

## C-reactive Protein as a Predictor of Prognosis in COPD

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Short statement on the impact of the research presented: New biomarkers are needed to better assess the probability of future COPD. In this paper we test the predictive value of serum CRP > 3mg/L on risk of COPD hospitalization and death in individuals with airway obstruction. Our data suggests that serum CRP is a strong long-term predictor of clinical COPD outcomes in individuals with airway obstruction.

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## Abstract

**Rationale:** Patients with COPD have an ongoing systemic inflammation, which can be assessed by measuring serum C-reactive protein (CRP).

**Objective:** To determine whether increased serum CRP in individuals with airway obstruction predict future hospitalization and death from COPD.

**Methods:** We performed a cohort study with a median of 8-years follow-up of 1,302 individuals with airway obstruction selected from the ongoing Copenhagen City Heart Study.

**Measurements and Main Results:** We measured serum CRP at baseline, and recorded COPD admissions and deaths as outcomes. During follow-up, 185 (14%) individuals were hospitalized due to COPD and 83 (6%) died from COPD. Incidences of COPD hospitalization and COPD death were increased in individuals with baseline CRP >3mg/L vs. ≤3mg/L (Log-rank:Ps<0.001). After adjusting for gender, age, FEV<sub>1</sub> % predicted, tobacco consumption, and ischemic heart disease, the hazard ratios for hospitalization and death due to COPD were increased at 1.4 (95% CI: 1.0-2.0) and 2.2 (1.2-3.9) in individuals with baseline CRP >3mg/L vs. ≤3mg/L. After close matching for FEV<sub>1</sub> % predicted and adjusting for potential confounders, baseline CRP was on average increased by 1.2 mg/L (ANOVA: P=0.002) and 4.1 mg/L(P=0.001) in those who were subsequently hospitalized or died from COPD, respectively. The absolute 10-year risks for COPD hospitalization and death in individuals with CRP above 3mg/L amounted to 54% and 57% among those older than 70 years, with a tobacco consumption above 15g/day and FEV<sub>1</sub> % predicted less than 50%.

**Conclusions:** CRP is a strong and independent predictor of future COPD outcomes in individuals with airway obstruction.

Key words: Cohort study; Lung diseases, obstructive; Airway obstruction; Inflammation; Biological markers. Word count: 250 (abstract)

## **Introduction**

Chronic obstructive pulmonary disease (COPD) is a leading and increasing cause of morbidity and mortality worldwide (1,2). The airflow limitation in COPD is associated with an abnormal inflammatory response of the lungs to noxious particles or gases (1), and it is increasingly recognised that in addition to an inflammatory process in the lung itself, also systemic inflammation play an important role in COPD (3-5). Systemic inflammation is thought to lead to loss of body mass in general and lean body mass in particular, each of which are associated with increased mortality in COPD (6-9). Following this, more direct measures of systemic inflammation like acute phase reactants could provide good markers of prognosis in COPD.

The clinically most common used acute phase reactant, C-reactive protein (CRP), binds bacteria (10-11), oxidised lipids (12-13), and apoptotic cells (13-14) and facilitates their clearance via the innate immune system. Slightly increased serum CRP levels have been shown to associate with presence of inflammation in atherosclerosis and with increased risk of coronary heart disease and myocardial infarction (15). Mounting evidence now suggests that increased serum CRP levels also associate with lung inflammation in stable COPD (5,16-18). It is therefore possible that serum CRP as a systemic marker of ongoing lung inflammation could be used as a predictor of future COPD outcomes.

In a cohort study, we here test the hypothesis that increased concentrations of serum CRP predict increased risk of hospitalization and death from COPD in individuals with airway obstruction. For this purpose we measured lung function in 9,259 individuals from a general population sample and determined baseline serum CRP in individuals with the presence of airway obstruction. During a median follow-up period of 8 years, we recorded COPD admissions and deaths as outcomes.

## **Methods**

### *Study design*

Subjects participated in the 1991-94 examination of the Copenhagen City Heart Study, a prospective epidemiological study initiated in 1976-78 (19-21). Participants aged 20 years and above were selected randomly after age stratification into 5-year age groups from residents of central Copenhagen. Of the 17,180 individuals invited, 10,135 participated, and 9,259 gave blood. Of these 1,561 had airway obstruction defined as  $FEV_1/FVC < 0.7$ , and 1,302 had never been hospitalized for COPD or asthma prior to the 1991-94 examination. More than 99% were white and of Danish descent. All participants gave written informed consent, and Herlev University Hospital and the ethics committee for Copenhagen and Frederiksberg approved the study (# 100.2039/91).

### *Questionnaire and COPD outcomes*

Participants reported whether they were current smokers, ex-smokers, or never-smokers, and all current smokers provided information on the type and daily amount of tobacco they consumed. Information on hospitalizations due to COPD (ICD8:491-492;ICD10:J41-44) was drawn from the Danish National Hospital Discharge Register from May 1<sup>st</sup> 1976 through December 31<sup>st</sup> 2000; hospital data prior to CRP measurements was used to exclude individuals who already had a diagnosis of COPD or asthma (ICD8:493;ICD10:J45-46). Data on deaths due to COPD were drawn from the Danish National Register of Causes of Death (ICD8:491-492;ICD10:J41-44) from April 1<sup>st</sup> 1992 to December 31<sup>st</sup> 1999; individuals with asthma (ICD8:493;ICD10:J45-46) as a contributory cause of death on the death certificate were excluded. We followed the COPD definition used in previous studies of Danish COPD patients (22). Three COPD hospitalizations and no COPD deaths were identified by adding ICD8 490 to our COPD definition, and including these cases in the analysis did not change the results presented. The ICD8 496 code was never implemented in the Danish ICD8 version. Written approval for data linkage was obtained from the Danish National Registers. ICD8 was used until the end of 1993 in Denmark, followed by ICD10; ICD9 was never implemented in Denmark. Twelve and 6 of the study participants died from COPD in 1993 (ICD8) and 1994 (ICD10), respectively. Of the 83 deaths with COPD listed on the death certificate, 57

(69%) had COPD as the major cause of death; 12 (14%) had other causes (I54.1,A169,C159,D696,E107,C619,C809,K265,K519,R989,R999,W190), 7 (8%) lung cancer (I62.1,C349), and 7 (8%) cardiovascular disease (I219,I249,I350,I519,I709,I710), with COPD as a contributory cause of death.

### *Laboratory Measurements*

Serum CRP was measured by high sensitivity CRP assay (Dade Behring Diagnostica, Rødovre, Denmark). FEV<sub>1</sub> and FVC were measured with a dry wedge spirometer (Vitalograph, Maidenhead, UK). The highest set out of three sets of FEV<sub>1</sub> and FVC measurements was used as percentage of predicted value using internally derived reference values based on a subsample of healthy never-smokers (23).

### *Statistical Analysis*

When relating CRP to outcomes (hospital admission and death), baseline CRP concentration was categorized using 2 cut-points, 1 and 3 mg/L. These cut-points were used rather than quartiles, as stratifying into smaller groups may increase the risk of spurious findings, and as these cut-points are simple and clinically useful and have been used previously in cardiovascular medicine (24).

Statistical analysis was performed with SPSS;  $p < 0.05$  on a two-sided test was considered significant. Pearson's  $\chi^2$ -test, Mann Whitney U test, or Student's t-test were used for two-group comparisons, depending on data distribution. Cumulative incidence of COPD outcomes as a function of age were compared using the log-rank test. Cox regression analysis was used to examine time to COPD hospitalization or death using hazard ratio and 95% confidence interval; the multiple adjusted model included gender, age (in deciles), FEV<sub>1</sub>%predicted (in deciles), tobacco consumption (in deciles), and ischemic heart disease (ICD8:410-414 or ICD10:I20-I25); adjusting for deciles implies categories (9 variables in the regression model). For each case of COPD hospitalization, COPD death, and death by any cause, controls in the same decile of

FEV<sub>1</sub>%predicted were selected using a computer matching program for SPSS. After matching, baseline CRP concentration (logarithmically transformed) was estimated by ANOVA adjusting for gender, age (in deciles), tobacco consumption (in deciles), and ischemic heart disease. Estimated absolute risks for COPD outcomes were calculated using the regression coefficients from a Poisson regression model with FEV<sub>1</sub>%predicted, tobacco consumption, age, and CRP. Absolute risks are presented as estimated incidence rates (events/10 years) in percentages. The dependent variables for the Poisson regressions are number of COPD hospitalizations or COPD deaths during the subsequent 10 years.

## Results

A total of 1,302 individuals with airway obstruction defined as FEV<sub>1</sub>/FVC<0.7 were included in the study; these individuals had not previously been diagnosed with COPD in the Danish National Hospital Discharge Register. During a median duration of 8 years follow-up, 185 individuals (14%) were hospitalized due to COPD and 83 (6%) died from COPD. Of the 83 COPD deaths, 41 (49%) were preceded by a hospital admission for COPD. The baseline characteristics of the participants in whom a COPD outcome subsequently developed are shown in Table 1. As expected, participants who had any COPD outcome had lower FEV<sub>1</sub> % of predicted at baseline than those who remained free of COPD outcomes, and they were more likely to be older and have a higher daily tobacco use.

### *Baseline CRP and COPD*

Baseline serum levels of CRP were higher in individuals who subsequently had a COPD outcome than in those who did not (Table 1). The difference was largest for those who subsequently died from COPD, 4.3 vs. 2.3 mg/L (p<0.001). The prevalence of ischemic heart disease did not differ significantly by COPD outcome status (Table 1;  $\chi^2$ : P=0.27). The cumulative incidence of COPD hospitalization and COPD death was higher in those with CRP>3 mg/L vs.  $\leq$ 3 mg/L (Fig 1; log-rank: p<0.001 and p<0.001). The equivalent cumulative incidences overall also increased with

increasing baseline CRP concentration from <1 mg/L to 1-3 mg/L to >3 mg/L; however, the cumulative incidence of COPD outcomes for CRP of 1-3 mg/L vs. <1 mg/L did not differ significantly ( $p=0.19$  and  $p=0.07$ ).

To assess the independent predictive value of baseline CRP >3mg/L on COPD hospitalization and death, we adjusted our analyses according to potential confounders. Prior to adjustment, the crude hazard ratios for hospitalization and death due to COPD were increased at 1.7 (95%CI:1.2-2.4) and 2.7 (1.6-4.7) in individuals with baseline CRP >3mg/L vs.  $\leq 3$  mg/L (Table 2). After adjusting for age, the equivalent hazard ratios for COPD hospitalization and COPD death were 1.6 (1.2-2.3) and 2.5 (1.5-4.4). In a multifactorial analysis including gender, age, FEV<sub>1</sub> % of predicted, tobacco consumption, and ischemic heart disease, the equivalent hazard ratios for COPD hospitalization and COPD death were increased at 1.4 (1.0-2.0) and 2.2 (1.2-3.9).

Increased serum CRP may also increase the risk of all-cause mortality in individuals with pulmonary dysfunction (25). The unadjusted hazard ratio for all-cause mortality was increased at 1.8 (1.4-2.2) in individuals with baseline CRP >3mg/L vs.  $\leq 3$  mg/L (Table 2). In an age-adjusted and multifactorial analysis, the equivalent hazard ratios for all-cause mortality were increased at 1.7 (1.4-2.1) and 1.4 (1.1-1.8), respectively.

FEV<sub>1</sub> % predicted is the most important predictor of future COPD outcomes. To ensure that CRP predicted COPD outcomes independently of FEV<sub>1</sub>, we also performed cross-sectional analyses with matching for FEV<sub>1</sub> % predicted. In an analysis matching for FEV<sub>1</sub> % predicted and adjustment for gender, age, tobacco consumption, and ischemic heart disease, baseline CRP was on average increased by 1.2 mg/L in those who were hospitalized for COPD (ANOVA:  $P=0.002$ ), 4.1 mg/L in those who died from COPD ( $P=0.001$ ), and 1.9 mg/L in those who died by any cause ( $P<0.001$ ).

*Absolute Risk for COPD outcomes*

The lowest absolute 10-year risks for COPD hospitalization and death were 5.7% and 1.0%, respectively, among individuals with CRP  $\leq$ 3mg/L, age  $\leq$ 70 years, tobacco consumption  $\leq$ 15 g/day, and FEV<sub>1</sub> % predicted above 79% (Fig. 2). Absolute risk increased with increasing serum CRP, increasing tobacco consumption, increasing age and decreasing FEV<sub>1</sub> % predicted. The highest absolute 10-year risks for COPD hospitalization and death were 54% and 57% among individuals with CRP >3mg/L, age >70 years, tobacco consumption >15 g/day, and FEV<sub>1</sub> % predicted less than 50%.

## **Discussion**

This 8-year follow-up study of a large and ethnically homogenous population with airway obstruction shows that increased serum CRP is a strong long-term predictor of COPD hospitalization and death, independent of smoking and lung function. The results expand the observations of increased CRP levels in stable COPD (5,17,18,26). Gan et al. aggregated data from 5 cross-sectional studies and estimated an average mean increase in serum CRP of 1.85 mg/L in individuals with stable COPD (5). Increased CRP has also been associated with all-cause mortality in patients with mild to moderate COPD, with reduced lung function, and greater FEV<sub>1</sub> decline (25,27-29). Our data now indicates that increased CRP predicts clinical COPD outcomes in individuals with airway obstruction during 8 years of follow-up.

Serum CRP at baseline was increased the most in those who subsequently died from COPD, and CRP was also a stronger predictor of COPD mortality than of COPD hospitalization. Consistent with this, elevated serum CRP has been found to mark metabolic and functional impairment in advanced COPD (30,31). CRP correlates with other inflammatory markers but in addition Broekhuizen et al have shown that it correlates with a reduced exercise capacity, a reduced 6-minute walk distance, as well as with health-related quality-of-life (31). In addition, Sin and Man showed that levels of CRP were predictive of adverse cardiac events in patients with COPD in the NHANES studies, measured as subsequent raised Cardiac Infarction Injury Score based on ECG

readings (32). Our findings differ from these as we have looked at more directly related COPD endpoints, as the predictive value of CRP was not driven by cardiac events, and as the effect of CRP seemed less dependent of level of lung function.

In the literature, there are strong arguments for CRP increasing thrombotic risk and cardiovascular deaths (15). However, this could not explain the current findings, as there was no higher prevalence of ischemic heart disease in participants who had a COPD outcome than in those free of an event (Table 1). Also, cardiovascular disease tended to occur less frequently as a contributing cause of death among those who died from COPD than among those who died from other causes (39% vs. 47%,  $\chi^2$ :P=0.19). Hence in individuals with airway obstruction CRP seems a strong predictor of COPD outcomes independent of cardiovascular events.

FEV<sub>1</sub> % predicted is the most important predictor of future clinical COPD outcomes. After adjustment with or without matching for FEV<sub>1</sub> % predicted, serum CRP remained a significant predictor of clinical COPD outcomes adding to the prognostic value of FEV<sub>1</sub> in predicting COPD. This corroborates with the idea that airflow limitation and airway inflammation are separate and independent factors in the pathophysiology of COPD (33), and suggests that serum CRP predicts future COPD in individuals with airway obstruction independent of lung function.

In the lung CRP has protective functions in innate immune responses against bacteria and apoptotic cells. CRP enters the lung from plasma and is primarily produced by hepatocytes in response to IL-6 stimulation. Activated epithelial cells and increased numbers of alveolar macrophages and other inflammatory cells in COPD may release IL-6 into the circulation (34-36). This stimulates an acute phase response and increases the level of plasma CRP. Consistent with our CRP data and a potential role for IL-6 in COPD pathogenesis, two other IL-6 regulated acute phase reactants (fibrinogen and  $\alpha_1$ -antitrypsin) are also associated with features of COPD (37,38). In further support of a role for IL-6 in COPD development, studies indicate that 1) IL-6 increases the number of lung CD4 cells, CD8 cells, B cells, neutrophils, and macrophages (34-36,39-44) consistent with the changes observed in human COPD pathology (45), 2) overexpression of IL-6

lead to emphysema-like airspace enlargement, peribronchiolar collections of mononuclear cells, thickening of airway walls, subepithelial fibrosis, and airway hyperresponsiveness (39,40,46), 3) intravenous IL-6 injections into rats lead to respiratory and peripheral skeletal muscle wasting (47), in line with the IL-6-associated reduced muscle strength observed in humans (29), and 4) lung injury is attenuated by the absence of IL-6 after exposing animals to ozone (44,48).

Plasma CRP may therefore be associated with IL-6-related processes in the airways that over time lead to progression of COPD with severe clinical implications. Further studies using rigorous molecular biological methodology is required to determine specifically any potential roles of IL-6 in COPD pathology. Plasma CRP may not only be used to assess inflammation during the course of COPD, but may also be useful as a marker to monitor inflammation during COPD treatment, as increased serum CRP in stable COPD seems to be reduced by treatment with an inhaled corticosteroid (49).

Because we studied a sample of individuals with airway obstruction from the adult Danish general population, generalisability of our data to other populations or races may potentially be constrained. Bias caused by investigators' knowledge of disease or risk factor status is unlikely, because we measured CRP and other basic characteristics at baseline and followed the study participants prospectively.

Another important implication of this paper is that we may now calculate 10 year risks for death or hospitalization in COPD patients on what would appear to be sound basis, as is done in cardiology for myocardial infarction and cardiac death. This may be useful for counseling COPD patients in the clinical setting. In conclusion, serum CRP is a strong long-term predictor of future COPD outcomes in individuals with airway obstruction.

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## **Figure legends:**

**Figure 1.** Cumulative incidence of COPD events according to baseline serum CRP levels.

Cumulative incidences of COPD hospitalization and death were increased in individuals with baseline CRP  $>3$  mg/L vs.  $\leq 3$  mg/L.

**Figure 2.** Absolute 10-year risks for COPD hospitalization and COPD death according to FEV<sub>1</sub>%

predicted, tobacco consumption, age, and serum CRP. The dependent variables for the Poisson regressions are number of COPD hospitalizations or COPD deaths during the subsequent 10 years.

The highest absolute 10-year risks for COPD hospitalization and death - 54% and 57% - were found among individuals with CRP  $>3$ mg/L, age  $>70$  years, tobacco consumption  $>15$  g/day, and FEV<sub>1</sub> % predicted less than 50%.

Table 1. Baseline characteristics of the study participants

	COPD outcomes during follow-up			
	None	Any	Hospitalization	Death
Female/male	490/604	107/101	102/83 <sup>†</sup>	38/45
Age, years	66 (58-73)	68 (63-73)*	68 (63-72)	70 (64-75) <sup>‡</sup>
FEV <sub>1</sub> , % of predicted	74 ±19	57 ±19 <sup>‡</sup>	57 ±19 <sup>‡</sup>	49 ±19 <sup>‡</sup>
Tobacco consumption, g/day	11 (0-20)	15 (4-20) <sup>†</sup>	15 (6-20) <sup>†</sup>	14 (0-20)
Ischemic heart disease**	148 (14%)	37 (18%)	35 (19%)	13 (16%)
CRP, mg/L	2.3 (1.0-4.9)	3.4 (1.7-7.5) <sup>‡</sup>	3.3 (1.6-7.4) <sup>‡</sup>	4.3 (2.1-7.8) <sup>‡</sup>

Values are numbers (%), median (25th percentile-75th percentile), or mean ±SD. \*p<0.05, <sup>†</sup>p<0.01, or <sup>‡</sup>p<0.001 on Pearson's  $\chi^2$  test, Mann Whitney U-test, or Student's t-test; reference group is individuals without COPD outcomes during follow-up. \*\*Ischemic heart disease = individuals ever hospitalized due to ICD8 codes 410-414 or ICD10 codes I20-I25. COPD = chronic obstructive pulmonary disease. FEV<sub>1</sub> = forced expiratory volume in one second. CRP = C-reactive protein.

Table 2. Risk of COPD outcomes and all-cause mortality according to baseline serum CRP level

	Events, n	CRP concentration >3mg/L vs. ≤3mg/L		
		Crude	Age*	Multiple†
COPD hospitalization	139	1.7 (1.2-2.4)	1.6 (1.2-2.3)	1.4 (1.0-2.0)
COPD death	58	2.7 (1.6-4.7)	2.5 (1.5-4.4)	2.2 (1.2-3.9)
All-cause mortality	329	1.8 (1.4-2.2)	1.7 (1.4-2.1)	1.4 (1.1-1.8)

Values are hazard ratios and 95% confidence interval. \*Adjusted for age (deciles). †Adjusted for gender, age (deciles), FEV<sub>1</sub> % predicted (deciles), tobacco consumption (deciles), and ischemic heart disease (ICD8: 410-414 or ICD10: I20-I25). COPD = chronic obstructive pulmonary disease. CRP = C-reactive protein.

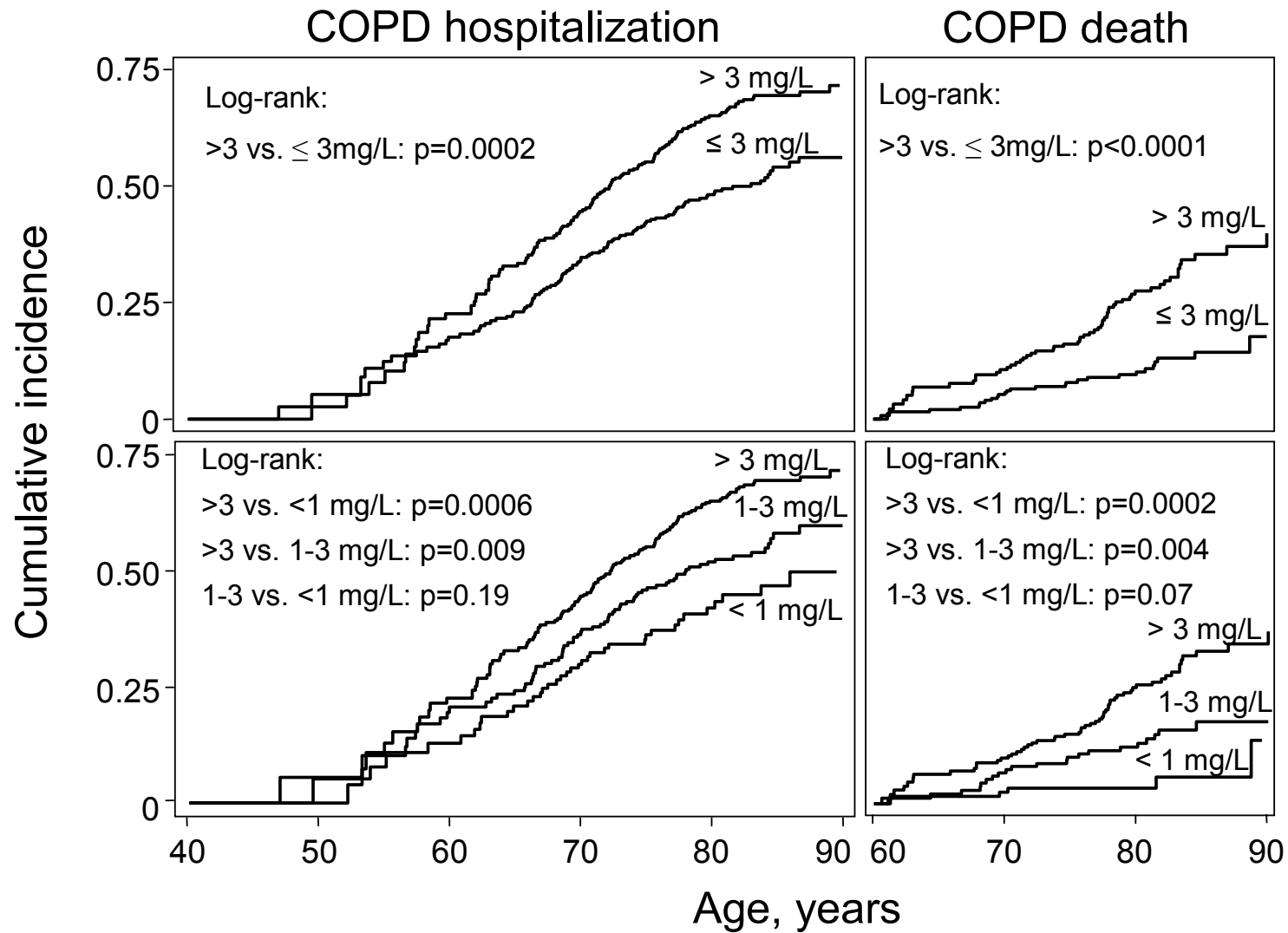
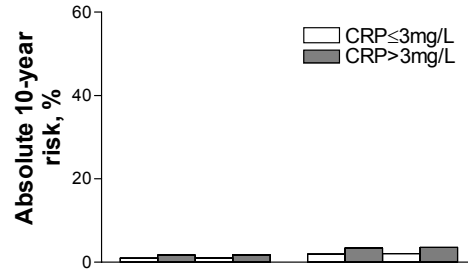
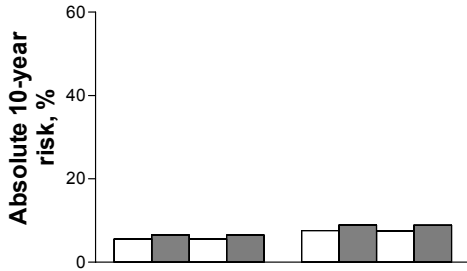


Fig. 1

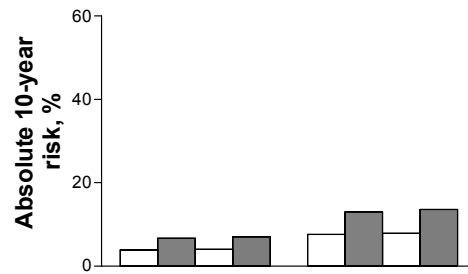
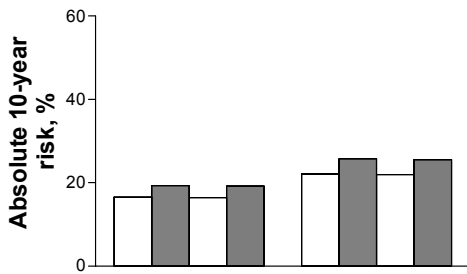
## COPD hospitalization

## COPD death

### FEV<sub>1</sub> % predicted >79%



### FEV<sub>1</sub> % predicted 50-79%



### FEV<sub>1</sub> % predicted <50%

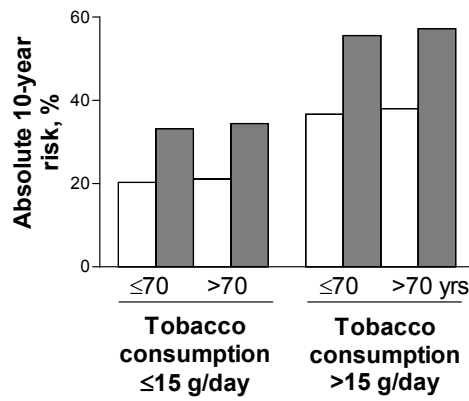
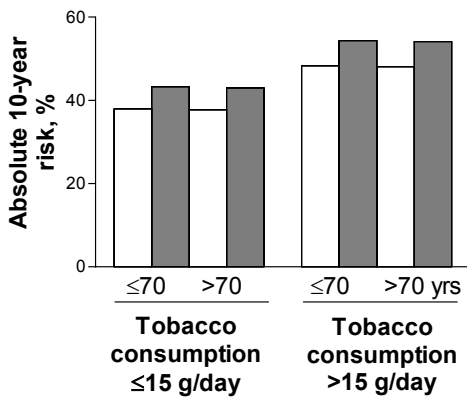


Fig. 2