The Interactions Between Cigarette Smoking and Reduced Lung Function on Systemic Inflammation

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Chest 2005;127;558-564
DOI: 10.1378/chest.127.2.558

The Interactions Between Cigarette Smoking and Reduced Lung Function on Systemic Inflammation*

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Background: **Low-grade systemic inflammation is commonly observed in conditions associated with reduced FEV_1. Active cigarette smoking, which is a leading risk factor for decreased FEV_1, can also independently induce systemic inflammation.**
Study objectives: **To determine the independent contributions of active cigarette smoking and reduced FEV_1 (as well as their potential interactions) on systemic inflammation.**
Design: **Cross-sectional survey.**
Setting: **The US general population.**
Participants: **A total of 7,685 adult participants, ≥ 40 years of age, in the Third National Health and Nutrition Examination Survey, who had acceptable data on spirometry and laboratory measurements such as serum C-reactive protein (CRP).**
Measurements: **The participants were stratified into four equal groups (quartiles) based on the percent predicted FEV_1 values. Each group was further categorized as active smokers or nonsmokers according to serum cotinine level (*ie*, ≥ 10 or < 10 ng/mL). Serum levels of CRP, plasma fibrinogen, blood leukocytes, and platelets were compared across the predicted FEV_1 quartile groups and across smoking status using multiple logistic regression models.**
Results: **We found that active smoking by itself increased the odds of having elevated CRP levels by 63% (adjusted odds ratio [OR], 1.63; 95% confidence interval, 1.28 to 2.09). The adjusted OR for reduced FEV_1 was 2.27 (95% confidence interval, 1.92 to 2.70). Having both risk factors increased the OR to 3.31 (95% confidence interval, 2.73 to 4.02). Similar findings were observed for blood leukocytes and plasma fibrinogen.**
Conclusion: **These findings suggest an additive effect of active smoking and reduced FEV_1 on markers of systemic inflammation and suggest their potential interactions in the pathogenesis of systemic complications observed in patients with poor lung function.**
(CHEST 2005; 127:558–564)

Key words: C-reactive protein; epidemiology; FEV_1; smoking; systemic inflammation

Abbreviations: BMI = body mass index; CRP = C-reactive protein; NHANES 3 = Third National Health and Nutrition Examination Survey; OR = odds ratio

Individuals who have reduced FEV_1 are at increased risk of morbidity and mortality from various disorders, including ischemic heart disease, stroke, arrhythmias, respiratory failure, and cachexia.[1–4] Although the exact mechanism for these relationships is still unknown, many individuals with COPD and other conditions associated with reduced FEV_1 consistently demonstrate both airway inflammation[5] and systemic inflammation[6–13] in a severity-dependent fashion. Low-grade systemic inflammation is a known risk factor for atherosclerosis,[14] muscle loss, and cachexia.[12,13] In the community, the single most important risk factor for reduced FEV_1 is cigarette smoking.[15] Since cigarette smoking by itself also can lead to systemic inflammation,[16,17] the observed relationship between reduced FEV_1 and systemic inflammation may be confounded by cigarette smoke exposure. Furthermore, there is little information on whether reduced FEV_1 and cigarette smoking have additive, synergistic, or no combined

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Dr. Sin was supported by a Canada Research Chair and a Michael Smith/St. Paul's Hospital Foundation Professorship. Drs. Sin and Man have received honoraria and research funding from GlaxoSmithKline, AstraZeneca, and Merck Frosst.
Manuscript received December 15, 2003; revision accepted August 3, 2004.

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effects on systemic inflammation. We used data from the Third National Health and Nutrition Examination Survey (NHANES 3) to determine, first, whether reduced FEV_1, independent of active cigarette smoking, is associated with systemic inflammation in the adult population that is ≥ 40 years of age, and, second, whether cigarette smoking has an additive (or even a synergistic) effect on systemic inflammation among those with reduced FEV_1.

Materials and Methods

Study Sample

NHANES 3 was conducted from 1988 to 1994 in the United States by the National Center for Health Statistics of the Centers for Disease Control and Prevention. This was a cross-sectional, multistage, probability representative sample of the civilian noninstitutionalized US population.[18] Once chosen, study participants were asked to complete a questionnaire and a comprehensive physical examination, which included spirometric measurements either in the household or at a specially equipped mobile examination center. The data were then collated and entered into a database. The full sampling methods and the survey protocols have been described elsewhere.[18] From the larger data set of approximately 20,000 Americans, we restricted the present analysis to the participants of NHANES 3 who were ≥ 40 years of age to minimize the influences of age on markers of systemic inflammation. Of the 11,448 participants aged ≥ 40 years, we excluded those who did not have reported values for smoking status, body mass index (BMI), FEV_1, or serum cotinine level. This process left 7,685 participants for the present study. Of these, 4,291 participants were either active or ex-smokers (as indicated by the participants' own history).

Measurements

The laboratory procedures used in the NHANES 3 have been described previously.[19] Briefly, pulmonary function testing was performed in study participants according to the standards of the American Thoracic Society.[20] Each study participant performed five to eight forced expiratory maneuvers. To adjust for height, age, and gender, we used published prediction equations for FEV_1 and FVC, which were derived from the NHANES 3 population.[21] Serum cotinine level was measured by using high-performance liquid chromatography atmospheric-pressure chemical ionization tandem mass spectrometry.[22] We used serum cotinine level to differentiate active smokers from nonsmokers because cotinine is widely considered to be the best marker for monitoring tobacco exposure in either actively or passively exposed individuals.[22] In contrast to nicotine, which has a serum half-life of only 1 to 2 h, cotinine (a major metabolite of nicotine) has a half-life of 18 to 20 h.[22] Accordingly, by measuring serum cotinine levels we can monitor tobacco exposure over the preceding 2 to 3 days. This avoids the misclassification of smokers who refrain from tobacco exposure just hours prior to the examination because their serum cotinine levels will still be elevated. The serum nicotine levels may be falsely negative in such individuals. In this study, we chose a serum cotinine level of ≥ 10 ng/mL to indicate active cigarette smoking. A previous study[23] using the NHANES 3 population showed that < 5% of nonsmokers have serum cotinine levels of > 10 ng/mL, and a similar proportion of individuals who actively smoke have cotinine levels of < 10 ng/mL. Thus, by using 10 ng/mL as the threshold, very few individuals in our study were misclassified.[23,24]

We chose C-reactive protein (CRP) as one of the markers of systemic inflammation for several reasons. First, CRP is an acute-phase protein that originates predominantly from hepatocytes in response to tissue damage or inflammation and, therefore, reflects the total systemic burden of inflammation of individuals.[25] The half-life of CRP is about 19 h, and is constant under all conditions of health and disease, so the major determinant of serum CRP is hepatic synthesis rate.[25] Second, CRP is stable and has little or no seasonal or diurnal variation, except during exacerbations or infections.[25] The self-correlation coefficient of CRP levels measured years apart is 0.5, a value that is similar to what would be expected for serum cholesterol levels.[25] Most importantly, in the community, serum CRP is a well-established independent risk factor for cardiovascular mortality and all-cause mortality.[26–28]

Because most participants had CRP levels below the lowest detectable limit for this assay (*ie*, 2.1 mg/L), CRP levels were categorized as undetectable (≤ 2.1 mg/L) or elevated (> 2.1 mg/L). Plasma fibrinogen levels, and blood leukocyte and platelet counts were also determined using standard assays, as previously described.[19] Blood leukocyte count, platelet count, and fibrinogen levels were deemed to be elevated if their values exceeded the 85th percentile for each marker. For leukocytes, the 85th percentile was ≥ 9.1×10^9 cells/L, for platelets it was ≥ 339.0×10^9 cells/L, and for fibrinogen it was ≥ 3.9 g/L.

Statistical Analysis

The population was divided into four equal groups (quartiles) based on the percentage of predicted FEV_1 values. Statistical comparisons of baseline characteristics of the study population in quartiles of FEV_1 were performed, using a χ^2 test for binary variables and a *t* test for continuous variables. To evaluate the effects of active cigarette smoke exposure on the relationship between FEV_1 and various systemic inflammatory markers, we further classified persons in the study population according to their serum cotinine levels (active smoker, ≥ 10 ng/mL; nonsmokers, <10 ng/mL). The latter group was composed of life-time nonsmokers and ex-smokers. Using those with serum cotinine levels of < 10 ng/mL and the best FEV_1 (quartile 4) as the referent, we performed multiple logistic regression analyses. To this model we added age, sex, race, and BMI as covariates. The latter was divided into quintiles and was expressed in kilograms per square meter. We also performed similar analyses using blood levels of leukocytes, platelets, and fibrinogen as the dependent variables. To test the robustness of the findings, in another model, we included all of these variables plus the presence of self-reported heart disease, cancer, diabetes, arthritis, hypertension, high cholesterol, and active use of systemic corticosteroids and aspirin. All tests were two-tailed in nature and were performed using statistical software (SAS, version 8.2; SAS Institute; Cary, NC; and SUDAAN, release 8.0; Research Triangle Institute; Research Triangle Park, NC). Analyses were performed with and without NHANES 3 weights. As the results were similar, we presented data from the unweighted analysis for parsimony.

Results

The baseline characteristics of the study population are summarized in Table 1. Quartile 1 (lowest FEV_1) contained more whites, more active smokers,

Table 1—*Characteristics of Participants by Quartiles of FEV_1***

Variable	Quartiles of FEV_1 % Predicted				p Value†
	4th Quartile (> 107.1%)	3rd Quartile (95.6–107.1%)	2nd Quartile (83.2–95.6%)	1st Quartile (≤ 83.2%)	
Age, yr	58.7 ± 14.0	57.6 ± 13.3	59.3 ± 13.0	64.8 ± 12.6	< 0.001
Male sex	35.1	45.5	52.9	59.5	< 0.001
White race	61.6	75.3	78.7	79.0	< 0.001
Current smoker	16.0	19.2	23.2	32.0	< 0.001
BMI	27.6 ± 5.3	27.8 ± 5.3	27.9 ± 5.6	27.6 ± 6.0	0.709
FEV_1					
L	2.98 ± 0.83	2.83 ± 0.76	2.58 ± 0.67	1.91 ± 0.64	< 0.001
% predicted	117.7 ± 9.6	101.1 ± 3.3	89.7 ± 3.5	68.2 ± 13.6	< 0.001
FVC					
L	3.76 ± 1.04	3.66 ± 1.02	3.46 ± 0.95	2.89 ± 0.93	< 0.001
% predicted	117.9 ± 11.5	104.2 ± 8.7	95.1 ± 9.4	80.7 ± 14.8	< 0.001
Pack-yr	17.5 ± 17.0	20.2 ± 21.9	24.6 ± 25.5	35.2 ± 34.0	< 0.001
Leukocytes, $\times 10^9$ cells/L	6.7 ± 2.0	7.1 ± 2.7	7.2 ± 2.1	7.6 ± 2.5	< 0.001
Elevated leukocyte level‡	10.2	13.7	16.4	21.2	< 0.001
Platelet, $\times 10^9$ cells/L	270.4 ± 69.3	271.3 ± 72.5	269.9 ± 74.4	268.7 ± 77.3	0.477
Elevated platelet level‡	14.5	15.0	14.9	15.8	0.239
Fibrinogen, g/L	3.05 ± 0.81	3.06 ± 0.86	3.14 ± 0.86	3.34 ± 0.94	< 0.001
Elevated fibrinogen level‡	11.6	12.7	14.3	21.1	< 0.001
Serum CRP,§ mg/L	3.0	3.3	3.5	4.0	< 0.001
Elevated CRP level‡	31.5	35.6	39.1	48.3	< 0.001

*Values given as mean ± SD or %, unless otherwise indicated.
†The 1st quartile compared with the 4th quartile.
‡Elevated levels of serum leukocyte, platelet, and fibrinogen were defined as ≥ 85th percentile of respective variable. Elevated CRP level was defined as > 2.1 mg/L.
§Geometric mean.

and more men than quartile 4 (highest FEV_1). Individuals in quartile 1 tended to be older than those in quartile 4. There were no significant differences in the BMI across the quartiles. Crudely, those in quartile 1 had higher leukocyte, fibrinogen, and CRP levels than those in quartile 4 (Table 1). Adjustments of various factors such as age, sex, BMI, race, and smoking status made little difference to the overall results (Table 2). There was a clear gradient in the levels of leukocytes, fibrinogen, and CRP

Table 2—*ORs and 95% Confidence Intervals for Elevated Levels of Blood Leukocytes, Platelets, Fibrinogen, and CRP by Quartiles of FEV_1 and Serum Cotinine Level***

Variable†	Quartiles of FEV_1 % Predicted			
	4th Quartile (> 107.1%)	3rd Quartile (95.6–107.1%)	2nd Quartile (83.2–95.6%)	1st Quartile (≤ 83.2%)
Leukocytes				
Cotinine < 10 ng/mL	1 (Reference)	1.41 (1.10–1.81)	1.50 (1.17–1.93)	2.36 (1.84–3.03)
Cotinine ≥ 10 ng/mL	3.40 (2.47–4.69)	3.77 (2.80–5.07)	4.97 (3.79–6.52)	5.11 (3.97–6.59)
Platelets				
Cotinine < 10 ng/mL	1 (Reference)	1.10 (0.89–1.36)	1.16 (0.94–1.44)	1.50 (1.20–1.88)
Cotinine ≥ 10 ng/mL	1.14 (0.83–1.56)	1.40 (1.05–1.88)	1.50 (1.14–1.96)	1.60 (1.25–2.05)
Fibrinogen				
Cotinine < 10 ng/mL	1 (Reference)	1.20 (0.96–1.52)	1.36 (1.08–1.71)	1.84 (1.47–2.31)
Cotinine ≥ 10 ng/mL	1.58 (1.13–2.21)	2.02 (1.47–2.76)	2.03 (1.52–2.70)	2.96 (2.32–3.78)
CRP				
Cotinine < 10 ng/mL	1 (Reference)	1.31 (1.12–1.54)	1.56 (1.32–1.84)	2.27 (1.92–2.70)
Cotinine ≥ 10 ng/mL	1.63 (1.28–2.09)	2.12 (1.69–2.67)	2.35 (1.90–2.92)	3.31 (2.73–4.02)

*Values given as OR (95% confidence interval). All values have been adjusted for age, sex, race, and BMI. Participants in the 4th FEV_1 quartile group with a serum cotinine level < 10 ng/mL are the reference category.
†Elevated levels of leukocytes, platelets, and fibrinogen were defined as ≥ 85th percentile of the respective variable. Elevated CRP was defined as a value > 2.1 mg/L.

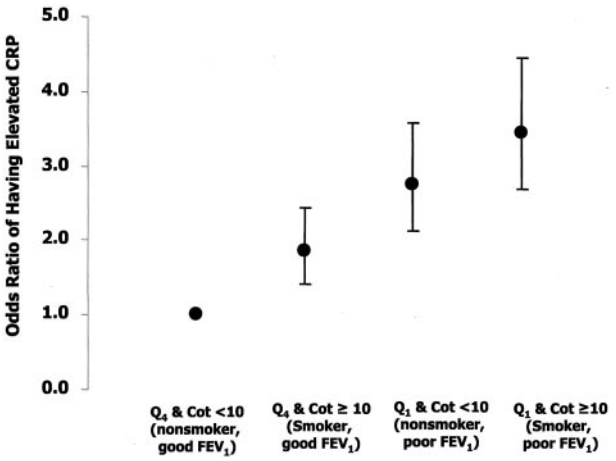

FIGURE 1. The impact of active smoking and reduced FEV_1 on circulating CRP levels. A serum cotinine level of ≥ 10 ng/mL indicates active smoking. Q, quartile based on FEV_1 percentage of predicted (Q_1, lowest FEV_1 percentage of predicted; Q_4, highest FEV_1 percentage of predicted); Cot, serum cotinine (in nanograms per milliliter).

across the FEV_1 quartiles, such that those in quartile 4 had the lowest values, while those in quartile 1 had the highest values for both active smokers and nonsmokers (Table 2). More importantly, there appeared to be an additive effect between serum cotinine values and FEV_1 quartile groups. For instance, using those in quartile 4 (best FEV_1) with serum cotinine levels of < 10 ng/mL (nonsmokers) as the referent group, active smoking (*ie*, serum cotinine level, ≥ 10 ng/mL) was associated with an odds ratio (OR) of 1.63 for having elevated CRP levels. The OR for those in quartile 1 (worst FEV_1) having serum cotinine levels of < 10 ng/mL was 2.27. However, in quartile 1, for those who had a serum cotinine level of ≥ 10 ng/mL, the OR was 3.31, indicating an additive effect of reduced FEV_1 and active smoking on CRP levels (Fig 1). Similar findings were observed for blood leukocyte and plasma fibrinogen levels. Consistently, those in quartile 1 and with serum cotinine levels of ≥ 10 ng/mL had the highest odds of having elevated levels of systemic markers of inflammation. Adjustments for age, sex, BMI, comorbidities, and select medications did not materially change the overall findings (Table 3).

The findings were similar between those with an FEV_1/FVC ratio of < 0.7, indicating obstructive airways disease (Table 4), and those without obstructive disease (FEV_1/FVC ratio ≥ 0.7) [Table 5]. In both groups, the group that had elevated serum cotinine levels and the lowest FEV_1 had the highest levels of inflammatory markers, while the group that had a normal serum cotinine level and the highest FEV_1 had the lowest levels of inflammatory markers. When we restricted the above analysis by using 4,291 active smokers and ex-smokers (as indicated on the participant's history), the results were similar to those of the main analysis (Table 6).

DISCUSSION

The most important and novel finding of this study was that active cigarette smoking and poor FEV_1 had an additive effect on systemic markers of inflammation. Individually, active smoking (as defined by a

Table 3—*ORs and 95% Confidence Intervals for Elevated Levels of Blood Leukocytes, Platelets, Fibrinogen, and CRP by Quartiles of FEV_1% Predicted and Serum Cotinine Level Adjusted for Comorbidities and Select Medications***

Variable†	Quartiles of FEV_1 % Predicted			
	4th Quartile (> 107.1%)	3rd Quartile (95.6–107.1%)	2nd Quartile (83.2–95.6%)	1st Quartile (≤ 83.2%)
Leukocytes				
Cotinine < 10 ng/mL	1 (Reference)	1.34 (1.03–1.74)	1.54 (1.19–1.98)	1.97 (1.54–2.52)
Cotinine ≥ 10 ng/mL	3.72 (2.65–5.22)	3.28 (2.39–4.51)	4.75 (3.58–6.31)	5.61 (4.37–7.21)
Platelets				
Cotinine < 10 ng/mL	1 (Reference)	1.00 (0.80–1.25)	1.18 (0.95–1.48)	1.35 (1.08–1.67)
Cotinine ≥ 10 ng/mL	1.18 (0.84–1.66)	1.25 (0.91–1.71)	1.43 (1.07–1.90)	1.59 (1.25–2.03)
Fibrinogen				
Cotinine < 10 ng/mL	1 (Reference)	0.96 (0.78–1.19)	1.09 (0.89–1.35)	1.46 (1.20–1.77)
Cotinine ≥ 10 ng/mL	1.23 (0.89–1.70)	1.56 (1.16–2.11)	1.78 (1.36–2.32)	2.59 (2.09–3.21)
CRP				
Cotinine < 10 ng/mL	1 (Reference)	1.36 (1.14–1.62)	1.46 (1.23–1.74)	2.02 (1.71–2.40)
Cotinine ≥ 10 ng/mL	1.73 (1.31–2.27)	2.29 (1.78–2.94)	2.12 (1.69–2.67)	3.33 (2.75–4.05)

*Values given as OR (95% confidence interval). All values have been adjusted for age, sex, race, BMI, comorbidities, and drug use (see "Materials and Methods" section for detail). Participants in the 4th FEV_1 quartile group with a serum cotinine level < 10 ng/mL are the reference category.
†Elevated levels of serum leukocyte, platelet, and fibrinogen were defined as ≥ 85th percentile of respective variable. Elevated CRP was defined as > 2.1 mg/L.

Table 4—*ORs and 95% Confidence Intervals for Elevated Levels of Blood Leukocytes, Platelets, Fibrinogen, and CRP by Quartiles of FEV_1% Predicted and Serum Cotinine Level Among Individuals With FEV_1/FVC Ratio of < 0.7**

Variable†	Quartiles of FEV_1 % Predicted (n = 1,890)			
	4th Quartile (> 91.5%)	3rd Quartile (79.6–91.5%)	2nd Quartile (65.0–79.6%)	1st Quartile (≤ 65.0%)
Leukocytes				
Cotinine < 10 ng/mL	1 (Reference)	0.91 (0.48–1.73)	1.68 (0.94–2.99)	2.84 (1.65–4.89)
Cotinine ≥ 10 ng/mL	4.20 (2.28–7.76)	3.93 (2.21–6.99)	4.17 (2.38–7.31)	4.02 (2.31–7.02)
Platelets				
Cotinine < 10 ng/mL	1 (Reference)	1.26 (0.77–2.06)	1.17 (0.70–1.97)	2.24 (1.40–3.58)
Cotinine ≥ 10 ng/mL	1.41 (0.78–2.56)	1.30 (0.74–2.28)	1.38 (0.80–2.35)	2.07 (1.26–3.42)
Fibrinogen				
Cotinine < 10 ng/mL	1 (Reference)	1.38 (0.78–2.41)	2.11 (1.24–3.59)	2.32 (1.37–3.93)
Cotinine ≥ 10 ng/mL	3.38 (1.83–6.23)	2.57 (1.40–4.71)	2.91 (1.64–5.15)	4.85 (2.85–8.25)
CRP				
Cotinine < 10 ng/mL	1 (Reference)	1.46 (1.02–2.08)	1.71 (1.19–2.45)	3.13 (2.19–4.47)
Cotinine ≥ 10 ng/mL	1.77 (1.14–2.75)	2.02 (1.34–3.05)	3.03 (2.05–4.48)	3.66 (2.49–5.39)

*Values given as OR (95% confidence interval). All values have been adjusted for age, sex, race, and BMI. Participants in the 4th FEV_1 quartile group with a serum cotinine level < 10 ng/mL are the reference category.

†Elevated levels of leukocytes, platelets, and fibrinogen were defined as ≥ 85th percentile of the respective variable. Elevated CRP was defined as a value > 2.1 mg/L.

serum cotinine level of ≥ 10 ng/mL) and reduced FEV_1 (as defined by an FEV_1 of ≤ 83.2% predicted) were associated with 1.6 and 2.3 increased odds of elevated CRP, respectively. For individuals with both of these risk factors, the odds increased by 3.3-fold, indicating an additive response. Similar findings also were observed for serum leukocyte and plasma fibrinogen levels. These findings are consistent with previous observations,[16,17] demonstrating that cigarette smoking contributes significantly to persistent low-grade systemic inflammation in susceptible individuals. As well, our findings suggest that, independent of active smoking, poor lung function is an important risk factor for low-grade systemic inflammation.

The mechanism for the latter observation is not entirely clear. However, there is compelling evidence to suggest that disorders such as COPD, one of the leading causes of reduced FEV_1 in the general population, have a strong inflammatory component in the airways,[5,29] which persists even after smoking cessation.[30,31] It is highly plausible that this inflammatory component may "spill over" into the systemic circulation, leading to a state of low-grade systemic

Table 5—*ORs and 95% Confidence Intervals for Elevated Levels of Blood Leukocytes, Platelets, Fibrinogen, and CRP by Quartiles of FEV_1% Predicted and Serum Cotinine Level in Those With FEV_1/FVC Ratio ≥ 0.7**

Variable†	Quartiles of FEV_1 % Predicted (n = 1,890)			
	4th Quartile (> 110.1%)	3rd Quartile (99.7–110.1%)	2nd Quartile (89.1–99.7%)	1st Quartile (≤ 89.1%)
Leukocytes				
Cotinine < 10 ng/mL	1 (Reference)	1.42 (1.07–1.89)	1.65 (1.24–2.19)	2.12 (1.60–2.80)
Cotinine ≥ 10 ng/mL	4.04 (2.82–5.80)	2.97 (2.06–4.28)	4.89 (3.55–6.73)	5.76 (4.25–7.80)
Platelets				
Cotinine < 10 ng/mL	1 (Reference)	1.03 (0.81–1.31)	1.28 (1.01–1.62)	1.19 (0.92–1.52)
Cotinine ≥ 10 ng/mL	1.18 (0.82–1.70)	1.32 (0.93–1.87)	1.47 (1.07–2.04)	1.44 (1.06–1.97)
Fibrinogen				
Cotinine < 10 ng/mL	1 (Reference)	1.07 (0.83–1.38)	1.39 (1.08–1.79)	1.48 (1.15–1.89)
Cotinine ≥ 10 ng/mL	1.35 (0.92–1.98)	1.71 (1.17–2.48)	1.57 (1.10–2.23)	2.41 (1.79–3.25)
CRP				
Cotinine < 10 ng/mL	1 (Reference)	1.38 (1.15–1.67)	1.49 (1.23–1.80)	2.09 (1.73–2.53)
Cotinine ≥ 10 ng/mL	1.72 (1.29–2.30)	2.33 (1.76–3.07)	2.04 (1.57–2.65)	3.39 (2.66–4.34)

*Values given as OR (95% confidence interval). All values have been adjusted for age, sex, race, and BMI. Participants in the 4th FEV_1 quartile group with a serum cotinine level < 10 ng/mL are the reference category.

†Elevated levels of leukocytes, platelets, and fibrinogen were defined as ≥ 85th percentile of the respective variable. Elevated CRP was defined as a value > 2.1 mg/L.

Table 6—*ORs and 95% Confidence Intervals for Elevated Levels of Blood Leukocytes, Platelets, Fibrinogen, and CRP by Quartiles of FEV_1% Predicted and Serum Cotinine Level Among Current and Former Smokers***

Variable†	Quartiles of FEV_1 % Predicted (n = 5,795)			
	4th Quartile (> 103.8%)	3rd Quartile (92.1–103.8%)	2nd Quartile (78.9–92.1%)	1st Quartile (≤ 78.9%)
Leukocytes				
Cotinine < 10 ng/mL	1 (Reference)	1.39 (0.90–2.12)	1.53 (0.99–2.35)	2.82 (1.88–4.24)
Cotinine ≥ 10 ng/mL	3.32 (2.19–5.06)	4.81 (3.24–7.14)	5.07 (3.46–7.43)	5.04 (3.45–7.38)
Platelets				
Cotinine < 10 ng/mL	1 (Reference)	1.05 (0.75–1.47)	1.38 (0.98–1.93)	1.57 (1.11–2.23)
Cotinine ≥ 10 ng/mL	1.09 (0.76–1.56)	1.34 (0.95–1.88)	1.49 (1.07–2.06)	1.48 (1.07–2.05)
Fibrinogen				
Cotinine < 10 ng/mL	1 (Reference)	1.18 (0.82–1.71)	1.39 (0.97–1.99)	1.63 (1.15–2.33)
Cotinine ≥ 10 ng/mL	1.73 (1.17–2.56)	1.84 (1.25–2.70)	2.09 (1.47–2.99)	2.64 (1.89–3.68)
Serum CRP				
Cotinine < 10 ng/mL	1 (Reference)	1.48 (1.15–1.90)	1.59 (1.22–2.05)	2.75 (2.11–3.57)
Cotinine ≥ 10 ng/mL	1.85 (1.40–2.44)	2.18 (1.66–2.86)	2.64 (2.04–3.43)	3.44 (2.67–4.44)

*Values given as OR (95% confidence interval). All values have been adjusted for age, sex, race, and BMI. Participants in the 4th FEV_1 quartile group with a serum cotinine level < 10 ng/mL are the reference category.

†Elevated levels of leukocytes, platelets, and fibrinogen were defined as ≥ 85th percentile of the respective variable. Elevated CRP was defined as a value > 2.1 mg/L.

inflammation.[32–35] The intensity of the systemic inflammation is further amplified by active smoking. We also found that individuals with reduced FEV_1 on the basis of a restrictive disorder had evidence of systemic inflammation, suggesting that lung inflammation in general, regardless of the exact cause, may result in systemic inflammation.

The present study has several strengths. First, it was conducted using a large representative sample of the US population, providing sufficient statistical power to evaluate the potential interaction between active smoking and reduced FEV_1 on various markers of systemic inflammation. Second, due to the very nature of NHANES 3, we were able to use a validated biochemical marker of tobacco exposure, serum cotinine, thereby minimizing smoke exposure misclassification, which has been seen in studies that exclusively rely on patient history. Third, we were able to control for important confounders such as age, sex, race, and BMI, making our findings reliable and valid.

There were several limitations to the current study. First, because NHANES 3 was a cross-sectional study, the temporal nature of the relationships among active smoking, reduced lung function, and elevated levels of inflammatory markers is uncertain. It is plausible, though unlikely, that systemic inflammation may lead to reduced lung function and not the other way around. Future prospective studies are needed to better understand the temporal associations of these relationships. Second, although the study adjusted for many factors, due to the observational nature of the study, residual confounding by these and other variables might still play a role. Third, the NHANES 3 database did not adequately capture information on active infections or exacerbations. Since CRP and other inflammatory markers may increase during these episodes, confounding by these factors may have been present. However, it is unlikely that this would have materially affected the overall results since a vast majority of individuals in this survey were stable at the time of the examination. Finally, the NHANES 3 database did not have extensive information on comorbidities or medications. However, it was reassuring that the inclusion of self-reported conditions such as heart disease, cancer, diabetes, arthritis, hypertension, high cholesterol, and active use of systemic corticosteroids and aspirin into the regression model did not materially alter the overall findings of the study. This suggests that the findings were not confounded by these factors.

In conclusion, our study findings suggest an additive effect of active smoking and reduced FEV_1 on various markers of systemic inflammation. Since persistent low-grade systemic inflammation is associated with various complications, including cachexia and cardiovascular morbidity and mortality, our findings may explain why certain disorders, such as COPD, are associated with these systemic complications and why active smoking accelerates the risk of such complications in these patients. These data further emphasize the value of smoking cessation in patients with reduced lung function. However, our findings also suggest that smoking cessation alone helps to maintain, but may be insufficient to fully normal-

ize, blood levels of CRP and other inflammatory biomarkers if compromised lung function has already developed.

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