

The influence of BMI in asthma. Which traits are due to obesity and which to asthma and obesity phenotype?

Short Title: The influence of BMI in asthma

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Abstract

Background: Characteristics of the asthma and obesity phenotype have been described by cluster studies, but they 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. This will allow 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 with a 2,514 patients database. Data was collected on the first visit to the Allergy clinic of all patients who underwent a correct spirometry maneuver due to suspected asthma between November 2014 and November 2017. All BMI, sex and age groups were represented.

Results: BMI influence over asthma differed in different age groups and genders. All spirometric results and FeNO were influenced by BMI.

Concerning asthma characteristics only a later asthma onset with higher BMI values was observed. No other differences were found between different BMI groups.

Conclusions: The effect of BMI on asthma is age dependent, so it should be corrected for age. The most important variations are on FeNO and spirometric 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 women prevalence or being late-onset or non-eosinophilic asthma, are non-specific 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, sólo 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 ésta. Además, las variaciones más importantes ocurren sobre el FeNO y los valores espirométricos, teniendo que ser estos valores corregidos por IMC.

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

Introduction

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

Obesity causes pulmonary physiological changes such as reduced lung volumes, gas exchange impairment, and collapse of the pulmonary airways [7]. It also influences asthma traits in phenotypic studies. Cluster studies have shown the existence of a specific asthma phenotype among severe asthmatics called "asthma and obesity" [8], and SARP III found an association with age [9]. This phenotype is characterized by late-onset, predominantly non-eosinophilic asthma, with a high prevalence in women, and highly symptomatic patients with poor response to asthma treatments [8].

However, subsequent studies have not fully corroborated these traits. Bibi et al [10] suggested that these patients have a higher rate of symptoms because they are not actually asthmatic, which explains the poor response to treatment and leads to overdiagnosis of asthma [10].

Sin et al [11] suggested that significant self-diagnosis was present among obese patients, but there were 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]. Even Schacter et al [14] reported that BHR is increased in patients with lower BMI with respect to obese subjects.

In contrast, other studies found BHR among obese patients and higher symptom perception, as expected, in these patients [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 non-eosinophilic, even before receiving anti-inflammatory treatment that could modify eosinophil counts [19]. In fact, this phenotype is considered to be dependent on interleukin-17 (IL-17) and IL-33 [20]. However, there are studies linking obesity and eosinophilic asthma. They even show that obesity can modify asthma differently depending on whether it is eosinophilic or non-eosinophilic [21].

The higher prevalence of women in the asthma and obesity phenotype is controversial in the existing literature. Some studies support the higher prevalence of women [22] and consider that obesity increases the risk of developing asthma in adolescent women but not in men [23]. Other studies suggest that there are no differences in the prevalence of sex in patients with asthma and obesity [24], or even that there is a higher prevalence of men in this phenotype [25].

Regarding asthma onset, the mere definition of late-onset asthma represents a problem in itself [26]. Different groups have established different cut-off points such as 12 [27], 18-20 [28], or 65 [29] years. 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. Holguin et al [27] suggested that obesity acts as a comorbidity in early-onset asthma and as a causal agent in late-onset asthma, using 12 years as the cut-off point.

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 strongly affected, while the influence in the elderly population is weaker [28].

The existing literature has already studied the relationship between asthma and obesity, despite the lack of specific conclusions, but other BMI groups have been poorly studied. Without adequate knowledge of the effect of all BMI groups on asthma, a proper differentiation between the effect of obesity on asthma and the specific features of the asthma and obesity phenotype cannot be made.

Our aim was to deeply explore the influence of obesity in asthma encompassing all BMI groups. Understanding how BMI affects asthma will allow analyzing the effect of obesity on asthma and, therefore, defining the specific asthma traits of obese asthma patients. Once these characteristics have already been described they will be compared to the asthma and obesity phenotype features and the differentiation between obese asthma patients and asthma patients with asthma and obesity phenotype will be possible.

Methods

Study

To study the relationship between asthma and obesity, we conducted a retrospective observational, real-world study. All patients who underwent spirometry for suspected asthma between November 2014 and November 2017 were recruited. The criteria for performing spirometry and clinical practice were not influenced by the study, following daily practice with existing hospital protocols. This study was approved by the Ethics Committee of the hospital.

Subjects

All patients between 3 and 99 years of age who attended the Allergy Clinic of the General Hospital of Villalba (Madrid, Spain) and underwent a good quality spirometric maneuver due to suspected asthma were included. All the clinical charts of the patients were analyzed. Only those with clear information for the diagnosis of asthma were included. Patients unable to perform an adequate spirometric 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 containing 2514 patients.

Studied variables

Anthropometric characteristics and respiratory functional variables obtained from spirometries performed according to the ERS/ATS criteria [31] were recorded. The GLI equations were used as reference values [32] and the percentage with respect to predicted value (Zapletal 2 references were used to for this matter) and the z-score were calculated. Bronchodilator test was considered positive when FEV₁ increase was higher 12% and > 200 ml. A FEV₁ increase < 12% and/or < 200 ml with a FVC increase >10% or an FEF₂₅₋₇₅ increase >35% was considered as partial bronchodilator response.

As inflammatory variables, peripheral blood eosinophil count and FeNO were recorded. FeNO was obtained using a Fenompro® testing device and its determination was performed following the ERS/ATS recommendations [33].

The following asthma characteristics were also recorded: time since diagnosis, age of asthma onset, allergic asthma, persistent asthma, patient is exposed to asthma trigger/patient is in symptomatic period and symptoms when spirometry is performed. 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 I] and treatment used in 48 hours prior to the 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 the asthma guidelines [34-36]. Only the first visit for each patient was included in the study [36]. Allergy tests were performed on all patients [36].

Database analysis

Patients were divided into asthmatics or non-asthmatics. They were also distributed into 4 BMI groups (<20, 20-25, 25-30 and >30). Variables were classified into gaussian and non-gaussian distributions [36] and were described according to its features [36]. [Detailed information on this data analysis is described in the supplementary appendix, Methods; data analysis section].

Results

Asthmatic patients

When the analysis between genders was performed, several statistically significant differences were found in several variables. These differences persisted after normalization for age and corticosteroid treatment [Table II]. It was observed that women were more prevalent among asthmatic patients in all BMI

groups (64% 20-25, 56% 25-30 and 60% >30), except in <20 where the prevalence of women was 49%.

The men were younger, with higher height and weight, but lower BMI. Men also had higher lung volumes, but 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 12 or 40 years. Men also had a higher rate of atopy. Persistent asthma and allergic contact dermatitis were more common among women.

Asthmatic patients stratified by sex

In both sexes, age was higher as BMI increased, with statistically significant differences being observed between the mean ages of the different BMI groups. Biometric parameters such as height, weight and spirometric 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 were also observed, which were more pronounced in men than in women. In fact, the women did not show a decrease in peripheral eosinophil counts and the decrease in total IgE disappeared after normalization.

Asthmatic patients stratified by age and sex

Differences in spirometric values (FEV₁, FVC and FEF₂₅₋₇₅ in total values and percentages and Z-score) were also evaluated, but they were not consistent between the different age groups. The <18-year-old group showed an increase in all these values as BMI increased. In the group of 40 to 64 years, a decrease was described in the BMI groups of 25 to 30 and >30. The group aged 19 to 39 years showed a decrease in these pulmonary function values in the extreme BMI groups (<20 and >30) compared to the central groups (20-25 and 25-30), and this was observed in both sexes but being only statistically significant in men.

Late-onset asthma increased with BMI using both cut-off points (12 and 40). These findings were significant in all age groups among women, while in men it was only significant in the <18 years group.

Asthmatic patients stratified by age

The differences found in the data stratified by sex for the spirometric values, and the Z-score were confirmed. However, FEV₁/FVC had a different behavior. FEV₁/FVC decreased with increasing BMI among patients <18 years and increased in extreme BMIs (<20 and >30) in both the 19-39 and 40-64 age groups. Among patients older than 65 years, all spirometric values, Z-score and FEV₁/FVC increased, as did BMI. However, the increase in FEV₁/FVC was not statistically significant [Supplementary appendix, Results section Tables III-VI].

Late-onset asthma prevalence was higher as BMI increased in all age groups except 19 to 39 years, where asthma starting before age 12 years remained stable across all BMI groups. The results in the group >65 years were not significant [Supplementary appendix, 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 the group <18 years.

Effect of BMI in the different variables

Analyzing the effect on each variable, both continuously and stratified, we observed that the stratified data in the four groups of BMI >20, 20-25, 25-30 and >30 was consistent with the analysis of continuous data for all variables.

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

The absolute values of the spirometric 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 were specular for genders. Men presented positive values

that increased as BMI increased, while women presented negative values that decreased as BMI increased.

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

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

BMI did not influence comorbidities, total serum IgE or peripheral eosinophils, but it did influence FeNO. FeNO values were lower at the extremes and higher at 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, asthma and obesity. However, there are no studies that exhaustively analyze the relationship and influence of BMI on asthma. The characteristics of asthma in obese patients (BMI > 30 or > 35) have been studied, but 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.

Nowadays, when knowledge increases and is channeled to properly phenotype patients [37], this study was designed to fill that unmet need. BMI is a biometric characteristic inherent to all patients, so the effect of BMI should not be investigated only in obese patients. The effect of all BMI groups on asthma should be studied to allow differentiation of asthma traits derived from the patient-specific BMI from unexpected ones.

To do this, the first question to address is whether the existing BMI groups (<20, 20-25, 25-30 and >30) are correct or should be modified or adapted to age or sex. After analyzing all the variables with continuous and stratified data, it is

concluded that the current groups perfectly define the trends of each variable, regardless of sex or age. Thus, we can establish that these groups are representative for each variable studied and type of patient, without the need to further modify them.

This study was conducted in an allergy clinic; therefore, an overestimation of allergic asthma could occur, introducing a bias. The prevalence of allergic asthma reported in 2016 was 67% [38], while this study shows a slightly higher prevalence of 80%. The main aeroallergens in Madrid are pollens, so intermittent asthma may be overrepresented. Allergic patients tend to be younger than non-allergic patients, so the sample size of >65 years is not large enough to draw firm conclusions.

On the contrary, this study has many strengths, including its design. There are few patients with comorbidities, most are non-respiratory, and almost no patients with COPD were found. Thus, the influence of other respiratory diseases has been minimized. In addition, the sample size is large, 2,514 patients, where 1,458 were asthmatic. All ages, BMI groups, and genders are represented, and a wide range of variables have been studied, allowing the results 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, pointing out that, in population terms, the important parameter to generate changes in BMI is weight. We can also observe that in all groups the mean age increases as the BMI increases, even after stratification by age. Therefore, there are few patients < 18 years of age who have a BMI > 30 and no patients > 65 years of age who have a BMI < 20. Henceforth, despite age stratification, it is treated as a covariate for all ANCOVA analysis.

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 this study. We observed differences when comparing age groups, but within each age stratum, the prevalence of women remains stable in all BMI groups. The only group where men are more frequent is <20 and this may be due to age. Therefore, we can establish that a higher prevalence of women is neither a specific characteristic of obese patients, nor of

asthma and obesity. It is an inherent characteristic of asthma and can be influenced by age, acting 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 <18 years. This observation might be due to the normal physiological development during this growing period, nevertheless, percentages respect predicted values are equally affected by this variation. The 19–39-year-old group shows a pattern with greater volumes in the 20-25 and 25-30 BMI groups and the 40–64-year-old group shows a decrease in the higher BMI groups (25-30 and >30). 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 are considered normal (between -2 and 2) and samples are not populational not assuring a complete homogeneity in the studied samples. Therefore, these differences should be further study to analyze its importance.

FEV₁/FVC acts differently from the rest of the parameters. Its evolution is inversely proportional to weight in the group of <18 years, while in the groups of 19-39 and 40-64 years it shows lower values in the central BMI groups (20-25 and 25-30) than in extreme groups (<20 and >30). Again, in <18 years old it can be directly related to expected development, having the same behavior that we could expect in healthy subjects.

These observations demonstrate that current expected spirometric values are not properly design to remove BMI effect over asthma. Therefore, they should be interpreted with an age dependent BMI correction. Particularly important is the fact that Z-score is affected by BMI variations. Z-score is meant to erase the effect of ethnic group, age, height and weight so results could be comparable for every patient. We can objectify that Z-score does not accomplish this goal for BMI, which is calculated using weight and height (Two features supposedly corrected by this coefficient). Consequently, we must review the appropriate formula for Z-score.

Weight weighting is very low in Z-score's formula and has no age correction. With this study's results it seems suitable to enlarge its importance of weight in this formula or include BMI as a parameter, applying an age correction for the chosen parameter.

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

When we analyze the Z-score we can observe that it is affected by variations in BMI. Z-score is intended to erase the effect of ethnicity, age, height, and gender and have been designed to evaluate a patient longitudinally, being able to evaluate the impact of weight through time. Therefore, these changes in Z-score are expected.

FeNO is being used for asthma phenotyping and is included in therapeutic algorithms, with 20-25 ppb as the cut-off point. In this study, it is shown that it is clearly influenced by BMI and depends on age. We observe how FeNO is lower in the extreme BMI (<20 and >30) in the groups of 19-39 and 40-64 years. However, all groups have an average FeNO greater than 20 ppb and only the group of 19-39 years have median values under 25 ppb in the extreme BMI groups (<20 and >30). Therefore, FeNO must be corrected by BMI, according to the patient's age, for adequate individual medication, but its effect on therapeutic algorithms may be limited.

In contrast, peripheral blood eosinophil counts and total IgE are not affected by BMI. The phenotype of asthma and obesity is assumed to be non-eosinophilic asthma [7], so it is important to determine that this parameter is not influenced by BMI. It is also important to note that eosinophil averages never exceed 300 eos/uL, so none of the groups could be considered as eosinophilic asthma [20]. Therefore, being non-eosinophilic is not a characteristic of asthma and obesity, nor is it characteristic of obese patients.

Regarding asthma traits, there is only one characteristic 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 only two groups where we do not observe this association are the 19-39 and >65 age groups. The group >65 years

is too small to draw adequate conclusions. The group of 19-39 is the furthest from the cut-off points, and when the onset of asthma occurred a long time ago and the patients have never been evaluated, they vaguely remember the exact time of onset of their asthma. Therefore, a recall bias could be important in this group. This finding suggests that late-onset asthma is related to high BMI and would be expected in all obese asthmatics. Therefore, it is not a trait for the asthma and obesity phenotype.

The literature indicates that in the asthma and obesity phenotype, patients are more symptomatic with fewer alterations in lung function tests and have a lower prevalence of atopy, rhinitis, and allergic asthma [8,9,19,20]. No differences have been observed when symptoms or bronchodilation test results have been analyzed and neither when studying rhinitis, atopy and allergy, including allergic asthma. Therefore, these traits suggest being specific to the asthma and obesity phenotype.

In conclusion, we can establish that the current BMI groups appear to be adequate and do not need modification. The effect of BMI is age dependent, so it should be corrected for age. The most important effects of BMI in asthma, whose results must be corrected by this parameter, are FeNO and spirometry results, including the Z-score.

The specific features 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 described characteristics, such as the predominance of women or being late-onset or non-eosinophilic asthma, are secondary to the effect of BMI in patients with asthma or are common in every BMI group.

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Conflict of interest statement:

- Ignacio Esteban-Gorgojo: IE-G is Co-founder of IgncyErto. Have received speakers and advisory board fees from Allergy Therapeutics, ALK, Leti, GSK, Astra Zeneca, Diater, Novartis, Chiesi, Orion, Merck, Stallergens and Shire.
- María Puy Gorgojo: MPG declares no conflict of interest
- Joaquín Sastre: JS reports having served as a consultant to Thermofisher, MEDA, Novartis, Sanofi, Leti, Faes Farma, Mundipharma, and GSK; having been paid lecture fees by Novartis, GSK, Stallergenes, Leti, and Faes Farma; as well as having received grant support for research from Thermofisher, Sanofi, and ALK.

- Francisco García-Río: FG-R has received speaker fees from Boehringer Ingelheim, Pfizer, Chiesi, GlaxoSmithKline, Menarini, Novartis and Rovi, and consulting fees from Boehringer Ingelheim, Pfizer, GlaxoSmithKline and Novartis.
- Santiago Quirce: SQ 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.

References

1. The global asthma report.
<http://www.globalasthmareport.org/burden/burden.php>, May 2020.
2. WHO asthma. <https://www.who.int/news-room/q-a-detail/asthma>, May 2020.
3. WHO obesity. <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>, May 2020.
4. Jacquelin A, Turiaf J, Blanchon P, Zizine L. Asthma, endocrine-genital disorders and obesity syndrome in women. *Sem Hop.* 1952;28(74):2980-3.
5. Figueroa JC. The asthma-endocrinogenital disorder-obesity syndrome in women. *Dia Med.* 1955;27(82):18-21.
6. Kallos P, Kallos-Deffner L. Investigations on the effect of an appetite-reducing compound (Tylinal) on overweight asthma patients. *Nutr Dieta Eur Rev Nutr Diet.* 1960;2:229-38.
7. Garcia-Rio F, Alvarez-Puebla MJ, Esteban-Gorgojo I, Barranco P, Olaguibel JM. Obesity and Asthma. Key Clinical Questions. *J Investig Allergol Clin Immunol.* 2019;29:262-71.
8. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med.* 2008;178(3):218-24.
9. Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, et al. Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: Differences with Age. *J Allergy Clin Immunol Pract.* 2018;6(2):545-54.
10. Bibi H, Shoseyov D, Feigenbaum D, Genis M, Friger M, Peled R, et al. The relationship between asthma and obesity in children: is it real or a case of over diagnosis. *J Asthma.* 2004;41(4):403-10.
11. Sin DD, Jones RL, Man SFP. Obesity is a risk factor for dyspnea but not for airflow obstruction. *Arch Intern Med.* 2002;162(13):1477–81.

12. Barranco P, García-Río F, Olivares J, López-Carrasco V, Alvarez-Sala R, Quirce S. Asthma diagnosis is not associated with obesity in a population of adults from Madrid. *J Investig Allergol Clin Immunol*. 2011;21(7):540-5.
13. Tantisira KG, Litonjua AA, Weiss ST, Fulhbrigge AL. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). *Thorax*. 2003;58:1036-41.
14. Schachter LM, Salome CM, Peat JK, Woolcock AJ. Obesity is a risk for asthma and wheeze but not airway hyperresponsiveness. *Thorax*. 2001;56(1):4-8.
15. Chinn S, Jarvis D, Burney P. Relation of bronchial responsiveness to body mass index in the ECRHS. *Thorax*. 2002;57(12):1028-33.
16. Sood A, Verhulst SJ, Varma A, Eagleton LE, Henkle JQ, Hopkins-Price P. Association of excess weight and degree of airway responsiveness in asthmatics and non-asthmatics. *J Asthma*. 2006;43(6):447-52.
17. Carpio C, Villasante C, Galera R, Romero D, de Cos A, Hernanz A, et al. Systemic inflammation and higher perception of dyspnea mimicking asthma in obese subjects. *J Allergy Clin Immunol*. 2016;137(3):718-26.e4.
18. Litonjua AA, Sparrow D, Celedon JC, DeMolles D, Weiss ST. Association of body mass index with the development of methacholine airway hyperresponsiveness in men: the Normative Aging Study. *Thorax*. 2002;57(7):581-5.
19. Soloveva IA, Sobko EA, Demko IV, Kraposhina AY, Loktionova MM, Gordeeva NV. Features of cellular structure of the induced sputum and profile of cytokines at sintropiya of bronchial asthma and obesity at young patients. *Ter Arkh*. 2018;90(3):25-32.
20. Esteban-Gorgojo I, antolín-Amérigo D, Domínguez-Ortega J, Quirce S. Non-eosinophilic asthma: current perspectives. *J Asthma Allergy*. 2018;11:267-81.
21. Mukadam S, Zacharias J, Henao MP, Kraschenewski J, Ishmael F. Differential effects of obesity on eosinophilic vs non-eosinophilic asthma subtypes. *J Asthma*. 2018;55(7):720-25.
22. Sutherland ER. Obesity and asthma. *Immunol Allergy Clin North Am*. 2008;28(3):589-602.

23. Ho WC, Lin YS, Caffrey JL, Lin MH, Hsu HT, Myers L, et al. Higher body mass index may induce asthma among adolescent with pre-asthmatic symptoms: a prospective cohort study. *BMC Public Health*. 2011;11:542.
24. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med*. 2007;175(7):661-6.
25. Postma DS. Gender differences in asthma development and progression. *Gend Med*. 2007; 4 Suppl B:S133-46.
26. Quirce S, Heffler E, Nenasheva N, Demoly P, Menzies-Gow A, Moreira-Jorge A, et al. Revisiting late-onset asthma: Clinical characteristics and association with allergy. *J Asthma Allergy*. 2020;13:743-52.
27. Holguin F, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Erzurum SC, et al. Obesity and asthma: an association modified by age of asthma onset. *J Allergy clin Immunol*. 2011;127(6):1486-93.
28. Nwaru BI, Ohlsson C, Bygdell M, Martikainen J, Kindblom JM. Pubertal BMI change and adul-onset asthma in men: Population-based cohort study in Sweden. *Clin Exp Allergy*. 2020;50(1):51-60.
29. Battaglia S, Benfante A, Spatafora M, Scichilone N. Asthma in the elderly: a different disease? *Breathe (Sheff)*. 2016;12(1):18-28.
30. Lang JE, Hossain J, Dixon AE, Shade D, Wise RA, Peters SP, et al. Does age impact the obese asthma phenotype? Longitudinal asthma control, airway function, and airflow perception among mild persistent asthmatics. *Chest*. 2011; 140(6):1524-33.
31. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardization of spirometry. *Eur Respir J*. 2005;26:319-38.
32. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the age range 3 to 95 years: the global lung function equations 2012. *Eur Respir J*. 2012;40(6):1324-43.
33. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med*. 2005;171:912-30.
34. GEMA 5.0. *J Invest Allergy Clin Immunol*. 2021;31:Supplement Suppl.1

35. Global Initiative for Asthma. <https://ginasthma.org>. May 2020.
36. Esteban-Gorgojo I, Gorgojo MP, Sastre J, Quirce S. Food allergy as an asthma comorbidity in children and adolescents: a practical approach through a real-world study. *Allergol Immunopathol (Madr)*. 2021;49(1):68-78.
37. Fitzpatrick AN, Moore WC. Severe Asthma Phenotypes – How Should They Guide Evaluation and Treatment. *J Allergy Clin Immunol Pract*. 2017;5(4):901-8.
38. Backman H, Räsänen P, Hedman L, Stridsman C, Andersson M, Lindberg A, et al. Increased prevalence of allergic asthma from 1990 to 2006 and further to 2016-results from three population surveys. *Clin Exp Allergy*. 2017;47:146-35.

Table 1. Comorbidities.

Comorbity	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 faringitis/larynghitis	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 anaphylaxia	4	0.2%
Anxiety	3	0.1%
Hereditary angioedema	1	0.0%
Escoliosis	1	0.0%
Multifactorial dyspnoea	1	0.0%
Histiocytosis X	1	0.0%
Lupus erythematosus	1	0.0%
Pachypleuritis with accesory lobe of the azygos	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%
Pytiriasis alba	1	0.0%
Pulmonary nodule with ground glass zone	1	0.0%

Table 2. Asthmatic patients.

	Women	Men	Men vs Women	ANCOVA	Odds Ratio	Relative risk men cohort	Relative risk women cohort
Sample size	845	613	-	-	-	-	-
Age	32,18 ± 16,10	26,51 ± 16,73	<0,001***	-	-	-	-
Weight (Kg)	62,85 ± 17,14	67,17 ± 25,99	<0,001***	<0,001***	-	-	-
Height (Cm)	158,90 ± 10,93	163,68 ± 19,84	<0,001***	<0,001***	-	-	-
BMI	24,56 ± 5,49	23,91 ± 5,91	0,032*	0,071	-	-	-
FEV ₁ (L)	2,73 ± 0,65	3,24 ± 1,12	<0,001***	<0,001***	-	-	-
FEV ₁ %	100,41 ± 14,79	97,94 ± 15,17	0,002**	0,001**	-	-	-
FEV ₁ Z-score	-1,21 ± 1,01	0,44 ± 1,31	<0,001***	<0,001***	-	-	-
FVC (L)	3,36 ± 0,77	4,11 ± 1,45	<0,001***	<0,001***	-	-	-
FVC %	106,3 ± 13,74	102,29 ± 13,33	<0,001***	<0,001***	-	-	-
FVC Z-score	-1,09 ± 0,93	0,93 ± 1,13	<0,001***	<0,001***	-	-	-
FEV ₁ /FVC (L)	81,49 ± 7,52	79,6 ± 8,24	<0,001***	<0,001***	-	-	-
FEV ₁ /FVC Z-score	-0,28 ± 1,07	-0,82 ± 1,04	<0,001***	<0,001***	-	-	-
FEF ₂₅₋₇₅ (L)	2,8 ± 1	3,07 ± 1,31	<0,001***	<0,001***	-	-	-
FEF ₂₅₋₇₅ %	80,18 ± 24,68	80,63 ± 24,95	0,733	0,409	-	-	-
+ Bronchodilation	74 (12%)	71 (16%)	0,075	-	1,365	1,151	0,843
* Bronchodilation	67 (11%)	50 (11%)	0,826	-	1,044	1,019	0,975
- Bronchodilation	490 (78%)	332 (73%)	0,098	-	0,790	0,903	1,143
Asthma onset prior 12 years old	248 (29%)	288 (47%)	<0,001***	-	0,469	0,715	1,524
Asthma onset prior 40 years old	703 (83%)	535 (87%)	0,032*	-	0,722	0,880	1,219
Allergic asthma	669 (79%)	501 (82%)	0,226	-	0,850	0,936	1,101
Asthma in symptomatic period	503 (60%)	342 (56%)	0,154	-	1,165	1,067	0,916
Persistent asthma	254 (30%)	152 (25%)	0,027*	-	1,303	1,114	0,854
Symptoms presence	257 (30%)	164 (27%)	0,128	-	1,197	1,077	0,900
Rhinitis	811 (96%)	585 (95%)	0,611	-	1,142	1,059	0,928
Atopy	778 (92%)	583 (95%)	0,022*	-	0,598	0,828	1,385
Food allergy	152 (18%)	104 (17%)	0,612	-	1,073	1,030	0,959
Drug allergy	50 (6%)	23 (4%)	0,061	-	1,613	1,193	0,740
NSAID vs other drugs	35 (70%)	18 (78%)	0,462	-	0,648	0,881	1,358
NSAID vs total drug allergy	35 (4%)	18 (3%)	0,225	-	1,428	1,145	0,802
Allergic contact dermatitis	25 (3%)	6 (1%)	0,010*	-	3,084	1,403	0,455
Comorbidities	105 (12%)	76 (12%)	0,951	-	1,010	1,004	0,994
FeNO (ppb)	30 (37,95)	37,60 (46,15)	<0,001***	<0,001***	-	-	-
Peripheral blood eosinophils (Eos/uL)	200 (200)	300 (300)	0,091	0,001**	-	-	-
Total IgE (kU/L)	195 (378,1)	260,5 (528,5)	<0,001***	0,016*	-	-	-

Data is presented as n (%) and mean ± standard deviation, FEV₁: Forced expiratory volume, FVC: Forced vital capacity, FEF₂₅₋₇₅: Forced expiratory flow between 25% and 75% of the spirometry, + Bronchodilation: Variation in FEV₁ >12% and >200 ml in bronchodilation test, * Bronchodilation: Variation in FVC >10% and/or variation in FEF₂₅₋₇₅ >30% with a variation in FEV₁ <12% and/or <200ml in bronchodilation test, - Bronchodilation: Variation in FEV₁ <12% and/or <200ml variation in FVC <10% and variation in FEF₂₅₋₇₅ <30%, %: Percentage, *: p<0.05, **: p<0.01, ***: p<0.001, ANCOVA: Negative for Levene test, **Results: Statistically significant.**