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Role of body anthropometry in severe asthmatic patients: Evidences from the Severe Asthma Network in Italy (SANI) registry

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ABSTRACT

Asthma and obesity are both chronic diseases. Obesity is a common comorbidity and a risk factor of severe asthma, associated with increased asthma exacerbation risk, poorer asthma control and reduced quality of life. However, the responsible mechanisms are poorly understood. The aim of this study was to detect parameters associated with obesity in patients with severe asthma in order to check different pattern of inflammation in obese asthmatics. Baseline data from the Severe Asthma Network in Italy (SANI) registry were analysed in 1922 patients with severe asthma. Demographic, clinical and functional features were compared, according to body mass index (BMI). The prevalence of overweight and obesity among severe asthma patients was 34,8 and 20,3, respectively. Females were more prevalent in the obese cluster ($p < 0.001$). Asthma onset age in overweight and obese patients was higher than in normal population ($p < 0.001$). Obese subjects reported less frequently chronic rhinosinusitis with nasal polyposis (CRSwNP) and more frequently impaired sleep quality, cardiovascular disease, and type-2 diabetes ($p < 0.001$). Severe asthma patients with obesity had lower predicted FVC values (89.0 ± 19.2 vs 93.5 ± 20.2; p 0.002) and higher FEV1/FVC ratio (69.9 ± 11.5 vs 66.9 ± 12.4; $p < 0.001$) than patients without obesity. Obese asthmatics had lower blood eosinophilic count, and fractional exhaled nitric oxide (FeNO) levels than non-obese asthmatics. Asthma control test (ACT) was significantly poorer in obese patients (17, IQR 12–21) than other subgroups. Regarding treatment, overweight and obese patients were more likely to receive a GINA-Step 5 therapy (p 0.023), with more than 20 of obese asthmatics having frequent exacerbations requiring oral corticosteroid (OCS). Patients with severe asthma and obesity presented different characteristics that support the existence of distinct asthma phenotype in obese patients.

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Keywords: Asthma, Obesity, BMI, Lung function

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INTRODUCTION

Asthma is a chronic respiratory disease, characterized by persistent airway inflammation, hyperresponsiveness and remodelling. The clinical presentation is characterized by variable expiratory airway obstruction and heterogeneous respiratory symptoms (eg, wheezing, shortness of breath, chest tightness and cough) that vary over time and in intensity.[1] Asthma affects 1–29 of the population in different countries with an increasing worldwide prevalence, and it is responsible for an increased health-care burden, especially in female and in higher income countries.[2,3] Around 5–10 of asthmatics suffer from severe asthma, which is defined as uncontrolled asthma despite regular treatment with high dose of inhaled corticosteroids–long-acting beta-agonists (ICS-LABA). According to European Respiratory Society/American Thoracic Society (ERS/ATS) criteria, severe asthma is characterized by frequent exacerbations, need for frequent boosts of oral steroids, unscheduled visits, accesses to emergency room and hospitalizations.[4] The Global Initiative for Asthma (GINA) recommends investigation for asthma comorbidities associated to poorer asthma-related outcomes.[1,5]

Obesity is a chronic disease defined by an excess of adipose tissue that induces an increase in body mass.[6] The diagnosis is obtained by calculating the body mass index (BMI): weight/height^2 (kg/m^2), thus stratifying patients into 4 categories: underweight ($<$18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese ($\geq$30 kg/m^2).[7] Over 890 million adults (1 in 8 people) are obese worldwide.[8] The rising obesity prevalence over the past few decades has led to a wide pressure on healthcare resources with an increased impact on outcomes in many of the most common lung diseases, such as asthma, chronic obstructive pulmonary disease (COPD) and obstructive sleep apnoea syndrome (OSAS).[9]

Obesity represents both a comorbidity and a risk factor of severe asthma.[1,10–13] Previous studies have shown that the prevalence of obesity in asthmatics ranges from 14 to 52.[14–16] Further studies suggest that patients with obesity and asthma have worse lung function with increased airflow limitation, an increased exacerbation rates and higher maintenance of oral corticosteroids (OCS) intake with a worse asthma control and worse quality of life than non-obese asthmatic subjects.[15–18] Obesity has been shown to change the response to third level drugs, like monoclonal antibodies. In this regard, recent studies showed that omalizumab effectiveness is reduced in asthmatic patients with obesity compared to non-obese patients.[19] On the other hand, further studies show that omalizumab reduces exacerbations in asthmatics despite their BMI.[20,21]

A significant association between obesity and asthma was already described in 1999 in a prospective cohort study on 61,000 asthmatic women registered in the Nurses Health Study II. The authors found that the relative risk of developing adult-onset asthma increased with higher BMI.[22]

Although the pathophysiological relation between obesity and asthma is poorly understood, the accumulation of body fat around the thoracic and abdominal cavities leads to a lung compression, favouring airway narrowing and resistance. In addition, it has been suggested that obesity directly changes lung mechanics affecting respiratory rate, inspiratory effort, and airway wall thickness.[23]

Aside from mechanistic considerations, it is worthwhile to underline the role of obesity in increasing the production of pro-inflammatory mediators that worsen airway inflammation with subsequent airway hyperreactivity.[12] The growth of adipose tissue performs an endocrine effect through the release of cytokines. For example, some studies reported in obese patients a significant increase of leptin, which can promote airway hyper-reactivity, and an important decrease of adiponectin, an anti-inflammatory mediator that normally reduces airway inflammation.[24–28] Tumor necrosis factor (TNF)-α and oxidative stress might have a role in the development of obesity-associated asthma.[29,30] Obesity is also associated with an increase in inflammatory cytokines such as interleukin (IL)-1β and IL-6, coming from adipose tissue.[24,31] This pro-inflammatory pattern in obese patients could be explained by the macrophage transition in adipose tissue from alternative activated M2 macrophages, normally involved in maintaining homeostasis, to classically activated M1 macrophages that promote inflammation by secreting

TNF- α, IL-1β, and IL-6.[32] A recent study describes that obesity-related elevation of leptin has pathogenic effects by increasing M1 macrophage polarization in obesity-related neutrophilic airway inflammation.[33] To better evaluate the association between these 2 conditions some observational and cross-sectional studies were already performed. A cross-sectional study on 2 different cohorts of patients from the University of California San Francisco (UCSF) and the Severe Asthma Research Program, described that increased concentrations of circulating IL-6 were associated with more severe asthma and a decrease of lung respiratory functions.[34] This study showed no association between IL-6 and markers of type-2 inflammation, suggesting that obese asthmatics probably have a different pattern of inflammation compared to non-obese patients.[24] Moreover, the involvement of type 3 innate lymphoid cells (ILC3s) was recently highlighted as pivotal for asthma onset and severity in obese patients. A chronical and persistent inflammation of the adipose tissue upregulates ILC3s, which, together with ILC2s, migrate to lungs, where they promote the production of IL-1β by macrophages, leading to an increased release of IL-17.[35,36] Particularly, an elevated level of the $CD69^{+}$ subset of ILC3s was found to be significantly related to asthma in obese patients compared to non-asthmatic obese control, as well as in severe asthma rather than in mild. Unsurprisingly, CD69 is not expressed in circulating ILCs, rather it is a marker of early tissue activation and residency.[35]

Severe Asthma Network in Italy (SANI) is a registry created to record patient epidemiology, symptoms, therapy, and treatment outcome in a long-term real-life setting.[37] Based on the data extrapolated from SANI, this study is aimed to characterize the role of body anthropometry in severe asthma in order to detect potential markers or risk factors for the different subsets of patients (under-/normal weight, overweight and obese).

METHODS

SANI is a web-based registry collecting demographic, clinical, lung functional, and inflammatory information of patients with diagnosis of severe asthma according to European Respiratory Society/American Thoracic Society (ERS/ATS) criteria,[4] enrolled in Italian accredited centres (Allergology and/or Pneumology Units).[37,38] The study was carried out according to the declarations of Helsinki and Oviedo. The SANI registry was set up according to the 3rd Edition Recommendation on registries for evaluating patient outcomes published by the Effective Health Care Program of the Agency for Healthcare Research and Quality (https://effectivehealthcare.ahrq.gov/topics/registries-guide-3rd-edition/research/). The protocol was performed according to the principles and procedures of the Good Clinical Practice (ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996; Directive 91/507. EEC, The Rules Governing Medical Products in the European Community) and according to the Italian laws (Legislative Decree n.211, June 24, 2003; Legislative Decree n.200 November 6, 2007; Health Ministry Decree, December 21, 2007). The registry protocol, as reported in detail elsewhere,[37] has been approved by the Central Ethics Committee with the Project Code OR00617 and the study number 1742; the enrolment in the other centres started upon approval of each local Ethics Committee. All adult participants or respective guardians subscribed written informed consent. No exclusion criteria were applied in order to have a realistic view of severe asthmatics patients in real life.

The data collected in the registry concerned: demographic and anthropometric characteristics (age, sex, height, weight, BMI), clinical features (age of onset of asthma, presence of allergies and other comorbidities, lung function, exacerbations, unscheduled visits), asthma control in the previous month according to the GINA (Global INitiative for Asthma) Guidelines,[1] and standardized questionnaires (asthma control test – ACT,[39] asthma control questionnaire – ACQ[40]), concomitant regular and on demand treatments (including biologic agents) and inflammatory markers (fractional exhaled nitric oxide – FeNO, eosinophils in the blood, total serum immunoglobulin E– IgE).[37] BMI was calculated as kg/m2 for each participant using the self-reported weight and height during the visit. All data were obtained in each center according to their standard procedures by trained and expert staff.

The current study is a cross-sectional analysis of baseline data of all patients recorded in the Severe Asthma Network in Italy (n = 1922) registry.[37] Three main subgroups were identified: underweight/normal weight, overweight and obesity. According to the AHA/ACC/TOS (American College of Cardiology/American Heart Association/The Obesity Society) guidelines, underweight/normal weight was defined as BMI $\leq$24,9 kg/m^2, overweight as BMI from 25 to 29.9 kg/m^2 and obesity as BMI $\geq$30 kg/m^2.[7]

Categorical variables are reported as absolute values and percentages. Continuous values are expressed as mean $\pm$ standard deviation or median (interquartile range) in case the distribution was not normal. Association between categorical variables and BMI groups was evaluated by χ^2 test, while *t*-test or Kruskal-Wallis test were used for continuous variable. Logistic regression models were used to predict poor asthma control per unit increase of BMI, after adjusting for sex, age, prolonged use of OCS and smoking habits. Statistical analysis was performed using Stata 18 (Stata Corporation, College Station, Texas).

RESULTS

Overall, 1922 patients with severe asthma were examined. According to BMI, 3 subgroups were identified: underweight/normal weight (44.8), overweight (34.8) and obese (20.4). Demographic data of the patients are shown in Table 1. Compared to the other groups, females were more prevalent in the obese group (72.1 vs 52.5 and 65.1 for the overweight and under-/normal weight groups, respectively; $p < 0.001$). Patients with BMI $\leq$24,9 kg/m^2 were significantly younger than overweight and obese subjects (52.9 $\pm$ 14.0 vs 57.1 $\pm$ 12.2 and 57.5 $\pm$ 12.3 years, respectively; $p < 0.001$). No significant differences among subgroups could be described concerning ethnicity and smoking habits, except for higher number of cigarettes packs consumed per year by obese patients [15 (IQ range 6–22.5) vs 10 (5–20) and 8 (3–17) in overweight and under-/normal weight groups, respectively; $p < 0.001$].

While the age of asthma onset in overweight and obese patients was higher than in underweight/normal ones (35 $\pm$ 17 in obese, 35.1 $\pm$ 16.9 in overweight and 32 $\pm$ 16 years in normal; $p < 0.001$), the median disease duration was not affected by weight (19 years in all subgroups).

Regarding treatment, overweight and obese patients were more likely to receive a GINA-Step 5 therapy than lean subjects (87.9 and 87.8 vs 83.1, respectively; p 0.023),[1] with more than 20 of obese asthmatic patients having frequent exacerbations requiring oral corticosteroid (OCS; p NS). No differences among subgroups were observed about the use of inhaled corticosteroids (ICS) and OCS for at least 6 months, and about the use of monoclonal antibodies therapy (approximately 10 in all subgroups).

As regards the prolonged use of OCS (defined as longer than 6 months), it was found to be related to an increased rate of infections compared to no or shorter resort to OCS, independently from BMI. As showed in Fig. 1, 10.36 of patients with prolonged OCS intake reported infections, while infections were described in 5.93 of patients with shorter or no OCS intake. More specifically, 7.23 of patients with prolonged uptake of OCS reported 1 infectious episode and 3.13 reported at least 2 episodes (versus 4.7 and 1.23, respectively, in case of shorter/non-use; p 0.004).

Table 2 shows the type 2 inflammation-related comorbidities. The obese subjects reported a significant lower rate of nasal polyposis compared to the other groups (37.2 vs 45.0 for overweight and 47.5 for under-normal weight; $p < 0.01$), hence with a lower resort to polypectomy. No differences among subgroups were observed concerning allergic rhinitis (both perennial and seasonal), atopic dermatitis and ASA/NSAID hypersensitivity.

A significant higher prevalence of impaired sleep quality assessed as snoring or OSAS (45.1 for obese, 22.8 in overweight and 20.7 in normal), cardiovascular disease (5.4, 3.4 and 1.4, respectively), and type-2 diabetes (11.4, 5.5 and 2.5) was observed in obese patients ($p < 0.001$ for each variable). Moreover, a higher prevalence of endoscopically confirmed gastroesophageal reflux disease (GERD) and peptic ulcer were described in obese patients compared to other groups, although without statistical significance. Other comorbidities such as bronchiectasis, anxious-depressive syndrome, osteoporosis and severe

Characteristic	Data available (n)	Overall (n = 1922)	Under-/Normal weight (n = 862)	Overweight (n = 669)	Obese (n = 391)	p-value[b]
Female, n (%)	1922	1194 (62.1)	561 (65.1)	351 (52.5)	282 (72.1)	<0.001
Ethnicity, n (%)						
Caucasian	1878	1822 (97.0)	826 (97.5)	630 (96.9)	366 (96.1)	0.375
Other		56 (3.0)	21 (2.5)	20 (3.1)	15 (3.9)	
Height, mean ± SD (cm)	1922	165.3 (9.6)	166.0 (9.3)	166.2 (9.7)	162.2 (9.7)	<0.001
Weight, mean ± SD (kg)	1922	71.9 (14.9)	61.2 (9.3)	75.5 (9.6)	89.1 (13.1)	<0.001
Age, mean ± SD (years)	1922	55.3 (13.2)	52.9 (14.0)	57.1 (12.2)	57.5 (12.3)	<0.001
Smoking habits, n (%)						
Non-smoker	1896	1332 (70.3)	607 (71.4)	457 (69.1)	268 (69.6)	0.420
Ex-smoker		484 (25.5)	202 (23.8)	181 (27.4)	101 (26.2)	
Current smoker		80 (4.2)	41 (4.8)	23 (3.5)	16 (4.2)	
Cigarettes packs/ years, median (Q1-Q3)[a]	532	10 (5–20)	8 (3–17)	10 (5–20)	15 (6–22.5)	<0.001
Age at asthma onset, mean ± SD (y)	1720	33.6 (16.9)	31.8 (16.5)	35.1 (16.9)	35.0 (17.3)	<0.001
Age at asthma diagnosis, mean ± SD (y)	1749	36.1 (16.9)	34.0 (16.3)	37.9 (16.9)	38.0 (17.8)	<0.001
Disease duration, median (Q1-Q3) (y)	1710	19 (10–32)	19 (9–30)	19 (10–33)	19 (10–33)	0.410
GINA Step 5, n (%)	1677	1437 (85.7)	641 (83.1)	500 (87.9)	296 (87.8)	0.023
Uncontrolled asthma, n (%)	1678	288 (17.2)	135 (17.5)	99 (17.4)	54 (16.0)	0.824
Frequent exacerbations requiring OCS, n (%)	1240	237 (19.1)	111 (19.1)	69 (16.8)	57 (22.9)	0.159
High dose ICS, n (%)	1922	1829 (94.7)	818 (94.9)	642 (96.0)	369 (94.4)	0.450
OCS for at least 6 months, n (%)	1922	454 (23.6)	211 (24.5)	162 (24.2)	81 (20.7)	0.315
Monoclonal antibodies, n (%)	1922	205 (10.7)	94 (10.9)	72 (10.8)	39 (10.0)	0.881

Table 1. Patients' characteristics by BMI group. *Abbreviations: GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; OCS: oral corticosteroids; Q: quartile; SD: standard deviation. [a]Calculated among current and ex-smokers. [b]T-test or Kruskal-Wallis test for quantitative variables, CHI2 test for categorical variables*

infections were equally distributed in all BMI categories.

Table 3 summarizes functional, clinical and laboratory data. Regarding spirometric findings, in the obese and overweight groups both pre- and post-bronchodilation (BD) FVC were lower than under/normal weight group (pre-FVC: 2.76 [0.88] L, 3.16 [0.99] L and 3.21 [1.00] L; post-FVC: 2.93 [0.98] L, 3.20 [0.95] L and 3.25 [0.98] L respectively), as well as FEV1 (pre: 1.93 [0.73] L, 2.11 [0.79] L and 2.16 [0.83] L; post: 2.07 [0.77] L, 2.16 [0.71] L and 2.28 [0.86] L, respectively). In contrast, the Tiffeneau index in pre-bronchodilation (FEV1/FVC ratio) was found higher in the obese group (66.9 [12.4] in normal, 66.8 [12.2] in overweight and 69.9 [11.5] in obese group). Obese patients had lower FVC% predicted pre-BD values and higher FEV1/FVC pre-BD ratio than patients without obesity. Pearson correlation underlined the lack of association between pre-bronchodilator FEV1%pred and BMI (rho = −0.04, p = 0.13) and a very weak association between FVC% pred and BMI (rho = −0.09, $p < 0.001$) (Fig. 2A and 2B**)**. No other significant differences could be described regarding the other functional variables.

Concerning the type 2 asthma endotype stakeholders, no differences among the subsets were recorded for the absolute eosinophil count, while a lower percentage eosinophil count was reported for the obese and overweight groups compared to the under-/normal weight group (respectively 4.0, IQR 1.6–7.1, 4.4, 1.8–8.1, and 5.3, 1.8–9.6; p 0.001).

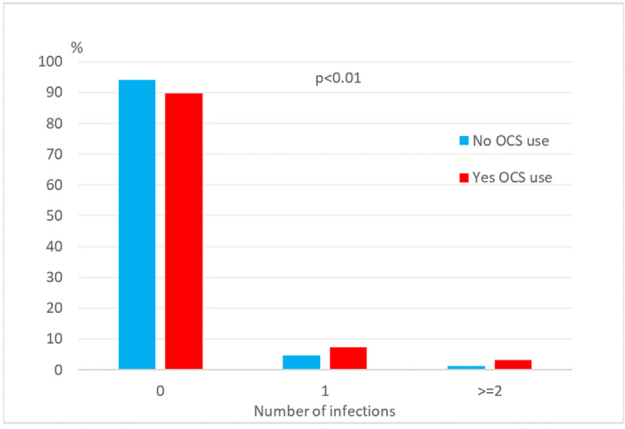

Fig. 1 Correlation between number of infections and use of oral corticosteroids (OCS). The prolonged use of OCS (>6 months) is related to an increased number of infections, independently from BMI*. *Pearson's chi-squared tests were performed.

Total serum IgE level was not affected by anthropometric characteristics. FeNO values were lower in obese patients.

Referring to level of asthma control according to the GINA guidelines[1] assessed through ACT, it was significantly poorer in obese patients (17, IQR 12–21) than in other subgroups (normal patients median 19, IQR 14–22; overweight median 18, IQR 14–22; p 0.001), but no other significant differences could be observed in other parameters including ACQ, number of exacerbations requiring steroid use, number of lost work days, admission in the emergency room and unscheduled visit (p NS for each parameter). The logistic regression confirmed the negative association between BMI and asthma control, showing that the unit increase in BMI leads to an increase in the odds of poor disease control by 3.0, even after adjusting for the use of OCS [OR (95%CI): 1.03 (1.0–1.1), p = 0.005].

DISCUSSION

Obesity represents not only an important risk factor for asthma, but also a disease modifying condition. As described in a recent review, obesity causes a mixed pattern of airway and systemic inflammation, contributing to the poor disease outcome in obese asthmatics.[24]

The main finding of the current study showed that more than a half of severe asthmatic patients is affected by excess weight, with a respective prevalence of 34.8 for overweight and 20.3 for obese. Our findings are slightly lower than the German Asthma Net describing that the prevalence of obesity was 29[15] but contrasts with the International Severe Asthma Registry and the Severe Asthma Research Program, reporting a higher prevalence of obesity (42 and 37, respectively).[5,41] Despite the differences in prevalence rates, our result is alarming and suggests that awareness-raising initiatives, early identification of obesity and overweight conditions, and weight loss promotion should be performed in asthma centres.

As widely reported in other studies,[15,17,41–45] we found that obesity was significantly more prevalent among female asthmatic patients (72). This disparity is most likely explained by elevated

Comorbidity	Data available (n)	Overall (n = 1922)	Under-/Normal weight (n = 862)	Overweight (n = 669)	Obese (n = 391)	p-value[c]
Allergic rhinitis, n (%)	1872	835 (44.6)	389 (46.1)	282 (43.0)	164 (44.1)	0.268
Periodicity of allergic rhinitis						
Perennial allergic rhinitis, n (%)[a]	835	620 (74.3)	297 (76.4)	211 (74.8)	112 (68.3)	0.136
Seasonal allergic rhinitis, n (%)[a]	835	255 (30.5)	117 (30.1)	87 (30.9)	51 (31.1)	0.963
Chronic rhinosinusitis without nasal polyps, n (%)	1831	520 (28.4)	243 (29.7)	181 (28.2)	96 (26.0)	0.427
Nasal polyposis last 12 months, n (%)	1888	841 (44.5)	404 (47.5)	295 (45.0)	142 (37.2)	0.003
Underwent polypectomy last 12 months, n (%)[b]	615 (of 1888)	488 (79.4)	245 (79.8)	170 (82.5)	73 (70.9)	0.053
Sleep quality last 12 months, n (%)						
Nothing to report	1756	1292 (73.6)	630 (79.3)	465 (77.2)	197 (54.9)	<0.001
Snoring		368 (21.0)	151 (19.0)	114 (18.9)	103 (28.7)	
OSAS		96 (5.4)	14 (1.8)	23 (3.8)	59 (16.4)	
Bronchiectasis, n (%)	1572	343 (21.8)	154 (21.8)	128 (22.7)	61 (20.2)	0.698
Atopic dermatitis, n (%)	1884	129 (6.9)	67 (7.9)	34 (5.2)	28 (7.4)	0.100
ASA/NSAID hypersensitivity, n (%)	1859	315 (16.9)	147 (17.6)	104 (16.0)	64 (17.1)	0.726
GERD diagnosis, n (%)						
No	1861	1140 (61.3)	528 (63.2)	397 (61.0)	215 (57.3)	0.308
Confirmed		513 (27.6)	222 (26.6)	175 (26.9)	116 (30.9)	
Suspected		208 (11.2)	85 (10.2)	79 (12.1)	44 (11.7)	

(continued)

Comorbidity	Data available (n)	Overall (n = 1922)	Under-/Normal weight (n = 862)	Overweight (n = 669)	Obese (n = 391)	p-value[c]
Cardiovascular disease, n (%)	1740	50 (2.9)	11 (1.4)	20 (3.4)	19 (5.4)	0.001
Anxious-depressive syndrome, n (%)	1736	80 (4.6)	39 (5.0)	27 (4.5)	14 (4.0)	0.743
Type-2 diabetes, n (%)	1746	94 (5.4)	20 (2.5)	33 (5.5)	41 (11.4)	<0.001
Peptic ulcer, n (%)	1729	29 (1.7)	13 (1.7)	6 (1.0)	10 (2.8)	0.116
Osteoporosis, n (%)	1578	250 (15.8)	118 (16.3)	80 (14.9)	52 (16.4)	0.773
Severe infections, n (%)	1713	120 (7.0)	46 (6.0)	50 (8.4)	24 (6.9)	0.220

Table 2. (Continued) Patients' comorbidities by BMI group. *Abbreviations: ASA: acetylsalicylic acid; GERD: gastroesophageal reflux disease; NSAID: non-steroidal anti-inflammatory drug; OSAS: obstructive sleep apnoea syndrome.* [a]*Calculated among patients with allergic rhinitis.* [b]*Calculated among patients with nasal polyposis in the last 12 months.* [c]*T-test or Kruskal-Wallis test for quantitative variables, CHI2 test for categorical variables*

blood estrogenic levels in obese women,[46] which mediate a role in lung inflammation and asthma by upregulating the expression of estrogenic receptors (ER) ERα and Erβ in human airway smooth muscle.[44,47]

In line with Klepaker et al,[42] subjects with severe asthma and overweight/obesity had an older age of asthma onset (mean 35 years of age) than lean asthmatic patients. Although Klepaker et al reported a lower mean age of asthma onset (16 years) in obese patients, probably due to its lower mean age of the overall study population, these findings could define an obese-asthma phenotype. Some studies described a late-onset nonatopic asthma in obese patients, more likely older obese women, characterized by non-T2 inflammation, poor-response to corticosteroids and more likely resolution with weight loss.[41,48–50]

Concerning the clinical control of asthmatic patients, in our study population overweight and obese asthmatics patients were more likely treated according to GINA Step 5.[1] This is consistent with the findings of the German Asthma Net, which described an increased prevalence of long-acting muscarinic antagonist (LAMA) therapy in obese asthmatics ($p < 0.001$) then lean ones.[15] In addition, although not statistically significant, we observed an increasing trend of exacerbations requiring OCS in obese patients, while no significant differences about OCS therapy were reported between the different subgroups. However, in our cohort, obesity did not appear to have a role in increasing the risk of infections related to the prolonged use of OCS. In line with our findings and other studies,[18,51] Bal et al detected an association of higher BMI with exacerbation rates.[15] These findings could be explained by the impaired response to standard asthma controller medications such as ICS-LABA, due to increased production of inflammatory cytokines in obesity, which have a negative effect on induction of mitogen-activated kinase phosphatase-1 (MAPK-1), a signalling protein involved in steroid responses.[52,53] Tashiro et al reported that a considerable proportion of obese asthmatic patients (44) have persistent symptoms despite more than a year of ICS/LABA therapy.[54] This reduced the response to ICS, together with the adverse effects related to the overuse of systemic corticosteroids[55] could lead to an

	Data available (n)	Overall (n = 1922)	Under-/Normal weight (n = 862)	Overweight (n = 669)	Obese (n = 391)	p-value[a]
Absolute eosinophil count (cell/L), median (Q1-Q3)	1486	0.37 (0.13–0.68)	0.39 (0.12–0.72)	0.35 (0.14–0.65)	0.33 (0.14–0.62)	0.340
Percentage eosinophil count, median (Q1-Q3)	1342	4.5 (1.7–8.7)	5.3 (1.8–9.6)	4.4 (1.8–8.1)	4.0 (1.6–7.1)	0.005
Higher blood eosinophil count (cell/L), median (Q1-Q3)	1076	0.62 (0.36–1.06)	0.65 (0.40–1.16)	0.60 (0.34–0.98)	0.56 (0.32–0.84)	0.007
Total serum IgE concentration, median (Q1-Q3)	1163	197 (74–483)	197 (75–456)	218 (86–491)	176 (63–484)	0.248
Chest CT last 2 years, n (%) no yes, altered yes, norma	1792	 980 (54.7) 499 (27.9) 313 (17.5)	 438 (54.7) 225 (28.1) 138 (17.2)	 332 (52.6) 182 (28.8) 117 (18.5)	 210 (58.3) 92 (25.6) 58 (16.1)	0.539
FVC pre-BD (L), mean ± SD	1408	3.10 (0.99)	3.21 (1.00)	3.16 (0.99)	2.76 (0.88)	<0.001
FVC predicted pre-BD mean ± SD	1390	91.4 (19.8)	93.5 (20.2)	90.2 (19.4)	89.0 (19.2)	0.002
FVC post-BD (L), mean ± SD	547	3.16 (0.98)	3.25 (0.98)	3.20 (0.95)	2.93 (0.98)	0.008
FVC predicted post-BD mean ± SD	538	94.3 (19.0)	95.5 (18.7)	93.4 (18.7)	93.5 (20.0)	0.462
FEV_1 pre-BD (L), mean ± SD	1412	2.10 (0.80)	2.16 (0.83)	2.11 (0.79)	1.93 (0.73)	<0.001

(continued)

	Data available (n)	Overall (n = 1922)	Under-/Normal weight (n = 862)	Overweight (n = 669)	Obese (n = 391)	p-value[a]
FEV_1 predicted pre-BD mean ± SD	1405	75.9 (21.1)	76.9 (22.2)	74.6 (20.3)	76.0 (19.8)	0.209
FEV_1 post-BD (L), mean ± SD	722	2.19 (0.79)	2.28 (0.86)	2.16 (0.71)	2.07 (0.77)	0.025
FEV_1 predicted post-BD mean ± SD	703	81.2 (21.0)	82.4 (21.4)	78.9 (20.2)	82.8 (21.1)	0.093
FEV_1/FVC pre-BD, mean ± SD	1398	67.5 (12.2)	66.9 (12.4)	66.8 (12.2)	69.9 (11.5)	<0.001
FEV_1/FVC post-BD, mean ± SD	543	68.3 (12.4)	68.1 (12.7)	67.3 (12.8)	70.3 (10.9)	0.097
FEV1/FVC predicted post-BD, mean ± SD	340	75.4 (17.1)	75.1 (17.5)	74.9 (16.7)	77.1 (17.0)	0.647
FeNO (ppb), median (Q1-Q3)	881	30.0 (16.0–58.0)	31.0 (17.0–63.0)	29.0 (16.0–55.4)	23.5 (13.5–50.5)	0.036
ACT, median (Q1-Q3)	1697	18 (14–22)	19 (14–22)	18 (14–22)	17 (12–21)	0.001
ACQ, median (Q1-Q3)	1272	2.27 (1.00–3.42)	2.14 (1.00–3.28)	2.42 (1.00–3.60)	2.19 (1.16–3.60)	0.209
N. days of work lost last 12 months, n (%)						
0	1121	698 (62.3)	330 (60.6)	239 (65.1)	129 (61.7)	0.618
1-7		154 (13.7)	78 (14.3)	44 (12.0)	32 (15.3)	
>7		269 (24.0)	137 (25.1)	84 (22.9)	48 (23.0)	
≥1 admission in the emergency room last 12 months, n (%)	1719	277 (16.1)	126 (16.1)	94 (15.7)	57 (16.9)	0.892

≥1 unscheduled visit last 12 months, n (%)	1451	431 (29.7)	207 (30.8)	145 (28.9)	79 (28.4)	0.688
N. Exacerbations with steroid use last 12 months (%)						
0	1649	580 (35.2)	247 (32.8)	210 (37.2)	123 (37.3)	0.317
1-2		516 (31.3)	253 (33.6)	164 (29.0)	99 (30.0)	
>2		553 (33.5)	254 (33.7)	191 (33.8)	108 (32.7)	

Table 3. (Continued) Patients' clinical characteristics by BMI group. *Abbreviations: ACT: asthma control test; ACQ: asthma control questionnaire; BD: bronchodilator; CT: computed tomography; FeNO: fractional exhaled nitric oxide; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; IgE: immunoglobulin E; Q: quartile; SD; standard deviation.* [a]*T-test or Kruskal-Wallis test for quantitative variables, CHI2 test for categorical variables*

increased need for advanced line treatments involving also monoclonal antibodies. Although this consideration, in line with other studies,[15,16] we did not detect any difference in monoclonal antibodies therapy between obese and non-obese asthmatics, but it is necessary to underline that the groups including patients in biological therapy were small. Since we did not stratify the study population based on respiratory symptoms (wheezing, coughing, shortness of breath, dyspnoea), we were unable to check their association with BMI in the present population.

As regards type 2 inflammation-related comorbidities, the SANI cohort patients with obesity were less likely to report a history of CRSwNP than the lower weight subgroups. Our findings are similar to the British Thoracic Society Difficult Asthma Registry, which observed a decreasing trend in prevalence of CRSwNP among obese patients with severe asthma, even if in that case only 10 of them suffered from CRSwNP.[18] In our study we did not find any significant differences concerning allergic rhinitis, atopic dermatitis and ASA/NSAID hypersensitivity between obese and non-obese patients. The absence in the investigated population of a clear association with type 2 inflammation-related diseases may contribute to reinforce the idea configuring asthma in obese subjects as a specific substrate. As reported by Orimo et al, in obesity-associated asthma also different inflammatory patterns have to be considered. Particularly, the activation of ILC3s promotes the release of IL-17, which is involved in airway neutrophilic infiltration.[36] However, type 2 inflammation-related conditions represent a fundamental evaluation parameter in clinical practice for the severe asthma therapy choice, independently of patients' weight.

Concerning systemic comorbidities, impaired sleep quality, including both snoring and OSAS, cardiovascular disease and type-2 diabetes were significantly reported more prevalent in the obese group. Furthermore, obese asthmatic patients were more likely to report a history of GERD. Considering only endoscopically confirmed diagnosis, in fact, GERD was reported by 30.9 of obese patients with severe asthma, a lower rate compared to the obese severe asthmatics of the British Thoracic Society Difficult Asthma Registry and the German Asthma Net (respectively, 53.9

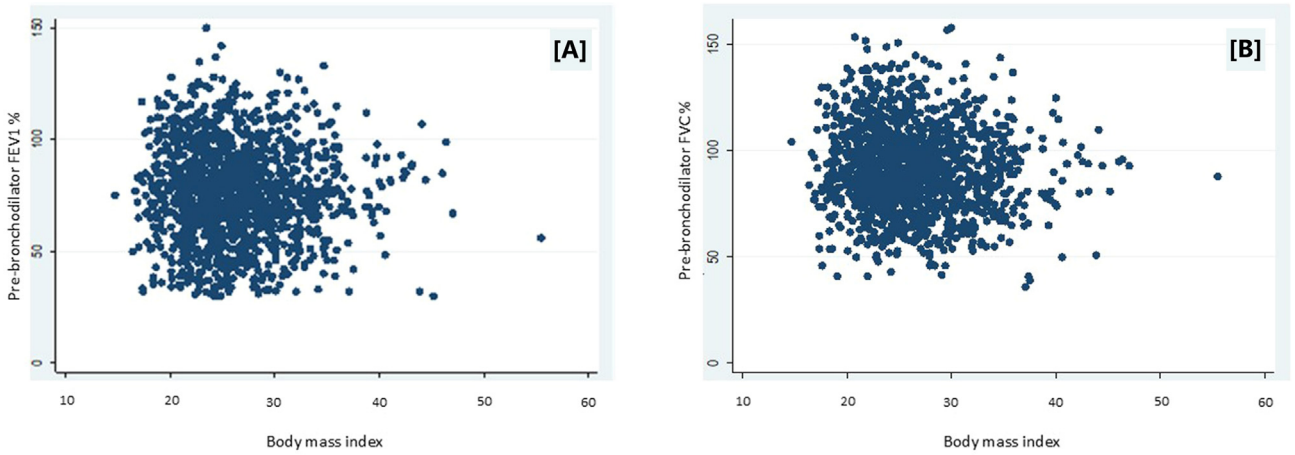

Fig. 2 Correlation between body mass index (BMI) and spirometry values among patients with asthma. Correlation between BMI kg/m^2 with forced expiratory volume in 1 s (FEV1) % [**A**] and forced vital capacity (FVC) % [**B**] were assessed*. *Pearson correlation analyses were performed.

and 40).[15,18] Despite the differences in prevalence, an increasing trend was highlighted in all mentioned studies. GERD and OSAS were described to affect asthma control trough micro aspiration, mechanical effects on lung function and systemic inflammation.[12] Although no further metabolic parameters were detected in our study, evidence suggests that hyperglycaemia and hyperinsulinemia may contribute to airway hyperresponsiveness and remodelling.[56] Whereas in our study we did not have the opportunity to investigate the effect of these comorbidities on asthma control, identifying and treating them is mandatory to improve disease control.

When assessing lung function, as observed in the German Asthma Net,[15] our findings reported a reduction in prebronchodilation FVC% of predicted with an increased prebronchodilator FEV1/FVC ratio in obese patients, probably because of FVC values. Although the British Thoracic Society Difficult Asthma Registry study reported similar data concerning FVC and FEV1/FVC ratio, it also observed a reduction in FEV1 in obese asthmatic patients compared to overweight and normal weight ones,[18] supporting other studies findings.[16,17] However, no differences were observed concerning prebronchodilator FEV1% of predicted between all groups in our cohort. According to this last value, we observed in all patients a mild airway obstruction, independently from BMI; since z-score was not considered in our study to confirm the degree of obstruction, additional analyses should be performed in future. It is known that obesity could induce an increased intraabdominal pressure on the diaphragm, leading to lower tidal volumes, functional residual capacity, and expiratory reserve volume. FEV1/FVC ratio may be normal, or elevated if gas trapping and airway closure reduce FVC.[23] Unfortunately, we did not detect other parameters, such as total lung capacity (TLC), maximal expiratory flow (MEF50 and MEF75), and diffusing capacity for carbon monoxide (DLCO), which could be important to evaluate the global lung function.

As regards type-2 inflammation markers, our study described a trend about lower blood eosinophilic count and total serum IgE concentration in obese asthmatics than other subgroups. Similar findings were reported by the British Thoracic Society Difficult Asthma Registry study,[18] whereas they are in contrast with the German Asthma Net, that did not find differences in blood eosinophilic count between obese and non-obese patients and observed a higher total serum IgE concentration in obese groups.[15] We found normal FeNO levels (median (Q1-Q3) 23.5 (13.5–50.5) ppb) in the obese subgroup, which resulted to be lower when compared with elevated FeNO levels in normal or overweight patients (normal weight median (Q1-Q3) 31,0 (17.0–63.0) ppb; overweight median (Q1-Q3) 29 (16.0–55.4) ppb). Other studies reported higher or normal FeNO levels in obese groups with no differences between obese and non-obese patients.[15,16,18] Our findings about type-2

inflammation markers are in line with a US multicenter study which revealed that obese asthmatic subjects have lower IgE levels, FeNO values, and blood eosinophil counts than all other groups.[57] The lower FeNO levels in obese patients may be functionally explained by altered nitric oxide (NO) metabolism in the airways, due to an increased airway oxidative stress in obese asthmatics.[58,59] Increased reactive oxygen species (ROS) in the obese airway promote the NO conversion into reduced forms which decrease the bioavailability of NO in the airways, consequently reducing FeNO levels.[59,60] A lower type-2 inflammatory profile in obese patients could be related to adipokine levels, which seems to have a role in alterations of eosinophil chemotaxis and survival.[30,61,62]

As widely reported in other studies,[15,42] poor asthma control remained significantly associated with BMI category. Our findings observed a significantly reduced median ACT score in obese patients than other subgroups. The lower prevalence of type-2 inflammation in obese patients may in part explain the poorer asthma control in obese than non-obese asthmatics.

Strength and limitations

A strength of this study is that a large cohort of asthma patients was analysed in detail, including information on pulmonary function, type-2 inflammation, and comorbidities. Furthermore, data from SANI allowed to assess the cohort in real life. Our study benefited of a similar cross-sectional design.

There are several limitations to this study that should be considered when interpreting our results. First, BMI is not the gold standard to assess body composition and fat content, and it may not be the best measure of the effect of adiposity on the lung,[23] even if, at the moment, it is a widely used measure to define overweight or obesity level in population-based studies and to monitor changes in body weight. In the future, research should include more complex anthropometric measures (eg, waist-circumference, or bioelectrical impedance analysis) that evaluate total body mass distribution, including body fat mass measure. Furthermore, the data came from a population distributed in different third level centres but living in the same nation (Italy); consequently, our data cannot be generalized to other continents or climate areas. The impact of external factors like pollution and personal habits other than smoke were not taken in consideration.

Finally, this was a cross-sectional study. Consequently, the causality between asthma and obesity as well as the effect of weight changes on asthma-related parameters could not be considered in our analysis. Future prospective studies should be performed to investigate these considerations.

CONCLUSIONS

In our cross-sectional multicentric study severe asthma in obese patients is associated to different inflammation pattern and a poor disease control, suggesting the existence of a peculiar phenotypical expression of the disease different from the one present in lean people, ie. older age of onset, and lower association to CRSwNP, lower eosinophilic blood count and lower FeNO levels. Despite this, obese patients report a lower control of asthmatic symptoms compared to patients with lower weight. These important differences between obese and non-obese asthmatic patients should be considered as a valuable support in real-life clinical practice in order to globally characterize patients and consequently improve strategies for therapy prescription and personalized management programs of patients with severe asthma, including the promotion of obesity prevention, healthy lifestyles, and weight loss, in order to achieve an effective asthma management.

List of abbreviations

AHA, American Heart Association; ACC, American College of Cardiology; ACT, asthma control test; ACQ, asthma control questionnaire; ASA, acetylsalicylic acid; ATS, American Thoracic Society; BD, bronchodilator; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; DLCO, diffusing capacity for carbon monoxide; ERS, European Respiratory Society; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; IQR, interquartile range; IgE, immunoglobulinE; IL, interleukin; ILC, innate lymphoid cell; LABA, long-acting beta-agonists; MAPK-1, mitogen-activated kinase phosphatase-1; MEF, maximal expiratory flow; NSAID, non-steroidal anti-inflammatory drugs; NS, not significant; OCS, oral corticosteroids; OSAS, obstructive sleep apnoea syndrome; ROS, reactive oxygen species; SANI, Severe Asthma Network Italy; SD, standard deviation;

TLC, total lung capacity; TNF, tumor necrosis factor; TOS, The Obesity Society.

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Data availability statement
Data and materials that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contribution
ER – conceptualization, writing original draft, review.
MO – conceptualization, data collection, elaboration of the tables, writing original draft, review.
FN – conceptualization, writing original draft, review.
FL – data collection, elaboration of the tables, editing of the figure, review.
LM, MM, NAC, FB, PP, EH, LB – review.
GWC – conceptualization, review.
GS – conceptualization, review.
MC – conceptualization, data collection, elaboration of the tables, editing of the figure, review.
All authors approved the submitted version and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

Authors' consent for publication
All authors have approved the submission of this manuscript. The results have not been previously published and are not being considered for publication in another journal.

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All other authors do not have any conflict of interest to declare.

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