Respiratory Medicine (2006) **100**, 2112–2120

respiratoryMEDICINE

Change in C-reactive protein levels and FEV_1 decline: A longitudinal population-based study ☆

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Received 9 November 2005; accepted 23 March 2006

KEYWORDS
C-reactive protein;
Epidemiology;
Forced expiratory volume in 1 s;
Longitudinal study

Summary Reduced pulmonary function is an important predictor of cardiovascular morbidity and mortality. The mechanisms underlying this association are unknown but may involve systemic inflammation. We assessed the cross-sectional and longitudinal relationships between C-reactive protein (CRP) levels and forced expiratory volume in 1 s (FEV_1) and its decline in the general population, over a period of 8.5 years.

The analyzes were based on 531 subjects (mean age at baseline: 37 ± 7 years, 50% women and 42% non-smokers), recruited at two French centers participating in the European Community Respiratory Health Survey. Lung function was expressed as a percentage of predicted FEV_1. CRP was measured centrally, by means of a highly sensitive assay.

In cross-sectional analysis, FEV_1 as a % of predicted values was negatively associated with serum CRP concentration ($P = 0.002$). Multivariate adjustment did not alter these results ($P = 0.002$). In longitudinal analysis, annual FEV_1 decline tended to increase from the lower to the upper tertile for baseline CRP concentration but the association was borderline significant ($P = 0.14$). Mean values of annual FEV_1 decline were 26 ± 32, 31 ± 32, and 34 ± 32 ml/year for the lower, middle and upper tertiles of baseline CRP concentration, respectively, after adjusting for potential confounders ($P = 0.09$). Changes in CRP levels during follow-up were associated with annual FEV_1 decline. The mean annual FEV_1 declines in subjects with increasing CRP, in those with stable CRP and in those with decreasing

Abbreviations: CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 s; BMI, body mass index

☆Data collected for the European Community Respiratory Health Survey in France (Paris and Grenoble) and supported by UCB Pharma, France and by the *Programme Hospitalier de Recherche Clinique-DRC* of Grenoble 2000 no. 2610.

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0954-6111/$ - see front matter
doi:10.1016/j.rmed.2006.03.027

CRP were 36±31, 30±31 and 24±31 ml/year, respectively ($P<0.001$). These findings were not affected by adjustment for potential confounders ($P=0.002$).

In conclusion, increases in CRP levels over time were associated with a steeper FEV_1 decline.

Introduction

Reduced pulmonary function, as assessed by peak expiratory flow, forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), is associated with an increase in the occurrence of vascular alterations and cardiovascular morbidity and mortality, in both smokers and non-smokers.[1–7]

Systemic inflammation may play a key role in the development of cardiovascular risk[8–10] and reduced pulmonary function.[11–14] There are various markers of systemic inflammation. C-reactive protein (CRP), an acute-phase reactant produced primarily in the liver in response to interleukin-6, is the best studied, and its concentration has consistently been shown to be strongly related to future cardiovascular risk in healthy subjects and in patients with peripheral and stable coronary artery diseases.[15–17]

Systemic inflammation may also be involved in lung function decline, as suggested by the results of the few available cross-sectional population-based studies. FVC has been reported to be inversely associated with levels of inflammation-sensitive serum proteins.[18] A lower FEV_1 and an increased risk of chronic obstructive pulmonary disease (COPD) have also been shown to be associated with high serum fibrinogen concentration.[12] High serum CRP concentrations have been reported in patients with COPD, which is a major cause of reduced FEV_1.[19] However, the relationships between serum CRP concentration and lung function have not been studied in detail. A few cross-sectional studies, including one carried out by our group, have investigated the association between serum CRP concentration and pulmonary function in the general population.[20,21] In these studies, FEV_1 was inversely associated with CRP concentration.

Cross-sectional studies cannot be used to determine direction- and time-dependent relationships. No longitudinal study has investigated the relationship between changes in CRP concentration and pulmonary function decline over time.

In this $8\frac{1}{2}$ year longitudinal study, conducted in 531 subjects aged between 20 and 44 years at baseline, recruited at two French centers participating in the European Community Respiratory Health Survey (ECRHS), we assessed the associations between changes in CRP concentration and annual FEV_1 decline.

Methods

The ECRHS is an international, longitudinal, multicenter epidemiological survey of asthma (prevalence, determinants, and management) in Europe. Full details of the original sampling protocol have been published elsewhere.[22,23] In the baseline study in 1991, 660 subjects (Paris) and 534 subjects (Grenoble) aged 20–44 years were randomly selected from the electoral rolls of Paris (18th *Arrondissement*) and Grenoble. These subjects were interviewed and examined. Subjects who had suffered from respiratory infection in the 3 weeks immediately preceding the examination were asked to postpone their examination if possible, as this was a criterion for exclusion. Each subject completed a standardized questionnaire and underwent standardized lung function and blood tests.

Between 1999 and 2001 (8.5 years of follow-up on average), all subjects from the baseline study were contacted again and asked to undergo examination again for the follow-up study. In the two centers, 684 subjects agreed to participate in the follow-up study. Participants and non-participants did not differ in sex distribution, body mass index (BMI) or lung function values. However, participants were slightly older (36.6±7.1 vs. 34.9±7.2 years, $P<0.001$) and more likely to be non-smokers (41.8% vs. 35.8%, $P<0.001$) (Table 1). The protocol was approved by the French Ethics Committee for Human Research and by the National Committee for Data Processing and Freedom. Informed written consent was obtained from all the subjects.

Data collection

At baseline and follow-up, trained interviewers used a standardized questionnaire to collect socio-demographic information and data concerning respiratory symptoms during the preceding 12

Table 1 Comparison of baseline characteristics among subjects participating and not participating in the follow-up study.

Baseline data	Participants* ($n = 684$)	Non-participants ($n = 510$)	$P^{\dagger}$
Age (year)[‡]	36.6 ± 7.1	34.9 ± 7.2	< 0.001
Men (%)	47.7	52.3	0.12
BMI (kg/m^2)[‡]	22.6 ± 3.1	22.7 ± 3.2	0.66
Smoking habits (%)			< 0.001
Never smokers	41.8	35.8	
Past smokers	25.0	24.2	
Light smokers	21.9	19.3	
Heavy smokers	11.3	20.8	
Atopy (%)	28.4	30.4	0.48
Asthma (%)	6.4	4.7	0.20
FEV_1% predicted[§]	104.9 ± 13.4	104.1 ± 13.3	0.27

*Subjects completed a questionnaire and underwent spirometry at follow-up study.
†For differences between the sexes, using Student's *t*-test for continuous variables and χ^2-tests for categorical variables.
‡Mean ± standard deviation.
§FEV_1% predicted = (observed FEV_1/predicted FEV_1) × 100.

months, smoking history, allergic symptoms, family history, home and work environment, and use of health-care services and medication. Subjects were classified as never having smoked, past smokers (those who had stopped smoking at least 1 year before the examination), heavy smokers (if their current tobacco consumption was at least 20 g per day) and light smokers (for those consuming up to 20 g of tobacco per day). Baseline "asthma" was defined as a positive response to any of the following questions: "Have you had an asthma attack in the last 12 months?" and/or "Are you currently taking any medication for asthma?". BMI was calculated as weight in kilograms divided by the square of height in meters.

Lung function measurements

FEV_1 was measured with a water-sealed bell spirometer (Biomedin srl, Padova, Italy). The highest of five technically acceptable FEV_1 readings was used for analysis. FEV_1 was expressed as a percentage of predicted values (FEV_1% predicted) calculated based on age and height for men and women, using ECSC reference equations.[24]

Biological measurements

Blood samples were collected at baseline and during follow-up studies and frozen at −80 °C. We determined the levels of IgE specific for house dust mite, cat, timothy grass and *Cladosporium* in serum samples. Tests for specific IgE were considered positive if values > 0.35 kU/l were obtained. "Atopy" was defined as at least one positive specific IgE test. Total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) concentrations were determined by enzymatic methods, using an automatic analyzer. Serum CRP concentrations were determined from frozen blood samples stored in the Biochemistry Department of Bichat Hospital, Paris, by means of an ultra-sensitive competitive immunoassay on a BN II analyzer (Dade Behring, Marburg, Germany). The intra- and inter-assay coefficients of variation were both < 10%.

Statistical analysis

Statistical analysis was carried out with SAS version 8.2 (SAS Institute Inc., Cary, NC, USA). Data are expressed as percentages for discrete variables and as means ± standard deviations for continuous variables. We considered *P*-values < 0.05 to be significant.

We carried out a cross-sectional analysis on data collected in 1991 (baseline). CRP concentrations were not normally distributed and analyzes were therefore performed with log-transformed values divided into tertiles (the tertile cut-off points for CRP concentration were 0.5 and 1.3 mg/l). We investigated the cross-sectional association between CRP and FEV_1% predicted by analysis of variance for univariate analyzes and analysis of covariance for multivariate analyzes (with FEV_1% predicted as the dependent variable). Cross-sectional multivariate analyzes were adjusted for sex, center, age, BMI, total cholesterol concentration, smoking habits (never, past, light, and heavy smokers), atopy and asthma.

For the longitudinal analysis, annual FEV_1 decline (ml/year) was calculated as the difference between follow-up and baseline observed FEV_1 values, divided by the number of months between the two surveys, multiplied by 12. The change in serum CRP concentration during follow-up was calculated by subtracting CRP concentration at follow-up from baseline CRP concentration. Subjects were divided into tertiles according to mean change in CRP concentration (tertile cut-off points for change in CRP concentration were -0.1 and 0.5 mg/l and mean $\pm$ SD for each tertile of CRP change were -1.8 ± 2.8, 0.1 ± 0.1, and 3.0 ± 4.4 mg/l, respectively). In the first tertile—"decrease"—CRP concentrations decreased over time. In the second tertile—"no change"—CRP concentrations remained stable and in the third tertile—"increase"—CRP concentrations increased over time.

Categories of change in smoking habits were derived, which included never smokers, sustained quitters, smokers (at each survey), quitters (stopped between surveys), and restarters.

We used analysis of variance and analysis of covariance to describe the differences in mean annual FEV_1 decline between the tertiles of both baseline CRP and change in CRP concentration, with and without adjustment for center, sex, and baseline age, BMI, total cholesterol concentration, smoking habits, atopy, asthma and FEV_1. In addition, changes in these confounding factors during follow-up were included in the multivariable model to assess its potential effects on this relationship.

We excluded 153 of the 684 subjects from the analysis, for the following reasons: missing data for serum CRP concentration ($n = 144$, due to the refusal of the subject to provide blood samples or technical and organizational difficulties) and/or missing pulmonary function tests ($n = 14$). This left 531 subjects for whom complete data were available for cross-sectional and longitudinal analysis. The 531 subjects with complete data were older at baseline (37.0 ± 7.0 vs. 35.6 ± 7.1 years, $P = 0.03$) than the excluded subjects and the percentage of men was higher (50.0% vs. 39.0%, $P = 0.01$). The mean duration of follow-up was 8.5 ± 0.8 years.

Men had a higher mean baseline FEV_1% predicted than women but serum CRP concentrations were similar in men and women.

Results

Mean baseline age ($\pm$ SD) for the 531 subjects (50% men) included in this study was 37.0 ± 7.0 years. About 42% of this population was non-smoker . As expected, mean BMI and mean total cholesterol concentrations were significantly higher in men than in women. Women had higher serum concentrations of HDL than men. Heavy smokers were more frequent in men than in women (results not shown). Men had a higher mean baseline FEV_1% predicted than women (107 ± 14 vs. 104 ± 13, $P < 0.01$) but serum CRP concentrations were similar in men and women (1.57 ± 2.5 vs. 1.60 ± 2.5, $P = 0.86$). Baseline characteristics were compared by tertiles of baseline CRP. CRP was positively associated with BMI ($P < 0.001$), smoking status ($P < 0.01$), total cholesterol ($P < 0.001$) and asthma ($P = 0.05$) (results available from authors).

Cross-sectional analysis

At baseline, FEV_1% predicted was negatively associated with serum CRP concentration. Crude mean values of FEV_1% predicted according to CRP tertiles were 106 ± 14%, 107 ± 13%, and 102 ± 14% for lower, middle and upper tertiles, respectively ($P = 0.002$).

Similar results were obtained in multivariate analyzes: the participants with the highest serum CRP concentrations had the lowest values of FEV_1% predicted (Table 2). This pattern applied to the various subgroups. The associations between CRP concentration and FEV_1% predicted were weaker (and not significant) in those who had never smoked. However, the interaction between CRP concentration and smoking habits was not statistically significant ($P = 0.5$).

Longitudinal study

A significant correlation was observed between baseline CRP and CRP at follow-up (correlation coefficient $= 0.50$, $P < 0.001$) and also between baseline FEV_1%predicted and FEV_1%predicted at follow-up (correlation coefficient $= 0.83$, $P < 0.001$).

Mean annual decline in FEV_1 ($\pm$ SD) was 30 ± 32 ml/year ($P < 0.001$). CRP concentration increased over time and the mean change in CRP concentration over the eight and a half years of follow-up was 0.5 ± 3.6 mg/l ($P = 0.004$). Baseline BMI, smoking and asthma were positively associated with change in CRP concentration over time. Baseline FEV_1 was not associated with CRP change (Table 3). Annual FEV_1 decline was positively associated with being female, age, smoking, and BMI at baseline (results available from the authors).

Table 4 shows the relationship between baseline CRP and FEV_1 decline. Annual FEV_1 decline tended to increase from the lower to the upper tertile for

Table 2 Cross-sectional analysis: multivariate relationships* between CRP concentration and FEV_1% predicted; in all subjects and in subgroups.

FEV_1% predicted	Baseline CRP by tertiles†			*P* for association	*P* for trend
	I Lower ($N = 179$)	II Middle ($N = 183$)	III Upper ($N = 169$)		
All ($n = 531$)	107 ± 14	107 ± 13	102 ± 14	0.002	0.006
Men ($n = 267$)	108 ± 15	108 ± 14	104 ± 14	<0.01	0.052
Women ($n = 264$)	105 ± 13	106 ± 13	100 ± 15	<0.05	0.075
Never smokers ($n = 224$)	107 ± 13	108 ± 13	105 ± 15	0.59	0.65
Current and past smokers ($n = 307$)	107 ± 13	106 ± 13	101 ± 13	0.002	0.002
Non-asthmatics ($n = 496$)	108 ± 13	107 ± 13	103 ± 15	0.005	0.002

*Models adjusted (where applicable) for center, age, sex, smoking habits, body mass index, cholesterol levels, atopy, and asthma.
†Cut-off points of tertiles: 0.5 and 1.3 mg/l.

Table 3 Relationship between change in CRP concentration and baseline factors.

Baseline variable	CRP change by tertiles*			*P*
	I Decrease ($N = 178$)	II No change ($N = 176$)	III Increase ($N = 177$)	
Paris (%)	53.4	48.3	40.7	0.05
Age (year)†	37.0 ± 7.1	36.9 ± 7.1	37.1 ± 7.1	0.99
Sex: men (%)	45.5	51.7	53.7	0.28
BMI (kg/m^2)†	22.7 ± 3.4	22.4 ± 2.4	23.2 ± 3.4	0.02
Total cholesterol (g/l)†	2.17 ± 0.5	2.11 ± 0.4	2.14 ± 0.5	0.50
HDL cholesterol (g/l)†	0.55 ± 0.15	0.56 ± 0.16	0.53 ± 0.14	0.14
LDL cholesterol (g/l)†	1.37 ± 0.45	1.31 ± 0.36	1.33 ± 0.41	0.42
Smoking habits (%)				<0.001
Never smokers	38.8	54.0	33.9	
Past smokers	22.5	25.6	27.7	
Light smokers	26.4	15.9	19.8	
Heavy smokers	12.4	4.6	18.6	
Asthma (%)	4.1	4.0	10.7	0.02
Atopy (%)	26.0	26.9	32.8	0.31
FEV_1% predicted‡	107 ± 14	107 ± 14	105 ± 14	0.34

*Cut-off points of CRP concentration change: −0.1 and 0.5 mg/l.
†Mean ± SD.
‡FEV_1% predicted = (observed FEV_1/predicted FEV_1) × 100.

baseline CRP concentration but this relationship did not reach statistical significance. After adjustment for covariates including, center, sex, baseline age, smoking habits, BMI, asthma, atopy, FEV_1 and change in CRP concentration, the association between baseline CRP and annual FEV_1 decline concentration was borderline significant ($P = 0.09$), but a significant difference in mean FEV_1 decline was seen between the highest and lowest tertiles for baseline CRP ($P = 0.03$).

Changes in CRP concentration during follow-up were negatively correlated with FEV_1 decline (correlation coefficient = −0.15, $P < 0.001$—Fig. 1). Mean annual FEV_1 decline was highest (36 ± 31 ml/year) for the upper tertile (increase in CRP concentration over time), lowest (24 ± 31 ml/year) for the lower tertile (decrease in CRP concentration over time), and intermediate (30 ± 31 ml/year) in the second tertile ($P < 0.001$). Similar results were obtained after adjustment for

Table 4 Longitudinal analyses: relationships between baseline C-reactive and annual decline in FEV_1.

FEV_1 decline (ml/year)	Baseline CRP by tertiles*			*P* for association	*P* for trend
	I	II	III		
Unadjusted	25 ± 31	31 ± 30	32 ± 31	0.14	0.07
Adjusted†	26 ± 32	31 ± 32	34 ± 32	0.09	0.02

*Cut-off points of tertiles: 0.5 and 1.3 mg/l.
†Models adjusted for center, sex, *baseline* age, smoking habits, body mass index, cholesterol levels, atopy, asthma, FEV_1 and change in CRP concentration.

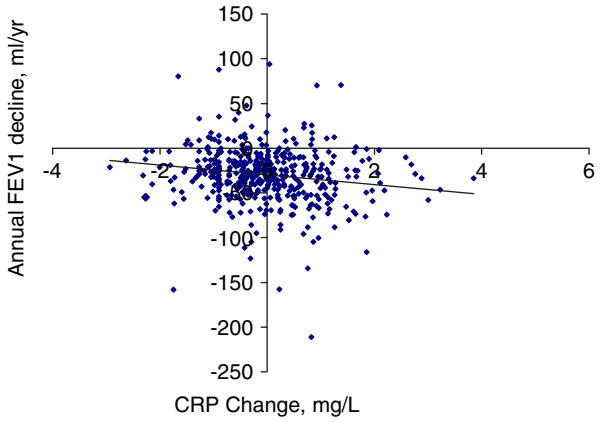

Figure 1 Relationship between CRP change during follow-up and annual FEV_1 decline (correlation coefficient = −0.15; $P<0.001$).

baseline factors ($P = 0.002$): the greater the increase in CRP concentration, the steeper the decline of FEV_1. Subjects in the upper tertile for changes in CRP concentration displayed a greater annual FEV_1 decline than subjects in the lower tertile (13 ml greater for men and 11 ml greater for women), whereas the annual decline in FEV_1 is around 30 ml/year in adults.[23] Adding changes over time in confounding factors (smoking habits, asthma, atopy, BMI, and lipid concentrations) to the multivariate model did not alter these findings (Table 5). Similar results were obtained if analyzes were carried out after excluding asthmatics, separately in men and in women, and according to baseline smoking habits (Table 5).

Discussion

In this population-based study, conducted in young and middle-aged subjects, FEV_1 and serum CRP concentration were negatively related both in cross-sectional and in longitudinal analyzes. These associations were independent of potential confounding factors (particularly smoking habits) and were observed in subgroups defined on the basis of sex, smoking habits and asthma status. This is the first longitudinal study to investigate the relationship between serum CRP concentration and lung function decline. Cross-sectional relationships between inflammation and lung function has been demonstrated previously in even larger population samples.[18,20] Some studies have shown that severe ($FEV_1 <$ 50% of predicted) and moderate (FEV_1 50–80% of predicted) COPD is associated with low-grade systemic inflammation.[24,25] Our study confirms and extends previous findings by demonstrating the presence of systemic inflammation even in subjects with modest decreases in pulmonary function. These associations seem to be relatively strong and may be considered clinically relevant. Subjects in the upper tertile for change in CRP concentration had an excess annual FEV_1 decline of 13 ml for men and 11 ml for women over subjects in the lower tertile.

Baseline CRP levels also tended to be related to annual FEV_1 decline. However, the association was of borderline statistical significance. This may reflect the low levels of variability in CRP responses in healthy young and middle-aged subjects. Moreover, analyzes based on a single baseline measurement and the within-person variability of CRP will tend to underestimate the effect of CRP on subsequent pulmonary function decline (regression dilution bias).[26]

The strengths of this study include the use of data from a general population sample with high-quality, standardized measurements, as part of the ECRHS.[27,28] We were able to confirm previously reported associations between annual FEV_1 decline and major risk factors, including baseline age, smoking habits and BMI, and the associations of CRP with BMI and with smoking habits observed are consistent with previously published results.[28–30]

Although the rate of participation in this study (around 60%) is acceptable for such a long follow-up study in the general population (mean of 8.5

Table 5 Longitudinal multivariate analyses: relationships between change in C-reactive protein concentration during follow-up and decline in FEV_1.

FEV_1 decline (ml/year)	CRP change by tertiles*			*P* for association	*P* for trend
	I Decrease	II No change	III Increase		
Unadjusted	24±31	30±31	36±31	0.009	0.002
Adjusted for confounding factors† at baseline	21±30	26±30	32±30	<0.01	0.002
Men	23±33	28±33	36±33	0.08	0.15
Women	20±26	25±26	31±26	0.02	0.01
Never smokers	24±28	32±28	38±28	0.02	0.01
Current and past smokers	25±32	28±32	36±32	0.04	0.02
Non asthmatics	25±29	30±29	39±29	0.001	0.001
Adjusted for confounding factors† at baseline and follow-up	26±32	30±31	35±32	0.04	0.01

*Cut-off points of CRP concentration change: −0.1 and 0.5 mg/l.
†Models adjusted (as appropriate) for center, sex, age, smoking habits, body mass index, cholesterol levels, atopy, asthma, and baseline FEV_1 and CRP.

years), we cannot rule out the possibility that there was a selection bias. Nevertheless, our population consisted mostly of young and middle-aged adults, so a significant proportion of the subjects lost to follow-up probably simply moved out of the area. Furthermore, our comparisons of participating and excluded subjects identified no differences in pulmonary parameters and CRP concentrations between these two groups.

We also analyzed the extent to which these associations were accounted for by confounding factors, such as smoking. It is now widely accepted that smoking is the main risk factor for reduced pulmonary function and COPD.[31] Compounds present in tobacco smoke also penetrate into the bloodstream, and are associated with a higher prevalence of coronary artery disease, endothelial dysfunction, and high serum concentrations of markers of systemic inflammation.[32–34] High CRP concentrations may reflect the effects of smoking, but adjustment for smoking habits had no effect on the observed association, and the observation that changes in CRP concentration were associated with FEV_1 decline in those who had never smoked renders it unlikely that this association is due to smoking.

Unknown or, to a lesser extent, unmeasured underlying conditions generating both high serum CRP concentrations and impaired pulmonary function via other mechanisms, may also result in confounding effects. The exclusion of subjects with CRP concentrations >10 mg/l ($n = 9$) had little or no effect on the reported associations.

The reasons for the inverse association between systemic inflammation and reduced pulmonary function are unclear but several mechanisms may be involved. Firstly, reduced lung function may be responsible for the observed systemic inflammation. Like hepatocytes, inflammatory lung or pulmonary epithelial cells, have been shown to express CRP and IL-6.[35,36] COPD, a leading cause of reduced FEV_1, is characterized by major lung inflammation.[37] This condition is associated with high serum concentrations of CRP and IL-6.[24,38] The production of IL-6 in the airways also increases in COPD.[41] IL-6 may reach the bloodstream, stimulating the production of CRP and other inflammatory mediators by the liver, sequentially activating pulmonary inflammatory cells during transit through the pulmonary circulation.[39] It was recently shown that inhaled corticosteroids may down-regulate IL-6 production in the airways, leading to a decrease in liver CRP production in patients with COPD.[40] An alternative mechanism—reverse causation—cannot be excluded. High levels of cytokines and acute-phase reactants in the peripheral circulation may be a cause rather than a consequence of poor lung function. There is increasing evidence that cytokines—especially IL-6, which is the chief stimulator of CRP production—play a major role linked to the activation and adhesion of inflammatory cells to the pulmonary capillary endothelium, leading to changes in endothelial function and increases in pulmonary vascular filtration.[41–43] The persistence of systemic inflammation, and pulmonary micro-filtration, may

result in damage to the airways, accelerating the age-related decline in FEV_1 and leading to COPD.

Conclusion

The results of this population-based study suggest, for the first time, that increases in serum CRP concentration over time are associated with a significant decline of pulmonary function, consistent with the hypothesis that low-grade systemic inflammation is associated with pulmonary impairment. However, the nature of these relationships is unclear and merits additional investigation. Further investigations are also needed to determine whether lowering serum CRP concentration could in itself slow FEV_1 decline.

Acknowledgments

We thank the Center of Clinical Investigations (CIC) of Bichat Teaching Hospital for its collaboration.

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