

## SUPPLEMENTARY MATERIAL

### Supplementary I

#### Methods:

Patients were categorized according to their functional pattern: air trapping (Residual volumen/ Total lung capacity, RV/TLC >120%) or obstructive (Forced expiratory volume in the first second, FEV1/FVC ratio ≤70%) and normal (FVC >80% and FEV1/FVC > 70%)<sup>8</sup>. Asthma was diagnosed based on the GINA guidelines and included a postbronchodilator FEV1 >12% on spirometry and/or methacholine PC20 <16 mg/ml. The ethics committees of each participating hospital approved this study. All subjects provided signed informed consent.

Study data included demographic and clinical characteristics, asthma treatment, asthma severity (following GINA guidelines<sup>1</sup>) and control (assessed using the Asthma Control Test), number and severity of exacerbations. Lung function tests (spirometry, plethysmography), sputum analysis, blood eosinophils (PBE), and FeNO were also collected. A full description of the MEGA cohort has been published previously<sup>10,11</sup>. Additionally, we examined the agreement between patients diagnosed with air trapping based on spirometric pattern (FVC <80% and/or FVC increase after bronchodilation ≥10%) and those patients diagnosed by plethysmography criteria (RV/TLC >120%).

Quantitative variables were described by mean and standard deviation, and qualitative variables by absolute and relative frequencies. Inter-group comparisons were performed using the chi-square test or Fisher's exact test for qualitative and ANOVA or Kruskal-Wallis for quantitative variables. Spearman's rank correlation coefficient was also used. Concordance estimated correlations were calculated by Cohen's kappa coefficient. Statistical analysis was carried out using the GraphPad Instat 6 (GraphPad Software Inc, San Diego, CA). P-values <0.05 were considered statistically significant.

## Supplementary II

Table I. Demographic, clinical, functional and inflammatory characteristics of patients studied.

**Table I.a. Demographic and clinical characteristics.**

	Normal	Obstruction	Air trapping	P value
<b>No. subjects (%)</b>	<b>253 (56.8)</b>	<b>105 (23.6)</b>	<b>87 (19.5)</b>	
<b>Demographic characteristics</b>				
Female sex, N (%)	183 (72.3)	62 (59.1)	50 (57.5)	0.008
Age, years, mean (SD)	45.8 (12.3)	54.4 (12.2)	45.4 (13.9)	<0.0001
Caucasian, N (%)	161 (63.6)	55 (52.4)	50 (57.5)	0.1
BMI, mean (SD)	26.9 (5.5)	27.7 (4.9)	26.8 (5.2)	0.1
Obesity <sup>1</sup> N (%)	42 (16.6)	26 (24.7)	20 (22.9)	0.1
Residency, urban area, N (%)	198 (78.3)	81 (77.1)	59 (67.8)	0.1
<b>Comorbidities, N (%)</b>				
Atopy <sup>2</sup>	177 (69.9)	73 (69.5)	79 (90.8)	0.0003
Allergic rhinitis	137 (54.1)	53 (50.5)	40 (45.9)	0.4
Bronchiectasis	11 (4.3)	15 (14.3)	7 (8.1)	0.004
CRSwNP	58 (22.9)	55 (52.4)	28 (32.2)	<0.0001
CRSsNP	26 (10.3)	10 (9.5)	9 (10.3)	0.9
Obstructive sleep apnea syndrome	12 (4.7)	6 (5.7)	2 (2.3)	0.5

(OSAS)				
<b>Smoking habit, N (%)</b>				
Never smoker	162 (64.0)	57 (54.3)	51 (58.6)	0.2
Current smoker	18 (7.1)	9 (8.5)	8 (9.2)	0.7
Former smoker	67 (26.5)	38 (36.2)	28 (32.2)	0.1
<b>Education level, N (%)</b>				
Higher education	193 (76.3)	67 (63.8)	71 (81.6)	0.01
Primary education	42 (16.6)	25 (23.8)	13 (14.9)	0.2
No studies	6 (3.9)	7 (6.7)	2 (2.3)	0.3
<b>Clinical characteristics</b>				
<b>Treatment, N (%)</b>				
ICS/LABA	196 (77.5)	94 (89.5)	66 (75.8)	0.01
Long-term OCS	15 (5.9)	21 (20.0)	8 (9.2)	0.0004
Biologicals	11 (4.3)	14 (13.3)	7 (8.1)	0.01
<b>Asthma severity<sup>3</sup>, N (%)</b>				
Intermittent	15 (5.9)	1 (0.9)	6 (6.9)	0.01
Mild persistent	52 (20.5)	9 (8.6)	18 (20.7)	0.01
Moderate persistent	94 (37.1)	37 (35.2)	16 (18.4)	0.003
Severe persistent	68 (26.9)	54 (51.4)	46 (52.9)	<0.0001 *
<b>Exacerbations, N (%)</b>				

Patients with asthma exacerbation during the previous year	108 (42.7)	71 (67.6)	37 (42.5)	0.0001
Severe asthma exacerbation	28 (11.1)	19 (18.1)	12 (13.8)	0.3
ED visits	0.5 (1.4)	0.9 (1.6)	0.6 (1.2)	0.02
ICU admission	0.1 (0.4)	0.2 (0.5)	0.06 (0.3)	0.08
<b>Asthma control in ACT N (%)</b>				
ACT ≤ 18 (non-controlled)	58 (22.9)	45 (44.1)	26 (30.2)	0.003
ACT ≥ 19 (controlled)	172 (67.9)	57 (55.9)	60 (69.8)	

**Table I.b. Functional characteristics.**

<b>Spirometry, Liters, mean (SD)</b>				
FEV1 (%)	95.9 (15.1)	70.1 (19.1)	80.8 (24.7)	<0.0001
FVC (%)	104.0 (15.2)	91.7 (19.1)	94.6 (23.6)	<0.0001
FEV1/FVC	90.6 (52.3)	60.1 (9.3)	76.6 (17.9)	<0.0001
<b>Positive spirometry bronchodilator test<sup>4</sup>, N (%)</b>	179 (73.4)	83 (79.0)	65 (74.7)	0.5
<b>Plethysmography, mean (SD)</b>				
TLC (%)	104.3 (18.1)	97.3 (29.8)	106.0 (26.4)	0.3

RV (%)	98.4 (29.9)	100.7 (34.8)	159.9 (37.9)	<0.0001
RV/TLC (%)	93.3 (21.5)	97.9 (24.9)	159.9 (63.5)	<0.0001
DLCO (%)	96.1 (22.3)	93.3 (30.3)	95.4 (20.4)	0.9
Methacholine challenge, PC20 mean (SD)	4.1 (7.3)	1.5 (1.4)	3.2 (6.8)	0.7

**Table I.c. Inflammatory biomarkers.**

<b>Total IgE, IU/mL, mean (SD)</b>	365.9 (735.5)	570.2 (1177)	308.6 (380.3)	0.04
<b>Blood eosinophils cells/<math>\mu</math>L mean (SD)</b>	335 (216.9)	355.8 (281.5)	369.3 (384.5)	0.91
<b>FeNO, ppb, mean (SD)</b>	40.2 (40.2)	50.3 (36.7)	37.4 (30.6)	0.006
<b>Sputum eosinophils, mean (SD)</b>	7.5 (13.5)	11.7 (21.8)	20.3 (27.8)	0.3
<b>Patients with sputum eosinophils&gt;3%, N (%)</b>	43 (16.9)	10 (9.5)	15 (17.2)	0.1
<b>Cellular profile, N (%)</b>				
Eosinophilic	36 (38.3)	10 (41.7)	12 (52.2)	0.5
Mixed	7 (7.4)	0 (0.0)	3 (13.0)	0.2
Neutrophilic	13 (13.8)	5 (20.8)	2 (8.7)	0.5
Paucigranulocitic	38 (40.4)	9 (37.5)	6 (26.1)	0.4

### Supplementary III

Table II. With clinical differences in air trapping diagnosis between spirometry and pletysmography.

	<b>Plethysmography</b>	<b>Spirometry</b>	
	<b>87 (19.5)</b>	<b>100 (22.5)</b>	
Female sex, N (%)	50 (57.5)	86 (86.0)	<0.001
Age, years, mean (SD)	45.4 (13.9)	52 (12.8)	0.006
Caucasian, N (%)	50 (57.5)	96 (96.0)	<0.001
Atopy <sup>2</sup>	79 (90.8)	70 (70.0)	0.0005
CRSwNP	28 (32.2)	40 (40.0)	NS
<b>Asthma severity<sup>3</sup>, N (%)</b>			
Intermittent	6 (6.9)	2 (2.0)	NS
Mild persistent	18 (20.7)	5 (5.0)	0.001
Moderate persistent	16 (18.4)	26 (26.0)	NS
Severe persistent	46 (52.9)	66 (66.0)	0.07
<b>Exacerbations, N (%)</b>			
Patients with asthma exacerbation during the previous year	37 (42.5)	66 (66.0)	0.001
<b>Asthma control in ACT, N (%)</b>			
ACT ≤ 18 (non-controlled)	26 (30.2)	51 (51.051)	0.004
ACT ≥ 19 (controlled)	60 (69.8)	49 (49.0)	0.007
<b>Total IgE, IU/mL, mean (SD)</b>	308.6 (380.3)	482.3 (939.0)	NS
<b>Blood eosinophils cells/μL mean (SD)</b>	369.3 (384.5)	359.5 (279.2)	NS
<b>FeNO, ppb, mean (SD)</b>	37.4 (30.6)	46.7 (34.1)	NS

<b>Sputum eosinophils, mean (SD)</b>	20.3 (27.8)	20.4 (26.3)	NS
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BMI: Body mass index, CRSwNP: Chronic rhinosinusitis with nasal polyps, CRSwNP: Chronic rhinosinusitis without nasal polyps, DLCO: carbon monoxide diffusing capacity, ED: Emergency department, FVC: Forced vital capacity, FeNO: Fractional exhaled nitric oxide, FEV1: Forced expiratory volume in the first second, ICU: Intensive care unit, NS: not significant, RV: Residual volume, TLC: Total lung capacity