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## Systemic inflammation and lung function: A longitudinal analysis

Robert J. Hancox<sup>a,\*</sup>, Andrew R. Gray<sup>a</sup>, Malcolm R. Sears<sup>b</sup>, and Richie Poulton<sup>c</sup>

<sup>a</sup>Department of Preventive & Social Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand <sup>b</sup>Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada <sup>c</sup>Department of Psychology, University of Otago, Dunedin, New Zealand

### Abstract

**Background**—Systemic inflammation is associated with impaired lung function in healthy adults as well as in patients with lung disease. The mechanism for this association is unknown and it is unclear if systemic inflammation leads to impaired lung function or if poor lung function leads to inflammation. We explored the temporal associations between blood C-reactive protein (CRP), fibrinogen, and white blood cells, and lung function in young adults.

**Methods**—Spirometry, plethysmography, and diffusion capacity were measured in a population-based cohort at ages 32 and 38 years. High-sensitivity CRP, fibrinogen, and white blood cells were measured at the same ages.

**Results**—Higher levels of CRP and, to a lesser extent, fibrinogen were associated with lower lung volumes in cross-sectional analyses at both ages 32 and 38 years. Higher CRP and fibrinogen at age 32 were associated with higher FEV<sub>1</sub> and FEV<sub>1</sub>/FVC at age 38, but not other measures of lung function. Lower lung volumes (total lung capacity, functional residual capacity, and residual volume) but not airflow obstruction (FEV<sub>1</sub>/FVC) at age 32 were associated with higher CRP at age 38. Associations between age 32 lung function and fibrinogen at follow-up were weaker, but consistent. There were no longitudinal associations between white blood cells and lung function.

**Conclusions**—We found no evidence that systemic inflammation causes a decline in lung function. However, lower lung volumes were associated with higher CRP and fibrinogen at follow-up indicating that pulmonary restriction may be a risk factor for systemic inflammation. The mechanism for this association remains unclear.

\*Corresponding author. bob.hancox@otago.ac.nz (R.J. Hancox).

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2015.12.007>.

#### Conflict of interest

None of the authors has a conflict of interest with the subject of this manuscript.

#### Contributors

RJH developed the idea for this study and was involved in data collection, analysis, and preparation of the manuscript. ARG was involved in the planning of the analyses, analysed the data, and helped to prepare the manuscript. MRS and RP collected data, contributed to the analyses, and critically reviewed the manuscript. All authors approved the manuscript prior to submission.

## Keywords

Cohort studies; C-reactive protein; Inflammation; Pulmonary function

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## 1. Introduction

There is a poorly understood association between systemic inflammation and reduced lung volumes [1–6]. This association is not only present among patients with chronic lung disease, but is also found in apparently healthy young adults. The mechanism(s) behind this association are unknown but may be important for a number of reasons. It is possible that chronic systemic inflammation from a non-respiratory cause leads to an accelerated decline in lung function. Conversely, unrecognised lung disease may result in systemic inflammation with deleterious effects on other aspects of health. Finally, confounding factors, such as obesity, may impact on both lung function and systemic inflammation [7,8]. Since systemic inflammation is implicated in the pathogenesis of cardiovascular diseases, the association may also help to explain the association between low lung function and cardiovascular mortality [9].

Most studies of lung function and systemic inflammation have been cross-sectional and it remains uncertain which comes first. Two studies found that higher levels of C-reactive protein (CRP) and fibrinogen in young adulthood were associated with a subsequent decline in lung volumes [5,10], but this was not found in other longitudinal studies [2,6,11]. One study found that high CRP levels were associated with subsequent lung function decline only in men [12]. Another suggested that the association between lung function and inflammation may be confounded by adiposity [13]. A recent study confirmed cross-sectional associations between CRP and spirometric lung function, and also found associations between changes in CRP and changes in lung function over 13 years of follow-up. However, baseline CRP levels did not predict lung function decline, nor did baseline lung function predict changes in CRP leaving the temporal sequence between CRP and lung function undetermined [14].

A large Mendelian randomisation study found that, although high levels of CRP were associated with COPD, participants with genetically elevated levels of CRP were not more likely to develop COPD or experience a greater decline in FEV<sub>1</sub> during follow-up [15]. This suggests that CRP does not directly mediate a decline in lung function, but it remains possible that CRP levels are an indirect marker of another inflammatory process that impacts on the lungs. A smaller (all male) cohort found an association between baseline CRP levels and FEV<sub>1</sub> decline, but this was not predicted by CRP genotype leading the authors to speculate that the association between CRP and lung function could be due to reverse causality –the possibility that impaired lung function causes elevation of CRP [16].

Although there has been considerable research interest in systemic inflammation and obstructive airways disease [17], studies of healthy populations suggest that the association between inflammation and lung function is equally strong for the FVC as the FEV<sub>1</sub> and appear to indicate lung restriction rather than airflow obstruction [2,11,14]. One study found an association between systemic inflammation and static lung volumes, but not with airflow

obstruction [3]. Most studies have reported spirometry only and we are not aware of any follow-up studies using a broad range of lung function tests.

We previously reported an association between blood CRP levels and reduced spirometric lung volumes in young adults [2]. We now report a 6-year follow-up of this cohort with pulmonary function tests of spirometry, static lung volumes, airways conductance, and gas transfer. Our primary aim is to assess whether CRP levels predict a subsequent decline in lung function or whether poor lung function predicts higher CRP at follow-up. We further aim to assess whether inflammation is associated with a restrictive or obstructive physiological impairment. We also considered blood fibrinogen [10,13,18] and white blood cell counts [19] as alternative measures of systemic inflammation that have also been associated with lung function.

## 2. Methods

Study members were born in Dunedin, New Zealand between April 1972 and March 1973 [20,21]. 1037 children participated in the first follow-up assessment at age 3 years, constituting the base sample of the study. This analysis examines the associations between CRP and lung function at ages 32 and 38 years. At each age, over 95% of living Study members were assessed (972/1015 at age 32 and 961/1007 at age 38), although not all consented to both blood and lung function tests. Study members are mostly of New Zealand/European ethnicity with 7.5% identifying as M ori at age 26 years. Few Study members identified with other ethnicities [22]. The Otago Ethics Committee approved the study. Written informed consent was obtained at each assessment.

Information about respiratory health was obtained at each age using questions from the American Thoracic Society and the European Community Respiratory Health Survey questionnaires [23,24]. Current smokers were defined as those who reported having smoked at least one cigarette a day for at least one month during the previous year. Former smokers were those who had smoked in the past but not within the previous year.

Cumulative smoking was calculated as the pack-years of cigarettes smoked up to each age (20 cigarettes/day for 1 year = 1 pack-year).

Height and weight were measured in light clothing without shoes to calculate Body Mass Index (BMI) in  $\text{kg/m}^2$ . Spirometry ( $\text{FEV}_1$  and FVC), static lung volumes (total lung capacity (TLC), functional residual capacity (FRC), residual volume (RV)), specific airways conductance ( $sG_{aw}$ ), single-breath diffusing capacity for carbon monoxide ( $DL_{CO}$ ), and alveolar volume by methane dilution ( $V_A$ ) were measured to European Respiratory Society/American Thoracic Society standards [25–30] using a body plethysmograph (CareFusion, Yorba Linda, CA). Spirometry was repeated after 200mcg salbutamol via large volume spacer. Participants were asked to avoid using their usual inhalers on the day of the test.

CRP was measured using a high-sensitivity immunoturbidimetric assay (Roche Diagnostics, Germany). Fibrinogen was measured using an automated coagulation analyser (Sysmex; Mahberg, Germany). Haemoglobin and white blood cell counts were measured on an

automated analyser (Sysmex Corporation, Japan). Exhaled carbon monoxide was measured twice using a Micro CO monitor, (Micromedical, UK) and the mean value was recorded.

## 2.1. Statistical methods

Previous analyses of this cohort suggest that associations between CRP and lung function may differ between men and women [2]. Interactions with sex were therefore investigated for all models. Pregnant women were excluded from all analyses. Because corticosteroids may suppress systemic inflammation and also influence lung function, participants using either oral or inhaled corticosteroids were also excluded.

Linear regression was used to examine cross-sectional associations between inflammation and lung function at ages 32 and 38 using all data available at each age. Analyses were stratified by sex and adjusted for height, BMI, and pack-years of smoking up to that age. Analyses of  $DL_{CO}$  and  $DL_{CO}/V_A$  also adjusted for exhaled carbon monoxide and haemoglobin.

For longitudinal analyses, linear regression was first used to assess associations between CRP at age 32 and changes in lung function at follow-up by using age 38 lung function values as the outcome while adjusting for the same measure at age 32. There was no evidence that sex was an effect modifier in these analyses, so analyses used the combined data set including sex as a covariate. Other covariates were height, changes in BMI, and the pack-years of cigarettes smoked between these assessments. Changes in exhaled carbon monoxide and haemoglobin were included when the outcome was  $DL_{CO}$  or  $DL_{CO}/V_A$ . Interactions between sex and each of baseline CRP, change in pack-years, change in BMI, and (for  $DL_{CO}$  and  $DL_{CO}/V_A$ ) change in haemoglobin were investigated and retained where statistically significant.

Next, the direction of the association was reversed and a second set of linear regression models used lung function at 32 to predict CRP levels at age 38 adjusting for age 32 CRP values using the same approach and covariates described above.

CRP was log-transformed for all analyses. Lung function values were also log transformed where this improved the normality and/or homoscedasticity of the residuals. In such cases, ratios of geometric means are reported rather than differences in arithmetic means.

The analyses were repeated using blood fibrinogen [10,13,18] and white blood cell counts. Both were log-transformed for all analyses.

Stata 13.1 (College Station TX) was used with statistical significance determined by two-sided  $p < 0.05$ . No adjustments were made for multiple comparisons and interpretation of results focuses on patterns rather than isolated instances of statistical significance.

## 3. Results

Participant characteristics are shown in Table 1.

### 3.1. Cross sectional associations at ages 32 and 38 years

There were several statistically significant interactions between sex and log-CRP levels and the cross-sectional associations are shown separately (Table 2). Higher log-CRP at age 32 was associated with lower spirometric volumes for both sexes, although the association with FVC was not significant among women. There was a statistically significant inverse association with the FEV<sub>1</sub>/FVC ratio only among women. Results for men were similar at age 38, but none of the associations between log-CRP and spirometry values were significant for women at this age. A similar pattern of findings was observed for post-bronchodilator spirometry (Appendix Table A.1).

Negative associations were found between log-CRP and TLC and FRC for men at both ages but not for women. Negative associations between log-CRP and DL<sub>CO</sub> were also found for men but not women, but the ratio of DL<sub>CO</sub>/V<sub>A</sub> was not associated with log-CRP in either sex.

The associations between lung function and fibrinogen were weaker and there were few statistically significant findings. There were no significant associations between fibrinogen and lung function in men at age 32. In women at 32, FEV<sub>1</sub>, FVC, TLC and DL<sub>CO</sub> were inversely associated with fibrinogen. In men at age 38 FVC and DL<sub>CO</sub> were inversely associated with fibrinogen. In women at age 38, DL<sub>CO</sub> was inversely associated with fibrinogen (Appendix Table A.2). White blood cell counts had even weaker associations with lung function: the only statistically significant findings were inverse associations with FEV<sub>1</sub> and DL<sub>CO</sub> at age 32 in women (Appendix Table A.2).

### 3.2. Longitudinal associations

**(i) Does baseline CRP predict lung function at follow up?**—Higher baseline log-CRP was associated with greater FEV<sub>1</sub> values and FEV<sub>1</sub>/FVC ratios at age 38. None of the associations between baseline log-CRP and other measures of lung function at age 38 were significant (Table 3).

There was also an association between higher log-CRP values at baseline and higher post-bronchodilator FEV<sub>1</sub>/FVC ratios at follow-up but other post-bronchodilator spirometry measures were not significantly associated with baseline CRP (Appendix Table A.4).

The longitudinal associations for fibrinogen and white blood cells are shown in Appendix Table A.5. Similar to CRP, higher fibrinogen at age 32 predicted higher FEV<sub>1</sub>/FVC ratios at age 38. White blood cell counts at age 32 were not significantly associated with lung function changes at age 38 aside from a negative association with RV (Appendix Table A.6).

**(ii) Does baseline lung function predict CRP at follow-up?**—Higher baseline lung volumes (TLC, FRC, and RV) were associated with lower follow-up log-CRP (Table 4). Gas transfer (DL<sub>CO</sub>) was also associated with higher log-CRP at follow-up, but not when it was corrected for alveolar volume (DL<sub>CO</sub>/V<sub>A</sub>). Neither pre- nor post-bronchodilator spirometry at baseline were associated with changes in CRP at follow up (Table 4 and Appendix Table A.7).

The associations between baseline lung function and change in fibrinogen levels are shown in Appendix Table A.8. Higher levels of FRC were associated with lower levels of fibrinogen at follow-up, but there were no other significant associations. There were no associations between baseline lung function and change in white blood cell counts (Appendix Table A.9).

### 3.3. Analysis among never-smokers

The analyses were repeated on the participants ( $n = 396$  at age 32 and  $n = 406$  at age 38) who had never smoked to exclude the possibility of residual confounding by smoking status. The results for CRP were similar to the full cohort with the following changes. The cross-sectional models revealed attenuated and non-significant associations at age 32 for men with respect to FEV<sub>1</sub> and FRC, and for women for FEV<sub>1</sub> and FEV<sub>1</sub>/FVC. For women at age 38, the association with FEV<sub>1</sub>/FVC was now statistically significant. In the longitudinal models, the association between baseline log-CRP and change in FEV<sub>1</sub> was attenuated and not statistically significant, while the inverse association between baseline DL<sub>CO</sub> and CRP at follow up was unchanged, but not statistically significant (results not shown).

## 4. Discussion

Cross sectional associations at both age 32 and 38 years in this population-based cohort confirm previous observations of an association between systemic inflammation and lower levels of lung function and extend these observations to include a broad range of lung function tests [1–6,14]. These were more apparent in men than women and were observed across a range of lung volume measurements. Although there were cross-sectional associations between higher CRP levels and lower FEV<sub>1</sub>/FVC ratios in women, the associations in men were more consistent with a restrictive rather than obstructive pattern. None of the associations with specific airway conductance (sG<sub>aw</sub>) were significant. Similarly, the association between CRP and lower DL<sub>CO</sub> in men was not found when corrected for alveolar volume (DL<sub>CO</sub>/V<sub>A</sub>) suggesting that the association was primarily due to reduced lung volume rather than impaired gas transfer *per se*.

From the longitudinal models, we did not find any evidence that systemic inflammation predicted a decline in lung function at follow-up. In fact higher levels of CRP at age 32 were associated with higher FEV<sub>1</sub> and FEV<sub>1</sub>/FVC ratios at age 38. Conversely, lower lung volumes at baseline predicted higher CRP levels at follow-up. These associations were found for plethysmographic lung volumes, but not for spirometry or airflow obstruction indicating that higher levels of systemic inflammation at follow up are predicted by a restrictive rather than obstructive lung function pattern.

Only a few studies have evaluated the temporal sequence between inflammation and reduced lung volumes. Some studies found no association between baseline CRP and decline in FEV<sub>1</sub> or FVC levels over 6–13 years follow-up [11,14,31], whereas other studies reported associations between higher levels of CRP at baseline and decline in spirometric lung function over follow-up of between 9 and 27 years [5,10,16,32]. Fewer studies have explored whether lung function at baseline predicts the subsequent change in CRP. We have previously found that a decline in FEV<sub>1</sub> between ages 26 and 32 was associated with an

increase in CRP, but this analysis was limited by the use of a low-sensitivity CRP assay at baseline [2]. Other studies have found no association between baseline FEV<sub>1</sub> and change in CRP [6,14], while a study in young Danish adults found that whereas baseline FEV<sub>1</sub> did not predict the change in CRP, the decline in FEV<sub>1</sub> predicted CRP at follow-up [5].

We found that associations between lung function and fibrinogen were generally weaker than the associations between lung function and CRP in both the cross-sectional and longitudinal analyses, whereas there were very few significant associations between lung function and white blood cell counts (Appendix Tables). Although, most of the identified associations were in a similar direction to those seen for CRP, this suggests that these measures of inflammation are less clearly associated with lung function. In contrast to our findings, a longitudinal study of elderly adults found that baseline fibrinogen, but not CRP, predicted a decline in the FEV<sub>1</sub>/FVC ratio [18]. In keeping with our findings, however, both CRP and fibrinogen were associated with higher levels of lung function at follow-up, which was interpreted as due to a survival bias. This would not apply to our younger cohort.

Our findings do not support the hypothesis that low-grade inflammation leads to lung damage. This is consistent with a large Mendelian randomisation study, which found that although high CRP levels were associated with worse lung function overall, those who were genetically predisposed to higher CRP levels did not have worse lung function [15]. Our findings extend these observations by showing that it is unlikely that CRP is a marker of an underlying inflammatory process that is causing lung damage. In fact, we found the opposite tendency – those with higher CRP at baseline tended to have improved spirometry values 6 years later. It seems unlikely that higher levels of CRP directly lead to improved lung function and one possible explanation is that a sub-clinical illness at the time of testing at age 32 could have led to both a higher CRP level and temporarily impaired spirometry.

By contrast, we found that lower lung volumes at baseline predicted higher inflammatory responses six years later. These findings were similar when the analyses were restricted to never smokers. This association could not be explained by the potential confounding influences of changes in body weight or smoking. It suggests that poor lung function leads to increased systemic inflammation, although whether this is a direct influence of the lungs on the inflammatory response or mediated by a third factor is unknown. The finding does, however, offer a potential explanation for the association between reduced lung volumes and cardiac disease, since CRP may be implicated in the pathogenesis of atherosclerosis [33].

There were sex-differences in the cross-sectional associations between poor lung function and systemic inflammation. For women, the associations were weaker than in men and generally not statistically significant. Several studies have found stronger association between CRP and lung function in men [4,5,32]. A possible explanation for this finding is that CRP tends to be higher in women and may fluctuate to a greater extent due to hormonal changes with the menstrual cycle. However, the strength of the association between CRP levels at 32 and 38 years was similar in men (Spearman's rho = 0.49) and women (rho = 0.53) suggesting that CRP levels are equally stable in both sexes. Hence, we cannot easily explain the sex difference and it remains to be seen if this persists with advancing age in future assessments of the cohort. We note, however, that the association between CRP and

cardiovascular disease appears to be stronger in men than women, and this is similar to our finding of stronger associations between CRP and lung function in men [34].

Strengths of this study include a broad range of measures of lung function taken six years apart in a population-based cohort with a very high follow-up rate. The fact that all Study members were the same age eliminates confounding by age. We also have information on potential confounding variables. A limitation of the study is that 6 years of follow-up data may not reflect changes in inflammation and lung function over a longer time.

In conclusion, cross-sectional analyses confirm the association between systemic inflammation and reduced lung function. Longitudinal analyses, however, provide no support for the hypothesis that systemic inflammation leads to lung function impairment. Conversely, lower lung volumes were associated with higher levels of inflammation at follow-up.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**

Participant characteristics at ages 32 and 38.

	Age 32		Age 38	
	Men	Women	Men	Women
	n = 429	n = 380	n = 420	n = 396
BMI <sup>a</sup>	26.0 (1.2)	25.3 (1.2)	27.0 (1.2)	26.1 (1.2)
<b>Smoking:</b>				
Current smoker	158 (36.8)	126 (33.2)	116 (27.6)	96 (24.2)
Former smoker	53 (12.4)	76 (20.0)	86 (20.5)	112 (28.3)
Never smoker	218 (50.8)	178 (46.8)	218 (51.9)	188 (47.5)
Pack-years <sup>b</sup>	10.2 (10.9)	8.2 (8.7)	12.7 (14.6)	8.7 (11.7)
<b>Inflammation</b>				
CRP mg/L <sup>a</sup>	1.1 (2.9)	1.4 (3.3)	1.1 (2.6)	1.4 (3.1)
<2	326 (76.3)	230 (60.8)	314 (74.8)	249 (62.9)
2-<5	67 (15.7)	85 (22.5)	77 (18.3)	87 (22.0)
5-<10	22 (5.2)	41 (10.8)	21 (5.0)	36 (9.1)
10	12 (2.8)	22 (5.8)	8 (1.9)	24 (6.1)
Fibrinogen (g/L) <sup>a</sup>	2.4 (1.2)	2.6 (1.2)	2.6 (1.2)	2.8 (1.2)
WBC ( $\times 10^9/L$ ) <sup>a</sup>	7.3 (1.3)	7.5 (1.3)	7.5 (1.3)	7.8 (1.2)
<b>Lung function (pre-bronchodilator)</b>				
FEV <sub>1</sub> (L)	4.5 (0.6)	3.3 (0.5)	4.2 (0.6)	3.2 (0.4)
FVC (L)	5.8 (0.8)	4.2 (0.6)	5.6 (0.7)	4.1 (0.5)
FEV <sub>1</sub> /FVC (%)	77.3 (6.2)	80.1 (5.8)	75.8 (6.1)	77.7 (5.9)
sG <sub>aw</sub> (mL/s/cmH <sub>2</sub> O/L) <sup>a</sup>	0.2 (1.7)	0.2 (1.6)	0.2 (1.4)	0.2 (1.3)
TLC (L) <sup>a</sup>	7.4 (1.1)	5.5 (1.1)	7.5 (1.1)	5.6 (1.1)
FRC (L)	3.4 (0.8)	2.8 (0.6)	3.1 (0.8)	2.6 (0.6)
RV (L) <sup>a</sup>	1.6 (1.3)	1.3 (1.3)	1.8 (1.2)	1.5 (1.3)
DL <sub>CO</sub> (mL/min/mmHg) <sup>a</sup>	33.7 (1.2)	23.7 (1.2)	31.2 (1.2)	22.4 (1.2)
DL <sub>CO</sub> /V <sub>A</sub> (mL/min/mmHg/L) <sup>a</sup>	4.8 (0.8)	4.6 (0.7)	4.7 (0.7)	4.5 (0.6)

<sup>a</sup>Geometric mean (geometric SD).<sup>b</sup>Median (IQR) for ever smokers.

**Table 2**

Cross-sectional adjusted associations between CRP and lung function.

	Age 32										Age 38																			
	Men					Women					Sex interaction					Men					Women					Sex interaction				
	n	Est	95% CI	p		n	Est	95% CI	p		n	Est	95% CI	p		n	Est	95% CI	p		n	Est	95% CI	p		n	Est	95% CI	p	
FEV <sub>1</sub>	422	-0.073	-0.123, -0.023	<b>0.004</b>	378	-0.056	-0.092, -0.021	<b>0.002</b>	0.446	420	-0.059	-0.117, -0.002	<b>0.043</b>	395	-0.016	-0.053, 0.021	0.389	0.205			420	-0.098	-0.166, -0.029	<b>0.006</b>	395	-0.000	-0.045, 0.045	0.989	<b>0.002</b>	
FVC	422	-0.104	-0.163, -0.046	<b>0.001</b>	378	-0.040	-0.083, 0.003	0.071	<b>0.029</b>	420	0.260	-0.403, 0.923	0.441	395	-0.370	-0.962, 0.222	0.220	<b>0.025</b>			420	0.260	-0.403, 0.923	0.441	395	-0.370	-0.962, 0.222	0.220	<b>0.025</b>	
FEV <sub>1</sub> /FVC	422	0.128	-0.443, 0.698	0.660	378	-0.601	-1.146, -0.056	<b>0.031</b>	0.037	420	0.260	-0.403, 0.923	0.441	395	-0.370	-0.962, 0.222	0.220	<b>0.025</b>			420	0.260	-0.403, 0.923	0.441	395	-0.370	-0.962, 0.222	0.220	<b>0.025</b>	
sG <sub>aw</sub> <sup>a</sup>	414	1.004	0.955, 1.055	0.879	370	0.987	0.947, 1.030	0.553	0.835	418	1.017	0.981, 1.054	0.362	392	0.979	0.953, 1.006	0.134	0.354			418	1.017	0.981, 1.054	0.362	392	0.979	0.953, 1.006	0.134	0.354	
TLC <sup>a</sup>	413	0.984	0.975, 0.993	<b>0.001</b>	370	0.995	0.986, 1.004	0.270	0.073	417	0.985	0.974, 0.996	<b>0.006</b>	393	0.999	0.989, 1.010	0.869	0.082			417	0.985	0.974, 0.996	<b>0.006</b>	393	0.999	0.989, 1.010	0.869	0.082	
FRC <sup>a</sup>	414	0.984	0.969, 0.998	<b>0.030</b>	370	0.998	0.984, 1.013	0.798	<b>0.004</b>	418	0.974	0.954, 0.994	<b>0.013</b>	393	0.987	0.970, 1.005	0.163	<b>0.027</b>			418	0.974	0.954, 0.994	<b>0.013</b>	393	0.987	0.970, 1.005	0.163	<b>0.027</b>	
RV <sup>a</sup>	413	0.992	0.973, 1.011	0.427	370	1.004	0.985, 1.024	0.672	0.221	418	0.986	0.965, 1.007	0.192	393	1.003	0.983, 1.024	0.767	0.347			418	0.986	0.965, 1.007	0.192	393	1.003	0.983, 1.024	0.767	0.347	
DL <sub>CO</sub> <sup>a</sup>	421	0.982	0.970, 0.995	<b>0.006</b>	369	0.995	0.982, 1.007	0.394	0.261	413	0.976	0.962, 0.990	<b>0.001</b>	383	0.991	0.978, 1.003	0.148	0.138			413	0.976	0.962, 0.990	<b>0.001</b>	383	0.991	0.978, 1.003	0.148	0.138	
DL <sub>CO</sub> /V <sub>A</sub>	421	-0.004	-0.065, 0.057	0.896	369	0.010	-0.050, 0.069	0.751	0.997	413	-0.028	-0.093, 0.036	0.383	383	-0.025	-0.085, 0.036	0.421	0.916			413	-0.028	-0.093, 0.036	0.383	383	-0.025	-0.085, 0.036	0.421	0.916	

p values < 0.05 are highlighted in bold.

<sup>a</sup>Log-transformed outcome so estimates and CIs are ratios of geometric means rather than differences of arithmetic means. Log-transformed CRP was used as the independent variable of interest. Analyses are adjusted for height, BMI, and pack years smoking. DL<sub>CO</sub> and DL<sub>CO</sub>/V<sub>A</sub> analyses are also adjusted for exhaled carbon monoxide and haemoglobin.

**Table 3**

Associations between baseline values of CRP and changes in lung function measures.

	n	Estimate	95% CI	p-value
FEV <sub>1</sub> <sup>b</sup>	729	0.020	0.006, 0.034	<b>0.005</b>
FVC <sup>b</sup>	729	0.005	-0.012, 0.021	0.586
FEV <sub>1</sub> /FVC <sup>b</sup>	729	0.340	0.130, 0.550	<b>0.002</b>
sG <sub>aw</sub> <sup>a</sup>	716	0.994	0.980, 1.007	0.353
TLC <sup>a,b</sup>	714	1.001	0.998, 1.004	0.358
FRC <sup>a,b</sup>	716	0.997	0.989, 1.006	0.581
RV <sup>a</sup>	715	0.996	0.985, 1.006	0.384
DL <sub>CO</sub> <sup>a</sup>	698	1.002	0.997, 1.008	0.409
DL <sub>CO</sub> /V <sub>A</sub>	698	0.023	-0.003, 0.049	0.088

p values < 0.05 are highlighted in bold.

<sup>a</sup>Log-transformed outcome so estimates and CIs are ratios of geometric means rather than differences of arithmetic means. Log-transformed CRP was used as the independent variable of interest. Analyses are adjusted for sex, height, changes in BMI and pack years smoking between ages 32 and 38 years. DL<sub>CO</sub> and DL<sub>CO</sub>/V<sub>A</sub> analyses are also adjusted for changes in exhaled carbon monoxide and haemoglobin.

<sup>b</sup>Sex-BMI interaction included in the model.

**Table 4**

Associations between baseline values of lung function measures and changes in CRP.

	n	Estimate	95% CI	p-value
FEV <sub>1</sub>	718	0.902	0.786, 1.035	0.142
FVC	718	0.915	0.817, 1.026	0.127
FEV <sub>1</sub> /FVC	718	1.000	0.989, 1.011	0.959
sG <sub>aw</sub>	711	1.221	0.769, 1.937	0.397
TLC	710	0.895	0.815, 0.983	<b>0.021</b>
FRC	711	0.758	0.684, 0.840	<b>&lt;0.001</b>
RV	710	0.793	0.654, 0.962	<b>0.018</b>
DL <sub>CO</sub>	703	0.981	0.966, 0.996	<b>0.012</b>
DL <sub>CO</sub> /V <sub>A</sub>	703	0.976	0.890, 1.070	0.605

CRP was log-transformed so estimates and CIs are ratios of geometric means rather than differences of arithmetic means. Analyses are adjusted for sex, height, changes in BMI and pack years smoking between ages 32 and 38 years. DLCO and DLCO/VA analyses are also adjusted for changes in exhaled carbon monoxide and haemoglobin.

p values < 0.05 are highlighted in bold.