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Obstructive and Restrictive Lung Disease and Markers of Inflammation: Data from the Third National Health and Nutrition Examination

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Although chronic obstructive pulmonary disease (COPD) and restrictive lung diseases are important causes of morbidity and mortality in the United States (1–3), a large proportion of the morbidity and mortality is not pulmonary (4). This raises the possibility that lung disease may be an indicator of susceptibility to the development of other diseases or may be associated with systemic inflammation that leads to other diseases (5,6). Previous analyses of the relation between lung function and markers of inflammation (7,8) have not looked at restrictive lung disease separately.

We applied spirometric criteria to define obstructive and restrictive lung disease in adults who had pulmonary function measurements obtained as part of the Third National Health and Nutrition Examination Survey (NHANES III). We then assessed the relation of impaired lung function to circulating levels of C-reactive protein and fibrinogen, adjusting for potential covariates that may also influence these measures.

METHODS

Study Sample

NHANES III was conducted from 1988 to 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention, Atlanta, Georgia (9). Our study sample was limited to 15,697 adults aged 17 years or older who had undergone pulmonary function testing either at home or at the mobile examination center, and had complete data on their race, smoking status, height, and presence of respiratory symptoms. Serum and plasma samples were obtained during the examination. Fibrinogen levels were available on 8342 adults aged ≥40 years.

Definition of Variables

Race was classified as white, black, Mexican American, or other, and was determined by self-report on the questionnaire. Other demographic variables included sex, education (<12 years, 12 years, or ≥13 years), and age. We defined subjects as being current, former, or never smokers, based on their responses to series of questions. Current pipe or cigar smokers were considered current smokers. We calculated pack-years of cigarette use by multiplying the average number of cigarettes smoked daily by the number of years smoked and dividing the product by 20.

We classified subjects as having a respiratory symptom if they gave a positive response to questions involving specific symptoms of cough, phlegm, wheeze, or dyspnea. Subjects were asked whether they had an upper respiratory or lower respiratory illness recently. We classified subjects as having or not having cardiovascular disease (physician diagnosis of stroke, myocardial infarction, or heart failure), diabetes mellitus (physician-diagnosed), or chronic inflammatory rheumatic disease (physician diagnosis of systemic lupus erythematosus or rheumatoid arthritis). Body mass index, which was calculated by dividing the weight (kg) by height (m^2), was divided into four strata: <18.5 kg/m^2, ≥18.5 to 24 kg/m^2, 25 to 29 kg/m^2, and ≥30 kg/m^2.

Pulmonary Function Data

Spirometry was conducted using procedures based on the 1987 American Thoracic Society recommendations (10). Values used in this analysis included the forced vital capacity (FVC), the forced expiratory volume in 1 second (FEV_1), and the FEV_1/FVC ratio. We used prediction equations to determine predicted values of FEV_1 and FVC (11). Using a modification of the Global Initiative for Chronic Obstructive Lung Disease criteria for COPD, we classified subjects into the following mutually exclusive categories using the FEV_1, the FVC, the FEV_1/FVC ratio, and the presence of respiratory symptoms as severe COPD (FEV_1/FVC <0.70 and FEV_1 <50% predicted), moderate COPD (FEV_1/FVC <0.70 and FEV_1 ≥50% to <80% predicted), mild COPD (FEV_1/FVC <0.70 and FEV_1 ≥80%), symptoms only (respiratory symptoms in the absence of any lung function abnormality), restrictive lung disease (FEV_1 ≥0.70 and FVC <80% predicted), or no lung disease (12).

Laboratory Measurements

C-reactive protein levels were measured using latex-enhanced nephelometry (13). The limit of detection for this assay was 3.0 mg/L; subjects with undetectable levels were assigned a level of 2.1 mg/L (3.0/1.41). Fibrinogen levels were measured using immunochemical methods on people aged ≥40 years (13).

Statistical Analysis

We calculated all estimates using the sampling weight to represent adults aged 17 years or older in the United States. We log-transformed fibrinogen and C-reactive protein levels for use in the linear regression models. We also used cutpoints of 3.0 mg/L to define "detectable"

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levels and ≥10.0 mg/L to define "highly elevated" levels in categorical analyses (14). Linear and logistic regression models were adjusted for age, race, sex, education level, smoking status, body mass index, and the presence of cardiovascular disease, diabetes mellitus, or inflammatory rheumatic disease. We exponentiated results from the log-transformed regression models to yield a percentage increase (from the reference value) for the outcome. For analyses, we used both SAS and SUDAAN, a program that adjusts for the complex sample design when calculating variance estimates (15,16).

RESULTS

Our final data set included 15,697 subjects, representing an estimated 170 million adults in the United States. The pulmonary function criteria classified 2% of subjects as having severe COPD, 5% as having moderate COPD, and 6% as having restrictive lung disease (Table 1).

Compared with subjects who had no lung disease, fibrinogen and C-reactive protein levels were elevated in those with any measure of lung disease, as were the proportions of those with C-reactive protein levels ≥3.0 mg/L or ≥10.0 mg/L (Table 2).

After adjustment for age, sex, race, smoking status, pack-years of smoking, body mass index, and the presence of chronic disease, every measure of lung disease, except mild COPD and respiratory symptoms, was associated with higher levels of fibrinogen and C-reactive protein, and with C-reactive protein levels ≥3.0 mg/L or ≥10.0 mg/L (Table 3). The effect of current or former smoking on C-reactive protein levels was less than that seen with moderate or severe COPD or restrictive lung disease.

When stratified by smoking status and lung function level, the proportion of participants with a C-reactive protein level ≥10 mg/L was increased in subjects with lung function impairment compared with in subjects who had no lung disease (Figure).

Table 1. Number and Weighted Percentage of Participants (n = 15,697) Included in Analysis, Stratified by Age, Race, Sex, Education Level, Smoking Status, Comorbid Disease, and Body Mass Index*

Characteristic	Number (Weighted Percentage)
Lung function	
Severe COPD†	228 (2)
Moderate COPD	878 (5)
Mild COPD	1260 (7)
Respiratory symptoms only	3286 (26)
Restrictive lung disease	1059 (6)
No lung disease	8446 (54)
Age (years)	
17–24	2599 (16)
25–44	5912 (45)
45–64	3690 (25)
65–74	1890 (9)
75–84	1258 (4)
≥85	348 (1)
Race	
White	6496 (77)
Black	4244 (10)
Mexican American	4342 (5)
Other	615 (8)
Sex	
Male	7384 (48)
Female	8313 (52)
Education (years)	
<12	6634 (26)
12	4461 (31)
≥13	4602 (43)
Smoking status	
Current smoker	4172 (30)
Former smoker	3586 (24)
Never smoker	7939 (46)
Comorbid diseases	
Cardiovascular disease	1127 (5)
Diabetes mellitus	1171 (5)
Rheumatic disease	633 (3)
Lower respiratory illness	765 (5)
Upper respiratory illness	2928 (18)
Body mass index (kg/m^2)	
<18.5	342 (2)
≥18.5 to 24	6112 (44)
25 to 29	5374 (32)
≥30	3869 (22)

* From the Third National Health and Nutrition Examination Survey, 1988–1994 (9).

† Severe COPD: $FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted; moderate COPD: $FEV_1/FVC < 0.70$ and $FEV_1 \geq 50\%$ to <80% predicted; mild COPD: $FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$; symptoms only: presence of respiratory symptoms in the absence of any lung function abnormality; restrictive lung disease: $FEV_1/FVC \geq 0.70$ and FVC <80% predicted.

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

DISCUSSION

In this analysis of a nationally representative sample of 15,697 U.S. adults, both obstructive and restrictive lung diseases were predictors of increased levels of plasma fibrinogen and serum C-reactive protein. This association remained significant after adjusting for several covariates related to fibrinogen, C-reactive protein, and lung function.

Patients with COPD have an increased risk of cardiovascular disease. The explanation for this association is unknown, but thought to be related to some of the factors associated with obstructive lung disease, such as smoking, chronic infection, or cor pulmonale (17–19). Recent work has focused on the systemic and inflammatory nature of COPD, such as its association with a catabolic state and chronic muscle wasting (20–22). The association be-

Table 2. Effects of Pulmonary Function on Fibrinogen and C-Reactive Protein Levels, and the Age-Adjusted Percentage of Subjects with C-Reactive Protein Levels ≥3.0 mg/L or ≥10.0 mg/L*

Lung Function	Fibrinogen (g/L)	C-Reactive Protein (mg/L)	Percentage with C-Reactive Protein ≥3.0 mg/L	Percentage with C-Reactive Protein ≥10.0 mg/L
	Geometric Mean ± Geometric SD			
Severe COPD	340 ± 67	4.7 ± 4.2	52	23
Moderate COPD	316 ± 58	3.6 ± 2.2	41	12
Mild COPD	292 ± 51	2.9 ± 1.3	27	6
Respiratory symptoms only	297 ± 55	3.1 ± 1.8	32	9
Restrictive lung disease	315 ± 50	3.7 ± 2.3	42	16
No lung disease	281 ± 47	2.7 ± 1.0	22	4

COPD = chronic obstructive pulmonary disease.
* Fibrinogen levels were not obtained on subjects aged <40 years.

tween elevated C-reactive protein and fibrinogen levels and cardiovascular disease has been well established (23,24). Thus, our findings provide a potential mechanism for the association between impaired lung function and cardiovascular health. Whereas previous research has demonstrated an association between emphysema (25), chronic bronchitis (8), or FEV_1 (7) and C-reactive protein levels, this analysis used the new criteria of the Global Initiative for COPD to define categories of impaired lung function (12).

A new finding in this analysis was the association of restrictive lung disease with elevated C-reactive protein and fibrinogen levels. Many pathologic mechanisms—ranging from obesity to interstitial lung disease to space-occupying lesions (2,26)—can cause restrictive lung disease. Inflammation is an important pathway for several different causes of restrictive lung disease, such as sarcoidosis or idiopathic pulmonary fibrosis (27). In addition, respiratory infections can also result in restrictive spirometric values.

C-reactive protein is mainly synthesized in hepatocytes, although it is also synthesized in lymphocytes and alveolar macrophages (28–30). C-reactive protein levels can also increase in response to an acute infection (31), but chronic infections such as periodontitis can also increase these inflammatory markers (32).

Fibrinogen is also an acute phase reactant that has been linked to cardiovascular disease (33). It is synthesized in the liver, and increased serum levels are related to both higher synthesis and lower degradation rates (34,35). In our analysis, the increase in fibrinogen levels related to impaired lung function was less than the increase in C-reactive protein levels (Table 3).

This analysis is subject to several limitations. Because this was a cross-sectional study, we cannot say that lung function abnormality results in increased C-reactive pro-

Table 3. Effects of Lung Function on Percentage Change in Fibrinogen and C-Reactive Protein Levels or the Risk of Having a C-Reactive Protein Level ≥3.0 mg/L or ≥10.0 mg/L*

Category	Change in Fibrinogen	Change in C-Reactive Protein	C-Reactive Protein ≥3.0 mg/L	C-Reactive Protein ≥10.0 mg/L
	Mean Percentage Change (95% Confidence Interval)		Odds Ratio (95% Confidence Interval)	
Lung function				
Severe COPD	15 (9 to 21)	54 (35 to 73)	2.9 (2.0 to 4.2)	4.3 (2.6 to 7.3)
Moderate COPD	6 (4 to 8)	16 (10 to 22)	1.7 (1.4 to 2.1)	2.0 (1.4 to 2.8)
Mild COPD	1 (−1 to 3)	2 (−2 to 6)	1.1 (0.9 to 1.4)	1.3 (0.9 to 2.0)
Respiratory symptoms only	1 (−1 to 3)	5 (3 to 7)	1.2 (1.0 to 1.3)	1.5 (1.2 to 1.9)
Restrictive lung disease	4 (0 to 8)	23 (17 to 29)	1.8 (1.5 to 2.2)	2.7 (1.9 to 3.8)
No lung disease	Reference	Reference	Reference	Reference
Smoking status				
Current smoker	6 (4 to 8)	6 (2 to 10)	1.3 (1.1 to 1.6)	1.5 (1.2 to 1.9)
Former smoker	0 (−2 to 2)	1 (−1 to 3)	1.1 (0.9 to 1.2)	1.2 (1.0 to 1.6)
Never smoker	Reference	Reference	Reference	Reference

COPD = chronic obstructive pulmonary disease.
* Adjusted for age, sex, race, smoking status (or lung function), pack-years of smoking, body mass index, and chronic disease (see Methods).

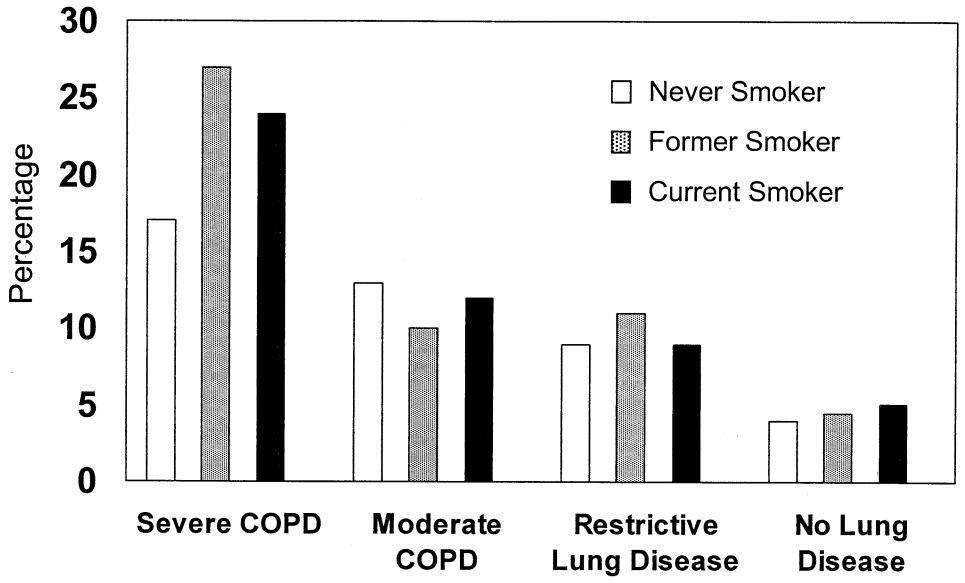

Figure. Percentages of subjects with C-reactive protein ≥10.0 mg/L, stratified by smoking status and lung function category (severe chronic obstructive pulmonary disease [COPD], moderate COPD, restrictive lung disease, and normal lung function). From the Third National Health and Nutrition Examination Survey, 1988–1994.

tein or fibrinogen levels. An alternative explanation might be that systemic inflammatory processes could result in impaired lung function. Another limitation is that the assay for C-reactive protein that we used had a limit of detection of 3 mg/L, and there is evidence of cardiovascular risk at levels below 3 mg/L (36).

In conclusion, our data demonstrate an association between both obstructive and restrictive lung disease and elevated levels of fibrinogen and C-reactive protein. This finding provides additional data linking respiratory disease to adverse outcomes outside of the pulmonary system.

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