Obesity is a risk for asthma and wheeze but not airway hyperresponsiveness

L M Schachter, G M Salome, J K Peat, A J Woolcock

Abstract

Background—A study was undertaken to assess whether the recent increases in prevalence of both asthma and obesity are linked and to determine if obesity is a risk factor for diagnosed asthma, symptoms, use of asthma medication, or airway hyperresponsiveness.

Methods—Data from 1971 white adults aged 17–73 years from three large epidemiological studies performed in NSW were pooled. Doctor diagnosis of asthma ever, history of wheeze, and medication use in the previous 12 months were obtained by questionnaire. Body mass index (BMI) in kg/m² was used as a measure of obesity. Airway hyperresponsiveness (AHR) was defined as dose of <3.9 µmol histamine required to provoke a fall in forced expiratory volume in one second (FEV₁) of 20% or more (PD₂₀FEV₁). Adjusted odds ratios (OR) were obtained by logistic regression.

Results—After adjusting for atopy, age, sex, smoking history, and family history, severe obesity was a significant risk factor for recent asthma (OR 2.04, p=0.048), wheeze in the previous 12 months (OR 2.6, p=0.001), and medication use in the previous 12 months (OR 2.83, p=0.005), but not for AHR (OR 0.87, p=0.78). FEV₁ and forced vital capacity (FVC) were significantly reduced in the group with severe obesity, but FEV₁/FVC ratio, peak expiratory flow (PEF), and mid forced expiratory flow (FEF₂₅₋₇₅) were not different from the group with normal BMI. The underweight group (BMI <18.5 kg/m²) had increased symptoms of shortness of breath, increased airway responsiveness, and reduced FEV₁, FVC, PEF, and FEF₂₅₋₇₅ with similar use of asthma medication as subjects in the normal weight range.

Conclusions—Although subjects with severe obesity reported more wheeze and shortness of breath which may suggest a diagnosis of asthma, their levels of atopy, airway hyperresponsiveness, and airway obstruction did not support the suggestion of a higher prevalence of asthma in this group. The underweight group appears to have more significant respiratory problems with a higher prevalence of symptoms, reduced lung function, and increased airway responsiveness without an increase in medication usage. This group needs further investigation.

Keywords: obesity; asthma; airway hyperresponsiveness; wheeze

In the past two decades there has been a significant increase in the prevalence of both asthma and obesity worldwide. Previous cross sectional studies have shown an association between obesity and both wheezing and diagnosed asthma. However, the nature of the relationship has not been established and, furthermore, if the association is causal, the direction of causation remains unknown.

There are several mechanisms by which obesity could cause either respiratory symptoms or more fundamental changes in the airways leading to asthma. In obese people symptoms of breathlessness and wheeze may be due to increased work of breathing. Alternatively, obesity may have a direct effect on the mechanical behaviour of the respiratory system by altering lung volume, airway calibre, or respiratory muscle strength. In obese subjects functional residual capacity (FRC) is reduced by approximately 500 ml. Changes in lung volume of this magnitude induced by voluntarily breathing below FRC and changes in posture have been shown to increase airway responsiveness in normal subjects.

On the other hand, factors associated with asthma could lead to an increase in obesity. Inactivity or inability to exercise in asthmatic subjects or those with atopy could cause weight gain. Medication required for treatment of severe asthma such as oral steroids may cause weight gain, which may cause asthmatic patients to become obese or to worsen pre-existing obesity.

In this paper we report an analysis of cross sectional data in a large population of white Australian adults. The aim of this analysis was to determine if obesity, as measured by body mass index (BMI), is associated firstly with an increase in the prevalence of wheeze, diagnosed asthma, or medication use for asthma and, secondly, with a reduction in lung function or an increase in the prevalence of atopy or airway responsiveness to histamine.
Table 1  Anthropometric and questionnaire data for subjects classified according to body mass index (BMI)

<table>
<thead>
<tr>
<th></th>
<th>Underweight (BMI &lt;18.5)</th>
<th>Normal (BMI 18.5–24.9)</th>
<th>Overweight (BMI 25.0–29.9)</th>
<th>Moderate obesity (BMI 30.0–34.9)</th>
<th>Severe obesity (BMI ≥35.0)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of subjects</td>
<td>52</td>
<td>1127</td>
<td>592</td>
<td>141</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>% male</td>
<td>17.3%</td>
<td>37.9%</td>
<td>60.1%</td>
<td>48.9%</td>
<td>30.5%</td>
<td>0.000</td>
</tr>
<tr>
<td>Age (years)</td>
<td>26.7 (24.4 to 29.0)</td>
<td>32.3 (31.7 to 32.9)</td>
<td>39.5 (35.2 to 36.6)</td>
<td>47.2 (39.0 to 54.4)</td>
<td>41.4 (38.7 to 54.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>% with family history of asthma</td>
<td>52.8 (39.4 to 66.2)</td>
<td>42.1 (39.2 to 45.0)</td>
<td>45.3 (41.3 to 49.3)</td>
<td>47.2 (39.0 to 54.4)</td>
<td>41.4 (38.7 to 54.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>% wheeze in last 12 months</td>
<td>33.3 (20.5 to 46.1)</td>
<td>20.4 (18.0 to 22.8)</td>
<td>19.8 (16.6 to 23.0)</td>
<td>25.9 (18.7 to 33.1)</td>
<td>37.9 (25.5 to 50.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>% SOBOE in last 12 months</td>
<td>40 (20.8 to 59.2)</td>
<td>17.7 (15.0 to 20.4)</td>
<td>21.2 (17.6 to 24.8)</td>
<td>29.2 (21.1 to 37.3)</td>
<td>49.0 (35.3 to 62.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>% recent asthma</td>
<td>17.0 (6.8 to 27.2)</td>
<td>12.3 (10.4 to 14.2)</td>
<td>10.4 (7.9 to 12.9)</td>
<td>14.6 (8.8 to 20.4)</td>
<td>21.7 (11.2 to 32.2)</td>
<td>0.06</td>
</tr>
<tr>
<td>% used medication in last 12 months</td>
<td>11.4 (2.8 to 20.0)</td>
<td>14.3 (12.3 to 16.3)</td>
<td>13.4 (10.7 to 16.1)</td>
<td>15.5 (9.5 to 21.5)</td>
<td>35.3 (23.1 to 47.5)</td>
<td>0.028</td>
</tr>
<tr>
<td>% current smoker</td>
<td>25 (13.2 to 36.8)</td>
<td>15.4 (13.3 to 17.5)</td>
<td>17.4 (14.3 to 20.5)</td>
<td>18.4 (12.0 to 24.8)</td>
<td>10.2 (2.5 to 17.9)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

SOBOE = shortness of breath on exertion.
Values are means and 95% confidence intervals or prevalence and 95% confidence intervals.
* Atopy was defined as a positive reaction of ≥3 mm to any of a panel of eight common Aeroallergens.

Table 2  Adjusted odds ratio for symptoms and airway hyperresponsiveness (AHR) in atopic and non-atopic subjects compared with a group of normal weight

<table>
<thead>
<tr>
<th></th>
<th>Underweight (BMI &lt;18.5)</th>
<th>Overweight (BMI 25–29.9)</th>
<th>Moderate obesity (BMI 30–34.9)</th>
<th>Severe obesity (BMI ≥35.0)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheeze in last 12 months</td>
<td>1.75 (0.80 to 3.82)</td>
<td>0.97 (0.68 to 1.38)</td>
<td>1.24 (0.70 to 2.20)</td>
<td>1.71 (0.73 to 4.02)</td>
<td></td>
</tr>
<tr>
<td>Atopics</td>
<td>0.57 (0.16 to 2.05)</td>
<td>1.31 (0.86 to 2.00)</td>
<td>2.37 (1.23 to 4.56)</td>
<td>5.10 (2.27 to 11.45)</td>
<td></td>
</tr>
<tr>
<td>Non-atopics</td>
<td>1.42 (0.59 to 3.45)</td>
<td>0.99 (0.65 to 1.51)</td>
<td>1.21 (0.62 to 2.35)</td>
<td>1.43 (0.54 to 3.79)</td>
<td></td>
</tr>
<tr>
<td>Recent asthma</td>
<td>0.38 (0.05 to 3.02)</td>
<td>0.90 (0.47 to 1.72)</td>
<td>2.21 (0.92 to 5.33)</td>
<td>4.08 (1.52 to 10.98)</td>
<td></td>
</tr>
<tr>
<td>SOBOE</td>
<td>2.34 (0.71 to 7.76)</td>
<td>1.18 (0.76 to 1.84)</td>
<td>1.89 (0.98 to 3.64)</td>
<td>2.96 (1.15 to 7.62)</td>
<td></td>
</tr>
<tr>
<td>Atopics</td>
<td>2.99 (0.86 to 10.31)</td>
<td>1.92 (1.23 to 2.97)</td>
<td>2.87 (1.51 to 5.49)</td>
<td>8.83 (3.79 to 20.58)</td>
<td></td>
</tr>
<tr>
<td>Non-atopics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication usage in previous 12 months</td>
<td>0.93 (0.37 to 2.32)</td>
<td>0.87 (0.59 to 1.27)</td>
<td>0.87 (0.47 to 1.64)</td>
<td>1.76 (0.75 to 4.16)</td>
<td></td>
</tr>
<tr>
<td>Atopics</td>
<td>0.85 (0.23 to 3.06)</td>
<td>1.15 (0.72 to 1.85)</td>
<td>1.80 (0.87 to 3.75)</td>
<td>3.30 (1.40 to 7.81)</td>
<td></td>
</tr>
<tr>
<td>Non-atopics</td>
<td>2.08 (0.91 to 4.73)</td>
<td>0.72 (0.46 to 1.12)</td>
<td>1.08 (0.56 to 2.08)</td>
<td>1.01 (0.36 to 2.81)</td>
<td></td>
</tr>
<tr>
<td>AHR (DRR &gt;8.1)</td>
<td>1.62 (0.34 to 7.70)</td>
<td>1.03 (0.44 to 2.40)</td>
<td>0.51 (0.05 to 3.88)</td>
<td>No subjects in this group</td>
<td></td>
</tr>
</tbody>
</table>

BMI = body mass index; SOBOE = shortness of breath on exertion; AHR = airway hyperresponsiveness; DRR = dose response ratio.
improved slightly during the challenge and this had a zero or negative DRR value, a constant of 3 was added to all DRR values to return a positive value for logarithmic conversion. Subjects with a fall in FEV1 of 20% or more with \( \leq 3.9 \) µmol histamine were defined as having airway hyperresponsiveness (AHR), which is equivalent to a DRR of >8.1. To compare those with and without AHR we used DRR as the measure of airway responsiveness in this study.

**BODY MASS INDEX**

Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in metres (kg/m\(^2\)). According to the WHO classification, a BMI of <18.5 kg/m\(^2\) is underweight, 18.5–24.9 kg/m\(^2\) is normal, and 25.0–29.9 kg/m\(^2\) is overweight. A BMI of \( \geq 30 \) kg/m\(^2\) is classified as obese and this group was further divided into moderate obesity (30.0–34.9 kg/m\(^2\)), severe obesity (35.0–39.9 kg/m\(^2\)), and very severe obesity (\( \geq 40.0 \) kg/m\(^2\)). In our sample only 12 subjects had a BMI of \( \geq 40 \) kg/m\(^2\) and their lung function, symptoms, and airway responsiveness were not significantly different from the group with severe obesity (BMI 35.0–39.9 kg/m\(^2\)). Data from subjects with very severe obesity (BMI \( \geq 40 \) kg/m\(^2\)) and severe obesity (BMI 35–39.9 kg/m\(^2\)) were combined for analysis. The groups of BMI were further subdivided to assess whether the effects on asthma were seen across the entire distribution of BMI or whether there were incremental effects as have been suggested in previous studies. As the results of the repeat analysis were no different from those in the initial analysis, the WHO classification of BMI groups was used.

**STATISTICAL METHODS**

Data were analysed using the statistical package SPSS (SPSS Inc, IL, USA). Geometric mean values are reported for DRR values, which were converted to base 10 logarithms before analysis. For all analyses p values of <0.05 were regarded as significant. Prevalence rates and mean values are reported with 95% confidence intervals. The \( \chi^2 \) test was used to determine the significance of differences in prevalence across all five BMI groups and between different BMI groups compared with the normal group (BMI 18.5–24.9 kg/m\(^2\)). Logistic regression was used to compute odds ratio for current asthma, wheeze, and AHR in the presence of obesity and adjusted for family history of asthma, age, sex, atopy status, and smoking history. Pearson's correlation coefficient was used to assess correlation between BMI and airway responsiveness.

A one way ANOVA was used to analyse means of grouped data. Duncan's post hoc analysis using the pooled variance was also performed to correct for multiple comparisons when comparing specific groups. We did not perform trend tests as the data did not suggest that there was a dose response trend. We also chose not to do multiple comparisons in order to reduce the type 1 error rate.

**Results**

Data from 1971 white adults were analysed. The response rate for Belmont was 57%, for Lismore was 66%, and for Wagga Wagga was 62%. All non-responders were telephoned and asked about their medication use for asthma. The rates of medication use between respondents and non-responders were not significantly different in any region, although they suggest that current asthmatics were slightly less likely to attend so that the prevalence rates reported may be an underestimate of the true disease rate. The BMI distribution in our sample (table 1) was similar to the distribution in the general population in Australia.

The prevalence of symptoms and medication use differed significantly between groups classified by BMI (table 1). Further analysis showed that, compared with normal weight subjects, subjects with severe obesity had a significantly higher prevalence of wheeze (\( \chi^2 = 16.65, p<0.01, \) fig 1), shortness of breath on exertion (\( \chi^2 = 39.40, p<0.001 \)), and medication use for asthma in the previous 12 months (fig 1).

**Table 3** Lung function and airway responsiveness as classified by body mass index (BMI)

<table>
<thead>
<tr>
<th>BMI Class</th>
<th>Underweight (BMI &lt;18.5)</th>
<th>Normal (BMI 18.5–24.9)</th>
<th>Overweight (BMI 25.0–29.9)</th>
<th>Moderate obesity (BMI 30.0–34.9)</th>
<th>Severe obesity (BMI ≥35.0)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 (% pred)</td>
<td>95.0 (91.9 to 98.1)*</td>
<td>102.0 (101.3 to 102.7)</td>
<td>100.5 (99.5 to 101.5)</td>
<td>99.2 (97.3 to 101.1)</td>
<td>98.1 (95.2 to 101.0)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FVC (% pred)</td>
<td>94.2 (91.5 to 96.9)*</td>
<td>99.4 (98.7 to 101.1)</td>
<td>97.4 (96.4 to 98.4)</td>
<td>95 (93.1 to 97.9)</td>
<td>93.6 (90.7 to 96.5)*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PEV/FVC (%)</td>
<td>86.4 (84.3 to 88.5)</td>
<td>102.2 (101.1 to 103.3)</td>
<td>105.3 (104.1 to 106.9)</td>
<td>102.2 (103.2 to 109.2)</td>
<td>106.2 (101.8 to 110.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEF25–75 (% pred)</td>
<td>85.8 (85.7 to 91.9)*</td>
<td>97.1 (95.7 to 98.5)</td>
<td>98.5 (96.5 to 100.5)</td>
<td>101.2 (97.4 to 107.4)</td>
<td>101.2 (94.3 to 108.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>DRR (measure of AR)</td>
<td>6.32 (4.88 to 8.18)*</td>
<td>4.71 (4.52 to 4.92)</td>
<td>4.42 (4.23 to 4.62)</td>
<td>4.72 (4.28 to 5.21)</td>
<td>4.66 (4.08 to 5.33)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; PEF = peak expiratory flow; FEF25–75 = mid forced expiratory flow; DRR = dose response rate; AR = airway responsiveness.

All values are mean (95% confidence intervals).

*Significant difference compared with normal group.

Figure 1 Prevalence of self-reported wheeze in previous 12 months in subjects grouped according to BMI classification.
Obesity and asthma

Discussion

We have found that severe obesity, defined as a BMI of >35 kg/m², was associated with a higher prevalence of wheeze, diagnosed asthma, and medication use. Despite the fact that FEV₁ and FVC were significantly reduced in severely obese subjects, these subjects did not have evidence of airflow obstruction or reduced flow rates, nor was there any increase in airway responsiveness to histamine.

In this study we used data from a large number of randomly selected white adults in three rural towns in NSW. The distribution of BMI in these samples was representative of the general population in Australia. The methods and the IUATLD questionnaire were similar to those used in other large epidemiology studies and are well validated.

Obesity could increase the risk of asthma if the functional consequences of changes to the respiratory system were sufficient to modify airway behaviour and increase airway responsiveness in susceptible individuals. Reductions in lung volume induced by voluntarily breathing below FRC and changes in posture have been shown to increase airway responsiveness in normal subjects. The response to methacholine is altered when the FRC is reduced by approximately 500 ml, a level of reduction which is commonly found in obese or severely obese subjects. Changes in compliance or elastic recoil resulting from low lung volume could decrease the tidal fluctuations of airway smooth muscle and enhance contractility, and thus shift the dose response curve or increase the level of the maximal response. We found no evidence of any reduction in flow rates or any increase in airway responsiveness in obese subjects.

Alternatively, the anatomical changes could cause increased symptoms of wheeze and shortness of breath without altering airway behaviour. It has been reported that obese subjects are more likely to report asthma-like symptoms without an increase in AHR or prevalence of atopy. Breathlessness and wheeze might be attributable to other causes in obese subjects such as increased work of breathing or deconditioning.

Severe obesity may cause changes in the upper airway and wheeze may result from extrathoracic obstruction caused by fat deposition. Obstructive sleep apnoea is also increased in severe obesity and the combination of asthma-like symptoms plus waking at night with shortness of breath or choking may be misinterpreted as asthma. Finally, the high level of reported wheeze in the obese group may be related to the lack of specificity of the question regarding the presence of wheeze.

Although the prevalence of wheeze and shortness of breath was increased in the severely obese, there was no airway narrowing on spirometric testing, no reduction in flow rates, and no increase in airway responsiveness. While the increased rate of diagnosis of asthma in this group probably reflects the increase in prevalence of symptoms, there is little objective evidence to support the diagnosis. If the definition of asthma includes airway inflammation, then it is unlikely that this group genuinely have asthma since there is no evidence that obesity is associated with increased airway inflammation. It is also unlikely

Figure 2 Prevalence of population reporting medication use for treatment of asthma in previous 12 months in subjects grouped according to BMI classification.
that the asthmatic group selectively became obese, either as a result of increased medication use or reduced activity levels, since the prevalence of atopy was not increased in the obese group.

Medication use, particularly inhaled corticosteroids, may have affected the outcome of the study if the severely obese group were receiving sufficient treatment to normalise airway responsiveness.22 Although we do not have detailed information of the type or dose of medication taken, this seems an unlikely explanation. Despite the fact that a greater proportion of severely obese subjects had taken anti-asthma medication, as a group they continued to have symptoms, suggesting that the medication was inadequate or inappropriate to control their symptoms.

If symptoms in this group are due to causes unrelated to asthma, then asthma medication would be unlikely to affect their symptoms. The high level of medication use in the severely obese subjects probably reflects a high level of presentation for medical intervention. Symptoms alone do not appear to be a good guide for asthma treatment in this group.

The underweight group appeared to have more respiratory problems. Their increased prevalence of symptoms was associated with poorer lung function, indicated by a reduction both in FVC and in flow rates, and an increase in airway responsiveness. There are several possible causes for this. The high levels of airway responsiveness and low levels of medication use suggest that they may have under-treated asthma. Reduction in respiratory muscle strength and function may also be a potential cause. The causes for these abnormalities are unknown and deserve further investigation.

This study has significant clinical implications. We found that obese people with symptoms of dyspnoea and wheeze are frequently diagnosed with asthma even though there is no evidence of airway obstruction, reduced flow rates, or airway hyperresponsiveness. It is likely that the prevalence of asthma in this group is similar to that in the rest of the population. It is important that obese patients are fully assessed with measurement of lung function, reversibility or airway responsiveness if they present for health care with symptoms consistent with asthma. If treatment for asthma is commenced, clinical and adverse effects should be closely monitored as treatment with either oral or high dose inhaled steroids may cause further weight gain and may be an inappropriate mode of treatment for this group.

We would like to thank Elena Belousova for help with data management and Wei Xuan for statistical advice.

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