Gender differences in the association between C-reactive protein, lung function impairment, and COPD

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Abstract: Individuals with COPD have systemic inflammation that can be assessed by measuring C-reactive protein (CRP). In this paper we evaluated whether CRP is related to COPD, lung function and rate of lung function decline.

We included 1237 randomly selected subjects (mean age 42, range 28–56 years) from three centers in the European Community Respiratory Health Survey: Reykjavik, Uppsala and Tartu. CRP was measured at the end of the follow-up (mean 8.3 years) and the values were divided into 4 quartiles.

Fifty-three non-asthmatic subjects fulfilled spirometric criteria for COPD ($FEV_1/FVC < 70\%$). COPD occurred more often in the 4th CRP quartile (OR (95% CI) 3.21 (1.13–9.08)) after adjustment for age, gender, body weight and smoking. High CRP levels were related to lower FEV_1 values in both men (–437 (–596, –279) mL) and women (–144 (–243, –44) mL). The negative association between CRP and FEV_1 was significantly larger in men than women ($p = 0.04$). The decline in FEV_1 was larger (16 (5, 27) mL) in men with high CRP levels whereas no significant association between CRP and FEV_1 decline was found in women.

Higher CRP values are significantly associated with COPD and lower lung function in men and women. In men higher CRP values are related to a larger decline in FEV_1.

Keywords: C-reactive protein, COPD, body mass index, spirometry, ECRHS

Introduction

Chronic obstructive lung disease (COPD) is characterized by a progressive airflow limitation and is associated with an abnormal inflammatory process in the lungs (Pauwels et al 2001). COPD is a major cause of morbidity and disability (Murray and Lopez 1996). Forced expiratory volume in one second (FEV_1) is a marker of COPD used in staging and evaluating prognosis of the disease and correlates with mortality and health status (Jones and Agusti 2006). Factors associated with decline in FEV_1 are of interest as they might have prognostic importance in COPD.

C-reactive protein (CRP) is a sensitive marker of inflammation, infection and tissue damage which contributes to host defenses against infection by activating complement pathways (Pepys and Hirschfield 2003). Highly sensitive assays for CRP are available and reflect low grade inflammation (Wilkins et al 1998).

Elevated levels of CRP have been reported in overweight adults (Visser et al 1999; Danesh et al 2004). Adiposity and weight change have been associated with an unfavorable development in respiratory function (Burchfiel et al 1996; Chinn et al 1996; Wang et al 1997). In a study estimating the effects of smoking and weight change a gender difference was reported where weight gain seems to diminish the benefit of smoking cessation by 38% in men and by 17% in women (Chinn et al 2005).

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Studies have demonstrated elevated levels of CRP and fibrinogen in patients with COPD (Mannino et al 2003; Gan et al 2005) and a meta-analysis by Gan et al (2004) confirmed a significant increase in CRP levels in COPD patients compared with controls indicating a persistent systemic inflammation in subjects with COPD. Donaldson et al (2005) examined 148 patients with moderate to severe COPD and showed that high levels of inflammatory markers are associated with a faster decline in lung function.

Smoking is the major contributor to COPD and a fast decline in FEV_1 (Anthonisen et al 2002). Numerous reports have shown current smokers to have higher CRP levels than non-smokers (Tamakoshi et al 2003; Danesh et al 2004; Gan et al 2005) and a positive association with the number of pack-years smoked (Frohlich et al 2003) but interestingly smoking and reduced lung function seem to have independent effects on CRP levels (Gan et al 2005).

The aim of this paper was to explore the relationship between CRP, smoking, COPD and lung function in a population sample of young and middle aged adults from Iceland, Estonia and Sweden.

Methods

Population

The European community respiratory health survey (ECRHS) is an international multi-centre epidemiological study of asthma and allergy. The first part, ECRHS I, was conducted in 1990–1994 and the follow-up study, ECRHS II, in 1999–2001. The design of ECRHS I and ECRHS II has been published elsewhere (Burney et al 1994; Anon 2002).

The present study includes data from three of the 29 centers in the ECRHS II: Reykjavik in Iceland, Tartu in Estonia and Uppsala in Sweden – where 2033 subjects participated in stage 2 of ECRHS I (Ólafsdóttir et al 2005). The number of subjects in the present analysis was 1289 (age range 28–56 years), of which 512 subjects were from Reykjavik, 288 from Tartu and 489 from Uppsala (participation rate 63.4%). Mean time between first (ECRHS I) and second spirometry (ECRHS II) was 8.3 ± 0.8 years. Only subjects with CRP measurement and an acceptable spirometry were included in the study (n = 1237).

Subjects were asked to postpone their examination if they had suffered from respiratory infection in the 3 weeks immediately preceding the examination, as this was a criterion for exclusion. Written informed consent was obtained from each subject before inclusion in the study. The relevant ethics authorities in each of the participating research centers approved the protocol.

Smoking

A questionnaire administered on each occasion provided information on smoking history. Those who answered "yes" to the lead question ("Have you ever smoked for as long as a year?") were asked "Do you smoke now, as of one month ago?" Those that answered yes to the first question and no to the second were considered to be ex-smokers. Additional questions were asked on age at starting, amount smoked currently, whether they had stopped or cut down, and amount smoked previously. Based on this information the subjects were classified into Never-smoker, Ex-smoker and Smokers. Lifetime and between survey exposure to smoking was calculated as pack years (Chinn et al 2005).

Spirometry

In all three centers lung function was performed using the same spirometer in ECRHS I and II. The maximum FEV_1 and maximum forced vital capacity (FVC) of up to five technically acceptable blows were determined, and also whether FEV_1 and FVC each met the American Thoracic Society criterion for reproducibility (Anon 1995). Decline in FEV_1 and FVC was expressed per year of follow-up (ECRHS I value minus ECRHS II value) (Chinn, Jarvis et al 2005). Predicted values for forced expiratory volume in one second (FEV_1) were calculated based on the European Coal and Steel Union reference values (Anon 1983).

Definition of COPD

The criterion for COPD in the present study was a $FEV_1/FVC < 70\%$ (Pauwels et al 2001; de Marco et al 2004). Subjects with an $FEV/FVC \geq 70\%$ that reported usually having cough or bringing up phlegm at least three months each year were defined as being at risk for COPD (Global initiative for chronic obstructive lung disease (GOLD) stage 0) (Pauwels et al 2001; de Marco et al 2004). Subject with a self-reported history of physician's diagnosed asthma were not considered as having COPD or GOLD stage 0.

Body mass index

BMI was calculated as weight in kilograms divided by the square of height in meters.

CRP measurements

CRP was measured at the end of the follow-up period. The analysis was carried out at the Dept. of Clinical Biochemistry, Landspitali University Hospital Iceland. All serum samples were stored frozen at –20 ºC. High sensitivity CRP concentrations were measured on a Hitachi 911 analyzer using a

commercially available latex-enhanced immunoturbidimetric assay from Roche. The lower detection limit of the assay is 0.1 mg/L. Two internal control specimens provided by the reagent manufacturer were measured in each batch of samples. The total coefficient of variation for CRP measurements of the internal controls was 1.1% at a concentration of 3.73 mg/L and 1.9% at a concentration of 0.68 mg/L.

Statistical analyses

Log-transformed values of CRP were used when analysing the relationship between CRP and pack years and the association between CRP and FEV_1 in subjects with COPD. The subjects were divided into four groups according to the quartile distribution of the CRP values ($\leq$0.45, 0.46–0.96, 0.97–2.21 and $>$2.21) when estimating risk association. Test for trend was used when analysing associations between CRP-quartiles and age, sex, smoking and BMI in the univariate analyses. Odds ratios for the relationship between COPD and CRP were calculated using logistic regression while multiple linear regressions were used to examine the association between lung function and CRP. Analyses of sex interaction were performed. Analyses of the association between CRP and lung function was performed separately in men and women as a significant sex interaction was found in the association between CRP and FEV_1. The adjusted risk ratios and adjusted estimates of the linear regressions with a 95% confidence interval (CI) were first analyzed on pooled data from all three centers, adjusting for centre and then calculated separately at each centre. Potential heterogeneity between centers was examined using standard methods for random-effects meta-analysis.

Results

The study population (n = 1237) included 595 men and 642 women, mean age 42 (range 28–56) years, 29.7% ex-smokers and 26.4% current smokers. CRP values ranged from $<$0.1 to 70.0 mg/L. Characteristics of the study population divided in CRP quartiles are presented in Table 1. There were no significant centre or gender differences in CRP levels, but there was a statistically significant positive correlation between CRP and current smoking, pack years and BMI (Table 1). The positive association between the number of pack years smoked and CRP was found in both ex- and current smokers (Figure 1).

CRP and COPD

Fifty-three participants (4.2%, 25 men and 28 women) fulfilled the criteria for having COPD and additionally 87 (7.0%) were defined as being at risk for COPD (GOLD stage 0). Eleven subjects had GOLD stage II or more. The lowest prevalence of subjects fulfilling the criteria for COPD was in those with the lowest CRP values and remained significant after adjusting for centre, age, sex, BMI and pack years (Table 2). There was no significant relation between CRP and GOLD stage 0. There was a correlation between COPD severity expressed as FEV_1 as % of the predicted and CRP in the 53 subjects with COPD (Figure 2). No significant gender interaction (p = 0.91) or centre heterogeneity was found in the associations between CRP and COPD (p for heterogeneity = 0.31).

CRP and lung function

Men and women with CRP values above 0.46 mg/L had significantly lower FEV_1 and FVC values than subjects with CRP values within the first quartile (Table 3, Figure 3). The negative association between CRP and FEV_1 was significantly larger in men than women (p = 0.04), whereas no gender difference in the association between CRP and FVC was found (Figure 3). The mean annual decline in FEV_1 was 44 mL in men and 31mL in women. Men with higher CRP values than 0.46 mg/L had a significantly larger decline in FEV_1 while no significant association between CRP and decline in lung function was found in women (Table 4). Decline in FEV_1, when not adjusted for CRP, was also significantly related to elevated BMI in both men and women and to the intensity of smoking between the surveys in women (Table 4). In men the association between change in BMI and FEV_1 decline increased when not adjusting for CRP [13 (6, 21) mL/year for each 5 unit increase in BMI, (adjusted effect (95% CI)], while no similar effect was found in women.

No significant interaction was found between CRP, smoking and change in body mass index in relation to lung function and decline in FEV_1. No centre heterogeneity was found in the associations between CRP and lung function with one exception. A significantly larger decline in FEV_1 was found in women with the highest CRP values in Uppsala [15 (6–24) mL/year] (p for heterogeneity = 0.002). No such association was found in the other centres.

Non-participants

Subjects that participated in both surveys (n = 1289) were slightly older (33.7 ± 7.2 vs 32.1 ± 7.0 years), had a higher BMI (23.9 ± 4.0 vs 23.3 ± 3.7 kg/m^2) ($p < 0.0001$) and were less often smokers (32.4 vs 37.0, p = 0.03) in the ECRHS I than the subjects that only participated in the first survey (n = 744).

Table 1 Characteristics of the study population in relation to CRP values

CRP (mg/L)	1st quartile: <0.46	2nd quartile: 0.46–0.96	3rd quartile: 0.97–2.21	4th quartile: >2.21	P for trend
Age (years)	40.5 ± 7.0	42.5 ± 7.2	42.6 ± 7.2	42.6 ± 7.4	0.0002
Women (%)	54.7	51.6	43.2	57.7	0.96
Ex-smokers (%)	28.6	30.8	24.8	34.0	0.38
Current smokers (%)	23.3	24.6	27.4	31.1	0.02
Pack years	5.0 ± 7.7	8.2 ± 13.3	9.1 ± 13.5	12.6 ± 16.6	<0.0001
BMI (kg/m^2)	23.3 ± 2.9	24.9 ± 3.5	26.3 ± 4.0	27.9 ± 5.2	<0.0001

Discussion

This study focuses on a well-defined general population. It demonstrates a strong association between elevated CRP levels and the prevalence of COPD and lower lung function (FVC and FEV_1). The negative association between CRP and FEV_1 was stronger in men than women and an association between faster decline of FEV_1 and higher CRP levels was found in men but not women.

Our results are in accordance with a cross sectional study from the Third National Health and Nutrition Survey where CRP levels, independent of smoking, were found to be related to reduced FEV_1 (Gan et al 2005). Broekhuizen et al (2006) showed that in 102 clinically stable COPD patients, 48 had elevated CRP levels (>4.21 mg/l) and these high levels where strongly associated with impaired energy metabolism and distress due to respiratory symptoms. A comparison of 88 COPD patients with 33 smokers and 38 non-smokers controls, showed higher levels of CRP in COPD patients (Pinto-Plata et al 2006). In assessing the association between CRP and lung function Shaaban et al (2006) looked at cross-sectional and longitudinal changes between CRP and FEV_1 decline. Their analysis included 531 subjects demonstrating a negative association between FEV_1 and CRP ($p = 0.002$) and higher CRP levels over time were associated with a faster FEV_1 decline. Similarly a recent study found CRP levels associated with accelerated decline in FEV1 and mortality in patients with mild to moderate COPD indicating that CRP measurements might enable identification of patients at a high risk of disease progression and mortality (Man et al 2006).

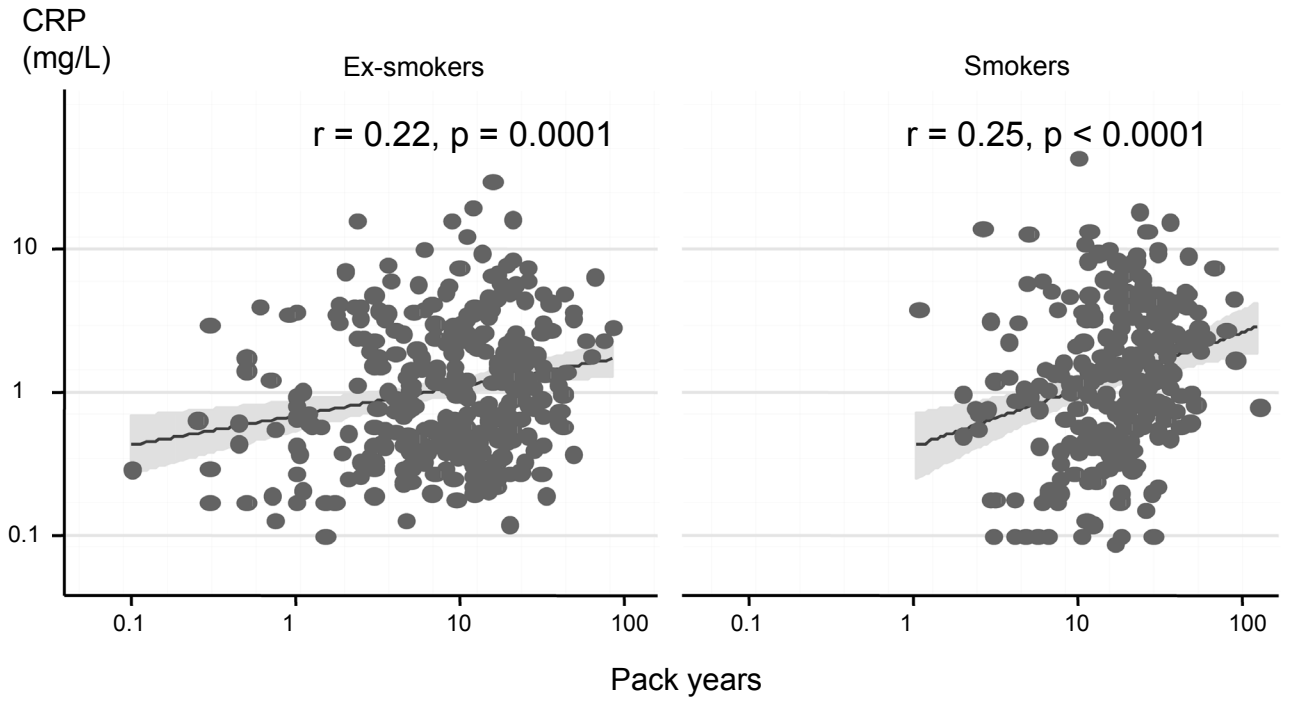

Figure 1 Correlation between pack years and CRP in ex- and current smokers.

Table 2 Prevalence of GOLD stage 0 and COPD and the independent association to CRP

	Stage 0		Stage 1+	
CRP (mg/L)	**Prevalence (%)**	**OR* (95% CI)**	**Prevalence (%)**	**OR* (95% CI)***
1st quartile: <0.46	6.9	1	2.2	1
2nd quartile: 0.46–0.96	5.5	0.78 (0.38–1.59)	5.2	2.90 (1.09–7.73)
3rd quartile: 0.97–2.21	6.9	0.95 (0.48–1.94)	3.9	1.94 (0.67–5.66)
4th quartile: >2.21	8.6	1.19 (0.59–2.39)	5.7	3.21 (1.13–9.08)

*The values are adjusted for centre, age, height, BMI and pack years.

The present study underscores the link between systemic inflammation and COPD. Many of prior studies have been focused on hospitalized subjects or COPD patients with severe COPD (GOLD III or IV). Our study implies that systemic inflammation is a factor even in the early phase of the COPD process. The exact role of inflammation in the pathogenesis of COPD is not fully understood. Lower airway bacterial colonization (Wilkinson et al 2003) and possibly upper airway bacterial inflammation (Hurst et al 2005) might provoke a systemic inflammatory response in COPD patients. Elevated levels of inflammatory markers such as plasma fibrinogen have been associated with reduced FEV_1, accelerated decline in lung function and increased risk of COPD hospitalizations in the future (relative risk 1.7 (95% CI: 1.1–2.6)) (Dahl et al 2001). A prospective study by Wilkinson et al (2003) including 30 patients with moderate COPD over 12 months, showed that FEV_1 decline was related to an increase in airway bacterial load ($r = 0.59$, $p = 0.001$) and higher sputum Il–8 was associated with greater declines in FEV_1 ($p = 0.03$). However, CRP was not reported in these studies. Faster decline in FEV_1 has also been associated with more frequent exacerbations of COPD (Donaldson et al 2002)

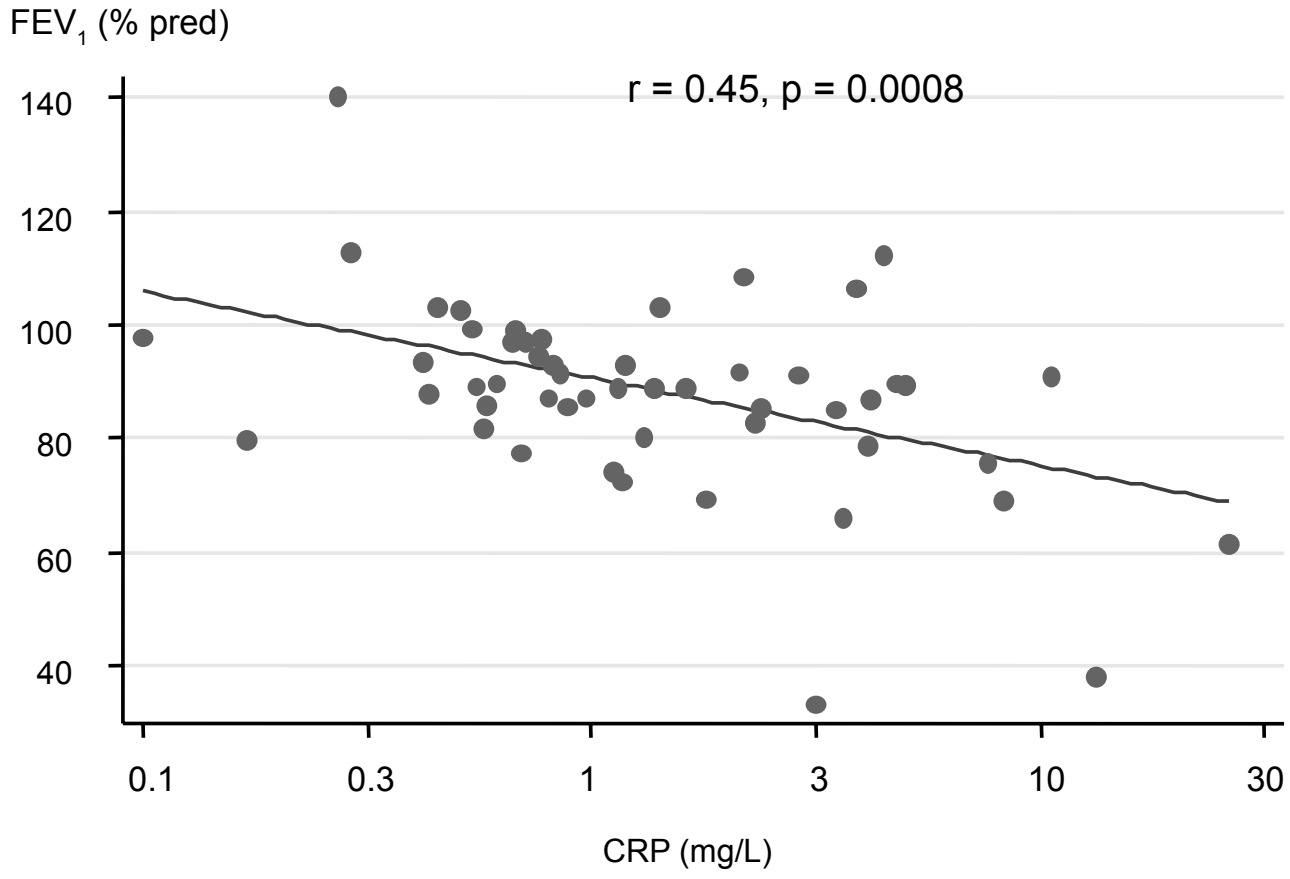

Figure 2 Correlation between CRP values and FEV_1 expressed as % of the predicted in subjects with COPD (n = 53).

Table 3 Estimated effect (95% CI) of CRP on lung function. Subjects with CRP value ≤0.45 mg/L are the reference group. The values are adjusted for centre, age, $(age)^2$, height, BMI and pack years (estimate in mL (95% CI))

CRP (mg/L)	2nd quartile CRP: 0.46–0.96	3rd quartile CRP: 0.97–2.21	4th quartile CRP > 2.21
Men			
FEV_1 (mL)	–216 (–358, –73)	–205 (–343, –66)	–437 (–596, –279)
FVC (mL)	–163 (–327, 1)	–181 (–340, –21)	–334 (–517, –152)
Women			
FEV_1 (mL)	–83 (–175, –10)	–161 (–261, –61)	–144 (–243, –44)
FVC (mL)	–96 (–208, 16)	–120 (–242, 1)	–222 (–343, –101)

and a recent publication suggested that the chronic deterioration in FEV_1 decline is explained by the acute events in COPD causing a faster rate of rise in airway inflammation (Donaldson et al 2005).

In our study men with higher CRP values had significantly larger decline in FEV_1 than men with low CRP whereas no such association was found in women. In an epidemiological follow-up study like ours the fast rate of lung function decline and the diagnosis of COPD are strongly interrelated and in other studies it has usually been described as one of the deleterious consequences of smoking (Lange et al 1989; Townsend et al 1991; Xu et al 1994; Burchfiel et al 1995). Chinn et al studied the effects of smoking cessation and weight gain on lung function in 6654 subjects. They showed gender differences with a significantly faster rate of lung function decline in relation to weight gain in men than women (Chinn et al 2005).

We found that the association between weight change and FEV_1 decline decreased when adjusting for CRP in men. This might indicate that weight-related effect on change in FEV_1 could partly be mediated through increased systemic inflammation. The strong relationship between increased body fat and lower lung function raises the question whether elevated CRP reflects inflammatory processes in the airways that overflow into the systemic circulation, promoting a generalized inflammatory reaction (Gan et al 2004). However in a recent review Wouters (2005) concluded that the inflammatory process in the airways and the systemic circulation were two independent processes. It is also possible that smoking induces CRP elevation, as a significant relationship was found between number of pack years and CRP levels in both ex- and current smokers in the present study. Alternatively elevated CRP may reflect a genetic or constitutional factor predisposing individuals with COPD to both systemic and pulmonary inflammation (Barnes 2000; Hersh et al 2006).

Previously we published that CRP in the same study population is increased in non-allergic but not allergic asthma (Ólafsdóttir et al 2005). In this report COPD was significantly more common in subjects with higher CRP quartiles. Despite adjustments for centre, age, sex, body mass index and pack years, a positive correlation was found between the severity of COPD (FEV_1%) and CRP values. The relatively young age of our study population (mean age 42, range 28–56 years) is of great clinical importance, as they have not yet reached the age with repeated hospitalizations due to exacerbations of COPD but do show rapid lung function decline.

The strengths of this study include the use of data from a general population, gathered and assessed with high quality and standardized methods as part of the ECRHS. The limitations merit some discussion. Firstly CRP was only measured at the end of our study while FEV_1 was measured at two time points and our assumptions on FEV_1 decline are based on these measurements. However, CRP levels measured at multiple time points have been stable in many studies (Macy et al 1997; Ockene et al 2001; Ridker et al 2005). Secondly we found that the participants were less likely to be smokers and slightly more obese than the non-participants. We cannot rule out selection bias but do not believe that those limitations undermine our work.

The present study indicates that subjects with elevated CRP levels are at greater risk of having COPD and impaired lung function. A significant gender difference was found where men with higher CRP values had a more rapid decline in FEV_1 during the study period. Future studies will reveal whether lowering elevated levels of CRP in COPD patients with drugs such as statins (Ridker et al 2005) or inhaled corticosteroids in high doses (Sin et al 2004) will slow the clinical progress of the main outcome variables in COPD, namely, decline in lung function, number of exacerbations, health related quality of life and mortality. Treatment of a younger population like the one we studied is of particular interest as at their age lung function is rapidly decreasing but loss of health related quality of life is not yet an irreversible fact.

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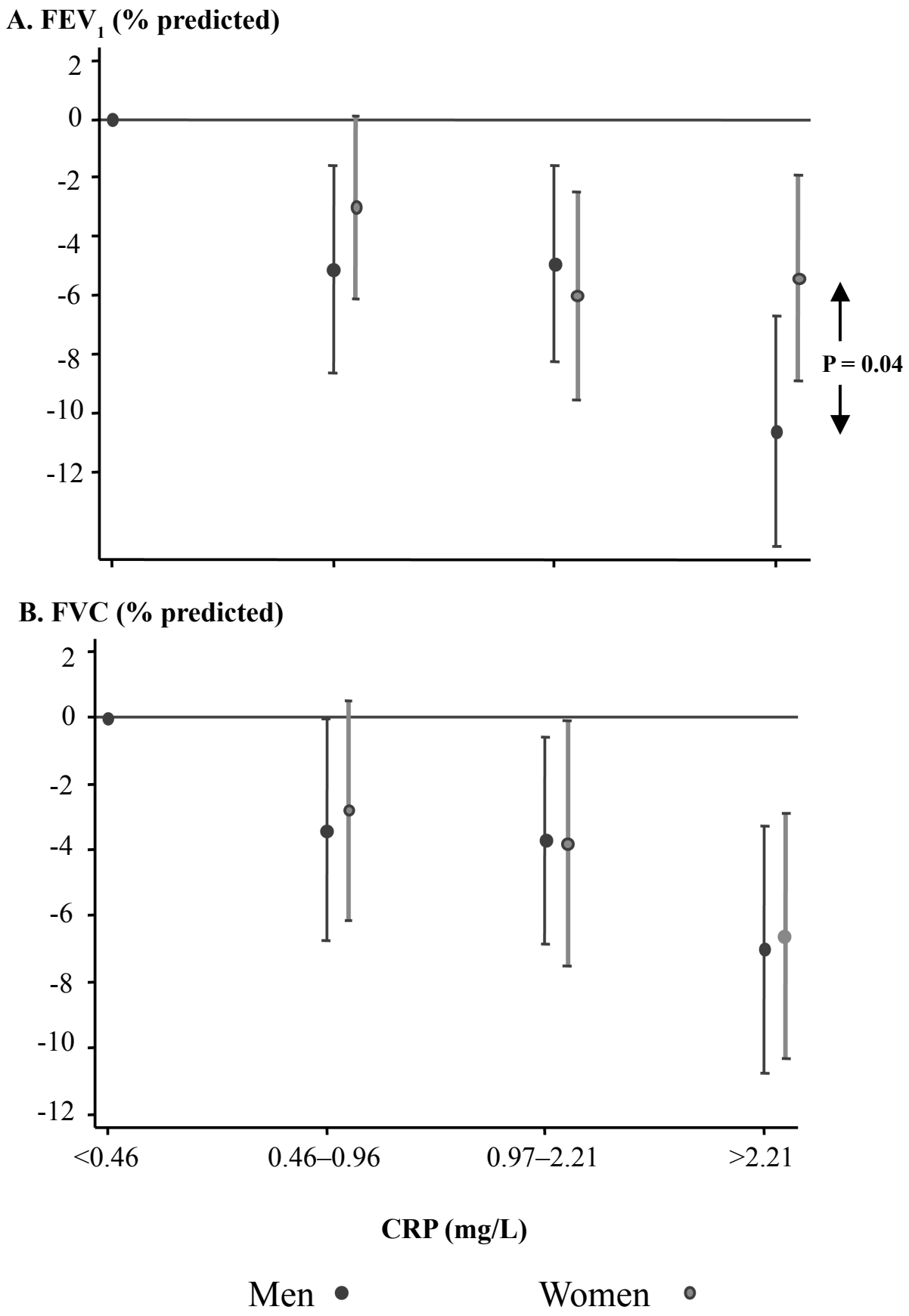

Figure 3 Estimated difference in FEV_1 (**A**) and FVC (**B**) between subjects with different CRP values, where subjects in the 1st CRP quartile are the reference. The estimates are adjusted for age, sex, BMI and pack years.

Table 4 Estimated effect (95% CI) of CRP on annual decline in FEV_1 (mL/year). Subjects with CRP value ≤0.45 mg/L are the reference group. The values are adjusted for centre, age, $(age)^2$, height, BMI at baseline, change in BMI and pack years

	Men	Women
	mL/year (95% CI)	mL/year (95% CI)
CRP		
2nd quartile: 0.46–0.96	10.7 (0.5, 20.8)	4.8 (–4.9, 12.6)
3rd quartile: 0.97–2.21	11.0 (1.1, 20.9)	1.4 (–7.0, 9.9)
4th quartile: >2.21	15.9 (4.6, 27.1)	–1.1 (–9.5, 7.3)
BMI at base line*	2.5 (–2.9, 7.8)	3.6 (–0.1, 7.3)
Change in BMI*	9.4 (1.9, 17.0)	5.2 (0.1, 10.2)
Pack years during the study period*	3.3 (–0.6, 7.1)	5.3 (0.3, 10.2)

* Per 5 unit increase.

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