Adiposity, asthma, and airway inflammation

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Background: Several studies have found obesity to be associated with an increased prevalence of asthma. For reasons that remain unclear, this association has often been reported to be stronger in women than in men. One possible explanation might be that these studies have used body mass index to identify adiposity, which might be a less reliable measure of body fat in men than in women.

Objective: We sought to explore the association between body fat percentage measured by means of bioelectrical impedance analysis and asthma, airflow obstruction, and airway inflammation in men and women.

Methods: Respiratory questionnaires, spirometry, bronchodilator response, exhaled nitric oxide level, and percentage of body fat were measured in a population-based cohort of approximately 1000 individuals at age 32 years.

Results: There was a significant association between the percentage of body fat and asthma in women ($P = .043$) but not in men ($P = .75$). Airflow obstruction was associated with percentage of body fat in women ($P = .046$), but there was an inverse association in men ($P = .010$). Bronchodilator responsiveness was also associated with lower body fat in men ($P = .004$). Airway inflammation, measured by means of exhaled nitric oxide, was not associated with body fat in either women ($P = .17$) or men ($P = .25$).

Conclusion: Adiposity is associated with asthma and airflow obstruction in women. This does not appear to be mediated by airway inflammation. In men airflow obstruction and bronchodilator responsiveness are associated with a lower percentage of body fat.

Clinical implications: In women, but not in men, obesity is associated with asthma and airflow obstruction, but there was no association with airway inflammation. (J Allergy Clin Immunol 2007;119:634-9.)

Key words: *Asthma, obesity, exhaled nitric oxide, body mass index, airway inflammation*

Numerous studies have shown a relationship between an increased body mass index (BMI) and asthma.[1] Several studies have found a stronger association in women, with only weak or nonsignificant associations in men.[2-4] The mechanism for the association between asthma and obesity and the reasons for the apparent difference between men and women remain unclear. Because both asthma and obesity are characterized by inflammation, a common inflammatory pathway has been proposed as a plausible explanation for the association between the 2 conditions.[5] The link might appear stronger in women either because for any given body weight women have a higher percentage of body fat or because BMI is a less accurate measure of body fat in men.[6]

Most studies to date have used BMI to determine overweight and obesity according to the World Health Organization definition.[7] BMI is used in epidemiologic studies and in clinical practice because it is easy and cheap to measure, but this assumes that body mass is associated with body fat and does not allow for those overweight because of large muscle mass or those with high body fat levels and normal weight for height. Hence BMI might not be an accurate measure of body fat, particularly in men.[6] This misclassification of body fat could potentially explain why the association between BMI and asthma appears weaker in men than in women.

A further problem with most studies of obesity and asthma is that they have relied on self-reported asthma, which might have been diagnosed on the basis of symptoms alone. It is possible that these symptoms could be the result of the increased work of breathing associated with obesity rather than airway inflammation and airway hyperresponsiveness. Studies of airway responsiveness provide conflicting findings, with some finding no link between obesity and airway responsiveness,[8,9] whereas another found an association that was stronger in men.[10] Studies using markers of airway inflammation and obesity have also been conflicting. Although one study found no correlation between fractional exhaled nitric oxide and obesity in either asthmatic or nonasthmatic subjects,[11] the analyses did not report separate associations for male

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Abbreviations used
BMI: Body mass index
FVC: Forced vital capacity
OR: Odds ratio
ppb: Parts per billion

and female subjects. Two smaller studies reported higher exhaled nitric oxide levels with increasing BMI in nonasthmatic adults, and no differences were found when adjusted for sex.[12,13]

We have previously reported an association between BMI, asthma, atopy, and airflow obstruction in a population-based sample of 26-year-old women, but not men, participating in the Dunedin Multidisciplinary Health and Development Study.[9] We now report findings from an assessment of the same cohort at age 32 years, which included measurement of body fat percentage by using bioelectrical impedance analysis and of exhaled nitric oxide in addition to BMI, asthma symptoms, and lung function. We hypothesized that body fat percentage, as a better indicator of adiposity than BMI, would be associated with asthma, airflow obstruction, and airway inflammation, as indicated by exhaled nitric oxide levels, in both men and women.

METHODS

The Dunedin Study has been described in detail elsewhere.[14] Briefly, this is a longitudinal study in a birth cohort of 1037 individuals born in Dunedin in 1972-1973. The cohort represents the full range of socioeconomic status in New Zealand's South Island, and Study members are mostly of New Zealand/European ethnicity. A broad range of health, behavioral, and developmental assessments has been conducted at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, and 32 years. At the assessment at 32 years of age, 972 (96%) of the 1015 living Study members were assessed. The Otago Ethics Committees approved this study, and written informed consent was obtained.

BMI and body fat percentage

Height and weight were measured in light clothing without shoes for calculation of BMI in kilograms per square meter.

The Tanita BC-418MA (Tokyo, Japan) segmental body composition analyzer was used to measure body fat percentage by means of bioelectrical impedance analysis. This uses a 50-Hz current source with electrodes on each hand and foot to measure impedance to electrical conductivity as it passes through body fluids and calculate total and segmental (trunk and each limb) fat mass.

Respiratory questionnaires

At each assessment since age 9 years, questions were asked about current and prior asthma and asthma symptoms using previously developed questionnaires.[15] Current asthma is defined as self-reported diagnosed asthma at age 32 years with symptoms in the previous 12 months and current wheeze as episodes of wheezing in the last year, excluding those with only 1 or 2 episodes, each lasting less than 1 hour. Cumulative smoking history to age 32 years was updated from previous assessments. One pack-year is defined as the equivalent of 20 cigarettes a day for 1 year. Current smoking was defined as smoking cigarettes daily for at least 1 month in the previous year.

Exhaled nitric oxide

Fractional exhaled nitric oxide levels were measured with a Logan LR2000 chemiluminescence analyzer (Rochester, United Kingdom). After maximal inhalation and without breath holding, study members exhaled at a flow rate of 50 mL/s.[16] Exhaled nitric oxide in parts per billion (ppb) was recorded continuously throughout expiration. Individual results were read at the first nitric oxide plateau, and the mean of 2 acceptable tests was recorded. The first 44 Study members were tested using a flow rate of 250 mL/s, and results were adjusted to 50 mL/s by using a previously validated formula.[17]

Spirometry

Spirometric measurements were performed to meet American Thoracic Society standards[18] by using a Sensormedics 6200 plethysmograph with Vmax version 4.3b software (Yorba Linda, Calif). Study members were seated in the plethysmograph and wore nose pegs. At least 3 acceptable maneuvers were obtained, with the best FEV_1 and forced vital capacity (FVC) from any of the acceptable tests reported and used for calculation of FEV_1/FVC ratio. A portable spirometer (Spiropro, Sensormedics) was used to test Study members ($n = 27$) who refused to sit in the plethysmograph or were unable to attend the research unit. Participants were asked to avoid using any of their inhalers on the day of the test. All test results were reviewed by a senior technician to ensure that only acceptable and reproducible results were entered for analysis. Testing equipment was calibrated daily, and weekly quality control measures were obtained to ensure the accuracy and precision of the test equipment.

Bronchodilator response

Spirometric measurements were repeated 15 minutes after administration of 200 μg of salbutamol (albuterol) through a metered-dose inhaler and a Volumatic spacer device (Allen & Hanburys, Stockley Park, Middlesex, United Kingdom). A 10% increase in FEV_1 over baseline was considered a significant bronchodilator response.

Skin prick tests

Skin prick tests were performed for house dust mite *(Dermatophagoides pteronyssinus)*, rye grass, cat, dog, horse, wool, *Aspergillus fumigatus*, *Penicillium* species, *Cladosporium* species, *Alternaria* species, kapok, and cockroach (ALK Allergens, Allergy Canada, Thornhill, Ontario, Canada). A wheal measurement was taken as the mean of the greatest length and the width at 90°. A diameter of at least 2 mm larger than that produced by the saline control was considered positive. Atopy was defined as a positive response to 1 or more allergens.

Statistical analysis

Associations between body fat percentage and the dependent variables of asthma, wheeze, FEV_1/FVC ratio, bronchodilator responsiveness, atopy, and exhaled nitric oxide level were analyzed by using linear and logistic regression. Because of our previous findings with BMI,[9] men and women were analyzed separately, and because smoking might affect both respiratory symptoms and adiposity, analyses of respiratory outcomes were adjusted for current and lifetime (pack-years) smoking history and tested for interactions between current smoking and adiposity. Analyses were repeated by using BMI and trunk fat measurements as the independent predictors. Body fat measurements were approximately normally distributed. Exhaled nitric oxide results were transformed to log values to approximate a

TABLE I. Cross-tabulation of individuals according to body fat percentage and BMI categories

	Body fat (%)					
	Women (n = 437)			Men (n = 487)		
BMI (kg/m^2)	Normal (<33%)	Overfat (33% to 38.9%)	Obese (≥39%)	Normal (<20%)	Overfat (20% to 24.9%)	Obese (≥25%)
Normal (BMI <25.0)	195	37	3	155	40	5
Overweight (BMI 25.0-29.9)	11	66	39	57	110	48
Obese (BMI ≥30.0)	0	6	81	1	10	61

Body fat percentage categories are defined according to the predicted body fat percentage for white and African American subjects.[6]

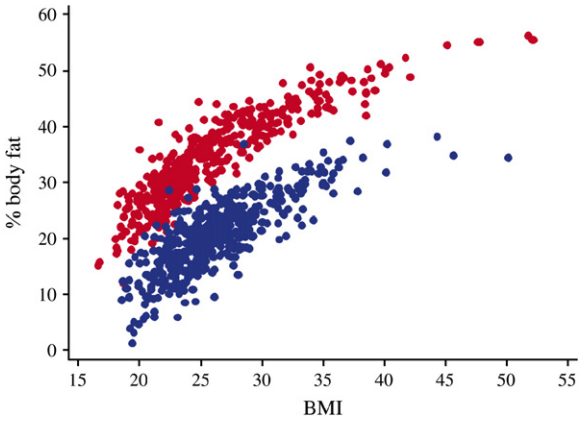

FIG 1. Plot of body fat percentage and BMI values for women and men. *Red circles*, women; *blue circles*, men.

normal distribution. The linearity assumption of the models was tested by using a quadratic term for "%bodyfat^2" and by means of visual inspection by quartiles of fat percentage. Pregnant women (n = 31) and those without body fat measurements were excluded from all analyses. *P* values of .05 or less were considered significant. Analyses were performed with Stata version 9.1 software (College Station, Tex).

RESULTS

Adiposity

Body fat percentage was used to determine adiposity and was measured in 438 nonpregnant women and 487 men. Women had a higher mean body fat than men (34.2% [SD, 8.0%] vs 20.7% [SD, 6.2%], respectively; $P < .001$). Current smokers had lower body fat percentages than nonsmokers (women: 33.3% vs 34.7%, $P = .081$; men: 19.1% vs 21.6%, $P < .001$). Similar differences were found for percentage of trunk fat. Mean BMI was not significantly different between women (25.9 kg/m^2 [SD, 5.6 kg/m^2]) and men (26.3 kg/m^2 [SD, 4.3 kg/m^2]). Strong correlations were found between BMI and body fat percentage in women ($r = 0.89$) and men ($r = .80$), but there was a wide range of body fat measurements within BMI categories, with a large amount of crossover between BMI and body fat groups (Table I[6] and Fig 1).[19] According to standard definitions,[7] 44% of men and 26% of women were overweight (BMI, 25-29.9 kg/m^2), and an additional 15% of men and 20% of women were obese (BMI, ≥30 kg/m^2).

Adiposity, asthma diagnosis, and wheezing symptoms

Current asthma was reported by 72 (16%) of 438 nonpregnant women and 89 (18%) of 487 men. Current wheeze was reported by 120 (27%) of 438 women and 138 (28%) of 487 men. In women there was a significant association between body fat percentage and current asthma (Table II and Fig 2). There was no association between body fat percentage and current wheeze in either sex (Table II).

Adiposity, airflow obstruction, and bronchodilator responsiveness

In women there was a significant inverse association between the FEV_1/FVC ratio and body fat percentage, indicating greater airflow obstruction in those with higher body fat (Table II and Fig 2). There was no significant association with bronchodilator responsiveness to salbutamol, which was present in 28 (6.6%) of 426 of women. By contrast, in men there was a significant positive association between FEV_1/FVC ratio and body fat percentage, indicating that those with less fat were more likely to have airway obstruction. There was also a significant association between lower body fat percentage and bronchodilator responsiveness, which was present in 61 (12.9%) of 474 of men.

There was evidence that the association between the FEV_1/FVC ratio and body fat in men was nonlinear (*P* value for %bodyfat^2 term = .014). There was also an interaction between smoking and body fat percentage for the FEV_1/FVC ratio in men ($P = .041$). Subgroup analysis by current smoking status indicated that the positive association between fat percentage and the FEV_1/FVC ratio was most prominent in smokers (n = 176, coefficient = 1.51, $P = .002$), with a weaker and nonsignificant positive association in nonsmokers. The association between higher fat percentage and reduced bronchodilator responsiveness was also stronger in men who smoked (n = 173; odds ratio [OR], 0.48; $P = .002$) than in nonsmokers, although the statistical interaction between smoking and fat

TABLE II. Associations between body fat and asthma, wheeze, lung function, and exhaled nitric oxide level

	Women				Men			
	n	OR	95% CI	*P* value	n	OR	95% CI	*P* value
Asthma	437	1.30	1.01 to 1.68	.043	487	0.96	0.76 to 1.22	.75
Wheeze	437	0.93	0.75 to 1.16	.51	487	1.00	0.82 to 1.22	1.00
BDR	422	0.96	0.64 to 1.45	.86	471	0.65	0.49 to 0.87	.004
	Women				Men			
	n	Coefficient	95% CI	*P* value	n	Coefficient	95% CI	*P* value
FEV_1/FVC	430	−0.60	−1.18 to −0.01	.046	477	0.82	0.20 to 1.44	.010
Ln eNO	421	−0.04	−0.10 to 0.02	.17	468	−0.03	−0.09 to 0.02	.25

Results from linear and logistic regression analyses by using body fat percentage as the predictor variable and adjusted for current and lifetime smoking history. Body fat measurements were expressed as SD scores. FEV_1/FVC ratio was expressed as a percentage. ORs indicate the change in odds of having the outcome, and coefficients indicate the change in the outcome measure for each SD change in body fat percentage (an OR of 1 or a coefficient of 0 indicates no difference). *OR*, Odds ratio from logistic regression; *BDR*, bronchodilator response (10% or greater increase in FEV_1 after salbutamol); *coefficient*, coefficient from linear regression; *Ln eNO*, natural logarithm of the exhaled nitric oxide level in parts per billion.

percentage was of borderline significance ($P = .08$). There were no interactions between smoking and body fat percentage for the FEV_1/FVC ratio ($P = .79$) or for bronchodilator responsiveness ($P = .37$) in women.

Adiposity and airways inflammation

Exhaled nitric oxide levels were significantly higher in those with asthma (geometric mean women: 14.9 ppb [95% CI, 12.4-18.0 ppb]; men: 20.6 ppb [95% CI, 17.3-24.6 ppb]) compared with levels in those without asthma (women: 11.1 ppb [95% CI, 10.4-11.8]; men: 14.3 ppb [95% CI, 13.4-15.3 ppb]). Current cigarette smokers had lower exhaled nitric oxide levels than nonsmokers ($P <$ .001 for both sexes). No association was found between exhaled nitric oxide and body fat percentage for either sex (Table II and Fig 2). The lack of association remained when the analysis was adjusted for current use of inhaled or oral corticosteroids and when current smokers were excluded (data not shown).

Adiposity and atopy

A positive skin prick response to at least 1 allergen was found in 251 (58%) of 436 women and 294 (61%) of 479 men. There was a nonsignificant trend toward a positive association between body fat percentage and atopy in women (n = 433; OR, 1.18; $P = .10$). There was no significant association in men (n = 476; OR, 1.09; $P = .38$).

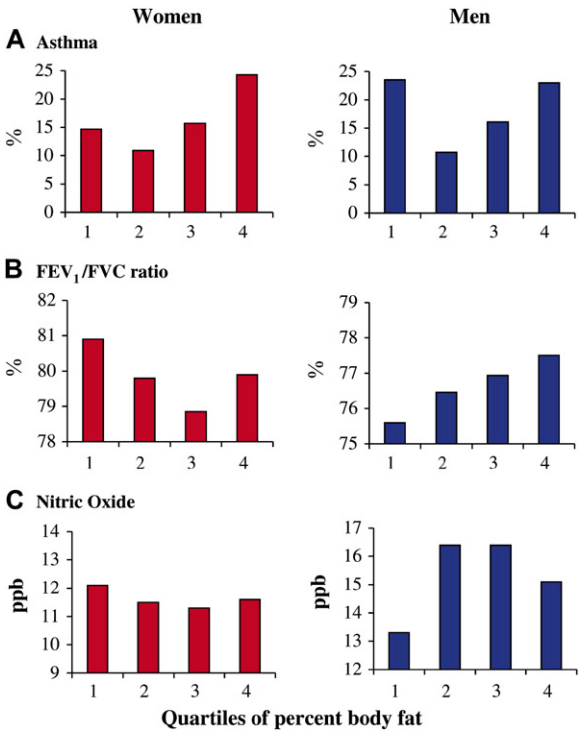

FIG 2. Asthma (**A**), mean FEV_1/FVC ratio (**B**), and mean exhaled nitric oxide level (**C**) according to quartiles of body fat percentage in women and men. Exhaled nitric oxide values are presented as geometric means.

DISCUSSION

These results confirm that there is an association between obesity and asthma in adult women. They extend earlier observations by using body fat percentage in place of BMI as the measure of adiposity. No association was found between asthma and adiposity in men by using either BMI or body fat percentage. In women, a higher body fat percentage was also associated with airflow obstruction on spirometry but not with bronchodilator responsiveness to salbutamol. By contrast, we found a lower body fat percentage in men to be associated with both airflow obstruction on spirometry and a positive bronchodilator response. There was no association between body fat and airway inflammation, as measured on the basis of exhaled nitric oxide levels, in either sex.

Several reports have found an association between obesity and asthma in women but not in men.[2-4] A possible explanation for this sex difference is that BMI is a poor measure of adiposity in men. Indeed, we found that the correlation between BMI and body fat percentage was lower in men ($r = 0.80$) than in women ($r = 0.89$). An

association between adiposity and asthma could be obscured if a substantial proportion of men are misclassified as overweight or obese when, in fact, their increased BMI is due to increased muscle mass rather than adipose tissue. Use of body fat percentage avoids this misclassification, and our findings suggest that there is a genuinely different association between adiposity and asthma in men and women. In fact, for all of our analyses, a similar pattern of results was observed when we used BMI instead of body fat percentage (see Table E1 in the Online Repository at www.jacionline.org).

It remains possible that fat tissue has similar biological properties with respect to asthma in both men and women, but the association is only observed in women because they have a greater body fat percentage for any given body weight. In other words, if men had similar body fat percentages as women, the association between asthma and adiposity might become apparent. However, this would only occur in men with extreme obesity. Moreover, increased body fat was significantly associated with a higher FEV_1/FVC ratio in men, indicating that men with high body fat had less airflow obstruction, the opposite of what was found in women, again suggesting that the interaction between adiposity and airway function is different in men and women. Men with more body fat were also less likely to have a significant response to bronchodilators. The reasons for the associations between body fat and a higher FEV_1/FVC ratio and reduced bronchodilator responsiveness in men are not clear, although both of these associations were stronger among smokers.

An association between adiposity and asthma in men could also be obscured by means of a nonlinear association. Several studies have reported a U-shaped relationship between BMI and asthma, with both underweight status and obesity being associated with an increased prevalence of respiratory symptoms and asthma.[8,20] In some studies this has been observed only in men.[21,22] Although we found no statistical evidence of a nonlinear association between body fat and asthma (the term for %bodyfat^2 was not significant), men in the lowest and highest quartiles of body fat percentage had the highest numerical prevalence of asthma (Fig 2). There was also statistical evidence for a nonlinear association between the FEV_1/FVC ratio and body fat in men, which was due to reduced ratios in a few individuals at the low end of the percentage of fat distribution.

To our knowledge, this is the first large study to examine the association between exhaled nitric oxide measurement and obesity in adults. The level of nitric oxide in exhaled air is a useful surrogate marker of airway inflammation in asthma, which correlates well with sputum eosinophilia and airway hyperresponsiveness.[23] We found no significant association between exhaled nitric oxide and body fat percentage in either sex. Thus despite overweight and obese women reporting more diagnosed asthma and having increased airways obstruction, there was no evidence of increased airway inflammation. It is possible that airflow obstruction in the overweight and obese women affected the nitric oxide readings: exhaled nitric oxide levels might be influenced by airway caliber[16] because the reduction in airflow that occurs with obstruction allows more time for diffusion of nitric oxide from airway walls. However, this should bias the findings toward increased exhaled nitric oxide levels with increasing adiposity. Our findings support those of Leung et al,[11] who found no difference in exhaled nitric oxide levels between obese and nonobese asthmatic or control subjects aged 7 to 18 years.

Why adiposity is associated with asthma in women remains unclear. The finding that adiposity is associated with a low FEV_1/FVC ratio but not with higher exhaled nitric oxide levels suggests that airflow obstruction might be due to a mechanical, rather than inflammatory, mechanism. One possibility is that the distribution of body fat affects breathing symptoms and lung function. However, we used a bioelectrical impedance device that measures segmental fat distribution, and analyses with trunk fat percentage provided very similar results to those with total body adiposity (see Table E2 in the Online Repository at www.jacionline.org). It seems unlikely that differences in the distribution of body fat between men and women explain the differences in the association with asthma.

In this analysis there was a nonsignificant trend toward an association between body fat percentage and atopy in women (n = 433; OR, 1.18; $P = .10$). An earlier analysis of this cohort also found a weak association between BMI and atopy in an unadjusted analysis.[9] Other studies have had mixed findings on the association between atopy and obesity, and the issue needs to be investigated further.[24-27] If an association between adiposity and atopy were to be confirmed, this would be more consistent with a biologically active role of fat tissue rather than a simple mechanical one.

Surprisingly, we found no association between body fat percentage and current (past year) wheezing symptoms. This differs from a previous analysis of this cohort using data collected between the ages of 9 and 26 years, which found significant associations between current wheeze and BMI in both women and men.[9] However, the finding that wheeze was not associated with adiposity suggests that the observed association between adiposity and asthma in women is unlikely to be due to overdiagnosis of asthma on the basis of nonspecific respiratory symptoms.

The associations that we have found among adiposity, asthma, and lung function were independent of childhood asthma (see Table E3 in the Online Repository at www.jacionline.org). We also found no evidence that having had a diagnosis of asthma in childhood was associated with increased body fat at age 32 years.

The present study has a number of strengths. It is a large population-based study of young adults with detailed information about their respiratory history, direct measurement of lung function, and airway inflammation. We also measured body fat percentage rather than using BMI as a surrogate measure of adiposity. Although bioelectrical impedance analysis might not be as accurate as a gold standard measure, such as dual-energy x-ray absorptiometry scanning, the real differences in fat

measurement between these techniques are small.[28-30] Body impedance tends to slightly overestimate fat mass,[28] but for large epidemiological studies, body impedance analysis is regarded as a simple and valid measure of determining body composition.[31] We believe that it is unlikely that our findings are due to errors in the measurement of body fat percentage.

In summary, this analysis has confirmed that there is an association between adiposity and asthma and airflow obstruction in women. This was not found in men, despite the use of a more accurate measure of body fat percentage instead of BMI to assess adiposity. However, we found no association between body fat and airway inflammation, as measured on the basis of exhaled nitric oxide levels, in either men or women. The findings suggest that although being overweight or obese might cause asthma symptoms and airflow obstruction in women, this is not likely to be mediated by an increase in airway inflammation.

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