

High-sensitive C-reactive protein is associated with reduced lung function in young adults

Finn Rasmussen^{*1}, Dennis Mikkelsen², Robert J Hancox³, Jess Lambrechtsen⁴, Mads Nybo⁵, Henrik Steen Hansen², Hans Christian Siersted¹.

1. Department of Respiratory Diseases, Odense University Hospital, Denmark
2. Department of Cardiology, Odense University Hospital, Denmark
3. Dunedin Multidisciplinary Health and Development Research Unit, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand
4. Department of Medicine, Svendborg Hospital, Denmark
5. Department of Biochemistry, Pharmacology and Genetics, Odense University Hospital, Denmark

* Corresponding author: Finn Rasmussen, M.D., Ph.D; Department of Respiratory Diseases, Odense University Hospital, 5000 Odense C; Tel:+45 6611 3526; Fax:+45 6541 2728; E-mail: Finn.Rasmussen@dadlnet.dk

Key words: Inflammation, Fitness, C-reactive protein, Lung Function, cohort studies

ABSTRACT

Question of the study. Systemic inflammation has been associated with low lung function. However, data on the inter-relationships between lung function and inflammation are sparse, and it is not clear if low-grade inflammation leads to reduced lung function.

Methods. Associations between high-sensitive CRP, and spirometric lung function were assessed in a population-based cohort of approximately 1000 Danes at ages 20

Results. In men, the average decline in FEV₁ in the highest CRP quintile was 23ml/year versus 1.6ml/year in the lowest quintile ($p < 0.0001$). In women, the average decline was -6.2ml/year in the highest CRP quintile versus an increase of 1.8ml/year in the lowest CRP quintile ($p = 0.25$). In a multiple regression analysis adjusted for sex, body mass index, cardio-respiratory fitness, smoking, asthma, airway hyperresponsiveness, and serum eosinophil cationic protein, higher levels of CRP at age 20 were associated with a greater reduction in both FEV₁ ($p = 0.04$) and FVC ($p = 0.04$) between ages 20 and 29 years.

Answer. Our findings shows that higher levels of CRP in young adults are associated with subsequent decline in lung function, suggesting that low-grade systemic inflammation in young adulthood may lead to impaired lung function independently of the effects of smoking, obesity, cardio-respiratory fitness, asthma and eosinophilic inflammation.

INTRODUCTION

Blood C-reactive protein (CRP), a marker of systemic inflammation, has consistently been found to be associated with excess mortality and adverse cardiovascular outcomes independently of confounding factors such as age and smoking (1). Increased systemic inflammation has also shown to be associated with lower spirometric lung function (2)3 . Moreover, a low spirometric value predicts not only mortality from respiratory disease but is also a risk factor for all-cause mortality (3). This raises the possibility that the association between poor lung function and mortality may be mediated by an inflammatory mechanism.

The inter-relationships between poor lung function and inflammation is poorly understood. Smoking, asthma and airway hyperresponsiveness are all associated with decline in lung function (4;5) and while smoking is associated with increased CRP levels (6), it seems that asthma and airway hyperresponsiveness influence lung function through other pathways (7). Obesity and poor cardio-respiratory fitness are other factors that are associated with higher CRP levels (8) and reduced lung function and could possibly help to explain these associations (9). The temporal relationship systemic inflammation and low lung function is also unclear. Although several studies have explored this association (1;10-15), each of these studies had certain limitations. Some of these studies were cross-sectional in nature and unable to assess the temporal relationships (10;11). Longitudinal studies have found that lung function decline was associated with raised levels of CRP at follow-up, but found little or no evidence that high levels of CRP predicted a subsequent decline in lung function. However, these studies have mostly been conducted in middle-aged individuals (13) or elderly subjects (1;15), or high sensitivity CRP measurements were not used on both occasions and the influence of low-grade inflammation may have been missed (12;14).

We explored the temporal relations between changes in lung function decline and CRP levels in a population-based cohort-study of young adults using high-sensitivity assays. We hypothesized that high levels of CRP would be associated with the subsequent decline in lung function after adjusting for the potential confounding influences of body mass index, cardio-respiratory fitness, smoking, asthma, airway hyperresponsiveness, and serum eosinophil cationic protein as a marker of eosinophilic inflammation.

METHODS

Additional details on the methods are provided in the online supplement.

POPULATION

The Odense Schoolchild study is a prospective community-based study of a cohort of 1369 schoolchildren first investigated during their third grade in 1985. The recruitment of the cohort is described in detail elsewhere (16). This report uses data collected at ages 20 and 29 years. At age 20, 1134 out of 1348 eligible subjects (84%) and at age of 29, 976 out of 1338 eligible subjects (73%) were assessed 870 subjects (65%) were seen at on both time points and 705 of these (53%) had full laboratory data. The subjects had mean ages of 20.1 and 29.3 years with a mean follow-up period of 9.2 years. No significant differences were found between the baseline characteristics (at age 9 years) of those who did and did not participate in these follow-up assessments (online supplement). All subjects gave informed content before participating. The study was approved by the local research ethics committee and the Danish Data Surveillance Authority.

QUESTIONNAIRES

Asthma diagnosis was defined by the question: “*Have you been told by a doctor that you have asthma?*” Tobacco smokers were defined as those who admitted smoking 1 or more cigarettes daily for at least 1 year at the age of 20 years or older.

PULMONARY FUNCTION TESTS

Forced Expiratory volume in 1 second (FEV₁) and Forced Vital capacity (FVC) were measured using a pneumotachometer (Vitalograph Compact) as previously described (17). Methacholine provocation tests were performed using an inhalation-triggered dosimeter (ME.FAR MB3 dosimeter; ME.FAR, Medicali, Brescia, Italy) at age 20 (17). The test results were expressed as a dose response slope (DRS) according to O’Connor et al.(18). Airway hyperresponsiveness (AHR) defined as greater than the value delimiting the 5% with the highest fall in FEV₁ amongst never-smoking subjects with no previous history of asthma or asthma-like symptoms (19). The upper 5th percentile in the reference group was 0.68 %/ μ mol. Predicted values of FEV₁ and FVC were calculated by sex-specific linear regression equations derived from the same reference study members.

CARDIO-RESPIRATORY FITNESS

Cardio-respiratory fitness test was measured at both assessments using the same progressive maximal progressive exercise test on an electrically braked cycle ergometer. The work load was increased every 3 minutes by increments based on the subject's weight and exercise data from a questionnaire. . Subjects were encouraged to provide a maximal effort and the effort was accepted as maximal when the subject exceeded the individual 85% of their expected maximal heart rate, which was calculated as 220-age in years. Cardio-respiratory fitness was measured as the maximum

workload ($W.kg^{-1}$) attained. This test has been shown to provide accurate and valid estimate of maximal oxygen consumption (20).

BLOOD SAMPLING

Blood samples at age 20 and at 29 were collected and analyzed at the Department of Biochemistry, Pharmacology and Genetics, Odense University Hospital. Samples were stored at $-70\text{ }^{\circ}\text{C}$ until analyzed. Eosinophil cationic protein (ECP) at age 20 was analyzed as previously reported (17). CRP was analyzed on a Modular Analytics P (Roche Diagnostics, Switzerland) using a particle-enhanced turbidimetric immunoassay. The lower limit of detection was 0.03 mg/L . The intra- and interassay were 0.43% and 2.1% , respectively.

STATISTICAL METHODS

Differences in dichotomous and in continuously distributed variables were evaluated using a χ^2 tests, and t tests respectively. Two-tailed tests were used with a 5% significance level. Arithmetic means (95% confidence intervals) of each variable were calculated except for CRP and ECP which had skewed distributions and were log-transformed before analysis. These values were transformed back to geometric means and 95% CI.

To test the hypothesis that systemic inflammation leads to decline in lung function, multiple linear regression (entry method) was used to assess the associations of log-CRP (at age 20) with lung function at age 29 (FEV_1 ; FVC; FEV_1/FVC) and the change in FEV_1 and FVC between age 20 and 29 years. These analyses adjusted for sex, height, log-ECP, asthma, cardio-respiratory fitness, smoking and BMI at age 20. The analysis used absolute values of lung function and adjusted for height in the analysis rather than using percent predicted (21). BMI was categorized as $<25\text{kgm}^{-2}$

(normal), $\geq 25 < 30 \text{ kgm}^{-2}$, (overweight) and $\geq 30 \text{ kgm}^{-2}$ (obese) to avoid possible co-linearity with cardio-respiratory fitness in the regression equations (repeat analyses using BMI as a continuous variable did not change the results).

To test the alternative hypothesis that the decline in FEV₁ leads to an increase in systemic inflammation we used multiple linear regression to test whether the change in FEV₁ between ages 20 and 29 years predicted log-CRP at age 29, adjusting for the same potential confounding variables.

The linearity assumptions of the models were checked by fitting quadratic and cubic terms for log-CRP.

Pregnant women were excluded from all analyses (age 20, n=3; age 29, n=38). Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS-PC 14.0; SPSS Inc, Chicago, Ill.) and with Medstat ver. 2.12.

RESULTS

CRP levels, lung function, BMI, cardio-pulmonary fitness, asthma and smoking findings from ages 20 and 29 years are shown in table 1 CRP levels increased between the ages in men but not in women. Despite this, CRP levels were higher in women than men at both ages. The sex-adjusted partial correlation coefficients between CRP measurements at ages 20 and 29 was $r=0.39$ ($p<0.001$).

Table 1. Characteristics of men and women at age 20 and 29. Findings are presented as means and 95% confidence intervals except where indicated. Pregnant women are excluded.

	Men (n=344)			Women (n=323)		
	Age 20	Age 29	p	Age 20	Age 29	p

*CRP (ug/L)	0.61 (0.55;0.68)	0.81 (0.73;0.89)	<0.0001	1.40 (1.24;1.58)	1.37 (1.22;1.55)	0.91
FEV ₁ (L)	4.65 (4.59;4.71)	4.56 (4.49;4.63)	<0.0001	3.42 (3.38;3.47)	3.38 (3.34;3.43)	<0.0001
FVC (L)	5.82 (5.74;5.90)	5.98 (5.89;6.07)	<0.0001	4.11 (4.06;4.16)	4.29 (4.23;4.34)	0.01
FEV ₁ percent of predicted (%)	99.1 (97.9;100.3)	99.0 (97.6;100.3)	0.69	99.6 (98.4;100.8)	99.1 (97.9;100.3)	0.31
FVC percent of predicted (%)	100.1 (99.1;101.2)	100.4 (99.1;100.6)	0.54	99.7 (98.5;100.9)	100.4 (99.1;100.7)	0.12
FEV ₁ /FVC (%)	80.3 (79.5;81.0)	76.6 (75.9;77.3)	<0.0001	83.7 (83.0;84.3)	79.5 (78.9;80.2)	<0.0001
BMI (kgm ⁻²)	23.2 (22.9;23.5)	25.9 (25.5;26.3)	<0.0001	23.0 (22.6;23.3)	24.7 (24.2;25.2)	<0.0001
Cardio-pulmonary fitness(W.kg ⁻¹)	48.7 (48.0;49.4)	40.6 (39.8;41.4)	<0.0001	37.7 (37.1;38.3)	33.4 (32.6;24.2)	<0.0001
Asthma (%)	10.3 (7.7;13.4)	12.3 (9.5;15.6)	0.39	12.1 (9.2;15.6)	13.9 (10.6;17.6)	0.52
Smoking (%)	35.0 (30.6;39.5)	35.5 (31.2;40.0)	0.92	37.8 (33.3;42.5)	29.6 (25.2;34.3)	0.01

* Geometric mean.

Higher levels of log-CRP at age 20 were associated with lower values of FEV₁, FVC and FEV₁/FVC ratio at age 29, and greater declines in FEV₁ and FVC between 20 and 29 after controlling for cardio-respiratory fitness, BMI, AHR, ECP, asthma, smoking, sex, and height at 20 years (Table 2). The association between log-CRP at age 20 and the change FEV₁/FVC ratio between age 20 and 29 did not reach formal significance (p=0.06).

Table 2. Adjusted associations of risk factors (coefficients* and their 95% confidence intervals) with FEV₁, FVC and FEV₁/FVC at age 29 and change in FEV₁, FVC and FEV₁/FVC between age 20 and 29 years.

	FEV ₁ at age 29 years (mL)	Change in FEV ₁ between age 20 and 29 years (mL)	FVC at age 29 (mL)	Change in FVC between age 20 and 29 years (mL)	FEV ₁ /FVC at age 29 years (%)	Change in FEV ₁ /FVC between age 20 and 29 years	
log-CRP at age 20 years (µg/L)	Coefficient CI(95) p	-139 (-224;-53) p=0.001	-49 (-97;-1) p=0.04	-11.1 (-27;-3.5) p=0.04	-68 (-130;-5) p=0.04	-0.14 (-0.26;-0.003) 0.01	-0.004 (-0.011;0.002) 0.06
Cardio-respiratory fitness at age 20 years (W.kg-1)	Coefficient CI(95) p	13 (6;20) p<0.0001	-0.65 (-4.5;3.1) p=0.84	1.9 (1.0;2.7) p<0.0001	2.6 (-2.3;7.5) p=0.29	0.00002 (-0.001;0.001) 0.96	-0.0009 (-0.001;0.001) 0.77
AHR at age 20 years †	Coefficient CI(95) p	-189 (-327;-51) p=0.007	-20 (-100;60) p=0.62	-9.9 (-27;7.4) p=0.25	-41 (-143;60) p=0.41	-0.026 (-0.044;-0.007) 0.008	-0.001 (-0.13;0.012) 0.93
log-ECP at age 20 years (µg/L)	Coefficient CI(95) p	-125 (-39;-289) p=0.04	43 (-52;138) p=0.38	24 (3.5;44.7) p=0.02	-23 (-144;98) p=0.71	-0.00003 (-0.022;0.022) 0.98	0.024 (0.009;0.039) 0.002
Asthma at age 20 years	Coefficient CI(95) p	-101 (-234;32) 0.14	2.7 (-74;79) p=0.93	7.8 (-9;25) p=0.36	111 (12;209) p=0.03	-0.023 (-0.41;-0.005) 0.01	-0.011 (-0.023;-0.002) 0.04
BMI at age 20 years (kgm ⁻²) ‡	Coefficient CI(95) p	70 (-21;163) p=0.13	-61 (-115;-8) p=0.02	16 (4;27) p=0.01	-53 (-122;14) p=0.12	-0.0062 (-0.019;0.006) 0.32	0.001 (-0.008;0.009) 0.90
Smoking	Coefficient CI(95) p	4.2 (-21;30) p=0.75	-3.5 (-18;11) p=0.64	2.1 (-1.1;5.4) p=0.20	11 (-9;30) p=0.28	-0.001 (-0.009;0.006) 0.76	-0.003 (-0.008;0.002) 0.23
Sex	Coefficient CI(95) p	414 (275;552) p<0.0001	-63 (-143;17) p=0.12	57.1 (39.6;74.7) p=0.01	-64 (-167;39) p=0.17	-0.14 (-0.033;0.004) 0.13	-0.001 (-0.014;0.012) 0.88

*Adjusted for all factors tabulated and height. †AHR= airway hyperresponsiveness (DRS#0.68%/µmol); ‡BMI (normal:<25; overweight:≥25<30; obese≥30).

The FEV₁ at age 20 did not predict the level of CRP at age 29 nor the change in CRP between age 20 and 29 (Table 3). When the change in FEV₁ between age 20 and 29 was used as the independent (predictor) variable in the regression a significant association was found with CRP at age 29 ($p < 0.0001$) and a trend to an association with the change in CRP between age 20 and 29 ($p = 0.09$). Stratification for sex or smoking did not alter the regression results (data not shown).

Table 3. Adjusted associations of risk factors (coefficients* and their 95% confidence intervals) with CRP at age 29 and change in CRP between age 20 and 29.

		CRP at age 29 years (ug/L)	Change in CRP between age 20 and 29 years (ug/L)
FEV ₁ at age 20 years	Coefficient CI(95) p	0.16 (-0.12;0.84) 0.76	0.095 (-0.21;0.21) 0.10
Cardio-respiratory fitness at age 20 years (W.kg ⁻¹)	Coefficient CI(95) p	-0.0059 (-0.13;-0.001) 0.05	0.0074 (0.001;0.016) 0.04
AHR at age 20 years †	Coefficient CI(95) p	0.17 (0.02;0.32) 0.02	-0.038 (-0.22;0.13) 0.66
ECP at age 20 years (µg/L)	Coefficient CI(95) p	0.093 (-0.79;0.27) 0.28	-0.24 (-0.44;0.30) 0.12
Asthma at age 20 years	Coefficient CI(95) p	-0.090 (-0.23;0.053) 0.22	0.049 (-0.12;0.22) 0.56
BMI at age 20 years (kg/m ²) ‡	Coefficient CI(95) p	0.22 (0.13;0.32) $p < 0.0001$	0.12 (0.001;0.23) 0.04
Smoking	Coefficient CI(95) p	-0.02 (-0.079;0.039) 0.51	-0.24 (-0.99;0.45) 0.50
Sex	Coefficient CI(95) p	-0.11 (-0.26;0.039) 0.15	-0.43 (-0.62;0.14) 0.66

*Adjusted for all factors tabulated and height. †AHR= airway hyperresponsiveness (DRS#0,68%/µmol); ‡ BMI (normal:<25;overweight:≥25<30;obese≥30).

The average change in FEV₁ per year was -23ml/year versus -1.6ml/ year in the highest and lowest CRP quintiles in men ($p < 0.0001$) and -6.2ml/yr versus 1.8ml/yr in the highest and

lowest CRP quintiles in women ($p=0.25$) (further data are provided in the online supplement). To assess whether this association was likely to be due to respiratory disease, the changes in lung function between age 20 and 29, and the FEV₁/FVC ratio at age 29 were compared according to CRP in quintiles at age 20 for non-asthmatic, non-smoking participants without respiratory symptoms. While no significant associations were seen in women (data not shown) higher levels of CRP at age 20 were significantly associated with decline in FEV₁ in men (figure 1). CRP levels at age 20 did not predict the change in the FEV₁/FVC ratio, but there was a trend to an association with lower FEV₁/FVC ratios at age 29.

The change in FEV₁ between ages 20 and 29 amongst non-asthmatic, non-smoking men without respiratory symptoms was associated with CRP values at age 29 ($p<0.0001$), but not with changes in CRP values between ages 20 and 29 ($p=0.29$) (Figure 2).

Excluding subjects with very high CRP levels (>10 mg/L) and a split half of the data to test the stability of regression equations did not change the findings (these were performed for all regressions).

DISCUSSION

We have investigated the relation between blood C-reactive protein (CRP) and lung function in an unselected cohort of young adults at ages 20 and at 29 years. We found that higher levels of CRP at age 20 predicted the subsequent decline in lung function by 29 years. This association

was independent of smoking, BMI, cardio-respiratory fitness, airway hyperresponsiveness, asthma, and serum ECP. The findings indicate that there is an association between systemic inflammation and the decline in lung function that is not explained by asthma, smoking-related lung disease, poor fitness or obesity.

Cross-sectional associations between low lung function and CRP have previously been shown in COPD patients (22-24) and in healthy subjects (2;13-15;25). Longitudinal studies have also demonstrated that the decline in lung function predicts CRP levels at follow-up (14;15). However, this is the first study to show an association between CRP and subsequent decline in lung function. By contrast, neither the longitudinal study of young adults by Hancox et al. (14) nor the study of older adults by Fogarty et al. (15) found that CRP levels predicted the subsequent decline in lung function. This might be because Hancox et al.(14) used a low-sensitivity CRP assay in their initial assessments of subjects in their population based cohort from New Zealand –The main difference between the present study and that of Fogarty et al.(15) is age of the subjects. That study used a very wide age range (age: 18-70), with 70% being older than 40 years at baseline and relatively few subjects under age 30. It is also possible that that study may have been biased by survival. In accordance with our findings, Shaaban et al. (13) found an association between CRP at baseline and a decline in FEV₁ in middle aged subjects (average age 37) over a follow-up period of 8.5 years, although this association did not reach formal significance (p=0.07). Additionally, plasma fibrinogen, another marker of systemic inflammation, was found to predict subsequent lung function decline in a 5-year follow-up study of young American adults (12). This indicates that different markers of systemic inflammation may be similar in predicting changes in lung function. Although we found a trend to an association between inflammation and FEV₁ and FVC decline in both sexes,

this was only significant in men in the stratified analysis (online data). A similar sex-difference in the association between lung function decline and CRP levels at follow-up has been reported from the European Community Respiratory Health Survey (26), and these findings suggest that there may be a sex difference in the pulmonary response to systemic inflammation.

The association between CRP at age 20 and subsequent change in FEV₁/FVC ratio did not reach formal statistical significance (p=0.06). Thus, although systemic inflammation predicts lung function decline, it remains uncertain if it is a risk factor for the development of airflow obstruction in young adults. Further studies with a longer follow-up are needed to confirm this.

CRP is produced primarily in the liver in response to interleukin-6, and its concentration has consistently been shown to be related to increased cardiovascular risk (1). Studies suggest that individuals who are able to produce high levels of IL-6 are disadvantaged for longevity (27). ~~study~~ this cohort, CRP increased from age of 20 to 29 in men, but there was no significant change in women.- This may be partly explained by the bigger change in factors known to increase CRP levels such as BMI, blood pressure, cardio-respiratory fitness, and cholesterol in men together with a more pronounced decrease in smoking among women between baseline and follow-up. Despite this, CRP levels in women remained higher than in men. A recent study (28) found that BMI was the strongest clinical predictor of CRP levels. Furthermore, Aronson et al.(29) found that smoking and metabolic perturbations, cardio-respiratory fitness, BMI, cholesterol, blood pressure are separate and largely independent factors in the pathophysiology of chronic, low-grade inflammation. In the light of these observations, it is not surprising that

BMI and cardio-respiratory fitness predicted CRP change whereas lung function did not. We also found that BMI and cardio-respiratory fitness were associated with lung function values although only BMI was significantly associated with the decline in lung function. Thus, it is possible that BMI and cardio-respiratory fitness influence lung function indirectly via CRP.-

The associations between CRP and lung function were independent of asthma, airway hyperresponsiveness and serum eosinophil cationic protein (ECP). A direct assessment of airway inflammation than ECP would have been preferable (e.g. pathological biopsies) but for obvious reasons these are not suitable in a large epidemiological study. However, we have previously shown that ECP is a risk factor for developing asthma (17). Asthma and ECP were also associated with the decline in the FEV₁/FVC ratio. Thus our data suggest that the association between a high CRP and decline in lung function is unlikely to be mediated through immunopathological mechanisms associated with asthma or allergic respiratory disease.

The strengths of the present study include an unselected population-based cohort of young adults who were all of the same age, repeated assessments using the same methods, objective measures of physical fitness and BMI, controlling for smoking and several markers for ongoing asthma/eosinophil-induced inflammation. Although the rate of participation in this study (around 70%) is acceptable for a longitudinal study over 9.2 years, a selection bias is possible. However, comparisons of participating and non-participating subjects identified no obvious differences between these two groups (online supplement). As in previous studies, our study only used two time points, which limits the capacity to unravel a temporal sequence where the temporal relationship between variables is complex or even bidirectional. Furthermore, there are

likely to be other important factors such as diet, hormonal contraceptive use, vitamins, and environmental exposures that may influence CRP or lung function that we did not measure.

In summary, we have identified a significant association between higher levels of CRP and subsequent decline in lung function in young adults independently of sex, smoking, asthmatic-inflammation, BMI and cardio-respiratory fitness. These findings suggest that low-grade systemic inflammation early in adult life may lead to a decline in lung function.

ACKNOWLEDGMENTS

We thank to the Study members and families of the Odense schoolchild study for their continuing support. Per Venge who kindly analyzed ECP.

CONFLICTS OF INTEREST

None

FUNDING

The study was supported by the Danish Lung Association, The Danish Medical Research Council, University of Southern Denmark, Odense University, The Hørslev Foundation and Else and Mogens Wedell-Wedellsborg Foundation.

References

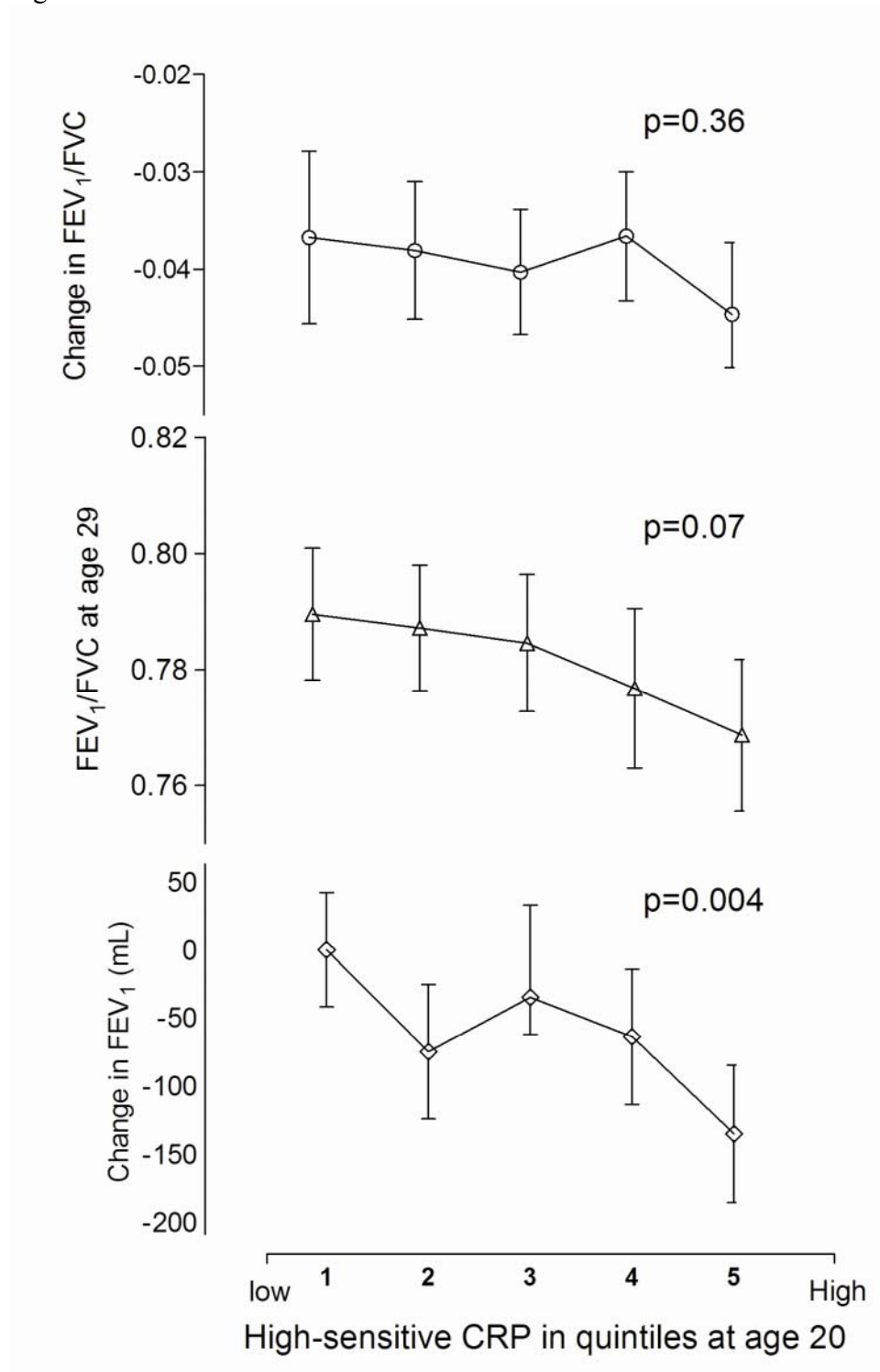
- (1) Tice JA, Browner W, Tracy RP, Cummings SR. The relation of C-reactive protein levels to total and cardiovascular mortality in older U.S. women. *The American Journal of Medicine* 2001 February 15;114(3):199-205.
- (2) Yende S, Waterer GW, Tolley EA, Newman AB, Bauer DC, Taaffe DR, Jensen R, Crapo R, Rubin S, Nevitt M, Simonsick EM, Satterfield S, Harris T, Kritchevsky SB. Inflammatory markers are associated with ventilatory limitation and muscle dysfunction in obstructive lung disease in well functioning elderly subjects. *Thorax* 2006 January 1;61(1):10-6.
- (3) Schroeder EB, Welch VL, Couper D, Nieto FJ, Liao D, Rosamond WD, Heiss G. Lung Function and Incident Coronary Heart Disease: The Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2003 December 15;158(12):1171-81.

- (4) Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998 October 22;339(17):1194-200.
- (5) Rijcken B, Schouten JP, Xu X, Rosner B, Weiss ST. Airway hyperresponsiveness to histamine associated with accelerated decline in FEV1. *Am J Respir Crit Care Med* 1995 May;151(5):1377-82.
- (6) Gan WQ, Man SFP, Sin DD. The Interactions Between Cigarette Smoking and Reduced Lung Function on Systemic Inflammation. *Chest* 2005 February 1;127(2):558-64.
- (7) Boulet LP, Chakir J, Dube J, Laprise C, Boutet M, Laviolette M. Airway inflammation and structural changes in airway hyper-responsiveness and asthma: an overview. *Can Respir J* 1998 January;5(1):16-21.
- (8) Williams MJ, Milne BJ, Hancox RJ, Poulton R. C-reactive protein and cardiorespiratory fitness in young adults. *Eur J Cardiovasc Prev Rehabil* 2005 June;12(3):216-20.
- (9) Jakes RW, Day NE, Patel B, Khaw KT, Oakes S, Luben R, Welch A, Bingham S, Wareham NJ. Physical inactivity is associated with lower forced expiratory volume in 1 second : European Prospective Investigation into Cancer-Norfolk Prospective Population Study. *Am J Epidemiol* 2002 July 15;156(2):139-47.
- (10) Engstrom G, Lind P, Hedblad B, Wollmer P, Stavenow L, Janzon L, Lindgarde F. Lung Function and Cardiovascular Risk: Relationship With Inflammation-Sensitive Plasma Proteins. *Circulation* 2002 November 12;106(20):2555-60.
- (11) Kony S, Zureik M, Driss F, Neukirch C, Leynaert B, Neukirch F. Association of bronchial hyperresponsiveness and lung function with C-reactive protein (CRP): a population based study. *Thorax* 2004 October 1;59(10):892-6.
- (12) Thyagarajan B, Jacobs DR, Apostol GG, Smith LJ, Lewis CE, Williams OD. Plasma fibrinogen and lung function: the CARDIA Study. *Int J Epidemiol* 2006 August 1;35(4):1001-8.
- (13) Shaaban R, Kony S, Driss F, Leynaert B, Soussan D, Pin I, Neukirch F, Zureik M. Change in C-reactive protein levels and FEV1 decline: A longitudinal population-based study. *Respiratory Medicine* 2006 December;100(12):2112-20.
- (14) Hancox RJ, Poulton R, Greene JM, Filsell S, McLachlan CR, Rasmussen F, Taylor DR, Williams MJA, Williamson A, Sears M. Systemic inflammation and lung function in young adults. *Thorax* 2007 June 29;62(12):1064-8.
- (15) Fogarty AW, Jones S, Britton JR, Lewis SA, McKeever TM. Systemic inflammation and decline in lung function in a general population: a prospective study. *Thorax* 2007 June;62(6):515-20.
- (16) Hansen HS, Hyldebrandt N, Nielsen JR, Froberg K. Blood pressure distribution in a school-age population aged 8-10 years: the Odense Schoolchild Study. *J Hypertens* 1990 July;8(7):641-6.

- (17) Rasmussen F, Lambrechtsen J, Siersted HC, Hansen HS, Hansen NC. Increased eosinophil cation protein level in sensitized nonasthmatics is linked to subsequent hyperresponsiveness to methacholine. The Odense Schoolchild Study. *Int Arch Allergy Immunol* 2000 February;121(2):129-36.
- (18) O'Connor G, Sparrow D, Taylor D, Segal M, Weiss S. Analysis of dose-response curves to methacholine. An approach suitable for population studies. *Am Rev Respir Dis* 1987 December;136(6):1412-7.
- (19) Godfrey S, Springer C, Noviski N, Maayan C, Avital A. Exercise but not methacholine differentiates asthma from chronic lung disease in children. *Thorax* 1991;46(7):488-92.
- (20) Hansen HS, Froberg K, Nielsen JR, Hyldebrandt N. A new approach to assessing maximal aerobic power in children: The Odense School Child Study. *Eur J Appl Physiol* 1989;618-24.
- (21) Vollmer WM, Johnson LR, McCamant LE, Buist AS. Methodologic issues in the analysis of lung function data. *J Chronic Dis* 1987;40(11):1013-23.
- (22) Gan WQ, Man SFP, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004 July 1;59(7):574-80.
- (23) Broekhuizen R, Wouters EFM, Creutzberg EC, Schols AMWJ. Raised CRP levels mark metabolic and functional impairment in advanced COPD. *Thorax* 2006 January 1;61(1):17-22.
- (24) Pinto-Plata VM, Mullerova H, Toso JF, Feudjo-Tepie M, Soriano JB, Vessey RS, Celli BR. C-reactive protein in patients with COPD, control smokers and non-smokers. *Thorax* 2006 January 1;61(1):23-8.
- (25) Aronson D, Roterman I, Yigla M, Kerner A, Avizohar O, Sella R, Bartha P, Levy Y, Markiewicz W. Inverse association between pulmonary function and C-reactive protein in apparently healthy subjects. *Am J Respir Crit Care Med* 2006 September 15;174(6):626-32.
- (26) Olafsdottir IS, Gislason T, Thjodleifsson B, Olafsson I, Gislason D, Jogi R, Janson C. Gender differences in the association between C-reactive protein, lung function impairment, and COPD. *Int J Chron Obstruct Pulmon Dis* 2007;2(4):635-42.
- (27) Bonafè M, Olivieri f, Cavallone I, Giovagnetti s, Francesca Marchegiani, Cardelli m, Pieri c, Marra m, Antonicelli r, Franceschi m. A gender-dependent genetic predisposition to produce high levels of IL-6 is detrimental for longevity. *European Journal of Immunology* 2001;31(8):2357-61.
- (28) Kathiresan S, Larson MG, Vasan RS, Guo CY, Gona P, Keaney JF, Jr., Wilson PWF, Newton-Cheh C, Musone SL, Camargo AL, Drake JA, Levy D, O'Donnell CJ, Hirschhorn JN, Benjamin EJ. Contribution of Clinical Correlates and 13 C-Reactive Protein Gene Polymorphisms to Interindividual Variability in Serum C-Reactive Protein Level. *Circulation* 2006 March 21;113(11):1415-23.

- (29) Aronson D, Avizohar O, Levy Y, Bartha P, Jacob G, Markiewicz W. Factor analysis of risk variables associated with low-grade inflammation. *Atherosclerosis* 2008 February 1.

Fig 1



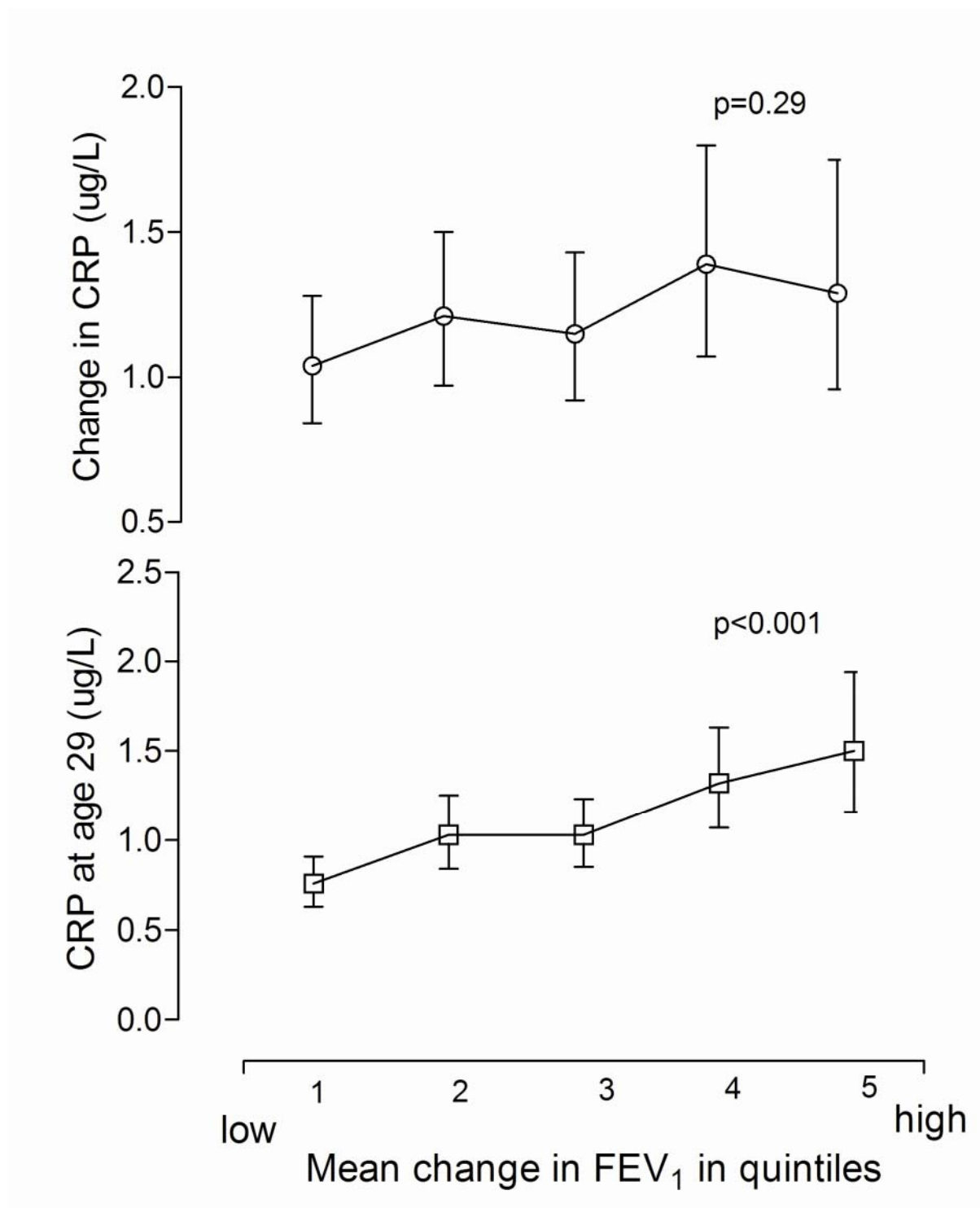


Fig 2