

## Differences between Asthma-COPD overlap syndrome (ACOS) and adult-onset asthma

### Supplementary tables

**Table S1. The inclusion and exclusion criteria of SAAS study [e1]**

Inclusion criteria	<ul style="list-style-type: none"><li>• a diagnosis of new-onset asthma made by a respiratory specialist</li><li>• diagnosis confirmed by at least one of the following objective lung function measurements<sup>u</sup>:<ul style="list-style-type: none"><li>○ FEV<sub>1</sub> reversibility in spirometry of at least 15 % and 200 mL</li><li>○ diurnal variability (≥ 20 %) or repeated reversibility (≥ 15 % / 60 L / min) in PEF-follow-up</li><li>○ a significant decrease in FEV<sub>1</sub> (15 %) or PEF (20 %) in response to exercise or allergen</li><li>○ a significant reversibility in FEV<sub>1</sub> (at least 15 % and 200 ml) or significant mean PEF in response to a trial with oral or inhaled glucocorticoids</li></ul></li><li>• symptoms of asthma</li><li>• age ≥ 15 years</li></ul>
Exclusion criteria	<ul style="list-style-type: none"><li>• physical or mental inability to provide signed informed consent</li><li>• diagnosis of asthma below the age of 15 years</li><li>• of note:<ul style="list-style-type: none"><li>○ patients with comorbidities, either other lung disease or any other significant disease were not excluded</li><li>○ patients were not excluded because of smoking, alcohol use or any other lifestyle factor</li><li>○ respiratory symptoms or any other disease during childhood was not a reason to exclude patients, but a diagnosis of asthma at age &lt;15 years was an exclusion criteria</li></ul></li></ul>

<sup>u</sup>The objective lung function criteria reflect those of national and international guidelines valid in 1999-2002 and may not exactly follow those valid at the moment [e2, e3].

Table S2. Characteristics of the included and excluded patients

	Included patients n=188	Excluded patients n=15	p-value
Age years	58.7 ±13.5	51.7 ±13.7	0.053
BMI kg·m <sup>-2</sup>	28 (24-31)	27 (25-32)	0.934
Gender male n(%)	79 (42.0)	6 (40.0)	> 0.999
Asthma control according to GINA n(%)			0.940
Controlled	64 (34.0)	5 (33.3)	
Partly controlled	69 (36.7)	5 (33.3)	
Uncontrolled	55 (29.3)	5 (33.3)	
LABA in daily use n(%)	93 (49.5)	3 (20.0)	<b>0.032*</b>
≥2 oral steroid courses in 2 years n(%)	24 (13.0)	3 (20.0)	0.433
ICS daily use n(%)	149 (79.3)	6 (40.0)	<b>0.002**</b>
ICS dose/day bud eq <sup>§</sup>	800 (400-1000)	1000 (520-1550)	0.438
ACT score	22 (19-24)	22 (18-24)	0.586
CAT score	11 (6-17)	10 (5-17)	0.754
AQ20 score	4 (1-7)	4 (2-7)	0.797
DLco % predicted	94 ±18	87 ±16	0.171
DLco/VA % predicted	95 ± 16	93 ± 15	0.536
B-Neutrophils x10 <sup>9</sup> /L	3.70 (2.90-4.78)	3.80 (3.50-5.10)	0.562
B-Eosinophils x10 <sup>9</sup> /L	0.16 (0.10-0.27)	0.26 (0.11-0.28)	0.269
IgE kU/l	61 (24-169)	54 (26-93)	0.684
FeNO ppb	11 (5-18)	11 (5-30)	0.551
Smoking status n(%)			<b>&lt;0.001***</b>
Never smoker	96 (51.1)	0 (0)	
Ex-smoker	68 (36.2)	9 (60.0)	
Current smoker	24 (12.8)	6 (40.0)	
FEV <sub>1</sub> % predicted <sup>δ</sup>	90 (80-98)	92 (84-102)	0.732
FEV <sub>1</sub> /FVC <sup>δ</sup>	0.75 (0.68-0.81)	0.78 (0.74-0.81)	0.319
FVC % predicted <sup>δ</sup>	98 (88-108)	97 (89-103)	0.620

Data is shown as n (%), mean ± SD, or median (interquartile range).<sup>§</sup>: budesonide equivalent, of daily users  
<sup>δ</sup>: post bronchodilator, BMI= Body mass index, GINA= Global Initiative for Asthma, ICS= inhaled corticosteroids, LABA= long acting beta agonists, ACT= Asthma Control Test score, CAT= COPD Assessment Test, AQ20= Asthma Questionnaire 20, DLco = Diffusing capacity of the lung for carbon monoxide, VA= Alveolar volume, B= blood, IgE= Immunoglobulin E, FeNO= Exhaled nitric oxide.

**Table S3. Pre bronchodilator lung function**

	Never and ex-smokers with <10 pack-years n=122	Non-obstructive patients with ≥10 pack-years n=32	ACOS ≥10 pack-years FEV <sub>1</sub> /FVC<0.7 n=34	p-value <sup>Φ</sup>
FEV <sub>1</sub> L	2.68 (2.24-3.17)	2.98 (2.26-3.47)	2.16 (1.63-2.80)##	<0.001***
FEV <sub>1</sub> % predicted	90.0 (82.8-99.0)	86.0 (75.5-92.8)	72.5 (55.0-83.5) ##	<0.001***
FEV <sub>1</sub> /FVC	0.75 (0.69-0.79)	0.75 (0.73-0.80)	0.61 (0.51-0.65) ##	<0.001***
FVC L	3.65 (3.07-4.31)	3.87 (3.04-4.78)	3.63 (3.23-4.40)	0.822
FVC % predicted	98.0 (89.8-110.0)	93.0 (79.5-101.0) †	94.0 (87.8-105.3)	0.026*

Data is shown as median (interquartile range)

Φ: p-value across all groups

†: as compared to group 1. (Never and ex-smokers with <10 pack-years) p<0.05

#: as compared to group 2. (Non-obstructive patients with ≥10 pack-years) p<0.05

**Table S4. Characteristics of the groups of ACOS and obstructive asthma**

	Obstructive asthma <10 pack-years and FEV <sub>1</sub> /FVC<0.7 n=19	ACOS ≥10 pack-years FEV <sub>1</sub> /FVC<0.7 n=34	p-value
Age years	62.3 ± 11.7	65.0 ± 10.7	0.391
Gender male n(%)	8 (42.1)	24 (70.6)	0.077
BMI kg·m <sup>-2</sup>	27.6 (24.6-30.9)	28.1 (24.2-30.7)	0.904
Asthma control according to GINA n(%)			0.115
controlled	5 (26.3)	5 (14.7)	
partly controlled	9 (47.4)	10 (29.4)	
uncontrolled	5 (26.3)	19 (55.9)	
ACT	22 (21-24)	21 (16-23)	0.125
CAT	12 ± 7	16 ± 7	0.049*
AQ20	4 (1-8)	4 (2-8)	0.787
ICS daily use n(%)	17 (89.5)	27 (79.4)	0.463
ICS dose/day bud eq <sup>§</sup>	800 (713-1000)	800 (800-1200)	0.567
≥2 oral steroid courses in 2 years n(%)	3 (16.7)	4 (12.1)	0.686

LABA in daily use n(%)	13 (68.4)	21 (61.8)	0.768
LAMA, LTRA or theophylline in daily use n(%)	7 (36.8)	8 (23.5)	0.351
Use of oral steroid courses ever n(%)	8 (44.4)	7 (21.2)	0.112
Skin-prick positive <sup>μ</sup> n(%)	4 (21.1)	5 (20.0)	>0.999
Continuous rhinitis n(%)	8 (42.1)	8 (23.5)	0.215
Allergic conjunctivitis or rhinitis n(%)	11 (57.9)	15 (45.5)	0.565

Data is shown as n (%), mean  $\pm$  SD, or median (interquartile range). <sup>§</sup>: budesonide equivalent, of daily users, <sup>μ</sup>: at the moment of diagnosis (1999-2002) [e1], GINA= Global Initiative for Asthma, ACT= Asthma Control Test, CAT= COPD Assessment Test, AQ20= Asthma Questionnaire 20, ICS= inhaled corticosteroids, LABA= long acting beta agonists, LAMA= long acting muscarinic antagonists, LTRA= leukotriene antagonists

**Table S5. Lung function in groups of ACOS and obstructive asthma**

	Obstructive asthma <10 pack-years and FEV <sub>1</sub> /FVC<0.7 n=19	ACOS ≥10 pack-years FEV <sub>1</sub> /FVC<0.7 n=34	<i>p</i> -value
<b>Post bronchodilator</b>			
FEV <sub>1</sub> L	2.42 (1.97-3.24)	2.32 (1.80-2.98)	0.528
FEV <sub>1</sub> % predicted	84.0 (78.0-94.0)	75.0 (57.5-85.5)	0.103
FEV <sub>1</sub> /FVC	0.64 (0.62-0.68)	0.62 (0.54-0.67)	0.334
FVC L	3.93 (3.11-5.04)	3.92 (3.41-4.47)	0.867
FVC % predicted	103.0 (95.0-116.0)	98.5 (91.0-106.5)	0.334
<b>FEV<sub>1</sub> reversibility<sup>Ω</sup></b>			
mL	155.8 $\pm$ 122.3	135.6 $\pm$ 149.9	0.619
%	7.2 $\pm$ 5.0	6.7 $\pm$ 7.7	0.779
<b>FVC reversibility<sup>Ω</sup></b>			
mL	133.2 $\pm$ 128.1	151.2 $\pm$ 239.7	0.723
%	3.6 $\pm$ 3.4	4.3 $\pm$ 6.6	0.618

Data is shown as mean  $\pm$  SD, or median (interquartile range), <sup>Ω</sup>: change from pre- to postbronchodilator

**Table S6. Comorbidities in the groups of ACOS and obstructive asthma**

	<b>Obstructive asthma &lt;10 pack-years and FEV<sub>1</sub>/FVC&lt;0.7 n=19</b>	<b>ACOS ≥10 pack-years FEV<sub>1</sub>/FVC&lt;0.7 n=34</b>	<b>p-value</b>
<b>Number of comorbidities</b>	1 (0-1)	2 (1-3)	<b>0.030*</b>
<b>Obesity<sup>§</sup></b>	5 (26.3)	10 (29.4)	>0.999
<b>Hypertension</b>	7 (36.8)	18 (52.9)	0.390
<b>Coronary heart disease</b>	3 (15.8)	7 (20.6)	>0.999
<b>Hypercholesterolemia</b>	3 (15.8)	12 (35.3)	0.205
<b>Diabetes</b>	3 (15.8)	8 (23.5)	0.726
<b>Systemic rheumatoid disease</b>	0	1 (2.9)	>0.999
<b>Thyroidal disease</b>	0	4 (11.8)	0.284
<b>Depression</b>	1 (5.3)	3 (8.8)	>0.999
<b>Painful condition</b>	3 (15.8)	4 (11.8)	0.691
<b>Treated dyspepsia</b>	1 (5.3)	3 (8.8)	>0.999
<b>Number of other medications<sup>Ω</sup></b>	2 (0-3)	3 (1-7)	0.100

Data is shown as n (%), or median (interquartile range), <sup>§</sup>: BMI ≥30, <sup>Ω</sup>: Other than medications for asthma or allergy

E-table references:

e1. Kankaanranta H, Ilmarinen P, Kankaanranta T, Tuomisto LE. Seinäjoki adult asthma study (SAAS): a protocol for a 12-year real-life follow-up study of new-onset asthma diagnosed at adult age and treated in primary and specialised care. NPJ Prim Care Respir Med 2015;25:15042

e2. Haahtela T, Lehtimäki L, Ahonen E, Harju T, Jartti T, Kankaanranta H et al. Update on current guidelines: asthma. Duodecim 2013; 129: 994–995.

e3. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention. Updated 2016. <http://www.ginasthma.org/>. Date last accessed: November 15<sup>th</sup> 2016.