

The Reciprocal Influences of Asthma and Obesity on Lung Function Testing, AHR, and Airway Inflammation in Prepubertal Children

Nicola P. Consilvio, MD, Sabrina Di Pillo, MD, Marcello Verini, MD, Tommaso de Giorgis, MD, Anna Cingolani, MD, Valentina Chiavaroli, MD, Francesco Chiarelli, PhD, and Angelika Mohn, MD*

Summary. Although asthma and obesity are among the major chronic disorders their reciprocal or independent influences on lung function testing, airways hyperresponsiveness (AHR) and bronchial inflammation has not been completely elucidated. In 118 pre-pubertal Caucasian children anthropometric measurements functional respiratory parameters (flow/volume curves at baseline and after 6-minute walk test [6MWT]) together with bronchial inflammatory index (FeNO) were assessed. The study population was divided into four groups according to BMI and the presence or absence of asthma: Obese asthmatic (ObA) Normal-weight asthmatic (NwA), Obese non-asthmatic (Ob), non-asthmatic normal-weight children (Nw). Baseline PEF and MEF₇₅ (%-expected) were significantly different across the four groups with significantly lower values of MEF₇₅ in ObA and Ob children when compared to Nw children ($P=0.004$ and $P=0.0001$, respectively) and this independent role of obesity on upper respiratory flows was confirmed by multiple analysis of covariance. After 6 MWT respiratory parameters decreased only in ObA and NwA children and 12 children presented a positive fall in FEV₁, in contrast no changes of respiratory function testing were detected in Ob and Nw children, and only 2 Ob children presented a significant fall in FEV₁. FeNO analysis demonstrated significantly higher values in ObA and NwA children when compared to Ob ($P=0.008$ and $P=0.0002$, respectively) and Nw children ($P=0.0001$ and $P=0.0003$, respectively), although a significant difference was found between Ob and Nw children ($P=0.0004$). Multiple analysis of covariance confirmed an independent role of asthma on this parameter. In conclusion while AHR and airway inflammation are clearly associated with an asthmatic status, obesity seems to induce reduction of upper airways flows associated with a certain degree of pro-inflammatory changes. **Pediatr Pulmonol.**

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INTRODUCTION

Over the past several decades the prevalence of obesity has steadily increased reaching epidemic proportions. Current estimates of childhood obesity coming from the National Health and Nutrition Examination Survey (NHANES) revealed an increase from 13.8% in 1999–2000 to 16.0% in 2003–2004 for American females and from 14.0% to 18.2% in American males subjects.¹ In Europe, Italy together with other Mediterranean countries explicates the highest rate of obesity in children aged between 7 and 11 years, reaching almost 17%.² This has been accompanied by a similar rise in the rates of asthma. In fact, the CDC National Surveillance for Asthma revealed that its prevalence in children has risen from 3.5% to 7.5% over a period ranging from 2001 to 2003.³ Similarly in developing countries undergoing their epidemiological transition phase comparable significant rises have been observed.⁴ Accordingly, the World Health

Organization (WHO) includes both obesity and asthma among the major chronic disorders representing worldwide public health priorities.⁵

Given this dramatic rise in the prevalence of obesity and asthma, it is not surprising that there has been an increasing body of literature on the association between body mass index (BMI) and asthma.⁶

Department of Pediatrics, University of Chieti, Chieti, Italy.

*Correspondence to: Angelika Mohn, MD, Department of Pediatrics, University of Chieti, Via Dei Vestini 5, 66100 Chieti, Italy.
E-mail: amohn@unich.it

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Obesity may have effects on both the upper and lower airway,⁷ and this hypothesis is supported to a certain extent by the observation that BMI, the best single measure of body adiposity,⁸ seems to be a reliable predictor of allergic respiratory symptoms and airways hyperresponsiveness (AHR).⁹ In fact, recent literature emphasizes the role of obesity in inducing a pro-inflammatory state due to increased levels of different pro-inflammatory cytokines. This might be implicated in the genesis of chronic inflammation of the airway system¹⁰ similar to those observed in asthma which is characterized by persistent infiltration of eosinophils, T-lymphocytes and mast cells combined with different cytokines. In this respect exhaled nitric oxide (eNO) has been shown to tightly reflect this airway inflammation¹¹ and its fractional concentration in exhaled air (FeNO) has been recently accepted by the PRACTALL Consensus Report for the Diagnosis, Management and Treatment of Childhood Asthma as a logical complementary item in the follow-up of bronchial inflammation.¹² The reported association between increased BMI and onset of AHR has been elegantly demonstrated by Litonjua et al.¹³ in a longitudinal study of aging and has been further confirmed by two large cross-sectional studies performed in adults.^{14,15} This is in contrast with other epidemiological studies performed in childhood where this association has not been universally observed.^{16–18} This represents an important discordance of the recent literature as it might indicate that different factors such as duration of obesity and subsequent physiological changes of airway structures might play an important role in the development of obesity induced AHR.

Pre-pubertal children are a special study population as the shorter duration combined with better control of both diseases eliminates confounding factors commonly present in older subjects. In fact, this kind of population offers the exclusive opportunity to tangle whether obesity and asthma explicate an independent effect on lung function testing or influence themselves in a reciprocal manner.

Therefore, with the primary aim to establish the possible dependent or independent role of asthma and obesity on airway system function we evaluated AHR and bronchial inflammation expressed by FeNO in a group of obese and nonobese asthmatic children in comparison to non-asthmatic obese and normal-weight pre-pubertal children.

MATERIALS AND METHODS

Study Subjects

Clinical, anthropometric measurements and respiratory parameters of a group of 118 Caucasian pre-pubertal children referred to the Children Obesity Clinic, to the Paediatric Allergy and Respiratory Clinic and to the

Department of Paediatrics, University of Chieti, Italy, were sequentially evaluated between May 2008 and August 2008.

Asthma was classified according to Global Initiative for Asthma (GINA) guidelines¹⁹ as intermittent asthma, mild persistent, moderate persistent and severe persistent asthma. The diagnosis was established by a single paediatric respiratory physician on the basis of a clinical history of repeated episodes of coughing, dyspnoea and wheezing, according to American Thoracic Society–European Respiratory Society (ATS–ERS) criteria.²⁰ Only subjects who fulfilled the definition of intermittent/mild persistent asthma were recruited. Low dose inhaled corticosteroids (ICSs) therapy was withdrawn for not more than weeks before the study evaluation. Over this period all children were closely monitored by the medical staff of the Paediatric Allergy and Respiratory Clinic, none experienced any adverse event and at the time of the study evaluation all subjects were symptom-free.

Obesity was defined as body mass index (BMI) above 2 standard deviations (SD) for the mean of age and sex.²¹ In all subjects endocrine diseases as cause for obesity were excluded prior to study entry. None of the non-asthmatic obese children had a personal history for asthma and allergic diseases.

We recruited as controls a group of healthy children, comparable for age, gender, and pubertal stage, who were admitted to the Department of Paediatrics for minor diseases. None of the children had a personal history for asthma and allergic diseases, and all were otherwise in a good health. Anthropometric measurement and respiratory function were assessed only after complete recovery of the disease.

Exclusion criteria for all children were: presence of upper or lower respiratory infections including asthma during the previous 4 weeks, congenital abnormalities of cardio-respiratory system, chest or skeletal deformities, or neuromuscular system disease, chronic and autoimmune disease, gastro-oesophageal reflux, presence of medical condition in which exercise was forbidden. None of the children was taking any medication.

Based on the presence or absence of asthma and according to BMI, the study population was divided into four groups:

1. Obese asthmatic children (ObA) (16 boys and 14 girls).
2. Normal-weight asthmatic children (NwA) (16 boys and 14 girls).
3. Non-asthmatic obese children (Ob) (14 boys and 16 girls).
4. Non-asthmatic normal-weight children [Nw] (14 boys and 14 girls).

All children underwent a complete physical examination including anthropometric parameters (height, weight).

Pubertal stage was defined on the basis of breast development in girls and genital development in boys according to the criteria of Tanner (all subjects had pre-adolescent characteristics corresponding to stage 1). Respiratory function was assessed by standard Flow/Volume curves at baseline and after six-minute walk test (6MWT), and respiratory inflammatory status was assessed by FeNO. Only asthmatic children performed allergy evaluation by skin prick test (SPT), and blood sample was taken for specific IgE measurement.

Written informed consent was obtained from all parents and oral consent from all children.

The study was approved by Ethical Committee of University of Chieti.

Methods

Anthropometric Measurements

Body weight was determined to the nearest 0.1 kg, and height was measured in triplicate with Harpenden stadiometer to the nearest 0.1 cm. As fatness indices, we used BMI (the weight in kilograms divided by the square of the height in meters). SDS-height and BMI-SDS were calculated as difference between the individual observed value and the reference mean for age and sex, divided by the corresponding standard deviation.²²

Spirometric and Flowmetric Measurements

Baseline flow/volume curves. Lung function evaluation was performed by Flow/Volume curves (KitMicro Spirometer 7.3a—COSMED) in the standing position with nose-clip until two consecutive technically acceptable curves were achieved, according to ATS/ERS Guidelines.²³ The main spirometric parameters included: forced expiratory volume in 1 sec (FEV₁), forced vital capacity (FVC), FEV₁/FVC, and Forced Expiratory Flows between 25% and 75% of the FVC (FEF_{25–75}) and the results are expressed as Z-scores according to Stanojevic et al.²⁴ Peak expiratory flow (PEF) and maximal expiratory flows at 75% of the FVC (MEF₇₅) were expressed as a percentage of theoretical values for age, gender, and height according to Quanjer et al.²⁵

Six-minute walk test (6MWT). In order to estimate the bronchial hyperresponsiveness, after baseline lung function testing, a 6MWT was performed according to standard protocol.²⁶ The target of the test was to achieve 6 min of free walk until the heart-rate was 80–90% of the predicted maximum (calculated as 220—age in years), according to ATS/ERS recommendations for exercise challenge test in older children.²⁷ Spirometry was performed in duplicate sets at 1, 3, 5, 10, and 20 min post-exercise. The better of the two curves was selected as

the representative value at each interval, but differences between the two values of FEV₁ had to be <5%. Exercise response was defined as the greatest decrease in FEV₁ expressed as a percentage of the baseline values. A bronchial obstruction response to exercise was considered positive when the FEV₁ reduction from baseline was greater than 12%.²⁸

Allergic Sensitization

Skin prick test (SPT) were performed and serum specific IgE were measured for the most common respiratory allergens: Dust Mite (*Dermatophagoides Pteronyssinus* and *Farinae*), Grass, *Parietaria*, *Artemisia Vulgaris*, Olive, Cypress, Lime, Stone, Elm, Plane, Cat and Dog dander, *Alternaria Alternata* and *Aspergillus Fumigatus* (moulds). Determination of Allergen-Specific IgE was made by an Immunoenzymatic Allergo-sorbent Test (Cap test Pharmacia).^{29,30}

Respiratory Inflammation Marker

FeNO was determined with an on-line method using a single breath exhalation and a sensitive chemiluminescence assay (Ecomedics CLD 88), according to ATS—ERS.³¹ Patients made an inspiration of eNO-free air via a mouthpiece immediately followed by full exhalation at a constant rate (50 ml/sec) for at least 5 sec. The mean of three readings at the end of the expiration (plateau phase) was taken as the representative value for each measurements. Twelve part per billion or more were considered positive, according to ATS—ERS criteria.³²

Statistical Analysis

All values were expressed as median and interquartile range.

Kruskal–Wallis test was performed for evaluating differences between the four groups (ObA, NwA, Ob, Nw). Statistical significance level was $P < 0.05$. Subsequently, differences within the single groups were tested by Mann–Whitney Test, adjusting the significance level by $P < 0.008$. Differences in functional respiratory baseline parameters and after 6MWT within each group were analyzed using Wilcoxon signed ranks test. Categorical variables were tested by Pearson's Chi-square (χ^2) test.

A multiple analysis of covariance (MANCOVA) was performed to investigate the independent effect of obesity and asthma on respiratory indices (PEF, MEF₇₅ and FEV₁/FVC) and bronchial inflammation (FeNO), after adjusting for gender, age, and height.

Statistical significance level was $P < 0.05$.

All calculations were made with the computer program Statistical Package for the Social Science (SPSS), version 16.0 software for Windows.

TABLE 1—Anthropometric Measurements and Respiratory Parameters of the Study Population

	ObA	NwA	Ob	Nw	<i>P</i> ¹
Clinical and anthropometric characteristics					
Gender (M/F)	16/14	16/14	14/16	14/14	NS*
Age (years)	7.03 [6.05–8.02]	7.06 [6.77–8.05]	8.04 [7.05–9.02]	6.1 [6.03–8.09]	NS
Weight (kg)	35 [31–45.25]	25.75 [22–30.2]	42 [36.5–48]	24 [21–31.5]	0.0001
SDS-height	0.5 [0.06–1.2]	0.5 [0.05–1.1]	0.56 [0.05–1.55]	0.48 [0.051–1.2]	NS
SDS-BMI	4.6 [3.85–5.45]	0.4 [–0.25 to 1.3]	5 [4.55–7.1]	0 [–0.4 to 0.1]	0.0001
Respiratory inflammation marker					
FeNO (ppb)	5.1 [2.8–10.3]	7.4 [3.5–17]	3.5 [2.3–4.3]	2.3 [2.1–2.4]	0.0002
Baseline respiratory functional parameters					
FVC (Z-score)	–0.26 [–0.78 to 0.53]	–0.11 [–0.48 to 0.33]	–0.28 [–1.12 to 0.02]	0.25 [–0.76 to 1.99]	NS
FEV ₁ (Z-score)	–0.14 [–0.84 to 0.31]	0.025 [–0.35 to 0.44]	0.12 [–0.74 to 0.73]	–0.13 [–0.66 to 2.01]	NS
FEV ₁ /FVC (Z-score)	0.11 [–0.57 to 0.69]	0.27 [–0.58 to 1]	0.69 [–0.37 to 1.45]	0.85 [0.62–1.10]	0.025
FEF _{25–75} (Z-score)	–0.13 [–0.49 to 0.25]	0.05 [–0.32 to 0.75]	0.35 [–0.30 to 0.93]	0.4 [0.08–0.56]	NS
Respiratory functional parameters after “free run” exercise challenge test					
Post-FEV ₁ (Z-score)	–0.97 [–2.12 to 0.33]	–1.11 [–1.60 to –0.37]	0.09 [–0.69 to 0.85]	–0.03 [–1.57 to –0.03]	0.009
Post-FVC (Z-score)	–1.01 [–1.71 to 0.31]	–1.15 [–1.53 to –0.30]	–0.43 [–1.15 to 0.36]	0.20 [–1.11 to 0.96]	NS
Post-FEV ₁ /FVC (Z-score)	–0.63 [–1.12 to 0.48]	0.18 [–0.80 to 0.81]	0.68 [–0.14 to 1.95]	1.35 [–0.61 to 1.53]	0.01
Post-FEF _{25–75} (Z-score)	–0.22 [–0.65 to 0.13]	–0.06 [–0.55 to 0.51]	0.3 [–0.21 to 0.49]	0.42 [–0.91 to 0.62]	NS
Fall in FEV ₁ >12%	5/30 (16.7%)	7/30 (23.3%)	2/30 (6.7%)	0/28 (0%)	0.008*

Values are median [interquartile range]. NS, no significant difference ($P > 0.05$). M, male; F, female.

BMI, body mass index; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 sec; FEV₁/FVC, forced expiratory volume in 1 sec/forced vital capacity; FEF_{25–75}, forced expiratory flows between 25% and 75% of the forced vital capacity.

All the tests are expressed as Z-score.

*Pearson's Chi-square (χ^2) test.

¹Kruskal–Wallis test.

RESULTS

Anthropometric measurements and respiratory functional data of the whole study population are reported in Table 1. The four groups were similar for age, gender, and SDS-height.

As expected BMI-SDS was similar between ObA and Ob children, but was significantly different between obese children and normal-weight children (ObA vs. NwA $P = 0.0004$; ObA vs. Nw: $P = 0.0008$; Ob vs. NwA $P = 0.0001$; Ob vs. Nw: $P = 0.0002$).

All the asthmatic children were sensitized to *Derma-topagoides Pteronyssinus*.

Baseline Respiratory Functional Parameters

No significant differences were found for FVC, FEV₁, and FEF_{25–75} Z-scores between the four groups, whereas FEV₁/FVC Z-score resulted significantly different (Table 1). In fact, this parameter was significantly lower in the ObA group compared to the Nw group ($P = 0.005$). Moreover a significant difference was detected between the four groups in terms of PEF ($P = 0.03$) and MEF₇₅ ($P = 0.001$) (Fig. 1). By comparing the four groups directly no further significances could be detected for PEF, whereas MEF₇₅ was significantly lower in the ObA group and the Ob group compared to the Nw group ($P = 0.004$ and $P = 0.0001$, respectively).

Respiratory Functional Parameters After 6MWT

After 6MWT no significant differences were found in post-FVC and post-FEF_{25–75} Z-scores among the four groups (Table 1). Although post-FEV₁/FVC Z-scores resulted significant different between the four groups, no further differences were detected by comparing the four groups directly. In contrast, post-FEV₁ Z-score resulted significantly lower in NwA children when compared to Ob children and Nw children ($P = 0.006$ and $P = 0.006$, respectively). Post-PEF and post-MEF₇₅ resulted significantly different between the four groups ($P = 0.01$, both). In fact, post-PEF was significantly lower in ObA children when compared to Nw children ($P = 0.002$). This was associated with significantly lower values of post-MEF₇₅ in the ObA group and the Ob group when compared to the Nw group ($P = 0.003$ and $P = 0.007$, respectively).

Changes in respiratory parameters after 6MWT within each group are shown in Table 2. Post-FEV₁/FVC Z-score was significantly lower in the ObA group, while in NwA children a significant reduction was detected for post-FEV₁, post-FVC and post-FEF_{25–75} Z-scores. In contrast no changes were detected for the Ob and Nw groups.

A positive response to exercise challenge was found in 5 ObA children and 7 NwA children compared to only 2 Ob children. As expected none of the healthy control children experienced a fall in FEV₁ greater than 12%.

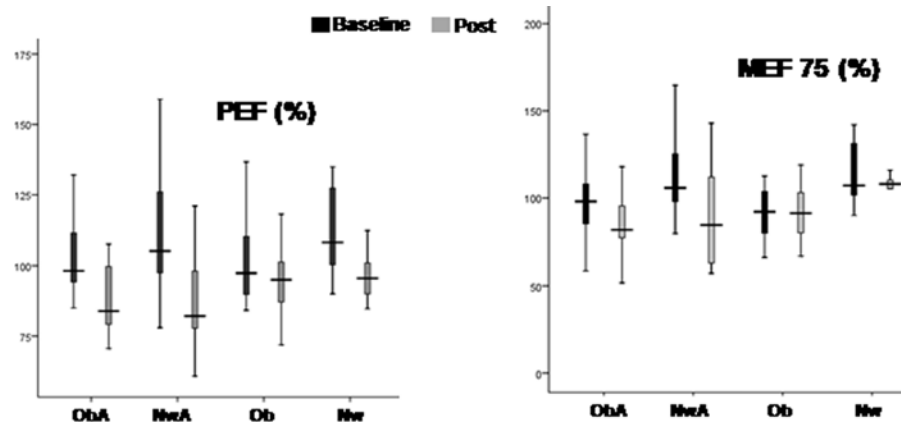


Fig. 1. Differences in PEF and MEF₇₅ obtained at baseline and after 6MWT. Values are median [interquartile range]. PEF, peak expiratory flow, MEF₇₅, maximal expiratory flow at 75% of the forced vital capacity. All the tests are expressed as %-predicted.

Respiratory Inflammation Marker

FeNO values were significantly different across all four groups ($P = 0.0002$) (Table 1).

In fact FeNO values were significantly higher in the ObA group and the NwA group compared to the Ob group ($P = 0.008$ and $P = 0.0002$, respectively) and to the Nw group ($P = 0.0001$ and $P = 0.0003$, respectively).

Furthermore FeNO was significantly higher in the Ob group when compared to the Nw group ($P = 0.0004$). In contrast no differences were detected between the two asthmatic groups.

Effect of Asthma and Obesity on Respiratory Functional Parameters and Bronchial Inflammation

In order to investigate the role of asthma and obesity on resulted significant different baseline respiratory variables

and FeNO, a multiple analysis of covariance was performed. Asthma was significantly and independently related to FeNO values, whereas no association was found for obesity. In contrast obesity was significantly and independently related to PEF and MEF₇₅. In the same model no relationship was found for asthma and obesity on FEV₁/FVC Z-score (Table 3).

DISCUSSION

Although the effect of obesity on pulmonary function tests has been extensively investigated in adults, the number of similar studies in children is limited and confirm the controversial results observed in adults between obesity and AHR. In this study we compare for the first time obese asthmatic with obese non-asthmatic pre-pubertal children and healthy controls with the aim to analyze the reciprocal influences of obesity and asthma on

TABLE 2—Comparison of the Respiratory Parameters After the 6MWT Within Each Group

	ObA	NwA	Ob	Nw
FVC (Z-score)	-0.26 [-0.78 to 0.53]	-0.11 [-0.48 to 0.33]	-0.28 [-1.12 to 0.02]	0.25 [-0.76 to 1.99]
Post-FVC (Z-score)	-1.01 [-1.71 to 0.31]	-1.15 [-1.53 to -0.30]	-0.43 [-1.15 to 0.36]	0.20 [-1.11 to 0.96]
P^1	NS	0.0001	NS	NS
FEV ₁ (Z-score)	-0.14 [-0.84 to 0.31]	0.025 [-0.35 to 0.44]	0.12 [-0.74 to 0.73]	-0.13 [-0.66 to 2.01]
Post-FEV ₁ (Z-score)	-0.97 [-2.12 to 0.33]	-1.11 [-1.60 to -0.37]	0.09 [-0.69 to 0.85]	-0.03 [-0.75 to 2.46]
P^1	NS	0.0001	NS	NS
FEV ₁ /FVC (Z-score)	0.11 [-0.57 to 0.69]	0.27 [-0.58 to 1]	0.69 [-0.37-1.45]	0.85 [0.62-1.10]
Post-FEV ₁ /FVC (Z-score)	-0.63 [-1.12 to 0.48]	0.18 [-0.80 to 0.81]	0.68 [-0.14 to 1.95]	1.35 [-0.61 to 1.53]
P^1	0.03	NS	NS	NS
FEF ₂₅₋₇₅ (Z-score)	-0.13 [-0.49 to 0.25]	0.05 [-0.32 to 0.75]	0.35 [-0.30 to 0.93]	0.4 [0.08-0.56]
Post-FEF ₂₅₋₇₅ (Z-score)	-0.22 [-0.65 to 0.13]	-0.06 [-0.55 to 0.51]	0.3 [-0.21 to 0.49]	0.42 [-0.91 to 0.62]
P^1	NS	0.02	NS	NS

Values are median [interquartile range]. NS, no significant difference ($P > 0.05$).

FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 sec; FEV₁/FVC, forced expiratory volume in 1 sec/forced vital capacity; FEF₂₅₋₇₅, forced expiratory flows between 25% and 75% of the forced vital capacity.

All the tests are expressed as Z scores.

¹Wilcoxon signed ranks test.

TABLE 3—Independent Effect of Asthma and Obesity on Lung Function and Bronchial Inflammation

Source	Dependent variable	Type III sum of squares	<i>F</i>	<i>P</i> ¹
Asthma	FeNO	655,174	3.957	0.048
	MEF ₇₅ (%)	505,481	1.038	NS
	PEF (%)	33,466	0.184	NS
	FEV ₁ /FVC (Z-score)	18,871	0.623	NS
Obesity	FeNO	119,116	0.719	NS
	MEF ₇₅ (%)	4,156,102	8.534	0.005
	PEF (%)	1,131,609	6.232	0.015
	FEV ₁ /FVC (Z-score)	5,290	0.175	NS

NS, no significant difference ($P > 0.05$).

FeNO, fractional exhaled nitric oxide; MEF₇₅, maximal expiratory flow at 75% of the forced vital capacity;

PEF, peak expiratory flow; FEV₁/FVC, forced expiratory volume in 1 sec/forced vital capacity.

FEV₁/FVC ratio are expressed as Z-score.

MEF₇₅ and PEF are expressed as percentage of theoretical values for age, gender, and height.

¹Multiple analysis of covariance (MANCOVA).

lung function and bronchial inflammation. Our findings clearly demonstrate that while an asthmatic status is tightly and directly involved in AHR and bronchial inflammation, obesity mainly affects the upper airways flows.

As obese children often experience dyspnoea and breathlessness during physical activities it is a crucial clinical question as to whether these symptoms are effectively related to AHR such as in asthmatic children. In order to explore this possibility a 6MWT was performed. While basal values of spirometric indices were normal in all examined groups, in ObA and NwA children exercise challenge induced AHR documented by the reduction of functional respiratory parameters. In contrast in Ob and Nw children no changes of any of the obtained variables were detected. This is confirmed by the number of children exhibiting a positive response to exercise defined as fall in FEV₁ greater than 12%. In fact within the asthmatic children 12 subjects met this definition compared to only 2 obese children. In agreement with our data, epidemiological studies do not uniformly support the conclusions that obesity leads to airflow limitation, AHR or asthma. In this respect Schachter et al.¹⁶ showed in a group of 1971 adults, that although BMI was associated with a clinical diagnosis of asthma and subjective symptoms of dyspnoea and wheeze, airflow obstruction or AHR subsequent to histamine challenge could not be detected in the sole obese subjects. Similar findings were obtained by Bibi et al.¹⁷ who demonstrated in a large population of pre-pubertal children that bronchodilation could not be induced by salbutamol inhalation in non-asthmatic obese subjects.³³ These data demonstrate that obesity should not be considered as being a risk factor for AHR in pre-pubertal children. Furthermore asthma like symptoms especially during physical activity should not be overestimated by parents and medical staff. This is of paramount relevance

as it might induce inappropriate treatment and refrain children from performing sports leading to a vicious circle impeding improvement of both obesity and respiratory symptoms.

Interestingly in the ObA and Ob groups we documented lower basal values of MEF₇₅ when compared to healthy controls. Furthermore PEF values were significantly different across the four groups with a tendency of lower values in the two obese groups. In fact, by performing a multiple analysis of covariance obesity was significantly and independently related to MEF₇₅ and to PEF, while this association was not found for asthma. Similar data were documented by two previous studies^{34,35} where obesity was associated with a significant reduction in FEV_{25–75}. These data suggests that obesity might play a primary role on upper airway flows, and despite being possibly explained by fatty infiltration of muscles narrowing directly the upper airway, recent literature suggest that this functional parameter might be used as an early predictor of sub-clinical asthma.³⁶

In order to obtain a complete evaluation of the bronchial status we performed also FeNO analysis. In effect, recent studies revealed that FeNO is a potentially useful measure to evaluate the role of airways inflammation in asthma, as it represents the forerunner of the most important event namely remodeling of bronchial airways,³⁷ offering therefore a logical complementary item to the only use of clinical and functional data. In our study, as expected, both groups of asthmatic children presented highly elevated FeNO values when compared to Ob children and normal controls reflecting the underlying bronchial inflammation process. However, data from animal and human studies clearly demonstrate that the enhancement of normal adipose tissue in obesity leads to a systemic pro-inflammatory state.³⁸ Adipose tissue from obese individuals expresses a number of pro-inflammatory molecules, such as leptin, tumor necrosis factor- α , IL-6, transforming

growth factor- β 1, and C-reactive protein, and there appears to be significant overlap between the immune function of adipocytes and the function of T-lymphocytes and macrophages, particularly with respect to the elaboration of inflammatory cytokines.^{39,40} Although a conclusive relationship between obesity and airway inflammation has not yet to be described, it could be argued that the role of the pro-inflammatory state underlying the main metabolic and cardiovascular complications in obesity might play a pivotal role in determining airways inflammation independently of any allergic mechanisms. This might explain the findings of our study where FeNO values were significantly higher in Ob children when compared to healthy controls, and the findings of Santamaria et al.⁴¹ who found a positive correlation between FeNO and BMI in healthy children. However it needs to be acknowledged that in the multiple analysis of covariance obesity was not a predictor for increased FeNO values as only asthmatic status remained as such. This apparent contrasting findings might be partially explained by the age group of our study population as obesity related inflammation might not have reached its full implication and a possible involvement of the respiratory system might require a long standing history of obesity.

In this respect an important limitation of this study is the cross sectional design which does not allow to speculate on the full clinical implications of our findings. In fact, as puberty is a well known risk factor for developing obesity related complications it might be of crucial interest to obtain longitudinal data starting in pre-puberty and lasting through all pubertal stages. This would allow to fully explore this intriguing relationship and to not underestimate the possible role of obesity on the development of bronchial inflammation.

In conclusion, while AHR and airways inflammation are clearly associated to an asthmatic status, obesity seems to induce reduction of upper airway flows combined with a certain degree of early pro-inflammatory airways changes. Longitudinal data are required in order to clarify whether these changes might represent risk factor for asthma later on in life.

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