The Relation of Body Mass Index to Asthma, Chronic Bronchitis, and Emphysema*

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Background: Recent studies have suggested a relationship between asthma and obesity. Despite these reports, the effect of being underweight or overweight as a risk factor for airway obstructive diseases (AODs) is not clear.

Objectives: To determine whether a relation of body mass index (BMI) to asthma, chronic bronchitis (CB), or emphysema exists (analysis 1), and, if so, whether the association between obesity and asthma is modified by gender (analysis 2).

Design: Nested case-control study from the longitudinal cohort of the Tucson Epidemiologic Study of Airways Obstructive Diseases.

Patients: Analysis 1: physician-confirmed incident cases of asthma (n = 102), CB (n = 299), or emphysema (n = 72) who denied any prior AODs. Analysis 2: all 169 incident cases of asthma, regardless of any previous AODs, stratified by gender and by other potential effect modifiers. In both analyses, we selected only subjects at least 20 years old who had weight and height measured during the study.

Measurements: BMI and other risk factors were assessed prior to the onset of the AOD (cases) or prior to the last completed survey (control subjects).

Results: A diagnosis of emphysema was significantly associated with a BMI < 18.5 (odds ratio [OR], 2.97; 95% confidence interval [CI], 1.33 to 6.68, when compared to healthy control subjects). A BMI ≥ 28 increased the risk of receiving a diagnosis of asthma (OR, 2.10; 95% CI, 1.31 to 3.36) and CB (OR, 1.80; 95% CI, 1.32 to 2.46). About 30% of the patients with asthma and 25% of the patients with CB (vs 16% of the control subjects, p < 0.001) were preobese or obese, regardless whether BMI was assessed before the diagnosis or before the onset of respiratory symptoms. The relation of elevated BMI to asthma was significant only among women.

Conclusions: Patients with emphysema are more likely to be underweight, and patients with CB are more likely to be obese. However, the temporal relationship between abnormal BMI and the onset of COPD is uncertain. Preobese and obese women are at increased risk of acquiring asthma. This relation, particularly if it is causal, has potentially relevant public health implications. (CHEST 2002; 122:1256–1263)

Key words: asthma; body mass index; chronic bronchitis; COPD; emphysema; obesity

Abbreviations: AOD = airway obstructive disease; BMI = body mass index; CB = chronic bronchitis; CI = confidence interval; OR = odds ratio

The effect of body mass index (BMI) on the incidence and prevalence of airway obstructive diseases (AODs)—asthma, chronic bronchitis (CB), and emphysema—is not clear. The nature of the relationship between BMI and AODs is also complicated by the potential effect respiratory symptoms can have on appetite and physical activity. For example, subjects with AOD may be more likely to avoid exercise, adopt a sedentary lifestyle and, in turn, gain weight. If this were the case, obesity would be a result rather than a cause of obstructive diseases. This issue has not been clarified, as most of the previous studies have been cross-sectional or retrospective.

Chen et al found that a BMI < 20 among male subjects and a BMI ≥ 28 among female subjects were associated with an increased prevalence of COPD (CB or emphysema). However, the potential
confounding effect of comorbid asthma was not addressed and, within the COPD group, no distinction was made between a diagnosis of CB and emphysema.

The relationship to an abnormal BMI has been more extensively studied for asthma than COPD. Higher levels of BMI and higher proportions of obese subjects have been found among patients with asthma than control subjects, both in pediatric and adult populations. Several studies have reported this association to be stronger among female than male subjects.

To our knowledge, only one study used longitudinal data to address the relationship between obesity and asthma among adults. In that study, within a longitudinal community population, three working hypotheses: (1) an abnormally low or high BMI is associated with AODs among adults, (2) the relation of abnormal BMI to asthma and CB does not differ between female and male subjects.

Based on this previous evidence, we aimed to test, in a longitudinal community population, three working hypotheses: (1) an abnormally low or high BMI is associated with AODs among adults, (2) the relation of abnormal BMI to asthma and CB does not differ when weight is assessed before the onset of respiratory symptoms rather than before the diagnosis, and (3) the association between abnormal BMI and asthma does differ between female and male subjects.

MATERIALS AND METHODS

We used data that were collected as part of the Tucson Epidemiologic Study of Airways Obstructive Diseases, a prospective cohort study on a stratified cluster sample of white non-Mexican American households enrolled between March 1972 and April 1973. Details of the enrollment process and interview techniques have been previously reported. Briefly, square blocks in the Tucson area were stratified based on the age of the head of the household, ethnic group, and socioeconomic status, and represented the sampling frame of the study. The initial participants numbered 3,905 from 1,655 households, but new enrollees were added by marriages and births over time.

Between 1972 and 1992, participating subjects were monitored in 12 periodic surveys, obtained approximately 1.5 to 2 years apart. During each survey, they completed a standardized questionnaire providing information on respiratory symptoms, pulmonary diseases, occupation, smoking history, as well as histories of other diseases. Except during survey 4, participants also had their weight and height measured by the study nurses with standardized equipment.

BMI was computed as weight divided by the square of height, and was grouped into four categories: underweight (BMI < 18.5), normal (BMI ≥ 18.5 and < 25), mild overweight (BMI ≥ 25 and < 30), and obese/obese (BMI ≥ 30). Allergy skin-prick tests for the most common allergens in the Tucson area were performed up to three times for each subject during the study period. A subject was considered atopic if a reaction at least 2 mm greater than the size of the control was recorded for at least one of the tested allergens. Blood samples were obtained and serum IgE levels were measured up to three times for each subject at least 6 years old during the study. The paper radioimmunoassay test (PRIST; Pharmacia Diagnostics; Piscataway, NJ) method was used for the measurement of total serum IgE.

Analysis 1

Among subjects who had weight and height measured, we selected subjects at least 20 years old without any previous AODs and with a new physician-confirmed diagnosis of asthma (n = 102), CB (n = 299), or emphysema (n = 72) during the study period (incident cases). In order to code our cases as physician confirmed, we required them not only to report the presence of asthma, CB, or emphysema, but also to have been seen, diagnosed, or treated for such a disease by a doctor.

Control subjects were represented by 1,475 subjects who reported no AOD diagnosis and no respiratory symptoms (shortness of breath with wheezing, or cough and phlegm for at least 3 months in 2 consecutive years) both at enrollment and during the entire study period. Control subjects were also required to have completed at least two surveys, to have weight and height measured during the study, and be ≥ 20 years old at the last completed survey.

For cases, the presence of potential risk factors was assessed at the last nonmissing survey preceding the first report of asthma, CB, or emphysema. Similarly, among the control subjects, potential risk factors were assessed prior to the last completed survey.

As it could be argued that subjects with AOD are more likely to avoid exercise and gain weight because of their respiratory symptoms, in a limited number of cases we also assessed BMI before the onset of respiratory symptoms (shortness of breath with wheezing for asthmatics, and chronic cough and phlegm for patients with CB). These were cases in which the diagnosis of AOD had been preceded by the onset of the specific respiratory symptoms during the study and for whom information on the BMI before the onset of respiratory symptoms was available.

Comparisons between normally distributed continuous variables were performed using parametric tests, including t test for independent samples. Not-normally distributed variables were compared by means of the Mann-Whitney test. Comparisons between proportions were performed using the χ² test, and the strength of the association between BMI categories and AOD was quantified by the odds ratio (OR) and tested for statistical significance using 95% confidence intervals (CIs).

Analysis 2

To study the effect of gender on the association between BMI and asthma and in order to have a sample size suitable for stratification, we compared all 160 cases of new physician-confirmed asthma, regardless of the presence of any previous AOD, to 1,903 control subjects who reported no asthma or shortness of breath with wheezing.

The association between being preobese or obese and the onset of asthma was tested in logistic regression models adjusted for other risk factors, including the presence of CB and/or emphysema. Stratification by gender and other variables was performed according to the Mantel-Haenszel method. The presence of effect modification was detected through the test for homogeneity; testing the null hypothesis that the ORs in the different strata were equal. Adjusted ORs for the association
between any BMI category and asthma were also computed separately for female and male subjects. An \( \alpha = 0.05 \) level of significance was chosen for all the performed statistical tests both in analysis 1 and in analysis 2.

**RESULTS**

**Analysis 1**

In Table 1, each of the AOD groups is compared to the control group. Unlike the asthma and CB groups, the proportion of male subjects in the emphysema group was significantly higher than in the control group. As expected, asthmatics were more likely to be atopic and had higher total IgE levels than control subjects. Patients with CB and patients with emphysema also had higher levels of total IgE than control subjects, but their geometric means were lower than those of patients with asthma, and their atopic status did not differ from that of control subjects. Subjects in each of the AOD groups were more likely to be smokers than control subjects, but the percentages varied widely. Approximately 85% of patients with emphysema, 69% of patients with CB, and 61% of patients with asthma were current or past smokers, vs 49% of control subjects. The mean BMI did not differ between emphysema patients and control subjects. Patients with asthma and patients with CB had significantly higher mean BMIs than control subjects.

Table 2 shows the distribution by BMI categories among control subjects and patients with asthma, CB, and emphysema. Within each AOD group, the ORs refer to the risk of acquiring the disease associated with the specific BMI category as compared with the normal BMI category (BMI, 18.5 to 24.9). A BMI < 18.5 was associated with emphysema (OR, 2.97; 95% CI, 1.33 to 6.68), while patients with asthma and patients with CB were more likely to have a BMI \( \geq 28 \) (OR, 2.10; 95% CI, 1.31 to 3.36; and OR, 1.80; 95% CI, 1.32 to 2.46, respectively).

The upper part of Table 3 shows that, when adjusting for other risk factors, the ORs for the association between BMI \( \geq 28 \) (as compared with BMI < 28) and asthma or CB were still significant. The adjusted ORs were even higher than the crude ORs, particularly for asthma, suggesting the presence of an inverse confounding effect.

The lower part of Table 3 shows that 30.8% of asthmatics and 23.8% of patients with CB had a BMI \( \geq 28 \) before the onset of respiratory symptoms—the first report of “shortness of breath with wheezing” for asthma cases and of “chronic cough and phlegm” for CB cases. The respective percentages were 30.4% and 25.1% when BMI was assessed before the diagnosis of the disease. Therefore, the proportion of subjects with BMI \( \geq 28 \) and the relative crude and adjusted ORs were similar whether the BMI levels were measured before the diagnosis of the disease or before the onset of respiratory symptoms.

**Analysis 2**

Table 4 shows that the magnitude of the crude and adjusted ORs for the association between BMI \( \geq 28 \) and asthma was higher among young than older subjects, among nonatopics than atopics, among nonsmokers than smokers, and among subjects with co-presence of COPD than subjects without it. However, the test for homogeneity was not significant for any of these potential effect modifiers.

In contrast, gender was a significant effect modifier, since the crude ORs for the association between BMI \( \geq 28 \) and asthma was statistically higher for women than for men, according to the test for homogeneity (\( p = 0.056 \)). Being preobese or obese increased significantly the risk of acquiring asthma among female subjects (adjusted OR, 3.45; 95% CI, 2.10 to 5.67) but not among male subjects (adjusted OR, 1.69; 95% CI, 0.88 to 3.27).

The effect modification by gender is also shown in Figure 1, where the adjusted ORs for the association

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**Table 1—Demographics and Risk Factors for AODs Among Control Subjects and Among New Cases of Physician-Confirmed Asthma, CB, or Emphysema**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Subjects</th>
<th>Asthma (p Value)</th>
<th>CB (p Value)</th>
<th>Emphysema (p Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, No.</td>
<td>1,475</td>
<td>102</td>
<td>290</td>
<td>72</td>
</tr>
<tr>
<td>Age, yr, mean ± SD†</td>
<td>53.6 ± 21</td>
<td>46.9 ± 19 (0.002)</td>
<td>51.6 ± 19 (NS)</td>
<td>68.7 ± 12 (&lt; 0.001)</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>44.8</td>
<td>36.3 (NS)</td>
<td>39.1 (NS)</td>
<td>61.1 (0.007)</td>
</tr>
<tr>
<td>Ever smoking, %</td>
<td>48.6</td>
<td>60.8 (0.017)</td>
<td>69.2 (&lt; 0.001)</td>
<td>84.7 (&lt; 0.0001)</td>
</tr>
<tr>
<td>Positive skin-prick test results, %</td>
<td>41.6</td>
<td>68.4 (&lt; 0.001)</td>
<td>41.8 (NS)</td>
<td>32.9 (NS)</td>
</tr>
<tr>
<td>IgE in IU/mL, geometric mean</td>
<td>23.0</td>
<td>47.3 (&lt; 0.001)</td>
<td>28.5 (0.025)</td>
<td>34.5 (0.020)</td>
</tr>
<tr>
<td>BMI, mean ± SD‡</td>
<td>24.26 ± 3.9</td>
<td>25.40 ± 4.6 (0.016)</td>
<td>25.00 ± 4.6 (0.010)</td>
<td>24.12 ± 4.8 (NS)</td>
</tr>
</tbody>
</table>

*All risk factors, except age, are reported as they were assessed before onset of the AOD (cases) or before the last completed survey (control subjects). NS = not significant.

†Mann-Whitney test. Age was at first report of AOD (cases) or at last completed survey (control subject).

‡t test for independent samples.
between any BMI category, as it refers to normal weight, and asthma are computed separately for female and male subjects. Preobese or obese females are at increased risk for acquiring asthma, whereas the ORs for preobese or obese males reach only a borderline significance.

**Discussion**

There is an increasing interest in the relationship between obesity and asthma; however, there is a lack of prospective studies on the issue. By using a large longitudinal cohort, we were able to confirm the association between obesity and asthma. We found, in fact, that subjects with a BMI \( \geq 28 \) had an increased risk of acquiring asthma. The potential confounding effect of COPD on this association was addressed by excluding asthmatic patients with other previous AOD in analysis 1 and by adjusting the ORs for the presence of COPD in analysis 2.

After excluding subjects with emphysema or CB and after adjusting for other risk factors, Young et al. found BMI categories linearly correlate with prevalence rates of asthma in a large military population. A dose-response relationship between BMI levels and asthma was evident in other cross-sectional studies on adults, as well as in the prospective Nurses Health Study II.

We found asthmatic patients more likely to be preobese or obese (BMI \( \geq 28 \)) than control subjects, but we did not find the ORs for the association with asthma linearly increase across the BMI categories. However, when we performed the stratification by gender, a BMI \( \geq 28 \) was a significant risk factor for asthma only among female subjects, and the ORs did increase as BMI increased in the female group.

These findings are consistent with those of previous studies reporting the association between high BMI and asthma to be stronger among female than male subjects. Findings from the National Population Health Survey in Canada and the 1970 British Cohort Study showed that among adult women, but

### Table 2—ORs for the Association With Each AOD Across Different BMI Categories

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Subjects, No.</th>
<th>Asthma</th>
<th>CB</th>
<th>Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. OR (95% CI)</td>
<td>No. OR (95% CI)</td>
<td>No. OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Underweight (BMI &lt; 18.5)</td>
<td>62</td>
<td>5</td>
<td>1.31 (0.51–3.41)</td>
<td>15</td>
</tr>
<tr>
<td>Normal (BMI, 18.5 to 24.9): reference</td>
<td>830</td>
<td>51</td>
<td>1.00</td>
<td>144</td>
</tr>
<tr>
<td>Mild overweight (BMI, 25.0 to 27.9)</td>
<td>343</td>
<td>15</td>
<td>0.71 (0.39–1.28)</td>
<td>65</td>
</tr>
<tr>
<td>Preobese/obese (BMI ( \geq 28 ))</td>
<td>240</td>
<td>31</td>
<td>2.10* (1.31–3.36)</td>
<td>75</td>
</tr>
</tbody>
</table>

*p < 0.001.
†p < 0.001.
‡p < 0.05.

### Table 3—Crude and Adjusted ORs for the Association Between the Development of Asthma or CB and BMI \( \geq 28 \), as Assessed Both Before the Diagnosis of the Disease and Before the Onset of Respiratory Symptoms

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Subjects, No.</th>
<th>Asthma</th>
<th>CB</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI as assessed before the first report of the disease, No. of subjects (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 28</td>
<td>1,235 (83.7)</td>
<td>71 (69.6)</td>
<td>224 (74.9)</td>
</tr>
<tr>
<td>( \geq 28 )</td>
<td>240 (16.3)</td>
<td>31 (30.4)</td>
<td>75 (25.1)</td>
</tr>
<tr>
<td>Crude OR (95% CI)</td>
<td>2.25† (1.44–3.50)</td>
<td>1.72† (1.28–2.32)</td>
<td></td>
</tr>
<tr>
<td>Adjusted OR† (95% CI)</td>
<td>2.50† (1.75–4.48)</td>
<td>1.90† (1.11–3.28)</td>
<td></td>
</tr>
</tbody>
</table>

| BMI as assessed before the first report of respiratory symptoms, No. of subjects (%) | | |
| < 28 | 1,235 (83.7) | 36 (69.2) | 64 (76.2) |
| \( \geq 28 \) | 240 (16.3) | 16 (30.8) | 20 (23.8) |
| Crude OR (95% CI) | 2.29† (1.25–4.19) | 1.61 (0.95–2.71) |
| Adjusted OR† (95% CI) | 3.27† (1.70–6.27) | 1.90† (1.11–3.28) |

*Shortness of breath with wheezing for asthma cases; cough and phlegm for at least 3 months in 2 consecutive years for CB cases.
†OR adjusted for age, gender, atopic status, and smoking.
‡p value < 0.001.
§p value = 0.01.
‖p value < 0.05.
not men, the ORs for the association with asthma increased with increasing BMI categories. In the Canadian study, in the highest BMI category (BMI ≥ 28), the adjusted OR for asthma was 1.89 (95% CI, 1.33 to 2.68) for women vs 0.93 (95% CI, 0.62 to 1.38) for men. In the latter study, the OR comparing young women in the highest quintile of BMI with those in the lowest quintile was 2.00 (95% CI, 1.36 to 2.94) vs 1.39 (95% CI, 0.89 to 2.17) for men.

Our findings do not support the hypothesis that obesity is the result rather than a cause of asthma through a reduction of physical activity related to the respiratory impairment. Due to the longitudinal nature of our data, in fact, we could assess the presence of an abnormal BMI among asthmatic patients both prior to the asthma diagnosis and prior to the onset of respiratory symptoms. In both cases, the proportion of preobese or obese subjects was significantly higher than among control subjects. We identified the onset of respiratory symptoms with the first report of shortness of breath with wheezing, as these symptoms have been shown to strongly relate to asthma. However, it should be stated that the assessment of the temporal sequence between obesity and asthma is complex, as asthma can be associated to respiratory symptoms other than shortness of breath with wheezing, and it is very difficult to distinguish with any certainty incident from recurrent asthma cases in an adult population.

Several explanations for the association between obesity and asthma are possible. First, the presence of potential confounders should be taken into account. Obese people can be more likely to be exposed to negative dietary factors, such as a deficiency of antioxidant vitamins, potentially related, in turn, to asthma. They could also be more likely to adopt sedentary lifestyle and to spend more time indoors. A sedentary lifestyle has been suggested to affect breathing patterns, reduce airway caliber, and increase exposure to environmental tobacco and

**Table 4—Crude and Adjusted ORs for the Association Between BMI ≥ 28 and Asthma After Stratification**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted* OR (95% CI)</th>
<th>Test of Homogeneity†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.57 (0.87–2.83)</td>
<td>1.69 (0.88–3.27)</td>
<td>0.056</td>
</tr>
<tr>
<td>Female</td>
<td>3.18 (2.07–4.88)</td>
<td>3.45 (2.10–5.67)</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–49</td>
<td>2.91 (1.77–4.79)</td>
<td>3.56 (2.03–6.22)</td>
<td>0.318</td>
</tr>
<tr>
<td>≥ 50</td>
<td>2.05 (1.27–3.30)</td>
<td>2.06 (1.19–3.58)</td>
<td></td>
</tr>
<tr>
<td>Atopic status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.81 (1.10–2.97)</td>
<td>2.19 (1.28–3.74)</td>
<td>0.142</td>
</tr>
<tr>
<td>No</td>
<td>3.07 (1.85–5.11)</td>
<td>3.62 (2.02–6.48)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.04 (1.31–3.19)</td>
<td>2.22 (1.34–3.68)</td>
<td>0.328</td>
</tr>
<tr>
<td>No</td>
<td>2.90 (1.69–5.00)</td>
<td>3.55 (1.88–6.70)</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.81 (1.51–5.22)</td>
<td>2.89 (1.51–5.51)</td>
<td>0.462</td>
</tr>
<tr>
<td>No</td>
<td>2.11 (1.36–3.28)</td>
<td>2.35 (1.58–4.11)</td>
<td></td>
</tr>
</tbody>
</table>

*ORs are adjusted for all the other factors included.
†The test for homogeneity tests the null hypothesis that the crude ORs in the two strata are equal.

**Figure 1.** ORs for the association with asthma and their 95% CIs across different BMI categories for female and male subjects. Normal weight is the referent category. ORs are adjusted for age, atopic status, smoking, and presence of COPD and/or emphysema.
indoor allergens strongly associated with asthma.\textsuperscript{14,15} However, obesity has been shown to be a risk factor for asthma even after adjusting for diet and physical activity.\textsuperscript{9}

Alternatively, it is possible that the association between obesity and asthma is affected by misclassification. Obesity leads to an increased work of breathing and predisposes to sleep disorders. The breathlessness associated with these conditions could be misinterpreted by the patients as asthma symptoms leading to misclassification. However, many studies have used physician-confirmed asthma as main outcome or even stricter definitions, reducing the risk of misclassification.

In elderly populations, the potential misclassification of cardiac diseases as asthma cases should be also taken into account. Congestive heart failure, in fact, is one of the most common causes of dyspnea in the elderly,\textsuperscript{16} and has been associated with bronchial hyperresponsiveness.\textsuperscript{17} Obesity is a known risk factor for cardiac diseases. However, if our findings were explained by such a misclassification, we would expect the association between obesity and asthma to be stronger among the subjects at increased risk of cardiac diseases, such as in older subjects. Instead, we found the ORs for the association between obesity and asthma to be higher in the group of 20- to 49-year-old subjects than in the group of older subjects.

Several mechanisms have been proposed for a potential causal relationship between obesity and asthma. Obesity can directly affect the airway caliber through the chest wall restriction. Narrowing of airways and a reduction of lung volumes have been associated with bronchial hyperreactivity.\textsuperscript{18} Obesity also predisposes to gastroesophageal reflux disease, a known risk factor for asthma.

According to these potential mechanisms, however, the effect of obesity on asthma would be expected to be similar in both sexes, whereas the association between obesity and asthma was significant only among women. The effect modification by gender suggests that sex hormones could be involved in the causal pathway. Estrogen and progesterone levels are affected by obesity and are related to asthma as well. By assessing BMI at age 11 years and presence of wheezing at age 11 years and 13 years, Castro-Rodriguez et al\textsuperscript{2} found that the association between overweight status and asthma was stronger among girls whose puberty started before the age of 11 years than among girls whose puberty started later. Also, among adult females, at least postmenopausal women, BMI has been shown positively associated with plasma estrogen that, in turn, could increase the risk of acquiring asthma.\textsuperscript{19}

We found emphysema associated with a BMI < 18.5 and CB associated with a BMI ≥ 28. The temporal sequence between abnormal BMI and COPD (emphysema or CB) is complex to assess. COPD and smoking, in fact, are likely to affect weight according to a bidirectional relationship. We assessed BMI before the diagnosis of COPD and, for patients with CB, before the onset of chronic cough and phlegm (clinical definition\textsuperscript{20}). However, as the onset of smoking habits dated back to the years preceding the enrollment in the study for most COPD patients, we could not assess the temporal sequence of smoking, abnormal BMI, and onset of COPD, despite the longitudinal nature of our data. Further research is required to clarify this complex interrelationship.

The association between emphysema and malnutrition is known but not fully understood. Recent findings from the Baltimore Longitudinal Study of Aging\textsuperscript{21} suggest that low BMI could itself be a risk factor for COPD. In this study, men in the lowest BMI tertile at baseline were almost three times more likely to receive a diagnosis of COPD during the follow-up period than men in the highest tertile. In another study,\textsuperscript{22} underweight patients with COPD were found to have lower carbon monoxide diffusing capacity and higher dyspnea scores than normal-weight patients with COPD. These characteristics are traditionally attributed primarily to the more emphysematous form of COPD.\textsuperscript{23} Emphysema patients can progressively lose weight due to several mechanisms. For instance, it has been hypothesized that the oxygen cost of breathing is increased in these patients\textsuperscript{24,25} and the caloric intake is reduced since large meals can induce shortness of breath. Although we assessed the BMI before the AOD diagnosis in our study, it is likely that most of the patients with emphysema experienced a gradual onset of the pulmonary obstructive disease years before receiving the diagnosis. In this case, the effect of the disease on the nutrition status, rather than the effect of malnutrition on the disease, could explain the association between low BMI and emphysema.

Our data also confirm that the association between BMI and COPD is largely affected by the type of diagnosis. In a prospective epidemiologic study, Higgs et al\textsuperscript{26} found leanness to have a predictive value for developing AODs among men but not women. Similarly, in a cross-sectional study,\textsuperscript{1} a BMI < 20 among male subjects and a BMI ≥ 28 among female subjects were associated with an increased prevalence of COPD. However, since no distinction was made between emphysema and CB, it is possible that these findings were related to the different distribution of the two types of COPD within the genders. Male subjects, in fact, have been shown to be more likely to have a diagnosis of emphysema and
female subjects a diagnosis of CB. In our study, we broke down the COPD group according to these diagnoses (emphysema or CB) and found emphysema associated with low BMI categories and CB with high BMI categories. However, we acknowledge that an epidemiologic distinction between the two diseases is difficult and that a physician’s diagnosis of COPD itself could be influenced by the weight of the patients, according to the traditional distinction of “plethoric” CB and “thin” emphysema. The risk of misclassification may be particularly relevant for CB patients. We have previously shown that the vast majority of subjects with new onset of CB do not satisfy the symptom criteria of chronic cough and phlegm at the first report of the disease, and, consistently, less than one third of our CB cases had chronic cough and phlegm at any time before receiving the diagnosis. Nevertheless, by restricting the analysis to these patients with CB, we were still able to confirm the association between obesity and CB. Of note, by combining patients with CB and patients with emphysema in a single COPD category, we would find a U-shaped risk trend, meaning that both low and high BMIs increase the risk for the disease.

To reduce the risk of misclassification, we selected only physician-confirmed cases, but the physician-confirmed diagnosis was still reported by the patient and could be sensitive to recall bias and lack of specificity or sensitivity. This problem cannot be completely ruled out, as some limitations to the specificity and sensitivity of case definition are intrinsic to the design of large epidemiologic studies.

In conclusion, emphysema is associated with being underweight; asthma and CB are associated with being preobese or obese. The temporal sequence between smoking, abnormal BMI, and development of COPD (emphysema or CB) is complex to assess. In contrast, the development of asthma seems to be temporally associated to a BMI ≥ 28, as patients with asthma are more likely to be obese both after and before the onset of respiratory symptoms. The association between elevated BMI and asthma is significant only among female subjects.

ACKNOWLEDGMENT: The authors thank Margaret Kurzius-Spencer, MS, MPH, for her comments and suggestions.

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