

The Influence of BMI in Asthma: Which Traits Are due to Obesity and Which to the Asthma and Obesity Phenotype?

Esteban-Gorgojo I¹, Gorgojo MP², Sastre J^{3,4,5}, García-Río F^{4,5,6,7}, Quirce S^{4,5,7,8}

¹Department of Allergy, Hospital General de Villalba, Madrid, Spain

²CS Universitat, Zaragoza, Spain

³Department of Allergy, Fundación Jiménez Díaz, Madrid, Spain

⁴Department of Medicine, Universidad Autónoma de Madrid, Madrid, Spain

⁵CIBER of Respiratory Diseases (CIBERES), Instituto de Salud Carlos III, Madrid, Spain

⁶Department of Pulmonology, La Paz University Hospital, Madrid, Spain

⁷IdiPAZ, Madrid, Spain

⁸Department of Allergy, La Paz University Hospital, Madrid, Spain

J Investig Allergol Clin Immunol 2024; Vol. 34(1): 30-37

doi: 10.18176/jiaci.0865

■ Abstract

Background: The characteristics of the asthma and obesity phenotype have been described in cluster studies but have not been subsequently confirmed. Specific characteristics of this phenotype have not been differentiated from those inherent to the patient's body mass index (BMI).

Objectives: This study aims to assess the effect of BMI on asthma in order to identify which traits could define the asthma and obesity phenotype and which are inherent to the patient's BMI.

Methods: A real-life retrospective observational study was conducted based on data from 2514 patients with suspected asthma collected at the first visit to the allergy clinic between November 2014 and November 2017. All patients had to perform an appropriate spirometry maneuver. All BMI, sex, and age groups were represented.

Results: The influence of BMI on asthma differed according to age group and sex. All spirometry results and FeNO were influenced by BMI. The only notable asthma characteristics were later onset of asthma with higher BMI values. No other differences were found between the BMI groups.

Conclusions: The effect of BMI on asthma is age-dependent; therefore, it should be corrected for age. The most important variations are in FeNO and spirometry results. The specific characteristics of the asthma and obesity phenotype are a greater perception of symptoms with fewer alterations in respiratory function tests and a lower prevalence of atopy, rhinitis, and allergy, including allergic asthma. Other characteristics of this phenotype, such as a higher female prevalence or late-onset or noneosinophilic asthma, are nonspecific for this phenotype.

Key words: Asthma. Obesity. BMI. Phenotype. Severe asthma. Asthma and obesity.

■ Resumen

Antecedentes: Las características del fenotipo asma y obesidad han sido descritas mediante estudios de tipo clúster, pero no han sido plenamente corroboradas en estudios posteriores. Las características específicas de este fenotipo no se han diferenciado de las inherentes al propio índice de masa corporal (IMC) del paciente.

Objetivos: Este estudio tiene como objetivo evaluar el efecto del IMC sobre el asma. Esto permitirá identificar qué rasgos podrían definir el fenotipo de asma y obesidad, y cuáles son inherentes al IMC del paciente.

Métodos: Se realizó un estudio observacional retrospectivo en condiciones de práctica clínica habitual (vida real) con una base de datos de 2.514 pacientes. Se recogieron los datos en la primera visita a la consulta de Alergia de todos los pacientes a los que se les realizó una maniobra espirométrica correcta por sospecha de asma entre noviembre de 2014 y noviembre de 2017. Todos los grupos de IMC, sexo y edad están representados en el estudio.

Resultados: La influencia del IMC sobre el asma difirió en diferentes grupos de edad y género. Todos los valores espirométricos analizados y el FeNO se vieron influenciados por el IMC. En cuanto a las características del asma, solo se observó que cuánto mayor era el IMC más tardío era el comienzo del asma. No se encontraron otras diferencias significativas entre los diferentes grupos de IMC.

Conclusiones: El efecto del IMC sobre el asma es dependiente de la edad, por lo que debería realizarse una corrección de los datos por esta. Además, las variaciones más importantes ocurren sobre el FeNO y los valores espirométricos, teniendo que ser estos valores corregidos por el IMC.

Palabras clave: Asma. Obesidad. IMC. Fenotipo. Asma grave. Asma y obesidad.

Summary box

• What do we know about this topic?

Obesity is a comorbidity that can modify asthma. The asthma and obesity phenotype has been described, although its characteristics have not been differentiated from those of obesity itself. Moreover, the effect of other BMI groups has received little attention.

• How does this study impact our current understanding and/or clinical management of this topic?

We describe the effects of all BMI groups on asthma. We then define the effect of obesity on asthma, thus making it possible to define the specific traits of the asthma and obesity phenotype and of obesity itself.

Introduction

Asthma and obesity are widespread diseases whose prevalence is increasing [1-3]. Both conditions occur simultaneously in many patients, and this co-occurrence is expected to become more prevalent in the future. The relationship between asthma and obesity was first studied in the 1950s and 1960s [4-6] and has been extensively investigated ever since.

Obesity causes pulmonary physiological changes such as reduced lung volume, impaired gas exchange, and collapse of the pulmonary airways [7]. It also influences asthma traits in phenotypic studies. Cluster studies have demonstrated a specific asthma phenotype, asthma and obesity, among patients with severe asthma [8], and SARP III found an association with age [9]. This phenotype is characterized by late-onset and predominantly noneosinophilic asthma, with a high prevalence in women and highly symptomatic patients who respond poorly to asthma treatments [8].

However, subsequent studies have not fully corroborated these traits. Bibi et al [10] suggested that affected patients more frequently have symptoms because they are not actually asthmatic, thus explaining the poor response to treatment and overdiagnosis of asthma.

Sin et al [11] suggested that obese patients were characterized by significant self-diagnosis, despite there being no functional changes or signs of pulmonary obstruction. Other studies found that bronchial hyperresponsiveness (BHR) is not increased in obese adults [12] or children [13]. In fact, Schacter et al [14] reported that BHR is increased in patients with lower BMI than in obese individuals.

In contrast, other studies found BHR among obese patients and greater perception of symptoms, as expected [15-17]. Litonjua et al [18] found BHR among patients in the highest BMI quintile and in the underweight group.

It is widely accepted that this phenotype is noneosinophilic, even before administration of anti-inflammatory treatment that could modify eosinophil counts [19]. In fact, this phenotype is dependent on IL-17 and IL-33 [20]. However, some authors link obesity and eosinophilic asthma and even show that obesity can modify asthma differently depending on whether it is eosinophilic or noneosinophilic [21].

The higher prevalence of women in the asthma and obesity phenotype is controversial in the literature. Some studies report a higher prevalence of women [22] and consider that obesity increases the risk of asthma in adolescent women but

not in men [23]. Other studies suggest that there are no sex differences in patients with asthma and obesity [24] or even that the prevalence of men in this phenotype is higher [25].

The definition of late-onset asthma constitutes a problem in itself [26]. Different groups have established different cut-off points, for example, age 12 years [27], age 18-20 years [28], and age 65 years [29]. Each of these studies showed that BMI had a heterogeneous influence on asthma depending on whether it developed before or after each cut-off point. Using age 12 years as the cut-off point, Holguin et al [27] suggested that obesity acts as a comorbid condition in early-onset asthma and as a causal agent in late-onset asthma.

Despite the lack of a specific cut-off point, the literature shows that the relationship between asthma and obesity varies with age [30]. This relationship is heterogeneous, and it has been suggested that women and children are considerably affected, while the influence in the elderly population is weaker [28].

The literature shows a relationship between asthma and obesity, despite the lack of specific conclusions. However, other BMI groups have been poorly studied. Without adequate knowledge of the effect of BMI groups on asthma, it is not possible to correctly differentiate between the effect of obesity on asthma and the specific features of the asthma and obesity phenotype.

Our aim was to explore in depth the influence of obesity in asthma by analyzing all BMI groups. Understanding how BMI affects asthma will make it possible to assess the effect of obesity on asthma and, therefore, define the specific asthma traits of obese asthma patients. Once these characteristics have been described, they can be compared with those of the asthma and obesity phenotype, thus enabling differentiation between obese asthma patients and asthma patients with the asthma and obesity phenotype.

Methods

Study

We conducted a retrospective observational, real-world study to investigate the relationship between asthma and obesity. All patients who underwent spirometry for suspected asthma between November 2014 and November 2017 were recruited. Neither the criteria for performing spirometry nor clinical practice were affected by the study, since existing

hospital protocols were applied. This study was approved by the local ethics committee.

Patients

The study population comprised all patients aged between 3 and 99 years of age who attended the Allergy Clinic of Hospital General de Villalba, Madrid, Spain with suspected asthma and performed a successful spirometry maneuver. The results of spirometry performed for other reasons were not taken into account. All the clinical charts were analyzed, and only those with clear information for the diagnosis of asthma were included. Patients unable to successfully perform a spirometry maneuver were excluded. Other inclusion/exclusion criteria were not considered. BMI data were extracted from the measurements necessary to perform spirometry.

All records of included patients were reviewed and data collected to create a database comprising 2514 patients.

Study Variables

We recorded anthropometric characteristics and lung function values obtained from spirometry performed according to the criteria of the European Respiratory Society/American Thoracic Society (ERS/ATS) [31]. The Global Lung Function Initiative equations were used as reference values [32], and the percentage with respect to the predicted value (Zapletal 2 references) and the Z-score were calculated. The bronchodilator test result was considered positive when the increase in FEV₁ was >12% and >200 mL. An increase in FEV₁ <12% and/or <200 mL with an increase in FVC >10% or an increase in FEF₂₅₋₇₅ >35% was considered a partial bronchodilator response.

Inflammation-related variables included peripheral blood eosinophil count and FeNO. FeNO was determined using a Fenom Pro testing device following ERS/ATS recommendations [33].

A series of asthma characteristics were also recorded, as follows: time since diagnosis; age at onset; allergic asthma; persistent asthma; exposure to asthma trigger; symptomatic period; and symptoms when spirometry is performed. We also assessed evidence of rhinitis, atopy (defined as sensitization to any food or aeroallergen, independently of its clinical relevance), peripheral blood IgE, food allergy, drug allergy, allergic contact dermatitis, other concomitant comorbidities (Table 1) and treatment during the 48 hours prior to spirometry. Treatments were classified according to current asthma guidelines [34,35].

Asthma

All medical records were reviewed to confirm a robust diagnosis of asthma. Asthma was diagnosed and treated following asthma guidelines [34-36]. Only the first visit for each patient was included in the study [36]. All patients underwent allergy testing [36].

Database Analysis

Patients were divided into those with and without asthma. They were also distributed into 4 BMI groups (<20, 20-25, 25-30, and >30). Variables were classified into gaussian and

Table 1. Comorbidities

Comorbidity	Total number	Percentage
Atopic dermatitis	146	5.8%
Acute respiratory infections	63	2.5%
Spontaneous urticaria/angioedema	52	2.1%
Gastroesophageal reflux disease	31	1.2%
Chronic pharyngitis/laryngitis	25	1%
Nasal polyps	23	0.9%
Chronic obstructive pulmonary disease	15	0.6%
Eosinophilic esophagitis	10	0.4%
Sleep apnea syndrome	8	0.3%
Idiopathic anaphylaxis	4	0.2%
Anxiety	3	0.1%
Hereditary angioedema	1	0.0%
Scoliosis	1	0.0%
Multifactorial dyspnea	1	0.0%
Histiocytosis X	1	0.0%
Lupus erythematosus	1	0.0%
Pachypleuritis of the azygos lobe	1	0.0%
Sarcoidosis	1	0.0%
Diastolic dysfunction with aortic insufficiency	1	0.0%
Chronic fatigue syndrome	1	0.0%
Graves disease	1	0.0%
Pityriasis alba	1	0.0%
Pulmonary nodule with ground glass pattern	1	0.0%

nongaussian distributions [36] and were described according to their features [36]. Detailed information on this data analysis is provided in the Supplementary material (Methods; data analysis section).

Results

Asthma Patients

When the analysis was performed by sex, statistically significant differences were found for several variables. These differences persisted after normalization for age and corticosteroid treatment (Table 2). Women were more prevalent among asthma patients in all BMI groups (20-25, 64%; 25-30, 56%; and >30, 60%), except in <20, where women accounted for 49%.

Men were younger, with greater height and weight, but lower BMI. Men also had higher lung volumes, although the expected percentages were always lower than among women.

Early-onset asthma was more common in men than in women, regardless of whether the selected cut-off point was

Table 2. Asthma Patients.^a

	Women	Men	Men vs Women	ANCOVA	Odds ratio	Relative risk, men's cohort	Relative risk, women's cohort
Sample size	845	613	-	-	-	-	-
Age	32.18 (16.10)	26.51 (16.73)	<.001 ^b	-	-	-	-
Weight, kg	62.85 (17.14)	67.17 (25.99)	<.001 ^b	<.001 ^b	-	-	-
Height, cm	158.90 (10.93)	163.68 (19.84)	<.001 ^b	<.001 ^b	-	-	-
BMI	24.56 (5.49)	23.91 (5.91)	.032 ^b	.071	-	-	-
FEV ₁ , L	2.73 (0.65)	3.24 (1.12)	<.001 ^a	<.001 ^a	-	-	-
FEV ₁ , %	100.41 (14.79)	97.94 (15.17)	.002 ^d	.001 ^{d,e}	-	-	-
FEV ₁ Z-score	-1.21 (1.01)	0.44 (1.31)	<.001 ^a	<.001 ^a	-	-	-
FVC, L	3.36 (0.77)	4.11 (1.45)	<.001 ^a	<.001 ^a	-	-	-
FVC, %	106.3 (13.74)	102.29 (13.33)	<.001 ^a	<.001 ^{a,e}	-	-	-
FVC Z-score	-1.09 (0.93)	0.93 (1.13)	<.001 ^a	<.001 ^a	-	-	-
FEV ₁ /FVC, L	81.49 (7.52)	79.6 (8.24)	<.001 ^a	<.001 ^{a,e}	-	-	-
FEV ₁ /FVC Z-score	-0.28 (1.07)	-0.82 (1.04)	<.001 ^a	.001 ^{a,e}	-	-	-
FEF ₂₅₋₇₅ , L	2.8 (1)	3.07 (1.31)	<.001 ^a	<.001 ^a	-	-	-
FEF ₂₅₋₇₅ , %	80.18 (24.68)	80.63 (24.95)	.733	.409 ^e	-	-	-
+ Bronchodilation	74 (12%)	71 (16%)	.075	-	1.365	1.151	0.843
* Bronchodilation	67 (11%)	50 (11%)	.826	-	1.044	1.019	0.975
- Bronchodilation	490 (78%)	332 (73%)	.098	-	0.790	0.903	1.143
Asthma onset age <12 y	248 (29%)	288 (47%)	<.001 ^a	-	0.469 ^f	0.715 ^f	1.524 ^f
Asthma onset age <40 y	703 (83%)	535 (87%)	.032 ^c	-	0.722 ^f	0.880 ^f	1.219 ^f
Allergic asthma	669 (79%)	501 (82%)	.226	-	0.850	0.936	1.101
Asthma in symptomatic period	503 (60%)	342 (56%)	.154	-	1.165	1.067	0.916
Persistent asthma	254 (30%)	152 (25%)	.027 ^c	-	1.303 ^f	1.114 ^f	0.854 ^f
Presence of symptoms	257 (30%)	164 (27%)	.128	-	1.197	1.077	0.900
Rhinitis	811 (96%)	585 (95%)	.611	-	1.142	1.059	0.928
Atopy	778 (92%)	583 (95%)	.022 ^c	-	0.598 ^f	0.828 ^f	1.385 ^f
Food allergy	152 (18%)	104 (17%)	.612	-	1.073	1.030	0.959
Drug allergy	50 (6%)	23 (4%)	.061	-	1.613	1.193 ^f	0.740
NSAID vs other drugs	35 (70%)	18 (78%)	.462	-	0.648	0.881	1.358
NSAID vs total drug allergy	35 (4%)	18 (3%)	.225	-	1.428	1.145	0.802
Comorbidities	105 (12%)	76 (12%)	.951	-	1.010	1.004	0.994
FeNO, ppb	30 (37.95)	37.60 (46.15)	<.001 ^b	<.001 ^{a,e}	-	-	-
Peripheral blood eosinophils/μL	200 (200)	300 (300)	.091	.001 ^d	-	-	-
Total IgE, kU/L	195 (378.1)	260.5 (528.5)	<.001 ^b	.016 ^c	-	-	-

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; FEF₂₅₋₇₅, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume; FVC, forced vital capacity; NSAID, nonsteroidal anti-inflammatory drug; +, Bronchodilation, variation in FEV₁ >12% and >200 mL in the bronchodilation test; *, Bronchodilation, variation in FVC >10% and/or variation in FEF₂₅₋₇₅ >30% with a variation in FEV₁ <12% and/or <200 mL in bronchodilation test; -, Bronchodilation, variation in FEV₁ <12% and/or <200-mL variation in FVC <10% and variation in FEF₂₅₋₇₅ <30%.

^aData are shown as No. (%) and mean (SD).

^bP<.001.

^cP<.05.

^dP<.01

^eANCOVA, negative for Levene test.

^fStatistically significant.

12 or 40 years. Men also had a higher rate of atopy. Persistent asthma and allergic contact dermatitis were more common among women.

Asthma Patients Stratified by Sex

In both sexes, age was higher as BMI increased, with statistically significant differences observed between the mean ages of the different BMI groups. Biometric parameters such as height, weight, and spirometry values differed significantly in both sexes. Persistent and late-onset asthma were also more prevalent as BMI increased in both sexes.

A drop in total IgE, FeNO, and peripheral eosinophil counts was also observed; this was more pronounced in men than in women. In fact, no decrease in peripheral eosinophil counts was observed in women, and the decrease in total IgE disappeared after normalization.

Asthma Patients Stratified by Age and Sex

Differences in spirometry values (FEV₁, FVC, and FEF₂₅₋₇₅) in total values and percentages and Z-score) were also evaluated, although these were not consistent between the age groups. The values increased with BMI in patients aged <18 years. In the group aged 40-64 years, a decrease was reported in the 25-30 and >30 BMI groups. In patients aged 19-39 years, a decrease was observed in for the extreme BMI groups (<20 and >30) compared with the central groups (20-25 and 25-30). This was similar for both sexes, although differences were only statistically significant in men.

Late-onset asthma increased with BMI using both cut-off points (12 and 40 years). This finding was significant in all age groups among women, while in men it was only significant in patients aged <18 years.

Asthma Patients Stratified by Age

Differences in spirometry values and the Z-score by sex were confirmed. However, FEV₁/FVC behaved differently, decreasing with higher BMI among patients aged <18 years and increasing in extreme BMIs (<20 and >30) in both the 19-39 and 40-64 age groups. Among patients older than 65 years, all spirometry values, Z-score, and FEV₁/FVC increased, as did BMI. However, the increase in FEV₁/FVC was not statistically significant (Supplementary material, Results section Tables III-VI).

The prevalence of late-onset asthma was higher as BMI increased in all age groups except in patients aged 19 to 39 years, where onset of asthma before age 12 years remained stable across all the BMI groups. The results in patients aged >65 years were not significant (Supplementary material, Results section Tables III-VI).

Analyzing the prevalence by sex, we observe that asthma is always more frequent in women than in men and is not modified by BMI.

FeNO was lower in the extreme BMI groups (<20 and >30), except in patients aged <18 years.

Effect of BMI on the Variables

Analyzing the effect on each variable, both continuously and stratified, we observed that the stratified data in the 4 BMI

groups (<20, 20-25, 25-30, and >30) were consistent with the analysis of continuous data for all variables.

Weight increased in parallel with BMI, whereas height remained stable across all BMI groups.

The absolute values of the spirometry parameters (FEV₁, FVC, and FEF₂₅₋₇₅) were always higher among men, while the percentages were always higher among women. There were no significant changes between the different BMI strata. Z-score values mirrored those recorded for sex. Men presented positive values that increased as BMI increased, while women presented negative values that decreased as BMI increased.

FEV₁/FVC decreased progressively with increasing BMI in men, although it was lower at the extremes (<20 and >30) in women. Its Z-score was negative in both sexes but higher in men than in women. Although there was no specific trend among men, a trough was observed in women.

Asthma traits showed little variation with changes in BMI. The only change found was a decrease in the frequency of early-onset asthma, at both the 12- and the 40-year cut-off, when BMI increased.

BMI did not affect comorbidities, total serum IgE, or peripheral eosinophil counts, although it did affect FeNO. FeNO values were lower at the extremes and higher in the central BMI groups (20-25 and 25-30).

Discussion

It is widely accepted that asthma and obesity are related. International guidelines [34,35] describe obesity both as a comorbidity and as a cause of asthma, generating a specific phenotype, namely, asthma and obesity. However, no studies exhaustively analyze the relationship between BMI and asthma or the effect of BMI on asthma. The characteristics of asthma in obese patients (BMI >30 or >35) have been studied, although different and even opposite results have been obtained. In this scenario, it is unfeasible to distinguish patients who are only obese and asthmatic (as comorbid conditions) from those who have a specific asthma-obesity phenotype.

Increases in knowledge in this area led us to design this study with the aim of properly phenotyping patients [37]. Since BMI is a biometric characteristic inherent to all patients, its effect should not be investigated only in obese patients. The effect of all BMI groups on asthma should be studied to enable differentiation of asthma traits associated with the patient-specific BMI from unexpected ones.

First, we must address whether the current BMI groups (<20, 20-25, 25-30, and >30) are correct or should be modified or adjusted for age or sex. After analyzing all the variables with continuous and stratified data, we conclude that the current groups perfectly define trends for variables, regardless of sex or age. Thus, we can establish that these groups are representative for each variable studied and type of patient, with no need for further modification.

The present study was conducted in an allergy clinic and is therefore subject to bias resulting from a potential overestimation of the frequency of allergic asthma. The prevalence of allergic asthma reported in 2016 was 67% [38]; we recorded a slightly higher prevalence of 80%. Given that the main aeroallergens in Madrid are pollens, intermittent asthma

may be overrepresented. Allergic patients tend to be younger than nonallergic patients, with the result that a sample size of >65 years is not large enough to draw firm conclusions.

Our study also has many strengths, including its design. Few patients had comorbidities, most comorbidities were nonrespiratory, and almost no patients had chronic obstructive pulmonary disease. Thus, the influence of other respiratory diseases has been minimized. In addition, the sample was large, comprising 2514 patients, of whom 1458 had asthma. All ages, BMI groups, and sexes were represented, and a wide range of variables were studied, thus making it possible to broadly explore the relationship between BMI and asthma.

The first finding is that weight increases in parallel with BMI, while height remains stable in all BMI groups, indicating that, in population terms, the main parameter that generates changes in BMI is weight. We can also observe that in all groups, the mean age increases with BMI, even after stratification by age. Therefore, few patients aged <18 years have a BMI >30 and no patients aged >65 years have a BMI <20. Henceforth, despite being stratified, age is treated as a covariate in the analysis of covariance.

Cluster studies [8,9] and subsequent asthma and obesity studies [22] established a higher prevalence of females as one of the main features of this phenotype. This contrasts with the data obtained in the present study. We observed differences when comparing age groups, although within each age stratum, the prevalence of women remained stable for all BMI groups. The only group where men were more frequent was <20, and this may be because of age. Therefore, we can establish that a higher prevalence of women is neither a specific characteristic of obese patients, nor a specific characteristic of asthma and obesity. It is an inherent characteristic of asthma and can be influenced by age, which acts as a confounding variable.

Spirometry results are the variables most influenced by changes in BMI. FEV₁, FVC, FEF₂₅₋₇₅, and FEV₁/FVC (absolute value, percentage, and Z-score) change based on the patient's BMI. Moreover, these changes are age-dependent. FEV₁, FVC, and FEF₂₅₋₇₅ increase in parallel to BMI in the group aged <18 years. This observation might be due to normal physiological development during this growing period, although the percentages reported for predicted values are equally affected by this variation. Greater volumes in the 20-25 and 25-30 BMI groups are observed among patients aged 19 to 39 years, and a decrease in the higher BMI groups (25-30 and >30) has been observed in patients aged 40 to 64 years. The sample size of the >65-year-old group is not large enough to draw adequate conclusions.

It is important to highlight that all Z-score values were considered normal (between -2 and 2). However, our data were not population-based but from a specific sample and cannot be considered homogeneous. Therefore, these differences should be further studied at population level to analyze their importance.

FEV₁/FVC acted differently from the other parameters. It was inversely proportional to weight in the group aged <18 years, while in the groups aged 19-39 years and 40-64 years, lower values were observed for the central BMI groups (20-25 and 25-30) than for the extreme groups (<20 and >30). Again, in patients aged <18 years, this may be directly

related to expected development, which would mirror that of healthy individuals.

These observations demonstrate that current expected spirometry values are not properly designed to remove the effect of BMI on asthma. Therefore, they should be interpreted after application of an age-adjusted BMI correction. Particularly important is the fact that the Z-score is affected by variations in BMI. The Z-score is meant to erase the effect of ethnicity, age, height, and weight so that results are comparable. We believe that the Z-score does not accomplish this goal for BMI, which is calculated using weight and height (both of which are supposedly corrected by this coefficient). Consequently, we must review the appropriate formula for the Z-score.

Weighting for body weight is very low in the Z-score formula and has no age correction. The results of the present study indicate that it is suitable to enlarge the importance of weight in this formula or include BMI as a parameter, with application of an age correction for the chosen parameter.

These observations demonstrate that current expected spirometry values are not adequately designed to eliminate the effect of BMI on asthma. Therefore, they should be interpreted with an age-dependent BMI correction.

Analysis of the Z-score shows that it is affected by variations in BMI. The Z-score is intended to erase the effect of ethnicity, age, height, and sex and is designed to evaluate a patient longitudinally, through assessment of the impact of weight over time. Therefore, consequent changes in the Z-score are expected.

FeNO is used for asthma phenotyping and included in therapeutic algorithms, with 20-25 ppb as the cut-off point. In this study, we showed that FeNO is clearly affected by BMI and depends on age and that it is lower in the extreme BMI values (<20 and >30) in patients aged 19-39 years and 40-64 years. However, all groups have an average FeNO greater than 20 ppb, and only the group aged 19-39 years have median values under 25 ppb for extreme BMIs (<20 and >30). Therefore, FeNO must be adjusted for BMI according to age to tailor medication, although its effect on therapeutic algorithms may be limited.

In contrast, peripheral blood eosinophil counts and total IgE are not affected by BMI. Given that the asthma and obesity phenotype is assumed to be noneosinophilic asthma [7], it is important to ensure that this parameter is not influenced by BMI. It is also important to note that mean eosinophil count never exceeds 300/ μ L. Therefore, none of the groups could be considered eosinophilic asthma [20]. Being noneosinophilic is not a characteristic of asthma and obesity or of obese patients.

Regarding asthma traits, only 1 characteristic is influenced by BMI. Late-onset asthma is clearly more frequent in groups with higher BMI, regardless of the selected cut-off point (12 or 40 years). The 2 groups where we do not observe this association are 19-39 years and >65 years. The group aged >65 years is too small to enable adequate conclusions to be drawn. The group aged 19-39 years is the furthest from the cut-off points. Their asthma was first detected many years previously and had never been evaluated, with the result that patients only vaguely remember the exact time of onset, indicating that recall bias could be important. Late-onset

asthma seems to be related to high BMI, would be expected in all obese asthma patients, and as such, is not a trait for the asthma and obesity phenotype.

The literature indicates that patients with the asthma and obesity phenotype are more symptomatic, with fewer alterations in lung function tests and a lower prevalence of atopy, rhinitis, and allergic asthma [8,9,19,20]. No differences have been observed when symptoms or bronchodilation test results are analyzed or when rhinitis, atopy, and allergy, including allergic asthma, are studied. Therefore, these traits seem to be specific to the asthma and obesity phenotype.

In conclusion, current BMI groups appear to be adequate and do not need modification. As the effect of BMI is age-dependent, this variable should be corrected for age. The most important effects of BMI in asthma, where results must be adjusted for the variable, are FeNO and spirometry results, including the Z-score.

The specific features of the asthma and obesity phenotype are greater perception of symptoms with fewer alterations in lung function tests and a lower prevalence of atopy, rhinitis, and allergy, including allergic asthma. Other characteristics, such as the predominance of women or late-onset or noneosinophilic asthma, are secondary to the effect of BMI in patients with asthma or are common in all BMI groups.

Acknowledgments

We are very grateful to the doctors who evaluated the patients and to the staff of the respiratory medicine clinic who performed the pulmonary function tests for the quality of their work and their professionalism. Without their excellent contribution, this study could have never been performed.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

- Ignacio Esteban-Gorgojo is cofounder of IgncyErto. He has received speaker and advisory board fees from Allergy Therapeutics, ALK, Leti, GSK, Astra Zeneca, Diater, Novartis, Chiesi, Orion, Merck, Stallergenes, and Shire.
- Joaquín Sastre reports having served as a consultant to Thermo Fisher, MEDA, Novartis, Sanofi, Leti, Faes Farma, Mundipharma, and GSK. He has also received lecture fees from Novartis, GSK, Stallergenes, Leti, and Faes Farma and grant support for research from Thermo Fisher, Sanofi, and ALK.
- Francisco García-Río has received speaker fees from Boehringer Ingelheim, Pfizer, Chiesi, GSK, Menarini, Novartis, and Rovi and consulting fees from Boehringer Ingelheim, Pfizer, GSK, and Novartis.
- Santiago Quirce has been on advisory boards for and has received speaker's honoraria from AstraZeneca, GSK, Sanofi, Leti, MSD, Novartis, Chiesi, ALK, Allergy Therapeutics, and Teva.

- María Puy Gorgojo declares that she has no conflicts of interest.

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- *Manuscript received July 8, 2022; accepted for publication October 4, 2022.*
- **Ignacio Esteban-Gorgojo**
- Department of Allergy
Hospital General de Villalba
Carretera de Alpedrete a Moralzarzal M-608, Km 41
28400 Collado Villalba (Madrid), Spain
E-mail: igestebang@gmail.com