

ORIGINAL ARTICLE

Asthma and insulin resistance in obese children and adolescents

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Abstract

Background: Obese children and adolescents have an increased risk for asthma. A few studies have evaluated the association of insulin resistance and asthma in obese pediatric populations. We examined whether there was a relationship between high degrees of insulin resistance and the presence of asthma in obese children and adolescents.

Methods: A total of 153 patients aged 4–15 years with at or above the 95th percentile BMI for age were prospectively recruited. Assessments included diagnosis of asthma, skin prick test reactivity to common environmental aeroallergens, and HOMA estimated insulin resistance, with the median (2.22) used as a cutoff value to categorize insulin resistance.

Results: There were 56 (36.6%) asthmatic and 97 (63.4%) non-asthmatic patients. HOMA values were significantly associated with positive skin tests ($p = 0.008$) and allergic asthma diagnosis ($p = 0.016$). Baseline insulin value was significantly associated with the risk of presenting asthma with positive skin testing (odds ratio 1.084, $p = 0.037$). Differences in age, BMI, and waist circumference were found between the groups of HOMA-IR <2.22 and ≥ 2.22 . Waist circumference (WC) was significantly associated with FVC ($p = 0.0001$) and FEV₁ ($p < 0.0003$); the greater the WC, the lower FVC and FEV₁ values.

Conclusions: Insulin resistance is a risk for allergic asthma in obese children and adolescents. Waist circumference was related to CVF and FEV₁ impairment.

The increase in the prevalence of asthma worldwide has been coincident with the increase in obesity in children and adults. Observational studies have shown a higher risk of asthma in obese children compared with non-obese, as well as a dose-dependent relationship between body mass index (BMI) and the incidence of asthma (1,2). In a 12-month prospective asthma management study of 902 patients (473 pediatric and 429 adults), 45% of children were overweight/obese (28% with BMIs ≥ 95 th percentile) (3). The increase in BMI and/or adiposity in children has been associated with an increase in asthma symptoms, exacerbation episodes, and emergency visits (4,5). In a study carried out in Canada with data of 3804 students 10–11 years of age, a linear association between BMI and asthma with a 6% increase in prevalence per unit increase of BMI was reported (6). On the other hand, obesity probably

affects the respiratory system in a different manner according to age due to the involvement of different mechanisms. In a prospective cohort of 932 children, infants with the highest weight-for-length (WFL) z scores at 6 months had a greater risk of recurrent wheezing by age 3 years (7).

The underlying mechanisms linking excess adiposity to the risk of asthma remain unclear. The presence of comorbidities and the production of proinflammatory mediators in response to a chronic, low grade systemic inflammation related to the excess adiposity have been proposed (8–10). Adipocytokines secreted by adipose tissue in obese patients exert pleiotropic effects on a variety of tissues and play an important role in the pathogenesis of insulin resistance (11,12). Increased BMI is linked to the development of insulin resistance, a potential pathway for obesity-asthma

association (13,14). Obesity may be related to an increased risk of aeroallergen sensitization and allergic asthma through mechanisms also involved in the development of insulin resistance (15). In a 5-year prospective study of a random sample of adults from the general population, insulin resistance at baseline was associated with an increased risk of wheezing and asthma-like symptoms (16).

A few studies have examined the association between insulin resistance and asthma in obese pediatric patients. A retrospective cohort study showed that morbid obese asthma patients had a higher degree of insulin resistance than morbidly obese non-asthma patients (17). Also, a relationship between adipokines and insulin resistance in children with allergic asthma has been reported (18).

The aim of this study was to determine whether high degrees of insulin resistance were associated with asthma in obese children. The relationship between markers of obesity and spirometry-related variables was also investigated.

Methods

Study population

A prospective study was designed in which the study population was all overweight kids (BMI >95th percentile for age and gender) (19) between 4 and 15 years of age who visited the clinic between 2007 and 2011 and thus stood a chance of being recruited. Patients were visited at the outpatient clinics of the pediatric endocrinology and pneumology services of a regional hospital (60 km northeast of Barcelona, Spain) with a reference population of 200,000 inhabitants. Patients with known syndromes (i.e., Trisomy 21, Angelman, Fragile X) or other chromosomal abnormalities, diabetes, or those on diabetes-related medications including metformin were excluded. Two pediatric endocrinologists and one pediatric pneumologist of the same Service of Pediatrics participated in the recruitment of patients. Eligible patients were recruited consecutively at the time of scheduled control visits. All patients who were invited to participate in the study agreed to take part. The study was approved by the Clinical Research and Ethics Committee of 'Consorci Sanitari del Maresme', Xarxa Hospitalària d'Utilització Pública, Servei Català de la Salut, Barcelona (Spain). Written informed consent was obtained from the parents and/or legal guardians. Also, children aged 10 years or older were fully informed regarding the characteristics of the study.

The primary objective of the study was to determine whether there was a relationship between high degree of insulin resistance and asthma in obese children and adolescents. The secondary objective was to assess the relationship between markers of obesity and spirometric variables.

Assessment of asthma

Information on asthma was obtained from a five clinical criteria, which included the following: (i) more than three previous episodes of wheezing, (ii) more than three episodes of

wheezing treated with beta-2 adrenergic agonists in the past 12 months, (iii) exertional dyspnea (referred by the patient or the parents), (iv) maintenance treatment with inhaled steroids at the time of the study, and (v) previous use of inhaled steroid maintenance therapy. Allergic asthma was defined by the presence of at least three of the five criteria mentioned above together with sensitization to one or more common allergens. Family history of asthma was considered when at least one parent was asthmatic.

Assessment of passive tobacco exposure

Passive tobacco exposure was defined on the basis of parental active smoking and when at least one parent claimed to smoke at home. Also, we asked whether the mother had smoked during pregnancy, and the average number of cigarettes smoked per day.

Assessment of sensitization of aeroallergens

Allergic status was assessed by skin prick testing (Leti Laboratories, Barcelona, Spain) for the most prevalent aeroallergens in our environment, including dust mites, cat and dog dander, grass pollen, fungi, *Parietaria*, *Platanus*, pine tree, cypress, and olive tree. Positivity was defined by a papule ≥ 3 mm in diameter or greater to histamine.

Assessment of pulmonary function

Patients aged 6 years or older underwent a forced spirometry with bronchodilator reversibility testing using Datospir 120 spirometer (Sibelmed, Barcelona, Spain), with reference values for Spanish children aged 5–15 years available at the time of the study (20) and following the recommendations of the Spanish Society of Pediatric Pneumology (21).

Assessment of obesity

Height and weight were measured using a stadiometer (Harpender wall-mounted, Holtain Ltd, Crosswell, Crymych, Dyfed, Wales, UK), and BMI was calculated using weight in kilograms divided by square of the height in meters. Waist circumference (WC) was measured directly on the body surface midway between the lower rib margin and the iliac crest using an extendable metric tape at the end of normal expiration. WC was measured in duplicate and if there was variation >2 mm between duplicate readings, then a third measurement was taken. The mean value was used in case of two measurements and the median value in case of three measurements.

Assessment of insulin resistance

The degree of insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) using the following formula: $\text{HOMA-IR index} = (\text{fasting plasma glucose [mmol/l]} \times \text{fasting serum insulin [mU/l]}) / 22.5$ (22). HOMA-IR method is valid for estimating insulin resistance in children and adolescents (23).

Assessment of glucose, insulin, cholesterol, and triglycerides

Insulin was measured using automated solid-phase chemiluminescent immunoassay (Immulite® 2000, Siemens Healthcare Spain, Getafe, Madrid, Spain). Glucose concentrations were analyzed by an enzymatic method on a Roche Modular P analyzer. Serum cholesterol and triglycerides were measured using an enzymatic colorimetric method on a Roche Modular P analyzer.

Assessment of comorbidities

All patients underwent a standard lipid profile and measurement of blood pressure.

Statistical analysis

Summary data are presented as median (maximum–minimum) for quantitative variables and as percentages of each category for categorical data. The association between different independent variables and the diagnosis of asthma or HOMA-IR (dichotomized according to the median value into <2.22 or ≥ 2.22) was assessed by univariate logistic regression analysis, and expressed as odds ratio (OR) and 95% confidence interval (CI). Outliers regarding HOMA-IR, defined as those exceeding the sum of adding twice the interquartile range value to the third quartile, were excluded from the analysis of the relationship between HOMA-IR and having asthma. The relationship between obesity measurements (BMI and WC) and spirometry-related variables (forced vital capacity [FVC] and forced expiratory volume in one-second (FEV₁)) was evaluated by simple linear regression analysis. The chi-square test or the Fisher's exact test was used for the comparison of categorical variables, and the Kruskal–Wallis test for the comparison of one qualitative and one quantitative variable. The association between diagnostic criteria of asthma (clinical, skin prick testing, or both) and HOMA-IR values was estimated by multivariate logistic regression analyses, in which dichotomized HOMA-IR values, age, and family history of asthma were the independent variables. Also, the association between obesity-

related variables (BMI, WC, and waist-to-hip ratio) and HOMA-IR was assessed in a multivariate logistic regression analysis. All tests were two-tailed, and statistical significance was set at $p < 0.05$. The Statistical Analysis System (SAS Institute, Cary, NC, USA) version 9.2 for Windows was used for the analysis of data.

Results

A total of 178 were recruited but 25 were excluded due to the presence of Turner's syndrome in 1 and missing data in the remaining 24. Therefore, the sample population included 153 patients (73 boys, 80 girls), 56 (36.6%) of which were asthmatics and 97 (63.4%) non-asthmatics. Thirty-five percent of non-asthmatics at the time of the study had previous history of recurrent wheezing and 20% reported exertional dyspnea. There were no significant differences between patients with and without asthma, although age ($p = 0.0946$) and family history of asthma ($p = 0.0751$) showed a marginal risk for asthma (Table 1). The median insulin level was 11.80 $\mu\text{g IU/ml}$ in the asthmatic group and 9.70 $\mu\text{g IU/ml}$ in the non-asthmatic group, $p = 0.0844$.

There were 17 patients (7 asthmatics, 10 non-asthmatics) with outliers HOMA-IR values. These patients were significantly older (median age 12 years vs. 10 years, $p = 0.015$) and showed significantly higher median insulin levels (32.8 vs. 9.6 $\mu\text{g IU/ml}$, $p < 0.0001$) as compared to the remaining patients. Outliers were excluded in data presented in Tables 2 and 3.

As shown in Table 2, there was a statistically significant association between HOMA-IR values and positive skin prick tests to aeroallergens as well as the combination of asthma diagnosis and positive skin prick tests to aeroallergens. Also, there were significant differences between patients in the HOMA-IR groups of <2.22 and ≥ 2.22 in relation to age, BMI, and WC (Table 3). In the univariate analysis and without excluding patients with outliers HOMA-IR values, a marginally statistically significant association was found between asthma with positive skin prick tests to aeroallergens and either HOMA-IR (OR = 1.380, 95% CI 0.981–1.941, $p = 0.0641$) or

Table 1 Differences in the distribution of variables between obese children and adolescents with and without asthma

Variables	Study patients		Odds ratio (95% CI)	p-value
	With asthma (n = 56)	Without asthma (n = 97)		
Age in years, median (range)	11 (4–14)	10 (4–15)	1.10 (0.95–1.27)	0.0946
Females, n (%)	32 (57.1)	48 (49.5)	1.36 (0.70–2.64)	0.3609
Caucasian race, n (%)	49 (87.5)	79 (81.4)	1.60 (0.62–4.10)	0.3290
BMI, kg/m ² , median (range)	27.5 (22.9–37.2)	28.5 (22.6–44)	0.95 (0.87–1.03)	0.2434
Passive tobacco exposure, n (%)	40 (71.4)	71 (73.2)	0.92 (0.44–1.91)	0.814
Family history of asthma, n (%)	23 (41.1)	26 (27.1)	1.88 (0.93–3.77)	0.0751
Waist circumference, cm, median (range)	92 (73–114)	92.5 (70–122)	0.99 (0.96–1.02)	0.719
Waist-to-height ratio, median (range)	0.62 (0.48–0.74)	0.63 (0.51–0.75)	0.002 (0.001–1.86)	0.1135
Insulin level, $\mu\text{gIU/ml}$, median (range)	11.80 (2–48.8)	9.70 (1.5–47.2)	1.03 (0.996–1.070)	0.0840
HOMA-IR, median (range)	2.25 (0.42–4.45)	2.03 (0.28–4.97)	1.23 (0.89–1.69)	0.2058

Range: minimum–maximum values.

Table 2 Association between HOMA-IR values and diagnosis of asthma

Variables	HOMA-IR values		Odds ratio* (95% CI)	p-value
	<2.22 (n = 76)	≥2.22 (n = 60)		
Diagnosis of asthma, n (%)	23 (30.3)	26 (43.3)	1.76 (0.82–3.80)	0.152
Positive prick tests to aeroallergens, n (%)	32 (42.1)	39 (65.0)	2.40 (1.13–5.10)	0.023
Asthma diagnosis + positive prick tests to aeroallergens, n (%)	15 (19.7)	23 (38.3)	2.36 (1.01–5.49)	0.046

*Adjusted by dichotomized HOMA-IR value, age, and family history of asthma (independent variables) with diagnosis of asthma as the dependent variable.

Diagnosis of asthma, positive prick tests to aeroallergens, and asthma diagnosis plus positive prick tests to aeroallergens were the dependent variables in each of the logistic regression model.

Table 3 Distribution of variables in the groups of HOMA-IR values < 2.22 and ≥ 2.22

Variables	HOMA-IR values		Odds ratio (95% CI)	p-value
	< 2.22 (n = 76)	≥ 2.22 (n = 60)		
Age in years, median (range)	9.0 (4.0–14.0)	11.5 (6.0–15.0)	1.43 (1.20–1.71)	<0.0001
Females, n (%)	44 (57.9)	29 (48.3)	0.68 (0.34–1.34)	0.267
Caucasian race, n (%)	66 (86.8)	49 (81.7)	0.68 (0.27–1.72)	0.407
Family history of asthma, n (%)	26 (34.2)	16 (27.1)	0.72 (0.34–1.51)	0.377
Mother	11 (14.5)	6 (10.2)	0.67 (0.23–19.3)	0.455
Father	8 (10.5)	6 (10.2)	0.96 (0.32–2.94)	0.946
Brothers/sisters	10 (13.3)	7 (11.9)	0.88 (0.31–2.46)	0.799
Passive tobacco exposure, n (%)	56 (73.7)	42 (70.0)	0.83 (0.39–1.77)	0.635
Father (active smoker)	36 (47.4)	35 (58.3)	1.56 (0.79–3.08)	0.204
Mother (active smoker)	35 (46.1)	29 (48.3)	1.10 (0.56–2.16)	0.791
Smoking during pregnancy	14 (34.2)	17 (46.0)	1.64 (0.66–4.09)	0.288
BMI, kg/m ² , median (range)	27.0 (22.9–37.5)	29.3 (22.6–39.8)	1.18 (1.07–1.31)	0.0014
Waist circumference, cm, median (range)	88.5 (70.0–113)	98 (75–121)	1.11 (1.06–1.15)	<0.0001
Height-to-waist ratio, median (range)	0.62 (0.48–0.75)	0.64 (0.51–0.75)		0.014

Range: minimum-maximum values.

(log)HOMA-IR values (OR = 1.830, 95% CI 0.940–3.575, $p = 0.0754$). Baseline insulin level was significantly associated with asthma accompanied by positive aeroallergen sensitization (OR = 1.084, 95% CI 1.005–1.170, $p = 0.0378$).

In the multivariate analysis, there was a significant association between obesity-related variables and HOMA-IR (BMI, $p < 0.0001$; WC, $p < 0.0001$; waist-to-hip ratio, $p = 0.0439$).

There was an inverse relationship between HOMA-IR and spirometry-related variables (FVC, FEV₁, FEV₁/FVC ratio), although statistical significance was not reached. However, WC showed a significant association with FVC ($p = 0.0001$) (Fig. 1) and FVE₁ ($p = 0.0003$) (Fig. 2), that is, the larger WC, the lower FVC and FEV₁ (Table 4). A similar inverse relationship between WC and FEV₁/FVC ratio as well as between waist-to-height ratio and lung function parameters was observed, but statistical significance was not reached.

Discussion

Results of the present clinical study indicate that insulin resistance is a risk factor for allergic asthma in obese children. In contrast to the study of Al-Shawwa et al. (17), our patients

did not have underlying comorbid conditions. We found that in the presence of relatively low degrees of insulin resistance, there is an increase in the risk of allergic asthma. These findings are consistent with data reported by Ashi et al. (18) in 21 allergic asthmatics and 10 non-allergic healthy controls, aged 6–17.9 years, with insulin resistance defined as HOMA-IR index ≥ 1.77 , in which insulin resistance was only found in allergic asthma patients (42.8%). In our study, the median value of HOMA-IR index was 2.22, and although this cutoff value was higher than that used in the study of Ashi et al. (18) clearly discriminated the study patients into two groups: one group of patients with a higher risk of aeroallergen sensitization (positive prick tests) or combined aeroallergen sensitization and allergic asthma, and another group of patients with a lower risk. These groups showed significant differences in age, BMI, and WC.

A total of 38.3% of patients with HOMA-IR ≥ 2.22 had asthma with sensitization to aeroallergens (allergic asthma) as compared to 19.7% in those with HOMA-IR values <2.22. However, when the three variables were independently analyzed (asthma, positive prick testing, and asthma with aeroallergen sensitization), sensitization to aeroallergens was the

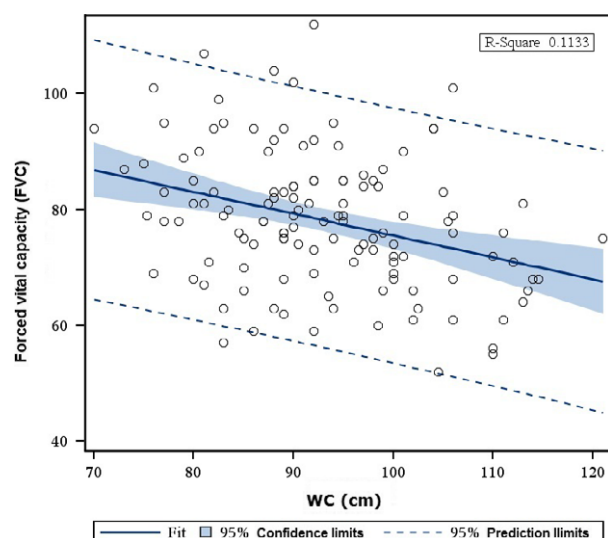


Figure 1 Relationship of waist circumference (WC) with forced vital capacity (FVC) (regression line equation: $FVC = 113.3 - 0.378 (WC \text{ in cm})$ ($p = 0.0001$)).

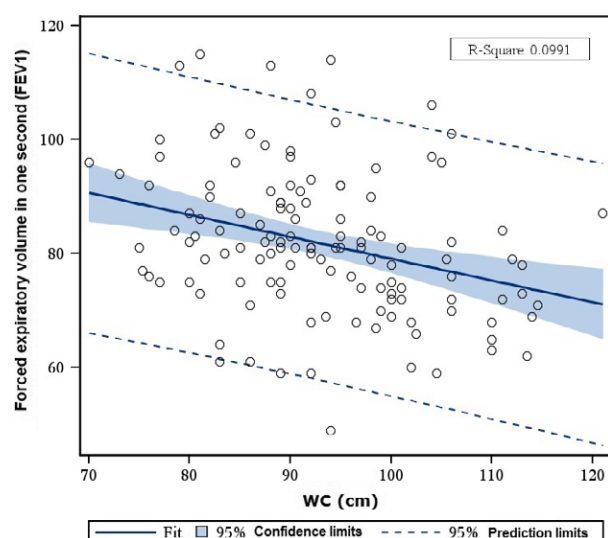


Figure 2 Relationship of waist circumference (WC) with forced expiratory volume in one-second (FEV_1) (regression line equation: $FEV_1 = 117.5 - 0.383 (WC \text{ in cm})$ ($p = 0.0003$)).

association with the highest statistical power. This is in agreement with the hypothesis that insulin resistance or the mechanisms conditioning resistance to insulin are those favoring development of asthma and sensitization to aeroallergens (15), probably in relation to a decrease of immunologic tolerance to antigens caused by changes in the levels of different adipokines secreted by the adipose tissue (chronic systemic inflammation theory) (24,25). However, at earlier ages as shown by the study of Bekkers et al. (26) in children of 4 years of age, the impact of BMI on asthma is independent of inflammatory markers. It is likely that a prolonged period of time may be needed to cause systemic inflammation, appearing therefore, later in life or in the presence of very important obesity at earlier age.

In different studies of asthma and obesity in childhood, the diagnosis of asthma is based on symptoms questionnaire filled out by the family and a few studies are based on objective measures. Because of the complexity of performing bronchial hyper-reactivity testing to all of the patients, a set of five clinical variables together with sensitization to one or more common allergens was established by consensus to accept or to exclude the presence of asthma.

There are controversial data regarding the role of obesity in the development of airflow obstruction, bronchial hyper-reactivity, or asthma (27,28). Spathopoulos et al. (29) in overweight ($BMI > 85$ th percentile) children aged 6–11 years found a significant reduction of FVC, FEV_1 , forced expiratory flow at 25%–75% (FEF_{25-75}), and FEV_1/FVC ratio as compared to children with normal weight. Also, the study of Chu et al. (30) showed that the FEV_1/FCV ratio decreased as BMI increased, both in boys and girls. Thus, from a point of view of pulmonary, obesity determined a mixed pattern in these patients. We found an inverse association between HOMA-IR values and FVC, FEV_1 and FEV_1/FVC ratio, although statistical significance was not reached probably due to the small sample size. However, a significant relationship between WC and FVC and FEV_1 was observed, so that the greater WC the lower the FVC and the FEV_1 .

The small sample size is a limitation of the study, which probably prevented to obtain significant differences in many of the study variables. Although comorbid conditions were not present in our patients, the study sample reflected the characteristics of obese children and adolescents attended by pediatricians or family physicians in the primary care setting in daily practice. It should be noted that most HOMA-IR values were < 5 except for 17 patients (7 asthmatics and 10

Table 4 Relationship between HOMA-IR values and waist circumference (WC) with lung function tests: simple linear regression models

	FVC (% of predictive)*				FEV ₁ (% of predicted)*			
	Regression coefficient	Standard error	R ² (%)	p-value	Regression coefficient	Standard error	R ² (%)	p-value
HOMA-IR†	−0.845	0.921	0.67	0.361	−1.253	0.997	1.25	0.210
WC†	−0.378	0.095	11.33	0.0001	−0.383	0.104	9.19	0.0003

*Dependent variables.

†Independent variables.

non-asthmatics) presenting extreme insulin values both in the decimal and logarithmic scales. These cases may suggest a different population subgroup as compared to the remaining patients in the study. Outliers were significantly older but given the small number ($n = 17$), a subanalysis taking into account differences in age could not be performed, nor age-HOMA-IR interaction could be included in the logistic regression models. This aspect may be examined in further studies with a larger sample population to determine whether these cases may be the result of sample fluctuations (randomness), an insufficient sample population to perform this analysis, or a specifically different subgroup of patients. For this reason, to assess the association between HOMA-IR and having asthma, outliers were excluded, given that the focus of our interest was to estimate this association in the pediatric population usually attended in daily practice. Also, outlier exclusion may account to the fact that comorbid conditions were not present in our patients.

The present results show that in the presence of even low degrees of insulin resistance, there is an increase in the risk of sensitization to aeroallergens and allergic asthma. The fact that mechanisms related to systemic inflammation are still not present at earlier ages offers an important opportunity to treat obesity at this age and to prevent future consequences. It seems that weight increases out from the critical period of an increase of adiposity does not involve a higher risk for asthma. The study of Schoeltens et al. (31) shows that children with an elevated BMI had a higher risk for asthma symptoms and bronchial hyper-reactivity at the age at which the child has an increased BMI. However, having an elevated BMI at early ages does not involve a higher risk in the future if BMI is normalized at ages 6–7 years.

The molecular mechanisms of obesity-associated asthma remain undefined. It has been shown that the NOD-like Receptor (NLR) family of innate immune cell sensors, such as the NLRP3 inflammasome, is implicated in recognizing certain non-microbial origin ‘danger-signals’ leading to caspase-1 activation with subsequent IL-1 β and IL-18 secretion, and contributing to obesity-induced inflammation and insulin resistance (32). Interestingly, Kim et al. (33) have recently shown for the first time in a mouse model that diet-induced

obesity leads to the development of airway hyper-reactivity through a pathway that required the NLRP3 inflammasome and IL-17, and that was facilitated by pulmonary IL-17 + ILC3 cells, a cell type that has not been linked previously with airways disease. These findings may explain why asthma associated with obesity appears to be distinct from other forms of asthma.

In summary, this study provides further evidence of the effect of insulin resistance as a risk factor for allergic asthma in obese children and adolescents. This risk increases with increasing the degree of insulin resistance. Moreover, WC was related to impairment of FCV and FEV₁.

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Conflict of interest

The authors declare no conflict of interests.

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Authors' contribution

J. Sánchez Jiménez has participated in study design, literature search, recruitment of patients, design of the database, statistical analysis, writing of the manuscript, and approval of the final draft. F.J. Herrero Espinet has participated in study design, recruitment of patients, data collection, interpretation of findings, critical review of the manuscript for intellectual content, and approval of the final draft. J.M. Mengibar Garrido has participated in recruitment of patients, collection of data, and approval of the final draft. J. Roca Antonio has participated in study design, statistical analysis and interpretation, and approval of the final draft. S. Peños Mayor has participated in performance of skin prick testing and pulmonary function tests, collection of data, and approval of the final draft. M.M. Peñas Boira, A. Roca Comas, and A. Ballester Martínez have participated in data collection, critical review of the manuscript, and approval of the final draft.

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