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ORIGINAL ARTICLE

Obesity is not Associated with Mild Asthma Diagnosis in a Population of Spanish Adults[†]

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Background. Several studies have suggested a relationship between asthma and obesity. Moreover, atopy is an important risk factor for asthma, but the relationship between obesity and atopy is uncertain. **Methods.** A cross-sectional multicenter study was conducted in a population of Spanish adults between November 2007 and July 2008. The subjects included had experienced asthma symptoms in the last year but had a forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) > 70%. Mild asthma diagnosis was confirmed by measuring airway hyperresponsiveness to methacholine. Body mass index in kg/m² was used as measure of obesity. Subjects were considered atopic when they had at least one positive skin prick test to common aeroallergens. Adjusted odd ratios (OR) were obtained by logistic regression. **Results.** A total of 662 subjects were included and 234 subjects (35.3%) were diagnosed with asthma (consistent symptoms and positive methacholine test). After adjusting the model for age, gender, atopy, baseline FEV₁, and FEV₁/FVC ratio, there was no association between overweight or obesity with asthma diagnosis, with OR of 0.889 (95% CI, 0.60–1.38) and 0.925 (95% CI, 0.577–1.48), respectively. A multivariable logistic regression analysis confirmed that atopy increases the risk of asthma ($p = 0.008$). The non-atopic obese group had an increased risk of asthma compared to the non-atopic group with normal weight or overweight ($p = 0.0032$). **Conclusions.** In this study obesity was not associated with a diagnosis of asthma. The presence of atopy was a risk factor for asthma, independent of obesity. Obesity, however, may be a risk factor for the development of asthma among non-atopic subjects.

Keywords asthma; obesity; body mass index; airway hyperresponsiveness; atopy

INTRODUCTION

Asthma and obesity are two frequent disorders that have an enormous impact on public health. It has been estimated that up to 65% of the adult population of the United States of America (USA) is obese or overweight (1), while in Spain about 15% of the population is obese and 39% is overweight (2)—figures that have all progressively increased in recent years. Although bronchial asthma affects a smaller proportion of people, its prevalence has also increased in the last several decades. According to the *Centers for Disease Control and Prevention*, the prevalence of asthma in North American children increased from 3.6% in 1980 to 5.8% in 2003 (3). In Spain, the prevalence of asthma increased 0.26% per year from 1991 to 2001 (4).

Recently, many studies have suggested a relationship between asthma and other factors present in western lifestyles, such as changes in diet and obesity (5–10). Epidemiological

data have led some researchers to suggest that obesity is a risk factor for the development of new-onset asthma, with odds ratios between 1.1 and 3.0, when comparing the highest with lowest body mass index (BMI) categories, with the effect apparently stronger in women (11). A meta-analysis of studies investigating overweight and obesity as a risk factor for incidental asthma showed that, overall, overweight and obesity increased the odds of incident asthma in a progressive manner (12, 13) and that the strength of this relationship was similar in men and women (13).

The exact nature of this association has not been fully elucidated, and methodological issues such as determining who has asthma versus who has symptoms that mimic asthma hamper many studies (3). However, mechanical factors or aspects of systemic inflammation related to obesity may contribute to asthma pathogenesis (2, 14–18). Atopy is an important risk factor for asthma, and several studies have examined the relationship between BMI and atopy, but the data are inconsistent (11, 15).

It is well known that simple obesity can cause an increase in airway resistance and a mild degree of airflow limitation (19). Thus, establishing a firm diagnosis of asthma in obese subjects with or without airflow limitation would require confirmation by an objective procedure, such as measurement

[†]On behalf of the Asthma Committee of the Spanish Society of Allergy and Clinical Immunology.

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of airway hyperresponsiveness (AHR). In this paper we report on a cross-sectional multicenter study of a population of Spanish adults studied for suspected asthma between November 2007 and July 2008. The aim of this study was twofold: (1) to determine whether obesity, measured by BMI, is associated with a diagnosis of asthma as established by the presence of symptoms and (2) demonstration of airway responsiveness to methacholine, as well as with the presence of atopy.

METHODS

Study Population

Patients were consecutively recruited from outpatient asthma clinics at six hospitals in Spain (Complejo Hospitalario, A Coruña; Carlos Haya, Málaga; La Paz and Fundación Jiménez Díaz, Madrid; Allergy and Asthma Centre, Palma de Mallorca; and Virgen Macarena, Sevilla) between November 2007 and July 2008. The subjects included were adults who, according to their allergist or pulmonologist, had presented symptoms suggestive of asthma (cough, shortness of breath, and/or wheezing) in the last year, with forced expiratory volume in 1 sec (FEV₁)/forced vital capacity (FVC) >70% and in whom it was necessary to establish the diagnosis of asthma by measuring AHR to methacholine. Subjects with contraindications to undergo methacholine challenge testing as outlined in the *American Thoracic Society* (ATS) guidelines (20) were excluded.

All subjects gave written informed consent and the study was approved by the Ethics Subcommittee of the Research Committee of Hospital Universitario La Paz, Madrid, Spain (code: HULP:PI-619).

Variables

The variables studied were age, gender, smoking status, height (meters), weight (kilograms), BMI, lung function (FVC, FEV₁, and FEV₁/FVC) measured immediately before the methacholine challenge test, results of the methacholine inhalation test (positive or negative), and the results of allergy skin prick testing.

Definitions

Asthma. Asthma was defined as a categorical dichotomous variable based on the presence of both consistent symptoms in the previous 12 months and a demonstration of AHR to methacholine.

Obesity. Weight and height of each subject were measured in street clothes without shoes immediately before performing the methacholine test. The BMI (weight in kilograms divided by the square of height in meters) was calculated for each subject. BMI was categorized as follows: normal weight, BMI <25 Kg/m²; overweight, BMI 25.0–29.9 Kg/m²; obese, BMI ≥ 30 Kg/m².

Atopy. The subjects were considered atopic when they had at least one positive skin prick test (≥3-mm diameter) with a panel of common aeroallergens (pollens, mites, molds, and animal epithelia).

Spirometry and Methacholine Inhalation Challenge

Spirometry was performed according to ATS recommendations (21).

Methacholine challenge tests were performed in the hospitals according to current guidelines (20, 22) and the spirometric reference values used in the six hospitals were those reported by the European Community of Coal and Steel and the European Respiratory Society in 1993 (23). In 3 centers (Virgen Macarena, Carlos Haya, and Complejo Hospitalario A Coruña), the methacholine test was performed following the Chatman method (22) using a DeVilbiss model 646 (Somerset, PA, USA) nebulizer. In one center (Fundación Jiménez Díaz) the methacholine test was performed according to ATS recommendations following the 2-minute tidal breathing dosing protocol using the DeVilbiss model 646, and in two centers (La Paz Hospital and Allergy and Asthma Center) the methacholine test was performed according to ATS recommendations following the five-breath dosimeter protocol (20) using an electronic dosimeter Spira Elektro (Respiratory Care Centre, Hameelinna, Finland) with an output of 0.45 μL and a nebulization time of 0.6 seconds. AHR was considered positive or present if there was a ≥ 20% decrease in FEV₁ from baseline with a provocative dose (PD₂₀ FEV₁) of four breaths of 25 mg/mL or less of methacholine (22), or provocative concentration (PC₂₀ FEV₁) of five breaths using dosimeter protocol or 2-minute tidal breathing dosing of 16 mg/mL or less of methacholine (20).

Because several methods of methacholine challenge were used, the results were interpreted only as positive or negative, and the data of PC₂₀ or PD₂₀ were not considered in the global analysis.

Statistical Analysis

Sample size. A logistic regression analysis of a binary dependent variable (asthma) on a binary independent variable (BMI) with a sample size of 662 observations (of which 35% were obese) achieved 80% power at a 0.05 significance level to detect a change in the probability from the baseline value of 0.350 to 0.447. This change corresponded to an odds ratio of 1.40.

Statistical analysis. Data are expressed as means (standard deviation) or percentages. Univariate relationships between dependent and independent variables were explored using *t* tests and one-way analysis of variance for normally distributed variables, non-parametric Wilcoxon rank sum tests for skewed variables, and X² tests for categorical variables. Univariate and multivariate conditional logistic regression models were created using the SAS statistical software package to determine the odds of having asthma in different BMI categories after adjusting for the other variables. For all analyses, two-tailed *p* values of less than 0.05 were considered significant. All analyses were performed with the SAS statistical software package (version 9.1.3, SAS Institute, Cary, NC, USA).

RESULTS

Study Population

A total of 662 subjects were included, distributed as follows: A Coruña 13 (2%), Málaga 65 (9.8%), Madrid 275 (41.6%) (La Paz 131 and Fundación Jiménez Díaz 144), Palma de Mallorca 49 (7.4%), and Sevilla 260 (39.3%).

Mean BMI was 25.5 kg/m² (SD 4.8). Normal weight was observed in 352 subjects (53.2%), overweight in 193 subjects

TABLE 1.—Baseline characteristics of study subjects.

	Non-Asthma	Asthma	Total	P value
Subjects, n	428	234	662	
Mean (SD) age (years)	36.61 (12.43)	37.98 (14.71)	37.09 (13.29)	0.226*
Mean (SD) BMI (kg/m ²)	25.67 (4.83)	25.36 (4.74)	25.56 (4.80)	0.432*
Gender, n (%):				0.67**
Male	163 (63.7%)	93 (36.3%)	256	
Female	265 (65.3%)	141 (34.7%)	406	
Smoking status, n (%):				0.08**
Non smoker	155 (51.3%)	147 (48.7%)	302	
Current smoker	32 (45.7%)	38 (54.35)	70	
Ex-smoker	21 (70%)	9 (30%)	30	
Atopy, n (%):				0.007**
Non-atopic	155 (72.4%)	59 (27.6%)	214	
Atopic	272 (61.7%)	169 (38.3%)	441	
Mean (SD) FEV ₁	84.25 (7.28)	84.29 (11.52)	84.26 (8.92)	0.963*
(% predicted)				
Mean(SD) FEV ₁ /FVC	83.53 (0.063)	82.99 (0.105)	83.34 (0.80)	0.470*
(% predicted)				

FEV₁ = forced expiratory in 1 second; FVC = forced vital capacity; BMI = body mass index.

*t test; **Chi-square analysis.

(29.1%), and obesity was observed in 117 subjects (17.7%).

A total of 234 subjects (35.3%) were diagnosed with asthma (symptoms and positive methacholine test). A univariate analysis according to asthma diagnosis is shown in Table 1. No significant differences were observed in age, gender, BMI, and smoking status according to asthma diagnosis, except in the frequency of atopy ($p = 0.007$). The mean values of the lung function parameters (FEV₁, FEV₁/FVC ratio) remained within the predicted normal range in the asthmatic and non-asthmatic groups, and no significant differences were observed between them (Table 1).

Relation of Asthma to Body Mass Index

Distribution of patients with confirmed asthma diagnosis in various BMI categories are shown in Table 2. After adjusting the model for age, gender, atopy, baseline FEV₁, and FEV₁/FVC ratio, there was no association between overweight or obesity with asthma diagnosis, with odds ratios of 0.889 (95% CI, 0.60–1.38) and 0.925 (95% CI, 0.577–1.48), respectively.

Effect of Other Variables

A multivariate analysis of gender distribution and smoking data for subjects classified according to BMI and asthma did not show any significant differences (Table 3).

Relationship of Atopy to BMI and Asthma

Data on atopic or non-atopic subjects classified according to BMI and asthma are shown in Table 4, and no significant differences were observed. The prevalence of atopy in the asthmatic group was 74.12% (169/228 subjects).

TABLE 3.—Sex and smoking status for subjects classified according to body mass index (BMI) and asthma.

BMI category	Asthma n (%)	Non-asthma n (%)	Total n (%)	p value
Sex				
Normal weight				p = 0.08
Male	30 (24%)	75 (33%)	105 (29.82%)	
Female	95 (76%)	152 (67%)	247 (70.18%)	
Total	125	227	352	
Overweight				p = 0.096
Male	41 (61.2%)	60 (47.6%)	101 (52.33%)	
Female	26 (38.8%)	66 (52.4%)	92 (47.67%)	
Total	67	126	193	
Obese				p = 0.12
Male	22 (52.4%)	28 (37.3%)	50 (42.74%)	
Female	20 (47.6%)	47 (62.7%)	67 (57.26%)	
Total	42	75	117	
Smoking Status				
Normal weight				p = 0.167
Non Smoker	75 (77.3%)	83 (70.9%)	158	
Current Smoker	20 (20.6%)	25 (21.4%)	45	
Ex-smoker	2 (2.1%)	9 (7.7%)	11	
Total	97	117	214	
Overweight				p = 0.139
Non Smoker	42 (72.4%)	44 (83%)	86	
Current Smoker	12 (20.7%)	4 (7.5%)	16	
Ex-smoker	4 (6.9%)	5 (9.4%)	9	
Total	58	53	111	
Obese				p = 0.265
Non Smoker	30 (76.9%)	28 (73.7%)	58	
Current Smoker	6 (15.4%)	3 (7.9%)	9	
Ex-smoker	3 (7.7%)	7 (18.4%)	10	
Total	39	38	77	

Chi-square analysis.

Note: sample size in smoker current and ex-smoker groups is small to compare between several categories of BMI.

When atopy was analyzed in subjects according to BMI, the multivariate logistic regression analysis confirmed that atopy increases the risk of asthma ($p = 0.008$). In addition, the group of non-atopic obese patients had an increased risk of asthma compared to the group of non-atopic patients with normal weight or overweight ($p = 0.0032$).

Results of skin testing with aeroallergens showed that 64.6% of the subjects studied were polysensitized, with pollen sensitization the most prevalent (83.45% to pollens, 38.32% to house dust mites, 29.25% to animal epithelia, and 13.60% to molds).

DISCUSSION

We found that obesity and overweight, defined as a BMI of 25 to 29 kg/m² and 25–29.9 kg/m², respectively, were not associated with a higher prevalence of a confirmed asthma diagnosis in patients with asthma symptoms and AHR to methacholine. In this study, we collected data from Caucasian adults from several cities of Spain with continental and coast climates. The distribution of BMI in this sample was similar

TABLE 2.—Association between initial BMI and presence of asthma (symptoms and AHR).

BMI category	Asthma n (%)	Non-asthma n (%)	Total n (%)	OR (95% CI)	Adjusted OR (95% CI)*
Normal weight:	125 (35.5%)	227 (64.5%)	352 (53.2%)		
Overweight:	67 (34.7%)	126 (65.3%)	193 (29.2%)	0.96(0.66–1.39)	0.889(0.60–1.38)
Obese:	42 (35.9%)	75 (64.1%)	117 (17.7%)	1.01(0.65–1.57)	0.925(0.577–1.48)
All BMI categories	234 (35.3%)	428 (64.7%)	662		

*Model adjusted for age, sex, atopy, initial FEV₁, and FEV₁/FVC.

TABLE 4.—Atopic or non atopic subjects classified according body mass index (BMI) and asthma.

Atopy	Non-asthma n (%)	Asthma n (%)	Total n (%)
Non atopic			
BMI:			$p = 0.07$
Normal weight	80 (75.5%)	26 (24.5%)	106 (49.5%)
Overweight	46 (76.7%)	14 (23.3%)	60 (28%)
Obese	29 (60.4%)	19 (39.6%)	48 (22.4%)
Total	155 (72.4%)	59 (27.6%)	214
Atopic			
BMI:			$p = 0.546$
Normal weight	146 (60.6%)	95 (39.4%)	241 (54.6%)
Overweight	80 (60.6%)	52 (39.4%)	132 (29.9%)
Obese	46 (67.7%)	22 (32.4%)	68 (15.4%)
Total	272 (61.7%)	169 (38.3%)	441

Chi-square analysis.

to the distribution among the general Spanish population (2).

Although obesity has been associated with severe asthma (24), the recent results of Severe Asthma Research Program (SARP) (25) did not find that obesity is more prevalent in severe asthma than in milder asthma, so further studies are necessary on this topic.

The population studied in this manuscript has a $FEV_1/FVC > 70\%$, with similar characteristics to the population reported in the main articles (26–28) that have previously studied the association of excess weight and AHR in subjects with symptoms of asthma.

In the European Community Respiratory Health Survey, AHR increases with increasing BMI in men but not in women²⁶. In a case-control study from participants in the Normative Aging Study, a high initial BMI was associated with the development of AHR to methacholine (OR 10; 95%CI, 2.6–37.9) when subjects in the highest BMI quintile were compared with those in the middle BMI quintile. There was also a linear relationship between increasing BMI over the study period and the subsequent development of AHR (27).

In contrast, Schachter et al. (28) showed that in a group of 1,971 adults, BMI was associated with the presence of asthma symptoms (dyspnea and wheezing) but not with air-flow obstruction or AHR. Another study by Tantisira et al. (29) showed similar results in a pediatric population.

Anatomical and respiratory function changes could cause increased symptoms of cough, shortness of breath, and wheezing without altering airway behavior. Sutherland et al. (30) studied 30 obese and non-obese adult women with asthma and observed that changes in respiratory function, especially dynamic hyperinflation, were greater in obese individuals with bronchoconstriction; however BMI was independently associated with changes in lung volume and AHR. Salome et al. (31) studied the effect on breathlessness and airway responsiveness to methacholine in 49 (23 obese and 26 non-obese) non-asthmatic subjects between 18 and 70 years. These authors found that obesity reduces lung volumes but does not alter the sensitivity or maximal response to methacholine. However, obese subjects have an enhanced perception of dyspnea, associated with greater apparent stiffness of the respiratory system, and may therefore be at greater risk of symptoms. Similar results were encountered by Machado et al. (32). In addition,

simulated obesity-related changes in lung volume increased airway responsiveness in lean, non-asthmatic subjects (33).

Some prospective studies have suggested that the relationship between obesity and asthma is stronger in women (34); however, the difference in the estimates of effect between men and women is usually small. In a random-effects meta-analysis of data from seven studies, a similar increase in the odds of incident asthma due to overweight and obesity was observed in men (OR, 146; 95% CI, 1.05–2.02) and women (OR, 168; 95% CI, 1.45–1.94) (13). In the present study, the prevalence of asthma was similar in men and women classified according to BMI.

In our study, atopy was significantly associated with asthma in all BMI categories. However, in the absence of atopy, an increased risk of asthma was found in obese subjects compared to subjects with normal weight or overweight. The cause of bronchial inflammation in those obese subjects with asthma appears to be different from atopy (35). It is now well established that obesity is a state of chronic low-grade systemic inflammation. Adipose tissue secretes important regulatory adipokines such as leptin, a proinflammatory adipokine, and adiponectin, which has anti-inflammatory properties (35). It has been suggested that leptin may contribute to the increased asthma prevalence observed among obese subjects (36), but recent studies indicate that the association between obesity and asthma is unlikely to be due to a direct effect of leptin on airway smooth muscle (37). In contrast, adiponectin-deficiency increases allergic airway inflammation and pulmonary vascular remodeling, and these data provide a possible mechanism for the association between obesity and asthma in adults (38).

In the present study, asthma diagnosis was confirmed in 35% of subjects with symptoms of cough, shortness of breath, and wheezing. Shawn et al. (39) reported similar results. Those authors found that about one third of obese and non-obese individuals with physician-diagnosed asthma did not have asthma when objectively assessed. This finding suggests that in developed countries asthma may be over-diagnosed. Moreover, if symptoms in this group are due to causes unrelated to asthma, then asthma medication would be unlikely to affect their symptoms. Symptoms alone do not appear to be a good guide for asthma diagnosis and treatment.

In conclusion, although our study has the limitations of cross-sectional studies, obesity was not associated with mild asthma diagnosis in a population of Spanish adults. The presence of atopy was a risk factor for asthma, independent of obesity. Moreover, further research is warranted to reveal the pathogenetic mechanisms of asthma in non-atopic obese subjects.

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DECLARATION OF INTEREST

Declaration of interest: none of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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