



Airflow limitation, lung volumes and systemic inflammation in a general population

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ABSTRACT: Although several levels of evidence have suggested an association between systemic inflammation and spirometric lung volumes, data addressing the potential interrelationship between airflow limitation and inflammatory markers are sparse and remain controversial.

Potential associations between high-sensitivity C-reactive protein (hsCRP), fibrinogen and lung function were investigated in 1,466 individuals aged 25–85 yrs, representing a general population. Within this cross-sectional population, data on body plethysmography, spirometry, helium dilution and diffusing capacity of the lung for carbon monoxide (DL_{CO}) were analysed.

After adjustment for potential confounding factors, such as smoking, obesity and cardio-respiratory fitness, there was an inverse association of hsCRP with forced expiratory and static lung volumes. In neither apparently healthy nor the entire population was inflammation associated with airflow limitation in central airways. In smokers only, higher hsCRP and fibrinogen were associated with an impaired DL_{CO} .

This study shows that higher levels of hsCRP are associated with decreased lung volumes in a general population over a wide age range. A consistent interrelationship of central airflow limitation and inflammation was not verifiable. Smoking is related to an impaired DL_{CO} in association with an increase in systemic inflammation.

KEYWORDS: C-reactive protein, diffusing capacity, inflammation, lung function, population-based studies

Several levels of evidence have consistently found significant association between markers of systemic inflammation and spirometric lung volumes [1–4]. Moreover, systemic inflammation as quantified by serum C-reactive protein (CRP) or fibrinogen is related to the longitudinal decline in spirometric lung volumes [2]. So far, the interrelationship between reduced lung volumes and inflammation remains poorly understood. CRP, as one of the most widely used serum markers of systemic inflammation, is associated with increased mortality and incidental adverse cardiovascular events independently of potential interfering factors [5]. Correspondingly, decreased lung volumes have also been shown to be consistently related to all causes of mortality [6, 7]. Thus, systemic inflammation has been discussed as one potential pathophysiological link between lung volumes and excess mortality [2].

Although the studies investigating the potential association of inflammation and lung volumes are numerous, each of these investigations had

limitations. First, some of these studies did not use high-sensitivity (hs)CRP and may have missed the influence of low-grade inflammation. Secondly, the majority of studies investigated pre-selected specific age decades, restricted either to young, middle-aged or elderly volunteers. Hence, none of these studies represented a general population. Thirdly, most studies are based on spirometric evaluations only and may be strongly biased by the volunteers' compliance.

In contrast to the evident association between lung volumes and inflammatory markers, investigations relating systemic inflammation to airflow limitation have shown controversial results. In general, diseases characterised by airflow limitation, such as chronic obstructive pulmonary disease (COPD), appear to be associated with systemic inflammation [8, 9]. Even if patients with COPD have increased CRP or fibrinogen compared with healthy controls, a continuous correlation between the level of inflammation and the extent of airflow limitation has not been

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shown and the relationship appears to be influenced by comorbidities, obesity and physical activity [9].

This investigation aimed to assess a potential link between low-grade systemic inflammation, quantified by hsCRP and fibrinogen, and lung function, based on a highly standardised setting within a population-based study representing a general population aged 25–85 yrs in the north-east of Germany: the Study of Health in Pomerania (SHIP). The main hypothesis to be investigated is that systemic inflammation, even within the low-grade range, is associated with airflow limitation, lung volumes and diffusing capacity, independently of potentially confounding factors, such as obesity, physical activity, cardiopulmonary diseases or smoking. In addition to spirometry, body plethysmography, helium dilution for measurement of alveolar volume and diffusing capacity of the lung for carbon monoxide (DL_{CO}) were applied to ensure additional physiological insight into the hypothesised link.

METHODS

Study population

The SHIP study is a population-based investigation in West Pomerania, a region in the north-eastern part of Germany. Study details are given elsewhere [10]. In brief, a sample from the population aged 20–79 yrs was drawn to be evaluated during baseline SHIP-0 from 1997 to 2001. Between March 2002 and September 2006, the 5-yr follow-up examinations (SHIP-1) were performed and comprised 3,300 participants (1,711 females). The study was reviewed by a board of independent scientists and approved by the Ethics Committee of the University of Greifswald (Greifswald, Germany). All participants provided written informed consent.

Blood samples to measure inflammatory markers were obtained during SHIP-0 and SHIP-1. Lung function examination, including body plethysmography and DL_{CO} , was offered to all participants and was performed on 1,809 individuals (885 males) during SHIP-1. The mean (range) time interval between core examination of SHIP-1 and lung function examination was 0.6 (0.0–2.5) months. Of these, we excluded 275 participants because of steroid intake or chronic use of nonsteroidal anti-rheumatics and 29 participants because of missing data. Levels of hsCRP $>10 \text{ mg}\cdot\text{L}^{-1}$, indicative of acute and active infection, systemic inflammatory processes or physical trauma, were defined as an additional exclusion criterion ($n=38$) [11]. In total, data from 1,466 participants were analysed.

Pre-exercise diagnostics

Sociodemographic and medical characteristics were assessed by computer-assisted personal interviews. Previous history of diseases was based on self-reported physician's diagnosis. According to tobacco consumption, participants were categorised into current (≥ 1 cigarettes·day⁻¹), former and nonsmokers. Data on medication were collected using the anatomical therapeutic chemical (ATC) code [12]. Height and weight were measured for the calculation of the body mass index (BMI; in $\text{kg}\cdot\text{m}^{-2}$). Waist circumference was measured to the nearest 0.1 cm using an inelastic tape midway between the lower rib margin and the iliac crest in the horizontal plane in standing position. The measurement was taken at the level of the narrowest part of the waist. Physical activity was assessed by standardised interview

(<2 or ≥ 2 h·week⁻¹). All interviews and measures were obtained at the time of lung function examination.

Blood sampling

For the laboratory examinations, nonfasting blood samples were drawn between 07:00 h and 16:00 h, during baseline examinations of SHIP-0 and SHIP-1. hsCRP was determined immunologically on a Behring Nephelometer II with commercially available reagents from Dade Behring (Dade Behring, Eschborn, Germany). Plasma fibrinogen concentrations were assayed according to the method of CLAUSS [13] using an Electra 1600 analyser (Instrumentation Laboratory, Barcelona, Spain).

To adjust DL_{CO} for the potential influence of blood haemoglobin levels, capillary blood from the ear lobe was drawn on the day of lung function testing. The capillary blood was collected in a 55- μL capillary (Clinitubes®; Radiometer, Copenhagen, Denmark) and immediately transferred to the blood gas and haemoglobin analyser (Radiometer ABL 510; Radiometer) to determine haemoglobin concentration.

Procedure and variables

The lung function examinations were conducted using a body plethysmograph equipped with a pneumotachograph (Master-Screen Body/Diff.; VIASYS Healthcare, JAEGER, Hoechst, Germany), which meets American Thoracic Society (ATS) criteria [14]. All calibrations and tests were carried out in the following order in accordance with European Respiratory Society (ERS) and ATS recommendations [15]: 1) static lung volume determination using variable-pressure body plethysmography; and 2) forced spirometry. The procedures were conducted with the subject in a sitting position and wearing a nose-clip. Pressure–flow and pressure–pressure diagrams were registered to obtain the specific and total airway resistance (R_{aw}). Functional residual capacity (FRC_{pleth}) was measured during expiration, breathing against a shutter near FRC. A series of gentle pants were obtained (three to five panting manoeuvres) against the shutter, followed by deep expiration to measure expiratory reserve volume (ERV) and inspiratory slow vital capacity (VC_{slow}). The residual volume (RV) was obtained by subtracting the ERV from the FRC_{pleth} . The total lung capacity (TLC) was computed from RV and VC_{slow} , and RV/TLC was calculated as a percentage. Forced spirometric manoeuvres were obtained to measure forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and the maximal expiratory flow at 75%, 50% and 25% of FVC ($MEF_{75\%}$, $MEF_{50\%}$ and $MEF_{25\%}$, respectively). At least three acceptable attempts at fulfilling reproducibility criteria for all variables according to the ATS/ERS guidelines were required (e.g. FRC variability $\leq 5\%$; R_{aw} variability $\leq 5\%$; FEV_1 , VC_{slow} and FVC variability $<150 \text{ mL}$) [15, 16].

After a break of ≥ 3 min, the assessment of DL_{CO} by a single-breath (SB) manoeuvre with CO was applied [17]. In parallel, alveolar volume (V_A) was measured using helium dilution [15]. DL_{CO} -SB was corrected for current haemoglobin (DL_{CO_c} -SB) and V_A (DL_{CO_c} - V_A).

Statistical analysis

Data on quantitative characteristics are expressed as median and interquartile range. Data on qualitative characteristics are expressed as percentages or absolute numbers, as indicated. Differences between males and females were tested by

Wilcoxon test for continuous data and by Chi-squared test for categorical data. Linear regression models were used to assess the association between inflammatory markers and pulmonary parameters. Fractional polynomials were applied to explore and graph nonlinear associations [18]. The dose–response relationship was found using fractional polynomials up to degree 2 with all possible combinations of powers selected from the set (-2, -1, -0.5, 0, 0.5, 1, 2, 3) and comparing them using the log likelihood to determine the best-fitting model. If none of the fractional polynomial models fitted the data significantly better than the linear model, linear regression was applied. All models were adjusted for age, sex, smoking status, BMI, heart failure (self-reported physician's diagnosis, echocardiographic evidence of left-ventricular or valvular dysfunction and/or in accordance with the Rotterdam Study heart failure definition (two-step approach, including the presence of shortness of breath at rest or on exertion, ankle oedema and pulmonary crepitations in addition to evidence of cardiac disease) [19]), COPD (self-reported physician's diagnosis), asthma (self-reported physician's diagnosis), and time between core and lung function examination. For sensitivity testing, BMI was substituted by waist circumference, height and weight. For additional sensitivity analyses, participants with the following were excluded: evidence of coronary artery disease (myocardial infarction, signs of ischaemia in ECG);

restrictive lung disease (TLC below the fifth percentile and FEV₁/VC_{slow} ratio above the fifth percentile); and airflow limitation (FEV₁/FVC and/or FEV₁/VC_{slow} ratios below the fifth percentile) [20, 21]. In addition, separate analyses were obtained for subjects with the following results below the fifth percentile: FEV₁/FVC and/or FEV₁/VC_{slow} ratios, TLC and DL_{CO_c}-VA. For this purpose, the reference equation for DL_{CO_c}-VA was assessed in accordance with the recommendations of the ERS [22]. Based on the methodology of lung function reference assessment within this population, the following reference equations were applied [21]:

$$DL_{CO_c}\text{-VA}_{(5th\ percentile)} = 1.6993 - (0.0074 \times \text{age}) + (0.0595 \times \text{sex}) - (0.001 \times \text{height})$$

$$TLC_{(5th\ percentile\ males)} = -11.2726 + (0.0027 \times \text{age}) + (0.0964 \times \text{height})$$

$$TLC_{(5th\ percentile\ females)} = -4.4949 + (0.0031 \times \text{age}) - (0.000045 \times \text{age}^2) + (0.0545 \times \text{height})$$

Height was expressed in cm, and for sex, males were given a value of 1, females 0. These reference equations were compared with those provided by QUANJER *et al.* [23] and COTES *et al.* [24].

As recommended for epidemiological studies with missing data, multiple imputations of missing data *via* chained equations

TABLE 1 Characteristics of the study population

	Males	Females	p-value [#]
Subjects n	752	714	
FVC mL	4531 (3880–5155)	3308 (2872–3768)	<0.001
FEV₁ mL	3847 (3244–4419)	2847 (2438–3260)	<0.001
FEV₁/FVC %	84.8 (80.4–88.2)	85.9 (82.4–89.1)	<0.001
MEF_{25%} L·s⁻¹	1.6 (1.2–2.2)	1.3 (1.0–1.8)	<0.001
MEF_{50%} L·s⁻¹	4.6 (3.6–5.6)	3.7 (3.0–4.5)	<0.001
MEF_{75%} L·s⁻¹	7.8 (6.7–9.0)	5.6 (4.8–6.5)	<0.001
R_{aw} kPa·s·L⁻¹	0.20 (0.15–0.24)	0.24 (0.19–0.30)	<0.001
TLC mL	7084 (6493–7867)	5470 (4980–5977)	<0.001
RV/TLC %	34.1 (28.5–40.5)	38.0 (31.9–43.6)	<0.001
DL_{CO_c}-VA mmol·kPa⁻¹·min⁻¹·L⁻¹	1.4 (1.3–1.6)	1.4 (1.3–1.6)	0.137
Age yrs	53.0 (41.0–63.0)	51.0 (41.0–61.0)	0.055
hsCRP mg·L⁻¹	1.08 (0.56–2.24)	1.26 (0.64–2.71)	0.003
Fibrinogen Clauss g·L⁻¹	2.84 (2.50–3.40)	3.08 (2.70–3.67)	<0.001
BMI kg·m⁻²	27.6 (25.4–30.5)	26.3 (23.6–30.0)	<0.001
Smoking status			
Former	336 (44.7)	131 (18.4)	<0.001
Current	176 (23.4)	139 (19.5)	
CHF	40 (5.3)	43 (6.0)	0.560
COPD	15 (1.9)	15 (2.1)	0.886
Physical activity[†]	320 (42.6)	337 (47.2)	0.074
Asthma	59 (7.7)	42 (5.7)	0.133
Time between core and pulmonary examination yrs	0.43 (0.00–2.50)	0.87 (0.00–2.53)	0.007

Data are presented as median (interquartile range) or n (%), unless otherwise stated. FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; MEF_{25%}, MEF_{50%} and MEF_{75%}: maximal expiratory flow at 25, 50 and 75% of FVC, respectively; R_{aw}: total airway resistance; TLC: total lung capacity; RV: residual volume; DL_{CO_c}-VA: diffusing capacity of the lung for carbon monoxide (single-breath), corrected for haemoglobin level and alveolar volume (assessed by helium dilution); hsCRP: high-sensitivity C-reactive protein; BMI: body mass index; CHF: congestive heart failure (self-reported physician's diagnosis); COPD: chronic obstructive pulmonary disease (self-reported physician's diagnosis). [#]: Wilcoxon test for continuous data and Chi-squared test for categorical data; [†]: subjects with physical activity for ≥2 h·week⁻¹.

were performed to reduce potential bias due to missing values in complete case analyses [25]. Imputations were performed by the imputation by chained equations (ICE) procedure with 20 runs [26]. In this imputation, parameters of lung function were predicted by age, sex, BMI, smoking status, chronic heart failure and physical activity. Afterwards, regression analyses were repeated using the imputed data.

Tests were considered statistically significant with a two-sided p-value of <0.05. All statistical analyses were performed using Stata 11.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Table 1 shows the characteristics of the study population stratified by sex. Compared with females, males had significantly higher values of FVC, FEV₁, FRC_{pleth} and TLC but lower values of FEV₁/FVC, *R*_{aw} and RV/TLC, while DL_{CO}-VA was comparable between sexes. Moreover, males were more often smokers and had a higher BMI, but had lower hsCRP and fibrinogen levels than females. The median (interquartile range) hsCRP was 1.17 (0.56–2.7) mg·L⁻¹ in non- and ex-smokers and 1.2 (0.6–2.49) mg·L⁻¹ in smokers. Increasing BMI was associated with increasing hsCRP levels (BMI <25 kg·m⁻²: 0.77 (0.4–1.7) mg·L⁻¹; BMI 25–30 kg·m⁻²: 1.15 (0.63–2.18) mg·L⁻¹; BMI >30 kg·m⁻²: 2.32 (1.14–4.87) mg·L⁻¹).

Comparing SHIP-0 and SHIP-1, a significant intercorrelation of both inflammatory markers was verified (Spearman correlation coefficients: hsCRP 0.62 and fibrinogen 0.69; both p<0.001).

To test for sex differences in the association between inflammatory markers and pulmonary variables, we added the interaction term between fibrinogen/hsCRP and sex to the fully adjusted models. These analyses revealed significant interaction terms for DL_{CO}-VA only. Consequently, regression analyses were performed in a sex-stratified manner for these variables, but not for the others.

Table 2 shows hsCRP and fibrinogen comparisons between subjects with normal and abnormal lung function (defined as central airflow limitation, lung volume restriction and DL_{CO} decrease). Subjects with central airflow limitation did not show different levels of hsCRP and fibrinogen, independent of the method of defining airflow limitation (FEV₁/FVC and/or FEV₁/VC_{slow} ratios below the fifth percentile (4.6% and 5.8% of the population, respectively)). The significant increase in hsCRP in subjects with DL_{CO}-VA below the fifth percentile was completely attributable to male smokers; the increase in fibrinogen was found in smokers of both sexes. Applying the reference equations formulated by QUANJER *et al.* [23] for TLC confirmed the results, whereas using the reference equations for DL_{CO} derived by COTES *et al.* [24] did not show statistical significance.

Table 3 shows the results of the multivariable regression analyses. In the entire population, hsCRP was significantly associated with FVC, FEV₁, MEF₂₅% and TLC, and fibrinogen was associated with FVC and FEV₁. Furthermore, hsCRP and fibrinogen were associated with DL_{CO}-VA in males; fibrinogen showed this association in females too (figs 1, 2 and 3). Data imputation confirmed associations of hsCRP with FEV₁, TLC and DL_{CO}-VA in males; for fibrinogen, association with DL_{CO}-VA was confirmed in both sexes.

TABLE 2 Comparison of subjects with and without restrictive lung disease, airflow limitation and diffusing abnormalities

	≥5th percentile [#]	<5th percentile [#]	p-value [†]
hsCRP mg·L⁻¹			
FVC	1.14 (0.59–2.49)	1.72 (0.75–3.75)	<0.001
FEV ₁ /FVC	1.21 (0.60–2.67)	1.63 (0.69–3.73)	0.132
FEV ₁ /VC _{slow}	1.23 (0.61–2.70)	1.02 (0.53–2.62)	0.446
TLC	1.18 (0.60–2.63)	1.99 (0.87–5.21)	<0.001
TLC [‡]	1.21 (0.60–2.66)	1.70 (0.83–4.07)	0.028
DL _{CO} -VA	1.18 (0.60–2.66)	1.47 (0.79–3.26)	0.025
Fibrinogen g·L⁻¹			
FVC	2.97 (2.59–3.50)	3.27 (2.80–3.89)	<0.001
FEV ₁ /FVC	3.00 (2.60–3.55)	3.25 (2.60–3.85)	0.062
FEV ₁ /VC _{slow}	3.00 (2.60–3.60)	2.81 (2.50–3.50)	0.192
TLC	3.00 (2.60–3.54)	3.20 (2.70–3.90)	0.050
TLC [‡]	3.00 (2.60–3.58)	3.11 (2.57–3.80)	0.527
DL _{CO} -VA	3.00 (2.60–3.51)	3.26 (2.63–4.00)	0.002

Data are presented as median (interquartile range), unless otherwise stated. hsCRP: high-sensitivity C-reactive protein; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; VC_{slow}: slow vital capacity; TLC: total lung capacity; DL_{CO}-VA: diffusing capacity of the lung for carbon monoxide (single-breath), corrected for haemoglobin level and alveolar volume (assessed by helium dilution). [#]: fifth percentiles defined by locally derived reference equations and by those from QUANJER *et al.* [23]; [†]: Wilcoxon test; [‡]: applying the reference equations from QUANJER *et al.* [23].

For sensitivity analysis, we excluded, in a stepwise manner, all participants with evidence of ischaemic heart disease (history of myocardial infarction, a pacemaker or electrocardiographic evidence of ischaemia), abnormal airflow limitation and restrictive lung disease. In this apparently healthy subgroup, no significant associations between lung volumes and inflammation were seen, independent of the applied reference equation for TLC. The stepwise exclusion revealed a major influence of TLC on the shown associations in the overall population. Substituting or adding height and/or weight and/or waist circumference did not alter the results substantially. In the subgroup of subjects with airflow limitation (FEV₁/FVC and/or FEV₁/VC_{slow} ratios below the fifth percentile), hsCRP was significantly associated with DL_{CO}-VA in males only (β=0.4, 95% CI 0.12–0.69; p<0.01), but no other associations were verifiable.

DISCUSSION

In terms of the hypothesis framing this study, systemic inflammation quantified by serum hsCRP and fibrinogen levels is not associated with the presence of airflow limitation in central airways, as inferred from FEV₁/FVC, FEV₁/VC_{slow} and *R*_{aw} in a general population. In adults aged 25–85 yrs, serum hsCRP is significantly associated with lung volumes as quantified by FEV₁ and TLC. In smokers only, DL_{CO} is associated with hsCRP and fibrinogen. These associations were independent of cardiorespiratory fitness, lung diseases, cardiac diseases, obesity and smoking and (based on data imputations) are representative of the general population.

TABLE 3 Associations between high-sensitivity C-reactive protein (hsCRP), fibrinogen and pulmonary variables

	Whole population [#]		Disease-free population [†]		Imputed data [‡]	
	Transformation [§]	β (95% CI)	Transformation [§]	β (95% CI)	Transformation [§]	β (95% CI)
FVC mL	log(hsCRP)	-56.91 (-91.74– -22.08)***	hsCRP ¹	-11.19 (-30.96–8.57)	log(hsCRP)	-42.98 (-87.84–1.88)
	Fibrinogen ¹	-60.08 (-109.03– -11.13)*	Fibrinogen ¹	-36.14 (-94.25–21.97)	Fibrinogen ¹	-43.74 (-111.28–23.81)
FEV₁ mL	log(hsCRP)	-60.28 (-90.92– -29.64)***	hsCRP ¹	-9.98 (-26.64–6.69)	log(hsCRP)	-43.66 (-82.98– -4.34)*
	Fibrinogen ¹	-56.72 (-99.90– -13.56)*	Fibrinogen ¹	-27.42 (-76.44–21.59)	Fibrinogen ¹	-39.63 (-98.87–19.60)
FEV₁/FVC %	hsCRP ¹	-0.10 (-0.26–0.07)	hsCRP ⁻¹	0.24 (-0.01–0.49)	hsCRP ¹	-0.07 (-0.29–0.15)
	Fibrinogen ¹	-0.11 (-0.60–0.38)	Fibrinogen ¹	0.18 (-0.32–0.69)	Fibrinogen ¹	-0.03 (-0.52–0.47)
FEV₁/VC_{slow}	hsCRP ¹	-0.00 (-0.00–0.00)	hsCRP ¹	-0.00 (-0.00–0.00)	hsCRP ¹	-0.00 (-0.00–0.00)
	Fibrinogen ¹	-0.00 (-0.01–0.00)	Fibrinogen ¹	-0.00 (-0.00–0.01)	Fibrinogen ¹	-0.00 (-0.01–0.00)
MEF_{25%} L·s⁻¹	hsCRP ¹	0.09 (0.03–0.15)*	hsCRP ^{-0.5}	0.07 (-0.00–0.14)	hsCRP ¹	0.05 (-0.02–0.13)
	Fibrinogen ¹	-0.03 (-0.07–0.02)	Fibrinogen ¹	-0.00 (-0.06–0.05)	Fibrinogen ¹	-0.01 (-0.06–0.04)
MEF_{50%} L·s⁻¹	hsCRP ¹	-0.02 (-0.05–0.01)	hsCRP ¹	-0.00 (-0.04–0.04)	hsCRP ¹	0.00 (-0.03–0.04)
	Fibrinogen ¹	-0.07 (-0.16–0.03)	Fibrinogen ¹	-0.00 (-0.11–0.11)	Fibrinogen ¹	-0.03 (-0.14–0.07)
MEF_{75%} L·s⁻¹	hsCRP ^{-0.5}	-0.03 (-0.07–0.01)	hsCRP ¹	-0.01 (-0.05–0.03)	hsCRP ^{-0.5}	-0.01 (-0.05–0.04)
	Fibrinogen ¹	-0.03 (-0.07–0.02)	Fibrinogen ¹	-0.07 (-0.20–0.06)	Fibrinogen ¹	-0.05 (-0.18–0.09)
FRC_{pleth} mL	hsCRP ¹	-0.00 (-0.01–0.01)	hsCRP ¹	-0.00 (-0.03–0.02)	hsCRP ¹	-0.00 (-0.01–0.01)
	Fibrinogen ¹	-0.00 (-0.06–0.06)	Fibrinogen ¹	-0.01 (-0.08–0.07)	Fibrinogen ¹	-0.01 (-0.09–0.07)
Raw kPa·s·L⁻¹	hsCRP ¹	0.00 (-0.00–0.00)	hsCRP ¹	-0.00 (-0.00–0.00)	hsCRP ¹	0.00 (-0.00–0.00)
	Fibrinogen ¹	0.00 (-0.00–0.01)	Fibrinogen ¹	-0.00 (-0.01–0.01)	Fibrinogen ¹	0.00 (-0.01–0.01)
TLC mL	hsCRP ³	-0.59 (-0.95– -0.24)*	hsCRP ¹	-24.85 (-52.98–3.28)	hsCRP ³	-0.42 (-0.80– -0.05)*
	Fibrinogen ¹	-52.10 (-125.26–21.07)	Fibrinogen ¹	-40.78 (-123.62–42.06)	Fibrinogen ¹	-53.84 (-141.19–33.52)
RV/TLC %	hsCRP ¹	-0.01 (-0.20–0.18)	hsCRP ¹	-0.07 (-0.28–0.13)	hsCRP ¹	-0.15 (-0.35–0.04)
	Fibrinogen ¹	0.52 (-0.04–1.07)	Fibrinogen ¹	0.22 (-0.38–0.83)	Fibrinogen ¹	0.34 (-0.27–0.95)
DL_{CO}-VA males	log(hsCRP)	-0.06 (-0.09– -0.04)***	hsCRP ¹	-0.01 (-0.03–0.00)	log(hsCRP)	-0.05 (-0.07– -0.02)***
	Fibrinogen ¹	-0.05 (-0.09– -0.02)*	Fibrinogen ¹	-0.03 (-0.08–0.01)	Fibrinogen ¹	-0.05 (-0.09– -0.02)*
DL_{CO}-VA females	hsCRP ¹	-0.00 (-0.01–0.01)	hsCRP ¹	-0.00 (-0.02–0.01)	hsCRP ¹	-0.01 (-0.02–0.00)
	Fibrinogen ¹	-0.04 (-0.08– -0.01)*	Fibrinogen ¹	-0.02 (-0.06–0.02)	Fibrinogen ¹	-0.05 (-0.09– -0.01)*

Linear regression using fractional polynomials for hsCRP and fibrinogen adjusted for age, sex, body mass index, physical activity (cut-off ≥ 2 h·week⁻¹), chronic obstructive pulmonary disease, asthma, former and current smoking, congestive heart failure, and time between core and pulmonary examination. FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 s; VC_{slow}: slow vital capacity; MEF_{25%}, MEF_{50%} and MEF_{75%}: maximal expiratory flow at 25, 50 and 75% of FVC, respectively; FRC_{pleth}: functional residual capacity measured by body plethysmography; Raw: total airway resistance; TLC: total lung capacity; RV: residual volume; DL_{CO}-VA: diffusing capacity of the lung for carbon monoxide (single-breath), corrected for haemoglobin level and alveolar volume (assessed by helium dilution). #: n=1,466; †: n=1,031; ‡: n=2,689; §: transformation of the exposure variable (hsCRP or fibrinogen) used. *: p<0.05; ***: p<0.001.

Our study further strengthens previously described associations of inflammatory markers and lung volumes [1–4]. Available evidence clearly shows associations of spirometrically assessable and, thus, mobile lung volumes. Both FEV₁ and FVC may be influenced by at least three mechanisms: airflow limitation, anatomical lung volume and respiratory muscle function [27]. Our study adds information from body plethysmographic and, thus, partly immobile and anatomically determined lung volumes. TLC, a reliable measure of lung size, is strongly associated with hsCRP. The strongest association of systemic inflammation with lung volumes and airflow restriction in the peripheral airways (FEV₁, FVC, MEF_{25%}) is shown for hsCRP at levels <3 mg·L⁻¹, while the FEV₁/FVC ratio, a measure of more central airflow limitation, is unaffected. Effects on TLC were detected at higher hsCRP levels. In contrast, associations of fibrinogen with FVC and FEV₁ showed a proportional decline over the full range of fibrinogen levels, even if these associations were not confirmed by imputed data

and may not be representative of the overall population. The described differences between hsCRP and fibrinogen associations may potentially be explained by differences in course and level of inflammatory responses. In contrast to fibrinogen, hsCRP is generally accepted to more rapidly adjust to inflammatory stimuli. Furthermore, CRP in its high-sensitivity determination potentially describes inflammation in the very low-grade range. Scientific evidence suggests some impact of cardiorespiratory fitness and BMI on the degree of systemic inflammation [9, 28]. However, even after adjusting for these potential influencing factors, associations between inflammatory markers and lung volumes remained. Thus, it is likely that systemic inflammation may influence lung volumes independently of these important confounders. Both lung volumes and hsCRP levels underlie genetic variants and pleiotropic effects and potential interactions may be possible [29, 30]. As a potential result, one may postulate that other factors, such as fetal and postnatal growth, may influence the potency of

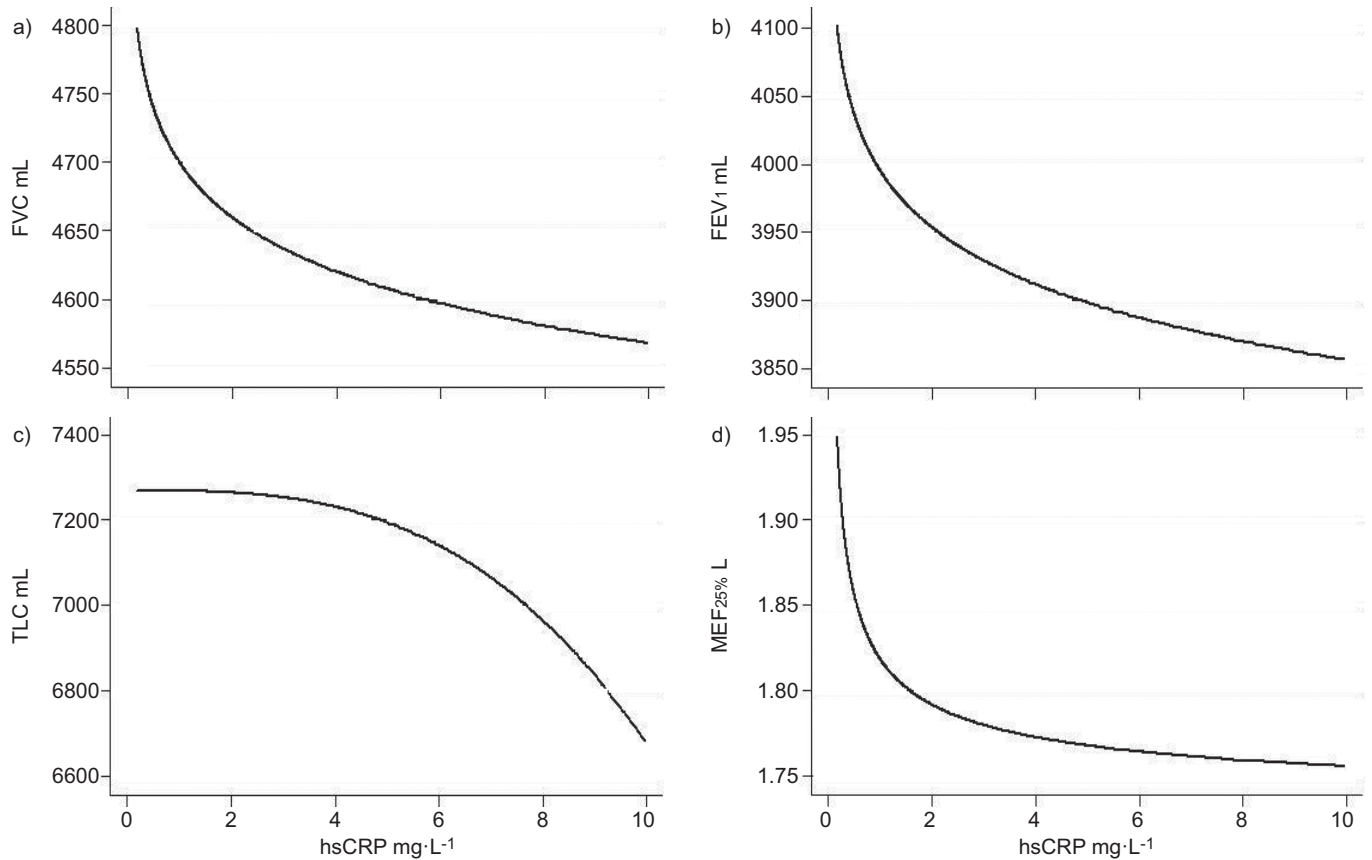


FIGURE 1. Significant associations between high-sensitivity C-reactive protein (hsCRP) and pulmonary variables in the overall population. a) Forced vital capacity (FVC), b) forced expiratory volume in 1 s (FEV₁), c) total lung capacity (TLC) and d) maximal expiratory flow at 25% of FVC (MEF_{25%}).

inflammatory responses, as well as affecting lung function development. This hypothesis is supported by the inverse association between birth weight and systemic inflammation [31], as well as by the association of low birth weight with

impaired lung volumes in adulthood [32]. However, this hypothesis has not yet been tested in a longitudinal observation.

Besides pulmonary anatomical structure and respiratory muscle strength, forced expiratory lung volumes are restricted by airflow limitation. Associations of inflammation with airflow limitation have been shown in selected populations suffering from COPD [8, 9]. Moreover, MELBYE *et al.* [33] reported significant associations between the degree of airflow limitation and blood CRP levels in a population sample of individuals aged ≥ 60 yrs. With respect to airflow limitation in central airways, these data contrast with our results. Neither subjects with impaired more central airflow limitation defined by a FEV₁/FVC or FEV₁/VC_{slow} ratio below the fifth percentile, nor healthy individuals, revealed any association between inflammation and airflow limitation (defined by FEV₁/FVC or FEV₁/VC_{slow} ratio and airway resistance). Correspondingly, pulmonary hyperinflation defined by the relation of RV to TLC was not associated with inflammatory markers. Interestingly, we found significant associations of MEF_{25%} and low-grade inflammation quantified by hsCRP. Even if this is small evidence, MEF_{25%} possibly reflects peripheral airway disease rather than central airflow limitation [34]. Thus, some influence of systemic inflammation on small airway function may be postulated, while central airways seem to be little affected. However, this association did not show robustness after data imputation and may not be representative for the overall SHIP population.

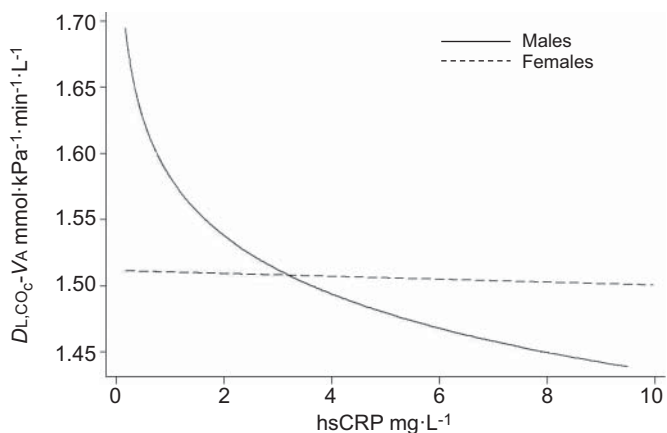


FIGURE 2. Significant associations between high-sensitivity C-reactive protein (hsCRP) and diffusing capacity of the lung for carbon monoxide (single-breath), corrected for haemoglobin level and alveolar volume (assessed by helium dilution) (DL_{c,CO_c}-VA), in the overall population. For this variable, hsCRP was significantly associated in males only.

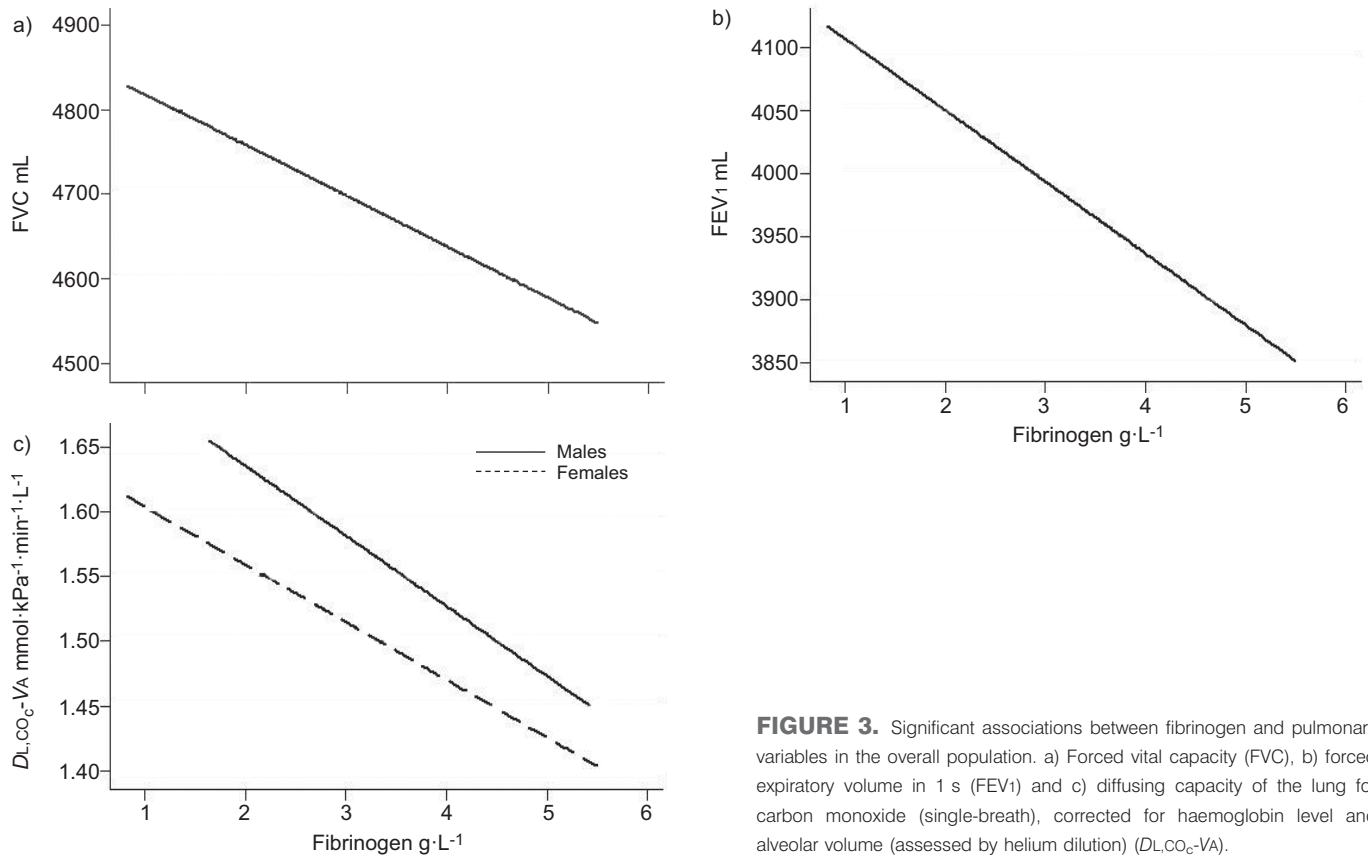


FIGURE 3. Significant associations between fibrinogen and pulmonary variables in the overall population. a) Forced vital capacity (FVC), b) forced expiratory volume in 1 s (FEV₁) and c) diffusing capacity of the lung for carbon monoxide (single-breath), corrected for haemoglobin level and alveolar volume (assessed by helium dilution) (DL_{CO_c-VA}).

In comparison with previously published data, this study applies more accurate definitions of airflow limitation. As a potential measure of lung ageing, the FEV₁/FVC ratio is substantially affected by age, resulting in an overestimation of airflow limitation in elderly individuals [35]. In addition, we applied the FEV₁/VC_{slow} ratio, as suggested by national authorities, resulting in a higher proportion of subjects with airflow limitation [36]. Thus, we assume that applying a more accurate definition of airflow limitation based on adjusted lower limits of normalcy and airway resistance is of substantial importance.

In smokers only, hsCRP and fibrinogen are significantly associated with DL_{CO} , suggesting a smoking-specific interaction. DL_{CO} is mainly affected by membrane and pulmonary vascular contributions [17]. In addition, ventilation–volume inhomogeneities [37] and ventilation–perfusion mismatching potentially affects DL_{CO} [38]. The reasons behind the links between smoking, inflammation and impaired DL_{CO} may be given by the observation that, predominantly, perfusion heterogeneity and low-grade airflow obstruction are observed in early stages of COPD, suggesting that in smokers, the smallest airways, parenchyma and pulmonary vessels are affected initially [38]. Moreover, there is scientific evidence that smoking will induce endothelial dysfunction in pulmonary vessels, resulting in pulmonary vasoconstriction and decreased pulmonary blood volume [39]. To what extent one or more of these pathophysiological mechanisms may contribute to the described associations remains unclear. None of the associations focused on DL_{CO} could be confirmed by applying previously published

reference equations [24]. Even if this study was neither designed nor powered to clarify this hypothesis, this further underlines the proposed ERS recommendation of applying regionally derived reference equations [22].

The major strengths of this study are: the population-based approach representing a general adult population; the highly standardised fashion of obtaining lung function, including body plethysmography and DL_{CO} ; and the adjustment for potential interfering factors. This study may be criticised for having a potential selection bias, but such a bias is almost inevitable in large-scale population-based studies. However, as the collected values were adjusted for numerous interfering factors, the differences between the general German population, the entire SHIP population and the lung function participants should be negligible. In addition, to minimise a potential recruitment bias, all associations have been re-assessed by imputed data. Based on data imputation, associations of hsCRP and lung volumes (FEV₁ and TLC) and DL_{CO} in males remained representative of the overall population; the same was the case for the fibrinogen– DL_{CO} interaction. However, as usual in cross-sectional population-based investigations, all measures are based on an assessment at a single point in time. The basic principle of the study is not designed to discover pathophysiological mechanisms. For example, it remains impossible to prove to what extent lung function affects inflammation or *vice versa*. Furthermore, there are likely to be additional factors interfering with inflammation and lung function that were possibly not measured. However, according to previously published literature, known

interfering factors for both lung function and inflammation have been included in the analyses [28].

Conclusion

In conclusion, a significant association of hsCRP as a surrogate of systemic inflammation and lung volumes in a general population has been identified, independently of obesity, age, sex, fitness or smoking. Central airflow limitation is not associated with systemic inflammation after adjustment for potential interfering factors, while peripheral lung structures may be involved. Further studies are needed to investigate the interaction of smoking, DLCO and inflammation.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

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