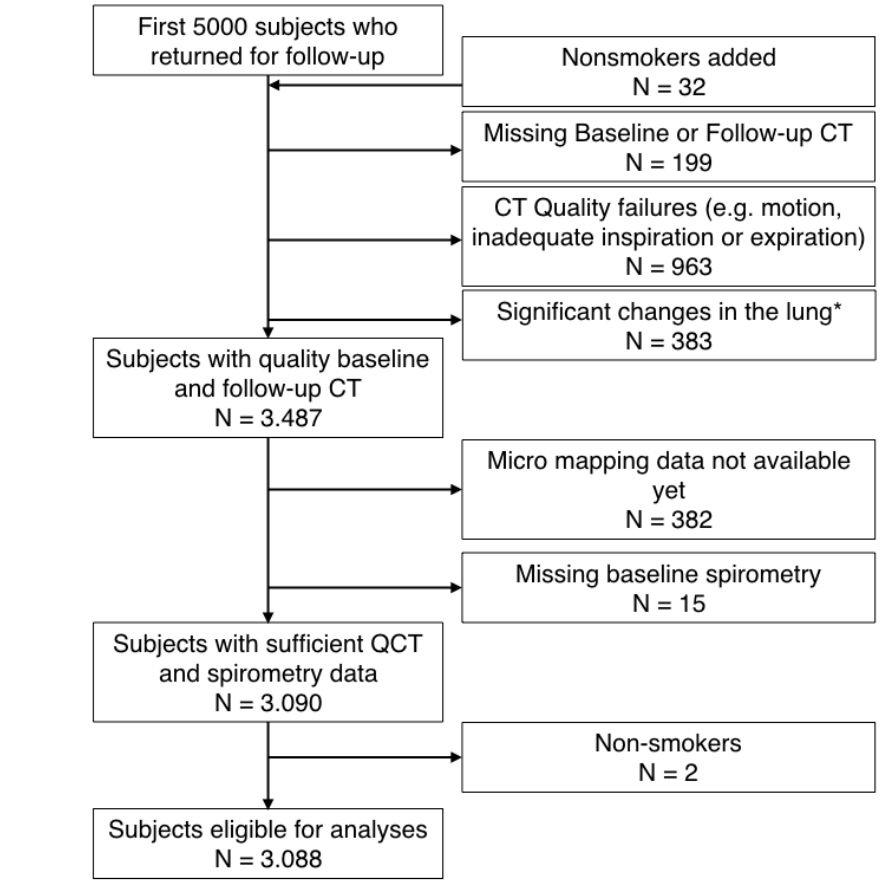
Online Supplement
Progression of Emphysema and Small Airways Disease in Cigarette Smokers

Figure S1. Consort diagram.



*Lobectomy or other surgery, pneumonia or other lung disease, other anatomic changes.

Figure S2. Change in fSAD among subjects in (A) GOLD 0, (B) GOLD 1, (C) GOLD 2, and (D) GOLD 3/4. The gray area depicts the 5th to 95th percentile of change in nonsmokers. The dark pink area denotes 5% of subjects that have the biggest change. The light pink area denotes all subjects that change more than nonsmokers. fSAD change appears quite similar across GOLD stages.

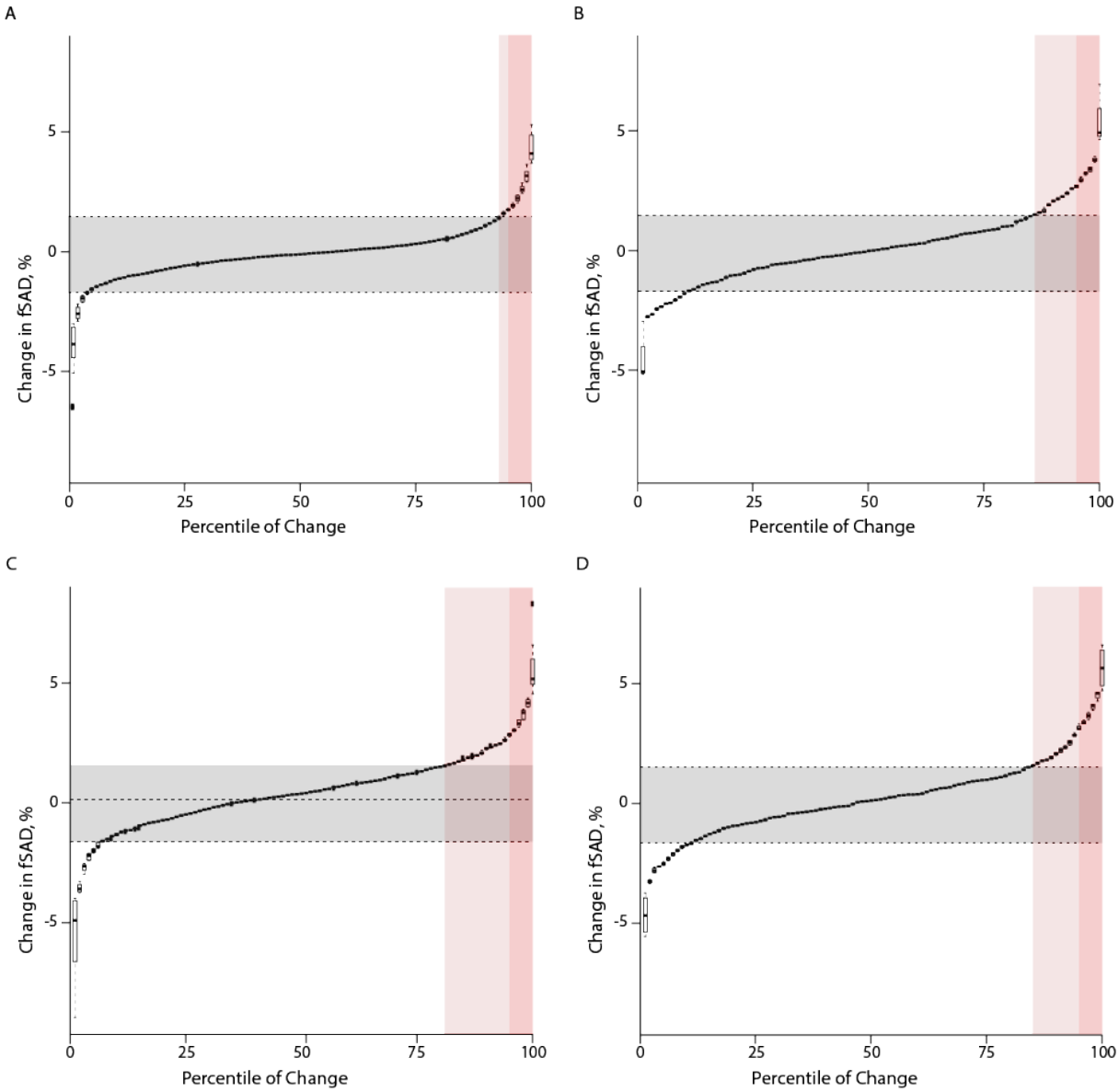


Figure S3. Change in (A) emphysema, (B) fSAD, and (C) FEV_1 in PRISm subjects (n = 305). The gray area depicts the 5^{th} to 95^{th} percentile of change in nonsmokers. The dark pink area denotes 5% of subjects that have the biggest change. The light pink area denotes all subjects that change more than nonsmokers.

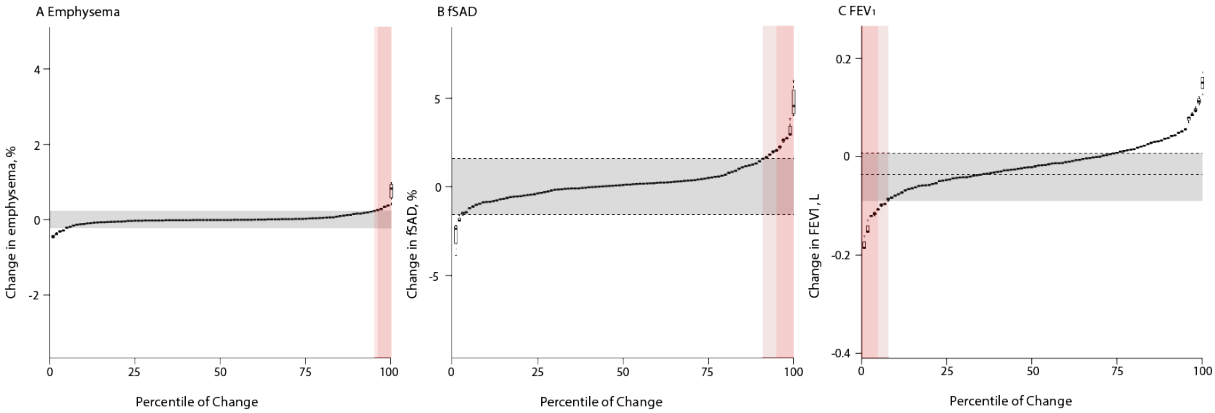


Table S1. Baseline characteristics (fSAD at baseline, 6MWD, SGRQ, MMRC, and exacerbations) for progressing and non-progressing subjects, stratified by GOLD stage (nonsmokers not included). Subjects were defined as 'progressing' when their emphysema and/or FEV_1 changed beyond the 95th percentile of change observed in nonsmokers (0.25% emphysema progression per year and 89 mL decrease in FEV_1 per year).

GOLD stage	Progression group	fSAD, %	6MWD, m	SGRQ	MMRC	Exacerbations, n (%)
GOLD 0	No progression (n = 1174)	8.0 (5.5 – 12.0)	488 (420 – 549)	7.6 (2.3 – 18.9)	0 (0 - 1)	92 (7.9%)
	Progression in emphysema (n = 89)	13.6 (8.5 – 19.3)	461 (411 – 518)	10.2 (3.8 – 24.1)	0 (0 - 2)	13 (14.6%)
	Progression in FEV_1 (n = 186)	9.2 (5.9 – 14.3)	480 (414 – 548)	8.2 (2.4 – 28.6)	0 (0 - 1)	17 (9.1%)
PRISm	No progression (n = 269)	7.9 (4.8 – 11.3)	425 (354 – 483)	18.9 (5.7 – 39.0)	1 (0 - 2)	54 (20.5%)
	Progression in emphysema (n = 16)	13.4 (9.7 – 14.8)	395 (325 – 482)	30.8 (9.9 – 43.7)	1.5 (0 - 3)	2 (12.5%)
	Progression in FEV_1 (n = 22)	9.8 (7.1 – 12.9)	441 (373 – 516)	20.4 (6.9 – 32.3)	1 (0 - 2)	7 (31.8%)
GOLD 1	No progression (n = 173)	14.4 (7.8 – 23.2)	489 (426 – 546)	9.2 (3.1 – 21.1)	0 (0 - 1)	16 (9.5%)
	Progression in emphysema (n = 61)	18.8 (13.8 – 23.3)	457 (372 – 522)	17.5 (7.2 – 28.5)	0 (0 - 1)	9 (14.8%)
	Progression in FEV_1 (n = 50)	18.5 (14.3 – 24.3)	484 (427 – 549)	13.7 (6.2 – 24.8)	0 (0 - 1)	8 (16.0%)
GOLD 2	No progression (n = 325)	17.5 (11.0 – 26.7)	438 (369 – 506)	23.2 (10.7 – 42.3)	1 (0 - 3)	78 (24.5%)

	Progression in emphysema (n = 235)	25.3 (16.8 – 31.9)	432 (367 – 495)	29.6 (13.6 – 46.1)	1 (0 - 3)	61 (26.0%)
	Progression in FEV_1 (n = 114)	26.9 (16.7 – 33.0)	416 (347 – 500)	29.5 (11.8 – 50.3)	1 (0 - 3)	29 (25.4%)
GOLD 3/4	No progression (n = 154)	33.4 (25.7 – 40.7)	376 (296 – 426)	40.7 (23.1 – 57.3)	2 (1 - 3)	55 (36.2%)
	Progression in emphysema (n = 238)	35.9 (28.2 – 41.1)	366 (297 – 429)	42.8 (30.0 – 56.0)	3 (2 - 3)	105 (44.1%)
	Progression in FEV_1 (n = 25)	33.5 (23.3 – 37.5)	357 (302 – 442)	47.3 (35.2 – 65.3)	3 (2 - 4)	9 (36.0%)

fSAD: functional small airways disease; 6MWD: six-minute walking distance; SGRQ: St. George's Respiratory Questionnaire; MMRC: British modified Medical Research Council dyspnea questionnaire; GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease; FEV_1: forced expiratory volume in one second; PRISm: preserved ratio impaired spirometry ($FEV_1 < 80\%$ and FEV_1/forced vital capacity ≥ 0.7)

Table S2. Multivariate linear mixed models using log(emphysema) as outcome. The model includes age, gender, race, BMI, smoking status, and pack years. By including an interaction with observation time, differences in the increase in log(emphysema) per year were calculated. Models were stratified based on GOLD status and were corrected for FRC/TLC and study center.

GOLD group	Parameter	Increment or comparison	Estimate (SE)	p-value
GOLD 0				
	Age	+ 1 year	0.043 (0.0059)	**< 0.001**
	Gender, female	Male	-0.90 (0.082)	**< 0.001**
	Race, African American	non-Hispanic white	-0.29 (0.12)	**0.016**
	BMI	+ 1 kg/m^2	-0.056 (0.0072)	**< 0.001**
	Smoking status, former smoker	Current smoker	-0.34 (0.10)	**< 0.001**
	Pack years	+ 1 pack year	-0.00048 (0.0021)	0.82
	Observation time	+ 1 year	-0.016 (0.059)	0.78
	Observation time * age	+ 1 year per year	0.0013 (0.00080)	0.10
	Observation time * gender, female	Male	-0.026 (0.011)	**0.024**
	Observation time * race, African American	non-Hispanic white	-0.00240 (0.016)	0.80
	Observation time * BMI	+ 1 kg/m^2 per year	-0.0016 (0.0010)	0.10
	Observation time * smoking status, former smoking	Current smoking	0.054 (0.014)	**< 0.001**
	Observation time * pack years	+ 1 pack year per year	0.00064 (0.00029)	**0.030**
PRISm				
	Age	+ 1 year	0.043 (0.014)	**0.0018**
	Gender, female	Male	-0.86 (0.18)	**< 0.001**
	Race, African American	non-Hispanic white	-0.12 (0.23)	0.58
	BMI	+ 1 kg/m^2	-0.020 (0.013)	0.13
	Smoking status, former smoker	Current smoker	-0.56 (0.22)	**0.011**
	Pack years	+ 1 pack year	0.0015 (0.0043)	0.72
	Observation time	+ 1 year	-0.23 (0.13)	0.086
	Observation time * age	+ 1 year per year	0.0048 (0.0018)	0.31
	Observation time * gender, female	Male	-0.015 (0.024)	0.53
	Observation time * race, African American	non-Hispanic white	0.060 (0.028)	**0.0057**
	Observation time * BMI	+ 1 kg/m^2 per year	-0.0018 (0.0017)	0.31
	Observation time * smoking status, former smoking	Current smoking	0.077 (0.028)	**0.0057**

	Observation time * pack years	+ 1 pack year per year	0.00064 (0.00054)	0.24
GOLD 1				
	Age	+ 1 year	0.017 (0.013)	0.17
	Gender, female	Male	-0.72 (0.18)	**< 0.001**
	Race, African American	non-Hispanic white	-0.086 (0.27)	0.75
	BMI	+ 1 kg/m^2	-0.081 (0.019)	**< 0.001**
	Smoking status, former smoker	Current smoker	-0.87 (0.21)	**< 0.001**
	Pack years	+ 1 pack year	0.015 (0.0042)	**< 0.001**
	Observation time	+ 1 year	0.082 (0.10)	0.41
	Observation time * age	+ 1 year per year	-0.00026 (0.0013)	0.84
	Observation time * gender, female	Male	-0.0052 (0.019)	0.78
	Observation time * race, African American	non-Hispanic white	-0.025 (0.028)	0.36
	Observation time * BMI	+ 1 kg/m^2 per year	-0.00065 (0.0019)	0.73
	Observation time * smoking status, former smoking	Current smoking	0.079 (0.021)	**< 0.001**
	Observation time * pack years	+ 1 pack year per year	-0.00012 (0.00043)	0.79
GOLD 2				
	Age	+ 1 year	0.028 (0.0087)	**0.0014**
	Gender, female	Male	-0.39 (0.12)	**0.0013**
	Race, African American	non-Hispanic white	-0.18 (0.19)	0.34
	BMI	+ 1 kg/m^2	-0.085 (0.011)	**< 0.001**
	Smoking status, former smoker	current smoker	-0.92 (0.14)	**< 0.001**
	Pack years	+ 1 pack year	0.010 (0.0026)	**< 0.001**
	Observation time	+ 1 year	0.15 (0.070)	**0.032**
	Observation time * age	+ 1 year per year	-0.00081 (0.00088)	0.36
	Observation time * gender, female	Male	-0.013 (0.012)	0.31
	Observation time * race, African American	non-Hispanic white	0.010 (0.017)	0.54
	Observation time * BMI	+ 1 kg/m^2 per year	-0.0018 (0.0011)	0.10
	Observation time * smoking status, former smoking	current smoking	0.043 (0.014)	**0.0028**
	Observation time * pack years	+ 1 pack year per year	0.00034 (0.00027)	0.21
GOLD 3/4				
	Age	+ 1 year	0.0071 (0.0076)	0.35
	Gender, female	Male	-0.11 (0.11)	0.31
	Race, African American	non-Hispanic white	-0.29 (0.15)	0.061
	BMI	+ 1 kg/m^2	-0.10 (0.0088)	**< 0.001**
	Smoking status, former smoker	Current smoker	-1,00 (0.12)	**< 0.001**
	Pack years	+ 1 pack year	0.0016 (0.0022)	0.48
	Observation time	+ 1 year	0.054 (0.055)	0.33

	Observation time * age	+ 1 year per year	-0.00081 (0.00071)	0.25
	Observation time * gender, male	Female	0.0085 (0.010)	0.40
	Observation time * race, African American	non-Hispanic white	-0.011 (0.014)	0.43
	Observation time * BMI	+ 1 kg/m^2 per year	0.0067 (0.00081)	0.41
	Observation time * smoking status, former smoking	Current smoking	0.051 (0.011)	**< 0.001**
	Observation time * pack years	+ 1 pack year per year	0.00038 (0.00021)	0.067

GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease; SE: standard error; BMI: body mass index; PRISm: preserved ratio impaired spirometry (FEV_1 < 80% and $FEV_1/FVC \geq 0.7$)

Table S3. Multivariate linear mixed models using (log)FEV_1 as outcome. The model includes age, gender, race, BMI, smoking status, and pack years. By including an interaction with observation time, differences in the increase in FEV_1 per year were calculated. Models were stratified based on GOLD status and were corrected for study center.

GOLD group	Parameter	Increment or comparison	Estimate (SE)	p-value
GOLD 0				
	Age	+ 1 year	-0.012 (0.00056)	**< 0.001**
	Gender, female	Male	-0.34 (0.0080)	**< 0.001**
	Race, African American	non-Hispanic white	-0.14 (0.011)	**< 0.001**
	BMI	+ 1 kg/m^2	-0.0039 (0.00071)	**< 0.001**
	Smoking status, former smoker	Current smoker	-0.025 (0.0098)	**0.010**
	Pack years	+ 1 pack year	-0.00019 (0.00021)	0.36
	Observation time	+ 1 year	-0.0085 (0.0049)	0.083
	Observation time * age	+ 1 year per year	-0.00020 (0.000066)	**0.0024**
	Observation time * gender, female	Male	-0.0011 (0.00095)	0.24
	Observation time * race, African American	non-Hispanic white	0.00070 (0.0013)	0.59
	Observation time * BMI	+ 1 kg/m^2 per year	0.00031 (0.000085)	**< 0.001**
	Observation time * smoking status, former smoking	Current smoking	-0.0031 (0.0012)	**0.0079**
	Observation time * pack years	+ 1 pack year per year	-0.00074 (0.000024)	**0.0025**
PRISm				
	Age	+ 1 year	-0.011 (0.0015)	**< 0.001**
	Gender, female	Male	-0.35 (0.020)	**< 0.001**
	Race, African American	non-Hispanic white	-0.20 (0.024)	**< 0.001**
	BMI	+ 1 kg/m^2	-0.0048 (0.0015)	**0.0015**

	Smoking status, former smoker	Current smoker	0.0040 (0.024)	0.87
	Pack years	+ 1 pack year	-0.00087 (0.00047)	0.066
	Observation time	+ 1 year	-0.026 (0.018)	0.14
	Observation time * age	+ 1 year per year	0.00026 (0.00023)	0.26
	Observation time * gender, female	Male	-0.0044 (0.0031)	0.16
	Observation time * race, African American	non-Hispanic white	0.0056 (0.0037)	0.14
	Observation time * BMI	+ 1 kg/m^2 per year	0.00018 (0.00023)	0.45
	Observation time * smoking status, former smoking	Current smoking	-0.00069 (0.0037)	0.85
	Observation time * pack years	+ 1 pack year per year	-0.00011 (0.000073)	0.12
GOLD 1				
	Age	+ 1 year	-0.012 (0.0013)	**< 0.001**
	Gender, female	Male	-0.39 (0.020)	**< 0.001**
	Race, African American	non-Hispanic white	-0.19 (0.030)	**< 0.001**
	BMI	+ 1 kg/m^2	-0.0042 (0.0020)	**0.038**
	Smoking status, former smoker	Current smoker	-0.014 (0.023)	0.55
	Pack years	+ 1 pack year	-0.00074 (0.00046)	0.11
	Observation time	+ 1 year	0.00089 (0.015)	0.95
	Observation time * age	+ 1 year per year	-0.00035 (0.00019)	0.062
	Observation time * gender, female	Male	-0.0023 (0.0028)	0.40
	Observation time * race, African American	non-Hispanic white	0.00041 (0.00041)	0.92
	Observation time * BMI	+ 1 kg/m^2 per year	0.00013 (0.00028)	0.65
	Observation time * smoking status, former smoking	Current smoking	-0.0094 (0.0032)	**0.0033**
	Observation time * pack years	+ 1 pack year per year	0.000019 (0.000064)	0.77
GOLD 2				
	Age	+ 1 year	-0.013 (0.0013)	**< 0.001**
	Gender, female	Male	-0.34 (0.019)	**< 0.001**
	Race, African American	non-Hispanic white	-0.18 (0.028)	**< 0.001**
	BMI	+ 1 kg/m^2	-0.0012 (0.0017)	0.47
	Smoking status, former smoker	current smoker	0.026 (0.022)	0.21
	Pack years	+ 1 pack year	-0.00033 (0.00040)	0.41
	Observation time	+ 1 year	-0.032 (0.017)	0.059
	Observation time * age	+ 1 year per year	-0.000012 (0.00021)	0.96
	Observation time * gender, female	Male	0.0020 (0.0029)	0.49
	Observation time * race, African American	non-Hispanic white	-0.0052 (0.0039)	0.18
	Observation time * BMI	+ 1 kg/m^2 per year	0.00043 (0.00026)	0.10
	Observation time * smoking status, former smoking	current smoking	-0.0054 (0.0034)	0.12
	Observation time * pack years	+ 1 pack year per year	-0.000080	0.20

		(0.000063)	
GOLD 3/4			
Age	+ 1 year	-0.0084 (0.0021)	**< 0.001**
Gender, female	Male	-0.33 (0.029)	**< 0.001**
Race, African American	non-Hispanic white	-0.042 (0.040)	0.29
BMI	+ 1 kg/m^2	0.0069 (0.0024)	**0.0036**
Smoking status, former smoker	Current smoker	0.091 (0.033)	**0.0066**
Pack years	+ 1 pack year	-0.00040 (0.00060)	0.51
Observation time	+ 1 year	-0.11 (0.024)	**< 0.001**
Observation time * age	+ 1 year per year	0.00077 (0.00031)	**0.015**
Observation time * gender, male	Female	0.00044 (0.0045)	0.92
Observation time * race, African American	non-Hispanic white	0.0017 (0.0061)	0.78
Observation time * BMI	+ 1 kg/m^2 per year	0.0013 (0.00036)	**< 0.001**
Observation time * smoking status, former smoking	Current smoking	0.0058 (0.0051)	0.26
Observation time * pack years	+ 1 pack year per year	-0.00012 (0.000091)	0.21

GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease; BMI: body mass index; PRISm: preserved ratio impaired spirometry (FEV_1 < 80% and $FEV_1/FVC \geq 0.7$)

Table S4. Multivariate results of logistic regression models with emphysema progression (yes/no) as outcome and clinical variables (fSAD, 6MWD, SGRQ, MMRC, and exacerbations) included as predictors. Subjects were defined as 'progressing' when their emphysema changed beyond the 95th percentile of change observed in nonsmokers (0.25% emphysema progression per year). Similarly, the presence of baseline emphysema was defined as having more than the 95th percentile in nonsmokers (>1.31%). All models were adjusted for age, gender, race, BMI, smoking status, and pack years. Bold numbers denote p-values < 0.05. Note that these p-values are not adjusted for multiple comparisons. In GOLD 0 there were 108 (7.6%) emphysema progressors, in GOLD 1 78 (29.2%), in GOLD 2 293 (47.6%), in GOLD 3/4 257 (64.6%), and 18 (5.9%) in subjects with Preserved Ratio Impaired Spirometry (PRISm). The low number of subjects progressing in PRISm did not allow for multivariate comparisons. These totals included subjects who progressed both in emphysema and FEV_1.

GOLD group	Parameter	Increment or comparison	OR (95% CI)	p-value
GOLD 0				
	Emphysema present	Emphysema not present	4.32 (2.30 – 8.14)	**< 0.001**
	fSAD	+ 1%	1.06 (1.04 – 1.09)	**< 0.001**
	fSAD, no baseline emphysema	+ 1%	1.06 (1.02 – 1.10)	**0.006**
	fSAD, with baseline emphysema	+ 1%	1.02 (0.99 – 1.04)	0.15
	6MWD	+ 100m	0.99 (0.99 – 0.99)	**0.007**
	SGRQ	+ 1 unit	1.02 (1.00 – 1.03)	**0.04**
	MMRC	+ 1 unit	1.26 (1.01 – 1.56)	**0.04**
	Exacerbations	No exacerbations	1.98 (1.32 – 2.96)	**< 0.001**
GOLD 1				
	Emphysema present	Emphysema not present	5.16 (2.89 – 9.22)	**< 0.001**
	fSAD	+ 1%	1.06 (1.03 – 1.10)	**< 0.001**
	fSAD, no baseline emphysema	+ 1%	1.17 (1.09 – 1.26)	**< 0.001**
	fSAD, with baseline emphysema	+ 1%	0.99 (0.94 – 1.04)	0.63
	6MWD	+ 100m	0.99 (0.99 – 0.99)	**< 0.001**
	SGRQ	+ 1 unit	1.03 (1.01 – 1.05)	**0.004**
	MMRC	+ 1 unit	1.16 (0.87 – 1.56)	0.31
	Exacerbations	No exacerbations	1.70 (0.82 – 3.54)	0.15
GOLD 2				
	Emphysema present	Emphysema not present	5.69 (2.48 –13.06)	**< 0.001**
	fSAD	+ 1%	1.04 (1.01 – 1.06)	**0.003**
	fSAD, no baseline emphysema	+ 1%	1.04 (0.98 – 1.10)	0.16
	fSAD, with baseline emphysema	+ 1%	0.99 (0.98 – 1.01)	0.40
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.49
	SGRQ	+ 1 unit	1.01 (1.00 – 1.02)	0.06
	MMRC	+ 1 unit	1.13 (0.97 – 1.30)	0.11
	Exacerbations	No exacerbations	1.20 (0.99 – 1.46)	0.06
GOLD 3/4				
	Emphysema present	Emphysema not present	5.55 (2.26 – 13.58)	**<0.001**
	fSAD	+ 1%	1.02 (0.99 – 1.04)	0.16
	fSAD, no baseline emphysema	+ 1%	1.08 (1.01 – 1.15)	**0.03**
	fSAD, with baseline emphysema	+ 1%	0.99 (0.97 – 1.01)	0.37
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.08
	SGRQ	+ 1 unit	1.01 (1.00 – 1.03)	0.15

	MMRC	+ 1 unit	1.22 (1.00 – 1.49)	0.05
	Exacerbations	No exacerbations	1.52 (1.09 – 2.11)	**0.01**

GOLD: Global Initiative for Obstructive Lung Disease; OR: odds ratio; CI: confidence interval; fSAD: functional small airways disease; 6MWD: six-minute walking distance; SGRQ: St. George's Respiratory Questionnaire; MMRC: British modified Medical Research Council dyspnea questionnaire

Table S5. Multivariate results of logistic regression models with FEV_1 progression (yes/no) as outcome and clinical variables (fSAD, 6MWD, SGRQ, MMRC, and exacerbations) included as predictors. Subjects were defined as 'progressing' when their FEV_1 changed beyond the 95^{th} percentile of change observed in nonsmokers (89 mL decrease in FEV_1 per year). Similarly, the presence of baseline emphysema was defined as having more than the 95^{th} percentile in nonsmokers (>1.31%). All models were adjusted for age, gender, race, BMI, smoking status, and pack years. Bold numbers denote p-values < 0.05. Note that these p-values are not adjusted for multiple comparisons. In GOLD 0 there were 205 (14.3%) FEV_1 progressors, in GOLD 1 67 (25.1%), and in GOLD 2 172 (27.9%). These totals included subjects who progressed both in emphysema and FEV_1. Multivariate analyses were not performed in GOLD 3/4 and PRISm subjects because of the small number of FEV_1 progressors (n = 44 and n = 24, respectively).

GOLD group	Parameter	Increment or comparison	OR (95% CI)	p-value
GOLD 0				
	fSAD	+ 1%	1.02 (0.99 – 1.05)	0.12
	fSAD, no baseline emphysema	+ 1%	1.03 (0.99 – 1.06)	0.14
	Emphysema present	Emphysema not present	1.27 (0.89 – 1.79)	0.19
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.34
	SGRQ	+ 1 unit	1.01 (1.01 – 1.02)	**< 0.001**
	MMRC	+ 1 unit	1.09 (0.97 – 1.22)	0.17

	Exacerbations	No exacerbations	1.44 (0.82 – 2.56)	0.21
GOLD 1				
	fSAD	+ 1%	1.05 (1.01 – 1.09)	**0.02**
	fSAD, no baseline emphysema	+ 1%	1.01 (0.97 – 1.06)	0.58
	Emphysema present	Emphysema not present	3.32 (1.49 – 4.59)	**0.003**
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.78
	SGRQ	+ 1 unit	1.02 (1.00 – 1.03)	0.07
	MMRC	+ 1 unit	1.35 (1.11 – 1.64)	**0.002**
	Exacerbations	No exacerbations	1.76 (0.66 – 4.71)	0.26
GOLD 2				
	fSAD	+ 1%	1.07 (1.06 – 1.09)	**< 0.001**
	fSAD, no baseline emphysema	+ 1%	1.06 (1.04 – 1.08)	**< 0.001**
	Emphysema present	Emphysema not present	4.09 (2.44 – 6.86)	**< 0.001**
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.06
	SGRQ	+ 1 unit	1.00 (0.99 – 1.02)	0.43
	MMRC	+ 1 unit	0.98 (0.80 – 1.20)	0.86
	Exacerbations	No exacerbations	1.29 (0.79 –2.11)	0.31

Sensitivity analysis

Table S6. Multivariate results of logistic regression models with emphysema progression (yes/no) as outcome and clinical variables (fSAD, 6MWD, SGRQ, MMRC, and exacerbations) included as predictors. Subjects were defined as 'progressing' when their emphysema changed beyond the 90th percentile of change observed in nonsmokers (0.14% emphysema progression per year). Similarly, the presence of baseline emphysema was defined as having more than the 90th percentile in nonsmokers (>0.80%). All models were adjusted for age, gender, race, BMI, smoking status, and pack years. Bold numbers denote p-values < 0.05. Note that these p-values are not adjusted for multiple comparisons. In GOLD 0 there were 195 (13.6%) emphysema progressors, in GOLD 1 109 (40.8%), in GOLD 2 363 (58.9%), in GOLD 3/4 285 (71.6%), and 44 (14.4%) in subjects with Preserved Ratio Impaired Spirometry (PRISm). These totals included subjects who progressed both in emphysema and FEV_1.

GOLD group	Parameter	Increment or comparison	OR (95% CI)	p-value
GOLD 0				
	Emphysema present	Emphysema not present	3.02 (1.57 – 5.82)	**< 0.001**
	fSAD	+ 1%	1.05 (1.03 – 1.08)	**< 0.001**
	fSAD, no baseline emphysema	+ 1%	1.10 (1.05 – 1.16)	**< 0.001**
	fSAD, with baseline emphysema	+ 1%	1.00 (0.97 – 1.02)	0.79
	6MWD	+ 100m	0.99 (0.99 – 0.99)	**0.01**
	SGRQ	+ 1 unit	1.02 (1.01 – 1.03)	**0.001**
	MMRC	+ 1 unit	1.13 (0.99 – 1.29)	0.06
	Exacerbations	No exacerbations	1.51 (1.03 – 2.19)	**0.03**
PRISm				
	Emphysema present	Emphysema not present	5.73 (1.98 – 16.61)	**0.001**
	fSAD	+ 1%	1.11 (1.05 – 1.18)	**< 0.001**
	fSAD, no baseline emphysema	+ 1%	1.20 (1.05 – 1.38)	**0.007**
	fSAD, with baseline emphysema	+ 1%	0.98 (0.88 – 1.10)	0.77
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.13
	SGRQ	+ 1 unit	1.01 (0.99 – 1.02)	0.50
	MMRC	+ 1 unit	1.11 (0.78 – 1.58)	0.57
	Exacerbations	No exacerbations	1.75 (1.06 – 2.87)	**0.03**
GOLD 1				
	Emphysema present	Emphysema not present	1.74 (0.64 – 4.68)	**< 0.001**
	fSAD	+ 1%	1.03 (1.00 – 1.08)	0.06
	fSAD, no baseline emphysema	+ 1%	1.15 (1.01 – 1.32)	**0.04**
	fSAD, with baseline emphysema	+ 1%	1.01 (0.97 – 1.06)	0.53
	6MWD	+ 100m	0.99 (0.99 – 0.99)	**< 0.001**
	SGRQ	+ 1 unit	1.03 (1.01 – 1.05)	**0.009**
	MMRC	+ 1 unit	1.21 (0.89 – 1.64)	0.23
	Exacerbations	No exacerbations	1.41 (0.77 – 2.57)	0.26
GOLD 2				
	Emphysema present	Emphysema not present	4.62 (1.63 –13.13)	**0.004**
	fSAD	+ 1%	1.03 (1.00 – 1.06)	**0.02**
	fSAD, no baseline emphysema	+ 1%	1.03 (0.98 – 1.09)	0.25
	fSAD, with baseline emphysema	+ 1%	1.00 (0.99 – 1.01)	0.57
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.91
	SGRQ	+ 1 unit	1.00 (0.99 – 1.01)	0.73
	MMRC	+ 1 unit	1.04 (0.93 – 1.16)	0.49

	Exacerbations	No exacerbations	1.03 (0.89 – 1.21)	0.71
GOLD 3/4				
	Emphysema present	Emphysema not present	3.50 (1.24 – 9.88)	**0.02**
	fSAD	+ 1%	1.01 (0.99 – 1.03)	0.39
	fSAD, no baseline emphysema	+ 1%	1.06 (0.95 – 1.18)	0.29
	fSAD, with baseline emphysema	+ 1%	0.99 (0.97 – 1.01)	0.46
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.11
	SGRQ	+ 1 unit	1.01 (1.00 – 1.02)	0.15
	MMRC	+ 1 unit	1.14 (1.00 – 1.30)	0.06
	Exacerbations	No exacerbations	1.30 (1.00 – 1.68)	0.05

GOLD: Global Initiative for Obstructive Lung Disease; OR: odds ratio; CI: confidence interval; fSAD: functional small airways disease; 6MWD: six-minute walking distance; SGRQ: St. George's Respiratory Questionnaire; MMRC: British modified Medical Research Council dyspnea questionnaire

Table S7. Multivariate results of logistic regression models with emphysema progression (yes/no) as outcome and clinical variables (fSAD, 6MWD, SGRQ, MMRC, and exacerbations) included as predictors. Subjects were defined as 'progressing' when their emphysema changed beyond the 97.5th percentile of change observed in nonsmokers (0.45% emphysema progression per year). Similarly, the presence of baseline emphysema was defined as having more than the 97.5th percentile in nonsmokers (>1.72%). All models were adjusted for age, gender, race, BMI, smoking status, and pack years. Bold numbers denote p-values < 0.05. Note that these p-values are not adjusted for multiple comparisons. In GOLD 0 there were 53 (3.7%) emphysema progressors, in GOLD 1 53 (19.9%), in GOLD 2 208 (33.8%), in GOLD 3/4 216 (51.0%), and 4 (1.3%) in subjects with Preserved Ratio Impaired Spirometry (PRISm). These totals included subjects who progressed both in emphysema and FEV_1. The low number of subjects progressing in PRISm did not allow for multivariate comparisons.

GOLD group	Parameter	Increment or comparison	OR (95% CI)	p-value
GOLD 0				
	Emphysema present	Emphysema not present	11.1 (5.71 – 21.68)	**< 0.001**

	fSAD	+ 1%	1.09 (1.06 – 1.12)	**< 0.001**
	fSAD, no baseline emphysema	+ 1%	1.06 (1.00 – 1.12)	0.067
	fSAD, with baseline emphysema	+ 1%	1.04 (1.00 – 1.08)	0.056
	6MWD	+ 100m	0.99 (0.99 – 0.99)	**0.009**
	SGRQ	+ 1 unit	1.04 (1.01 – 1.07)	**0.007**
	MMRC	+ 1 unit	1.59 (1.10 – 2.30)	**0.01**
	Exacerbations	No exacerbations	2.29 (1.22 – 4.28)	**0.01**
GOLD 1				
	Emphysema present	Emphysema not present	6.38 (2.76 – 14.74)	**< 0.001**
	fSAD	+ 1%	1.05 (1.01 – 1.10)	**0.01**
	fSAD, no baseline emphysema	+ 1%	1.13 (1.03 – 1.24)	**0.007**
	fSAD, with baseline emphysema	+ 1%	0.96 (0.90 – 1.03)	0.27
	6MWD	+ 100m	0.99 (0.99 – 0.99)	**< 0.001**
	SGRQ	+ 1 unit	1.04 (1.02 – 1.06)	**< 0.001**
	MMRC	+ 1 unit	1.24 (0.93 – 1.64)	0.14
	Exacerbations	No exacerbations	1.73 (0.57 – 5.21)	0.33
GOLD 2				
	Emphysema present	Emphysema not present	12.9 (5.06 –32.90)	**< 0.001**
	fSAD	+ 1%	1.05 (1.02 – 1.07)	**< 0.001**
	fSAD, no baseline emphysema	+ 1%	1.02 (0.98 – 1.06)	0.34
	fSAD, with baseline emphysema	+ 1%	1.00 (0.98 – 1.01)	0.69
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.80
	SGRQ	+ 1 unit	1.02 (1.00 – 1.03)	0.01
	MMRC	+ 1 unit	1.24 (1.10 – 1.41)	**< 0.001**
	Exacerbations	No exacerbations	1.43 (1.04 – 1.95)	**0.03**
GOLD 3/4				
	Emphysema present	Emphysema not present	12.36 (4.29 – 35.59)	**<0.001**
	fSAD	+ 1%	1.03 (1.03 – 1.05)	**0.02**
	fSAD, no baseline emphysema	+ 1%	1.00 (0.91 – 1.10)	0.95
	fSAD, with baseline emphysema	+ 1%	1.00 (0.98 – 1.02)	0.73
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.12
	SGRQ	+ 1 unit	1.01 (1.00 – 1.03)	0.14
	MMRC	+ 1 unit	1.27 (0.99 – 1.63)	0.06
	Exacerbations	No exacerbations	1.66 (1.16 – 2.38)	**0.006**

GOLD: Global Initiative for Obstructive Lung Disease; OR: odds ratio; CI: confidence interval; fSAD: functional small airways disease; 6MWD: six-minute walking distance; SGRQ: St. George's Respiratory Questionnaire; MMRC: British modified Medical Research Council dyspnea questionnaire

Table S8. Multivariate results of logistic regression models with FEV_1 progression (yes/no) as outcome and clinical variables (fSAD, 6MWD, SGRQ, MMRC, and exacerbations) included as predictors. Subjects were defined as 'progressing' when their FEV_1 changed beyond the 90^{th} percentile of change observed in nonsmokers (76 mL per year). Similarly, the presence of baseline emphysema was defined as having more than the 90^{th} percentile in nonsmokers (>0.80%). All models were adjusted for age, gender, race, BMI, smoking status, and pack years. Bold numbers denote p-values < 0.05. Note that these p-values are not adjusted for multiple comparisons. In GOLD 0 there were 304 (21.3%) FEV_1 progressors, in GOLD 1 95 (35.6%), in GOLD 2 238 (38.6%), in GOLD 3/4 66 (16.6%), and 34 (11.1%) in subjects with Preserved Ratio Impaired Spirometry (PRISm). These totals included subjects who progressed both in emphysema and FEV_1. The low number of subjects progressing in GOLD 3/4 did not allow for multivariate comparisons.

GOLD group	Parameter	Increment or comparison	OR (95% CI)	p-value
GOLD 0				
	fSAD	+ 1%	1.03 (1.01 – 1.05)	**< 0.001**
	fSAD, no baseline emphysema	+ 1%	1.04 (1.01 – 1.07)	**0.009**
	Emphysema present	Emphysema not present	1.25 (1.02 – 1.55)	**0.04**
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.73
	SGRQ	+ 1 unit	1.02 (1.01 – 1.02)	**< 0.001**
	MMRC	+ 1 unit	1.14 (1.03 – 1.25)	**0.01**
	Exacerbations	No exacerbations	1.35 (0.80 – 2.28)	0.26
PRISm				
	fSAD	+ 1%	1.00 (0.95 – 1.06)	0.97
	fSAD, no baseline emphysema	+ 1%	1.05 (0.96 – 1.14)	0.31
	Emphysema present	Emphysema not present	0.81 (0.34 – 1.94)	0.64
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.69
	SGRQ	+ 1 unit	1.00 (0.98 – 1.02)	0.92
	MMRC	+ 1 unit	1.19 (0.86 – 1.65)	0.28
	Exacerbations	No exacerbations	1.74 (0.76 – 3.99)	0.19

GOLD 1				
	fSAD	+ 1%	1.04 (1.00 – 1.07)	**0.04**
	fSAD, no baseline emphysema	+ 1%	1.03 (0.96 – 1.11)	0.44
	Emphysema present	Emphysema not present	2.48 (1.55 – 3.98)	**< 0.001**
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.78
	SGRQ	+ 1 unit	1.01 (1.00 – 1.02)	0.16
	MMRC	+ 1 unit	1.34 (1.07 – 1.67)	**0.01**
	Exacerbations	No exacerbations	1.77 (0.83 –3.77)	0.14
GOLD 2				
	fSAD	+ 1%	1.06 (1.04 – 1.08)	**< 0.001**
	fSAD, no baseline emphysema	+ 1%	0.99 (0.91 – 1.09)	0.85
	Emphysema present	Emphysema not present	4.47 (2.53 – 7.91)	**< 0.001**
	6MWD	+ 100m	1.00 (1.00 – 1.00)	**0.04**
	SGRQ	+ 1 unit	1.01 (1.01 – 1.02)	**< 0.001**
	MMRC	+ 1 unit	1.05 (0.91 – 1.23)	0.49
	Exacerbations	No exacerbations	1.74 (1.29 –2.34)	**< 0.001**

GOLD: Global Initiative for Obstructive Lung Disease; OR: odds ratio; CI: confidence interval; fSAD: functional small airways disease; 6MWD: six-minute walking distance; SGRQ: St. George's Respiratory Questionnaire; MMRC: British modified Medical Research Council dyspnea questionnaire

Table S9. Multivariate results of logistic regression models with FEV_1 progression (yes/no) as outcome and clinical variables (fSAD, 6MWD, SGRQ, MMRC, and exacerbations) included as predictors. Subjects were defined as 'progressing' when their FEV_1 changed beyond the 97.5th percentile of change observed in nonsmokers (100 mL per year). Similarly, the presence of baseline emphysema was defined as having more than the 97.5th percentile in nonsmokers (>1.72%). All models were adjusted for age, gender, race, BMI, smoking status, and pack years. Bold numbers denote p-values < 0.05. Note that these p-values are not adjusted for multiple comparisons. In GOLD 0 there were 148 (10.3%) FEV_1 progressors, in GOLD 1 49 (18.4%), and in GOLD 2 123 (20.0%). These totals included subjects who progressed both in emphysema and FEV_1. Multivariate analyses were not performed in GOLD 3/4 and PRISm subjects because of the small number of FEV_1 progressors (n = 30 and n = 17, respectively).

GOLD group	Parameter	Increment or comparison	OR (95% CI)	p-value
GOLD 0				
	fSAD	+ 1%	1.02 (0.99 – 1.05)	0.15
	fSAD, no baseline emphysema	+ 1%	1.03 (0.99 – 1.07)	0.17
	Emphysema present	Emphysema not present	1.25 (0.73 – 2.15)	0.42
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.10
	SGRQ	+ 1 unit	1.01 (1.01 – 1.02)	**0.001**
	MMRC	+ 1 unit	1.02 (0.86 – 1.22)	0.82
	Exacerbations	No exacerbations	1.52 (0.95 – 2.43)	0.08
GOLD 1				
	fSAD	+ 1%	1.06 (1.01 – 1.10)	**0.01**
	fSAD, no baseline emphysema	+ 1%	1.08 (1.00 – 1.16)	0.05
	Emphysema present	Emphysema not present	2.48 (1.30 – 4.74)	**0.006**
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.22
	SGRQ	+ 1 unit	1.02 (1.00 – 1.04)	0.10
	MMRC	+ 1 unit	1.44 (1.12 – 1.87)	**0.005**
	Exacerbations	No exacerbations	1.58 (0.50 – 4.99)	0.44
GOLD 2				

fSAD	+ 1%	1.05 (1.02 – 1.07)	**< 0.001**
fSAD, no baseline emphysema	+ 1%	1.02 (0.98 – 1.06)	0.34
Emphysema present	Emphysema not present	12.90 (5.06 – 32.90)	**< 0.001**
6MWD	+ 100m	1.00 (1.00 – 1.00)	0.80
SGRQ	+ 1 unit	1.02 (1.00 – 1.03)	**0.005**
MMRC	+ 1 unit	1.24 (1.10 – 1.41)	**< 0.001**
Exacerbations	No exacerbations	1.43 (1.04 –1.95)	**0.03**

GOLD: Global Initiative for Obstructive Lung Disease; OR: odds ratio; CI: confidence interval; fSAD: functional small airways disease; 6MWD: six-minute walking distance; SGRQ: St. George's Respiratory Questionnaire; MMRC: British modified Medical Research Council dyspnea questionnaire

Table S10. Multivariate results of logistic regression models with FEV_1 progression (yes/no) as outcome and clinical variables (fSAD, emphysema, 6MWD, SGRQ, MMRC, and exacerbations) included as predictors. Subjects were defined as 'progressing' when their FEV_1 declined by 2% per year, for a total decline of approximately 10% from baseline over the 5 years of the study. The presence of baseline emphysema was defined as having more than the 95th percentile in nonsmokers (>1.31%). All models were adjusted for age, gender, race, BMI, smoking status, and pack years. Bold numbers denote p-values < 0.05. Note that these p-values are not adjusted for multiple comparisons. In GOLD 0 there were 495 (35.0%) FEV_1 progressors, in PRISm 87 (29.1%), in GOLD 1 129 (49.0%), in GOLD 2 309 (51.2%), and GOLD 3/4 226 (57.7%). These totals included subjects who progressed both in emphysema and FEV_1.

GOLD group	Parameter	Increment or comparison	OR (95% CI)	p-value
GOLD 0				
	fSAD	+ 1%	1.02 (1.01 – 1.03)	**< 0.001**
	fSAD, no baseline emphysema	+ 1%	1.02 (1.00 – 1.04)	**0.026**
	fSAD, with baseline emphysema	+ 1%	1.01 (0.97 – 1.05)	0.67
	Emphysema present	Emphysema not present	1.34 (1.08 – 1.66)	**0.008**
	6MWD	+ 100m	1.00 (1.00 – 1.00)	**0.027**
	SGRQ	+ 1 unit	1.01 (1.01 – 1.02)	**< 0.001**
	MMRC	+ 1 unit	1.05 (0.96 – 1.16)	0.29
	Exacerbations	No exacerbations	1.25 (0.94 – 1.66)	0.13
PRISm				
	fSAD	+ 1%	1.03 (1.00 – 1.06)	0.085
	fSAD, no baseline emphysema	+ 1%	1.06 (1.02 – 1.10)	**0.0033**
	fSAD, with baseline emphysema	+ 1%	0.92 (0.83 – 1.03)	0.13
	Emphysema present	Emphysema not present	1.00 (0.48 – 2.08)	0.99
	6MWD	+ 100m	1.00 (1.00 – 1.00)	0.23
	SGRQ	+ 1 unit	1.00 (0.99 – 1.01)	0.98

	MMRC	+ 1 unit	1.10 (0.97 – 1.25)	0.12
	Exacerbations	No exacerbations	1.55 (1.06 – 2.26)	**0.024**
GOLD 1				
	fSAD	+ 1%	1.02 (0.99 – 1.06)	0.14
	fSAD, no baseline emphysema	+ 1%	1.05 (1.00 – 1.10)	0.069
	fSAD, with baseline emphysema	+ 1%	0.98 (0.92 – 1.05)	0.64
	Emphysema present	Emphysema not present	1.59 (0.89 – 2.86)	0.12
	6MWD	+ 100m	1.00 (1.00 – 1.00)	**0.0048**
	SGRQ	+ 1 unit	1.01 (1.00 – 1.03)	0.074
	MMRC	+ 1 unit	1.19 (0.96 – 1.48)	0.12
	Exacerbations	No exacerbations	1.69 (0.80 –3.59)	0.17
GOLD 2				
	fSAD	+ 1%	1.07 (1.05 - 1.08)	**< 0.001**
	fSAD, no baseline emphysema	+ 1%	1.04 (1.01 - 1.07)	**0.0026**
	fSAD, with baseline emphysema	+ 1%	1.05 (1.03 - 1.07)	**< 0.001**
	Emphysema present	Emphysema not present	3.55 (2.63 - 4.78)	**< 0.001**
	6MWD	+ 100m	1.00 (1.00 - 1.00)	**0.0024**
	SGRQ	+ 1 unit	1.01 (1.01 - 1.02)	**< 0.001**
	MMRC	+ 1 unit	1.14 (1.03 - 1.26)	0.**010**
	Exacerbations	No exacerbations	1.65 (1.23 - 2.20)	**< 0.001**
GOLD 3/4				
	fSAD	+ 1%	1.02 (1.00 - 1.03)	**0.019**
	fSAD, no baseline emphysema	+ 1%	1.04 (0.99 - 1.09)	0.13
	fSAD, with baseline emphysema	+ 1%	1.00 (0.98 - 1.02)	0.72
	Emphysema present	Emphysema not present	2.29 (1.11 - 4.74)	**0.025**
	6MWD	+ 100m	1.00 (1.00 - 1.00)	**< 0.001**
	SGRQ	+ 1 unit	1.00 (0.99 - 1.02)	0.57
	MMRC	+ 1 unit	1.19 (0.97 - 1.45)	0.10
	Exacerbations	No exacerbations	0.78 (0.47 - 1.28)	0.33

GOLD: Global Initiative for Obstructive Lung Disease; OR: odds ratio; CI: confidence interval; fSAD: functional small airways disease; 6MWD: six-minute walking distance; SGRQ: St. George's Respiratory Questionnaire; MMRC: British modified Medical Research Council dyspnea questionnaire

Table S11. Multivariate results of logistic regression models with FEV_1 progression (yes/no) as outcome and clinical variables (fSAD, emphysema, 6MWD, SGRQ, MMRC, and

exacerbations) included as predictors. Subjects were defined as 'progressing' when their FEV_1 declined by 4% per year, for a total decline of approximately 20% from baseline over the 5 years of the study. The presence of baseline emphysema was defined as having more than the 95th percentile in nonsmokers (>1.31%). All models were adjusted for age, gender, race, BMI, smoking status, and pack years. Bold numbers denote p-values < 0.05. Note that these p-values are not adjusted for multiple comparisons. In GOLD 0 there were 107 (7.6%) FEV_1 progressors, in GOLD 2 178 (29.5%), and GOLD 3/4 139 (35.5%). These totals included subjects who progressed both in emphysema and FEV_1. The number of subjects progressing in the PRISm and GOLD 1 group did not allow for multivariate analyses (n = 29 and n = 45, respectively).

GOLD group	Parameter	Increment or comparison	OR (95% CI)	p-value
GOLD 0				
	fSAD	+ 1%	1.01 (0.98 – 1.04)	0.69
	fSAD, no baseline emphysema	+ 1%	1.01 (0.96 – 1.07)	0.64
	fSAD, with baseline emphysema	+ 1%	1.03 (0.97 – 1.09)	0.27
	Emphysema present	Emphysema not present	0.73 (0.46 – 1.16)	0.19
	6MWD	+ 100m	1.00 (1.00 – 1.00)	**0.038**
	SGRQ	+ 1 unit	1.02 (1.01 – 1.04)	**< 0.001**
	MMRC	+ 1 unit	1.12 (0.94 – 1.34)	0.20
	Exacerbations	No exacerbations	1.47 (0.93 – 2.34)	0.10
GOLD 2				
	fSAD	+ 1%	1.08 (1.06 - 1.09)	**< 0.001**
	fSAD, no baseline emphysema	+ 1%	1.02 (0.97 - 1.07)	0.37
	fSAD, with baseline emphysema	+ 1%	1.06 (1.04 - 1.08)	**< 0.001**
	Emphysema present	Emphysema not present	5.77 (3.80 - 8.77)	**< 0.001**
	6MWD	+ 100m	1.00 (1.00 - 1.00)	**0.0022**
	SGRQ	+ 1 unit	1.01 (1.01 - 1.02)	**< 0.001**
	MMRC	+ 1 unit	1.10 (0.97 - 1.24)	0.14

	Exacerbations	No exacerbations	1.99 (1.59 - 2.50)	**< 0.001**
GOLD 3/4				
	fSAD	+ 1%	1.02 (1.01 - 1.03)	**< 0.001**
	fSAD, no baseline emphysema	+ 1%	1.04 (1.00 - 1.09)	**0.043**
	fSAD, with baseline emphysema	+ 1%	1.01 (0.99 - 1.03)	0.17
	Emphysema present	Emphysema not present	1.90 (0.79 - 4.56)	0.15
	6MWD	+ 100m	1.00 (1.00 - 1.00)	0.77
	SGRQ	+ 1 unit	1.01 (0.99 - 1.02)	0.31
	MMRC	+ 1 unit	1.06 (0.94 - 1.20)	0.34
	Exacerbations	No exacerbations	1.15 (0.73 - 1.81)	0.56

GOLD: Global Initiative for Obstructive Lung Disease; OR: odds ratio; CI: confidence interval; fSAD: functional small airways disease; 6MWD: six-minute walking distance; SGRQ: St. George's Respiratory Questionnaire; MMRC: British modified Medical Research Council dyspnea questionnaire

Table S12. List of robust parameters with significant associations in all sensitivity analyses.

GOLD group	Parameter
GOLD 0	6MWD
	SGRQ
PRISm	fSAD, no baseline emphysema
	Exacerbations
GOLD 1	6MWD
GOLD 2	fSAD
	Emphysema present
	Exacerbations
GOLD 3/4	-

GOLD: Global Initiative for Obstructive Lung Disease; fSAD: functional small airways disease; 6MWD: six-minute walking distance; SGRQ: St. George's Respiratory Questionnaire

Voxel analysis

Table S13. Percentage of voxels shifting from Phase 1 to Phase 2 in GOLD 0 subjects. The table is stratified by progression status (no progression, progression in emphysema, progression in FEV_1). Data on subjects progressing in both emphysema and FEV_1 (n = 11) are not shown. Numbers show mean percentages of lung tissue and relative percentages for each row between brackets. For example, 82.48% of all lung voxels categorized as normal tissue at Phase 1 were also categorized as normal tissue at Phase 2 (93.39% of all normal voxels at Phase 1), whereas 4.95% of all lung voxels categorized as normal tissue at Phase 1 shifted to fSAD at Phase 2 (5.60% of all normal voxels at Phase 1). The total amount of normal tissue, fSAD, emphysema, and rest tissue at Phase 1 can be found at the right side of the table and the total amount of voxels categorized at Phase 2 can be found at the bottom of the table. All together the voxels of both Phase 1 or Phase 2 compile 100% of all lung voxels.

GOLD 0 subjects without progression (n = 1218)

Phase 1	Phase 2				
	Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Normal	82.48% (93.39%)	4.95% (5.60%)	0.17% (0.19%)	0.72% (0.82%)	88.32%
fSAD	5.63% (61.20%)	3.27% (35.54%)	0.16% (1.74%)	0.14% (1.52%)	9.20%
Emphysema	0.36 (45.57%)	0.25% (31.65%)	0.12% (15.19%)	0.06% (7.59%)	0.79%
Rest	1.34% (77.91%)	0.19% (11.05%)	0.05% (2.91)	0.14% (8.14%)	1.72%
Total	89.81%	8.66%	0.51%	1.06%	100%

GOLD 0 subjects with progression (n = 109)

Phase 1	Phase 2				
	Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Normal	65.02% (79.25%)	13.60% (16.58%)	1.41% (1.72%)	2.01% (2.45%)	82.04%
fSAD	4.93% (36.46%)	6.87% (50.81%)	1.33% (9.84%)	0.39% (2.88%)	13.52%
Emphysema	0.28% (13.73%)	0.63% (30.88%)	0.97% (47.55%)	0.16% (7.84%)	2.04%
Rest	1.02% (42.86%)	0.49% (20.59%)	0.41% (17.23%)	0.46% (19.33%)	2.38%
Total	71.25%	21.59%	4.12%	3.02%	100%

GOLD 0 subjects with FEV_1 progression (n = 89)

Phase 1	Phase 2				
	Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Normal	79.37% (91.96%)	5.87% (6.80%)	0.26% (0.30%)	0.81% (0.94%)	86.31%
fSAD	6.32% (60.48%)	3.78% (36.17%)	0.21% (2.01%)	0.14% (1.34%)	10.45%
Emphysema	0.45% (36.89%)	0.44% (36.07%)	0.27% (22.13%)	0.06% (4.92%)	1.22%
Rest	1.55% (77.50%)	0.26% (13.00%)	0.06% (3.00%)	0.13% (6.50%)	2.00%
Total	87.69%	10.35%	0.80%	1.14%	100%

Table S14. Percentage of voxels shifting from Phase 1 to Phase 2 in PRISm subjects. The table is stratified by progression status (no progression, progression in emphysema, progression in FEV_1). Data on subjects progressing in both emphysema and FEV_1 (n = 2) are not shown. Numbers show mean percentages of lung tissue and relative percentages for each row are shown between brackets. For example, in PRISm subjects without progression, 83.63% of all lung voxels categorized as normal tissue at Phase 1 were also categorized as normal tissue at Phase 2 (92.92%% of all normal voxels at Phase 1), whereas 5.58% of all lung voxels categorized as normal tissue at Phase 1 shifted to fSAD at Phase 2 (6.20% of all normal voxels at Phase 1). The total amount of normal tissue, fSAD, emphysema, and rest tissue at Phase 1 can be found at the right side of the table and the total amount of voxels categorized at Phase 2 can be found at the bottom of the table. All together the voxels of both Phase 1 or Phase 2 compile 100% of all lung voxels.

PRISm subjects without progression (n = 267)

		Phase 2				
		Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Phase 1	**Normal**	83.63% (92.92%)	5.58% (6.20%)	0.18% (0.20%)	0.61% (0.68%)	90.00%
	fSAD	5.33% (63.30%)	2.81% (33.37%)	0.16% (1.90%)	0.12% (1.43%)	8.42%
	Emphysema	0.22% (43.14%)	0.17% (33.33%)	0.09% (17.65%)	0.03% (5.88%)	0.51%
	Rest	0.82% (73.87%)	0.19% (17.12%)	0.03% (2.70%)	0.07% (6.31%)	1.11%
	Total	90.00%	8.75%	0.46%	0.83%	100%

PRISm subjects with emphysema progression (n = 26)

		Phase 2				
		Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Phase 1	**Normal**	65.42% (78.43%)	14.47% (17.35%)	1.29% (1.55%)	2.23% (2.67%)	83.41%

	fSAD	5.16% (40.28%)	6.13% (47.85%)	1.11% (8.67%)	0.41% (3.20%)	12.81%
	Emphysema	0.29% (15.85%)	0.59% (32.24%)	0.81% (44.26%)	0.14% (7.65%)	1.83%
	Rest	0.91% (46.43%)	0.45% (22.96%)	0.29% (14.80%)	0.31% (15.82%)	1.96%
	Total	71.78%	21.64%	3.50%	3.09%	100%

PRISm subjects with FEV_1 progression (n = 10)

	Phase 2					
		Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Phase 1	**Normal**	82.55% (93.17%)	5.71% (6.44%)	0.07% (0.08%)	0.27% (0.30%)	88.60%
	fSAD	6.32% (67.23%)	2.94% (31.28%)	0.08% (0.85%)	0.06% (0.64%)	9.40%
	Emphysema	0.33% (60.00%)	0.18% (32.73%)	0.03% (5.45%)	0.01% (1.82%)	0.55%
	Rest	1.29% (89.58%)	0.11% (7.64%)	0.01% (0.69%)	0.03% (2.08%)	1.44%
	Total	90.49%	8.94%	0.19%	0.37%	100%

Table S15. Percentage of voxels shifting from Phase 1 to Phase 2 in GOLD 1 subjects. The table is stratified by progression status (no progression, progression in emphysema, progression in FEV_1). Data on subjects progressing in both emphysema and FEV_1 (n = 14) are not shown. Numbers show mean percentages of lung tissue and relative percentages for each row are shown between brackets. For example, 70.08% of all lung voxels categorized as normal tissue at Phase 1 were also categorized as normal tissue at Phase 2 (89.49% of all normal voxels at Phase 1), whereas 6.95% of all lung voxels categorized as normal tissue at Phase 1 shifted to fSAD at Phase 2 (8.87% of all normal voxels at Phase 1). The total amount of normal tissue, fSAD, emphysema, and rest tissue at Phase 1 can be found at the right side of the table and the total amount of voxels categorized at Phase 2 can be found at the bottom of the table. All together the voxels of both Phase 1 or Phase 2 compile 100% of all lung voxels.

GOLD 1 subjects without progression (n = 178)

		Phase 2				
		Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Phase 1	**Normal**	70.08% (89.49%)	6.95% (8.87%)	0.38% (0.49%)	0.90% (1.15%)	78.31%
	fSAD	9.06% (55.89%)	6.19% (38.19%)	0.62% (3.82%)	0.34% (2.10%)	16.21%
	Emphysema	0.89% (30.38%)	0.95% (32.42%)	0.83% (28.33%)	0.26% (8.87%)	2.93%
	Rest	1.68% (65.63%)	0.40% (15.63%)	0.16% (6.25%)	0.32% (12.50%)	2.56%
	Total	81.71%	14.49%	1.99%	1.82%	100%

GOLD 1 subjects with emphysema progression (n = 57)

		Phase 2				
		Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Phase 1	**Normal**	55.51%	15.04% (20.24%)	1.97% (2.65%)	1.78% (2.40%)	74.30%

	(74.71%)				
fSAD	5.87% (32.09%)	9.70% (53.03%)	2.30% (12.58%)	0.42% (2.30%)	18.29%
Emphysema	0.42% (9.35%)	0.97% (21.60%)	2.81% (62.58%)	0.29% (6.46%)	4.49%
Rest	0.93% (31.63%)	0.53% (18.03%)	0.78% (26.53%)	0.70% (23.81%)	2.94%
Total	62.73%	26.24%	7.86%	3.19%	100%

GOLD 1 subjects with FEV_1 progression (n = 18)

	Phase 2				
	Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Normal	65.04% (86.64%)	8.38% (11.16%)	0.59% (0.79%)	1.06% (1.41%)	75.07%
fSAD	9.25% (54.93%)	6.59% (39.13%)	0.67% (3.98%)	0.33% (1.96%)	16.84%
Emphysema	1.26% (33.60%)	1.52% (40.53%)	0.75% (20.00%)	0.22% (5.87%)	3.75%
Rest	2.66% (61.43%)	0.98% (22.63%)	0.34% (7.85%)	0.35% (8.08%)	4.33%
Total	78.21	17.47	2.35%	1.96%	100%

Phase 1

Table S16. Percentage of voxels shifting from Phase 1 to Phase 2 in GOLD 2 subjects. The table is stratified by progression status (no progression, progression in emphysema, progression in FEV_1). Data on subjects progressing in both emphysema and FEV_1 (n = 39) are not shown. Numbers show mean percentages of lung tissue and relative percentages for each row are shown between brackets. For example, in GOLD 2 subjects without progression, 64.49% of all lung voxels categorized as normal tissue at Phase 1 were also categorized as normal tissue at Phase 2 (83.98% of all normal voxels at Phase 1), whereas 10.07% of all lung voxels categorized as normal tissue at Phase 1 shifted to fSAD at Phase 2 (13.11% of all normal voxels at Phase 1). The total amount of normal tissue, fSAD, emphysema, and rest tissue at Phase 1 can be found at the right side of the table and the total amount of voxels categorized at Phase 2 can be found at the bottom of the table. All together the voxels of both Phase 1 or Phase 2 compile 100% of all lung voxels.

GOLD 2 subjects without progression (n = 333)

		Phase 2				
		Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Phase 1	**Normal**	64.49% (83.98%)	10.07% (13.11%)	0.93% (1.21%)	1.30% (1.69%)	76.79%
	fSAD	8.43% (45.72%)	7.96% (43.17%)	1.58% (8.57%)	0.47% (2.55%)	18.44%
	Emphysema	0.43% (12.91%)	0.89% (26.73%)	1.81% (54.35%)	0.20% (6.01%)	3.33%
	Rest	0.67% (46.85%)	0.32% (22.38%)	0.23% (16.08%)	0.21% (14.69%)	1.43%
	Total	74.02%	19.24%	4.55%	2.18%	100%

GOLD 2 subjects with emphysema progression (n = 213)

		Phase 2				
		Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Phase 1	**Normal**	46.50%	6.82% (12.47%)	0.56% (1.02%)	0.81% (1.48%)	54.69%

	(85.02%)				
fSAD	14.97% (49.07%)	12.96% (42.48%)	1.91% (6.26%)	0.67% (2.20%)	30.51%
Emphysema	2.16% (17.68%)	4.06% (33.22%)	5.20% (42.55%)	0.80% (6.55%)	12.22%
Rest	1.34% (52.14%)	0.51% (19.84%)	0.30% (11.67%)	0.42% (16.34%)	2.57%
Total	64.97%	24.35%	7.97%	2.70%	100%

GOLD 2 subjects with FEV_1 progression (n = 31)

	Phase 2				
	Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Normal	50.87% (78.33%)	11.35% (17.48%)	1.24% (1.91%)	1.48% (2.28%)	64.94%
fSAD	13.43% (46.02%)	11.96% (40.99%)	2.79% (9.56%)	1.00% (3.43%)	29.18%
Emphysema	0.61% (14.06%)	1.25% (28.80%)	2.14% (49.31%)	0.34% (7.83%)	4.34%
Rest	0.57% (37.01%)	0.31% (20.13%)	0.39% (25.32%)	0.27% (17.53%)	1.54%
Total	65.48%	24.87%	6.56%	3.09%	100%

Phase 1

Table S17. Percentage of voxels shifting from Phase 1 to Phase 2 in GOLD 3 and 4 subjects. The table is stratified by progression status (no progression, progression in emphysema). Data on subjects progressing in both emphysema and FEV_1 (n = 10) and in FEV_1 only (n = 1) are not shown. Numbers show mean percentages of lung tissue and relative percentages for each row are shown between brackets. For example, in GOLD 3/4 subjects without progression, 38.59% of all lung voxels categorized as normal tissue at Phase 1 were also categorized as normal tissue at Phase 2 (78.32%% of all normal voxels at Phase 1), whereas 9.41% of all lung voxels categorized as normal tissue at Phase 1 shifted to fSAD at Phase 2 (19.10% of all normal voxels at Phase 1). The total amount of normal tissue, fSAD, emphysema, and rest tissue at Phase 1 can be found at the right side of the table and the total amount of voxels categorized at Phase 2 can be found at the bottom of the table. All together the voxels of both Phase 1 or Phase 2 compile 100% of all lung voxels.

GOLD 3/4 subjects without progression (n = 145)

		Phase 2				
		Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Phase 1	**Normal**	38.59% (78.32%)	9.41% (19.10%)	0.76% (1.54%)	0.51% (1.04%)	49.27%
	fSAD	12.55% (38.37%)	16.49% (50.41%)	3.23% (9.87%)	0.44% (1.35%)	32.71%
	Emphysema	1.65% (10.31%)	5.20% (32.50%)	8.73% (54.56%)	0.42% (2.63%)	16.00%
	Rest	0.95% (46.80%)	0.62% (30.54%)	0.29% (14.29%)	0.17% (8.37%)	2.03%
	Total	53.74%	31.72%	13.01%	1.54%	100%

GOLD 3/4 subjects with emphysema progression (n = 242)

		Phase 2				
		Normal	**fSAD**	**Emphysema**	**Rest**	**Total**
Phase 1	**Normal**	28.85% (64.11%)	13.45% (29.89%)	2.04% (4.53%)	0.66% (1.47%)	45.00%

fSAD	7.09% (20.31%)	19.52% (55.92%)	7.84% (22.46%)	0.46% (1.32%)	34.91%
Emphysema	0.73% (3.99%)	3.78% (20.64%)	13.47% (73.57%)	0.33% (1.80%)	18.31%
Rest	0.44% (24.58%)	0.52% (29.05%)	0.62% (34.64%)	0.21% (11.73%)	1.79%
Total	37.11%	37.27%	23.97%	1.66%	100%