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

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

L M Schachter, C 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.
Methods

SAMPLES AND SELECTION CRITERIA
Data from three large epidemiological studies conducted in three rural regions of NSW, Australia (Belmont, Lismore, and Wagga Wagga) between 1991–7 were pooled. Details of the population, response rates, and information about non-responders have been published previously.12 13 The same two senior researchers were present at all studies and trained and supervised all other staff involved. A large random group of adults aged 17–73 years was studied. Less than 5% of the sample were non-white and their data were excluded from the analysis. Subjects were included in the current analyses if data available included height, weight, age, and a measure of airflow responsiveness. Diagnosis of asthma ever, history of wheeze, smoking history, and family history of asthma had been obtained by a self-administered questionnaire which all subjects completed. The questionnaire was a modified version of the International Union against Tuberculosis (IUATLD) questionnaire.

All of our raw data (questionnaires, lung function tests, and allergy testing) were taken from these three studies and no new interventions were made. The methodology for collecting all of the questionnaire data, lung function, and allergy testing were identical in all three studies.

Table 2  Adjusted odds ratio for symptoms and airways 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>
</tr>
</thead>
<tbody>
<tr>
<td>Wheeze in last 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopics</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>
</tr>
<tr>
<td>Non-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>
</tr>
<tr>
<td>Recent asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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>
</tr>
<tr>
<td>Non-atopics</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>
</tr>
<tr>
<td>SOBOE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopics</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>
</tr>
<tr>
<td>Non-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>
</tr>
<tr>
<td>Medication usage in previous 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atopics</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>
</tr>
<tr>
<td>Non-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>
</tr>
<tr>
<td>AHR (DRR ≥8.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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>
</tr>
<tr>
<td>Non-atopics</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>
</tr>
</tbody>
</table>

BMI = body mass index; SOBOE = shortness of breath on exertion; AHR = airways 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 \( \leq 3.9 \mu \text{mol histamine} \) 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 \(<18.5 \text{ kg/m}^2\) is underweight, 18.5–29.9 kg/m\(^2\) is normal, and 25.0–29.9 kg/m\(^2\) is overweight. A BMI of \( \geq 30 \text{ kg/m}^2\) 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 (\( \geq 40 \text{ kg/m}^2\)). In our sample only 12 subjects had a BMI of \( \geq 40 \text{ kg/m}^2\) 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\(^2\)).

The response rate for Belmont was 57%, for Lismore was 66%, and for Wagga Wagga 62%. All non-responders were telephoned and asked about their medication use for asthma. The rates of medication use between responders 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.\(^{13}\)

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 \( (\chi^2 = 16.65, p<0.01, \text{fig 1}) \), shortness of breath on exertion \( (\chi^2 = 39.40, p<0.001) \), and medication use for asthma in the previous 12 months in subjects grouped according to BMI classification.

**RESULTS**

Data from 1971 white adults were analysed. The response rate for Belmont was 57%, for Lismore was 66%, and for Wagga Wagga 62%. All non-responders were telephoned and asked about their medication use for asthma. The rates of medication use between responders 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.\(^{13}\)

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![Figure 1](https://www.thoraxjnlp.com)
Obesity and asthma measured by PEF and FEF 25–75, and a higher comparison showed a reduction in flow rates, and wheeze (table 1). In this group post hoc increase in symptoms of shortness of breath di
dese showed that there were no significant
weight, moderate, and severely obese groups
group and FVC was reduced in the under-
reduced in the underweight and severely obese
months (\( \chi^2 = 12.33, p<0.05 \), fig 2). There was
no difference between the groups in the preva-
ience of atopy (\( \chi^2 = 4.42, \) NS). Separate analy-
ses showed that there were no significant
differences between atopic and non-atopic
subjects (table 2) or between men and women
in the strength of the associations between BMI
and recent asthma, wheeze in the previous 12
months, medication use, or AHR. There did,
however, appear to be a trend in the increase in
symptoms in non-atopic subjects compared
with atopic subjects but this was not significant
and may be due to the small numbers in the
severe obesity group (table 2).

There were significant differences between
groups in lung function parameters including
FEV\(_1\), FVC, PEF, FEF\(_{25-75}\), and DRR, although
the mean values of the groups remained within
the predicted normal range (table 3). Post hoc
comparison showed that FEV\(_1\) was significantly
reduced in the underweight and severely obese
group and FVC was reduced in the under-
weight, moderate, and severely obese groups
(\( p<0.05 \)). There was no significant difference
in FEV\(_1\)/FVC\% between the groups. In the
underweight group there was a significant
increase in symptoms of shortness of breath and
wheeze (table 1). In this group post hoc
comparison showed a reduction in flow rates,
measured by PEF and FEF\(_{25-75}\) and a higher
prevalence of AHR (table 3). In the group with
severe obesity flow rates and airway responsive-
ness were not different from the normal group.

After adjusting for atopy, sex, age, smoking
history, and family history, severe obesity was
a significant risk factor for recent asthma, de-
 fined as recent wheeze plus a previous diag-
nosis of 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). Furthermore, obesity was a sig-
nificant risk for wheeze without AHR (OR
3.33, p=0.0001) but not for wheeze in the
presence of AHR (OR 0.72, p=0.73). There
was no significant correlation between BMI
and airway responsiveness (\( r=-0.041, p=0.07 \)).

Discussion
We have found that severe obesity, defined as a
BMI of >35 kg/m\(^2\), was associated with a higher
prevalence of wheeze, diagnosed asthma, and medication use. Despite the fact
that FEV\(_1\) 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.\(^{15}\) The methods
and the IUATLD questionnaire were similar to
those used in other large epidemiology studies
and are well validated.\(^{16}\)

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 respon-
siveness in susceptible individuals. Reductions
in lung volume induced by voluntarily breath-
ing below FRC\(^{16}\) and changes in posture\(^{11}\) have
been shown to increase airway responsiveness
in normal subjects. The response to metha-
choline 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 elas-
tic recoil resulting from low lung volume could
decrease the tidal fluctuations of airway
smooth muscle and enhance contractility,\(^{17}\) 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 sub-
jects.

Alternatively, the anatomical changes could
cause increased symptoms of wheeze and
shortness of breath without altering airway
behaviour. It has been reported that obese sub-
jects are more likely to report asthma-like
symptoms without an increase in AHR or
prevalence of atopy.\(^{16}\) Breathlessness and
wheeze might be attributable to other causes in
obese subjects such as increased work of
breathing or deconditioning.\(^{6}\)

Severe obesity may cause changes in the
upper airway\(^{20}\) and wheeze may result from
extrathoracic obstruction caused by fat deposi-
tion. Obstructive sleep apnoea is also increased
in severe obesity\(^{20}\) 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.\(^{21}\)

Although the prevalence of wheeze and
shortness of breath was increased in the
severely obese group, there was no airway nar-
rowing on spirometric testing, no reduction in
flow rates, and no increase in airway respon-
siveness. 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 diagno-
sis. 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 in-
creased airway inflammation. It is also unlikely

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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. 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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