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

Short running title: Lung function and inflammation

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Abstract

Although several levels of evidence suggested an association of 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-sensitive C-reactive protein, fibrinogen and lung function were investigated in 1466 individuals, aged 25 – 85 years, representing a general population. Within this cross-sectional population based study data on bodyplethysmography, spirometry, helium dilution and diffusing capacity for carbon monoxide were analyzed.

After adjustment for potential confounding factors such as smoking, obesity and cardiorespiratory fitness, there was an inverse association of high-sensitive C-reactive protein with forced expiratory and static lung volumes. Neither in apparently healthy nor in the entire population inflammation was associated with airflow limitation in central airways. In smokers only, higher high-sensitive C-reactive protein and fibrinogen were associated with an impaired diffusing capacity.

This study shows that higher levels of high-sensitive C-reactive protein 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 diffusing capacity in association to an increase in systemic inflammation.

Introduction

Several levels of evidence have consistently found significant associations of markers of systemic inflammation and spirometric lung volumes [1-4]. Moreover, systemic inflammation as quantified by serum C-reactive protein (CRP) or fibrinogen are related to the longitudinal decline in spirometric lung volumes [2]. So far, the interrelationship between reduced lung volumes and inflammation remains poorly understood. C-reactive protein, 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-cause 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 apply high-sensitivity CRP (hsCRP) and may have missed the influence of low-grade inflammation. Second, the majority of studies investigated pre-selected specific age decades, restricted either to young, middle-aged or elderly volunteers. Hence, none of these studies did represent a general population. Third, the majority of studies is based on spirometric evaluations only and may be strongly biased by 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 characterized by airflow limitation such as chronic obstructive pulmonary disease (COPD) appear to be associated with

systemic inflammation [8, 9]. Even if patients with COPD may have increased CRP or fibrinogen than healthy controls, a continuous correlation between the level of inflammation and the extent of airflow limitation has not been shown and appears to be influenced by co-morbidities, obesity and physical activity [9].

This investigation aims to assess a potential link between low-grade systemic inflammation quantified by hsCRP and fibrinogen with lung function based on a highly standardized setting within a population based study representing a general population aged 25 to 85 years 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, bodyplethysmography, helium dilution for measurement of alveolar volume and diffusing capacity measurement for carbon monoxide were applied to assure additional physiological insight into the hypothesized link.

Methods

Study population

The Study of Health in Pomerania (SHIP) 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 years was drawn to be evaluated during baseline SHIP-0 from 1997 to 2001. Between March 2002 and September 2006, the 5-year follow-up examinations (SHIP-1) were performed and comprised 3300 participants (1711 women). The study was reviewed by a board of independent scientists and approved by the Ethics Committee of the University of Greifswald. All participants provided written informed consent.

Blood samples to measure inflammatory markers were obtained during SHIP-0 and SHIP-1. Lung function examination including bodyplethysmography and diffusing capacity measurement for carbon monoxide was offered to all participants and was performed on 1809 individuals (885 males) during SHIP-1. The mean time interval between core examination of SHIP-1 and lung function examination was 0.6 months (range 0.0; 2.5 months). Of these we excluded 275 participants because of steroid intake or chronic use of non-steroidal anti rheumatics and 29 participants because of missing data. Levels of hsCRP >10 mg/L indicative for acute and active infection, systemic inflammatory processes or physical trauma were defined as additional exclusion criterion (n=38) [11]. In total data of 1466 participants were analyzed.

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 categorized into current (one or more cigarettes per day), former, and non-smokers. 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 = body weight (kg) / height^2 (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 standardized interview (no or less 2h per week or ≥ 2 h per week). All interviews and measures were obtained at the time of lung function examination.

Blood sampling

For the laboratory examinations, non-fasting blood samples were drawn between 07:00 a.m. and 04:00 p.m. during baseline examinations of SHIP-0 and SHIP-1. High-sensitive CRP 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 Clauss using an Electra 1600 analyzer (Instrumentation Laboratory, Barcelona, Spain).

To adjust diffusing capacity for the potential influence of blood hemoglobin levels, capillary blood from the ear lobe was drawn at the day of lung function. The capillary blood was collected in a 55 µl capillary (Clinitubes ®, Radiometer, Copenhagen, Denmark) and immediately transferred to the blood gas and hemoglobin analyzer (Radiometer ABL 510, Radiometer, Copenhagen, Denmark) to determine hemoglobin concentration.

Procedure and variables

The lung function examinations were conducted using a bodyplethysmograph equipped with a pneumotachograph (VIASYS Healthcare, MasterScreen Body/Diff., JAEGER, Hoechberg, Germany) which meets the American Thoracic Society (ATS) criteria [13]. All calibrations and tests were carried out in the following order in accordance to European Respiratory Society (ERS) and ATS recommendations [14]: (1) static lung volumes determination using a variable pressure bodyplethysmography and (2) forced spirometry. The procedures were conducted in a sitting position and with wearing a nose clip. Pressure-flow diagrams and pressure-pressure diagrams were registered to obtain the specific airway resistance (sRtot) and total airway resistance (Rtot). Functional residual capacity (FRC_{pleth}) was measured during expiration, breathing against a shutter near FRC. A series of gentle pants were obtained (3 – 5 panting manoeuvres) against the shutter, followed by

deep expiration to measure expiratory reserve volume (ERV) and inspiratory vital capacity ($_{slow}$VC) measurement. 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 and RV/TLC (%) calculated. Forced spirometric manoeuvres were obtained to measure forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and the expiratory flow at 75, 50 and 25% of FVC (MEF75, 50, 25, respectively). At least 3 acceptable attempts fulfilling reproducibility criteria for all variables according to the ATS-ERS guidelines were required (e.g. FRC variability ≤5%; RAW variability ≤5%; FEV1, $_{slow}$VC and FVC variability <150 ml) [14, 15].

After a break of at least 3 minutes the assessment of diffusing capacity by a single breath manoeuvre with carbon monoxide (CO) was applied [16]. In parallel, alveolar volume (VA) using Helium dilution was measured [14]. TLCO-SB was corrected for current haemoglobin (TLCOc-SB) and VA (TLCOc-VA).

Statistical analysis

Data on quantitative characteristics are expressed as median and inter-quartile range. Data on qualitative characteristics are expressed as percent values or absolute numbers, as indicated. Differences between males and females were tested by Wilcoxon test for continuous data and by χ2 test for categorical data. Linear regression models were performed to assess the association between inflammatory markers and pulmonary parameters. Fractional polynomials were applied to explore and graph nonlinear associations [17]. The dose-response relation 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 compare them using the log

likelihood to determine the best-fitting model. If none of the fractional polynomials 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 physicians diagnosis, echocardiographic evidence of left ventricular or valvular dysfunction and/or in accordance to 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) [18], chronic obstructive pulmonary disease (self reported physicians diagnosis), asthma (self reported physicians 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 the following participants were excluded: evidence of coronary artery disease (myocardial infarction, signs of ischemia in ECG); restrictive lung disease (TLC below the 5th percentile and FEV1/VC ratio above the 5th percentile); airflow limitation (FEV1/FVC and/or FEV1/$_{slow}$VC ratio below the 5th percentile) [19, 20]. In addition, separate analyses were obtained for the following subjects with results below the 5th percentile: FEV1/FVC and/or FEV1/$_{slow}$VC ratio, TLC and TLCOc-VA. For this purpose, reference equation for TLCOc-VA has been assessed in accordance to the recommendations of the ERS [21]. Based on the methodology of lung function reference assessment within this population, the following reference equations had been applied [20]:

$$TLCOc\text{-}VA_{(5th\ percentile)} = 1.6993 - 0.0074 \times age + 0.0595 \times sex^{(1=males;0=females)} - 0.001 \times height^{(cm)}.\ TLC_{(5th\ percentile\ males)} = -11.2726 + 0.0027 \times age + 0.0964 \times height$$

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

These reference equations had been compared to those provided by Quanjer [22] and Cotes [23].

As recommended for epidemiological studies with missing data, multiple imputations of missing data via chained equations were performed to reduce potential bias due to missing values in complete case analyses [24]. Imputations were performed by the ice procedure with 20 runs [25]. In this imputation parameters of lung function were predicted by age, sex, body mass index, smoking status, chronic heart failure and physical activity. Afterwards regressions analyses were repeated using the imputed data.

Tests were considered statistically significant at a two-sided p<0.05. All statistical analyses were performed using Stata 11.0 (Stata Corporation, College Station, TX, U.S.A.).

Results

Table 1 shows the characteristics of the study population stratified by sex. Compared to females, males had significantly higher values of FVC, FEV1, FRC_{pleth} and TLC but lower values of FEV1/FVC, Rtot and RV/TLC while TLCOc-VA was comparable between sexes. Moreover males were more often smokers, had a higher BMI, but lower hsCRP and fibrinogen levels than females. Mean hsCRP was 1.17 mg/L (0.56; 2.7) in non- and ex-smokers and 1.2 in smokers (0.6; 2.49). Increasing BMI was

associated with increasing mean hsCRP levels [BMI <25 kg/m^2 0.77 mg/L (0.4; 1.7); 25 – 30 kg/m^2 1.15 (0.63; 2.18); >30 kg/m^2 2.32 (1.14; 4.87)].

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

To test for sex differences on 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 TLCOc-VA only. Consequently, regression analyses were performed sex-stratified for these variables, but not for the other ones.

Table 2 shows hsCRP and fibrinogen comparisons between subjects with normal and abnormal lung function defined as central airflow limitation, lung volume restriction and diffusing capacity. Subjects with central airflow limitation did not show different levels of hsCRP and fibrinogen, independent of the way of defining airflow limitation [FEV1/FVC ratio < 5^{th} percentile (4.6% of the population) and/or $FEV1/_{slow}VC$ ratio < 5^{th} percentile (5.8%)]. The significant increase of hsCRP in subjects with TLCOc-VA below the 5^{th} percentile was completely attributable to male smokers, the one in fibrinogen in smokers of both sexes. Applying Quanjer's reference equations for TLC did confirm the results, whereas using reference equations for TLCO derived by Cotes 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, fibrinogen was associated with FVC and FEV1. Furthermore, hsCRP and fibrinogen were associated with TLCOc-VA in males; fibrinogen showed this association in females, too (figures 1, 2 and 3). Data imputation confirmed associations of hsCRP

to FEV1, TLC and TLCOc-VA in men (concerning fibrinogen TLCOc-VA in both sexes were confirmed).

For sensitivity analysis we furthermore step wisely excluded all participants with evidence of ischemic heart disease [history of myocardial infarction, pacemaker, electrocardiographic evidence of ischemia], abnormal airflow limitation and restrictive lung disease. In this apparently healthy subgroup, no significant associations between lung volumes and inflammation were seen, independent by 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 ratio < 5^{th} percentile and/or $FEV1/_{slow}VC$ ratio < 5^{th} percentile] hsCRP was significantly associated with TLCOc-VA in men 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, $FEV1/_{slow}VC$ and Rtot in a general population. In adults aged 25 to 85 years serum hsCRP is significantly associated with lung volumes as quantified by FEV1 and TLC. In smokers only, diffusing capacity 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 for a general population.

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 [26]. Our study adds information from bodyplethysmographic and, thus, partly immobile and anatomically determined lung volumes. Total lung capacity as a reliable measure of lung size is strongly associated with hsCRP. The strongest association of systemic inflammation with lung volumes and airflow restriction at peripheral airways (FEV1, FVC, MEF25) is shown for hsCRP levels at levels below 3 mg/l - leaving FEV1/FVC ratio as a measure of more central airflow limitation unaffected. Effects on TLC were detected at higher hsCRP levels. In contrast, associations of fibrinogen to 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 for 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 as more rapidly adjusting 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, 27]. 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 underlay genetic variants and pleiotropic effects and potential interactions may be possible [28, 29]. As a potential result, one may postulate that other factors such as fetal and postnatal growth may

influence the potency of inflammatory responses, as well as they may affect lung function development. This hypothesis is supported by the inverse association between birth weight and systemic inflammation [30] as well as by the association of low birth weight with impaired lung volumes in adulthood [31]. However, this hypothesis has not been tested in a longitudinal observation yet.

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. reported significant associations between the degree of airflow limitation and blood CRP levels in a population sample of individuals aged 60 years and older [32]. With respect to airflow limitation in central airways these data are contrasted by our results. Neither subjects with impaired more central airflow limitation defined by a FEV1/FVC or $FEV1/_{slow}VC$ ratio below the 5^{th} percentile, nor healthy individuals revealed any association between inflammation and airflow limitation (defined by FEV1/FVC or $FEV1/_{slow}VC$ ratio and airway resistance). Correspondingly, pulmonary hyperinflation defined by the relation of residual volume to total lung capacity was not associated with inflammatory markers. Interestingly, we found significant associations of MEF25 and low-grade inflammation quantified by hsCRP. Even if of small evidence, MEF25 possibly reflects peripheral airway disease rather than central airflow limitation [33]. 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.

In comparison to previously published data this study applies more accurate definitions of airflow limitation. As a potential measure of lung aging, FEV1/FVC ratio is substantially impacted by age, resulting in an overestimation of airflow limitation in

elderly individuals [34]. In addition, we applied $FEV1/_{slow}VC$ ratio as suggested by national authorities as well, resulting in a higher proportion of subjects with airflow limitation [35]. 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 diffusing capacity suggesting a smoking specific interaction. Diffusing capacity for carbon monoxide is mainly impacted by membrane and pulmonary vascular contributions [16]. In addition, ventilation-volume inhomogeneities [36] and ventilation perfusion mismatching potentially impacts diffusing capacity [37]. The reasons behind smoking, inflammation and impaired diffusing capacity may be given by the observation, that predominantly perfusion heterogeneity and low grade airflow obstruction is observed in early stages of COPD, suggesting that in smokers initially the smallest airways, parenchyma, and pulmonary vessels are affected [37]. Moreover, there is scientific evidence that smoking will induce endothelial dysfunction in pulmonary vessels, resulting in pulmonary vasoconstriction and decreased pulmonary blood volume [38]. To what extent one or more of these pathophysiological mechanisms may contribute to the described associations remains unclear. All association focusing TLCO could not be confirmed by applying previously published reference equations [23]. Even if this study was neither designed nor powered to clarify this hypothesis this further underlines the proposed ERS recommendation to apply regionally derived reference equations [21].

The major strengths of this study are: the population based approach representing a general adult population; the highly standardized fashion in obtaining lung function including bodyplethysmography and diffusing capacity and the adjustment for potential interfering factors. This study may be criticized 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 minimize 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 diffusing capacity in males remained representative for the overall population; the same belonged to the fibrinogen diffusing capacity interaction. However, as usual in cross sectional population based investigations, all measures are based on a single point in time assessment. The basic principle of the study is not designed to answer pathophysiological mechanisms. For example, it remains impossible to proof to what extent lung function impacts inflammation or the other way around. Furthermore, there are likely to be additional factors interfering with inflammation and lung function that were possibly not measured. However, according to previous literature known interfering factors on both, lung function and inflammation, have been included in the analyses [27].

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, diffusing capacity and inflammation.

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Disclosures

All authors state to have nothing to disclose.

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Tables:

Table 1. Characteristics of the study population

	Men (n=752)	Women (n=714)	p*
FVC in ml	4531 (3880; 5155)	3308 (2872; 3768)	<0.001
FEV1 in ml	3847 (3244; 4419)	2847 (2438; 3260)	<0.001
FEV1/FVC in %	84.8 (80.4; 88.2)	85.9 (82.4; 89.1)	<0.001
MEF25	1.6 (1.2; 2.2)	1.3 (1.0; 1.8)	<0.001
MEF50	4.6 (3.6; 5.6)	3.7 (3.0; 4.5)	<0.001
MEF75	7.8 (6.7; 9.0)	5.6 (4.8; 6.5)	<0.001
Rtot in kPa/s * l	0.20 (0.15; 0.24)	0.24 (0.19; 0.30)	<0.001
TLC in ml	7084 (6493; 7867)	5470 (4980; 5977)	<0.001
RV/TLC in %	34.1 (28.5; 40.5)	38.0 (31.9; 43.6)	<0.001
TLCOc-VA in mmol/kPa/min/l	1.4 (1.3; 1.6)	1.4 (1.3; 1.6)	0.137
Age in years	53.0 (41.0; 63.0)	51.0 (41.0; 61.0)	0.055
highsensitive CRP in mg/L	1.08 (0.56; 2.24)	1.26 (0.64; 2.71)	0.003
Fibrinogen Clauss in g/L	2.84 (2.50; 3.40)	3.08 (2.70; 3.67)	<0.001
Body mass index in kg/m^2	27.6 (25.4; 30.5)	26.3 (23.6; 30.0)	<0.001
Smoking Status			

- former smoker	336 (44.7%)	131 (18.4%)	<.001
- current smoker	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 in years	0.43 (0.00; 2.50)	0.87 (0.00; 2.53)	0.007

Data are given as numbers (percentage) or median (25^{th} and 75^{th} percentile). Physical activity is given as percentage of subjects with sportive activity of ≥ 2 hours per week.
* Wilcoxon test for continuous data and χ^2 test for categorical data.
FVC-forced vital capacity; FEV1-forced expiratory volume in one second; Rtot-total airway resistance; MEF – maximal expiratory flow at 75, 50 and 25% of FVC; TLC-total lung capacity; RV/TLC-residual volume to total lung capacity ratio; TLCOc-VA-diffusing capacity for carbon monoxide (single breath), corrected for hemoglobin level and ventilated area (assessed by Helium dilution); CRP-C-reactive protein; CHF-congestive heart failure (patients reported physicians diagnosis); COPD-chronic obstructive pulmonary disease (patients reported physicians diagnosis).

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

	≥ 5th percentile	< 5th percentile	p*
	hsCRP		
FVC	1.14 (0.59; 2.49)	1.72 (0.75; 3.75)	<0.001
FEV1/FVC	1.21 (0.60; 2.67)	1.63 (0.69; 3.73)	0.132
FEV1/$_{slow}$VC	1.23 (0.61; 2.70)	1.02 (0.53; 2.62)	0.446
TLC in ml	1.18 (0.60; 2.63)	1.99 (0.87; 5.21)	<0.001
TLC in ml (Quanjer)	1.21 (0.60; 2.66)	1.70 (0.83; 4.07)	0.028
TLCOc/VA	1.18 (0.60; 2.66)	1.47 (0.79; 3.26)	0.025
	Fibrinogen		
FVC	2.97 (2.59; 3.50)	3.27 (2.80; 3.89)	<0.001
FEV1/FVC	3.00 (2.60; 3.55)	3.25 (2.60; 3.85)	0.062
FEV1/$_{slow}$VC	3.00 (2.60; 3.60)	2.81 (2.50; 3.50)	0.192
TLC in ml	3.00 (2.60; 3.54)	3.20 (2.70; 3.90)	0.050
TLC in ml (Quanjer)	3.00 (2.60; 3.58)	3.11 (2.57; 3.80)	0.527
TLCOc/VA	3.00 (2.60; 3.51)	3.26 (2.63; 4.00)	0.002

Values are given as median (25th; 75th percentile). 5th percentile defined by locally derived reference equations and by those provided by Quanjer [22]; *p by Wilcoxon test.
FVC-forced vital capacity; FEV1-forced expiratory volume in one second; TLCOc-VA-diffusing capacity for carbon monoxide (single breath), corrected for hemoglobin level and ventilated area (assessed by Helium dilution); hsCRP – high sensitive C-reacting protein.

Table 3. Associations between hsCRP, fibrinogen and pulmonary variables

	Whole population (n=1466)		Disease-free population (n=1031)		Imputed data (n=2689)	
	Transformation	β (95%-CI)	Transformation	β (95%-CI)	Transformation	β (95%-CI)
FVC in 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 in 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 in %	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)
$FEV1/_{slow}VC$	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)
MEF25 in l/sec	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)

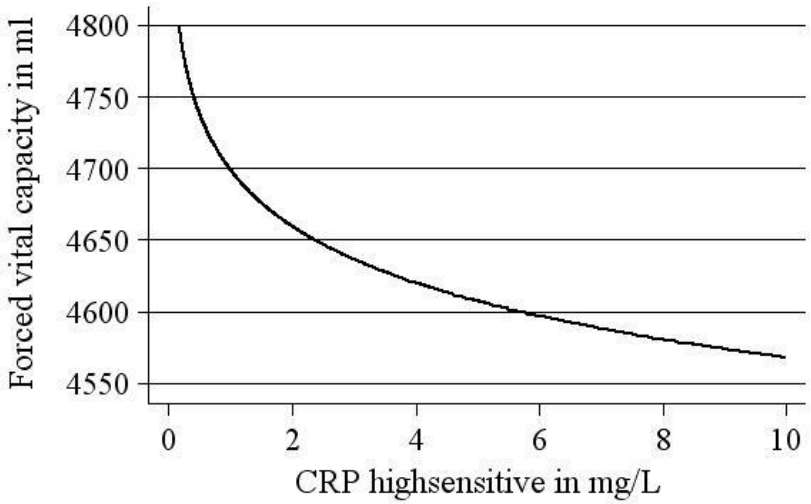
	Fibrinogen[1]	-0.03 (-0.07; 0.02)	Fibrinogen[1]	-0.00 (-0.06; 0.05)	Fibrinogen[1]	-0.01 (-0.06; 0.04)
MEF50 in l/sec	hsCRP[1]	-0.02 (-0.05; 0.01)	hsCRP[1]	-0.00 (-0.04; 0.04)	hsCRP[1]	0.00 (-0.03; 0.04)
	Fibrinogen[1]	-0.07 (-0.16; 0.03)	Fibrinogen[1]	-0.00 (-0.11; 0.11)	Fibrinogen[1]	-0.03 (-0.14; 0.07)
MEF75 in l/sec	$hsCRP^{-0.5}$	-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} in 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)
Rtot in kPa/s * l	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 in 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)

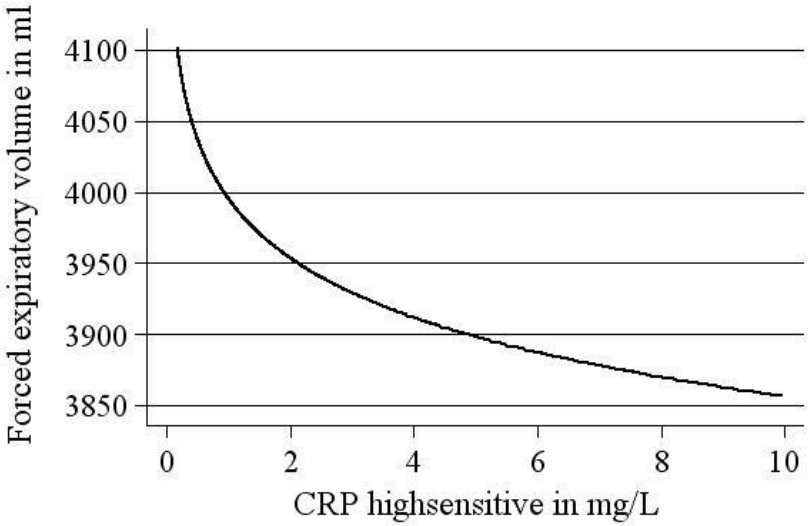
RV/TLC in %	hsCRP[1]	-0.01 (-0.20; 0.18)	hsCRP[1]	-0.07 (-0.28; 0.13)	hsCRP[1]	-0.15 (-0.35; 0.04)
	Fibrinogen[1]	0.52 (-0.04; 1.07)	Fibrinogen[1]	0.22 (-0.38; 0.83)	Fibrinogen[1]	0.34 (-0.27; 0.95)
TLCOc-VA in mmol/kPa/min/l males	log(hsCRP)	-0.06** (-0.09; -0.04)	hsCRP[1]	-0.01 (-0.03; 0.00)	log(hsCRP)	-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)
TLCOc-VA in mmol/kPa/min/l 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)

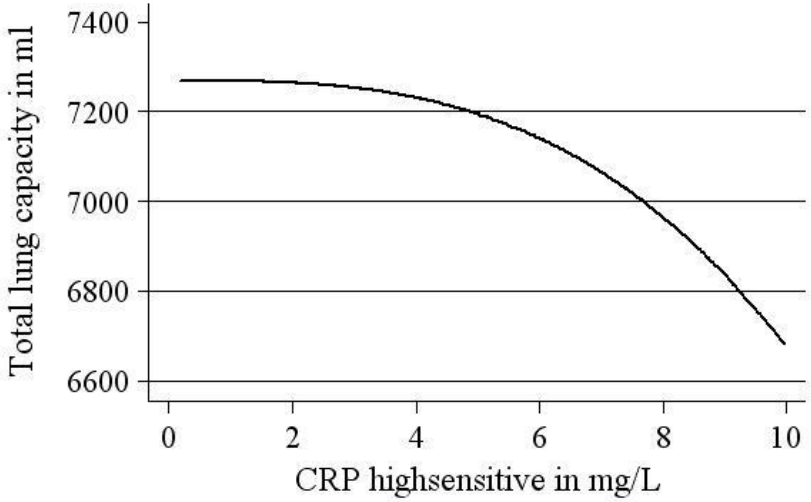
Linear regression using fractional polynomials for hsCRP and fibrinogen adjusted for age, sex, body mass index, physical activity (cut-off ≥2 hours/week), COPD, asthma, former and current smoking, congestive heart failure, and time between core and pulmonary examination. Transformation of the exposure variable (hsCRP, fibrinogen) used. *p<0.05; **p<0.001
FVC-forced vital capacity; $_{slow}$VC-slow vital capacity; FEV1-forced expiratory volume in one second; MEF – maximal expiratory flow at 75, 50 and 25% of FVC; Rtot-total airway resistance; TLC-total lung capacity; RV/TLC-residual volume to total lung capacity ratio; FRC_{pleth} – functional residual capacity derived bodyplethysmography; TLCOc-VA-diffusing capacity for carbon dioxide (single breath), corrected for hemoglobin level and ventilated area (assessed by Helium dilution);
CI confidence interval

Figure legends:

Figure 1: Significant associations between hsCRP and pulmonary variables in the overall population.
Volumes are given in milliliters (ml); MEF25 for maximal expiratory flow at 25% of forced vital capacity (FVC) is given in liters


Forced vital capacity in ml
4800
4750
4700
4650
4600
4550
0
2
4
6
8
10
CRP highsensitive in mg/L


Forced expiratory volume in ml
4100
4050
4000
3950
3900
3850
0
2
4
6
8
10
CRP highsensitive in mg/L


Total lung capacity in ml
7400
7200
7000
6800
6600
0
2
4
6
8
10
CRP highsensitive in mg/L

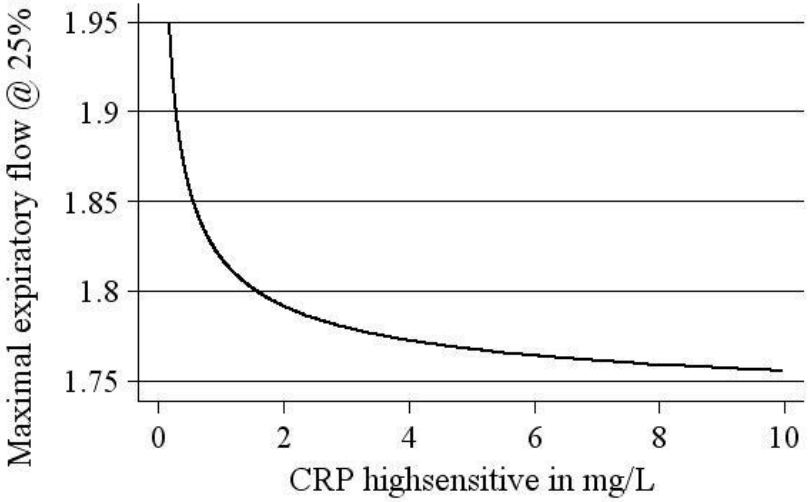

Maximal expiratory flow @ 25% FVC
1.95
1.9
1.85
1.8
1.75
0
2
4
6
8
10
CRP highsensitive in mg/L

Figure 2: Significant associations between hsCRP and diffusing capacity for carbon monoxide in the overall population. Straight line represents males and the dashed line females, for this variable hsCRP was significantly associated in males only.
Diffusing capacity for carbon monoxide (single breath in mmol/kPa/min/l), corrected for hemoglobin level and alveolar volume (assessed by Helium dilution)

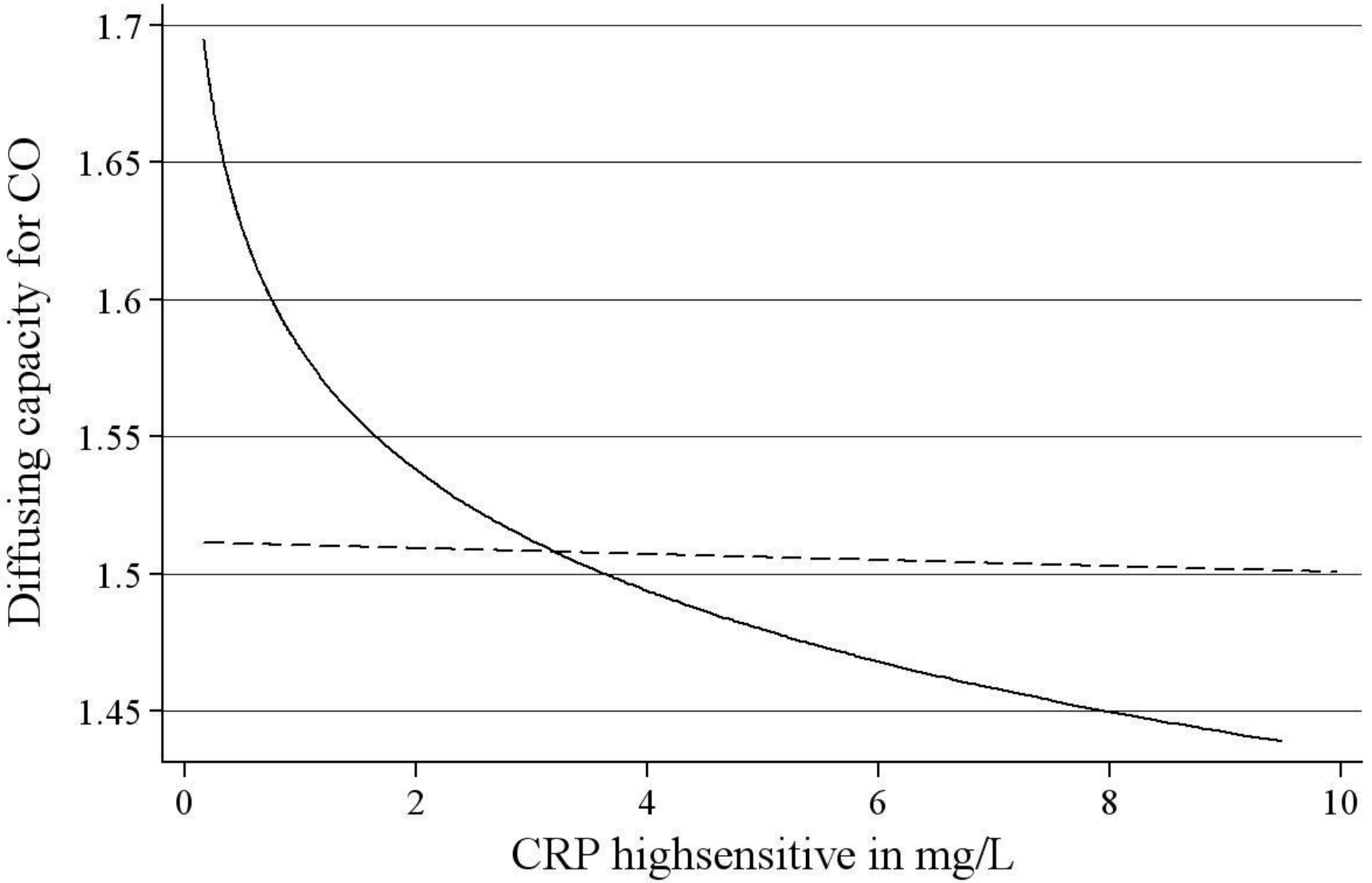
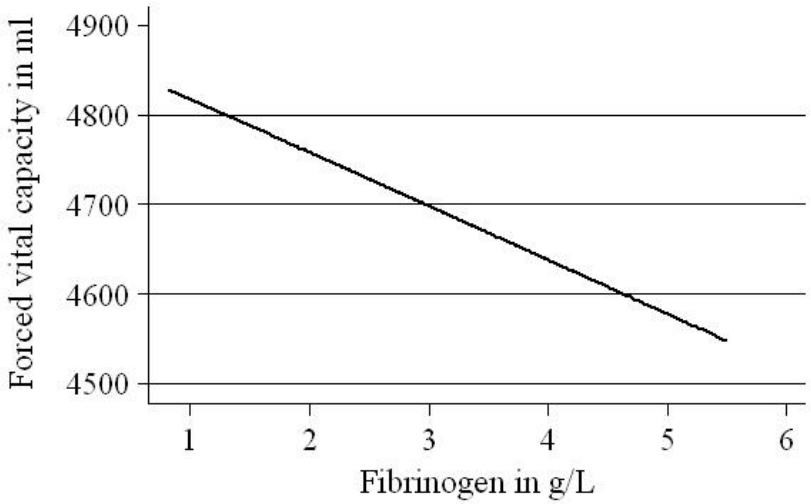
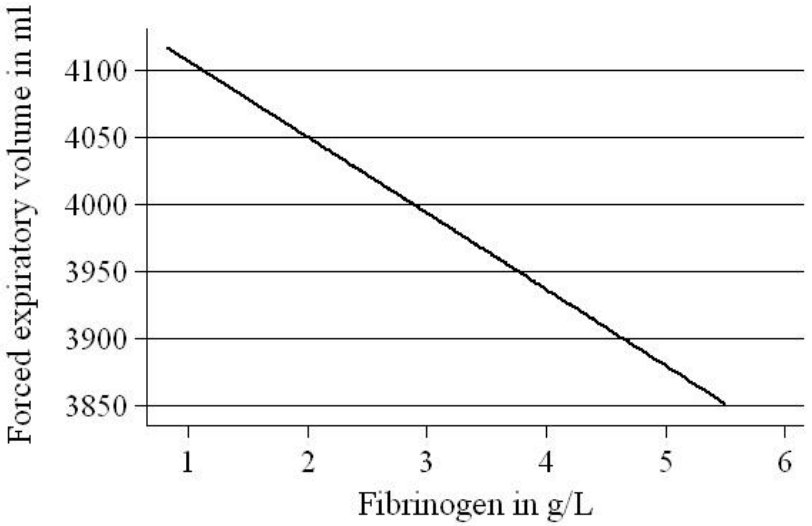
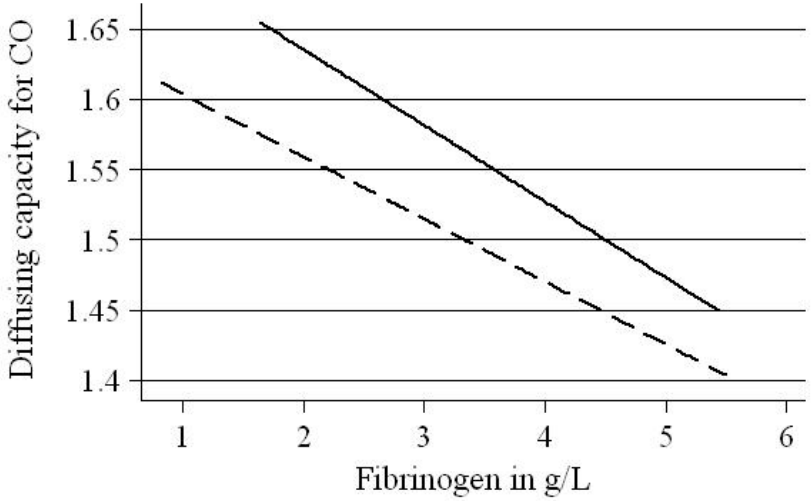

Diffusing capacity for CO
1.7
1.65
1.6
1.55
1.5
1.45
0
2
4
6
8
10
CRP highsensitive in mg/L

Figure 3: Significant associations between fibrinogen and pulmonary variables in the overall population. In the figure with diffusing capacity the straight line represents males and the dashed line females.
Volumes are given in milliliters (ml); diffusing capacity for carbon monoxide (single breath in mmol/kPa/min/l), corrected for hemoglobin level and alveolar volume (assessed by Helium dilution)


Forced vital capacity in ml
4900
4800
4700
4600
4500
1
2
3
4
5
6
Fibrinogen in g/L


Forced expiratory volume in ml
4100
4050
4000
3950
3900
3850
1
2
3
4
5
6
Fibrinogen in g/L


Diffusing capacity for CO
1.65
1.6
1.55
1.5
1.45
1.4
1
2
3
4
5
6
Fibrinogen in g/L