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Association of CRP and IL-6 with lung function in a middle-aged population initially free from self-reported respiratory problems: the Whitehall II study

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Abstract

To assess whether two inflammatory markers, C-reactive protein (CRP) and interleukin-6 (IL-6), and change in their concentrations over 12 years, are associated with lung function (FVC and FEV_1) 12 years after baseline. Data are from over 1,500 participants free from self-reported respiratory problems in a large-scale prospective cohort study of white-collar male and female civil servants. CRP and IL-6 measured at baseline (1991–1993) and follow-up (2002–2004) and FVC and FEV_1, measured at follow-up. Results adjusted for sociodemographic and anthropometric characteristics, health behaviours, biological factors, chronic conditions and

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medications, and corrected for short-term variability in CRP and IL-6 concentrations. Higher baseline levels of CRP and IL-6 were strongly associated with lower FVC and FEV_1, independent of potential confounders. A 10% increase serum CRP from baseline to follow-up was associated with lower values of FVC and FEV_1 at follow-up, 4.7 and 3.0 ml, respectively. The corresponding values for a 10% increase in IL-6 were 12.6 ml for FVC and 7.3 ml for FEV_1. Systemic low-grade inflammation is associated with only slightly poorer pulmonary function in a population free from self-reported respiratory problems 12 years earlier. These data provide evidence linking inflammation to adverse outcomes beyond cardiovascular disease. Interventions targeting inflammation may prevent lung function impairment.

Keywords

Inflammation; Pulmonary function; Cohort study; Epidemiology

Introduction

Poor lung function is associated with an increased risk of all-cause mortality [1] and, in particular, cardiovascular death [2]. The systemic inflammatory response predicts coronary heart disease [3, 4] and it has also been hypothesized to represent one of the pathophysiological processes predicting reduced lung function [5, 6]. It is well known that inflammation contributes to reduced lung function [7] and certain pulmonary conditions such as asthma [8]; and the therapeutic use of anti-inflammatory agents is considered as a standard treatment for diseases such as persistent asthma and advanced chronic obstructive pulmonary disease [9]. However, it is less certain whether inflammation predicts general lung function in populations free from self-reported respiratory problems [10]. If so, interventions targeting the inflammatory response might prove effective in preventing lung function impairment beyond their use in specific pulmonary conditions [11].

Inflammatory responses are the subject of active research and previous work has found that high levels of inflammatory markers are associated with reduced lung function. However, only a few longitudinal studies have previously examined this relationship with contradictory findings. Two studies with a 9-year follow-up period found an inverse trend between inflammatory markers and lung function [12, 13] while other studies with similar [14, 15] or longer [16] follow-up did not. In addition, most studies have focused specifically on chronic obstructive pulmonary disease [17-22] and either lacked extensive control for confounding factors or did not take account of measurement error, leading to less accurate estimates of the levels of inflammatory markers and their associations with lung function [23]. Finally, despite the vast array of serologic markers of systemic inflammation, studies have typically assessed only one marker, C-reactive protein (CRP). Although CRP is a general marker of inflammatory processes, interleukin-6 (IL-6), which regulates the synthesis of CRP [24], may be a more sensitive and appropriate marker of systemic inflammation. However, research on IL-6 in relation to lung function is scarce [19, 25].

The aim of this study was to assess whether CRP and IL-6 at baseline, and change in CRP and IL-6 concentrations over 12 years, are associated with lung function 12 years after baseline. To achieve this aim, we used data from the Whitehall II study, an ongoing large-scale prospective occupational cohort study of the white-collar male and female employees of 20 London-based Civil Service departments with the potential to adjust for many potential confounders and correct for short-term variability in the concentrations of CRP and IL-6.

Methods

Participants

The Whitehall II study sample recruitment (Phase 1) took place between late 1985 and early 1988 among all office staff, aged 35–55, from 20 London-based Civil Service departments [26]. The response rate was 73% (6,895 men and 3,413 women), although the true response rate is likely to be higher since around 4% of those invited were ineligible. Since Phase 1 there have been six further data collection phases. Odd-numbered phases include both a self-administered questionnaire and clinical examination, while even-numbered phases are limited to completion of a questionnaire [27]. Participants gave written informed consent and the University College London Medical School Committee on the Ethics of Human Research approved the protocol.

We aimed to select participants from the original Whitehall II cohort [26, 27] (n = 10,308) who were free from self-reported respiratory problems at baseline (Phase 3, 1991–1993). Of the 6,966 participants with measures of inflammatory markers either at baseline and/or follow-up (Phase 7, 2002–2004), 4,818 participants had completed lung function measures at follow-up. Of these, we excluded the following participants: those reporting respiratory health problems at Phase 3 (i.e., diseases of the respiratory system according to the ICD-10 or respiratory-related symptoms such as cough, catarrh or phlegm, shortness of breath or wheezing in the last 14 days, n = 1,938); those taking medication for asthma, anti-inflammatory drugs or other respiratory-related medication at baseline (n = 184) or with missing data in these variables (n = 197); and those with recent cold/flu (n = 595). Any single or combination of the above variables was regarded as self-reported respiratory problems. Further, we excluded participants with CRP > 10 mg/L, either at baseline or follow-up (n = 63), since these values are suggestive of acute inflammation and immune activation due to current illness, and are thus likely to reflect short-term inflammatory responses [28]. Those with missing data on the covariates under consideration were also excluded (n = 184). For each regression analysis we used the maximum available sample for each particular combination of inflammatory marker, respiratory outcome and phase under analysis, so the final analytical sample varied between 1,566 and 1,415 participants (see Tables 2 and 3 for detailed samples). Overall, excluded participants had lower lung function values and higher concentration levels of inflammatory markers than the final samples.

Inflammatory markers

CRP was measured using a high-sensitivity immunonephelometric assay in a BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK) and IL-6 was measured using a high-sensitivity ELISA assay (R&D Systems, Oxford, UK) [29]. Both markers were only measured in phases 3 and 7. Blood samples were collected between 8 am and 1 pm, stored at −80°C and were not thawed or refrozen during storage. In order to avoid systematic errors, stored serum samples from both phases were analysed at the same time and in the same laboratory for CRP and IL-6 in 2005. Values below the detection limit (0.154 mg/L for CRP and 0.08 pg/mL for IL-6) were assigned a value equal to half the detection limit. To measure short-term biological variation and laboratory error, a repeat sample was taken from a subset of 150 participants for CRP and 241 for IL-6 at baseline (average elapsed time between samples was 32 (SD = 10.5 days), and 533 for CRP and 329 for IL-6 at follow-up (average elapsed time between samples was 24 (SD = 11.0 days). Intra- and inter-assay coefficients of variation were 4.7 and 8.3% for CRP, and 7.5 and 8.9% for IL-6 at baseline and follow-up, respectively. Reliability between samples was assessed with Pearson's r correlation coefficients: r = 0.77 at baseline and r = 0.72 at follow-up for CRP, and r = 0.61 and 0.63, respectively, for IL-6. Mean follow-up was 11.8 years (range 9.6–13.8).

Lung function testing

At follow-up, participants were asked to perform spirometry as a part of the clinical examination using a portable flow spirometer (MicroPlus Spirometer, Micro Medical Ltd, Kent, UK) to measure the forced vital capacity (FVC in L) and the forced expiratory volume in one second (FEV_1 in L) [30, 31]. Following recommended procedures [31], the largest FVC and FEV_1 values from the three manoeuvres were used. All testing was conducted by nine trained nurses, and performed with the participant standing. Senior personnel conducted random supervisions to ensure that the testing protocol was correctly followed. Following the reproducibility criteria recommended by the American Thoracic Society at the time the spirometry was conducted, we checked whether the difference between the two largest FVC and FEV_1 values varied by more than 200 ml, respectively [31]. The 13.9% of the participants who did not achieve this reproducibility criterion had greater FVC than participants who met the criterion (3.91L vs. 3.82L; $P = 0.020$); there was no significant difference in FEV_1. As recommended, this criterion was set as a goal during data collection, but was not used to invalidate a test [30].

We included in the analysis the only one additional item on respiratory symptoms available at the follow-up questionnaire. This item asked about the presence or absence of shortness of breath in the previous 14 days; 132 (8.0%) participants reported having this symptom.

Covariates

Baseline sociodemographic characteristics, behavioural and biological factors, medical conditions and medication use (Table 1), known or suspected to be associated with inflammation and/or lung function, were measured as covariates [32-35].

Sociodemographic data included age using five-year age bands, sex and ethnicity (White, South Asian, Black and other categories). Participants' adult socioeconomic position (SEP) was based on their last known Civil Service employment grade at Phase 3, a measure of prestige, income and employment relations. Participants were classified from high to low SEP as follows: unified grade 1–6, unified grade 7, senior executive officer, higher executive officer, executive officer, and clerical and support staff [27]. As a marker of early life circumstances, father's social class was determined at Phase 1, using Phase 6 for missing values, following the UK Registrar General's social class classification (i.e., I Professional occupations, II Managerial and lower professional occupations, IIIN Non-manual skilled occupations, IIIM Manual skilled occupations, IV Semi-skilled occupations, and V Unskilled occupations).

Health-related behaviours were categorized as follows: alcohol consumption over the recommended limits (>14 units for women and >21 units for men); [36] good or poor diet based on bread, milk type, and fruit and vegetable consumption [37], vigorous/moderate or none/mild leisure-time physical activity based on energy utilization [37], and smoking grouped as never, former and current smokers. Smoking data from earlier phases were used to validate never-smoking status in Phase 3. The following biological measures were assessed: blood pressure (mmHg) was measured twice after 5 min rest using a Hawksley random zero sphygmomanometer (Hawksley and Sons, Lancing, England); to calculate total to high density lipoprotein (Total: HDL) cholesterol ratio, total and HDL-cholesterol, were measured within 72 h in serum stored at 4°C using enzymatic colorimetric methods [38]; waist and hip circumferences, to calculate waist-to-hip ratio, and weight (in kg) and height (in m) from which Body Mass Index (BMI in kg/m^2) was calculated, were measured using standard protocols [39].

Health conditions included any coronary heart disease (CHD), as previously reported [40], up to and including Phase 3, and, Type-2 diabetes mellitus based on self-reports and glucose

tolerance tests [37]. Medication use included CHD, diabetes and central nervous system medication, and non-CHD related analgesics.

Statistical analysis

Differences in lung function values and levels of inflammatory markers between the excluded and the included participants at each stage were studied with *t* tests and the Wilcoxon rank-sum (Mann–Whitney). To explore cross-sectional and longitudinal relationships between inflammation and lung function with linear regression analysis, CRP and IL-6 values were transformed by natural logarithm given their skewed distributions. All models were adjusted for age, sex, ethnicity and height. Final models were additionally adjusted for other covariates including sociodemographic characteristics, behavioural and biological factors, medical conditions and medication use (see Table 1 for details) [35, 41] Curvilinear effects for BMI were tested, but the quadratic term was dropped from the model due to statistical non-significance. To correct for short-term biological variation and measurement error, we computed regression dilution ratios (RDR) based on data from repeat subsample using the Rosner method [42] and corrected coefficients for inflammatory markers and all biological covariates by dividing the uncorrected regression coefficient by the RDR. Coefficients were directly obtained using the "errors-in-variables regression by regression calibration" (regcal) procedure (available at http://www.mrc-bsu.cam.ac.uk). Finally, the relationship between inflammatory markers and self-reported shortness of breath was examined by computing the relative risk (RR), implementing Zou's method for analyses of dichotomous outcomes [43]. All analyses were performed using STATA/SE v.9.2® [StataCorp 2005].

Results

Table 1 presents the characteristics of the participants with data on lung function and either CRP or IL-6 at baseline (n = 1,657). A similar covariate pattern was observed in the separate samples of CRP and IL-6 at baseline (data not shown). Participants were middle-aged, mostly men, of white ethnicity, from the higher and medium employment grades, and from a non-manual class background. A poor diet, none/mild leisure-time physical activity or being an ex-smoker was reported by approximately one-third of the participants, while one-seventh reported alcohol consumption above the recommended amounts or being a current smoker. Only a minority had a history of coronary heart disease, diabetes or used medications.

Table 2 shows all the linear regression coefficients (i.e., β) of the association between the levels of the inflammatory markers (i.e., CRP and IL-6) and the lung function values (i.e., FVC and FEV_1). Given that the inflammatory markers have been log-transformed, β represents the change in lung function values, in $\beta/100$ units, per each one percent increase in the original untransformed levels of inflammatory markers, while holding all other covariates constant. Thus, a 10% increase in the average CRP level at baseline, 0.67 mg/L (SD = 2.95), would result in an average level of 0.74 mg/L (SD = 3.25). Similar changes at follow-up, would result in an average level of 1.15 mg/L (SD = 2.93) from a value of 1.04 mg/L (SD = 2.66). Corresponding 10% increases in IL-6 at baseline would result in an average level of 1.51 pg/mL (SD = 1.93) from 1.37 pg/mL (SD = 1.75); and at follow-up, the average would be 1.94 pg/mL (SD = 1.91) from 1.77 pg/mL (SD = 1.74). Finally, a 10% increase in the average level of the differences from baseline to follow-up values would result in a difference in CRP levels of 1.77 mg/L (SD = 2.95) from 1.61 mg/L (SD = 2.68). For IL-6, the average difference would be 1.43 pg/L (SD = 1.99) from 1.30 pg/mL (SD = 1.80).

Analyses of the relationship of CRP and IL-6 with lung function values, adjusting for age, sex, ethnicity and height, showed there was a prospective inverse association (higher CRP, lower lung function) between CRP at baseline and both FVC ($\beta = -0.083$, $P < 0.001$) and FEV_1 ($\beta = -0.056$, $P < 0.001$) at follow-up. Stronger inverse associations were observed between CRP and lung function at Phase 7. In analyses additionally adjusted for CRP at baseline, an increase in CRP levels between baseline and follow-up was associated with lower levels of FVC ($\beta = -0.058$, $P < 0.001$) and FEV_1 ($\beta = -0.035$, $P = 0.003$) at follow-up. Corresponding to CRP, IL-6 at baseline was associated with lower lung function values at follow-up; inverse cross-sectional associations were observed at Phase 7; and an increase in IL-6 levels between baseline and follow-up, additionally adjusted for baseline IL-6, was associated with low FVC ($\beta = -0.172$, $P < 0.001$) and FEV_1 ($\beta = -0.114$, $P < 0.001$) at follow-up.

Associations including adjustments for all covariates between CRP and IL-6 and lung function values are also presented in Table 2. These models showed the relationship between baseline CRP and both FVC ($\beta = -0.055$, $P = <0.001$) and FEV_1 ($\beta = -0.054$, $P = <0.001$) was attenuated a little bit and associations at follow-up were very similar to the models adjusted only for age, sex, ethnicity and height. The estimators of the increase in CRP levels between baseline and follow-up on lung function were slightly reduced ($\beta = -0.047$, $P = 0.006$ for FVC and $\beta = -0.030$, $P = 0.047$ for FEV_1). Thus, each 10% increase in the level of serum CRP from baseline to follow-up was associated with lower FVC and FEV_1 values, 4.7 and 3.0 ml, respectively, after adjustment for all covariates.

Overall, corresponding results for IL-6 showed increases in the estimates of both the inverse association between baseline IL-6 and lung function values at follow-up and the inverse cross-sectional associations at follow-up; as well as reductions of the estimators of the increase in IL-6 levels between baseline and follow-up on FVC ($\beta = -0.126$, $P < 0.001$) and FEV_1 ($\beta = -0.073$, $P = 0.002$). Thus, each 10% increase in the level of serum IL-6 from baseline to follow-up was associated with lower FVC and FEV_1 values, 12.6 and 7.3 ml, respectively, after adjustment for all covariates.

The associations between CRP and IL-6 and shortness of breath at follow-up are presented in Table 3. A pattern similar to the one with lung function levels could be observed in relation to shortness of breath, although the prospective association, adjusted for all covariates, between baseline inflammation and shortness of breath was not statistically significant. Increases in the average inflammatory marker levels between baseline and follow-up still were associated with greater risk of recent shortness of breath at follow-up for both CRP (RR = 1.67; 95%CI: 1.35–2.08) and IL-6 (RR = 1.53; 95%CI: 1.16–2.03) after adjustment for all covariates.

Discussion

The present prospective study demonstrates an association of higher levels of two systemic inflammatory markers, CRP and IL-6, and their change in 12 years, with slightly poorer lung function, measured as FVC and FEV1, in a well-characterized cohort of middle-aged men and women free from self-reported respiratory problems at baseline. Initial serum levels of CRP and IL-6 were found to be associated with FVC and FEV_1 12 years after baseline, independently of other determinants of lung function, such as sociodemographic characteristics, behavioural and biological factors, medical conditions and medication use. After final adjustment, each 10% increase in the level of CRP from baseline to follow-up was associated with lower FVC and FEV_1, 4.7 and 3.0 ml respectively. Corresponding values for IL-6 were 12.6 ml for FVC and 7.3 ml for FEV_1.

Plausible mechanisms linking inflammation with the development of pulmonary impairment have been described. Cytokines (e.g., IL-6) and the acute phase-reactants they stimulate (e.g., CRP) may be associated with the activation and adhesion of inflammatory cells in the pulmonary capillary endothelium, leading to changes in endothelial function and increasing pulmonary vascular microfiltration which may, in turn, result in damaged airways and accelerated decline in lung function [12, 44]. Few studies have purposely investigated this pathway [14, 22,45, 46].

Additionally, while the majority of previous studies have primarily assessed only the role of CRP, we have extended coverage to IL-6, a more sensitive marker of systemic inflammation. Whereas many prior studies suggest that reduced lung function is responsible for systemic inflammation [6], our findings are consistent with a pathway from systemic inflammation to impaired lung function in a population initially free from self-reported respiratory problems.

Higher levels of CRP have been found to be associated with lung function decline among young adults [12, 13]—lack of association in another study has been attributed to using a low-sensitivity CRP assay [15]—and middle-aged adults [12], including our study, but not in much older (i.e., 65 and older) samples [16]. In addition, a prior population-based prospective study of UK people aged 18–70 [14], found cross-sectional inverse associations between CRP levels and FVC and FEV_1 at both baseline and follow-up and inconsistent prospective associations between changes in CRP over 9 years (i.e., no association between continuous measures of CRP and FEV_1 change but an inverse association using tertiles). Given these findings it may be that the association between CRP and lung function appears in young adulthood, if not earlier, then it weakens during middle adulthood, as the weak association we found suggests, and even disappears in old age, possibly due to survival bias. Nevertheless, despite that diversity in sample composition and covariate adjustment limits direct comparisons with prior studies, the consistency of our findings with prior observations of an inverse association between inflammation and lung function, the extension of the findings to IL-6, the existence of a potential explanatory pathophysiological mechanism, and our broad adjustments, suggest that our results are not spurious.

Our analyses focused on FVC and FEV_1 at follow-up in a cohort free from self-reported respiratory disease and/or symptomatology at baseline. After sample exclusions, the small number of participants in our sample who developed lung disease (ICD-10 coding) at the follow-up examination, precluded a detailed analysis. We conducted an exploratory nested case–control analysis with cases of ICD-10 diseases of the respiratory system (between 48 and 55 cases depending on the inflammatory marker), matched for sex, age (5-years groups) and smoking status (data not shown). Increases in the levels of both CRP (OR = 1.34; 95% CI: 0.89–2.02) and IL-6 (OR = 1.27; 0.67–2.41) between baseline and follow-up were non-significantly associated with greater likelihood of respiratory diseases. However, cases were self-reported, included a miscellaneous mixture of acute and chronic cases, and it is also possible that the time interval of 12 years was insufficient for the development of a sufficient number of clinical lung disease cases to reach statistical significance. Continued follow-up of this prospective cohort will be necessary to further explore the relationship between inflammation and clinically diagnosed cases of respiratory disease.

Nevertheless, we found that increased levels of both CRP and IL-6 were associated with greater risk of recent self-reported shortness of breath at follow-up. The prospective association, adjusted for age, sex, ethnicity and height, between baseline inflammation and recent shortness of breath at follow-up became not statistically significant after all covariates were considered. Only about eight percent of the participants reported this symptom, limiting the statistical power of our analyses. Also, our questionnaire did not distinguish

between acute and chronic shortness of breath. Exclusion of persons with a cold/flu at the time of follow-up makes it more likely that reported shortness of breath reflected longstanding dyspnoea. Despite these shortcomings, the observed associations of inflammatory marker levels with a clinical respiratory symptom, and the indication of associations with diseases of the respiratory system, taken together with the findings on lung function, provide additional support for our primary findings.

The strengths of this study include the use of repeat measurements to correct for short-term biological variation and measurement error. Prior cross-sectional studies based on a single baseline measurement of levels of inflammatory markers tend to underestimate the association of inflammation with subsequent pulmonary function (i.e., regression dilution bias). In addition, we aimed our analyses to participants with complete lung function testing at follow-up, inflammatory markers measured either at baseline or follow-up and free from self-reported respiratory problems at baseline. Further, participants with CRP values (i.e., >10 mg/L) at baseline or follow-up, indicating acute inflammation and immune activation due to current illness, were also excluded since these are likely to reflect short-term inflammatory responses. From this reduced eligible sample (n = 1,841), between 74 and 82% participants were included in the final analyses [28]. Unfortunately, no baseline measure of lung function was available for this study, thus, some of the exclusions were based on self-reported symptoms, not lung function, and some participants with low lung function may have reported no symptoms. However, because of all the exclusions, the possibility of reverse causation, that is, that impaired lung function is responsible for inflammation, is less likely. If anything, our exclusions may have biased our results towards an underestimation of the association between inflammation and lung function, since excluded participants had higher levels of inflammatory markers and lower lung function values than participants with full data.

Our cohort may have limited representativeness of the total British population because of the singular type of employees (i.e., white-collar civil servants) and their single location (i.e., London). The observed associations are likely to be smaller than in the overall population because occupational cohorts are, by their very nature, healthier than their general population [47], and therefore the range of lung function might be narrower. This being the case, the associations reported herein will, if anything, be an underestimate of the associations in the general population, which includes those not in employment. This does not necessarily mean, however, that the reported associations are an underestimate of the true association between the level of inflammatory markers and lung function. In addition, participants were mainly white women and men working in white-collar occupations [48], thus results may have limited generalizability to other ethnic groups and occupations. But given the increasing percentage of workers in affluent societies employed in white-collar occupations, our sample may be largely representative. Future research in more diverse samples should extend the generalizability of our findings.

In summary, findings from a large-scale, prospective, British occupational cohort suggest that, in a population free from self-reported respiratory problems at baseline, higher levels of inflammation, and their 12-year change, are associated with only slightly poorer lung function. It is already well known that age, together with height, weight, sex and race, explain the majority of the lung function differences between two individuals [30]. And so, the contribution of other factors, such as CRP and IL-6, to these differences will be comparatively small. However, the differences in lung function associated with increases in CRP and IL-6 levels were robust to adjustment and with small p-values providing strong evidence against the null hypothesis (that is, of no relationship between inflammation and lung function). Thus, one should consider that the relatively small differences attributed to increases in the levels of inflammatory makers would occur on top of natural changes

already occurring. While we cannot stop the biological age clock, we could conceivably take steps to reduce and/or control biological contributing factors to decline, such as inflammation. Given that causality cannot be firmly established from our study, it may be premature to promote the development of intervention therapies targeting inflammation to prevent lung function impairment [49]. Overall, we believe it is important to continue the study of the association of inflammation with lower lung function in order to confirm the possibility of a systemic low-grade inflammation mechanism of pulmonary impairment as suggested by our findings.

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Table 1

Characteristics of the sample at baseline (1991–1993) (n = 1,657)

Baseline characteristics	Percent or mean (standard deviation)
Lung function measures	
Forced expiratory volume in one second (FEV_1, in L)	3.0 (0.80)
Forced vital capacity (FVC, in L)	4.0 (0.97)
Inflammatory markers	
C-reactive protein (mg/L)†	0.67 (2.9)
Interleukin-6 (pg/mL)†	1.37 (1.7)
Sociodemographics	
Age (years)	49.2 (6.0)
Sex (female)	27.3%
Ethnicity (White)	92.8%
Employment grade	
Unified grade 1–6	19.7%
Unified grade 7	23.2%
Senior executive officer	15.9%
Higher executive officer	16.5%
Executive officer	13.9%
Clerical and support staff	10.9%
Father's social class	
I Professional occupations	8.9%
II Managerial and lower professional occupations	36.2%
IIIN Non-manual skilled occupations	16.4%
IIIM Manual skilled occupations	28.3%
IV Semi-skilled occupations	7.4%
IV Unskilled occupations	2.8%
Health related behaviours	
Alcohol consumption (over the recommended limits)	13.5%
Diet (Poor)	33.1%
Exercise (None/mild)	31.5%
Current smokers	14.1%
Former smokers	33.1%
Biological factors	
Height (in cm)	172.9 (9.2)
Waist-to-hip ratio	0.86 (0.08)
Body mass index (kg/m^2)	24.6 (3.2)
Systolic blood pressure (mmHg)	119.7 (13.3)
Diastolic blood pressure (mmHg)	78.7 (9.3)

Baseline characteristics	Percent or mean (standard deviation)
Total:HDL cholesterol ratio	4.7 (1.5)
Health conditions	
Coronary heart disease	5.1%
Diabetes	2.1%
Medication use	
Coronary heart disease	6.0%
Diabetes	0.3%
Central nervous system	2.4%
Analgesics (Not for coronary heart disease)	2.2%

Sample with data on lung function measures at follow-up and baseline measurement of either C-reactive protein or interleukin-6 and complete data on the other variables shown in the table

†Geometric mean and geometric standard deviation

Table 2

Relationship between inflammatory markers (C-reactive protein and interleukin-6) with lung function values

Inflammatory markers	n	Lung function at Phase 7 (2003–2004)					
		Adjusted for age, sex, ethnicity and height			Adjusted for all covariates[a]		
		β[b]	(SE)[c]	*P*-value	β[b]	(SE)[c]	*P*-value
	FVC						
CRP							
Phase 3 (1991–1993)	1565	−0.083	(0.013)	<0.001	−0.055	(0.015)	<0.001
Phase 7 (2003–2004)	1,566	−0.155	(0.019)	<0.001	−0.131	(0.025)	<0.001
Change score[d]	1,484	−0.058	(0.016)	<0.001	−0.047	(0.017)	0.006
IL-6							
Phase 3 (1991–1993)	1,561	−0.179	(0.033)	<0.001	−0.150	(0.055)	0.006
Phase 7 (2003–2004)	1,495	−0.515	(0.058)	<0.001	−0.516	(0.076)	<0.001
Change score[d]	1,415	−0.172	(0.028)	<0.001	−0.126	(0.027)	<0.001
	FEV_1						
CRP							
Phase 3 (1991–1993)	1,565	−0.056	(0.011)	<0.001	−0.054	(0.013)	<0.001
Phase 7 (2003–2004)	1,566	−0.096	(0.017)	<0.001	−0.100	(0.022)	<0.001
Change score[d]	1,484	−0.035	(0.013)	0.003	−0.030	(0.015)	0.047
IL-6							
Phase 3 (1991–1993)	1,561	−0.144	(0.029)	<0.001	−0.198	(0.047)	<0.001
Phase 7 (2003–2004)	1,495	−0.349	(0.051)	<0.001	−0.383	(0.067)	<0.001
Change score[d]	1,415	−0.114	(0.024)	<0.001	−0.073	(0.024)	0.002

CRP C-reactive protein, *IL-6* Interleukin-6, *FVC* forced vital capacity (in L), FEV_1 forced expiratory volume in one second (in L)

[a] Adjusted for all covariates shown in Table 1

[b] Linear regression coefficients. Given that the inflammatory markers have been log-transformed, the format for interpretation of the linear regression coefficients is that a one percent increase in the original untransformed scale in the levels of inflammatory markers changes the lung function variables by (β/100) units while all other variables in the model are held constant

[c] Standard error

[d] Change score = Phase 7 value minus Phase 3 value; additionally adjusted for Phase 3 value

Table 3

Relationship between inflammatory markers (CRP and IL-6) with shortness of breath

Inflammatory markers	Shortness of breath at Phase 7 (2003-2004)						
	Adjusted for age, sex, ethnicity and height				Adjusted for all covariates[a]		
	n	RR[b]	(95%CI)	*P*-value	RR[b]	(95%CI)	*P*-value
CRP							
Phase 3 (1991–1993)	1,561	1.24	(1.04–1.47)	0.016	1.05	(0.86–1.29)	0.612
Phase 7 (2003–2004)	1,562	1.76	(1.42–2.06)	<0.001	1.58	(1.29–1.93)	<0.001
Change score[c]	1,480	1.72	(1.40–2.13)	<0.001	1.67	(1.35–2.08)	<0.001
IL-6							
Phase 3 (1991–1993)	1,557	1.33	(1.04–1.69)	0.023	1.10	(0.83–1.47)	0.498
Phase 7 (2003–2004)	1,492	1.74	(1.39–2.19)	<0.001	1.45	(1.12–1.87)	0.004
Change score[c]	1,412	1.72	(1.32–2.24)	<0.001	1.53	(1.16–2.03)	0.003

CRP C-reactive protein, *IL-6* Interleukin-6, FEV_1 forced expiratory volume in one second (in L), *FVC* forced vital capacity (in L)

[a] Adjusted for all covariates shown in Table 1

[b] Relative Risk. Given that the inflammatory markers have been log-transformed, then the RR is the risk of having shortness of breath associated with scaling up the levels of inflammatory markers, in the original untransformed scale, by a factor of $e = \exp(1)$, which is approximately 2.718281828, while all other variables in the model are held constant

[c] Change score = Phase 7 value minus Phase 3 value; additionally adjusted for Phase 3 value