Body Mass Index and the Risk of COPD*

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Background: Previous studies have documented the prognostic value of low body weight in patients with COPD and also in general populations. However, it is not clear whether low body weight is a risk factor for COPD or a consequence of established disease.

Study objective: To determine whether asymptomatic subjects with low initial body mass were at a greater risk of having COPD develop during subsequent follow-up.

Design and subjects: Observational retrospective study of 458 male and 192 female participants (age range, 40 to 73 years) in the Baltimore Longitudinal Study of Aging. At baseline, the participants did not have COPD. After mean follow-up periods of 10.2 years for the men and 6.4 years for the women, 40 men and 7 women received a diagnosis of COPD.

Methods: Cox proportional-hazards regression models were used to assess the relationship between COPD diagnosis and baseline body mass index (BMI) in men.

Results: The risk of COPD developing in men varied inversely with baseline BMI, even after adjusting for other risk factors, including cigarette smoking, age, FEV\textsubscript{1} percent predicted, abdominal obesity, and educational status. In men, the relative risk of COPD developing for the lowest BMI tertile relative to the highest tertile was 2.76 (95% confidence interval, 1.15 to 6.59). The small number of women who had COPD did not allow us to draw conclusions regarding BMI as a risk factor for COPD.

Conclusion: After controlling for confounding variables, men with low BMI are at increased risk for getting COPD.

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Key words: body mass index; body weight; lung diseases, obstructive

Abbreviations: BLSA = Baltimore Longitudinal Study of Aging; BMI = body mass index; CI = confidence interval; RR = relative risk; WHR = waist-hip ratio

Nutritional depletion and weight loss are features of COPD. Using the criteria of weight < 90% of ideal body weight or weight loss of 5 to 10% of initial body weight, the incidence of malnutrition is 24 to 35% in patients with moderate-to-severe COPD.\textsuperscript{1} Several studies\textsuperscript{2–4} have documented the association between low body mass and poor prognosis and mortality in patients with established COPD. Wilson et al\textsuperscript{2} found that in male patients with COPD, weight was a significant predictor of survival even after adjusting for FEV\textsubscript{1}. Gray-Donald et al\textsuperscript{3} reported that in patients with severe COPD, low body weight was associated with respiratory mortality. Additionally, in a large study of patients with COPD receiving domiciliary oxygen therapy or mechanical ventilation, Chailleux et al\textsuperscript{4} found that lower body mass index (BMI) was an independent negative determinant of survival in patients with COPD.

More recently, body weight has been shown to predict respiratory mortality in general population samples. Results from the Honolulu Heart Program\textsuperscript{5} indicated that in elderly Japanese-American men, age-adjusted mortality was highest in those with both BMI < 21 kg/m\textsuperscript{2} and FEV\textsubscript{1} percent predicted < 70%. Furthermore, the Adventist Mortality Study of nonsmoking men and women demonstrated that low BMI was associated with an increased risk of respiratory disease mortality.\textsuperscript{6,7} In another general population study, Landbo et al\textsuperscript{8} selected subjects with COPD from the Copenhagen City Heart Study. Their results showed that low BMI predicted poor survival after adjustment for age, ventilatory function, and smoking.

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The relationship between body mass and pulmonary function is complex and is influenced by several factors that include age, gender, and smoking status, among others. Recently, we have shown that abdominal obesity has a negative effect on pulmonary function that is more prominent in men than women. In addressing the association between body mass and lung function, Nemery et al. raised the possibility that subjects who are susceptible to chronic obstructive lung disease may be leaner than subjects who were not susceptible. Thus, it is not clear whether low body weight is a risk factor for COPD or merely a consequence of established lung disease. Therefore, we examined this question using the Baltimore Longitudinal Study of Aging (BLSA), a long-term aging study, which afforded us the opportunity to find out whether asymptomatic subjects with lower initial body mass were at a greater risk of COPD developing during subsequent follow-up.

Materials and Methods

Study Population

The BLSA was started in 1958 as a long-term multidisciplinary study of normal human aging conducted by the intramural research program of the National Institute on Aging. The open-panel study continuously recruits community-dwelling volunteers, predominantly from the Washington-Baltimore area. In 1978, women began enrolling in the BLSA. The BLSA study participants are generally well educated and in good health, and entry into the study. All participants give written informed consent as approved by the Institutional Review Board. Participants return approximately every 2 years for 2 days of comprehensive clinical, physiologic, and psychological measurements, including spirometry. From the BLSA population of 1,227 men and 645 women with smoking histories who underwent spirometry, physical examination, and anthropometric measurements, we selected 877 men and 424 women between the ages of 40 years and 75 years. From this sample, the following subjects were excluded: 224 men and 132 women because of nonreproducible spiromograms; 33 and 36 men and women who had smoked less than daily within the past 2 years and who did not meet the definition of a never-smoker. Three to five packages of pipe tobacco during their lifetime. Former smokers were those who had quit smoking > 2 years before the visit date. Never-smokers were those who had smoked cigarettes every day or who had quit smoking < 2 years before the visit date. If a participant subsequently received a diagnosis of COPD at the first visit and 5 men and 5 women because of a diagnosis of COPD at the first visit and 5 men who received a diagnosis of COPD and did not have abnormal spirometry findings. This resulted in a final study group of 458 men and 192 women who had a minimum of two visits and did not have COPD at baseline. The earliest available BLSA examination that included the relevant study information was considered the baseline visit. If a participant subsequently received a diagnosis of COPD, the visit at which the diagnosis was made became, for the purpose of this study, the last visit. However, for participants who did not have COPD throughout the period of observation, the most recent visit with complete data was considered the last visit.

Spirometry

Spirometric testing in the BLSA started in 1962 for men and in 1978 for women, and continued until 1994. Testing was performed as previously described with a volume-displacement water-sealed spirometer that met the accuracy criteria of the American Thoracic Society. After 1987, measurements were digitally recorded to permit automated determination of quality and reproducibility. Spirometry tracings that were collected before 1987 were digitized to allow computerized assessment of quality and reproducibility. Only those participants who demonstrated two acceptable quality maneuvers that were reproducible within 5% of the largest value were included in the present study. Reproducibility criteria were met when the second-lowest FEV1 was within 5% of the largest value. FEV1 percent predicted was calculated by dividing the observed FEV1 by the corresponding predicted FEV1 values derived from the BLSA sex- and race-specific cross-sectional FEV1 prediction equation.

Anthropometric Measurements

Anthropometric measurements were obtained at each visit. Measurement of height was made using a clinical stadiometer in bare or stocking feet. Body weight was measured with a calibrated precision scale with subjects wearing a hospital gown. BMI, defined as weight (kilograms) divided by the square of height (meters), was calculated. Men were classified into tertiles of baseline BMI. Waist-hip ratio (WHR) was measured in the standing position, as previously reported, using a flexible metal tape.

Smoking and Socioeconomic Status

Smoking histories were obtained from the subjects and classified as reported previously. Current cigarette smokers were those who smoked cigarettes every day or who had quit smoking < 2 years before the visit date. Never-smokers were those who had not smoked > 5 to 10 packs of cigarettes, 50 to 75 cigars, or three to five packages of pipe tobacco during their lifetime. Former smokers were those who had quit smoking > 2 years before the visit. Occasional smokers were defined as those who had smoked less than daily within the past 2 years and who did not meet the definition of a never-smoker. Pipe and cigar smokers were those who were currently smoking pipes or cigars at the time of the examination. In this study, the effect of smoking was evaluated by comparing current smokers with those who were not currently smoking. Detailed information on pack-years of smoking was not available. Education was used as a surrogate for socioeconomic status. Because the participants were generally well educated, we assessed the effect of socioeconomic status by comparing college graduates with nongraduates.

COPD

At each visit, the BLSA medical staff performed physical examinations on the participants and recorded clinical diagnoses. Specific diagnosis was determined by the clinical staff based on medical history, including the American Thoracic Society Division of Lung Diseases pulmonary questionnaire, physical examination, pulmonary function testing, and chest radiography. In this study, COPD was considered to be present if the participants received any of the following diagnoses during follow-up: emphysema, chronic bronchitis, or chronic airway obstruction, and if FEV1/FVC was < 0.7 during follow-up. Among the five cases of emphysema in men, two cases were based on chest radiography, and one case was based on hyper-
inflation of the lungs and increased anterior-posterior chest diameter. The rationale for the remaining two emphysema cases was not stated specifically. Participants who received a diagnosis of asthma at any visit were excluded from the study cohort.

Statistical Analysis

We used the Cox proportional-hazards model to assess the relationship between baseline BMI and the diagnosis of COPD by computing the disease-specific risk ratios for BMI tertiles 1 and 2 relative to tertile 3 in male participants. Because of the small number of women who had COPD, the analysis was limited to men. In addition to tertiles of baseline BMI, candidate independent predictors included the following baseline variables: age, FEV1 percent predicted, current cigarette smoking status (1 = current smoker, 0 = not currently smoking), WHR, and education (1 = > 15-year education, 0 = ≤ 15-year education). For participants with COPD, time was calculated as the difference between age at entry and at diagnosis; for disease-free subjects, time was defined as the difference between age at entry and age at last visit. The final model was determined by backward elimination of the nonsignificant variables. Coefficients were considered significant at p ≤ 0.05. In addition, standard statistical methods including Student’s t test, analysis of variance, and the Cochran-Armitage trend test were used (Tables 1, 2). All statistical analyses were performed using SAS software (SAS Institute; Cary, NC).

Results

Participant Characteristics

Table 1 shows the characteristics of the final study group by gender. At baseline, the men ranged in age from 40 to 73.2 years (mean age, 53.1 years) and the women ranged in age from 40 to 73.2 years (mean age, 53.1 years). On average, the men had higher BMI, were better educated, and had a larger proportion of smokers than the women. After a mean follow-up of 10.2 years for the men and 6.4 years for the women, the proportion of participants with COPD was lower in women than in men (3.6% vs 8.7%, respectively). Due to the small number of women with COPD (n = 7), statistical comparisons of women in this group with their male counterparts, or with women without COPD were not performed. Overall, the women with COPD were all either current or former smokers, had lower lung function measures, and were heavier and slightly better educated than the disease-free women.

Table 1 also shows that, as expected, the men with COPD had lower BMIs and FEV1/FVC ratios at baseline and at their last visit. In the few COPD subjects in whom FEV1/FVC was > 0.7 at the time of diagnosis, the ratio fell to < 0.7 during follow-up. Although WHR was also lower in the group with COPD, the difference between the two groups was not significant. Table 1 also shows that, as expected, the men with COPD had a higher proportion of smokers both at baseline and at follow-up. The education level was similar in the two groups.

Effect of Baseline BMI on the Risk of Getting COPD

To explore the relationship between baseline BMI and subsequent development of COPD, we classified the men into tertiles by BMI at first visit (Table 2). Tertile 1 was defined as BMI ≤ 24.29 kg/m², and

Table 1—Descriptive Statistics for BLSA Participants*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men Without COPD, n = 418</th>
<th>Men With COPD, n = 40</th>
<th>Women Without COPD, n = 185</th>
<th>Women With COPD, n = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first visit, yr</td>
<td>53.1 ± 10.0</td>
<td>53.0 ± 8.1</td>
<td>55.5 ± 10.2</td>
<td>55.4 ± 4.2</td>
</tr>
<tr>
<td>Age at last visit, yr</td>
<td>63.2 ± 9.3</td>
<td>65.1 ± 7.0</td>
<td>61.9 ± 9.8</td>
<td>62.9 ± 3.8</td>
</tr>
<tr>
<td>FEV1% predicted at first visit</td>
<td>100.5 ± 11.9</td>
<td>97.1 ± 14.7</td>
<td>100.4 ± 13.2</td>
<td>91.4 ± 12.2</td>
</tr>
<tr>
<td>FEV1% predicted at last visit†</td>
<td>95.6 ± 13.4</td>
<td>88.2 ± 16.9</td>
<td>99.6 ± 13.4</td>
<td>83.8 ± 13.8</td>
</tr>
<tr>
<td>FEV1/FVC at first visit†</td>
<td>0.79 ± 0.06</td>
<td>0.76 ± 0.06</td>
<td>0.80 ± 0.06</td>
<td>0.75 ± 0.06</td>
</tr>
<tr>
<td>FEV1/FVC at last visit†</td>
<td>0.76 ± 0.06</td>
<td>0.68 ± 0.07</td>
<td>0.76 ± 0.05</td>
<td>0.68 ± 0.05</td>
</tr>
<tr>
<td>BMI at first visit, kg/m²†</td>
<td>25.8 ± 3.1</td>
<td>24.4 ± 2.1</td>
<td>24.5 ± 4.4</td>
<td>25.4 ± 3.5</td>
</tr>
<tr>
<td>BMI at last visit, kg/m²†</td>
<td>26.3 ± 3.6</td>
<td>25.0 ± 2.9</td>
<td>25.2 ± 4.5</td>
<td>26.0 ± 4.5</td>
</tr>
<tr>
<td>WHR at first visit</td>
<td>0.919 ± 0.056</td>
<td>0.903 ± 0.054</td>
<td>0.762 ± 0.068</td>
<td>0.780 ± 0.053</td>
</tr>
<tr>
<td>WHR at last visit</td>
<td>0.939 ± 0.057</td>
<td>0.931 ± 0.053</td>
<td>0.776 ± 0.076</td>
<td>0.812 ± 0.037</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD or %. See “Materials and Methods” section for description of COPD.
†Comparison between men with and men without obstructive disease (p ≤ 0.05); comparisons for women were not done because of the small No. of affected women.
tertile 3 was defined as BMI > 26.63 kg/m², with tertile 2 in between the two levels. The mean ages of the men, both at baseline and at last visit, were similar in all three tertiles. Table 2 shows that as baseline BMI tertile increased, the percentage of subjects with COPD progressively decreased, while the ratio of FEV₁/FVC increased. Thus, the third tertile had the highest FEV₁/FVC and the smallest proportion of men with obstructive disease. The inverse association of baseline BMI and subsequent COPD was significant (p = 0.004 for trend). The lower FEV₁ percent predicted in the heaviest tertile, although of borderline significance (0.06), is probably caused by the higher proportion of current smokers and by the inverse relationship between abdominal obesity, as measured by WHR and FEV₁. It is interesting that the proportion of current smokers was highest in the third BMI tertile.

To determine the effect of lowering the cutoff value of the group with the lowest BMI, we performed another analysis using a cutoff point for BMI of 22 kg/m². When this was done without changing the other cutoff points, we found that the frequency of COPD diagnosis in group 1 was 14.6% (6 of 41 patients), in group 2 was 10.2% (27 of 265 patients), and in group 3 was 4.6% (7 of 152 patients). The frequencies for groups 1 and 2 were slightly larger than those reported in Table 2. Checking for trend effect using the Cochran-Armitage test gave a p value of 0.008, which was similar to that originally reported in Table 2.

The Cox proportional-hazards model, as described in the “Materials and Methods,” allowed us to adjust for the effect of smoking, age, and other baseline variables in determining the relationship between baseline BMI and the risk of getting COPD. Figure 1 shows that the risk of COPD decreased as baseline BMI tertile increased, and that the risk associated with the lightest tertile (tertile 1) relative to the heaviest tertile was significant (relative risk [RR], 2.76; 95% confidence interval [CI], 1.15 to 6.59). As expected, current cigarette smoking conferred the highest risk (RR, 3.81; 95% CI, 1.92 to 7.54). Moreover, the RR associated with increased baseline age was 1.12/yr (95% CI, 1.07 to 1.18/yr) and 3.10/decade (1.12/decade). High baseline FEV₁ percent predicted was protective, with RR of 0.97 per 1% predicted (95% CI, 0.94 to 0.99) and 0.73 (0.97/decade) per 10% predicted. Years of education and WHR were not significantly associated with the risk of COPD diagnosis in this group of men.

To determine whether the effect of the variables on the risk of COPD is similar in younger men and older men, we classified the men into two groups by age at first visit: younger (40 to 55 years) and older (> 55 years). After adjustment for the effect of smoking and other baseline variables as previously described, the age-stratified proportional-hazards model gave essentially the same results as above.

**Discussion**

The major finding of this study is that middle-aged and older men with low body weight, as measured by BMI, are at a substantially higher risk of COPD developing even after adjusting for other potential risk factors, including cigarette smoking, age, FEV₁.
percent predicted, abdominal obesity, and educational status. The inverse relationship between baseline BMI and the incidence of COPD is in agreement with the results of Higgins et al\textsuperscript{19} from the Tecumseh Community Health Study, who reported that after an average follow-up period of 15 years, the incidence rate of obstructive airway disease, defined as FEV\textsubscript{1} percent predicted <65\%, was highest in lean men and lowest in overweight men. Our finding is also consistent with results from studies of patients with established COPD of Schols and colleagues,\textsuperscript{20} and other investigators,\textsuperscript{2-4} and also from general population studies,\textsuperscript{5-8} all of which demonstrated the association between low body mass and increased respiratory disease mortality.

There is compelling evidence that poor nutritional status at birth or during early infancy is associated in adulthood with impaired lung function or the development of COPD. Follow-up studies revealed that in 60- to 70-year-old men born in Hertfordshire, England, low birth weight was a risk factor for impaired lung function after adjusting for smoking status and social class. The men in this study were also more likely to have died from COPD if their weight was low at the age of 1 year.\textsuperscript{21} The effect of low birth weight on respiratory disease is further underscored by the finding that despite its association with obesity,\textsuperscript{22-23} adult asthma is more likely to occur in individuals of low birth weight.\textsuperscript{23}

Malnutrition is probably the main cause of poor

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**Figure 1.** RR for BMI tertiles 1 and 2 relative to tertile 3. The relative risk of getting COPD was determined by tertile of baseline BMI for 458 men from the BLSA who were without COPD at baseline. Analysis was performed using the Cox proportional-hazards model that included the following baseline variables: smoking status, age, FEV\textsubscript{1} percent predicted, education, and body fat distribution.

\( * p < 0.05. \)
gestational growth that was observed in the Hertfordshire study. Evidence that nutritional depletion during the fetal and neonatal periods can lead to permanent structural and functional changes in the lung is derived from studies in laboratory animals such as the rat and the guinea pig. Deprivation of calories or protein in neonatal rats caused retardation in lung growth, reduced elastin, enlargements in airspaces and alveoli, and decreases in elastic recoil, all of which are similar to findings in emphysema.

Another possible explanation for the association between low baseline BMI and the increased risk of COPD in adult men is the finding that deficits in cell-mediated immunity and circulating T-lymphocyte numbers that result from protein-energy malnutrition can cause increased susceptibility to infection. This is of special importance for patients with COPD in whom a relatively minor respiratory infection can greatly compromise lung function. It is also consistent with the observation that low body mass is a risk factor for tuberculosis and other chronic lung infections.

The effect of malnutrition on pulmonary function is mediated in part by its effect on respiratory muscles. Arora and Rochester showed that nutritional depletion reduced respiratory muscle strength in patients without lung diseases. This is probably caused by the positive correlation between body weight and isometric length of different muscle groups and by the fact that changes in body weight affect diaphragm muscle mass. Thurlbeck suggested that malnutrition, which often occurs in COPD, causes respiratory muscle wasting, as demonstrated by diaphragm weight in emphysematous patients being lower than expected for body weight. This muscle loss, coupled with the altered thoracic configuration, further compromises the action of the diaphragm in obstructive pulmonary disease.

Another possible explanation for the observed inverse association between BMI and the risk of COPD developing is that low body weight in men who are susceptible to disease may be attributable to the lower caloric intake by the cigarette smokers. If true, then a decreased body weight may be a sensitive indicator of the biological effects of cigarette smoke. However, it is unlikely that a smoking-induced low caloric intake can completely account for low BMI, because the association of leanness with a higher risk of respiratory mortality was also observed in lifetime never-smoking men and women in the Adventist Mortality Study.

Energy expenditure in excess of energy intake leads to weight loss. There is evidence that resting energy expenditure and the oxygen cost of augmented ventilation are higher in patients with COPD who lose weight than in patients who have stable weight, or in healthy control subjects. Hugli et al reported that even though resting energy requirements were higher in patients with COPD, total energy expenditure was about the same as in control subjects because of the reduction of activity by the former. The relevance of these observations to the present study is not clear because our study subjects were selected to be clinically free of COPD at baseline.

A somewhat surprising result of this study is our finding that men with high baseline body mass had a lower risk of getting COPD. Although this finding is consistent with previous reports in the literature, which demonstrated that the obese subjects had lower COPD mortality rates, it is at variance with our previous finding that individuals with greater central obesity, as measured by WHR, tended to have lower lung function, and also with the finding that increased BMI is positively associated with the risk of adult-onset asthma. Perhaps the effect of central obesity is predominately restrictive, causing a reduction in both FVC and FEV₁.

A major strength of the present study is that it provided prospective, comprehensive data over a long follow-up interval in a group of initially healthy, community-dwelling individuals. In contrast to previous studies, all of our study participants were deemed to be without clinical lung disease at the time of first evaluation. Moreover, the diagnosis of COPD was based on a comprehensive evaluation that included history, physical examination, pulmonary function testing, and chest radiography.

However, the study has limitations that must be acknowledged. First, even though our finding that women with COPD were heavier than those without COPD is consistent with the findings of Chen et al, there are an insufficient number of women with COPD in this study to enable us to draw conclusions regarding body weight as a risk factor for lung obstruction in women. Second, this study was composed largely of a higher socioeconomic, white population. Although this limits our ability to extend these findings to other racial and socioeconomic groups, it permits us to conclude that our results were not confounded by poverty, which is itself a risk factor for COPD.

In summary, we have found that low body weight as indicated by BMI is an important risk factor for subsequent development of COPD in men. This finding cannot be accounted for by smoking or other clinical and demographic measures. The source of this relationship is unclear but raises the possibility that early nutritional intervention may prevent or delay the occurrence of COPD.
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REFERENCES