Background
Several studies have demonstrated an association between obesity and asthma. However, it is uncertain if fraction of exhaled nitric oxide (FENO), which is used as a marker of airway inflammation, and atopy are associated with BMI. The aim of this study was to examine if obese subjects with asthma symptoms have a different phenotype of asthma than nonobese subjects as indicated by FENO.

**Methods**

The subjects (N = 2,187) consisted of women and men, aged 25 to 74, living in Gothenburg, Sweden, who participated in the randomly selected INTERGENE study cohort. Measurements included anthropometric measures, bioelectric impedance, FENO, pulmonary function, and blood samples for IgE; questionnaires included items on respiratory symptoms. Obesity was defined as BMI ≥ 30 kg/m². In this cross-sectional analysis, general linear models were used to analyze how FENO was associated with anthropometry, body composition, wheezing, and atopy.

**Results**

In nonobese subjects, wheezing was associated with raised FENO and atopy, whereas in contrast, obese subjects who reported wheezing had lower FENO than obese subjects without wheezing (16.1 vs 19.1 parts per billion, P < .01). The prevalence of atopy was similar in both of those subgroups (25.0% vs 20.7%, P = .4). Similarly, in 395 subjects (19%) who reported wheezing, FENO was negatively associated with BMI, waist-to-hip ratio, and percentage of body fat, whereas no significant relationships were observed in those without respiratory symptoms.

**Conclusions**

Wheezing was significantly associated with reduced FENO in obese subjects, whereas there was a positive association between wheezing and FENO among the nonobese subjects, indicating a possible difference in asthma phenotype, based on body weight.

**Abbreviations**

FENO
- fraction of exhaled nitric oxide

NO
- nitric oxide

ppb
- parts per billion

WHR
- waist-to-hip ratio

Several observational studies have demonstrated an association between obesity and asthma, and weight-loss studies have shown improvements in symptoms, medication use, and lung function. Moreover, a meta-analysis of prospective studies on BMI and incidence of asthma demonstrated a dose-response relationship. However, the specific mechanism of this association is unclear. Tantisira and Weiss suggest that obesity may affect asthma through mechanical effects, by enhancing the immune response, through related genetic mechanisms, and/or by gender-specific influences, including the hormone estrogen. The relation between obesity and asthma might also be affected by physical activity, dietary factors, and birth weight.

A new hypothesis regarding the association between obesity and asthma is that insulin resistance and atopic asthma share common inflammatory pathways. The association with insulin resistance does not seem to be present in nonatopic asthma, indicating that the underlying mechanism is different in this form of asthma. Studies reporting on the association between anthropometric measures and nonatopic vs atopic asthma, on the other hand, show inconsistent results. Moreover, in some populations, a relationship between BMI and atopy is found, whereas in others, it is not.
Fraction of exhaled nitric oxide (FENO) is being used increasingly as a marker of airway inflammation. Levels of FENO are raised in subjects with atopic asthma, but to determine whether it is a useful measure in nonatopic asthma calls for further investigation. Furthermore, more research is needed on how FENO varies with body weight, abdominal obesity, and body composition. Adipose tissue is considered to be an endocrine organ that plays an inflammatory role, and inflammatory markers in the circulation are increased in obese individuals. Obesity has been linked with the systemic inflammation associated with insulin resistance and cardiovascular disease but less is known about the possible role of adipose tissue in the development of asthma. There have been have conflicting results from studies on the relation between BMI and FENO in asthma patients, and more research is needed on how FENO varies with body weight, abdominal obesity, and body composition. Adipose tissue is considered to be an endocrine organ that plays an inflammatory role, and inflammatory markers in the circulation are increased in obese individuals. Obesity has been linked with the systemic inflammation associated with insulin resistance and cardiovascular disease but less is known about the possible role of adipose tissue in the development of asthma.

Given the inconsistent findings of previous studies, the aim of the present investigation was to explore whether obese subjects with asthma symptoms have a different phenotype of asthma than nonobese subjects as indicated by FENO, by examining how BMI, waist-to-hip ratio (WHR), and percentage of body fat are related to atopy and FENO in a population-based study and whether these associations are different in subjects with and without asthma symptoms.

Materials and Methods

Population

Adult Onset Asthma and Nitric Oxide (ADONIX) is a subproject within the population-based research program INTERGENE, which assesses the interplay between genetic susceptibility and environmental factors for the risk of chronic diseases in western Sweden. The survey started in April 2001 and continued until December 2004. The study population consisted of randomly selected women and men, aged 25 to 74 years at the time of sampling, living in the Västra Götaland Region. Altogether, the sample consisted of 8,625 eligible subjects. The overall response rate of the invited cohort was 3,610 (1,908 women [44%] and 1,702 men [39%]). The mean age was 51.2 years for women and 51.6 years for men. For the purpose of this study, pregnant women (n = 16) were excluded. Lung function and exhaled nitric oxide (NO) were examined only in the 2,187 subjects living in the Gothenburg area. Participants were asked not to eat during the last 4 h and not to smoke during the last hour before the clinical examination. In the analyses of FENO, participants who reported recent consumption of nitrate-rich foods were excluded (n = 25). The INTERGENE/ADONIX research program study procedures were approved by the ethical review board of the University of Gothenburg (No. 237/2000) and have been described by Berg et al and Strandhagen et al and at http://www.medicine.gu.se/english/phcm/public_health_and_community_medicine/research_areas/Intergene/. The FENO measurements have been described by Olin et al.

Lung Function and NO in Expired Air

FENO was measured using a chemiluminescence analyzer (NIOX-system; Aerocrine AB; Solna, Sweden) to measure exhaled NO during a slow, single exhalation against an oral pressure of 5 cm H2O. NO was measured for 10 s, aiming at an exhalation flow rate of 50 mL/s (± 10%) from second 6 to second 10 of the exhalation phase. All measurements were performed in duplicate, all within 10% deviation, and the mean concentration in parts per billion (ppb) was registered. FENO was measured before spirometry.

Spirometry was performed with a dry wedge spirometer (Vitalograph; Buckingham, England) to provide estimates of FVC, which is the maximum volume of air expired during forced expiration, and FEV1. Results are presented as percent predicted values based on age, gender, and height.

Anthropometry and Body Composition

Using World Health Organization guidelines, obesity was defined as BMI ≥ 30 kg/m2 and abdominal fatness risk zone as WHR > 0.85 for women and WHR > 1.0 for men. There is no corresponding consensus risk zone for percentage of body fat. Thus, cutoff values for high-percentage body fat were set to ≥ 40 for women and ≥ 30 for men, based on body fat percentage predicted from a BMI of 30 kg/m2 in adult populations.

Body height and weight were measured to the nearest centimeter and 0.1 kg, with the subjects in light clothing and without shoes. Waist circumference was measured at a level midway between the lower rib margin and the iliac crest, and the hip was measured as the maximal perimeter over the buttocks.
Body composition was estimated using bioelectrical impedance analysis. Whole-body electrical resistance was measured using BIA series 3-4, 50 kHz (BIACOM Gesundheitsberatung GmbH; Köln, Germany), following the instructions given by the manufacturer. The subjects rested in a supine position for 10 min before being measured with electrodes on the dorsal surfaces of the right hand, wrist, ankle, and foot. The percentage of body fat was derived from body weight and fat-free mass, using prediction equations for fat-free mass from a Danish population.[43]

**Laboratory Analysis**

Whole blood was stored at -70°C in 1.5-mL aliquots for later analysis. Atopy was defined as the presence of specific IgE antibodies to any of the following allergens: house dust mite, cat, timothy grass, and a local allergen. Class 0 was regarded as negative, and class 1 was considered positive (Phadiatop; Phamacia; Uppsala, Sweden).

**Questionnaires**

The following definitions [20], [44] of asthma and asthma-like symptoms were based on affirmative answers in a questionnaire: Physician-diagnosed asthma: Have you ever had asthma diagnosed by a physician? Current asthma: Have you had an asthma attack in the last 12 months? Asthma symptoms during the previous month: Have you had an asthma attack during the past month? Wheezing: Have you since the age of 15 ever noticed wheezing or whistling in your chest? The use of inhaled steroids was based on the reporting of the current use of medicines for asthma classified as inhaled steroids. Based on items in the questionnaire, smoking status was categorized as current smokers, ex-smokers, and never smokers.

**Statistical Analysis**

The FENO distribution was positively skewed; therefore, the analyses were performed on the natural logarithmic transformed FENO values. To calculate bootstrap mean, SD, and CI, we used the SAS macro %jackboot.sas (http://support.sas.com/kb/24/982.html) and gave the results for 1,000 resamples and bias correction. Differences between nonobese and obese subjects were tested with the \( \chi^2 \) test and the two-sample Student \( t \) test.

The associations between atopy and wheezing were examined in logistic regressions adjusted for age and gender, together with the Hosmer and Lemeshow test of model adequacy. Differences in geometric mean FENO values were assessed using general linear models. The models were adjusted for age, gender, height, atopy, reported use of inhaled steroids, and smoking status. The interactions between gender and anthropometric measures, and wheezing and anthropometric measures, were tested by including the interaction term in separate models. Women and men were analyzed together because no gender interactions were present, whereas separate analyses were performed for subjects with and without wheezing. Statistical analyses were performed using Statistical Analysis Software, version 9.1 (SAS Institute; Cary, North Carolina).

**Results**

The characteristics of obese and nonobese subjects are shown in Table 1. Obese participants were older, had decreased lung function, and were more likely to report wheezing than were those who were not obese. In women, obesity was also associated with physician-diagnosed asthma and no current smoking.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. [b] (%), Age, y</td>
<td>963 (87) (55.7 (12.8)</td>
<td>915 (85) (54.1 (12.0)</td>
</tr>
<tr>
<td>Self-reported physician-diagnosed asthma</td>
<td>6 (13) &lt; .001</td>
<td>6 (13.1) &lt; .001</td>
</tr>
<tr>
<td>Wheezing during adulthood</td>
<td>17 (32) &lt; .001</td>
<td>17 (25) &lt; .05</td>
</tr>
<tr>
<td>Respiratory symptoms last month</td>
<td>4 (10) &lt; .01</td>
<td>4 (3) ns</td>
</tr>
<tr>
<td>Respiratory symptoms last year</td>
<td>8 (17) &lt; .01</td>
<td>8 (6) ns</td>
</tr>
<tr>
<td>Reported use of inhaled corticosteroids</td>
<td>2 (3) ns</td>
<td>2 (2) ns</td>
</tr>
<tr>
<td>Atopy</td>
<td>21 (20) ns</td>
<td>27 (26) ns</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>100.1 (12.1) 94.7 (12.3) &lt; .001</td>
<td>95.3 (12.4) 88.6 (13.0) &lt; .001</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Nonobese</td>
<td>Obese</td>
</tr>
<tr>
<td>---------------</td>
<td>----------</td>
<td>-------</td>
</tr>
<tr>
<td>FEV1, % predicted</td>
<td>96.8 (13.1)</td>
<td>92.5 (13.9)</td>
</tr>
<tr>
<td>FENO, ppb</td>
<td>17.6 (12.8)</td>
<td>18.2 (13.1)</td>
</tr>
<tr>
<td>WHR</td>
<td>0.81 (0.06)</td>
<td>0.88 (0.06)</td>
</tr>
<tr>
<td>Percentage of body fat</td>
<td>32.6 (6.2)</td>
<td>45.3 (2.9)</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>22</td>
<td>13</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or %, unless otherwise indicated. FENO = fraction of exhaled nitric oxide; ns = not statistically significant; ppb = parts per billion; WHR = waist-to-hip ratio.

Fraction of Exhaled NO

Obese men had lower FENO values than did nonobese men, but there was no difference between obese and nonobese women (Table 1). Table 2 shows how FENO varies with the presence of asthma, and Table 3 shows how it varies with wheezing in obese and nonobese subjects. There was no difference in FENO between the obese subjects with or without physician-diagnosed asthma. The hypothesis was that the association between asthma and FENO differed with the presence or absence of obesity. However, the number of obese subjects with asthma was low. Therefore, wheezing, which is more prevalent but less specific, was used in further analyses. The prevalence of physician-diagnosed asthma among those with wheezing (26%) did not significantly differ between the obese and nonobese.

**Table 2 -- Asthma [a] in Relation to Atopy [b] and FENO in Nonobese and Obese Subjects (Unadjusted Analyses)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Asthma (n = 1,768)</th>
<th>Asthma (n = 110)</th>
<th>P Value</th>
<th>No Asthma (n = 279)</th>
<th>Asthma (n = 30)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy (n = 2,187)</td>
<td>22.7</td>
<td>46.4</td>
<td>&lt; .001</td>
<td>22.6</td>
<td>26.7</td>
<td>.6</td>
</tr>
<tr>
<td>FENO (n = 2,165), ppb</td>
<td>19.2</td>
<td>25.4</td>
<td>&lt; .05</td>
<td>18.1</td>
<td>20.3</td>
<td>.9</td>
</tr>
<tr>
<td></td>
<td>(18.5–19.8)</td>
<td>(20.8–30.0)</td>
<td>(16.9–19.4)</td>
<td>(14.4–26.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as % or bootstrap mean (95% CI). See Table 1 for expansion of abbreviations.

- **a** Self-reported physician-diagnosed asthma.
- **b** Presence of specific IgE antibodies to house dust mite, cat, timothy grass, or a local allergen.
- **c** χ² test and Student t test (natural logarithm FENO) within group.
- **d** χ² test and Student t test (natural logarithm FENO), nonobese subjects compared with obese subjects in those reporting asthma.

**Table 3 -- Wheezing [a] in Relation to Atopy [b] and FENO in Nonobese and Obese Subjects (Unadjusted Analyses)**

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Wheezing (n = 1507)</th>
<th>Wheezing (n = 316)</th>
<th>P Value</th>
<th>No Wheezing (n = 213)</th>
<th>Wheezing (n = 84)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy (n = 2,120)</td>
<td>21.7</td>
<td>36.7</td>
<td>&lt; .001</td>
<td>20.7</td>
<td>25.0</td>
<td>.4</td>
</tr>
<tr>
<td>FENO, all (n = 2,100), ppb</td>
<td>18.7 (18.1–19.4)</td>
<td>23.5 (20.8–26.2)</td>
<td>.05</td>
<td>19.1 (17.6–20.6)</td>
<td>16.1 (13.7–18.5)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>FENO in atopics (n = 502), ppb</td>
<td>22.1 (20.4–23.8)</td>
<td>27.1 (23.2–31.0)</td>
<td>.06</td>
<td>18.7 (15.7–21.7)</td>
<td>16.8 (12.7–21.0)</td>
<td>.3</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or %, unless otherwise indicated. FENO = fraction of exhaled nitric oxide; ns = not statistically significant; ppb = parts per billion; WHR = waist-to-hip ratio.

- **a** χ² and Student t test (FENO values were natural logarithmic transformed).
- **b** Numbers differ slightly because of missing values in some variables.
Wheeving was associated with increased FENO in the nonobese group only. In contrast, in the obese group, the mean FENO value was significantly lower among those with wheezing. This tendency was similar for atopic and nonatopic subjects (Table 3). These results were confirmed in multivariable analyses, and the same pattern (although not statistically significant) was observed when examining central obesity and high percentage of body fat (Table 4). Wheezing was significantly associated with raised FENO (Δ1.9 ppb, \( P < .001 \)) in the nonobese subjects (BMI < 30 kg/m²). In contrast, in the obese subjects with wheezing, FENO was, on average, 2.1 ppb lower (\( P < .05 \)) than in the obese subjects without wheezing (Fig 1).

### Table 4 -- Differences Between Means in Natural Logarithm FENO Values (Participants With Wheezing in Comparison With Those Without Wheezing Stratified for Obesity, Abdominal Obesity, and High Percentage of Body Fat)

<table>
<thead>
<tr>
<th>Analyzed Group</th>
<th>No.</th>
<th>Mean Difference ( [a] ) (95% CI)</th>
<th>Geometric Mean Difference FENO, ( [b] ) ppb</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt; 30</td>
<td>1,790</td>
<td>0.12 (0.05, 0.19)</td>
<td>1.9</td>
<td>.0007</td>
</tr>
<tr>
<td>BMI ≥ 30</td>
<td>294</td>
<td>-0.15 (-0.30, -0.01)</td>
<td>-2.1</td>
<td>.03</td>
</tr>
<tr>
<td>WHR ≤ 0.85 women, WHR ≤ 1 men</td>
<td>1,626</td>
<td>0.07 (-0.003, 0.15)</td>
<td>1.1</td>
<td>.06</td>
</tr>
<tr>
<td>WHR &gt; 0.85 women, WHR &gt; 1 men</td>
<td>385</td>
<td>-0.007 (-0.13, 0.11)</td>
<td>-0.1</td>
<td>.9</td>
</tr>
<tr>
<td>%BF &lt; 40 women, %BF &lt; 30 men</td>
<td>1,284</td>
<td>0.12 (0.04, 0.20)</td>
<td>1.8</td>
<td>.004</td>
</tr>
<tr>
<td>%BF ≥ 40 women, %BF ≥ 30 men</td>
<td>454</td>
<td>-0.08 (-0.20, 0.04)</td>
<td>-1.3</td>
<td>.2</td>
</tr>
</tbody>
</table>

From general linear models adjusted for age, gender, height, smoking status, atopy, and treatment with inhaled corticosteroid. %BF = percentage body fat. See Table 1 for expansion of the other abbreviations.

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\( a \) Difference in mean values of natural logarithm FENO (wheezing vs nonwheezing).

\( b \) Difference in geometric mean values of FENO, ppb (wheezing vs nonwheezing).
Figure 1  Geometric means of fraction of exhaled nitric oxide (FENO) by wheezing, from general linear models stratified for obesity adjusted for age, gender, height, smoking status, atopy, and inhaled corticosteroid. The geometric mean values of FENO are smaller than the arithmetic mean values because of the skewness of the distribution of FENO. ppb = parts per billion.

BMI, WHR, and percentage of body fat were also used as continuous variables to predict FENO in adjusted general linear models (Table 5, full models are shown in e-Tables 1-3). BMI was not significantly associated with FENO, but there was a significant interaction between wheezing and BMI, in that the relation between BMI and FENO differed between subjects with and without wheezing. Accordingly, stratified analyses were performed in which FENO was negatively associated with BMI among those with wheezing, whereas no significant relationship was observed in those without wheezing. Likewise, FENO decreased significantly with increasing WHR and percentage of body fat only in those reporting wheezing. For WHR, the negative association with FENO was also significant for all participants. Adjusting for FEV\textsubscript{1}% and FVC% did not change the results significantly (data not shown).

Table 5  -- General Linear Models With Natural Logarithm FENO Values as Dependent Variable (Models Including All Participants and Analyses Stratified by Wheezing)

<table>
<thead>
<tr>
<th>Analyzed Group</th>
<th>Predictor Variable</th>
<th>No.</th>
<th>β</th>
<th>P Value</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>BMI</td>
<td>2,084</td>
<td>-0.0042</td>
<td>.2</td>
<td>.0003</td>
</tr>
<tr>
<td>No wheezing</td>
<td>BMI</td>
<td>1,689</td>
<td>0.0033</td>
<td>.4</td>
<td></td>
</tr>
<tr>
<td>Wheezing</td>
<td>BMI</td>
<td>395</td>
<td>-0.023</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>WHR</td>
<td>2,011</td>
<td>-0.59</td>
<td>.002</td>
<td>.01</td>
</tr>
<tr>
<td>No wheezing</td>
<td>WHR</td>
<td>1,628</td>
<td>-0.33</td>
<td>.1</td>
<td></td>
</tr>
<tr>
<td>Wheezing</td>
<td>WHR</td>
<td>383</td>
<td>-1.56</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>%BF</td>
<td>1,738</td>
<td>0.00043</td>
<td>.8</td>
<td>.02</td>
</tr>
<tr>
<td>No wheezing</td>
<td>%BF</td>
<td>1,415</td>
<td>0.0041</td>
<td>.08</td>
<td></td>
</tr>
<tr>
<td>Wheezing</td>
<td>%BF</td>
<td>323</td>
<td>-0.012</td>
<td>.03</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, gender, height, smoking status, atopy, and treatment with corticosteroid. See full models in e-Tables 1–3. See [Table 1] , [Table 4] for expansion of abbreviations.

Atopy

The prevalence of atopy did not differ significantly between obese and nonobese subjects (Table 1). Asthma and wheezing were significantly associated with atopy in the nonobese subjects, whereas no corresponding associations were observed in obese subjects (Tables 2, 3). Thus, the prevalence of atopy was significantly lower among the obese subjects with wheezing than in their nonobese counterparts. In the nonobese group, the risk of wheezing was higher in atopic than in nonatopic subjects (OR, 2.1; 95% CI, 1.6-2.7; \( P < .0001 \)) when adjusting for age and gender in logistic regression, whereas no corresponding association was found in the obese group (OR, 1.3; 95% CI, 0.7-2.5; \( P = .35 \)).
Discussion

This population study confirms a negative association between BMI and FENO in subjects with asthma symptoms, which has been suggested previously by studies in nonsmoking, asthmatic adults and adolescents. In the obese group, wheezing was associated with reduced FENO, which was unexpected because it has been suggested that adiposity causes a systemic proinflammatory state that would initiate or augment airway inflammation rather than prevent inflammation in the airways. The same tendency was found in both nonatopic and atopic obese subjects with wheezing, indicating a different phenotype of asthma/wheezing in obese subjects.

In general, FENO is associated with eosinophilic airway inflammation. Recent research suggests a reclassification of asthma based on inflammatory phenotypes. We know that FENO is a marker for eosinophilic airway inflammation and is associated with atopy but it seems to be less valid as a marker of nonatopic asthma. At least one-half of all asthma cases in adults are attributable to nonallergic mechanisms, whether defined as the absence of eosinophils in the airways or as the presence of atopy, according to a review by Douwes et al. In the present study, obesity was not associated with atopy, and in the obese group, asthma and wheezing were not related to atopy. Thus, the decreased FENO values in obese subjects might indicate that wheezing is not mediated by allergic mechanisms in the most frequent subgroup of the obese. The finding that both atopic and nonatopic obese subjects with wheezing have decreased FENO, compared with those with normal weight, further supports the theory that obese subjects with wheezing have a different inflammatory phenotype that is independent of the presence of atopy.

Most studies have used BMI as a measure of overweight status. In the present study, we also assessed body fat and WHR as measures of adiposity and abdominal obesity. All three measures were inversely related to FENO in those with wheezing, indicating that body fat percentage as well as location of fat are of importance. For WHR, the negative association with FENO was significant for all participants, which might indicate an association in the total population that BMI does not catch.

Reduced FENO might be a result not only of reduced production of NO in the airway, but also of increased metabolism of NO. One explanation might be that more NO is being formed in the airway but much of it is being oxidized prior to exhalation. In fact, in patients with cystic fibrosis characterized by profound airway inflammation, FENO has been observed to be lower than in healthy controls, and is associated with the degree of structural changes in the peripheral airways. Perhaps both low and high FENO may signal respiratory disease, with increased levels associated with eosinophilic airway inflammation and decreased levels indicating disrupted epithelial lining and oxidative stress, as suggested previously by Lundberg et al and supported by Keen et al. An alternative explanation for the negative association with WHR might be that a mechanical effect on breathing pattern may influence FENO values so that increased NO values will not be detected in expiration. If so, the observed association is a matter of methodology.

A limitation of the present study is that, in order to increase power, we analyzed wheezing instead of physician-diagnosed asthma. Wheezing is a common symptom in asthma but may reflect conditions other than airway inflammation. On the other hand, is it an advantage to use this symptom instead of physician-diagnosed asthma because detection bias might play a role in the previously observed associations in patients. Obese individuals might be more likely to be diagnosed than nonobese individuals if they have more contact with the health-care system as a result of comorbidities. The present study implies that the negative association between BMI and FENO previously shown in asthma patients is not a result of such bias. It is hence a strength that the present study is based on data from a randomly selected population, even if wheezing is an imprecise measure.

Conclusions

In conclusion, the present epidemiologic data, together with results from previous studies in patients, suggest a negative association between BMI and FENO in subjects with asthma or wheezing. In addition, the present study demonstrates negative associations with WHR and percentage of body fat. The results do not support the hypothesis that sex hormones play a major role in the association between obesity and FENO because no gender interactions were present. Furthermore, the results indicate that wheezing in obesity is not associated with atopy. This might indicate that wheezing as a result of obesity is not associated with eosinophilic airway inflammation, but rather, is a reflection of other inflammatory processes or mechanical effects.

Acknowledgments

Author contributions: Dr Berg: contributed to the development of the research question, the data analysis, the interpretation of the results, and the writing of the manuscript.

Dr Thelle: contributed to the initiation and direction of the INTERGENE research program, and the writing and approval of the final version of the manuscript.
Dr Rosengren: contributed to the direction of the INTERGENE research program, and the writing and approval of the final version of the manuscript.

Dr Lissner: contributed to the direction of the INTERGENE research program, and the writing and approval of the final version of the manuscript.

Dr Torén: contributed to the direction of the INTERGENE research program, and the writing and approval of the final version of the manuscript.

Dr Olin: contributed to the development of the research question, the interpretation of the results, and the writing and approval of the final version of the manuscript.

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Additional information: The e-Tables can be found in the Online Supplement at http://chestjournal.chestpubs.org/content/139/5/1109/suppl/DC1.

Web Extra Material

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