

**Table S1** Participant demographic and clinical characteristics according to the smoking status

Variables	Smokers (n=314)			Never-smokers (n=167)		
	Control group (n=37)	SAD group (n=92)	GOLD I group (n=185)	Control group (n=48)	SAD group (n=65)	GOLD I group (n=54)
Demographic data						
Age, years	58±7	58±8	62±8*†	53±7	57±8*	61±8*†
Male sex	37 [100]	92 [100]	183 [99]	12 [25]	17 [26]	17 [32]
BMI, kg/m <sup>2</sup>	23.4±3.2	22.9±3.1	22.1±3.0	24.2±3.1	23.6±3.6	22.9±3.4
Smoking status						
Never						
Former	7 [19]	32 [35]	41 [22]†			
Current	30 [81]	60 [65]	144 [78]†			
Smoking index, pack×years	40±20	44±31	49±30			
Symptoms‡						
Chronic cough	9 [25]	30 [33]	54 [30]	6 [13]	8 [13]	10 [19]
Chronic sputum	6 [17]	32 [35]	64 [35]*	7 [15]	7 [11]	9 [17]
Dyspnea	0 [0]	0 [0]	2 [1]	1 [2]	4 [6]	3 [6]
Wheezing	1 [3]	10 [11]	15 [9]	2 [4]	7 [11]	6 [11]
Any symptom	10 [27]	40 [44]	77 [42]	7 [15]	15/65 [23]	16/54 [30]
Post-BD spirometry measures						
FEV <sub>1</sub> , L	3.00±0.40	2.50±0.40*	2.43±0.41*	2.48±0.53	2.08±0.45*	2.04±0.53*
FVC, L	3.77±0.57	3.41±0.57*	3.78±0.62*	3.00±0.67	2.74±0.68	3.09±0.77†
FEV <sub>1</sub> /FVC, %	80.0±4.2	73.7±3.9*	64.4±4.1*†	83.1±4.4	76.7±4.7*	66.2±3.4*†
FEV <sub>1</sub> %pred, %	107±12	92±11*	94±10*	108±12	97±16*	97±11*
MMEF, L	2.80±0.56	1.69±0.36*	1.16±0.37*†	2.60±0.58	1.55±0.33*	1.08±0.35*†
FEF50, L	3.69±0.67	2.41±0.49*	1.69±0.51*†	3.43±0.77	2.17±0.47*	1.57±0.49*†
FEF75, L	0.99±0.30	0.57±0.18*	0.38±0.17*†	0.97±0.43	0.51±0.16*	0.33±0.15*†
MMEF %pred, %	84±15	51±9*	37±10*†	82±16	52±10*	37±9*†
FEF50 %pred, %	92±16	61±12*	45±11*†	92±17	61±12*	44±11*†
FEF75 %pred, %	72±20	43±12*	32±14*†	68±25	39±12*	27±10*†

Data are mean ± standard deviation or n (%). The control group was defined as having normal lung function (non-COPD without SAD), the SAD group as having SAD but no COPD, and the GOLD I group as having mild COPD. Baseline characteristics were compared between the groups using one-way analysis of variance or Kruskal–Wallis test for continuous variables and chi-squared tests or Fisher's exact tests for categorical variables. Pairwise comparisons between groups were performed using the Bonferroni method. \*P<0.05 vs. the control group. †P<0.05 vs. the SAD group. ‡, numbers of participants with symptoms available: chronic cough =472, chronic sputum =478, wheezing =467. BMI, body mass index; FEF50, forced expiratory flow at 50% of vital capacity; FEF75, forced expiratory flow at 75% of vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MMEF, maximal mid-expiratory flow; SAD, small airway dysfunction.

**Table S2** Measurements at the anaerobic threshold and at the peak of symptom-limited incremental cycle exercise in smokers

Variables	Anaerobic Threshold †			Peak Exercise		
	Control	SAD	GOLD I	Control	SAD	GOLD I
Work rate, Watt	89±21	74±20*	70±22*	149±22	133±26*	123±25†
$\dot{V}O_2$ , L/min	1.10±0.19	1.01±0.23	0.99±0.23*	1.60±0.25	1.51±0.30	1.48±0.31
(% predicted maximum)	(59±10)	(55±14)	(58±14)	(86±11)	(82±13)	(86±15)
$\dot{V}O_2 < 84\%$ pred at peak exercise, n (%)				16 (43.2)	56 (60.9)	89 (48.1)
HR, beats/min	107±17	103±18	97±19 †	141±18	143±19	139±17
(% predicted maximum)	(66±10)	(64±12)	(62±13)	(87±10)	(88±11)	(88±10)
O <sub>2</sub> pulse, ml O <sub>2</sub> /beat	9.9±1.7	9.3±2.0	9.4±1.9	11.4±1.8	10.7±2.0	10.7±2.0
$\dot{V}_E$ , L/min	23.3±5.7	30.4±6.4	31.5±8.2	59.4±12.2	56.2±14.4	55.1±12.1
(% estimated MVV)	(32±6)	(36±10)	(38±11)*	(57±10)	(65±16)*	(66±14)*
$\dot{V}_E/\dot{V}CO_2$	32.1±4.0	33.4±4.7	35.3±5.4†	31.9±5.1	33.0±4.7	34.5±5.3*
$\dot{V}_E/\dot{V}CO_2 > 34$ at the anaerobic threshold, n (%)	11 (31.4)	38 (41.3)	101 (55.5)*†			
$\dot{V}_E/\dot{V}O_2$	30.4±3.9	30.0±4.1	31.3±5.1	37.0±5.6	37.1±6.3	37.4±5.9
PETCO <sub>2</sub> , mmHg	39.6±4.4	38.4±4.3	36.9±4.9†	39.5±5.5	38.5±5.1	37.3±5.7
f <sub>R</sub> , breaths/min	25±4	23±5	22±5*	32±5	33±6	34±7
R	0.95±0.06	0.90±0.08*	0.89±0.08*	1.17±0.11	1.13±0.09	1.10±0.10†
VT, L	1.35±0.28	1.29±0.28	1.32±0.28	1.84±0.34	1.66±0.32*	1.66±0.35*

Data are shown as the mean ± standard deviation or n (%). The control group was defined as having normal lung function [non-chronic obstructive pulmonary disease (COPD) without SAD], the SAD group as having SAD but no COPD, and the GOLD I group as having mild COPD. Measurements were compared between groups using one-way analysis of variance or Kruskal-Wallis test for continuous variables and chi-squared tests or Fisher's exact tests for categorical variables. Pairwise comparisons between groups were performed using the Bonferroni method. \*P<0.05 vs. the control group. †P<0.05 vs. the SAD group. ‡, anaerobic threshold could not be identified in 5 participants. GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, heart rate; PETCO<sub>2</sub>, end-tidal carbon dioxide partial pressure; f<sub>R</sub>, respiratory frequency; MVV, maximum ventilatory volume; R, respiratory exchange ratio; SAD, small-airway dysfunction;  $\dot{V}O_2$ , oxygen uptake;  $\dot{V}_E$ , minute ventilation volume;  $\dot{V}_E/\dot{V}CO_2$ , ventilatory equivalents for carbon dioxide;  $\dot{V}_E/\dot{V}O_2$ , ventilatory equivalents for oxygen; VT, tidal volume.

**Table S3** Measurements at the anaerobic threshold and at the peak of symptom-limited incremental cycle exercise in never-smokers

Variables	Anaerobic threshold <sup>‡</sup>			Peak exercise		
	Control	SAD	GOLD I	Control	SAD	GOLD I
Work rate, Watt	77±16	68±20	61±23*	129±30	116±29	113±32*
$\dot{V}O_2$ , L/min	0.98±0.23	0.90±0.23	0.88±0.23	1.40±0.35	1.29±0.29	1.30±0.37
(% predicted maximum)	(64±15)	(62±15)	(60±15)	(91±16)	(89±15)	(89±14)
$\dot{V}O_2 < 84\%$ pred at peak exercise, n (%)				12 (25.0)	27 (41.5)	19 (35.2)
HR, beats/min	117±18	107±17*	104±22*	147±16	141±19	140±17
(% predicted maximum)	(70±12)	(66±10)	(66±14)	(88±9)	(86±11)	(88±11)
O <sub>2</sub> pulse, ml O <sub>2</sub> /beat	8.3±1.9	8.3±2.3	8.0±2.1	9.6±2.1	9.3±2.2	9.2±2.5
$\dot{V}_E$ , L/min	27.4±6.8	25.8±6.2	25.6±7.2	47.9±15.9	45.5±11.7	44.7±15.2
(% estimated MVV)	(32±8)	(37±10)	(37±10)	(56±15)	(63±13)*	(63±14)*
$\dot{V}_E/\dot{V}CO_2$	30.4±3.5	32.1±3.5*	32.4±3.9*	29.5±3.2	30.8±3.7	32.9±6.1* <sup>†</sup>
$\dot{V}_E/\dot{V}CO_2 > 34$ at the anaerobic threshold, n (%)	6 (14.0)	15 (23.8)	11 (21.6)			
$\dot{V}_E/\dot{V}O_2$	27.8±3.8	28.3±3.5	28.5±3.7	33.8±3.8	34.3±4.9	35.6±8.1
PETCO <sub>2</sub> , mmHg	40.7±4.4	38.8±4.3	37.9±4.0*	41.3±4.8	40.0±4.9	37.6±4.2* <sup>†</sup>
f <sub>R</sub> , breaths/min	24±5	25±5	23±6	33±9	32±7	34±6
R	0.92±0.08	0.89±0.09	0.88±0.10	1.15±0.08	1.12±0.11	1.09±0.11*
VT, L	1.10±0.27	1.06±0.31	1.12±0.39	1.44±0.39	1.44±0.39	1.34±0.41

Data are shown as the mean ± standard deviation or n (%). The control group was defined as having normal lung function [non-chronic obstructive pulmonary disease (COPD) without SAD], the SAD group as having SAD but no COPD, and the GOLD I group as having mild COPD. Measurements were compared between groups using one-way analysis of variance or Kruskal-Wallis test for continuous variables and chi-squared tests or Fisher's exact tests for categorical variables. Pairwise comparisons between groups were performed using the Bonferroni method. \*P<0.05 vs. the control group. <sup>†</sup>P<0.05 vs. the SAD group. <sup>‡</sup>, anaerobic threshold could not be identified in 10 participants. GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, heart rate; PETCO<sub>2</sub>, end-tidal carbon dioxide partial pressure; f<sub>R</sub>, respiratory frequency; MVV, maximum ventilatory volume; R, respiratory exchange ratio; SAD, small-airway dysfunction;  $\dot{V}O_2$ , oxygen uptake; E, minute ventilation volume;  $\dot{V}_E/\dot{V}CO_2$ , ventilatory equivalents for carbon dioxide;  $\dot{V}_E/\dot{V}O_2$ , ventilatory equivalents for oxygen; VT, tidal volume.

**Table S4** Association between respiratory disease and impaired exercise capacity ( $\dot{V}O_{2peak} < 84\% \text{ pred}$ ) after excluding participants with preserved ratio impaired spirometry ( $FEV_1/FVC \geq 0.7$  and  $FEV_1\% < 80\%$ )

Groups	Participants (n)	$\dot{V}O_{2peak} < 84\% \text{ pred}$ , n (%)	Univariate		Adjusted*	
			OR (95% CI)	P value	OR (95% CI)	P value
Control group	85	28 (32.9)	1 (Ref.)		1 (Ref.)	
SAD group	135	68 (50.4)	2.07 (1.18–3.63)	0.012	2.23 (1.23–4.03)	0.008
GOLD I group	239	108 (45.2)	1.68 (1.00–1.82)	0.051	1.80 (1.00–3.23)	0.049

The control group was defined as having normal lung function (non-COPD without SAD), the SAD group as having SAD but no COPD, and the GOLD I group as having mild COPD. The risks of impaired exercise capacity ( $\dot{V}O_{2peak} < 84\%$  of predicted values) were evaluated using dichotomous logistic regression. \*, adjusted for sex, age, body mass index, smoking status, and smoking index. CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; OR, odds ratio; SAD, small airway dysfunction;  $\dot{V}O_{2peak}$ , peak oxygen uptake.

**Table S5** Association between respiratory disease and impaired exercise capacity ( $\dot{V}O_{2peak} < 84\% \text{ pred}$ ) after excluding participants with peak respiratory exchange rate lower than 1.10

Groups	Participants (n)	$\dot{V}O_{2peak} < 84\% \text{ pred}$ , n (%)	Univariate		Adjusted*	
			OR (95% CI)	P value	OR (95% CI)	P value
Control group	65	22 (33.8)	1 (Ref.)		1 (Ref.)	
SAD group	96	54 (56.3)	2.51 (1.31–4.83)	0.006	2.86 (1.44–5.71)	0.003
GOLD-I group	113	54 (47.8)	1.79 (0.95–3.37)	0.072	1.90 (0.93–3.87)	0.078

The control group was defined as having normal lung function (non-COPD without SAD), the SAD group as having SAD but no COPD, and the GOLD I group as having mild COPD. The risks of impaired exercise capacity ( $\dot{V}O_{2peak} < 84\%$  of predicted values) were evaluated using dichotomous logistic regression. \*, adjusted for sex, age, body mass index, smoking status, and smoking index. CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; OR, odds ratio; SAD, small airway dysfunction;  $\dot{V}O_{2peak}$ , peak oxygen uptake.

**Table S6** Association between respiratory disease and impaired exercise capacity ( $\dot{V}O_{2peak} < 84\% \text{ pred}$ ) when grouped according to the GLI 2012 reference equations

Groups	Participants (n)	$\dot{V}O_{2peak} < 84\% \text{ pred}$ , n (%)	Univariate		Adjusted*	
			OR (95% CI)	P value	OR (95% CI)	P value
Control group	111	40 (36.0)	1 (Ref.)		1 (Ref.)	
SAD group	134	74 (55.2)	2.19 (1.31–3.67)	0.003	1.94 (1.13–3.34)	0.017
GOLD-I group	244	112 (45.9)	1.51 (0.95–2.39)	0.082	1.27 (0.76–2.13)	0.360

The Global Lung Initiative (GLI) 2012 reference values were used. SAD is defined as a post-bronchodilator spirometry MMEF  $< 80\%$  of the predicted value. COPD is defined as a post-bronchodilator spirometry  $FEV_1/FVC < 0.70$  and mild COPD has a post-bronchodilator spirometry  $FEV_1 \geq 80\%$  of the predicted value. The control group was defined as having normal lung function (non-COPD without SAD), the SAD group as having SAD but no COPD, and the GOLD I group as having mild COPD. The risks of impaired exercise capacity ( $\dot{V}O_{2peak} < 84\%$  of predicted values) were evaluated using dichotomous logistic regression. \*, adjusted for sex, age, body mass index, smoking status, and smoking index. CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; OR, odds ratio; SAD, small airway dysfunction;  $\dot{V}O_{2peak}$ , peak oxygen uptake.