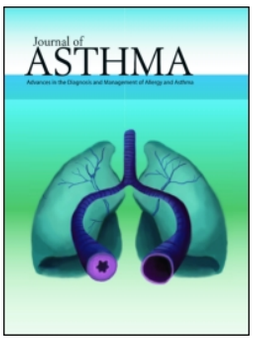

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Inspiratory muscle function in asthma.

Inspiratory muscle function in asthmatic and healthy subjects: influence of age, nutrition and physical activity.

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Abstract

Objective: To compare inspiratory muscle function (strength and endurance) between asthmatics and healthy controls, and the influence of age, nutritional status and physical activity on them.**Methods:** This is cross-sectional study. Asthmatic and healthy subjects, aged 6 to 18 years old, recruited from two public schools in Southern Brazil were included in the study. Asthmatic subjects were selected using the criteria presented by the International Study on Asthma and Allergies in Children and control subjects based on the absence of respiratory symptoms. Anthropometric data was measured, body mass index calculated and subjects classified as normal weight, overweight or obese. Physical activity levels, maximum inspiratory pressure

(MIP) and inspiratory muscle endurance (IME) were also evaluated. **Results**: A total of 314 participants were included, separated in control group (181) and asthmatics (133), with a total mean age of 11 years. When both groups were compared, there were no significant differences in both MIP and IME. However, when groups were analyzed subdivided in children and adolescents, IME was significantly reduced (p=0.003) in asthmatic adolescents. Indeed, when groups were also stratified considering the nutritional status, IME showed a reduction in asthmatic adolescents with overweight (p=0.042) and obesity (p=0.041) when compared to healthy controls. No effects of physical activity levels between groups were found. **Conclusions**: Results demonstrate a reduction in the IME in asthmatic adolescents with overweight and obesity, indicating an association between asthma, nutritional status and respiratory muscle function.

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Introduction

Asthma is a chronic inflammatory disease of the airways that affects practically all age groups, especially children [1]. It is characterized by recurrent episodes of wheezing, breathlessness, chest tightness and coughing, consequent to reversible airflow obstruction [1]. This airflow limitation decreases the exhaled tidal volume, leading to increased total lung capacity and airway resistance, with consequent air trapping and lung hyperinflation, compromising the biomechanics of the respiratory muscles [2, 3].

Among the mechanical disadvantages caused by this respiratory condition, the main factors include inspiratory muscle shortening, kinetic limitation caused by diaphragmatic flattening as a result of hyperinflation, as well as muscle weakness related to the effects of drug treatment with corticosteroids [4, 5]. Another factor that seems to cause loss of synchrony in the

pulmonary system is the presence of obesity, which can lead to decreased functional residual capacity and airway caliber, contributing to increased symptoms and recurrent periods of acute crisis [6]. Moreover, during an asthmatic crisis, subjects exhibit a marked increase in the respiratory work load caused by abnormal airflow resistance, while the ability of muscles to tolerate a load may be compromised by hyperinflation [7]. Also, it is already known that physical activity levels can influence muscle function [8]. However, although there are evidences on these effects upon peripheral muscles [9], little is known regarding its effects on respiratory muscle function.

Although the measurement of maximal static pressures is considered a simple, noninvasive and easy to perform method that provides important information on muscle strength [10], there are few and contradictory evidence about the influence of asthma on inspiratory muscle function in children and adolescents [2, 11-14]. Moreover, despite the fact that muscular strength and endurance are often related, the muscle strength evaluation does not necessarily allow an extrapolation of the IME, considering that the endurance is the ability of a muscle to sustain a given task over time, being directly related to fatigue mechanisms [15].

In this sense, previous studies have shown that the assessment of muscle endurance may be more important than strength in patients with chronic obstructive pulmonary disease due to the huge demand of the respiratory muscles during prolonged periods of acute crisis, making them more susceptible to fatigue and respiratory failure [12, 16]. Despite a recent systematic review [17] that demonstrated benefits with the use of muscle training, including an increase of inspiratory force, reduction of symptoms and medication use, there is still little information related to the basal function of inspiratory muscle endurance in this group of patients. In

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addition, there is a lack of evidence in the pediatric population on the real influence of age, nutritional status and physical activity levels on IME, which makes more difficult to assess and early detect possible respiratory muscle alterations.

Therefore, considering the different mechanisms involved in muscle mechanics, the conflicting findings regarding inspiratory muscle strength, and also the lack of information on muscular endurance, as well as the nutritional status and physical activity influence on these parameters, it is of relevance to further study the respiratory muscle strength and endurance in these patients. We hypothesized that inspiratory muscle function would be decreased in asthmatic subjects and that age, nutrition and physical activity could be significantly associated to these results. Thus, the objective of present study was to compare inspiratory muscle strength and endurance and to evaluate the influence of age, nutritional status and physical activity levels in asthmatic and healthy children and adolescents.

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Methods

Study design and participants

A cross-sectional study was performed including children and adolescents with or without the diagnosis of asthma, aged between 6 and 18 years old, enrolled at two public schools in the Southern Brazil (Porto Alegre, Rio Grande do Sul), in the period from June to December 2013. The study was approved by the Ethics in Research Committee of the Pontifical Catholic University of Rio Grande do Sul (n° 08823212.1.0000.5336). All legal guardians of the individuals signed the free and informed consent term prior to inclusion.

Firstly, a questionnaire with classic questions based on the International Study of Asthma and Allergies in Children (ISAAC) questionnaire [18] and the consent form were sent to the legal guardians of the students, through the school, inviting them to participate in the study. After completing and returning these instruments, the children were selected and called to carry out the tests at their school.

Subjects of the asthmatic group were selected based on responses to four different questions; three classic questions based on the ISAAC questionnaire study [18] and a further question regarding rescue medication use, as follows: (1) the presence of asthma symptoms (wheezing, shortness of breath or night awakening with cough) in the last 12 months; (2) medical diagnosis of asthma ever; (3) symptoms of asthma ever; and (4) use of rescue treatment for asthma in the past 12 months (bronchodilators or oral corticosteroids). Only individuals with all four positive responses were selected. On the other hand, participants in the control group were recruited based on the absence of respiratory symptoms. Subjects who had historic of cardiac or neuromuscular diseases, prematurity (<37 weeks), low birth weight (<2.500 grams) and cognitive or motor limitations were excluded of the present study.

After that, data regarding age, gender, ethnicity, anthropometric variables and physical activity levels were collected. Inspiratory muscle strength test to evaluate maximal inspiratory pressure (MIP) and the IME protocol were then performed. Participants were classified as children when younger than 12 years-old and adolescents when aged over 12 years-old.

Anthropometric measure

Weight and height were measured in triplicate and the average of measurements used, with no more than 5% variation between measurements allowed. Weight was measured using a

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digital scale (G-Tech Glass 1 FW, Rio de Janeiro, Brazil) with an accuracy of 100 grams. Height was obtained using a portable stadiometer (Alturaexata TBW, São Paulo, Brazil) with a precision of 1 mm. The body mass index (BMI: Weight (kg) / height (m^2)) was calculated and expressed in absolute value and z-score, adjusted for age. The students were classified by BMI into three categories: eutrophic (z-score between -2 and +1), overweight (z-score > +1 and <+2) and obese (z-score> +2) [19].

Physical activity levels

Physical activity levels were evaluated by using both a short questionnaire [20] and the triaxial accelerometer (Actigraph, Pensacola, Florida, United States of America). The questionnaire included information on physical activity, such as time spent from home to school or work, and the frequency and time spent in each physical activity during leisure. The students were classified according to the level of physical activity in active (>300 minutes/week) and inactive (≤300 minutes/week) [20]. Also, physical activity levels were evaluated through an objective measure using the triaxial accelerometer wGT3X-BT. All children and adolescents were encouraged to use the accelerometer during all day on the left side of the waist, between the period of Wednesday and Monday. Collected data were only included and analyzed when subjects used the device more than 4 consecutive days for at least 600 minutes/day. Periods with more than 60 consecutive minutes registering zero counts were excluded. The epoch was configured to collect information every 5 seconds [21]. Results of physical activity were expressed as the time spent (min/day) in accordance with its intensity: sedentary (<100 counts), light (≥100 counts), and moderate to vigorous (> 2296 counts) [22].

Manovacuometry

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Inspiratory muscle strength was evaluated using a digital manometer (MVD 500-Globalmed, São Paulo, Brazil) with a variation of ±500 cmH_2O. Maximal inspiratory pressure (MIP) was performed against an occluded valve, through a semi-rigid mouthpiece that had a hole (2 mm in diameter) to prevent the increase in intraoral pressure [10]. The measurements were performed in the sitting position using a nose clip. A maximum inspiratory effort from residual volume, sustained for at least 1 second, at intervals of approximately a minute between measurements, were performed [23]. A minimum of three and a maximum of nine measures were used for each test [10]. The test ended when technically correct maneuvers were obtained, including three acceptable measures (without air escaping) and two reproducible ones (variation of less that 10% between the two largest maneuvers). The higher value obtained in the test following the criteria above was used as final result. MIP was expressed in absolute value (cmH_2O) and as percentage of predicted, normalized by two reference equations according to the age range studied [10, 24].

Inspiratory muscle endurance protocol

A protocol of IME was performed through a linear load device (Threshold-IMT) during an incremental loading test [25]. The spring and structure of the apparatus were modified in order to obtain higher pressures than 41 cmH_2O. Thus, a new stainless steel spring was made with an elastic constant of 0.035 N/mm, allowing obtaining pressures up to 145 cmH_20. The patients began the protocol breathing against a fixed load of 30% of MIP during 2 minutes. To begin the inspiratory flow it was necessary to generate a sufficient inspiratory pressure to open the valve, in order to allow air to enter. Every 2 minutes the load was increased by 10% of MIP. The maximum load was defined as the highest percentage of MIP achieved and maintained for at

least 1 minute [25]. The breathing pattern was controlled and maintained at 20 respiratory incursions per minute. The interruption criteria of the protocol were intense fatigue and failure to open the valve at least 3 consecutive times.

Sample size estimation

Sample size estimation was performed considering the main variable of interest (IME). Adopting a significance level of 0.05, a power of 95% and a minimum difference between the expected averages of 5%, we have estimated approximately 300 children and adolescents to be distributed between the two groups.

Statistical analysis

The main variables of the study were evaluated by using the Kolmogorov-Smirnov test. Accordingly, data were expressed as mean/standard deviation, median/interquartile range or absolute/relative frequency. Inspiratory muscle function variables (MIP and IME) were compared by using Student's t test for independent samples. On the other hand, the Man Whitney U test was used to compare physical activity data between groups, as it presented asymmetric distribution. Categorical data were compared using Pearson's chi-square test. We have also further analyzed results by separating individuals by age, nutritional status and physical activity level. All analysis and data processing were performed using SPSS version 18.0 (SPSS Inc., USA). In all cases differences were considered significant when $p<0.05$.

Results

A total of 321 children and adolescents were selected. One of them did not consent to have the anthropometric data measured and six were not able to perform the IME test. Thus, the final study sample was composed of 314 participants. Of these, 181 were in the control group

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and 133 in the asthma group, being 50.2% and 47.3% male, respectively. There were no statistically significant differences ($p>0.05$) between the baseline characteristics evaluated in both groups (table 1).

Results in table 2 shows that no significant differences were observed between the control and asthma groups in relation to MIP ($p=0.20$), IME ($p=0.092$) and physical activity levels ($p=0.71$). Regarding to gender, there were no differences in the inspiratory muscle strength and endurance when female and male in both groups were compared. When control and asthmatic groups were compared (table 3) in relation to physical activity (active and inactive), no significant differences were found for MIP ($p=0.60$) and IME ($p=0.76$). Furthermore, no differences were observed when the results were stratified according to different classifications of nutritional status (table 4).

When groups were subdivided according to age, 106 children and 75 adolescents were in the control group and 89 children and 44 adolescents in the asthmatic group. Thus, when separately analysis only with children was performed, no significant differences were found in relation to MIP and IME between control and asthmatic groups. On the other hand, when the adolescents data was compared, MIP (%) demonstrated similar results between both groups but the IME (%) was significantly reduced in the asthmatic group (62.4 ± 13.6 vs. 55.1 ± 12.3; $p=0.003$), demonstrating a decreased ability of the inspiratory muscles to support a load over time in this group (figure 1). Furthermore, when MIP and IME were compared according to physical activity levels in both children and adolescents, no differences were found.

Finally, when both age groups were analyzed separately according to nutritional status, there were no significant differences in the measurements of MIP and IME in children. Also,

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MIP values in adolescents of different nutritional status were not changed. However, IME (%) was significantly reduced in both overweight (67.5±17.1 vs. 50.0±12.6; p=0.042) and obese asthmatic individuals (65.7±16.5 vs. 53.6±9.2; p=0.041) when compared to the control group (figure 2). MIP and IME were not different when separated by physical activity levels according to BMI classifications (data not shown).

Discussion

The results of present study partially confirm the hypothesis of decreased inspiratory muscle function in asthmatics, demonstrating that the adolescents with asthma presented significant reduction in the IME. However, when this group was stratified in relation to nutrition status classification, the reduction demonstrated was present only in overweight and obese adolescents, indicating that the changes in the IME depend of an association between the respiratory condition and the nutritional status alteration, considering that asthmatic adolescents with normal nutritional status did not show significant changes. Also, no significant influence of physical activity levels were found on the analysis performed.

Although the relationship between asthma and obesity is not fully elucidated, both independently influence the respiratory mechanical synchronism. Previous findings demonstrated that obesity induces changes in the elastic properties of the chest wall due to accumulation of fat in the thoracic-abdominal region, showing diaphragm and lung movement limitations and causing a reduction in the functional residual capacity [26-28]. This reduction results in decrease of expiratory reserve volume, which shifts the basal ventilation to smaller airways, generating an increase in airway resistance and consequent expiratory flow limitation [26, 29, 30]. Moreover, the ventilation in low lung volume appears to increase bronchial hyperresponsiveness of the

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airways of these patients [31]. Such changes may contribute to the increased respiratory demand, with higher work of breathing and decreased lung compliance, leading to inspiratory muscle mechanical disadvantage and reduced ability of a muscle to sustain a given task over time [30]. Taken together, these factors could help to explain the presence of IME reduction in the asthmatic individuals with overweight and/or obesity demonstrated in the present study. As far as we know, this is the first study demonstrating these changes and their interaction with nutritional status in the pediatric age group.

So far, there is very little evidence on the IME function in children and adolescents, which makes the results interpretation more difficult. Previous studies in the asthmatic adult population demonstrated that the significant reduction in the endurance may be related to the severity of pulmonary obstruction, malnutrition and due to acute treatment with steroids [12, 32, 33]. Likewise, studies in obese adults demonstrated deleterious effects on both strength and endurance in these subjects [34, 35]. Also, four studies evaluated respiratory endurance in subjects with cystic fibrosis [25, 36-38]. Three of these studies [25, 36, 37] included adolescents and/or adults and only one [38] recruited children and adolescents. One study showed an increased IME that was related to an adaptation of ventilating against the load generated by airway obstruction [36]. On the other hand, two studies demonstrated a decreased IME that was not related to nutrition, airway obstruction, hyperinflation, MIP or exercise capacity [25, 37]. In addition, in the pediatric population, we have also demonstrated that cystic fibrosis patients with no colonization by *P. aeruginosa* and normal lung function presented decreased endurance, a result that correlated with airway resistance [38]. Present results also show that IME is significantly lower in asthmatic adolescents, indicating the influence of respiratory changes on

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inspiratory muscle function. However, no significant differences were found in the IME between children of both groups evaluated. This result contributes to the hypothesis that age may also influence endurance, considering that this impairment seems to be worse and/or only manifest in adolescents. It is possible that in early stages of chronic respiratory diseases, there is less influence of "training" effects induced by airway obstruction.

Although previous studies have already shown an important impairment of the peripheral muscles in asthmatic patients and that this reduction is associated with physical performance [9, 39], it is still poorly understood how physical activity influences IME in asthmatic children and adolescents. As far as we know, this is the first study to evaluate the influence of physical activity levels on IME in this group. Our results showed that no significant differences were found on physical activity levels between control and asthmatic groups. Also, no influence was demonstrated on MIP and IME when participants were separated according to the presence or absence of sedentary behavior in both groups. Previous studies [40, 41] that evaluated the physical activity levels in asthmatic patients by using questionnaires and objective measurements, demonstrated that asthmatic individuals have similar levels of physical activity when compared to healthy children. This finding is likely to be attributed to the characteristics of the studied samples, including lower clinical severity, control of the disease and young age of the population [40]. In addition, we believe that the fact of more than half of present study sample have been considered inactive may have limited the evaluation of physical activity influence on IME.

The assessment of IME in asthmatic subjects with overweight and/or obesity may constitute in an important tool for better assessment and monitoring of inspiratory muscle mechanics in these

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patients, considering the pulmonary changes and the possible increased susceptibility to fatigue and respiratory failure during periods of acute crisis. Also, evidence suggests that pulmonary alterations are present in asthmatic individuals even in exacerbation-free periods [42] and airway remodeling process, including stable structural alterations, may be present and possibly associated with lung function [43], which together with the well-known effects of overweight/obesity could help to explain our results. Although previous studies suggest that the values of normality of IME range between 60 and 80% [25, 34], there are still no reference values for children and adolescents, which makes more difficult the interpretation of these results, considering that the main variables that influence the IME are still unknown. Thus, further studies are needed in order to generate reference values on IME for the pediatric population. The better understanding about the respiratory muscle function may help in early detection of muscular deficits, contributing to the elaboration of more specific muscle training programs.

The results of this study demonstrated that inspiratory muscle strength in children and adolescents with asthma was similar to healthy subjects. Moreover, even when participants were grouped separately according to the age group, there were no significant alterations. These results corroborate with previous studies demonstrating that the preservation of MIP values can be attributed to the fact that many patients with mild or moderate obstructive lung disease do not show significant changes in lung volumes, which prevents the diaphragmatic rectification [2, 14]. On the other hand, some studies demonstrated that muscle strength can be reduced in asthmatic patients and this could be related to lung hyperinflation, which is caused by air trapping as a consequence of airflow obstruction [5, 11, 13]. Furthermore, the continued use of

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high doses of corticosteroids also seems to be associated with the reduction of MIP [4]. In addition, inspiratory muscle strength was fairly studied in cystic fibrosis patients, although contradictory results demonstrating both increased [25, 44-46] and decreased [37, 47-49] levels of MIP were shown. Although the severity of airway obstruction and pulmonary volumes were not assessed in present study, it is possible that the young population studied, with normal values of muscle strength and in a school environment, represent a sample characterized by low pulmonary impairment, which may help to understand the results.

The absence of medical assessment in order to confirm the asthma diagnosis constitutes in a limitation of present study. However, the ISAAC questionnaire [18] has been often used worldwide for epidemiological studies and appears to be sensitive to identify asthmatic subjects, since it gives specific information on the presence of respiratory symptoms and the need of medication use. Moreover, the lack of pulmonary function evaluation and severity assessment in our sample may also represent another limitation. Nevertheless, considering that previous studies have shown that even severe children and adolescents with asthma can present nearly normal lung function values [50, 51], we believe that the absence of information on pulmonary obstruction may have not significantly influenced the results presented here.

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Conclusions

The results of this study demonstrated a reduction in the IME in asthmatic adolescents with overweight and obesity, indicating an association between asthma, nutritional status and respiratory muscle function. On the other hand, the respiratory muscle strength was similar

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between young asthmatics and healthy subjects. Physical activity levels seem not to influence respiratory muscle function in asthma.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Variables	Control group (n=181)	Asthmatic group (n=133)	p
Demographic characteristic			
Age, years	11.4 ± 2.5	11.0 ± 2.2	0.17
Gender male, n (%)	91 (50.2)	63 (47.3)	0.61
Weight, kg	44.5 ± 16.3	42.2 ± 15.3	0.20
Height, cm	146.3 ± 14.5	143.8 ± 12.9	0.10
Caucasian, n (%)	90 (49.7)	65 (48.9)	0.79

Table 1. Characteristics of the studied sample.

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Nutritional conditions			
BMI, absolute	20.1 ± 4.3	19.9 ± 4.9	0.67
BMI, z-score	0.74 ± 1.2	0.69 ± 1.3	0.73

Values expressed as mean ± standard deviation

Gender expressed as absolute and relative frequency

n = total number of participants

BMI: Body Mass Index.

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Variables	Control group (n=181)	Asthmatic group (n=133)	p
MIP			
cmH_2O	-106.5 ± 24.6	- 105.6 ± 20.0	0.73
% predicted	109.3 ± 22.2	112.5 ± 23.3	0.20
IME			
cmH_2O	-58.3 ± 12.3	-56.0 ± 11.3	0.08
% maximum load	62.5 ± 20.9	58.9 ± 15.5	0.09
Physical activity questionnaire			
Minutes per week	290.0 (120.0 – 600.0)	275.0 (112.0 – 600.0)	0.71
Active, n (%)	83 (45.9)	60 (45.1)	0.89
Accelerometer[#]			
Sedentary activity (min/day)	447.3 (368.3- 548.8)	472.6 (429.5- 536.4)	0.35
Light activity (min/day)	172.0 (145.6-231.8)	177.3 (129.2-221.4)	0.65
Moderate to vigorous activity (min/day)	33.3 (13.0 – 71.5)	35.4 (21.1 – 84.2)	0.37

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Table 2. Comparison of MIP, IME and physical activity levels between asthmatic and control groups.

Values expressed as mean ± standard deviation and median (interquartile range)

Physical activity questionnaire (active) expressed as absolute and relative frequency

n = total number of participants

MIP: maximal inspiratory pressure

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IME: inspiratory muscle endurance

[#]Available data from 60 subjects (30 in each studied group).

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Table 3. Comparison of MIP and IME results on different levels of physical activity measured by questionnaire in between asthmatic and control groups.

Variables	Control group (n=181)	Asthmatic group (n=133)	p
MIP (% predicted)			
Active	112.1 ± 24.6	110.1 ± 21.7	0.60
Inactive	108.9 ± 21.9	111.9 ± 23.5	0.39
IME (% maximum load)			
Active	55.9 ± 11.2	56.4 ± 9.7	0.76
Inactive	58.8 ± 12.9	57.6 ±12.9	0.53

Results are expressed as mean ± standard deviation

MIP: maximal inspiratory pressure

IME: inspiratory muscle endurance.

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Table 4. Comparison of MIP and IME results in different nutritional status classifications between asthmatic and control groups.

Variables	Control group (n=181)	Asthmatic group (n=133)	p
MIP (% predicted)			
Eutrophic	109.7 ± 22.4	113.3 ± 21.4	0.24
Overweight	110.5 ± 19.9	116.5 ± 28.2	0.34
Obese	106.4 ± 24.2	103.1 ± 18.3	0.55

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IME (% maximum load)			
Eutrophic	58.1 ± 11.4	56.8 ± 11.3	0.44
Overweight	58.3 ± 13.8	54.8 ± 12.7	0.28
Obese	59.0 ± 13.9	55.0 ± 10.2	0.22

Results are expressed as mean ± standard deviation

MIP: maximal inspiratory pressure

IME: inspiratory muscle endurance.

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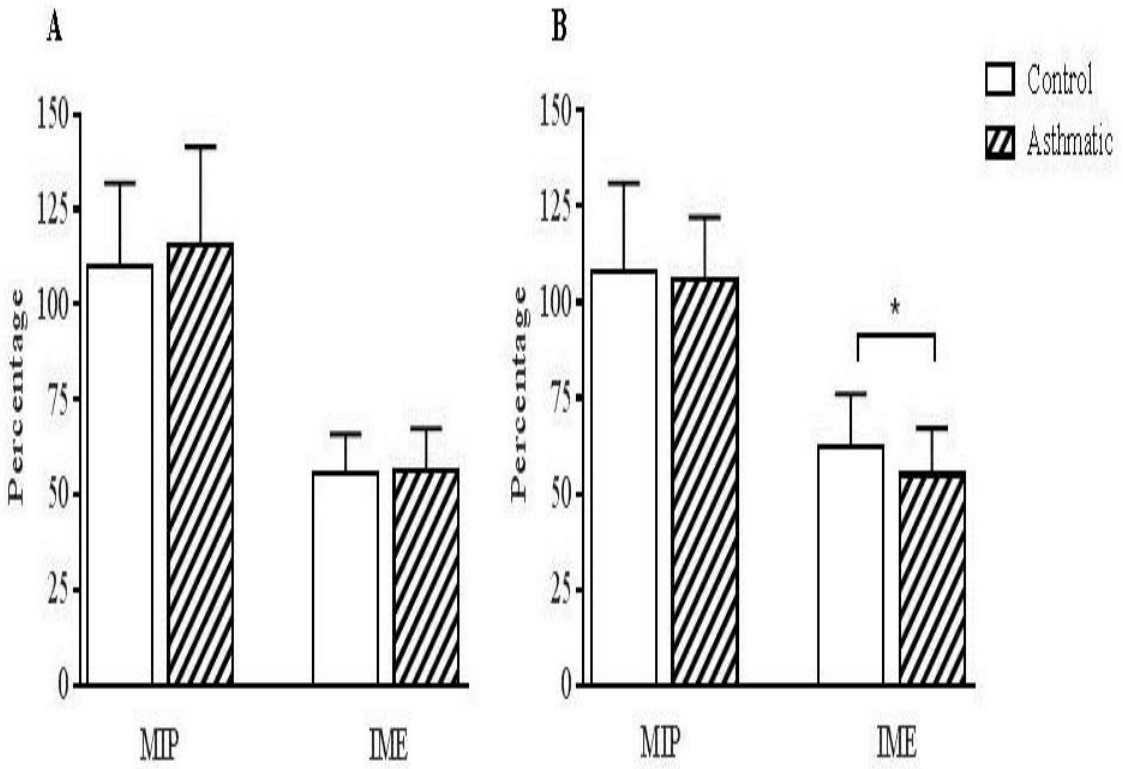

Figure 1. Comparison of MIP (% predicted) and IME (% maximum load) in children (1A) and adolescents (1B) between asthmatic and control subjects. *p=0.003.

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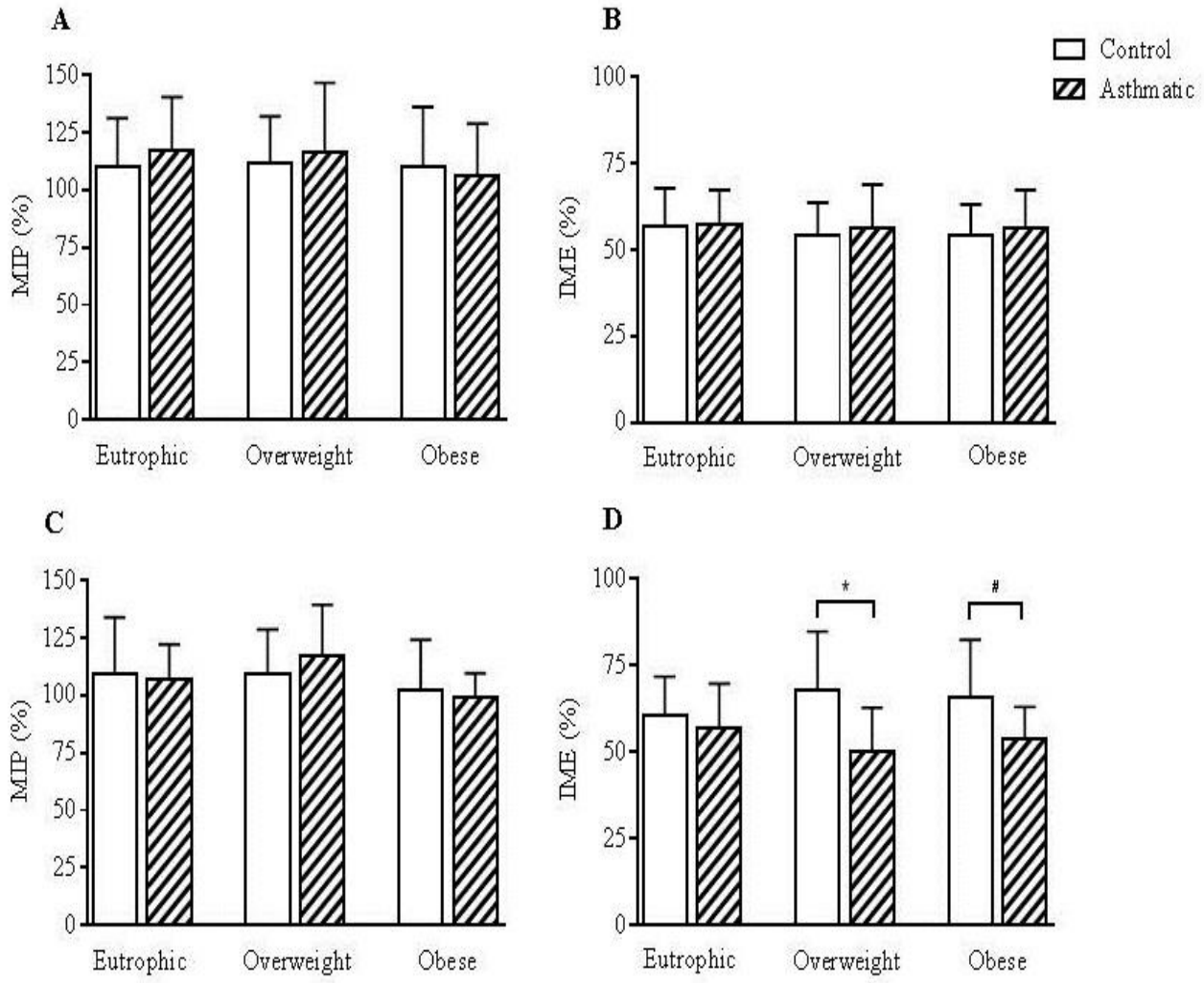

Figure 2. Comparison of MIP (% predicted) and IME (% maximum load) in children (2A, 2B) and adolescents (2C, 2D) with different nutritional status between asthma and control groups. *p=0.042; #p=0.041