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Association Between Combined Interleukin-6 and C-Reactive Protein Levels and Pulmonary Function in Older Women: Results from the Women's Health and Aging Studies I and II

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Abstract

OBJECTIVES—To determine whether combined higher interleukin-6 (IL-6) and C-reactive protein (CRP) levels are associated with lower pulmonary function levels in older women, accounting for chronic inflammatory diseases, physical function, and other factors associated with inflammation.

DESIGN—Cross-sectional study using data from two prospective cohorts.

SETTING—Baltimore, Maryland.

PARTICIPANTS—Eight hundred forty disabled and 332 higher-functioning community-dwelling women aged 65 and older from the Women's Health and Aging Studies (WHAS) I and II, respectively.

MEASUREMENTS—IL-6 and CRP, combined according to their tertile concentrations, and pulmonary function measures, assessed according to forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC).

RESULTS—In WHAS I and II, similar dose-response trends were observed between combined higher IL-6 and CRP levels and lower pulmonary function levels. In WHAS I (disabled women),

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the combined highest IL-6 and CRP levels were associated with the lowest levels of FEV₁ (mean 137.0 mL, 95% confidence interval (CI) = 128.4–145.7 mL) and FVC (mean 191.7 mL, 95% CI = 180.4–202.9 mL). Similarly, in WHAS II (higher-functioning women), the combined highest IL-6 and CRP levels were associated with the lowest levels of FEV₁ (mean 158.3 mL, 95% CI = 146.3–170.4 mL) and FVC (mean 224.2 mL, 95% CI = 209.9–238.5 mL).

CONCLUSION—Combined elevations in IL-6 and CRP were associated with the lowest pulmonary function levels in older women. These findings suggest that high IL-6 and CRP levels may be an indication of prevalent impaired pulmonary function. Future studies should determine whether measurement of IL-6 and CRP could enhance current methods of monitoring respiratory diseases beyond that provided by pulmonary function measures.

Keywords

pulmonary function; inflammation; older women

Deteriorating pulmonary function is associated with adverse clinical outcomes, including less physical activity, pneumonia, cardiovascular events, respiratory failure, and death.^{1–7} Pulmonary function, assessed according to forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC), gradually declines with aging. Accelerated pulmonary function decline indicates common lung diseases in older adults, such as chronic obstructive pulmonary disease (COPD), which is the fourth leading cause of death globally, with rising mortality rates in women.^{8–11}

Emerging evidence suggests that women may develop faster pulmonary function decline than men because of their greater vulnerability to the effects of environmental exposures associated with systemic inflammation, including cigarette smoking.^{12–15} High concentrations of systemic inflammatory biomarkers interleukin-6 (IL-6) and C-reactive protein (CRP) have been associated with lower levels of pulmonary function in observational studies,^{16,17} although little is known about how systemic inflammation is linked to poorer pulmonary function specifically in older women.

Prior research studies that have evaluated the relationship between systemic IL-6 and CRP concentrations and pulmonary function in older women have been rare and have limited their assessment to one inflammatory biomarker at a time.¹⁸ As an acute phase protein seen during proinflammatory states, the liver produces CRP directly in response to IL-6 activation. Given that IL-6 stimulates the hepatic production of CRP, it is important to understand how combined levels of systemic IL-6 and CRP correlate with pulmonary function in older women. Combined IL-6 and CRP levels may better reflect trends in pulmonary function levels than would levels of each inflammatory biomarker alone. It is uncertain whether higher IL-6 and CRP levels in combination are associated with lower pulmonary function levels. Because IL-6 regulates circulating CRP concentrations, this raises the possibility of whether the combined highest levels of IL-6 and CRP in older women may be associated with the poorest pulmonary function.

To the knowledge of the authors, no study has evaluated the association between IL-6 and CRP concentrations and pulmonary function in a population composed of exclusively older

women. Understanding how systemic IL-6 and CRP concentrations relate to pulmonary function in older women cross-sectionally would serve as the basis for determining whether, over time, these inflammatory biomarkers may be used adjunctively to monitor deteriorating pulmonary function, assess for clinical responses to treatment, and prognosticate adverse clinical outcomes, including pneumonia and respiratory failure, associated with poor pulmonary function from respiratory diseases.

In disabled and higher-functioning older women from two cohorts, this study sought to determine whether higher systemic IL-6 and CRP levels are associated with poorer pulmonary function and, if so, whether the combined highest IL-6 and CRP levels are associated with the poorest pulmonary function. It was hypothesized that similar trends in the relationships between IL-6 and CRP levels and pulmonary function in disabled and higher-functioning older women would be observed.

METHODS

Study Design and Population

Participants in the Women's Health and Aging Studies (WHAS) I and II, two cohorts of community-dwelling older women in Baltimore, Maryland, were included in this cross-sectional study. These cohorts were designed to investigate factors associated with the progression of physical disability. WHAS I, which consisted of 1,002 women aged 65 and older, represented the one-third most disabled women in Baltimore; WHAS II, composed of 436 women aged 70 to 79, was recruited from among the two-thirds least disabled in the same community.

The study cohorts were sampled using the Health Care Financing Administration's (now called Centres for Medicare and Medicaid Services) Medicare eligibility lists for 12 ZIP codes that spanned contiguous areas in eastern Baltimore City and Baltimore County. More extensive details about the sampling methods and study eligibility criteria have been previously published.^{19,20} Seventy-one percent of women in WHAS I and 49.5% of women in WHAS II who fulfilled study eligibility criteria consented to participate. The baseline evaluation for the two cohorts used in the current study included interviews, physical examinations, and blood testing. Baseline assessment occurred from November 1992 to February 1995 in WHAS I and from August 1994 to February 1996 in WHAS II.

Participants in WHAS I and II were studied separately to compare the association between systemic IL-6 and CRP and pulmonary function measures in a disabled population with that of a higher functioning population. Participants with acceptable spirometric measurements according to American Thoracic Society standards for whom IL-6 and CRP concentrations were available were included in this study.²¹ Of the 1,002 WHAS I participants, 162 were excluded because they did not meet medical or safety criteria for spirometry or did not complete testing, and 321 were excluded because of missing laboratory data, leaving 519 participants in the WHAS I analytical sample. Of the 436 WHAS II participants, 104 were excluded because they did not meet medical or safety criteria for spirometry or did not complete testing, and 34 were excluded because of missing laboratory data, leaving 298 participants in the WHAS II analytical sample. Supplementary analyses of the participants

with missing values showed that they were more likely to be older and less educated. They were also more likely to have more comorbid diseases and physical disability. Written informed consent was obtained from all participants. The Johns Hopkins Medical Institutions institutional review board approved the research protocols.

Laboratory Data

Nonfasting blood specimens were collected at participants' homes in WHAS I and at the Johns Hopkins General Clinical Research Center in WHAS II for measurement of hemoglobin concentration, serum creatinine, IL-6, and CRP. Assessment of IL-6 was performed using the High-Sensitivity Quantikine Kit (R&D Systems, Minneapolis, MN), a commercial enzyme-linked immunosorbent assay. Other laboratory data were analyzed at Quest Diagnostics Laboratories (Teterboro, NJ).

Chronic Inflammatory Diseases and Conditions

Prevalent chronic diseases and conditions were adjudicated and validated using algorithms involving systematic physician review of the study participants' medical history, as discussed in detail elsewhere.¹⁹ Chronic inflammatory diseases and conditions in WHAS were defined using previously published methods based upon two criteria: if they were associated with IL-6 or CRP and if sufficient literature was available to support an inflammatory etiology.²² Chronic kidney disease, cardiovascular disease, depressive symptoms, anemia, diabetes mellitus, peripheral artery disease, rheumatoid arthritis, and pulmonary disease, including obstructive (e.g., chronic bronchitis) and restrictive lung diseases, fulfilled these criteria for chronic inflammatory diseases and conditions. Chronic inflammatory disease count was dichotomized as 0 to 1 versus 2 or more. Chronic bronchitis, definite obstructive lung disease, and definite restrictive lung disease, whose adjudicated definitions were based primarily upon spirometry, were excluded from the disease count because pulmonary function measures served as the outcomes of the current study.

Pulmonary Function

FEV₁ and FVC are the standard measures used to assess pulmonary function. Measurements of pulmonary function were obtained using a PJ5 Spirometer with a pneumotachograph (Tamarac Systems, Denver, CO) and a connected notebook computer (Zeos International, Ltd., Minneapolis, MN). Trained nurse-examiners supervised participants as they attempted to produce three acceptable spirograms out of five or more forced expirations. Spirometry was not performed after administering a bronchodilator.

Spirograms were interpreted at the National Institute for Occupational Safety and Health reading center, according to guidelines established by the American Thoracic Society (ATS).²¹ As prescribed by ATS standards, the highest acceptable FEV₁ and FVC measurements were included in the analysis. Medical reasons (e.g., eye, chest, or abdominal surgery within 6 weeks or hospitalizations for respiratory infection within 3 weeks before examination) formed the basis for exclusion from spirometric testing.

Statistical Analyses

Descriptive statistics were calculated to describe the two study samples. The distributions of IL-6 and CRP levels were skewed and, for this reason, were distributed as equally as possible into three ordinal categories (low, mid, and high levels) based upon their concentrations. In each WHAS study sample, multivariable linear regression analyses were used to model the associations between the IL-6 and CRP variables and pulmonary function measures FEV₁ and FVC. The IL-6 and CRP variables were highly correlated in WHAS I (Kendall's tau-b = 0.40, $P < .001$) and in WHAS II (Kendall's tau-b = 0.33, $P < .001$) and were examined individually in the regression models.

To evaluate whether the combined highest IL-6 and CRP levels were associated with the poorest pulmonary function, a combined IL-6 and CRP variable was created. Although IL-6 induces CRP production, which is also regulated posttranscriptionally during the acute-phase inflammatory response, CRP itself could further amplify IL-6 signaling, forming a positive feedback mechanism for its heightened production that results in high serum CRP concentrations.^{23,24} For these reasons, four categories of combined low, mid, and high levels of IL-6 and CRP were developed, adapting the combination scheme described previously to reflect the regulatory relationship between IL-6 and CRP.²⁵ The highest category represented those with the highest levels of IL-6 and CRP. The lowest category represented those with the lowest levels of IL-6 and CRP. The two middle categories included those with mid levels of IL-6 or CRP or both, but neither in the highest levels, and those with the highest levels of IL-6 or CRP, but not the highest levels of both. Using multivariable linear regression analyses, the relationships between the combined IL-6 and CRP variable and pulmonary function measures FEV₁ and FVC were modeled. The least-squares means of FEV₁ and FVC were computed for each combined IL-6 and CRP category based upon these linear regression models.

Potential confounders were tested with bivariate analyses, examining their associations with each of the inflammatory biomarkers and pulmonary function measures. Fully adjusted models included age, race, smoking status, body mass index, summary physical performance score, anti-inflammatory medications (aspirin, statins, nonsteroidal anti-inflammatory drugs, and glucocorticosteroids), and chronic inflammatory disease count. Interactions between the covariates and inflammatory biomarkers were evaluated to determine potential differences in the associations between IL-6 and CRP and pulmonary function. Multicollinearity between independent variables was assessed by examining correlation matrices and variance inflation factors. Model fit was assessed using residual analysis and diagnostic statistics. Statistical significance was set at an alpha level of 0.05 or less. All data analyses were generated using SAS software version 9.2 (SAS Institute, Inc., Cary, NC) and Stata software version 9.2 (Stata Corp, College Station, TX).

RESULTS

Baseline Characteristics of WHAS I and II

Table 1 presents the major baseline characteristics of the study population in WHAS I (N = 840 disabled women) and WHAS II (N = 332 higher-functioning women). The mean age of

participants who successfully underwent spirometry was 78.1 ± 8.1 in WHAS I and 73.7 ± 2.8 in WHAS II. In WHAS I, 72.5% of women were white, as were 83.1% in WHAS II. Participants in WHAS I had on average less education, a higher body mass index, a lower functional performance score, poorer cognitive function, and more comorbid chronic inflammatory diseases than those in WHAS II. In both study populations, more than half of the participants had never smoked, and more than three-quarters did not have adjudicated chronic bronchitis or other obstructive lung disease. At least 95% of women from the two cohorts did not have adjudicated restrictive lung disease. WHAS II participants had lower median IL-6 and CRP concentrations and higher mean pulmonary function levels than those in WHAS I.

Association Between Individual Systemic Inflammatory Biomarkers IL-6 and CRP and Pulmonary Function

The relationships between IL-6 and CRP and each of the pulmonary function measures FEV₁ and FVC were assessed in the two cohorts (Table 2). In WHAS I (disabled), IL-6 was associated with FEV₁, although the association with FVC was not statistically significant, and CRP was associated with FEV₁ and FVC. Similar analyses in WHAS II (higher functioning) showed that IL-6 was associated with FVC, and CRP was associated with FEV₁. Neither the association between IL-6 and FEV₁ nor the association between CRP and FVC was statistically significant. Nevertheless, in WHAS I and II, the point estimates were similar in magnitude, as were their 95% confidence intervals (CIs) in range. There were no statistically significant interactions between age, smoking status, physical performance, and chronic inflammatory disease count and each of the inflammatory biomarkers.

Association Between Combined IL-6 and CRP Levels and Pulmonary Function

Whether combined highest IL-6 and CRP levels would be associated with the poorest pulmonary function was also evaluated. In WHAS I and II, similar trends were observed in the dose-response relationships between combined higher levels of IL-6 and CRP and lower levels of FEV₁ and FVC (Figure 1). In WHAS I (disabled), the combined highest levels of IL-6 and CRP were associated with the lowest levels of FEV₁ (mean 137.0 mL, 95% CI = 128.4–145.7 mL) and FVC (mean 191.7 mL, 95% CI = 180.4–202.9 mL). Similarly, in WHAS II (higher functioning), the combined highest levels of IL-6 and CRP were associated with the lowest levels of FEV₁ (mean 158.3 mL, 95% CI = 146.3–170.4 mL) and FVC (mean 224.2 mL, 95% CI = 209.9–238.5 mL). Women with the combined highest IL-6 and CRP levels showed the lowest FEV₁ and FVC levels, demonstrating significantly lower pulmonary function levels than those with the combined lowest IL-6 and CRP levels. This was evident in the nonoverlapping 95% CIs of FEV₁ (WHAS I and II) and FVC (WHAS II) comparing the combined highest and lowest IL-6 and CRP categories. Age, smoking status, physical performance, and chronic inflammatory disease count did not interact significantly with combined IL-6 and CRP levels to affect pulmonary function.

DISCUSSION

In this cross-sectional study, higher IL-6 and CRP levels were associated with poorer pulmonary function in disabled and higher-functioning older women, accounting for

comorbid disease burden and other factors associated with inflammation. Combined higher IL-6 and CRP levels also were correlated with poorer pulmonary function in a dose-response fashion. These findings suggest that the combination of high IL-6 and CRP concentrations in older women may be an indication of prevalent impaired pulmonary function. This study is notable for being the first to investigate the relationship between systemic inflammation and pulmonary function in disabled and higher-functioning older women. This is also the first study to assess for a dose-response relationship between combined IL-6 and CRP levels and pulmonary function. Although this study supports the findings of prior observational studies in well-functioning older adults, which showed that high levels of IL-6 and CRP were each associated with poor pulmonary function, it further demonstrates that these associations exhibit similar trends in disabled and higher-functioning older women.^{26–28} In addition, this study indicates that the assessment of combined IL-6 and CRP concentrations offers greater insight than the evaluation of each inflammatory biomarker alone into the association between heightened systemic inflammation and poor pulmonary function, whether from underlying obstructive or restrictive lung disease.

Environmental exposures, including cigarette smoking, and respiratory pathogens in the airways that may activate intrapulmonary inflammatory cells such as alveolar macrophages to secrete IL-6, which could lead to structural changes, resulting in deteriorating pulmonary function over time, could explain an association between combined higher levels of IL-6 and CRP and poorer pulmonary function.²⁹ Moreover, intrapulmonary IL-6 is believed to circulate into the periphery, activating the systemic inflammatory response, including hepatic production of CRP and other acute phase reactants. These systemic inflammatory mediators could return to the pulmonary circulation and cause parenchymal damage, inducing physiological alterations associated with impaired pulmonary function.

An important implication is that combined high IL-6 and CRP levels could identify preexisting pulmonary function impairment in older women with high or low physical function. Future research is needed to determine whether combined IL-6 and CRP levels have clinical utility in enhancing current methods of monitoring pulmonary function decline, evaluating responses to treatment, and risk-stratifying related adverse clinical outcomes. By delineating the cross-sectional associations between combined IL-6 and CRP levels and pulmonary function in older women, the current study also introduces the possibility that inflammatory biomarkers could serve as therapeutic targets for delaying the progression of pulmonary function decline. Interventions that reduce systemic inflammation, including structured exercise programs, could play a beneficial role, which are additive to smoking cessation and other treatments that could minimize deteriorating pulmonary function.

Although the findings may be generalized to community-dwelling older women, this study had several limitations. First, the cross-sectional study design limits the ability to make causal inferences about the effect that IL-6 and CRP concentrations have on pulmonary function. Second, it was not possible to assess the cumulative proinflammatory consequences of combined high IL-6 and CRP levels on pulmonary function. Additional proinflammatory pathways could be activated further downstream, leading to the induction of other proinflammatory mediators, which would affect pulmonary function. There are no available biostatistical methods that would allow the aggregated effects of multiple

inflammatory biomarkers to be addressed simultaneously.³⁰ Finally, the analyses used raw FEV₁ and FVC values, which do not discern between differences in height and waist circumference that can affect spirometric measurements of pulmonary function. Therefore, the dose-response trends observed between combined IL-6 and CRP levels and pulmonary function measures merely provide insight into how these factors are correlated with, rather than reflect, quantitative reductions in pulmonary function measures associated with IL-6 and CRP levels.

The progression of deteriorating pulmonary function can herald the presence of COPD, various interstitial lung diseases, and a higher risk of related adverse clinical outcomes, including pneumonia and respiratory failure. Given projected global increases in COPD prevalence and mortality, especially in women, it is of paramount importance that how declining pulmonary function is monitored and managed in this population be improved.^{9,11,31–33} Understanding how systemic inflammatory biomarkers, such as IL-6 and CRP, are related to pulmonary function over time may indicate whether these biomarkers could improve surveillance of declining pulmonary function, assessment of treatment effects, and prediction of related adverse clinical outcomes associated with respiratory diseases.

The results of this study demonstrate that combined higher IL-6 and CRP concentrations are associated with poorer pulmonary function in disabled and higher-functioning older women. As a next step, using larger cohort studies, it is planned to determine whether these dose-response relationships vary in older women depending on the type of respiratory impairment, namely airflow limitation (as seen in COPD) or restriction (as seen in interstitial lung disease) and in those with normal pulmonary function. The study findings further lay the foundation for future longitudinal studies to investigate whether changes in systemic IL-6 and CRP concentrations are associated with changes in pulmonary function in older women. Additional knowledge gained from these studies may lead to interventional trials that could evaluate whether specific treatments that reduce IL-6 and CRP concentrations would slow the progression of pulmonary function decline in older women and, subsequently, reduce the risk of related adverse clinical outcomes associated with respiratory diseases.

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Figure 1.

Association between combined interleukin-6 (IL-6) and C-reactive protein (CRP) levels and pulmonary function in the Women's Health and Aging Studies (WHAS) I and II. (A) and (B) show the mean forced expiratory volume in 1 second (FEV₁) according to combined IL-6 and CRP categories in each WHAS cohort. (C) and (D) show the mean forced vital capacity (FVC) according to combined IL-6 and CRP categories in each WHAS cohort. The four combined IL-6 and CRP categories were: (1) low IL-6 and CRP: concentrations in the lowest levels for IL-6 (WHAS I <2.77 pg/mL; WHAS II <2.27 pg/mL) and CRP (WHAS I <3 mg/L; WHAS II <3 mg/L); (2) mid IL-6 or CRP: concentrations in the middle levels for IL-6 (WHAS I 2.77–4.59 pg/mL; WHAS II 2.27–3.66 pg/mL) or CRP (WHAS I 3–7.49 mg/L; WHAS II 3–5.79 mg/L), but neither in the highest; (3) high IL-6 or CRP: concentrations in the highest levels for IL-6 (WHAS I 4.60 pg/mL; WHAS II 3.67 pg/mL) or CRP (WHAS I 7.50 mg/L; WHAS II 5.8 mg/L), but not both in the highest; and (4) high IL-6 and CRP: concentrations in highest levels for IL-6 (WHAS I 4.60 pg/mL; WHAS II 3.67 pg/mL) and CRP (WHAS I 7.50 mg/L; WHAS II 5.8 mg/L). The numbers above each bar graph represent the mean volumes in mL for FEV₁ and FVC, according to their corresponding combined IL-6 and CRP categories. The vertical lines represent the 95% confidence intervals. The means presented for each pulmonary function measure are calculated least-squares means adjusted for age, race, smoking status, body mass index, summary physical performance score, anti-inflammatory medications (aspirin, statins, nonsteroidal anti-inflammatory drugs), and number of comorbid inflammatory diseases.

Table 1

Baseline Characteristics of Women's Health and Aging Studies (WHAS) I and II Participants

Characteristic	WHAS I (N = 840)*	WHAS II (N = 332) [†]
Age, mean $\pm$ SD	78.1 $\pm$ 8.1	73.7 $\pm$ 2.8
Race, n (%)		
Black	230 (27.5)	56 (16.9)
White	607 (72.5)	275 (83.1)
Education, years, mean $\pm$ SD	9.9 $\pm$ 3.6	12.7 $\pm$ 3.3
Smoking status, n (%)		
Never	449 (53.5)	183 (55.1)
Former	300 (35.7)	119 (35.8)
Current	91 (10.8)	30 (9.0)
Body mass index, kg/m ² , mean $\pm$ SD	28.7 $\pm$ 9.0	26.3 $\pm$ 5.0
Summary Physical Performance score (range 0–12), mean $\pm$ SD [‡]	6.1 $\pm$ 3.3	8.8 $\pm$ 1.8
Mini-Mental State Examination score (range 18–30), mean $\pm$ SD	26.5 $\pm$ 3.0	28.9 $\pm$ 1.8
Chronic inflammatory diseases, n (%)		
Chronic kidney disease	333 (51.5)	131 (39.8)
Cardiovascular disease	276 (32.9)	49 (14.8)
Depressive symptoms	251 (30.0)	25 (7.5)
Anemia	126 (20.2)	28 (8.8)
Diabetes mellitus	129 (15.4)	21 (6.3)
Peripheral artery disease	165 (19.6)	13 (3.9)
Rheumatoid arthritis	21 (2.5)	2 (0.6)
Pulmonary disease, n (%)		
Chronic bronchitis or other obstructive lung disease	202 (24.0)	70 (21.1)
Restrictive lung disease	42 (5.0)	13 (3.9)
Number of comorbid chronic inflammatory diseases, n (%) [§]		
0 or 1	278 (45.4)	259 (82.2)
2	334 (54.6)	56 (17.8)
Anti-inflammatory medications, n (%) [#]		
No	320 (39.3)	105 (33.4)
Yes	495 (60.7)	209 (66.6)
Systemic inflammatory biomarkers, median (interquartile range)		
Interleukin-6 (pg/mL)	3.6 (2.4–5.6)	2.9 (2.1–4.1)
C-reactive protein (mg/L)	3.7 (2.0–8.1)	2.0 (2.0–5.5)
Spirometry, mean $\pm$ SD		
Forced expiratory volume in 1 second, mL	1,400 $\pm$ 500	1,800 $\pm$ 400
Forced vital capacity, mL	1,900 $\pm$ 600	2,500 $\pm$ 500

* All missing data were <10.5%, except for variables that were defined, using laboratory test results from peripheral blood specimens. These were chronic kidney disease, anemia, number of comorbid chronic inflammatory diseases, interleukin-6, and C-reactive protein. Up to 27% of blood data were missing.

† All missing data were <5.5%.

‡ Based on a series of physical performance tests assessing upper and lower extremity function; the higher the score, the better the physical function.

§ Chronic bronchitis or other obstructive lung disease and restrictive lung disease were excluded from the chronic inflammatory disease count, which was an adjustment variable in the regression analyses. Pulmonary function, the outcome of interest, was the basis of how these disease diagnoses were adjudicated.

Aspirin, statins, nonsteroidal anti-inflammatory drugs, and glucocorticosteroids. The maximum number any one subject was taking was three different types of these medications.

SD = standard deviation.

Table 2

Association Between Individual Interleukin-6 (IL-6) and C-Reactive Protein (CRP) Levels and Pulmonary Function

Inflammatory Biomarker [*]	Pulmonary Function Measure (95% Confidence Interval)			
	WHAS I		WHAS II	
	FEV ₁ (mL)	FVC (mL)	FEV ₁ (mL)	FVC (mL)
IL-6 [†]	-49.6 (-94.5 to -4.7) [‡]	-47.9 (-105.9–10.1)	-52.9 (-110.4–4.6)	-86.2 (-154.4 to -18.0) [‡]
CRP [§]	-56.6 (-100.5 to -12.7) [‡]	-61.2 (-117.7 to -4.7) [‡]	-59.5 (-116.8 to -2.2) [‡]	-57.6 (-126.0–10.9)

* There were two regression models for each outcome pulmonary function measure. IL-6 was the main predictor variable in one and CRP in the other. Both models were adjusted for age, race, smoking status, body mass index, summary physical performance score, anti-inflammatory medications (aspirin, statins, nonsteroidal anti-inflammatory drugs), and number of comorbid inflammatory diseases.

[†] Categorized as <2.77, 2.77–4.59, and 4.60 pg/mL in the (Women's Health and Aging Study (WHAS) I and <2.27, 2.27–3.66, and 3.67 pg/mL in WHAS II.

[‡] $P < .05$.

[§] Categorized as <3, 3–7.49, and 7.50mg/L in WHAS I and <3, 3–5.79, and 5.8mg/L in WHAS II.***** ML = milliliters.