Original Investigation

Cardiorespiratory fitness, inflammation and risk of chronic obstructive pulmonary disease: a cohort study

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Running title: Cardiorespiratory fitness, inflammation and chronic obstructive pulmonary disease

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Abstract

Purpose: Chronic obstructive pulmonary disease (COPD) is characterized by chronic lung inflammation. The relationship between cardiorespiratory fitness (CRF) and COPD has not been well characterized. We aimed to evaluate the independent and joint associations of inflammation (measured by high sensitivity C-reactive protein, hsCRP) and CRF with COPD risk in a cohort of Caucasian men.

Methods: In 2,274 men aged 42-61 yr at baseline, serum hsCRP was measured using an immunometric assay and CRF was assessed using a respiratory gas exchange analyser. hsCRP was categorized as normal and high (≤ 3 and >3 mg/L, respectively) and CRF as low and high. We corrected for within-person variability in exposure levels using repeat measurements taken several years apart.

Results: A total of 116 COPD cases occurred during a median follow-up of 26.0 yr. The age-adjusted regression dilution ratio (95% CIs) of hsCRP and CRF was 0.57 (0.50-0.64) and 0.58 (0.53-0.64), respectively. Comparing high vs normal hsCRP, the multivariable-adjusted HR (95% CI) for COPD was 1.79 (1.20-2.68). COPD risk decreased continuously with increasing CRF (*p*-value for nonlinearity=0.94). The multivariable-adjusted HR (95% CI) for COPD per 1 SD increase in CRF was 0.75 (0.60-0.95). Compared with men with normal hsCRP-low CRF, high hsCRP-low CRF was associated with an increased COPD risk 1.80 (1.12-2.89), with no evidence of an association for high hsCRP-high CRF and COPD risk 1.35 (0.68 – 2.69).

Conclusions: hsCRP and CRF are each independently associated with COPD risk. However, high CRF levels attenuate the increased risk of COPD related to high hsCRP levels.

Chronic obstructive pulmonary disease (COPD) is a respiratory condition that is characterized by chronic lung inflammation, resulting in progressive and irreversible airflow obstruction.[1] The airflow obstruction is reported to result from a combination of entities such as chronic bronchitis and emphysema. Chronic obstructive pulmonary disease is the third leading cause of death worldwide; it caused about 3.23 million deaths in 2019.[2] It is also a major cause of disability-adjusted life years and associated with significant health costs.[1] Though smoking is the principal risk factor for COPD, exposure to indoor air pollution, and occupational dusts, fumes, chemicals, and infections are also recognized as important risk factors.[2] Though COPD has no cure, it is a preventable and treatable disease; hence, modulation of risk factors could be essential in preventing COPD or delaying its progression. Chronic obstructive pulmonary disease is mediated by a chronic inflammatory process,[1] hence, it is no surprise that elevated levels of circulating inflammatory markers such as C-reactive protein (CRP) have been demonstrated to be associated with an increased risk of COPD.[3, 4] Physical activity has been identified as an important predictor of COPD outcomes; lower levels of physical activity are associated with a higher risk of exacerbations, hospitalizations, and all-cause mortality in patients with COPD.[5] Cardiorespiratory fitness (CRF), an index of cardiopulmonary function and habitual physical activity, is an established and independent risk marker for several vascular and non-vascular outcomes. High CRF levels have been shown to be strongly and independently associated with reduced risk of pneumonia.[6] Though a previous study has shown evidence of an association between higher levels of CRF and lower long-term risk of COPD,[7] the nature of the dose-response relationship and whether the association depends on inflammation is unknown. Furthermore, CRF has consistently been demonstrated to have the ability to offset the harmful effect of other risk factors,[8-12] however, whether high CRF levels also attenuate or offset the increased risk of COPD due to inflammation has not yet been explored. In this context, using a

population-based prospective cohort of 2,274 middle-aged Finnish men, we aimed to (i) confirm the existing association between inflammation (as measured by high sensitivity CRP, hsCRP) and COPD risk; (ii) evaluate the nature and magnitude of the relationship between CRF and COPD risk; and (iii) evaluate the joint effects of hsCRP and CRF on the risk of incident COPD.

METHODS

Study design and participants

We utilized the Kuopio Ischemic Heart Disease (KIHD) study, an ongoing population-based prospective cohort study comprising a representative sample of middle-aged men aged 42-61 recruited from Kuopio, eastern Finland. Baseline examinations were carried out between March 1984 and December 1989. Of a representative sample of 3,433 randomly selected men, 3,235 were found to be eligible; and of this number, 2,682 volunteered to participate, 186 did not respond to the invitation, and 367 declined to give informed consent. The data set analyzed in the present study includes 2,274 men with complete information on hsCRP, CRF, relevant covariates, and COPD outcomes. The research protocol was approved by the Research Ethics Committee of the University of Eastern Finland and all participants provided written informed consent. The investigation was concordant with the principles outlined in the Declaration of Helsinki and its future amendments.

Measurement of covariates and outcome ascertainment

Prior to blood specimen collections, participants were instructed to fast overnight, abstain from alcohol consumption for at least 3 days, and to abstain from smoking for at least 12 hours.[13-17] Serum hsCRP was measured using an immunometric assay (Immulite High-Sensitivity CRP assay, DPC, Los Angeles, CA).[18] Cardiorespiratory fitness, measured by maximal oxygen uptake (VO_{2max}), was assessed using a respiratory gas exchange analyzer (Medical Graphics, MCG, St. Paul, Minnesota) during cycle ergometer exercise testing.[16, 19, 20] Repeat measurements of hsCRP and CRF were performed in a random subset of participants 11 years after baseline. The assessment of age, smoking, alcohol consumption, socio-economic status (SES), prevalent diseases, and medication history employed the use of self-administered health and lifestyle questionnaires.[21] History of type 2 diabetes was defined

as having a clinical diagnosis of diabetes and regular treatment with diet or medications, fasting plasma glucose ≥ 7.0 mmol/l, or according to self-reports. History of CHD was based on a previous myocardial infarction, angina pectoris, the use of nitroglycerin for chest pain once a week or more frequently or chest pain. Adulthood SES was based on a summary index that combined income, education, occupational prestige, material standard of living, and housing conditions. The composite SES index ranged from 0 to 25, with higher values indicating lower SES. Alcohol consumption was assessed using the Nordic Alcohol Consumption Inventory. All incident cases of COPD occurring from study entry to 2014 were included. Outcomes were collected by linkage to the National Hospital Discharge Register. The diagnoses were made by qualified physicians based on the International Classification of Disease codes.

Statistical analysis

Baseline characteristics were presented as means (SD) or median (interquartile range) for continuous variables and percentages for categorical variables. Hazard ratios with 95% CIs for incident COPD were calculated using Cox proportional hazard models. Hazard ratios were adjusted for in two main models: model 1: age and model 2: model 1 plus smoking status, history of type 2 diabetes, prevalent CHD, history of asthma, history of chronic bronchitis, history of tuberculosis, alcohol consumption, energy intake, and SES. In a third model, there was alternate adjustment for each exposure. To explore a potential nonlinear dose-response relationship between CRF and COPD risk, we constructed a restricted cubic spline with knots at the 5th, 35th, 65th, and 95th percentiles of the distribution of CRF in a multivariable adjusted model. In addition to modelling CRF as a continuous variable, hsCRP was categorized into normal (≤ 3 mg/L) and high levels (> 3 mg/L) and CRF was categorized into low and high levels based on the median value to maintain consistency with previous

reports.[8, 16, 22] To quantify and correct for within-person variability (regression dilution bias) in levels of the exposures (hsCRP and CRF), which is, the extent to which an individual's measurements of these exposures vary around the long-term average exposure levels ("usual levels"),[23] adjusted regression dilution ratios (RDRs) were calculated by regressing available repeat measurements of the exposures on baseline values.[6, 20, 24, 25] This involved dividing the estimated disease association (log hazard ratio and its 95% confidence intervals) by the RDR. For the evaluation of the joint associations, study participants were divided into four groups according to hsCRP and CRF levels: normal hsCRP-low CRF; normal hsCRP-high CRF; high hsCRP-low CRF; and high hsCRP-high CRF. All statistical analyses were conducted using Stata version MP 16 (Stata Corp, College Station, Texas).

RESULTS

The overall mean (standard deviation, SD) age and CRF of men at baseline was 53 (5) yrs and 30.3 (8.0) ml/kg/min, respectively. The median (interquartile range, IQR) of hsCRP was 1.24 (0.69-2.36) mg/L (Table 1). Repeat measurements of hsCRP and CRF taken at 11 years after baseline were available in a random sample of 692 and 564 men, respectively. The overall age-adjusted RDR of hsCRP was 0.57 (95% CI: 0.50 to 0.64), suggesting that the association of hsCRP with COPD risk using baseline measurements of hsCRP only, could under-estimate the risk by [(1/0.57)-1]*100 = 75%. The overall age-adjusted RDR of CRF was 0.58 (95% CI: 0.53 to 0.64), suggesting that using baseline measurements of CRF to assess the association between CRF and COPD risk could under-estimate the risk by [(1/0.58)-1]*100 = 72%.

During a median (IQR) follow-up of 26.0 (18.5-28.1) yrs, 116 incident cases of COPD were recorded. Compared to men with normal hsCRP, high hsCRP was associated with an increased risk of COPD following adjustment for age, smoking status, prevalent type 2 diabetes, histories of CHD, asthma, chronic bronchitis and tuberculosis, alcohol consumption, energy intake, and socioeconomic status 1.94 (95% CI: 1.31-2.89) and the association was minimally attenuated after further adjustment for CRF 1.79 (95% CI: 1.20-2.68) (Table 2).

A multivariable restricted cubic spline curve showed that the risk of COPD decreased continuously with increasing CRF across the range 31-43 ml/kg/min (*p*-value for nonlinearity=0.94) (Figure 1). The HR for COPD per 1 SD increase in CRF in analysis adjusted for age, smoking status, prevalent type 2 diabetes, histories of CHD, asthma, chronic bronchitis and tuberculosis, alcohol consumption, energy intake, and socioeconomic status was 0.72 (95% CI: 0.57-0.91). On further adjustment for inflammation (hsCRP), a potential mediator of the association, the HR remained similar 0.75 (95% CI: 0.60-0.95). Comparing high versus low CRF, the corresponding adjusted HRs were 0.65 (95% CI: 0.43-0.98) and

0.68 (95% CI: 0.45-1.03), respectively. Correction for regression dilution bias strengthened the respective associations (Supplemental Digital Content).

Cumulative hazard curves showed a heightened risk of COPD among men with high hsCRP-low CRF compared with other groups (*p*-value for log-rank test < .001 for all; Figure 2). Compared with men with normal hsCRP-low CRF, high hsCRP-low CRF was associated with an increased risk of COPD in multivariable analysis 1.80 (95% CI: 1.12-2.89), with no evidence of an association for high hsCRP-high CRF and COPD risk 1.35 (95% CI: 0.68 – 2.69).

DISCUSSION

Consistent with previous reports,[3, 4] we have confirmed the independent associations of elevated levels of hsCRP with an increased risk of COPD. In this general population-based cohort of middle-aged Caucasian men, the results demonstrate a strong inverse dose-response relationship between objectively measured CRF and future risk of COPD. The association was independent of several risk factors including lifestyle factors and comorbidities. The association was also independent of inflammation, when CRF was appropriately modelled as a continuous variable. It should be noted that since COPD is characterized and mediated by chronic inflammation,[1] our adjustment for hsCRP may represent an overadjustment. New findings based on the joint associations of hsCRP and CRF with the risk of COPD showed that the risk of COPD was increased in men with elevated hsCRP and low CRF, but the increased risk of COPD due to elevated hsCRP was attenuated by increased levels of CRF. These findings add to the accumulating literature on the beneficial effects of CRF on chronic diseases and align with previous reports showing higher CRF levels attenuate or offset the increased risk of adverse outcomes due to other risk factors.[9, 10]

Though smoking is the major risk factor for COPD, only 20–25% of smokers develop COPD.[1] Chronic obstructive pulmonary disease is characterized by a chronic inflammatory process, which persists after smoking cessation. The main inflammatory mediators involved in COPD include tumor necrosis factor alpha (TNF-α), interleukin-1, interleukin-6, reactive oxygen species and proteases.[1] During the process of inflammation, CRP, an acute phase protein is produced by the liver in response to stimulation by inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α.[26] A distinct feature of COPD is the presence of acute exacerbations, which are typically associated with increased inflammation and are triggered by infections and environmental factors.[1] It has been demonstrated that consistently elevated levels of circulating CRP in the early stages of respiratory tract infections increase

the risk of progression to severe disease.[26] The mechanistic pathways that underlie the association between high levels of CRF and reduced incidence of COPD are not well understood, but may be via the effects of habitual physical activity, which confers good CRF, an index of better cardiopulmonary function. The protective effects of physical activity on COPD may be exerted via the anti-inflammatory effects of regular physical activity.[27] High levels of physical activity may reduce lung function decline, hence preventing or delaying the onset of COPD.[28] The increasing demand of ventilation during progressive physical activity may mechanically improve and increase the amount of ventilation in pulmonary airways, bronchioles and alveoli. Further research is needed to elucidate the mechanistic pathways underlying the relationship between CRF and COPD risk and if there is a causal relevance.

There are several strengths of the current evaluation, and these include the population-based prospective cohort design, large sample size, the long-term follow-up, the use of an objective gold standard measure of CRF, and ability to evaluate the dose-response relationship between CRF levels and COPD risk and correct for within-person variability in levels of both exposures. The limitations included the use of a relatively homogenous population consisting of predominantly white males which precluded generalization to women or other populations, repeat measurements of the exposures only available in a subset of the study participants, and potential for biases such as reverse causation and residual confounding.

CONCLUSIONS

In a middle-aged Finnish population, both hsCRP and CRF are each independently associated with the risk of COPD. The relationship between CRF and COPD risk is consistent with a graded dose-response relationship at CRF levels ranging from 31-43 ml/kg/min. However, high levels of CRF attenuate the increased risk of COPD related to high hsCRP levels.

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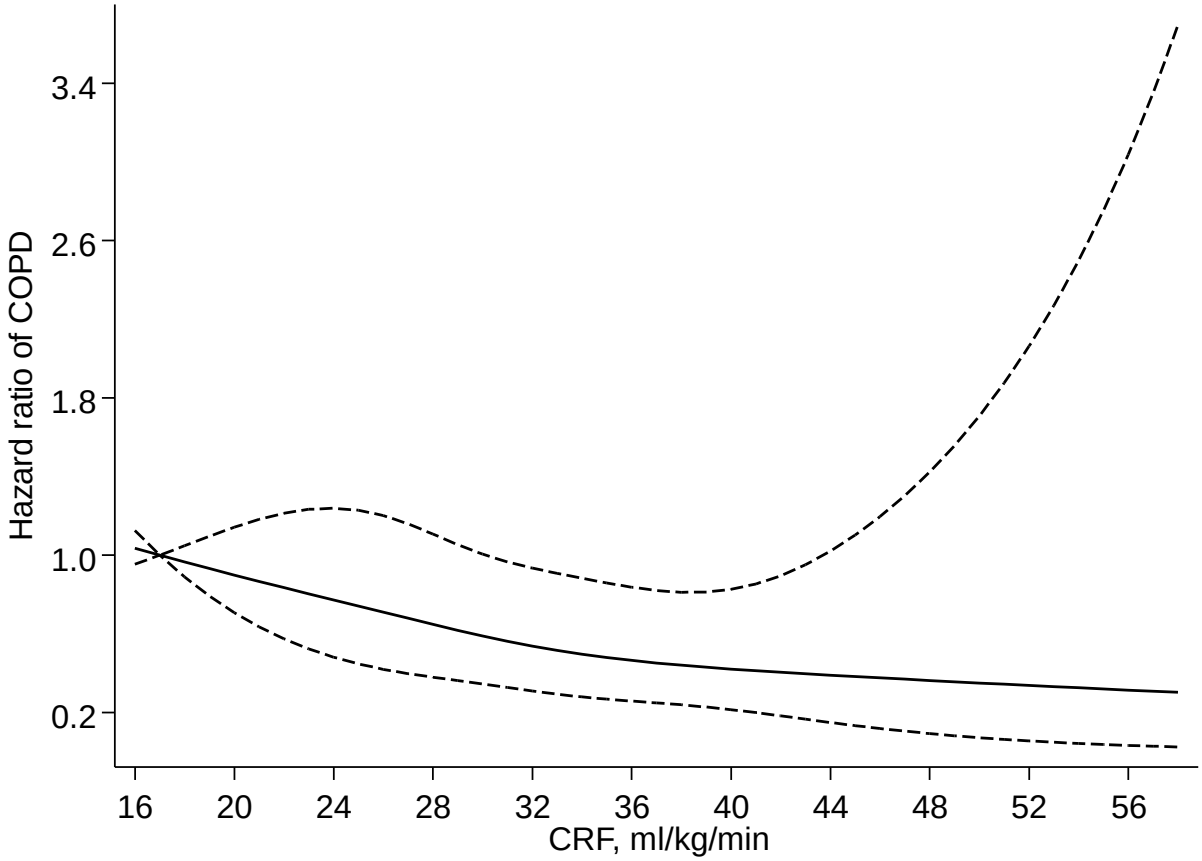
Figure Legends

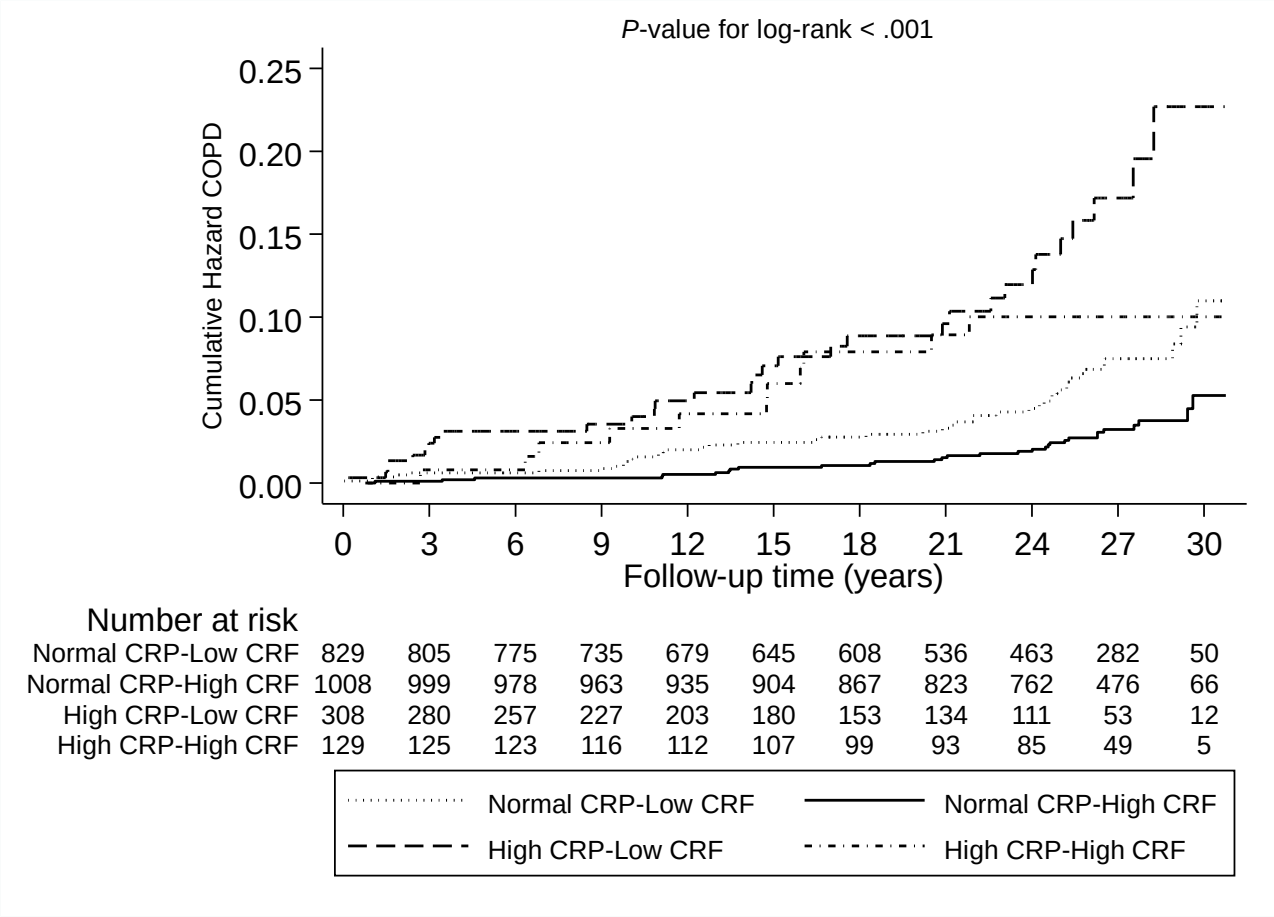
Figure 1. Restricted cubic spline of the hazard ratios of incident chronic obstructive pulmonary disease with cardiorespiratory fitness



Models were adjusted for age, smoking status, history of diabetes, prevalent coronary heart disease, history of asthma, history of chronic bronchitis, history of tuberculosis, total cholesterol, alcohol consumption, and socioeconomic status

COPD, chronic obstructive pulmonary disease

Figure 2. Cumulative Kaplan-Meier curves for COPD during follow-up according to joint categories of hsCRP and CRF



COPD, chronic obstructive pulmonary disease; CRF, cardiorespiratory fitness; hsCRP, high-sensitivity C-reactive protein

Table 1. Baseline characteristics of study participants

Characteristics	**Mean (SD) or median (IQR) or n (%)**
High sensitivity C-reactive protein (mg/l)	1.24 (0.69-2.36)
Cardiorespiratory fitness (ml/kg/min)	30.3 (8.0)
Questionnaire/Prevalent conditions	
Age (years)	53 (5)
Alcohol consumption (g/week)	31.9 (6.4-91.5)
Total energy intake, kJ/day	9904 (2572)
History of type 2 diabetes	76 (3.3)
Current smoking	710 (31.2)
History of CHD	535 (23.5)
History of asthma	76 (3.3)
History of chronic bronchitis	163 (7.2)
History of tuberculosis	86 (3.8)
Physical measurements	
BMI (kg/m^2)	26.9 (3.5)
SBP (mmHg)	134 (17)
DBP (mmHg)	89 (10)
Socio-economic status	8.41 (4.24)
Blood biomarkers	
Total cholesterol (mmol/l)	5.91 (1.07)
HDL-C (mmol/l)	1.29 (0.30)
Fasting plasma glucose (mmol/l)	5.33 (1.19)

BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; SD, standard deviation; SBP, systolic blood pressure

Table 2. Separate and joint associations of high sensitivity C-reactive protein and cardiorespiratory fitness with risk of chronic obstructive pulmonary disease

Exposure categories	Events/ Total	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
hsCRP (mg/L)							
Normal hsCRP (≤3)	74 / 1837	ref		ref		ref	
High hsCRP (>3)	42 / 437	3.15 (2.16 – 4.61)	< .001	1.94 (1.31 – 2.89)	.001	1.79 (1.20 – 2.68)	.005
CRF (ml/kg/min)							
Per 1 SD increase	116 / 2274	0.60 (0.48-0.74)	<.001	0.72 (0.57-0.91)	.006	0.75 (0.60-0.95)	.018
Low CRF (6.36-30.05)	75 / 1137	ref		ref		ref	
High CRF (30.06-65.40)	41 / 1137	0.51 (0.35 - 0.76)	.001	0.65 (0.43 - 0.98)	.04	0.68 (0.45-1.03)	.07
hsCRP (mg/L) and CRF (ml/kg/min) combination							
Normal hsCRP-Low CRF	44 / 829	ref		ref		NA	
Normal hsCRP-High CRF	30 / 1008	0.56 (0.35 – 0.90)	.018	0.67 (0.41 – 1.08)	.10	NA	
High hsCRP-Low CRF	31 / 308	2.66 (1.68 – 4.22)	<.001	1.80 (1.12 – 2.89)	.016	NA	
High hsCRP-High CRF	11 / 129	1.92 (0.98 – 3.75)	.058	1.35 (0.68 – 2.69)	.39	NA	

CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; hsCRP, high sensitivity C-reactive protein; NA, not applicable; ref, reference

Model 1: Adjusted for age

Model 2: Model 1 plus smoking status, history of type 2 diabetes, prevalent coronary heart disease, history of asthma, history of chronic bronchitis, history of tuberculosis, alcohol consumption, energy intake, and socioeconomic status

Model 3: Model 2 plus CRF for hsCRP or hsCRP for CRF

Supplemental Digital Content. Associations of high sensitivity C-reactive protein and cardiorespiratory fitness with risk of chronic obstructive pulmonary disease on correction for regression dilution bias

Exposure categories	**Events/ Total**	**Model 1**		**Model 2**		**Model 3**	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Usual hsCRP (mg/L)*							
Normal hsCRP (≤3)	74 / 1837	ref		ref		ref	
High hsCRP (>3)	42 / 437	7.50 (3.85 – 14.62)	< .001	3.21 (1.60 – 6.44)	.001	2.77 (1.37 – 5.62)	.005
Usual CRF (ml/kg/min)*							
Per 1 SD increase	116 / 2274	0.41 (0.28-0.59)	<.001	0.57 (0.38-0.85)	.006	0.61 (0.41-0.92)	.018
Low CRF (6.36-30.05)	75 / 1137	ref		ref		ref	
High CRF (30.06-65.40)	41 / 1137	0.32 (0.16 - 0.63)	.001	0.48 (0.23 - 0.97)	.04	0.52 (0.25-1.05)	.07

CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; hsCRP, high sensitivity C-reactive protein; NA, not applicable; ref, reference

*, indicates correction for within-person variability in values of the exposures, that is, the extent to which an individual's measurements of the exposures vary around a long-term average value (e.g. "usual CRF values")

Model 1: Adjusted for age

Model 2: Model 1 plus smoking status, history of type 2 diabetes, prevalent coronary heart disease, history of asthma, history of chronic bronchitis, history of tuberculosis, alcohol consumption, energy intake, and socioeconomic status

Model 3: Model 2 plus CRF for hsCRP or plus hsCRP for CRF