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Online Supplementary materials

TITLE: Prevalence of reduced lung diffusing capacity and CT scan findings in smokers without airflow limitation: A population-based study

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Supplementary Table 1. Demographic and clinical characteristics of the study subjects without airflow limitation*

	Non airflow subjects with DLCO determination (n=405)	Non airflow limitation subjects without DLCO determination (n=7610)	*P* value
Females, n (%)	218 (53.8)	4085 (53.7)	0.958
Age, yr	60 ± 11	59 ± 11	0.281
BMI, Kg/m^2	27.4 ± 4.8	27.6 ± 5.0	0.168
Level of studies, n (%)			0.177
No studies	0.7	1.8	
Primary education	19.0	20.8	
Secondary education	18.8	21.7	
University	61.2	55.3	
Lives alone, n (%)	68 (16.8)	1129 (14.8)	0.158
Pack-years	25 ± 21	24 ± 21	0.717
Comorbidity Charlson index	0.3 ± 0.8	0.3 ± 0.8	0.703
COTE index	1.1 ± 2.3	1.0 ± 2.2	0.173
Pre-bronchodilator FEV$_1$, z-score	0.10 ± 1.02	0.05 ± 1.03	0.314
Pre-bronchodilator FEV$_1$/FVC, z-score	-0.26 ± 0.81	-0.19 ± 0.76	0.143
Post-bronchodilator FEV$_1$, s-score	0.12 ± 0.99	0.07 ± 1.01	0.114
Post-bronchodilator FEV$_1$/FVC, z-score	-0.15 ± 0.79	-0.16 ± 0.80	0.246

*Data are mean ± standard deviation or number (percentage). Comparisons were made between groups using the Student's t-test or chi-squared test. *Abbreviations*: BMI, body mass index; FVC, forced vital capacity; FEV$_1$, forced expiratory volume in 1 second

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Supplementary Table 2. Comparison of diffusing capacity between subgroups of current or former smoker subjects*

	DLCO, z-score	DLCO/VA, z-score
Sex		
Males (n=83)	-0.34 ± 0.80	0.01 ± 0.12
Females (n=89)	-0.68 ± 0.57	-0.11 ± 0.12
P value	0.001	<0.001
Chronic cough		
Yes (n=39)	-0.67 ± 0.64	-0.03 ± 0.13
Non (n=131)	-0.47 ± 0.72	-0.06 ± 0.13
P value	0.130	0.289
Chronic bronchitis		
Yes (n=13)	-0.35 (-0.63- -0.05)	0.00 (0.07-0.12)
Non (n=146)	-0.53 (-0.95- -0.08)	-0.05 (-0.14-0.03)
P value	0.683	0.145
Chronic expectoration		
Yes (n=35)	-0.53 (-0.96- -0.22)	-0.04 (-0.11-0.03)
Non (n=135)	-0.50 (-0.94- -0.01)	-0.05 (-0.14-0.03)
P value	0.288	0.724
Dyspnoea		
Yes (n=22)	-0.37 (-0.91-0.25)	-0.04 (-0.12-0.07)
Non (n=147)	-0.53 (-0.94- -0.09)	-0.05 (-0.14-0.03)
P value	0.993	0.688
Wheezing		
Yes (n=69)	-0.62 ± 0.70	-0.06 ± 0.13
Non (n=102)	-0.45 ± 0.71	-0.05 ± 0.13
P value	0.132	0.614

*Data are mean ± standard deviation or median (interquartile range) according to their distribution. Comparisons were performed by t-Student or Mann-Whitney tests. *Abbreviations*: DLCO, lung diffusing capacity for carbon monoxide; VA, alveolar volume.

Supplementary Table 3. Relation between diffusion parameters and clinical, functional, and morphological variables in current smokers with a cumulative smoking exposure higher than 10 pack x years*

	DLCO, z-score		DLCO/VA, z-score	
	r	*P* value	r	*P* value
Age, years	0.170	0.145	0.139	0.235
BMI, Kg/m^2	0.051	0.664	**0.227**	**0.043**
Pack x years	-0.005	0.967	0.121	0.300
Fagerström test	**-0.253**	**0.030**	**-0.236**	**0.043**
Charlson comorbidity index	-0.051	0.666	0.132	0.259
COTE index	-0.061	0.605	-0.063	0.590
CAT total score	-0.080	0.494	0.001	0.991
mMRC dyspnoea scale	0.032	0.617	0.011	0.841
Baseline SaO$_2$, %	0.087	0.458	-0.053	0.652
Exhaled CO, ppm	**-0.278**	**0.017**	-0.184	0.116
Pre-bronchodilator FVC, z-score	**0.375**	**0.001**	**-0.232**	**0.045**
Pre-bronchodilator FEV$_1$, z-score	**0.360**	**0.002**	-0.159	0.177
Pre-bronchodilator FEV$_1$/FVC, z-score	0.062	0.594	0.133	0.256
6MWD, m	0.181	0.120	0.136	0.243
Haemoglobin, g/dl	0.146	0.222	**0.289**	**0.014**
Eosinophils, %	0.070	0.554	0.118	0.319
Fibrinogen, g/l	-0.001	0.992	-0.078	0.544
C-reactive protein, mg/l	-0.149	0.236	-0.150	0.234
Albumin, g/l	**0.680**	**0.031**	-0.219	0.544
BODE index	-0.089	0.448	0.035	0.767
YPAS - physical activity summary	0.098	0.594	0.010	0.958
Total emphysema volume, %	0.039	0.760	-0.004	0.978
Low density volume, %	-0.020	0.879	-0.058	0.651
P15, HU	-0.030	0.813	-0.047	0.715
Secondary bronchi WA, %	-0.092	0.475	-0.092	0.476
Pulmonary artery diameter, mm	**-0.3304**	**0.015**	**-0.400**	**0.001**
Pulmonary artery:aorta ratio	0.143	0.263	0.161	0.207

*Pearson correlation coefficient (r) and *P*-value are shown. *Abbreviations*: DLCO, lung diffusing capacity of carbon monoxide; VA, alveolar volume; BMI, body mass index; CAT, Chronic Obstructive Pulmonary Disease assessment test; SaO$_2$, oxygen saturation; CO, carbon monoxide; FVC, forced vital capacity; FEV$_1$, forced expiratory volume at 1 second; 6MWD, six-minute walk distance; BODE, Body Obstructive Dyspnoea Exercise; YPAS, Yale physical activity survey; P15, 15th percentile; HU, Hounsfield units; WA, wall area

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Supplementary Table 4. Correlation between diffusion parameters and clinical, functional, and morphological variables in former smokers with a cumulative smoking exposure higher than 10 pack x years*

	DLCO, z-score		DLCO/VA, z-score	
	r	*P* value	r	*P* value
Age, years	0.032	0.795	0.139	0.175
BMI, Kg/m^2	0.052	0.613	**0.302**	**0.003**
Pack-years	-0.089	0.384	-0.108	0.293
Charlson comorbidity index	-0.006	0.953	0.047	0.646
COTE index	-0.158	0.123	-0.006	0.956
CAT total score	-0.181	0.076	-0.047	0.650
mMRC dyspnoea scale	0.099	0.189	0.054	0.346
Baseline SaO$_2$, %	0.061	0.553	-0.083	0.420
Exhaled CO, ppm	-0.082	0.425	-0.070	0.497
Pre-bronchodilator FVC, z-score	**0.336**	**0.001**	-0.119	0.246
Pre-bronchodilator FEV$_1$, z-score	**0.399**	**<0.001**	0.014	0.891
Pre-bronchodilator FEV$_1$/FVC, z-score	0.187	0.067	**0.220**	**0.031**
6MWD, m	**0.202**	**0.048**	-0.118	0.249
Haemoglobin, g/dL	0.110	0.289	0.044	0.672
Eosinophils, %	-0.007	0.944	0.160	0.122
Fibrinogen, g/L	-0.111	0.335	-0.109	0.344
C-reactive protein, mg/L	-0.024	0.822	0.036	0.736
Albumin, g/L	-0.048	0.882	-0.274	0.389
BODE index	-0.024	0.818	**0.259**	**0.010**
YPAS - physical activity summary	0.221	0.108	0.167	0.227
Total emphysema volume, %	-0.051	0.639	-0.018	0.872
Low density volume, %	0.070	0.519	0.142	0.192
P15, HU	-0.132	0.226	-0.174	0.109
Secondary bronchi WA, %	0.098	0.368	0.046	0.676
Pulmonary artery diameter, mm	**-0.229**	**0.034**	**-0.314**	**0.003**
Pulmonary artery:aorta ratio	-0.053	0.627	0.017	0.876

*Pearson correlation coefficient (r) and *P*-value are shown. *Abbreviations*: DLCO, lung diffusing capacity of carbon monoxide; VA, alveolar volume; BMI, body mass index; CAT, Chronic Obstructive Pulmonary Disease assessment test; SaO$_2$, oxygen saturation; CO, carbon monoxide; FVC, forced vital capacity; FEV$_1$, forced expiratory volume at 1 second; 6MWD, six-minute walk distance; BODE, Body Obstructive Dyspnoea Exercise; YPAS, Yale physical activity survey; P15, 15th percentile; HU, Hounsfield units; WA, wall area.

Supplementary Table 5. Comparison between current smoker subjects according to their lung diffusing capacity*

		Reduced DLCO (n=20)	Normal DLCO (n=55)	*P*
Females, n (%)		15 (75.0)	31 (56.4)	0.115
Age, years		59 (52-59)	60 (59-65)	0.088
BMI, Kg/m^2		31.5 (30.2-34.4)	26.8 (16.8-29.2)	0.834
Level of studies				0.419
	No studies	0	0	
	Primary education	2 (10.0)	5 (9.1)	
	Secondary education	6 (30.0)	17 (30.9)	
	University	11 (55.0)	33 (60.0)	
Lives alone		1 (5.0)	13 (23.6)	0.060
Pack-years		24 (23-45)	34 (34-44)	0.161
Fagerström test		4 (4-6)	3 (3-4)	0.707
Charlson comorbidity index		0 (0-0)	0 (0-0)	0.730
COTE index		6 (3-6)	0 (0-0)	0.229
CAT total score		5 (5-16)	9 (8-12)	0.610
mMRC dyspnoea level				0.218
	0	13 (65.0)	41 (74.5)	
	1	6 (30.0)	14 (25.5)	
	2	0	0	
	3	1 (5.0)	0	
Chronic cough, n (%)		7 (36.8)	20 (36.4)	0.590
Chronic bronchitis, n (%)		2 (12.5)	8 (16.0)	0.544
Chronic expectoration, n (%)		5 (25.0)	16 (29.1)	0.485
Wheezing, n (%)		12 (60.0)	30 (55.6)	0.471
Baseline oxygen saturation, %		96 (95-97)	96 (95-97)	0.782
Exhaled CO, ppm		38 (32-46)	7 (6-21)	0.068
Pre-bronchodilator FVC, z-score		-0.41 (-1.00-0.42)	0.33 (-0.32-0.80)	0.013
Pre-bronchodilator FEV$_1$, z-score		-0.30 (-1.28- -0.02)	-0.15 (-0.72-0.80)	0.076
Pre-bronchodilator FEV$_1$/FVC, z-score		-0.62 (-0.83- -0.14)	-0.44 (-1.05-0.16)	0.815
6MWD, m		522 (512-562)	577 (554-600)	0.185
Haemoglobin, g/dl		14.3 (13.7-14.7)	16.4 (15.0-16.4)	0.203
Eosinophils, %		1.1 (0.6-2.8)	2.0 (1.6-2.8)	0.701
Fibrinogen, mg/dL		3.4 (3.1-3.6)	3.9 (3.5-3.9)	0.417
C-reactive protein, mg/L		0.2 (0.2-0.7)	0.4 (0.3-0.5)	0.420
Albumin		4.2 (4.2-4.3)	4.4 (4.4-4.6)	0.014
BODE index				0.068
	0-2 points (survival: 80%)	55 (100)	18 (90.0)	
	3-4 (survival: 67%)	0	2 (10.0)	
YPAS - physical activity summary		29 (26-42)	53 (43-61)	0.073
Total emphysema volume, %		0.5 (0.3-0.6)	0.2 (0.1-0.2)	0.987
Low density volume, %		41 (40-50)	17 (12-35)	0.528
P15, HU		-906 (-912 - -905)	-876 (-897 - -865)	0.670
Secondary bronchi WA, %		22.2 (21.0-24.0)	24.1 (22.2-25.8)	0.499
Pulmonary artery diameter, mm		28 (25-29)	24 (23-24)	0.014
Pulmonary artery:aorta ratio		0.77 (0.72-0.79)	0.70 (0.65-0.70)	0.269

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Supplementary Table 6. Comparison between former smoker subjects according to their lung diffusing capacity*

		Reduced DLCO (n=14)	Normal DLCO (n=83)	*P*
Females, n (%)		6 (42.9)	37 (44.6)	0.571
Age, years		63 (55-65)	63 (55-68)	0.541
BMI, Kg/m^2		28.3 (21.9-29.7)	27.8 (25.8-30.7)	0.426
Level of studies				0.028
	No studies	1 (7.1)	0	
	Primary education	5 (35.7)	19 (22.9)	
	Secondary education	0	14 (16.9)	
	University	8 (57.1)	50 (60.2)	
Live alone		4 (28.6)	18 (21.7)	0.395
Pack-years		25 (19-50)	27 (19-37)	0.750
Fagerström test		0 (0-0)	0 (0-0)	1.0
Charlson comorbidity index		0 (0-0)	0 (0-0)	0.794
COTE index		0 (0-0)	0 (0-0)	0.217
CAT total score		6 (1-10)	6 (3-11)	0.789
mMRC dyspnoea level				0.090
	0	10 (71.4)	64 (77.1)	
	1	2 (14.3)	16 (19.3)	
	2	1 (7.1)	3 (3.6)	
	3	1 (7.1)	0	
Chronic cough, n (%)		1 (7.1)	11 (13.4)	0.446
Chronic bronchitis, n (%)		0	3 (3.8)	0.633
Chronic expectoration, n (%)		2 (14.3)	12 (14.8)	0.661
Wheezing, n (%)		3 (21.4)	24 (28.9)	0.413
Baseline oxygen saturation, %		96 (96-97)	96 (95-97)	0.920
Exhaled CO, ppm		3 (1-6)	2 (2-4)	0.782
Pre-bronchodilator FVC, z-score		-0.48 (-1.24-0.40)	0.37 (-0.28-1.02)	0.008
Pre-bronchodilator FEV$_1$, z-score		-0.47 (-1.32- -0.30)	0.08 (-0.49-0.97)	0.003
Pre-bronchodilator FEV$_1$/FVC, z-score		-0.23 (-0.94-0.24)	-0.29 (-0.82-0.29)	0.666
6MWD, m		503 (448-541)	535 (464-590)	0.257
Haemoglobin, g/dl		-	15.1 (13.4-15.8)	-
Eosinophils, %		-	2.1 (0.1-3.6)	-
Fibrinogen, mg/dL		-	3.6 (3.4-4.6)	-
C-reactive protein, mg/L		-	0.4 (0.2-0.9)	-
Albumin		-	4.9 (4.6-40.7)	-
BODE index				0.054
	0-2 points (survival: 80%)	12 (85.7)	82 (98.8)	
	3-4 (survival: 67%)	2 (14.3)	1 (1.2)	
YPAS - physical activity summary		53 (44-55)	60 (47-87)	0.255
Total emphysema volume, %		2.2 (0.2-4.1)	1.1 (0.5-3.0)	0.640
Low density volume, %		58 (47-66)	52 (47-64)	0.615
P15, HU		-920 (-930 - -911)	-910 (-935 - -900)	0.343
Secondary bronchi WA, %		22.8 (20.9-31.5)	25.1 (22.1-28.2)	0.574
Pulmonary artery diameter, mm		25 (23-28)	24 (21-27)	0.097
Pulmonary artery:aorta ratio		0.76 (0.70-0.84)	0.75 (0.66-0.83)	0.806

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Supplementary Table 7. Multiple logistic regression model to detect reduced DLCO in current smoker subjects*

Variable	B	Standard error	*P*	OR	95%CI
Pre-bronchodilator FVC, z-score	-0.732	0.301	0.015	0.481	0.2675-0.867
Exhaled CO, ppm	0.026	0.048	0.039	1.014	1.001-1.028
Constant	-1.058	0.281	-	-	-

*Exhaled CO level, pre-bronchodilator FVC, pre-bronchodilator FEV_1, serum albumin level and pulmonary artery diameter were entered into the model. The BODE index was not entered because it was considered redundant and not strictly applicable to subjects without airflow limitation.
Abbreviations: FVC, forced vital capacity; CO, carbon monoxide; B, regression coefficient; OR, odds ratio; CI, confidence interval

Supplementary Table 8. Multiple logistic regression model to detect reduced DLCO in former smoker subjects*

Variable	B	Standard error	*P*	OR	95%CI
Pre-bronchodilator FVC, z-score	-0.993	0.345	0.004	0.371	0.188-0.729
Exhaled CO, ppm	0.018	0.023	0.047	1.016	1.000-1.034
Constant	-1.886	0.331	-	-	-

*Exhaled CO level, pre-bronchodilator FVC, pre-bronchodilator FEV_1, serum albumin level and pulmonary artery diameter were entered into the model. The BODE index was not entered because it was considered redundant and not strictly applicable to subjects without airflow limitation.
Abbreviations: FVC, forced vital capacity; CO, carbon monoxide; B, regression coefficient; OR, odds ratio; CI, confidence interval