Original articles

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/m^2 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 (FEV_1) of 20% or more ($PD_{20}FEV_1$). 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). FEV_1 and forced vital capacity (FVC) were significantly reduced in the group with severe obesity, but FEV_1/FVC ratio, peak expiratory flow (PEF), and mid forced expiratory flow ($FEF_{25–75}$) were not different from the group with normal BMI. The underweight group (BMI <18.5 kg/m^2) had increased symptoms of shortness of breath, increased airway responsiveness, and reduced FEV_1, FVC, PEF, and $FEF_{25–75}$ 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.**

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Keywords: obesity; asthma; airway hyperresponsiveness; wheeze

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In the past two decades there has been a significant increase in the prevalence of both asthma[1] and obesity[2] worldwide. Previous cross sectional studies have shown an association between obesity and both wheezing and diagnosed asthma.[3–5] 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.[6] 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.[7 8] In obese subjects functional residual capacity (FRC) is reduced by approximately 500 ml.[9] 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.[10 11]

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.[5] 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)

	Underweight (BMI <18.5)	*Normal (BMI 18.5–24.9)*	*Overweight (BMI 25.0–29.9)*	*Moderate obesity (BMI 30.0–34.9)*	*Severe obesity (BMI ⩾35.0)*	*p value*
No of subjects	52	1127	592	141	59	
% male	17.3%	37.9%	60.1%	48.9%	30.5%	0.000
Age (years)	26.7 (24.4 to 29.0)	32.3 (31.7 to 32.9)	35.9 (35.2 to 36.6)	36.5 (35.1 to 37.9)	34.6 (32.6 to 36.6)	
% atopic*	52.8 (39.4 to 66.2)	42.1 (39.2 to 45.0)	45.3 (41.3 to 49.3)	47.2 (39.0 to 54.4)	41.4 (38.7 to 54.1)	0.27
% with family history of asthma	25.0 (13.2 to 36.8)	21.8 (19.4 to 24.2)	24.2 (20.7 to 27.7)	19.9 (13.3 to 26.5)	28.8 (17.2 to 40.4)	0.51
% wheeze in last 12 months	33.3 (20.5 to 46.1)	20.4 (18.0 to 22.8)	19.8 (16.6 to 23.0)	25.9 (18.7 to 33.1)	37.9 (25.5 to 50.3)	0.002
% SOBOE in last 12 months	40 (20.8 to 59.2)	17.7 (15.0 to 20.4)	21.2 (17.6 to 24.8)	29.2 (21.1 to 37.3)	49.0 (35.3 to 62.7)	0.000
% recent asthma	17.0 (6.8 to 27.2)	12.3 (10.4 to 14.2)	10.4 (7.9 to 12.9)	14.6 (8.8 to 20.4)	21.7 (11.2 to 32.2)	0.06
% used medication in last 12 months	11.4 (2.8 to 20.0)	14.3 (12.3 to 16.3)	13.4 (10.7 to 16.1)	15.5 (9.5 to 21.5)	35.3 (23.1 to 47.5)	0.028
% current smoker	25 (13.2 to 36.8)	15.4 (13.3 to 17.5)	17.4 (14.3 to 20.5)	18.4 (12.0 to 24.8)	10.2 (2.5 to 17.9)	0.18

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.

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 airway 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.

DEFINITIONS

Recent wheeze was defined as a positive reply to questions on the presence of wheeze in the previous 12 months. Recent asthma was defined as recent wheeze plus a doctor diagnosis of asthma ever.

LUNG FUNCTION AND HISTAMINE INHALATION CHALLENGE

Lung function was recorded before and after saline inhalation using a Mijnhardt VRS dry rolling seal spirometer (Mijnhardt BV, Bunnik, The Netherlands) connected to an IBM compatible laptop computer running Scientific and Medical (S&M) data acquisition software. Forced expiratory manoeuvres were repeated until two measurements of forced expiratory volume in one second (FEV_1) within 100 ml of each other were obtained. The largest FEV_1 was used in the analysis. Subjects who had taken a β agonist less than six hours before the test were asked to make another appointment and to withhold treatment with this medication before testing.

Airway responsiveness was measured by histamine inhalation using the rapid method.[14] The dose of histamine that caused a 20% fall in FEV_1 ($PD_{20}FEV_1$) and the dose response ratio (DRR; percentage change in final FEV_1 from baseline divided by the total dose of histamine administered) were calculated. Because many subjects had an FEV_1 that remained stable or

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

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

BMI = body mass index; SOBOE = shortness of breath on exertion; AHR = airway hyperresponsiveness; DRR = dose response ratio.

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

	Underweight (BMI <18.5)	*Normal (BMI 18.5–24.9)*	*Overweight (BMI 25.0–29.9)*	*Moderate obesity (BMI 30.0–34.9)*	*Severe obesity (BMI ≥35.0)*	*p value*
FEV_1 (% pred)	95.0 (91.9 to 98.1)*	102.0 (101.3 to 102.7)	100.5 (99.5 to 101.5)	99.2 (97.3 to 101.1)	98.1 (95.2 to 101.0)*	<0.001
FVC (% pred)	94.2 (91.5 to 96.9)*	99.4 (98.7 to 101.1)	97.4 (96.4 to 98.4)	95 (93.1 to 96.9)*	93.6 (90.7 to 96.5)*	<0.001
FEV_1/FVC (%)	86.4 (84.3 to 88.5)	86.3 (85.9 to 86.7)	85.8 (85.4 to 86.2)	86.9 (85.9 to 87.9)	87.6 (86.1 to 89.1)	NS
PEF (% pred)	89.9 (85.7 to 94.1)*	102.2 (101.1 to 103.3)	105.5 (104.1 to 106.9)	106.2 (103.2 to 109.2)	106.2 (101.8 to 110.6)	<0.001
$FEF_{25–75}$ (% pred)	85.8 (79.7 to 91.9)*	97.1 (95.7 to 98.5)	98.5 (96.5 to 100.5)	101.4 (97.4 to 105.4)	101.2 (94.3 to 108.1)	0.001
DRR (measure of AR)	6.32 (4.88 to 8.18)*	4.71 (4.52 to 4.92)	4.42 (4.23 to 4.62)	4.72 (4.28 to 5.21)	4.66 (4.08 to 5.33)	0.017

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; PEF = peak expiratory flow; $FEF_{25–75}$ = mid forced expiratory flow; DRR = dose response rate; AR = airway responsiveness.
All values are mean (95% confidence intervals).
*Significant difference compared with normal group.

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 FEV_1 of 20% or more with ≤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 ≥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 (≥40.0 kg/m^2). In our sample only 12 subjects had a BMI of ≥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^3), so data from subjects with very severe obesity (BMI ≥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 χ^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 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.[15]

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 (χ^2 = 16.65, p<0.01, fig 1), shortness of breath on exertion (χ^2 = 39.40, p<0.001), and medication use for asthma in the previous 12

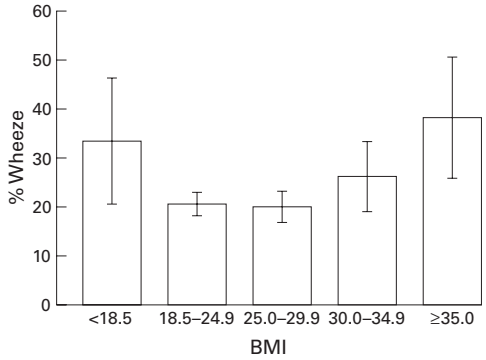

Figure 1 Prevalence of self-reported wheeze in previous 12 months in subjects grouped according to BMI classification.

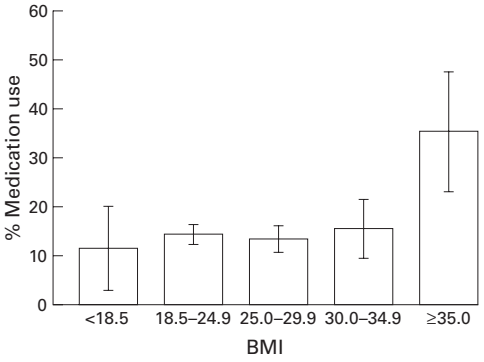

Figure 2 Prevalence of population reporting medication use for treatment of asthma in previous 12 months in subjects grouped according to BMI classification.

months (χ^2 = 12.33, p<0.05, fig 2). There was no difference between the groups in the prevalence of atopy (χ^2 = 4.42, NS). Separate analyses 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 underweight, 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 responsiveness 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, defined as recent wheeze plus a previous diagnosis 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 significant 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 responsiveness in susceptible individuals. Reductions in lung volume induced by voluntarily breathing below FRC[10] and changes in posture[11] 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,[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 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.[18] 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[19] and wheeze may result from extrathoracic obstruction caused by fat deposition. 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 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

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 undertreated 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.

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1 Woolcock AJ, Peat JK. Evidence for the increase in asthma worldwide. *Ciba Foundation Symposium* 1997;**206**:122–34.
2 WHO. *Obesity: preventing and managing the global epidemic*. Report of a WHO Consultation on Obesity. Geneva: WHO, 1997.
3 Shaheen SO, Sterne JA, Montgomery SM, *et al*. Birth weight, body mass index and asthma in young adults. *Thorax* 1999;**54**:396–402.
4 Seidell JC, De Groot LC, Van Sonsbeek JL, *et al*. Associations of moderate and severe overweight with self-reported illness and medical care in Dutch adults. *Am J Public Health* 1986;**76**:264–9.
5 Huang SL, Shiao G, Chou P. Association between body mass index and allergy in teenage girls in Taiwan. *Clin Exp Allergy* 1999;**29**:323–9.
6 Martinez FJ, Stanopoulos I, Acero R, *et al*. Graded comprehensive cardiopulmonary exercise testing in the evaluation of dyspnea unexplained by routine evaluation. *Chest* 1994; **105**:168–74.
7 Luce JM. Respiratory complications of obesity. *Chest* 1980; **78**:626–31.
8 Rochester DF. Respiratory muscles and ventilatory failure: 1993 perspective. *Am J Med Sci* 1993;**305**:394–402.
9 Jenkins SC, Moxham J. The effects of mild obesity on lung function. *Respir Med* 1991;**85**:309–11.
10 Ding DJ, Martin JG, Macklem PT. Effects of lung volume on maximal methacholine-induced bronchoconstriction in normal humans. *J Appl Physiol* 1987;**62**:1324–30.
11 Shardonofsky FR, Martin JG, Eidelman DH. Effect of body posture on concentration-response curves to inhaled methacholine. *Am Rev Respir Dis* 1992;**145**:750–5.
12 Peat JK, Toelle BG, Dermand J, *et al*. Serum IgE levels, atopy and asthma in young adults: results from a longitudinal cohort study. *Allergy* 1996;**51**:804–10.
13 Toelle BG, Peat JK, Salome CM, *et al*. Towards a definition of asthma for epidemiology. *Am Rev Respir Dis* 1992;**146**: 633–7.
14 Yan K, Salome C, Woolcock AJ. Rapid method for measurement of bronchial responsiveness. *Thorax* 1983;**38**:760–5.
15 Australian Bureau of Statistics. *How Australians measure up*. Report No 4359.0. Canberra: Australian Bureau of Statistics, 1995.
16 Burney PG, Laitinen LA, Perdrizet S, *et al*. Validity and repeatability of the IUATLD (1984) bronchial symptoms questionnaire: an international comparison. *Eur Respir J* 1989;**2**:940–5.
17 Fredberg JJ, Inouye DS, Mijailovich SM, *et al*. Perturbed equilibrium of myosin binding in airway smooth muscle and its implications in bronchospasm. *Am J Respir Crit Care Med* 1999;**159**:959–67.
18 Bai J, Peat JK, Berry G, *et al*. Questionnaire items that predict asthma and other respiratory conditions in adults. *Chest* 1998;**114**:1343–8.
19 Shepard JW Jr, Gefter WB, Guilleminault C, *et al*. Evaluation of the upper airway in patients with obstructive sleep apnea. *Sleep* 1991;**14**:361–71.
20 Van Boxem TJ, De Groot GH. Prevalence and severity of sleep disordered breathing in a group of morbidly obese patients. *Neth J Med* 1999;**54**:202–6.
21 Burney PG, Chinn S, Britton JR, *et al*. What symptoms predict the bronchial response to histamine? Evaluation in a community survey of the bronchial symptoms questionnaire (1984) of the International Union Against Tuberculosis and Lung Disease. *Int J Epidemiol* 1989;**18**:165–73.
22 Woolcock AJ, Yan K, Salome CM. Effect of therapy on bronchial hyperresponsiveness in the long-term management of asthma. *Clin Allergy* 1988;**18**:165–76.