Airway inflammatory and spirometric measurements in obese children

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Objectives To investigate the association between obesity and airway inflammation and spirometric parameters in local children.

Design Cross-sectional and observational study.

Setting Paediatric clinics of a university-affiliated teaching hospital in Hong Kong.

Patients Chinese subjects aged 6 to 18 years were recruited from the paediatric clinics. Obesity was defined as being 120% or more of the median weight-for-height.

Main outcome measures Airway inflammation assessed by exhaled nitric oxide concentration; lung function evaluated by measuring forced expiratory flow in 1-second and forced vital capacity using spirometry; and peak expiratory flow rate measured by using a mini-Wright peak flow meter.

Results Fifty-five subjects were recruited into four groups as follows: 13 non-obese controls, 16 obese non-asthmatics, 15 non-obese asthmatics, and 11 obese asthmatics. The median (interquartile range) exhaled nitric oxide concentrations of these groups were 17.6 (14.4-20.9), 33.3 (26.1-75.4), 65.7 (32.0-110.0) and 49.2 (41.1-82.6) parts per billion, respectively (P=0.001 for trend). Post-hoc analysis revealed higher exhaled nitric oxide concentration in the latter three groups (obese and/or asthmatic subjects) than controls (P=0.002). Exhaled nitric oxide concentration did not differ among obese non-asthmatics, non-obese asthmatics, and obese asthmatics (P>0.1 for all). In non-asthmatics, exhaled nitric oxide concentration correlated positively with age (P=0.048), weight-for-height z-score (P=0.001), and forced vital capacity (P=0.009). Weight-for-height z-score correlated positively with forced vital capacity (P=0.041), but inversely with the forced expiratory flow in 1-second/forced vital capacity ratio (P=0.049). Such correlations were not observed in asthmatic children.

Conclusion Increased airway inflammation as revealed by exhaled nitric oxide concentration was found in obese non-asthmatic children. Weight-for-height z-score as an indicator of childhood obesity correlated with exhaled nitric oxide concentration and spirometric parameters in children without asthma. Nonetheless, concomitant obesity does not influence exhaled nitric oxide concentration in asthmatic children. Further studies are needed to identify the pathophysiologic mechanisms for such associations.

Introduction

The prevalence of both asthma and obesity has increased over the past two decades. The highest prevalence rates of asthma in the Asia-Pacific were noted in more affluent locations such as Singapore, Japan, and Hong Kong. In the survey conducted by the Hong Kong Children Health Service, the respective prevalence rates of obesity in boys and girls from local schools increased from 12.7% and 10.4% in 1998 to 14.7% and 12.4% in 2001. A further increase in the obesity rate to 15.9% (boys: 18.1%; girls: 13.9%) in Hong Kong adolescents was observed in 2004. In view of the parallel increase in asthma and obesity, it has been suggested that these two common conditions are related to each other. A number of studies found that obesity was associated with a diagnosis of asthma, respiratory symptoms, and airway hyperresponsiveness. The review by Weiss proposed several mechanistic...
One likely explanation is that obesity, being a proinflammatory state, is associated with increased adipokines, and may up-regulate asthmatic airway inflammation. In recent years, measurement of nitric oxide in exhaled breath offers a non-invasive approach to assessing airway inflammation. Increased exhaled nitric oxide (eNO) concentration was found in patients with untreated asthma, and decreased following corticosteroid treatment. The concentration of eNO showed positive correlations with measures of eosinophilic inflammation in airway mucosa and eosinophilia in induced sputum. As airway inflammation is a cornerstone of childhood asthma, it appears prudent to define the confounding effects of obesity on airway inflammation in asthmatic patients. Such data can help to delineate whether obesity influences the clinical utility of eNO in diagnosing and monitoring asthma. From the above review, Weiss also suggested that obesity may be associated with asthma-like symptoms due to altered lung mechanics. Spirometry and peak expiratory flow (PEF) are common clinical tools for measuring lung volumes and the extent of airflow limitation. In this study, we hypothesised that the relationship between childhood asthma and obesity may be mediated either by abnormal airway inflammation or altered lung mechanics. We performed eNO concentration and lung function testing in obese and non-obese Chinese children to look for any evidence of altered airway inflammation and/or lung mechanics.

**Methods**

**Study population**

Chinese subjects aged 6 to 18 years were recruited from paediatric clinics of a university-affiliated teaching hospital. Each subject's asthma and allergy status were ascertained using the Chinese International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire, and grouped under four categories. These were: (1) non-obese, non-asthmatics (controls); (2) obese non-asthmatics; (3) non-obese asthmatics; and (4) obese asthmatics. The diagnosis of asthma in patients in groups 3 and 4 was made according to American Thoracic Society (ATS) guidelines. Specifically, these patients had a 6-month or longer history of recurrent chest symptoms, such as: cough, dyspnnea and wheeze, that were relieved by bronchodilator treatment. They also demonstrated reversible airflow limitation or bronchial hyperresponsiveness (BHR) to methacholine inhalation.

Obesity was defined according to the World Health Organization (WHO) criterion of weight exceeding 120% of the median weight-for-height. Wasting was defined as weight lower than 80% of the median weight-for-height, and such subjects were excluded. The weight-for-height z-score was based on published local growth standards. Thus the weight-for-height z-score was calculated as: (measured weight – expected mean weight for subject’s height and sex) / expected standard deviation in weight for subject’s height and sex. Body mass index (BMI) was also calculated as: weight in kg / height² in m².

Subjects with domestic tobacco smoke exposure, co-existing illnesses (eg systemic lupus erythematosus, bronchiectasis, epilepsy), allergic rhinitis, or pulmonary hypertension were excluded, as were asthmatics who had received inhaled corticosteroids (ICS) within 1 month. All subjects had to be free of any symptom of upper respiratory tract infection for 1 week before study. They were also questioned about recent food intake before the study procedures, because food and beverage might alter eNO readings. Informed consent was obtained from the subjects’ parents, and the entire study was performed in accordance with the ethical guidelines of the institutional review board.
approved by the Clinical Research Ethics Committee of our University. During the same clinic visit, each subject’s body weight and height were measured using an electronic device (Model 708; Seca, Germany) and a Harpenden stadiometer. All subjects underwent the same sequence of eNO testing followed by spirometric and PEF measurements.

### Exhaled nitric oxide measurement

The eNO concentration was measured online at an expiratory flow rate of 50 mL/s using a chemiluminescence analyser (NOA280i; Sievers Instruments, Boulder/CO/US) according to the European Respiratory Society (ERS)/ATS standard, and recorded as the average of three reproducible measurements.

### Spirometry

All subjects underwent spirometry (MasterScreen; Jaegers, Würzburg, Germany) according to ERS/ATS guidelines to measure the pre-bronchodilator forced expiratory volume in 1-second (FEV₁), forced vital capacity (FVC), forced expiratory flow at 25% (FEF25), 50% (FEF50) and 75% (FEF75) of vital capacity. Except for the FEV₁/FVC ratio which was taken as the best of three values, spirometric parameters were recorded as the best predicted percentage values as compared to local reference values.

### Peak expiratory flow

Peak expiratory flow was recorded as the best of three maximal expiratory efforts using a mini-Wright peak flow meter. This test was performed after eNO and spirometric measurements, and the results were compared to local PEF reference values.

### Statistical analyses

Data were expressed as median and interquartile ranges (IQRs), unless otherwise stated. The χ² test was used to compare categorical variables, and the Kruskal-Wallis test to analyse trends for numerical variables across all four subject groups, and a post-hoc analysis between the two subgroups was performed using the Mann-Whitney U test. The correlations pertaining to eNO concentrations, lung function variables, and anthropometric data (weight, height, weight-for-height z-score, and BMI) were analysed by Spearman correlations. All analyses were performed using the Statistical Package for the Social Sciences (Windows version 14.0; SPSS Inc, Chicago [IL], US), and a P value of lower than 0.05 was considered statistically significant.

### Results

#### Subjects

Fifty-five children, consisting of 13 controls (group

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**TABLE 1. Demographic and clinical characteristics of our subjects**

<table>
<thead>
<tr>
<th>Demographic/clinical characteristic</th>
<th>NONA (n=13)</th>
<th>ONA (n=16)</th>
<th>NOA (n=15)</th>
<th>OA (n=11)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>13.3 (9.4-17.0)</td>
<td>15.0 (12.1-16.2)</td>
<td>14.9 (12.9-16.3)</td>
<td>13.6 (8.0-17.3)</td>
<td>0.707</td>
</tr>
<tr>
<td>No. (%) of males</td>
<td>6 (46)</td>
<td>10 (63)</td>
<td>10 (67)</td>
<td>7 (64)</td>
<td>0.701</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>41.6 (26.7-62.6)</td>
<td>85.6 (49.2-94.9)</td>
<td>46.8 (41.2-49.8)</td>
<td>53.2 (32.9-83.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.55 (1.32-1.70)</td>
<td>1.60 (1.50-1.75)</td>
<td>1.63 (1.56-1.67)</td>
<td>1.49 (1.27-1.69)</td>
<td>0.430</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>17.3 (15.7-21.5)</td>
<td>31.5 (24.1-33.4)</td>
<td>17.3 (17.0-18.2)</td>
<td>23.4 (20.5-28.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight-for-height z-score</td>
<td>0.09 (-0.57 to 0.82)</td>
<td>3.72 (2.23 to 4.44)</td>
<td>-0.27 (-0.53 to -0.07)</td>
<td>2.06 (1.91 to 2.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eNO (ppb)</td>
<td>17.6 (14.4-20.9)</td>
<td>33.3 (26.1-75.4)</td>
<td>65.7 (32.0-110.0)</td>
<td>49.2 (41.1-82.6)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

#### Lung function parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NONA (n=13)</th>
<th>ONA (n=16)</th>
<th>NOA (n=15)</th>
<th>OA (n=11)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ predicted (%)</td>
<td>95 (87-107)</td>
<td>104 (96-108)</td>
<td>91 (83-98)</td>
<td>100 (91-107)</td>
<td>0.044</td>
</tr>
<tr>
<td>FVC predicted (%)</td>
<td>90 (78-101)</td>
<td>102 (92-107)</td>
<td>88 (85-93)</td>
<td>103 (88-112)</td>
<td>0.040</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>92 (86-96)</td>
<td>86 (822-91)</td>
<td>87 (85-93)</td>
<td>85 (81-88)</td>
<td>0.105</td>
</tr>
<tr>
<td>FEF25 predicted (%)</td>
<td>105 (67-117)</td>
<td>901 (77-106)</td>
<td>91 (73-101)</td>
<td>96 (88-105)</td>
<td>0.902</td>
</tr>
<tr>
<td>FEF50 predicted (%)</td>
<td>98 (78-136)</td>
<td>95 (85-109)</td>
<td>83 (70-101)</td>
<td>85 (71-99)</td>
<td>0.158</td>
</tr>
<tr>
<td>FEF75 predicted (%)</td>
<td>83 (53-110)</td>
<td>79 (67-107)</td>
<td>73 (55-90)</td>
<td>62 (52-92)</td>
<td>0.163</td>
</tr>
<tr>
<td>PEF predicted (%)</td>
<td>112 (106-126)</td>
<td>87 (79-112)</td>
<td>101 (88-111)</td>
<td>117 (99-142)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

* NONA denotes non-obese non-asthmatic, ONA obese non-asthmatic, NOA non-obese asthmatic, OA obese asthmatic, eNO exhaled nitric oxide concentration, ppb parts per billion, FEV₁ forced expiratory volume in 1-second, FVC forced vital capacity, FEF25/50/75 forced expiratory flow at 25%/50%/75%, and PEF peak expiratory flow

† Data are shown in median (interquartile range), unless otherwise stated
‡ Analysed by Kruskal-Wallis test, except for gender which was analysed by χ²
1), 16 obese non-asthmatics (group 2), 15 non-obese asthmatics (group 3), and 11 obese asthmatics (group 4), were recruited. Table 1 summarises their demographic and clinical characteristics. Concerning the diagnostic criteria for asthma in these 26 cases, 15 had reversible airflow limitation, four had BHR, and seven had both features. The median (IQR) FEV₁ reversibility in those with reversible airflow limitation was 15.7% (12.7-19.2%), whereas the provocative dose of methacholine causing a 20% drop in FEV₁ among patients with BHR was 1.20 (0.43-2.00) µmol. The four BHR subjects were matched for age and sex, and their median weight-for-height z-scores were 0.10, 3.72, -0.27, and 2.06.

**Exhaled nitric oxide measurement**

The median eNO concentrations for groups 1, 2, 3 and 4 were 17.6 parts per billion (ppb), 33.3 ppb, 65.7 ppb, and 49.2 ppb, respectively (P=0.001 for trend; Fig 1). Using the Mann Whitney U test, the eNO concentration was significantly higher in group 2 (P=0.002), group 3 (P<0.001) and group 4 (P=0.001) than in group 1. The eNO concentration did not differ between groups 2 and 4 (P= 0.141), groups 3 and 4 (P=0.612), and groups 2 and 3 (P=0.123).

**Spirometry and peak expiratory flow measurements**

The FEV₁ and FVC were significantly different among subjects in the four groups (P=0.044 and 0.040 for trend, respectively). The FEV₁ differed mainly between groups 2 and 3 (P=0.005), whereas the differences in FVC were significant between groups 2 and 3, and groups 3 and 4 (P=0.018 for both). There was no difference between the four groups with respect to FEF25, FEF50, and FEF75. The respective median PEF rates for the four groups were 112%, 87%, 101%, and 117% (P=0.023 for trend). This difference was caused by lower PEF values in obese non-asthmatics (group 2) and non-obese asthmatics (group 3) when each was compared to the controls in group 1 (P=0.005 and 0.025, respectively).

**Correlations between clinical and lung function variables**

In view of the above-mentioned statistical difference in the weight-for-height z-score and other parameters, we analysed correlations between variables in subgroups of children without asthma (groups 1 and 2) and with asthma (groups 3 and 4). Table 2 summarises Spearman correlation coefficients for factors associated with eNO concentration and weight-for-height z-score in 29 non-asthmatic children. Among these subjects, eNO concentration showed positive correlations with age (P=0.048), weight-for-height z-score (P=0.001; Fig 2), and FVC (P=0.009). Weight-for-height z-score correlated positively with FVC (P=0.041) but inversely with FEV₁/FVC ratio (P=0.049; Fig 3). On the contrary, there was

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**TABLE 2.** Spearman correlation analysis of factors associated with exhaled nitric oxide (eNO) concentrations and weight-for-height z-scores among non-asthmatic subjects

<table>
<thead>
<tr>
<th>Factor</th>
<th>eNO</th>
<th>Weight-for-height z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.391</td>
<td>0.048</td>
</tr>
<tr>
<td>Weight</td>
<td>0.536</td>
<td>0.006</td>
</tr>
<tr>
<td>Height</td>
<td>0.389</td>
<td>0.054</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.521</td>
<td>0.008</td>
</tr>
<tr>
<td>Weight-for-height z-score</td>
<td>0.613</td>
<td>0.001</td>
</tr>
<tr>
<td>eNO</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Lung function parameters**

<table>
<thead>
<tr>
<th>Factor</th>
<th>p</th>
<th>eNO value</th>
<th>Weight-for-height z-score value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁</td>
<td>0.375</td>
<td>0.065</td>
<td>0.262</td>
</tr>
<tr>
<td>FVC</td>
<td>0.510</td>
<td>0.009</td>
<td>0.388</td>
</tr>
<tr>
<td>FEV₁/FVC ratio</td>
<td>-0.378</td>
<td>0.062</td>
<td>-0.375</td>
</tr>
<tr>
<td>FEF25</td>
<td>0.011</td>
<td>0.959</td>
<td>-0.021</td>
</tr>
<tr>
<td>FEF50</td>
<td>0.049</td>
<td>0.817</td>
<td>-0.034</td>
</tr>
<tr>
<td>FEF75</td>
<td>0.057</td>
<td>0.787</td>
<td>-0.103</td>
</tr>
<tr>
<td>PEF</td>
<td>-0.078</td>
<td>0.718</td>
<td>-0.378</td>
</tr>
</tbody>
</table>

* FEV₁ denotes forced expiratory volume in 1-second, FVC forced vital capacity, FEF25/50/75 forced expiratory flow at 25%/50%/75%, and PEF peak expiratory flow.
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no significant correlation between anthropometric parameters and eNO concentrations or spirometric variables in 26 children with asthma.

Discussion

As aeroallergen sensitisation is an important intermediate phenotype of childhood asthma, our group recently studied the relationship between atopy, obesity indices, and systemic inflammatory biomarkers in 486 Chinese schoolchildren. These children were recruited in a population-based study on the epidemiology of obesity. We found that obesity status was not associated with asthma, allergic rhinitis or eczema, and atopy was not associated with age-adjusted BMI or waist circumference. Besides, the rates of both atopy and the presence of allergen-specific immunoglobulin E did not differ between overweight or obese children and those with normal BMI. These results suggested that the epidemiological association between childhood obesity and asthma was not mediated through enhanced allergen sensitisation, which prompted us to investigate the more direct effects of obesity on airway inflammation and lung mechanics.

Obesity is a proinflammatory state in which increased levels of leptin and proinflammatory cytokines (eg interleukin-6, interleukin-1, tumour necrosis factor-α) might up-regulate inflammation in the airway. There are limited data addressing whether obesity is associated with more intense airway inflammation. In a study of healthy non-smoking adults, eNO concentration (a marker of airway inflammation) correlated positively with BMI. On the contrary, our group could not detect any significant correlation between nitric oxide and leukotriene B4 concentrations in the exhaled breath of Chinese children and BMI or weight-to-height z-score. Another study extended our findings to Caucasian children. From the above, it is evident that most studies treated obesity indices as continuous variables and correlated them with airway inflammatory markers. Nonetheless, these studies lacked a group of significantly obese subjects to examine outcomes.

Santamaria et al studied 50 children with BMI values higher than the 95th percentile for age and sex, and 50 non-obese controls. Among obese children, median BMI and BMI z-scores were 34.5 kg/m² and 2.51, respectively, but there was an absence of airway inflammation as assessed by eNO concentration, even when their asthma or atopy status were taken into account. Nonetheless, their study was limited by the confounding effects of concurrent allergies among their subjects; 18 (36%) and 11 (22%) of the children had a history of asthma and seasonal rhinitis, respectively, and in six, asthma was active. Despite ours being a small sample, the present case-control study recruited 27 children who were obese (according to WHO criteria) and had asthma status classified (according to the standardised ISAAC questionnaire). Our results convincingly demonstrated that in obese children with or without asthma, eNO concentration was significantly higher than that in non-obese controls. Exhaled nitric oxide concentrations also yielded a positive correlation with weight-for-height z-score in children without asthma. These findings support the presence of increased airway inflammation in childhood obesity.
We found that eNO concentration did not differ between obese and non-obese asthmatics, nor did it correlate with anthropometric variables or the lung function of our asthmatic children. In our small study, obesity did not appear to be an important modulator of airway inflammation in childhood asthma. On the other hand, our results cast doubt on the clinical utility of measuring eNO concentration in obese children whenever asthma is suspected.

Obesity adversely affected lung volumes (as measured by spirometry) and PEF in non-asthmatic children. Moreover, FVC showed a positive correlation with weight-for-height z-score, as expected from published results of lung volumes and anthropometric parameters such as BMI and standing height.24,25 On the other hand, in the same group of subjects, the FEV/FVC ratio showed an inverse correlation with weight-for-height z-score. Such significant correlations were not observed in children with asthma. We also observed lower PEF rates in obese non-asthmatics than in controls, which was in keeping with an intervention study on obesity, showing that PEF increased following weight reduction.26 Another study that investigated the effects of weight loss on PEF variability, airway obstruction and lung volumes in obese patients with asthma, revealed a significant increase in morning PEF values.27 These findings pertaining to obesity, altered lung volume and airflow may be due to extraluminal compression of airways due to increase in soft tissues, as well as airway narrowing due to increase in inflammatory mediators (such as C-reactive protein and leptin). Notably, this study failed to detect any significant difference in FEF25, FEF50 and FEF75 between controls and obese subjects, which suggests that childhood obesity is not associated with small airway obstruction. However, thoracic computed tomography might be better at delineating the extent of air trapping and obstruction in small airways.28

Future studies should investigate airway inflammatory markers other than eNO in relation to obesity. Exhaled breath condensate (EBC) analysis is an emerging, non-invasive method for assessing airway inflammation. Airway inflammation increases the acidity of EBC, through the release of myeloperoxidase by neutrophils, resulting in the formation of the highly volatile hypochlorous acid. Release of HCl is also mediated by vacuolar hydrogen-adenosine triphosphatase in the vesicles of macrophages and eosinophils.29 Our recent studies revealed that EBC acidity and biomarkers such as leukotriene B4 were significantly increased in asthmatic children.30 We went on to show that biomarkers in EBC represent a distinct dimension, when compared to inflammatory mediators present in the circulation.31 It would be interesting to investigate whether childhood obesity is associated with altered presence of inflammatory biomarkers in EBC.

The main limitation of our study relates to its small sample size, leading to possible false-positive results between groups due to outliers. We attempted to reduce this problem by resorting to non-parametric statistical tests. Although we did encounter several significant results, the sample of 55 subjects may also have been insufficiently powered to detect differences in FEF25, FEF50 and FEF75 owing to the large variations in these parameters. Similarly, due to our small sample size, this study was not adequately powered to allow adjustment of outcomes for confounders of eNO concentration, such as environmental tobacco exposure and ambient air pollution. The observed association between obesity and lower PEF in non-asthmatics was limited by the fact that PEF is effort-dependent, and might not be a reliable measure in obese children. In addition, our study did not investigate whether increased airway inflammation in obese children was steroid-responsive, as our asthmatics were not currently in receipt of ICS treatment. Another group of obese and ICS-treated patients would be needed to address this issue.

Conclusions

This study demonstrated increased eNO concentrations compared to controls even in obese Chinese children without asthma, supporting our hypothesis that childhood obesity is associated with increased airway inflammation. The degree of obesity in our non-asthmatic children also correlated with eNO and several other lung function variables. By contrast, concomitant obesity did not appear to influence the relationship between childhood asthma and airway inflammation. Further studies with larger sample sizes are needed to define the exact relationship between childhood obesity, asthma, and airway inflammation and to delineate their underlying pathophysiologic mechanisms.

Acknowledgements

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References


14. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, November 1986. Am Rev Respir Dis 1987;136:225-44.

