

Online Supplement

Treatable Traits in Misdiagnosed Chronic Obstructive Pulmonary Disease: Data from the Akershus Cardiac Examination 1950 Study

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Supplementary table 1. Clinical characteristics of the Akershus Cardiac Examination 1950 population with FEV₁/FVC < LLN according to undiagnosed/diagnosed COPD.

	Undiagnosed COPD (n=187, 72.2%)	Diagnosed COPD (n=72, 27.8%)	P
Tobacco exposure, n (%)			
Current smoking	90 (48.1)	27 (37.5)	0.124
Never smokers	13 (7.0)	2 (2.8)	0.154
≥ 20 pack-years	99 (55.0)	59 (81.9)	<0.001
Lung function			
FEV ₁ , L	2.26 (1.83, 2.87)	1.83 (1.48, 2.32)	<0.001
FVC, L	3.73 (3.15, 4.96)	3.59 (2.80, 4.34)	0.016
FEV ₁ /FVC*	0.60 (0.55, 0.63)	0.55 (0.45, 0.62)	<0.001
FEV ₁ % of predicted*	84 (70, 97)	71 (53, 83)	<0.001
FVC % of predicted*	117 (103, 130)	104 (87, 118)	<0.001
FEV ₁ ≥80 % of predicted	106 (56.7)	24 (33.3)	0.001
FEV ₁ ≥50 - <80 % of predicted	68 (36.4)	32 (44.4)	0.151
FEV ₁ <50% of predicted	13 (7.0)	14 (19.4)	0.003
Respiratory symptoms, n (%)			
mMRC ≥2	16 (8.5)	29 (40.2)	<0.001
Cough	79 (43.2)	40 (56.3)	0.059
Expectorate	52 (29.2)	43 (60.6)	<0.001
Wheezing	59 (32.6)	40 (56.3)	0.001
One or more symptoms	102 (58.0)	60 (85.7)	<0.001
Respiratory infections, n (%)			
Antibiotics for lower respiratory infection last 3 years	68 (37.0)	42 (59.2)	0.001
Comorbidities, n (%)			

Inactivity/low activity	85 (45.4)	38 (52.7)	0.234
Obesity (BMI \geq 30)	26 (13.9)	17 (23.6)	0.060
Underweight (BMI <18.5) **	6 (3.2)	3 (4.2)	0.712
Coronary artery disease	14 (7.5)	10 (13.9)	0.111
Heart failure**	4 (2.1)	3 (4.2)	0.401
Atrial fibrillation**	8 (4.3)	5 (6.9)	0.359
Hypertension	107 (57.2)	47 (65.3)	0.237
Sleep-apnoea	15 (8.1)	7 (9.7)	0.669
Diabetes	12 (6.4)	7 (9.7)	0.361

Systemic inflammation

CRP \geq 3*	56 (30.3)	31 (43.1)	0.052
Blood eosinophil count \geq 300*	41 (21.9)	14 (19.4)	0.662

AB; antibiotics, BMI; body mass index, COPD; chronic obstructive pulmonary disease, CRP; c-reactive protein, FEV₁; forced expiratory volume during 1st second, FVC; forced vital capacity, LLN; lower limit of normal, mMRC; Modified Medical Research Council dyspnoea scale, *Median, Mann Whitney-U test, ** Fishers exact test.

Supplementary table 2. Clinical characteristics of the Akershus Cardiac Examination 1950 population according to previously undiagnosed and diagnosed COPD. Sensitivity analysis using COPD-definition defined by Global Lung Initiative 2012 reference values.

	Undiagnosed COPD	Diagnosed COPD	P
	n=230	n=77	
Tobacco exposure, n (%)			
Current smoking	102 (44.3)	28 (36.4)	0.233
Never smokers	22 (9.6)	2 (2.6)	0.051
≥ 20 pack-years	118 (53.4)	62 (80.5)	<0.001
Lung function			
FEV ₁ * (L)	2.30 (1.52, 2.46)	1.89 (1.52, 2.46)	<0.001
FVC*(L)	3.77 (3.25, 4.85)	3.66 (2.83, 4.38)	0.024
FEV ₁ /FVC*	0.62 (0.56, 0.64)	0.57 (0.46, 0.62)	<0.001
FEV ₁ % of predicted*	82 (68,93)	69 (49,81)	<0.001
FVC % of predicted*	106 (93,118)	93 (82,105)	<0.001
FEV ₁ ≥80 % of predicted	123 (53.5)	19 (24.7)	<0.001
FEV ₁ ≥50 - <80 % of predicted	86 (37.4)	39 (50.6)	0.045
FEV ₁ <50% of predicted	14 (6.1)	15 (19.5)	0.001
Respiratory symptoms, n (%)			
mMRC ≥2	20 (8.8)	30 (40.0)	<0.001
Cough	93 (41.2)	42 (55.3)	0.034
Expectorate	58 (26.2)	45 (59.2)	<0.001
Wheezing	65 (29.0)	41 (53.9)	<0.001
One or more symptoms	146 (63.8)	67 (88.2)	<0.001
Respiratory infections, n (%)			

Antibiotics for lower respiratory infection last 3 years	78 (34.4)	47 (61.8)	<0.001
Comorbidities, n (%)			
Inactivity/low activity	103 (45.2)	40 (53.3)	0.233
Obesity (BMI \geq 30)	35 (15.2)	18 (23.4)	0.117
Underweight (BMI <18.5)	6 (2.6)	3 (3.9)	0.696
Coronary artery disease	17 (7.4)	12 (15.6)	0.043
Heart failure	4 (1.7)	4 (5.2)	0.112
Atrial fibrillation	8 (3.5)	5 (6.5)	0.324
Hypertension	134 (58.3)	52 (67.5)	0.178
Sleep-apnoea	17 (7.4)	8 (10.4)	0.470
Diabetes	18 (7.8)	9 (11.7)	0.352
Systemic inflammation			
CRP \geq 3*	63 (27.6)	33 (42.9)	0.016
Blood eosinophil count \geq 300*	46 (20.0)	17 (22.1)	0.745

Supplementary table 3. P-values for comparison of diagnostic accuracy of various variables in undiagnosed COPD.

		Individual variables					
		Sputum	Cough	Wheezing	Current smoking	>20 packyear	Exacerbation last 3 yr
		AUC 0.577	AUC 0.612	AUC 0.610	AUC 0.688	AUC 0.661	AUC 0.599
Individual variables							
Dyspnea	AUC 0.502	0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Sputum	AUC 0.577		0.076	0.106	<0.001	<0.001	0.317
Cough	AUC 0.612			0.829	0.005	0.100	0.563
Wheezing	AUC 0.610				0.005	0.073	0.765
Current smoking	AUC 0.688					0.246	0.002
>20 packyear	AUC 0.661						0.023
Composite variables							
Cough or wheezing	AUC 0.647						
Any symptoms	AUC 0.652						

*Multivariate model consisting of current smoking, >20 packyears, wheezing, antibiotics for respiratory infection last 3 BMI<30.

Supplementary table 4. Determinants associated with undiagnosed COPD according to GLI 2012 reference sets in a general population based sample

	Univariate, OR (95% CI)	p	Multivariate, OR (95% CI)	p
Demographic data				
Male gender	0.88 (0.67, 1.15)	0.342	0.96 (0.71, 1.32)	0.816
Inactivity/low activity	1.33 (1.02, 1.75)	0.037	1.01 (0.73, 1.38)	0.974
Anthropometric data				
Underweight (BMI < 18.5)	3.26 (1.34, 7.96)	0.009	1.28 (0.38, 4.30)	0.688
Obesity (BMI ≥ 30)	0.60 (0.41, 0.86)	0.006	0.54 (0.36, 0.81)	0.003
Smoking history (n=3641)				
Current smoking	5.66 (4.28, 7.49)	<0.001	2.87 (1.99, 4.14)	<0.001
≥ 20 packyears	3.67 (2.78, 4.83)	<0.001	2.25 (1.59, 3.17)	<0.001
Respiratory symptoms				
mMRC ≥ 2	1.55 (0.96, 2.52)	0.072		
Regular cough	2.68 (2.03, 3.53)	<0.001	1.47 (1.02, 2.13)	0.041
Regular expectorate	2.19 (1.60, 3.02)	<0.001	0.85 (0.55, 1.30)	0.446
Regular wheezing	3.61 (2.65, 4.92)	<0.001	2.11 (1.40, 3.18)	<0.001
Respiratory infections				
Antibiotics for lower respiratory infection last 3 years	2.52 (1.89, 3.36)	<0.001	2.04 (1.46, 2.84)	<0.001

Comorbidities

Coronary artery disease	1.05 (0.63, 1.76)	0.841
Heart failure	1.09 (0.39, 3.03)	0.871
Atrial fibrillation	0.76 (0.37, 1.56)	0.453
Hypertension	0.84 (0.64, 1.11)	0.218
Sleep-apnoea	1.22 (0.73, 2.05)	0.440
Diabetes	0.91 (0.56, 1.50)	0.910

Laboratory tests

CRP $\geq 3^*$	1.47 (1.09, 1.99)	0.012	1.29 (0.91, 1.84)	0.149
Blood eosinophil cell count $\geq 300^*$	1.54 (1.10, 2.16)	0.012	1.05 (0.70, 1.57)	0.815

Supplementary Figure 1

