

Central obesity is associated with nonatopic but not atopic asthma in a representative population sample

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Background: Epidemiologic studies have consistently demonstrated the association between high body mass index (BMI) and asthma, yet the relationship between asthma and the alternative central obesity phenotypes, waist circumference (WC) and waist-to-hip ratio (WHR), has not been assessed in a representative population sample.

Objective: To determine the strength of the association of WC and WHR with current asthma and whether the association is modified by atopic status in a representative population sample.

Methods: The North West Adelaide Health Study, a biomedical population study of $n = 4060$, assessed current asthma, respiratory symptoms, and participant demographics by self-completed questionnaire. Clinic assessment included measures of WC and WHR, spirometry, and skin prick tests to a panel of allergens.

Results: Logistic regression analysis showed a significant, marginal increased adjusted risk of asthma associated with obese levels of WC and WHR and BMI ≥ 35.0 kg/m² in female subjects only. When the association was considered stratified according to atopic status, the relationship between obese levels of WC and WHR with asthma held only for the nonatopic population in both males (WC: odds ratio [OR] 5.7, 95% confidence interval [CI] 1.1-28.8; WHR: OR 6.2, 95% CI, 1.1-32.9) and females (WC: OR 2.3, 95% CI, 1.2-4.4; WHR: OR 3.0, 95% CI, 1.5-5.9). BMI ≥ 35.0 kg/m² showed an inconsistent pattern in the association with asthma.

Conclusion: Central obesity was significantly associated with an increased risk of nonatopic asthma only. The causal pathway is unknown, but this study suggests the involvement of different pathophysiological mechanisms requiring further investigation.

Clinical implications: Asthma should be considered in older, nonatopic, centrally obese, symptomatic individuals. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Asthma, asthma epidemiology, obesity, waist circumference, waist-to-hip ratio, atopy

Consistent with international findings,^{1,2} in Australia, the prevalence of obesity³ has increased. Asthma prevalence may have stabilized internationally,⁴ although this has not been a totally consistent finding.⁵ There is a large body of evidence suggesting that these increases are related, including longitudinal studies that have demonstrated an association of obesity with incident asthma.⁶⁻¹¹ Some studies have shown this relationship is modified by sex,^{7,9} suggesting a hormonal component in the etiology.

Most studies have used self-reported asthma and body mass index (BMI) to examine this relationship. Although asthma-like symptoms observed in obese people may be a result of asthma, it is important to establish that obesity-related dyspnea and wheeze are associated with airway hyperresponsiveness (AHR). Few studies have considered the asthma risk associated with weight in terms of AHR, and the evidence is inconsistent.¹²⁻¹⁶ An association between BMI and AHR¹² and incident AHR¹³ in men has been demonstrated. However, Schachter et al¹⁴ were unable to demonstrate an association, and have suggested that respiratory symptoms in obese people may be misdiagnosed as asthma. Consistent with these findings, weight loss in obese people with asthma was associated with improved lung function measures independent of changes in AHR, suggesting an effect of mass loading on the airways.^{17,18} This is supported by studies that have shown no association between BMI and atopy.^{14,19,20} Again there is inconsistency in the relationship between BMI and atopy, and some studies have shown an association only in female subjects.^{15,16}

It is intuitive that measures of central/abdominal obesity such as waist circumference (WC) or waist-to-hip ratio (WHR) may have a stronger association with asthma than BMI, through a greater modifying affect on airway smooth muscle function by mechanical factors.²¹ However, few population studies have examined the relationship between asthma and these alternate obesity phenotypes.^{8,11} Obesity phenotype may be an important component in the obesity–asthma association given that BMI criteria have the potential to misclassify individuals considered obese by WC, for example.^{22,23} Furthermore,

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Abbreviations used

AHR: Airway hyperresponsiveness
 BMI: Body mass index
 CLD: Chronic Lung Disease Index
 OR: Odds ratio
 SBR: Significant bronchodilator response
 WC: Waist circumference
 WHR: Waist-to-hip ratio

for a given value of WC, the risks of obesity-related metabolic disorders were found to be independent of BMI.²⁴

We have previously demonstrated an unadjusted association of current asthma with a BMI of at least 30 kg/m².²⁵ Therefore, the aim of this study was to examine the relationship between asthma and obesity with particular reference to the alternative obesity phenotypes WC and WHR in a representative population sample of 4060 people. We also examined the role of asthma phenotype in the relationship by considering asthma in terms of self-reported current asthma, and whether there was a modifying effect of atopy status on the association.

METHODS

Sample population and study method

The North West Adelaide Health Study is a representative biomedical population study of people age 18 years or older living in the northwestern suburbs of Adelaide, South Australia (regional population, 0.6 million), and the methods have been extensively described.²⁶ Households selected at random from the electronic *White Pages* telephone directory were eligible for inclusion in the study. In each household, the person age 18 years or older who was the last to have a birthday was asked to participate in the telephone interview and recruited to a clinical assessment. As many as 10 telephone calls were made to interview the selected person, with no replacement for refusal or for nonresponse.

Telephone interviews by trained health interviewers investigated self-reported health status (including asthma), smoking status, and demographic variables. A questionnaire was then sent to each participant for self-completion. This was composed of items on risk factor prevalence, respiratory symptoms, and more detailed demographic information. Smoking was categorized into self-reported current, former, or never-smoker. Respiratory symptoms were assessed with the Chronic Lung Disease Index (CLD).²⁷ This is a 6-item questionnaire, scored out of 100, with subscales relating to the frequency and intensity of dyspnea and wheeze, and frequency of coughing and volume of sputum production. Severity is categorized as follows: mild ≤ 43 , moderate = 44 to 62, and severe ≥ 63 .

Self-reported current asthma was defined as a positive response to all 3 of the following questions: (1) "Have you ever had asthma?" (2) "Was your asthma confirmed by a doctor?" and (3) "Do you still have asthma?" Spirometry was conducted in 2 hospital-based clinics (Microlab 3300 spirometer; Micro Medical LTD, Kent, United Kingdom) according to American Thoracic Society criteria.²⁸ Each subject performed at least 3 acceptable and reproducible forced vital capacity maneuvers. Reversibility of airway obstruction was defined by 2 criteria: the increase in FEV₁ after inhalation of 400 μ g salbutamol of at least 12% of baseline FEV₁ and 9% of predicted FEV₁²⁹

(assuming the increase exceeded 200 mL). The 9% of predicted criterion was chosen because of its ability to identify impairment in people without a current asthma diagnosis independent of age and sex.³⁰ Airway obstruction was defined as a postbronchodilator FEV₁/forced vital capacity ratio less than 2 SDs below that predicted for age and sex.³¹ Skin prick testing was conducted for the following allergens: rye grass, cat dander, house dust mite, *Alternaria*, feather, and cockroach. Lengths and widths of wheals and flares were measured after 15 minutes. The skin test panel was considered valid if the positive control (histamine) wheal was greater than 2 mm in diameter. An allergen-specific skin test response was considered positive if the mean of the length and width of wheal was at least 3 mm greater than the negative control response. Atopy was defined as having at least 1 positive reaction to this panel of allergens.

Medical assessment of participants included measurements of height (measured to the nearest 0.5 cm using a stadiometer), weight (measured to the nearest 0.1 kg in light clothing and without shoes using standard digital scales), WC (measured at minimal inspiration to the nearest 0.1 cm with an inelastic tape, midway between the last rib and iliac crest), and hip (measured at the level of the maximum posterior extension of the buttocks).

Waist circumference in centimeters³² and WHR (WC divided by hip circumference)³³ were categorized according to the following sex-specific international criteria.

WC. Normal/not at risk: male subjects, ≤ 94 cm, female subjects, ≤ 80 cm; overweight/risk level 1: male subjects, 95 to 101 cm, female subjects, 80 to 87 cm; obese/risk level 2: male subjects, ≥ 102 cm, female subjects, ≥ 88 cm.

WHR. Normal/not at risk: male subjects, ≤ 0.90 , female subjects, ≤ 0.80 ; overweight/risk level 1: male subjects, 0.91 to 0.99, female subjects, 0.81 to 0.84; obese/risk level 2: male subjects, ≥ 1.0 , female subjects, ≥ 0.85 .

BMI. Body mass index in kg/m² was categorized as follows³²: underweight, ≤ 18.49 ; normal, 18.5 to 24.9; overweight, 25.0 to 29.9; moderate obesity, 30.0 to 34.9; severe obesity, ≥ 35.0 .

Statistical analysis

Data obtained were weighted to the 1999 Estimated Residential Population for South Australia³⁴ by region, age group, sex, and probability of selection in the household, to provide population representative estimates. Data were analyzed using the Statistical Package for the Social Sciences (SPSS Version 13.0; SPSS Inc, Chicago, Ill). The correlation between obesity measures, adjusted for age and sex, was expressed as a partial correlation coefficient (partial *r*). Multiple analysis of variance was used to adjust mean continuous variables (eg, FEV₁ and CLD scores) for baseline covariates, including age and sex. The Student *t* test was used to determine statistically significant differences in mean values. Multiple logistic regression models were developed to adjust the risk of current asthma associated with obesity and overweight for age, annual household income, education, and smoking (including former smoking). For the remaining models, adjustment for confounders was limited to age and smoking status (including former smoking) because of small sample sizes. Approval for the North West Adelaide Health Cohort Study was obtained from institutional ethics committees of the North West Adelaide Health Service, and all subjects gave written informed consent.

RESULTS

Of the total eligible sample of 8213, 5850 (71%) completed the initial telephone interview. Of these, *n* = 4060 attended the clinic for the biomedical examination, representing 69% of those who completed the

TABLE I. Prevalence of people within different weight classifications among those with and without asthma

	Percent within different weight classifications				
	Total	No current asthma (n = 3438)		Current asthma (n = 380)	
		Male subjects (1722)	Female subjects (1716)	Male subjects (155)	Female subjects (225)
BMI (kg/m ²) [†]					
Underweight	1.3	1.1	1.5	0.0	0.9
Normal	35.5	31.6	40.0	29.9	38.7
Overweight	36.3	41.8	30.2*	46.1	27.5*
Obesity					
Moderate	17.5	18.7	17.2*	16.9	13.5
Severe	9.5	6.8	11.1*	7.1	19.4*
WC (cm) [‡]					
Not at risk	40.6	43.4	38.6	41.3	34.1
Risk level 1	22.1	22.8	21.5	23.2	20.0
Risk level 2	37.3	33.8	39.9*	35.5	45.9
WHR [§]					
Not at risk	46.4	41.0	52.4	40.7	44.4
Risk level 1	36.4	49.8	23.3*	46.4	26.7*
Risk level 2	17.3	9.2	24.3*	12.9	28.9*

**P* value < .05 vs male subjects.[†]BMI: underweight, ≤18.49; normal, 18.5 to 24.9; overweight, 25.0 to 29.9; moderate obesity, 30.0 to 34.9; severe obesity, ≥35.0.[‡]WC: not at risk: male subjects, ≤94 cm, female subjects, ≤80 cm; risk level 1: male subjects, 95 to 101 cm, female subjects, 80 to 87 cm; risk level 2: male subjects, ≥102 cm, female subjects, ≥88 cm.[§]WHR: not at risk: male subjects, ≤0.9, female subjects, ≤0.8; risk level 1: male subjects, 0.91 to 0.99, female subjects, 0.81 to 0.84; risk level 2: male subjects, ≥1.0, female subjects, ≥0.85.

telephone interview. Complete self-reported asthma and spirometry data were available on 4037 (99.4%) and 4018 (99.0%) participants, respectively. Measures of adiposity were available on 4058 participants. The mean age (SD) of the sample was 44.8 (18.2) years, and the prevalence of current and former smokers was 24.2% and 28.2%, respectively. Current asthma was reported by 9.4% (n = 380) of the study participants. Current asthma prevalence in males was 7.8% (n = 155), compared with 10.9% (n = 225) in females. The prevalence of significant bronchodilator responsiveness (SBR) in the absence of a doctor diagnosis of asthma was 4.6% (n = 183; males, n = 86; females, n = 97) according to the 9% predicted criterion and 2.7% (n = 109; males, n = 53; females, n = 56) according to the 12% of baseline FEV₁ criterion.³⁰

The significant age-adjusted partial correlations between adiposity measures were generally stronger in male subjects than in female subjects. BMI and WC showed the strongest correlation for both male and female subjects (partial *r* = 0.90). Male subjects showed a stronger correlation between WC and WHR (partial *r* = 0.80) than female subjects (partial *r* = 0.67). The lowest correlations were seen for WHR and BMI (male subjects, partial *r* = 0.66; female subjects, partial *r* = 0.39). Despite the strong correlations seen between adiposity measures, there was relatively poor agreement between the measures in the classification of obesity. Of the 1520 (37.5%) participants classified as obese by WC criteria, over half of these people (60.5%) were not identified by WHR obese criteria, and 35% were not identified by BMI obese criteria (≥30 kg/m²). The strongest agreement between the measures to identify obesity occurred between WC and BMI (κ = 0.66), then WC and WHR (κ = 0.39), and the lowest

agreement occurred between WHR and BMI (κ = 0.30). Accordingly, there was a large variation in obesity prevalence depending on the obesity criteria used, ranging from 17.3% according to WHR to 37.3% for WC in the overall population, as shown in Table I. Generally, female subjects were significantly less likely to be overweight and significantly more likely to be obese compared with male subjects.

Table II shows the sex-specific associations of current asthma with measures of obesity. After adjustment for age, annual household income, education, smoking, and recreational physical activity levels, at-risk levels of WC (≥88 cm) and WHR (>0.80) and BMI ≥ 35.0 kg/m² were associated with a significantly increased risk of asthma in female subjects. In these models, asthma was consistently associated with age less than 50 years (odds ratio [OR], 1.8; 95% CI, 1.2-2.4), low levels of household income (OR, 1.7; 95% CI, 1.2-2.3), and former smoking (OR, 1.4; 95% CI, 1.0-2.0). In male subjects, asthma was significantly associated with low levels of education (secondary school only; OR, 2.2; 95% CI, 1.5-3.1). With few exceptions (BMI < 18.0 kg/m² in female subjects and BMI 25.0-29.9 kg/m² in male subjects), there was no significant age-adjusted or smoking-adjusted association of either measure of obesity with having a significant bronchodilator response (in the absence of an asthma diagnosis; Table III). Positive associations were seen for risk level 1 and 2 of WHR, but these did not reach statistical significance.

The prevalences of atopy in the overall population, participants reporting asthma, and participants with no asthma or SBR were 61.7%, 76.6%, and 60.5%, respectively. Current asthma was significantly associated with atopy (adjusted OR, 2.1; 95% CI, 1.7-2.8). No

TABLE II. Sex-specific prevalence (%) and adjusted OR (95% CI) of current asthma associated with measures of obesity

	Male subjects (n = 1878)		Female subjects (n = 1940)	
	Percent	OR* (95% CI)	Percent	OR* (95% CI)
BMI (kg/m ²)†				
Underweight	0.0	—	11.2	1.0 (0.3-3.9)
Normal	7.8	1.0	7.1	1.0
Overweight	9.0	1.2 (0.8-1.9)	10.6	0.9 (0.6-1.4)
Obesity				
Moderate	7.5	0.9 (0.5-1.6)	9.2	0.9 (0.5-1.4)
Severe	8.6	1.2 (0.6-2.4)	18.4	1.8 (1.1-2.8)
WC (cm)‡				
Not at risk	7.8	1.0	10.4	1.0
Risk level 1	8.5	1.1 (0.7-1.7)	10.8	1.2 (0.8-1.9)
Risk level 2	8.6	1.1 (0.7-1.7)	13.1	1.5 (1.0-2.1)
WHR§				
Not at risk	8.2	1.0	10.0	1.0
Risk level 1	7.7	1.0 (0.7-1.6)	13.0	1.4 (1.0-2.1)
Risk level 2	11.2	1.3 (0.7-2.5)	13.6	1.5 (1.0-2.2)

*Adjusted for age, income, education, and smoking.

†BMI: underweight, ≤ 18.49 ; normal, 18.5 to 24.9; overweight, 25.0 to 29.9; moderate obesity, 30.0 to 34.9; severe obesity, ≥ 35.0 .

‡WC: not at risk: male subjects, ≤ 94 cm, female subjects, ≤ 80 cm; risk level 1: male subjects, 95 to 101 cm, female subjects, 80 to 87 cm; risk level 2: male subjects, ≥ 102 cm, female subjects, ≥ 88 cm.

§WHR: not at risk: male subjects, ≤ 0.9 , female subjects, ≤ 0.8 ; risk level 1: male subjects, 0.91 to 0.99, female subjects, 0.81 to 0.84; risk level 2: male subjects, ≥ 1.0 , female subjects, ≥ 0.85 .

significant association of atopy with central measures of obesity was found; however, overweight (BMI 25.0-29.9 kg/m²) and obesity (BMI ≥ 30.0 kg/m²) in male subjects younger than 50 years was associated with an increased risk of atopy (OR, 1.2; 95% CI, 1.0-1.4).

Demographic characteristics and respiratory indicators (lung function and symptoms) associated with asthma phenotype (asthma $\pm$ atopy) were examined. Current asthma was significantly associated with female sex (OR, 1.5; 95% CI, 1.2-1.8), and this relationship held for both atopic (OR, 1.3; 95% CI, 1.0-1.7) and nonatopic asthma (OR, 2.7; 95% CI, 1.7-4.4) after adjustment for age. Nonatopic subjects with asthma were significantly older than atopic subjects (52.7 vs 40.3 years; $P < .001$). After adjustment for age, nonatopic and atopic subjects with asthma showed no significant differences in the mean percentage predicted prebronchodilator FEV₁ (87.2% vs 88.4%, respectively) and percentage predicted postbronchodilator FEV₁ (92.0% vs 93.9%, respectively). In addition, nonatopic subjects with asthma were not significantly more likely (OR, 1.18; 95% CI, 0.6-2.5) to demonstrate postbronchodilator airways obstruction (17.6% vs 14.3%, respectively) compared with atopic subjects with asthma. In contrast, nonatopic subjects with asthma experienced worse respiratory symptoms than atopic subjects with asthma (CLD score, 42.6 vs 37.0; $P < .001$).

When the relationship between asthma and obesity was considered stratified according to atopic status (Table IV),

an association was generally observed only for the nonatopic population. All of these associations were significant with the exception of nonatopic female subjects, for whom the association did not reach statistical significance ($P = .13$). Severe obesity (BMI ≥ 35 kg/m²) was also significantly associated with an increased risk of asthma in atopic female subjects. A significant association with nonatopic asthma was also observed in male and female subjects for risk level 1 categories of WC and WHR, respectively. In these age-adjusted and smoking-adjusted models, in female subjects, atopic asthma was significantly associated with age younger than 50 years. Nonatopic asthma was also consistently significantly associated with former smoking in male subjects (OR, 3.6; 95% CI, 1.1-13.0) and female subjects (OR, 2.1; 95% CI, 1.2-3.7).

DISCUSSION

This study has revealed the association of nonatopic asthma with obesity among both men and women. Atopic asthma was associated with obesity (BMI ≥ 35 kg/m²) among women but not men. These associations were seen for both BMI and measures of central obesity (WC and WHR), although there were some differences in the patterns of association for these different measures. For both men and women, there was an association between a history of former smoking and nonatopic asthma.

Camargo et al⁸ reported that incident asthma was significantly associated with WC but did not remain so after adjustment of the models for BMI. Three recent studies have reported the asthma risk in relation to obesity according to atopic status. Ronmark et al¹⁰ reported that in both male and female subjects, incident asthma (with verified bronchial variability confirmed by methacholine responsiveness) was associated with several factors including hay fever, family history of asthma, former smoking, and overweight (BMI, 25.0-29.9 kg/m²) or obesity (BMI ≥ 30.0 kg/m²). The relationship between overweight and obesity with incident asthma held in both atopic and nonatopic subjects.¹⁰ Another Swedish study¹¹ reported significant unadjusted relative risks for incident asthma associated with obese levels of BMI and central adiposity as measured by WC in both men and women age 20 to 50 years. In contrast with the findings of Ronmark et al,¹⁰ but generally consistent with our results, Kronander et al¹¹ demonstrated an increasing risk of nonatopic asthma with obese levels of BMI and WC in both sexes, but not for atopic asthma. Recently, elevated C-reactive protein levels were shown to be associated with non-allergic asthma only, but in contrast with our findings, Olafsdottir et al³⁵ showed that a BMI ≥ 30 kg/m² was associated with both allergic and nonallergic asthma, where allergy was measured by specific and total serum IgE to 4 allergens. After adjustment for C-reactive protein, the association with BMI remained for the allergic asthma group only.

It is arguable that the observed association of central obesity with nonatopic but not atopic asthma only

TABLE III. Sex-specific prevalence (%) and OR (95% CI) of SBR in the absence of a current asthma diagnosis associated with measures of obesity

	SBR $\geq$ 9% predicted FEV ₁				SBR $\geq$ 12% baseline FEV ₁			
	Male subjects (n = 1878)		Female subjects (n = 1940)		Male subjects (n = 1812)		Female subjects (n = 1812)	
	Percent	OR* (95% CI)	Percent	OR* (95% CI)	Percent	OR* (95% CI)	Percent	OR* (95% CI)
BMI (kg/m ²)†								
Underweight	0.0	—	13.3	2.9 (1.0-8.7)	0.0	—	13.3	4.8 (1.5-14.9)
Normal	3.0	1.0	5.0	1.0	1.8	1.0	3.0	1.0
Overweight	6.7	1.9 (1.1-3.5)	5.8	1.1 (0.7-1.9)	3.8	1.6 (0.8-3.4)	2.7	0.7 (0.4-1.4)
Obesity								
Moderate	3.6	1.0 (0.5-2.1)	3.6	0.7 (0.4-1.4)	3.0	1.3 (0.5-3.3)	2.3	0.6 (0.2-1.3)
Severe	4.1	1.3 (0.5-3.4)	6.4	1.3 (0.7-2.5)	3.3	1.3 (0.4-4.6)	4.4	1.3 (0.6-2.8)
WC (cm)‡								
Not at risk	3.6	1.0	5.0	1.0	1.8	1.0	2.6	1.0
Risk level 1	4.9	1.2 (0.7-2.2)	4.4	0.8 (0.5-1.5)	2.9	1.2 (0.5-2.6)	3.6	1.2 (0.5-2.4)
Risk level 2	5.2	1.2 (0.7-1.9)	4.7	0.9 (0.6-1.5)	4.4	1.7 (0.8-3.3)	3.3	1.0 (0.5-2.0)
WHR§								
Not at risk	2.5	1.0	4.8	1.0	1.9	1.0	2.1	1.0
Risk level 1	5.4	1.6 (0.9-2.8)	4.2	0.9 (0.5-1.6)	3.4	1.1 (0.6-2.2)	4.0	1.7 (0.9-3.3)
Risk level 2	6.8	1.9 (0.9-4.1)	5.1	1.1 (0.7-1.8)	4.7	1.3 (0.5-3.2)	4.1	1.6 (0.8-3.1)

Subjects with current asthma have been excluded from the analysis.

*Adjusted for age and smoking.

†BMI: underweight, $\leq$ 18.49; normal, 18.5 to 24.9; overweight, 25.0 to 29.9; moderate obesity, 30.0 to 34.9; severe obesity, $\geq$ 35.0.‡WC: not at risk: male subjects, $\leq$ 94 cm, female subjects, $\leq$ 80 cm; risk level 1: male subjects, 95 to 101 cm, female subjects, 80 to 87 cm; risk level 2: male subjects, $\geq$ 102 cm, female subjects, $\geq$ 88 cm.§WHR: not at risk: male subjects, $\leq$ 0.9, female subjects, $\leq$ 0.8; risk level 1: male subjects, 0.91 to 0.99, female subjects, 0.81 to 0.84; risk level 2: male subjects, $\geq$ 1.0, female subjects, $\geq$ 0.85.**TABLE IV.** Prevalence (%) and adjusted* sex-specific risk of current asthma, OR (95% CI), associated with measures of obesity, stratified by atopy status

	Male subjects				Female subjects			
	Atopic† (n = 1220)		Nonatopic‡ (n = 657)		Atopic† (n = 1149)		Nonatopic‡ (n = 791)	
	Percent	OR (95% CI)	Percent	OR (95% CI)	Percent	OR (95% CI)	Percent	OR (95% CI)
BMI (kg/m ²)§								
Normal/underweight	11.2	1.00	1.3	1.0	13.4	1.0	7.6	1.0
Overweight	11.5	1.0 (0.7-1.6)	4.4	2.2 (0.6-8.2)	13.1	1.0 (0.7-1.6)	6.6	0.8 (0.4-1.7)
Obesity								
Moderate	9.6	0.8 (0.5-1.5)	2.7	1.7 (0.3-8.8)	8.5	0.7 (0.4-1.2)	10.9	1.3 (0.7-2.7)
Severe	9.6	0.8 (0.4-1.8)	8.7	5.0 (1.0-25.1)	22.6	1.9 (1.2-3.2)	12.4	1.7 (0.8-3.5)
WC (cm)								
Not at risk	11.5	1.0	0.7	1.0	13.6	1.0	5.5	1.0
Risk level 1	10.6	0.9 (0.6-1.5)	4.9	5.5 (1.0-29.2)	12.1	1.0 (0.6-1.6)	9.1	1.8 (0.9-3.8)
Risk level 2	10.4	0.9 (0.6-1.4)	5.4	5.8 (1.1-28.8)	14.8	1.3 (0.9-1.9)	10.8	2.0 (1.0-3.7)
WHR¶								
Not at risk	11.7	1.0	0.9	1.0	13.1	1.0	5.0	1.0
Risk level 1	9.9	0.9 (0.6-1.3)	4.1	3.2 (0.6-13.3)	14.2	1.2 (0.8-1.9)	11.3	2.4 (1.2-4.6)
Risk level 2	12.7	1.2 (0.6-2.2)	8.7	6.0 (1.1-31.0)	14.8	1.4 (0.9-2.2)	12.1	2.5 (1.3-4.7)

*Adjusted for age and smoking status.

†Atopic asthma, n = 291; male subjects, n = 133; female subjects, n = 158.

‡Nonatopic asthma, n = 89; male subjects, n = 22; female subjects, n = 67.

§BMI: underweight, $\leq$ 18.49; normal, 18.5 to 24.9; overweight, 25.0 to 29.9; moderate obesity, 30.0 to 34.9; severe obesity, $\geq$ 35.0.||WC: not at risk: male subjects, $\leq$ 94 cm, female subjects, $\leq$ 80 cm; risk level 1: male subjects, 95 to 101 cm, female subjects, 80 to 87 cm; risk level 2: male subjects, $\geq$ 102 cm, female subjects, $\geq$ 88 cm.¶WHR: not at risk: male subjects, $\leq$ 0.9, female subjects, $\leq$ 0.8; risk level 1: male subjects, 0.91 to 0.99, female subjects, 0.81 to 0.84; risk level 2: male subjects, $\geq$ 1.0, female subjects, $\geq$ 0.85.

observed in our study may be a result of the misdiagnosis as asthma of respiratory symptoms caused by physical deconditioning given the high prevalence of obesity in nonatopic subjects with asthma compared with atopic subjects with asthma (data not shown). We have demonstrated, however, that people with nonatopic current asthma have at least comparable respiratory impairment (in terms of FEV₁ % predicted and airways obstruction) to the atopic current asthma group, if not worse respiratory symptoms. Consistent with the literature,³⁶ nonatopic subjects with asthma were more likely to be older and female, with more severe clinical manifestations than atopic subjects with asthma. This argues that the asthma diagnosis reported in the nonatopic group is most probably valid. The etiology of this obesity-related nonallergic asthma is unclear. Atopy is an age-related phenomenon³⁷ and decreases with age. Therefore, it is possible that these subjects with nonatopic asthma may have been previously atopic, given that the nonatopic subjects with asthma were significantly older in our study.

Ford³⁸ has suggested a role for detection bias in the association of obesity and asthma (ie, obese people are more likely to have asthma diagnosed because they present to the general practitioner more frequently as a result of other comorbidities than normal-weight individuals). Arguing against a detection bias operating, we did not observe an increased risk of normal-weight participants demonstrating SBR and significant respiratory impairment in the absence of a diagnosis of asthma (probable undiagnosed asthma) compared with obese participants. To the contrary, there were positive associations between overweight or obesity and SBR in the absence of an asthma diagnosis, but most of these associations did not reach statistical significance, probably because of the small sample sizes in these groups. These associations should be viewed with caution, however, given that this is a proxy measure of undiagnosed asthma (significant reversibility in the presence of respiratory impairment) and not a clinical diagnosis. Consistent with the argument against a detection bias operating, we have previously shown that people demonstrating SBR in the absence of a current asthma diagnosis were equally exposed to primary care services as those with diagnosed asthma.²⁵

Olafsdottir et al³⁵ suggest a differing pathophysiological background for the asthma–obesity association between allergic and nonallergic asthma. Recent data have shown a strong correlation of a circulating adhesion molecule E-selectin with AHR and peak flow variability³⁹ in nonatopic compared with atopic asthma. Furthermore, atopic and nonatopic subjects with asthma differ in other respects,³⁶ including increased airway smooth muscle thickening⁴⁰ and higher levels of exhaled nitric oxide demonstrated in atopic subjects with asthma.^{41,42} However, comparisons of inflammatory cells in bronchial biopsies^{43–47} and asthma/allergy-related cytokines⁴⁸ of atopic and nonatopic subjects with asthma have not shown consistent differences. Interestingly, Zeibecoglou et al⁴⁷ have demonstrated increased mRNA expression of the anti-inflammatory cytokines IL-10 and IL-12 in induced sputum of atopic subjects with asthma compared with

nonatopic subjects with asthma and suggest that this represents a homeostatic mechanism to decrease bronchial inflammation in atopic subjects with asthma. This finding is consistent with the more severe presentation of symptoms in nonatopic asthma. Adiponectin, which is reduced in obesity,⁴⁹ has been shown to inhibit vascular smooth muscle proliferation⁵⁰ and increase IL-10 production to downregulate vascular inflammation.⁵¹ If such a mechanism also operates in airway smooth muscle, this may provide a pathway for the association of nonallergic inflammation and obesity.

The relationship between adiposity and traditional obesity-related comorbid conditions such as diabetes and cardiovascular disease is complex. In relation to these conditions, it has been suggested that BMI, WC, and hip circumferences measure different aspects of fat distribution given that large hip and thigh circumferences are protective against diabetes⁵² and cardiovascular disease⁵³ independent of WC and BMI. The variation that we observed in (1) the levels of agreement between the obesity measures and (2) the associations of obesity with asthma suggests that fat distribution may have an important role in the association of obesity with asthma, and that central measures of adiposity should be considered in future assessments of asthma risk. Our finding that those categorized by BMI as severely obese were all centrally obese, but not vice versa, emphasizes the importance of fat distribution.

Our study is limited by the use of self-report for a diagnosis of asthma. However, it is unlikely that participants self-reporting current asthma do not actually have the condition, because self-report is used widely and has been shown to be a valid measure of asthma.⁵⁴ Until follow-up data on the cohort are available, the cross-sectional nature of our study precludes any conclusions being drawn about the direction of the association. Our survey was limited to households with telephones, but because 97% of the households in the region have telephones,⁵⁵ and the demographic characteristics were representative of the population of profile of Adelaide overall,⁵⁶ the extent of any bias is likely to be small.

In summary, this study has shown a consistent association of obesity phenotypes with nonatopic asthma in male and female subjects. Among women but not men, high BMI (≥ 35 kg/m²) was also associated with atopic asthma. The pathways for these associations are unknown but are likely to be complex, involving genetic, environmental, and immunological factors. Given the relatively small number of nonatopic subjects with asthma in this study, it is important to reproduce this finding in other large, representative population samples.

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