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Reduced Lung Function, C-Reactive Protein, and Increased Risk of Cardiovascular Mortality

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Background: We explored whether reduced lung function is a predictor of mortality due to cardiovascular or coronary artery disease (CVD or CAD), and, if this hypothesis is correct, whether C-reactive protein (CRP), a systemic inflammatory marker, is responsible for this association in a general population-based cohort.

Methods and Results: We used the Third Nutrition and Health Examination Survey (NHANES Ⅲ) database and the NHANES Ⅲ Linked Mortality File. A total of 13,310 participants ≥20 years of age who completed a spirometric test at baseline examination were included. On comparison of the participants in the lowest forced vital capacity percent predicted (FVC% pred) quartile with those in the highest quartile, the hazard ratio (HR) was 2.1 (95% CI: 1.7–2.6) for cardiovascular mortality and 2.2 (95% CI: 1.6–3.2) for coronary mortality. A similar association was observed for forced expiratory volume in 1 s percent predicted (FEV_1% pred). When the participants with the highest FVC% pred or FEV_1% pred (Q4) and low CRP (≤0.22 mg/dl) were defined as the reference group, the adjusted HR for cardiovascular mortality was significantly increased in the individuals with the lowest spirometric volume (Q1), and the risk was prominent in individuals with high CRP (>0.22 mg/dl).

Conclusions: There is a significant association between lung function parameters and death from CVD and CAD in the general population. (*Circ J* 2014; **78:** 2309–2316)

Key Words: Coronary artery disease; Inflammation; Lung

Lung function decline is a significant predictor of adverse cardiovascular events. Many epidemiologic studies have demonstrated that poor lung function, as indicated by a low forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC), is associated with an increased risk of coronary artery disease (CAD), stroke, and cardiovascular death.[1–7] This risk is independent of cigarette smoking,[3,8,9] which is a shared risk factor for lung function and cardiovascular disease (CVD).[8,9] Moreover, lung function parameters are a powerful predictor of cardiovascular mortality compared with socioeconomic position, cardiovascular risk factors (ie, serum cholesterol and blood pressure),[7,10] and Framingham risk score alone.[11]

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The exact mechanisms responsible for the association between lung function and cardiovascular risk remain unclear. Low-grade systemic inflammation, however, has been identified as a plausible mechanistic pathway.[1,5,10] Subjects with a reduced FEV_1 or FVC have elevated levels of circulating inflammatory markers, such as C-reactive protein (CRP) and fibrinogen, compared with individuals with normal lung function.[12,13] The cardiovascular risk of subjects with low spirometric parameters significantly differs based on systemic inflammation level,[1,5] suggesting an interplay of systemic inflammation with reduced lung function in the development of cardiovascular events.

Although several studies have evaluated the association between lung function and cardiovascular events, evidence of a link between lung function, systemic inflammation, and cardiovascular mortality is still limited. In this study, we explored whether decline in lung function, as measured by FVC percent predicted (FVC% pred) and FEV_1 percent predicted (FEV_1% pred), is a predictor of mortality due to CVD or CAD, and, if this hypothesis is correct, whether CRP, a systemic inflammatory marker, is responsible for this association in a general population-based cohort.

Methods

Subjects

We used the Third Nutrition and Health Examination Survey (NHANES Ⅲ) database[14] and the NHANES Ⅲ Linked Mortality

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Table 1. Baseline Characteristics vs. FVC% Pred and FEV_1% Pred

	%FVC pred				
	Q1 (≤89.49)	Q2 (89.50–98.86)	Q3 (98.87–108.00)	Q4 (≥108.01)	P-value†
Age (years)					
20–29	507±16.9	856±28.6	874±29.2	758±25.3	<0.0001
30–39	488±17.4	752±26.8	811±28.9	757±27.0	
40–49	506±23.2	564±25.9	593±27.2	517±23.7	
50–59	484±32.3	386±25.7	334±22.3	297±19.8	
60–69	594±33.5	408±23.0	343±19.4	426±24.1	
≥70	635±30.7	385±18.6	417±20.2	632±30.6	
Gender					
Male	1,442 (23.4)	1,659 (26.9)	1,539 (24.9)	1,536 (24.9)	0.0004
Female	1,772 (24.8)	1,692 (23.7)	1,833 (25.6)	1,851 (25.9)	
Race/Ethnicity					
White	1,524 (26.6)	1,448 (25.3)	1,442 (25.2)	1,318 (23.0)	<0.0001
Black	892 (23.8)	870 (23.2)	912 (24.3)	1077 (28.7)	
Hispanic	798 (20.8)	1,033 (26.9)	1,018 (26.5)	992 (25.8)	
Education					
Less than high school	864 (29.0)	658 (22.1)	648 (21.7)	812 (27.2)	<0.0001
High school	1,575 (24.5)	1,650 (25.7)	1,671 (26.0)	1,523 (23.7)	
College or more	775 (19.8)	1,043 (26.6)	1,053 (26.8)	1,052 (26.8)	
Cigarette smoking					
Current smoker	902 (25.6)	933 (26.5)	907 (25.7)	782 (22.2)	<0.0001
Former smoker	855 (26.5)	720 (22.4)	783 (24.3)	863 (26.8)	
Never smoker	1,457 (22.2)	1,698 (25.8)	1,682 (25.6)	1,742 (26.5)	
History of disease					
Hypertension	1,288 (33.4)	872 (22.6)	828 (21.5)	870 (22.6)	<0.0001
Dyslipidemia	1,070 (27.3)	964 (24.6)	921 (23.5)	959 (24.5)	<0.0001
Diabetes	542 (40.3)	330 (24.6)	257 (19.1)	215 (16.0)	<0.0001
Asthma	283 (32.5)	205 (23.5)	190 (21.8)	194 (22.3)	<0.0001
COPD	340 (40.1)	190 (22.4)	169 (19.9)	150 (17.7)	<0.0001
Height (cm)	166.1±0.3	167.5±0.3	166.7±0.3	166.2±0.3	<0.0001
BMI (kg/m^2)	28.1±0.2	27.2±0.2	26.8±0.2	26.6±0.2	<0.0001
TC (mg/dl)	209.6±1.6	203.6±1.5	203.8±1.5	204.3±1.5	<0.0001
CRP (mg/dl)	0.6±0.0	0.5±0.0	0.4±0.0	0.4±0.0	<0.0001
Serum ferritin (ng/ml)	146.5±5.5	136.1±5.3	124.4±4.5	124.9±4.5	<0.0001

(Table 1 continued the next page.)

File, which was a mortality follow-up study that matched the NHANES III records with data available in the National Death Index as of 31 December 2006. The date and cause of death in the National Death Index were derived from death certificates.[15]

NHANES III is based on a complex multistage probability sampling design. Appropriate sampling weights are needed to estimate prevalence, means, medians, and other statistics. The sampling weights are used to produce correct population estimates because each sampled person does not have an equal probability of selection. The sampling weights incorporate the differential probabilities of selection and include adjustments for non-coverage and non-response.[14]

We initially included 14,994 study participants who were aged ≥20 years and who successfully completed a spirometric test at the time of examination. From this sample, 665 participants were excluded because they had a history of heart attack or cerebrovascular disease. We also excluded 1,019 participants who had missing variables for cardiovascular risk factors. The cohort analysis in the present study was thus based on 13,310 NHANES III participants.

NHANES is a publicly released dataset, so we did not need informed consent to use this dataset. This study was exempt from the Institutional Review Board approval of Ajou University Hospital.

Baseline Data Collection

The participants were interviewed in NHANES III to obtain information on age (20–29, 30–39, 40–49, 50–59, 60–69, or 70+ years), gender (male or female), race/ethnicity (white, black, Hispanic, or other), education (less than high school, high school graduate, or college or more), and smoking status (current, former, or never). Regarding disease history, hypertension was defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg, anti-hypertensive drug use, or prior physician diagnosis of hypertension. Hyper-cholesterolemia was defined as serum total cholesterol level ≥6.19 mmol/L, current medication use, or self-reported diagnosis by a physician.

	%FEV$_1$ pred				
	Q1 (≤86.84)	Q2 (86.85–97.16)	Q3 (97.17–106.74)	Q4 (≥106.75)	P-value†
Age (years)					
20–29	444±14.8	860±28.7	926±30.9	765±25.5	<0.0001
30–39	443±15.8	766±27.3	845±30.1	754±26.9	
40–49	467±21.4	611±28.0	581±26.7	521±23.9	
50–59	534±35.6	368±24.5	319±21.3	280±18.7	
60–69	641±36.2	389±22.0	328±18.5	413±23.3	
≥70	680±32.9	372±18.0	382±18.5	635±30.7	
Gender					
Male	1,550 (25.1)	1,646 (26.7)	1,514 (24.5)	1,466 (23.7)	<0.0001
Female	1,659 (23.2)	1,720 (24.1)	1,867 (26.1)	1,902 (26.6)	
Race/Ethnicity					
White	1,599 (27.9)	1,423 (24.8)	1,405 (24.5)	1,305 (22.8)	<0.0001
Black	900 (24.0)	913 (24.3)	856 (22.8)	1,082 (28.9)	
Hispanic	710 (18.5)	1,030 (26.8)	1,120 (29.2)	981 (25.5)	
Education					
Less than high school	873 (29.3)	672 (22.5)	677 (22.7)	760 (25.5)	<0.0001
High school	1,586 (24.7)	1,690 (26.3)	1,613 (25.1)	1,530 (23.8)	
College or more	750 (19.1)	1,004 (25.6)	1,091 (27.8)	1,078 (27.5)	
Cigarette smoking					
Current smoker	1,074 (30.5)	978 (27.8)	818 (23.2)	654 (18.6)	<0.0001
Former smoker	922 (28.6)	732 (22.7)	769 (23.9)	798 (24.8)	
Never smoker	1,213 (18.4)	1,656 (25.2)	1,794 (27.3)	1,916 (29.1)	
History of disease					
Hypertension	1,303 (33.8)	864 (22.4)	798 (20.7)	893 (23.2)	<0.0001
Dyslipidemia	1,081 (27.6)	958 (24.5)	908 (23.2)	967 (24.7)	<0.0001
Diabetes	475 (35.3)	346 (25.7)	285 (21.2)	238 (17.7)	<0.0001
Asthma	394 (45.2)	215 (24.7)	143 (16.4)	120 (13.8)	<0.0001
COPD	423 (49.8)	175 (20.6)	137 (16.1)	114 (13.4)	<0.0001
Height (cm)	166.9±0.3	167.7±0.3	166.4±0.3	165.6±0.3	<0.0001
BMI (kg/m^2)	27.8±0.2	27.2±0.2	26.9±0.2	26.8±0.2	<0.0001
TC (mg/dl)	210.2±1.6	203.6±1.5	202.8±1.5	204.8±1.5	<0.0001
CRP (mg/dl)	0.6±0.0	0.5±0.0	0.4±0.0	0.4±0.0	<0.0001
Serum ferritin (ng/ml)	147.7±5.7	136.4±5.1	124.3±4.6	123.6±4.4	<0.0001

Data given as n (%) or mean±SE. †Chi-squared test for categorical variables and ANOVA for continuous variables.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FEV$_1$% pred, forced expiratory volume in 1 s percent predicted; FVC% pred, forced vital capacity percent predicted; TC, total cholesterol.

Diabetes was defined as fasting plasma glucose ≥6.99 mmol/L, non-fasting plasma glucose ≥11.1 mmol/L, current insulin use, or prior physician diagnosis of diabetes. History of respiratory disease included asthma or chronic obstructive pulmonary disease (COPD) based on prior physician diagnosis. Anthropometric variables included height in centimeters and body mass index (BMI), which was calculated by dividing weight in kilograms by height in meters squared. Total cholesterol (mg/dl), CRP (mg/dl), and ferritin were included as biomarkers of mortality risk and were treated as continuous variables.

In addition, because most participants (56%) had CRP below the lowest detectable level of 0.22 mg/dl, CRP was categorized into 2 subgroups: low CRP (≤0.22 mg/dl) and high CRP (>0.22 mg/dl).

Mortality Follow-up

The International Classification of Diseases, 9th Revision (ICD-9) was used for deaths occurring from 1988 through 1998, and International Classification of Diseases, 10th Revision (ICD-10) was used for deaths occurring from 1999 through 2000. The underlying causes of death were grouped according to the coding system of the National Center for Health Statistics, and all deaths from 1988–1998 that were coded under the ICD-9 Clinical Modification guidelines were replaced by the ICD-10 underlying causes of death.[16] In addition to all-cause mortality, we studied the following specific causes of death: CVD (ICD-10 code I00–I99) and CAD (ICD-10 code I20–I25).

Lung Function Test

Lung function testing (spirometry) was preformed according to the 1987 American Thoracic Society recommendations.[17] A more detailed description is available in the Hankinson et al study.[18] Briefly, using screening questions, participants who had undergone chest or abdominal surgery within 3 weeks or had experienced heart problems (myocardial infarction or heart attack, angina or chest pain, or congestive heart failure) were excluded from testing. Body measurements were taken, in-

Table 2. Mortality According to FVC% Pred and FEV_1% Pred

	CVD mortality			CAD mortality		
	Standardized mortality (%)†	Model I Adjusted HR (95% CI)	Model II Adjusted HR (95% CI)	Standardized mortality (%)†	Model I Adjusted HR (95% CI)	Model II Adjusted HR (95% CI)
FVC% pred						
Q1 (≤89.49)	11.2 (10.2–12.1)	2.6 (2.1–3.2)	2.1 (1.7–2.6)	6.0 (5.3–6.7)	2.8 (2.0–3.8)	2.2 (1.6–3.2)
Q2 (89.50–98.86)	7.6 (6.7–8.6)	1.6 (1.3–2.0)	1.6 (1.3–1.9)	4.6 (3.9–5.3)	1.9 (1.4–2.7)	1.8 (1.2–2.5)
Q3 (98.87–108.00)	6.9 (6.1–7.8)	1.5 (1.2–1.9)	1.4 (1.2–1.8)	4.0 (3.4–4.7)	1.5(1.0–2.1)	1.4 (1.0–2.1)
Q4 (≥108.01)	6.2 (5.5–6.8)	Reference	Reference	3.3 (2.8–3.8)	Reference	Reference
P-trend		<0.0001	<0.0001		<0.0001	<0.0001
FEV_1% pred						
Q1 (≤86.84)	10.4 (9.5–11.3)	2.2 (1.8–2.6)	1.7 (1.4–2.1)	5.6 (5.0–6.3)	2.2 (1.7–3.0)	1.8 (1.4–2.4)
Q2 (86.85–97.16)	7.6 (6.6–8.5)	1.4 (1.1–1.7)	1.2 (0.9–1.6)	4.3 (3.6–5.0)	1.5 (1.1–2.1)	1.4 (1.0–2.0)
Q3 (97.17–106.74)	7.3 (6.4–8.2)	1.3 (1.0–1.6)	1.2 (1.0–1.5)	4.1 (3.4–4.7)	1.3 (0.9–1.9)	1.3 (0.9–1.9)
Q4 (≥106.75)	6.6 (5.9–7.3)	Reference	Reference	3.8 (3.3–4.3)	Reference	Reference
P-trend		<0.0001	<0.0001		<0.0001	0.0023

†Age- and gender-standardized mortality from CVD and CAD. Model I was adjusted for age, sex, race/ethnicity, and education. Model II was further adjusted for smoking, history of disease (hypertension, dyslipidemia, diabetes, asthma, or chronic obstructive pulmonary disease), height, BMI, TC, CRP, and ferritin.
CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio. Other abbreviations as in Table 1.

cluding standing height, weight, and sitting height. The testing procedure was explained to and demonstrated for each examinee by a spirometry technician.

A testing session consisted of repeated FVC maneuvers. The technicians were instructed to obtain between 5 and 8 maneuvers, ensuring that the subject produced the highest possible peak flows and that maximum exhalation continued for at least 6 s until there was a plateau in the volume-time curve. At the completion of each maneuver, a display was provided of all flow-volume curves: FVC; FEV_1; peak expiratory flow; expiratory time; and percentage difference between each FVC, FEV_1, and peak expiratory flow and the corresponding largest value. To classify test reliability, 2 senior quality technicians at the spirometry quality control center reviewed all tests.[19]

Statistical Analysis

To account for the complex sampling design, the weighted estimates of the population parameters were computed using the NHANES Analytic and Reporting Guidelines. All analysis was done using PROC SURVEY in SAS 9.2 (SAS Institute, Cary, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance level was set at α=0.05 (2-sided).

We used the largest FVC and FEV_1 and derived FVC% pred and FEV_1% pred using the Hankinson et al equation.[18] Overall risk analysis for CVD and CAD mortality involved calculating the quartiles of each FVC% pred and FEV_1% pred. Cox proportional hazards regression was used in the multivariate analysis of mortality, and the hazard ratios (HR) and 95% confidence intervals (95% CI) of the outcome variables for participants in the first (Q1), second (Q2), and third (Q3) quartiles were calculated relative to the fourth (Q4) quartile of each FVC% pred and FEV_1% pred. The model was adjusted for age, gender, race/ethnicity, and education. Additional adjustment was conducted for smoking, a history of disease (hypertension, dyslipidemia, diabetes, asthma, or COPD), height, BMI, total cholesterol, and CRP level. Adjusted Kaplan-Meier estimates, stratified by quartiles of spirometric volume, for cardiovascular and coronary mortality were determined and are presented as event curves.

To further assess whether CRP contributed to the association between lung function and mortality, we divided CRP into 2 subgroups, low CRP (≤0.22 mg/dl) and high CRP (>0.22 mg/dl), based on the detection limit. HR was calculated for the extreme quartiles (Q1) of each FVC% pred and FEV_1% pred in relation to CRP level, by classifying participants with the highest spirometric parameters (Q4) and low CRP as the reference group. The model was adjusted for age, gender, race/ethnicity, education, smoking, history of CVD or respiratory disease, height, BMI, and total cholesterol.

Results

Table 1 lists the frequency (%) and mean±SE for FVC% pred and FEV_1% pred, grouped by subject baseline characteristics. Significant trends in all characteristics were observed for both quartiles of FVC% pred and FEV_1% pred (P<0.05 for trend). Specifically, participants with the lowest FVC% pred or FEV_1% pred were more likely to be older, female, white, and have less than high school education. These participants had also a history of disease (ie, hypertension, dyslipidemia, diabetes, asthma, and COPD) and elevated BMI, total cholesterol, CRP, and serum ferritin. In this sample, the overall prevalence was 9.2% (n=1,224) for CVD mortality and 4.9% (n=657) for CAD mortality. The subject baseline characteristics with and without CVD or CAD mortality are provided in Table S1.

Table 2 lists age- and gender-standardized mortality and the HR (95% CI) for mortality from CVD and CAD based on the quartile of the spirometric volume at baseline. CVD and CAD mortality was the highest in the lowest quartile (Q1), and the mortality rate gradually decreased as the quartiles increased. On comparison of the participants in the lowest FVC% pred quartile with the individuals in the highest quartile, the adjusted HR was 2.1 (95% CI: 1.7–2.6) for cardiovascular mortality and 2.2 (95% CI: 1.6–3.2) for coronary mortality, after adjusting for CVD risk factors, including smoking, CVD history (ie, hypertension, dyslipidemia, and diabetes), BMI, total cholesterol, CRP, and ferritin level. The risk significantly increased, even in response to a small reduction (ie, Q2 and Q3) in FVC% pred. For FEV_1% pred, the corresponding HR were

Table 3. Lung Function Pattern and Mortality

Lung function	CVD mortality		CAD mortality	
	No. events (%)	Adjusted HR† (95% CI)	No. events (%)	Adjusted HR† (95% CI)
Normal FVC and FEV_1 (FVC1% ≥80, FEV_1% ≥80)	825 (7.4)	Reference	448 (4.0)	Reference
Normal FVC and low FEV_1 (FVC1% ≥80, FEV_1% <80)	119 (15.0)	1.4 (0.9–2.0)	57 (7.2)	1.1 (0.6–2.0)
Low FVC and normal FEV_1 (FVC1% <80, FEV_1% ≥80)	55 (18.8)	2.8 (1.5–5.2)	31 (10.6)	3.8 (1.9–7.8)
Low FVC and low FEV_1 (FVC1% <80, FEV_1% <80)	225 (21.5)	2.1 (1.5–2.8)	121 (11.6)	2.1 (1.3–3.2)

†Adjusted for age, sex, race/ethnicity, smoking, education, the history of disease, height, BMI, TC, CRP, and ferritin.
Abbreviations as in Tables 1,2.

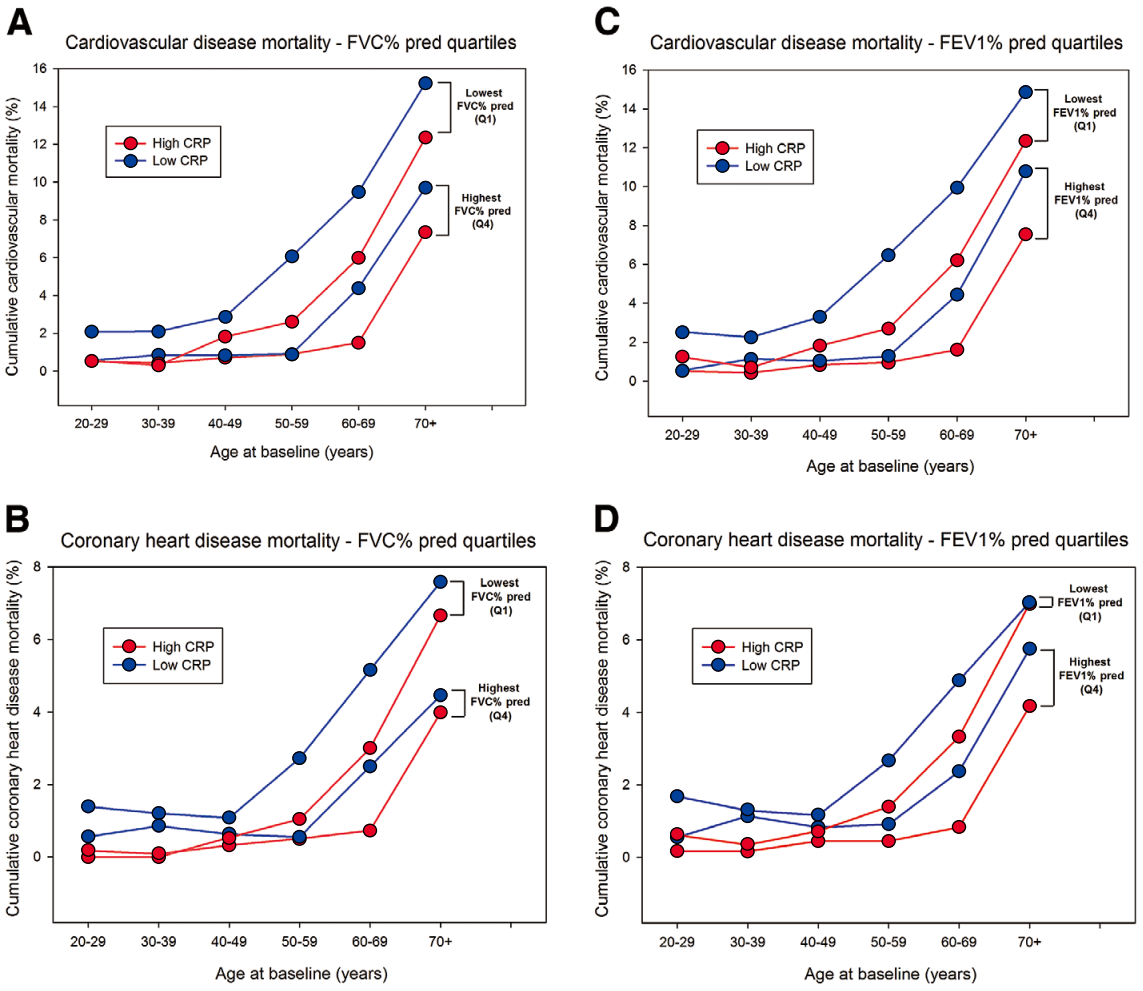

Figure. Cumulative (**A**,**C**) cardiovascular and (**B**,**D**) coronary artery disease mortality for extreme forced vital capacity percent predicted (FVC% pred) or forced expiratory volume in 1 s percent predicted (FEV_1% pred) quartiles and C-reactive protein (CRP). (●) High CRP (>0.22 mg/dl); (●) low CRP (≤0.22 mg/dl).

1.7 (95% CI: 1.4–2.1) for cardiovascular mortality and 1.8 (95% CI: 1.4–2.4) for coronary mortality. Significant overall trends in risk were observed for both FVC% pred and FEV_1% pred ($P<0.05$ for trend). In addition, subgroup analyses were conducted based on ever smoking (former and current smokers), age (<65 years or ≥65 years) and sex (**Tables S2–S4**). Except for the FEV_1% pred related to CVD and CAD mortality among adults (<65 years), there was an overall significant association between lung function and mortality from CVD and CAD.

Table 3 lists the distribution of CVD and CAD mortality by combination of FVC% pred and FEV_1% pred. Lung function was categorized into 4 groups: normal FVC and normal FEV_1 (FVC% pred ≥80, FEV_1% pred ≥80); normal FVC and low FEV_1 (FVC% pred ≥80, FEV_1% pred <80); low FVC and normal FEV_1 (FVC% pred <80, FEV_1% pred ≥80); and low FVC and low FEV_1 (FVC% pred <80, FEV_1% pred <80). As

Table 4. Mortality According to Extremes of Lung Volume and CRP

	CVD mortality		CAD mortality	
	No. events (%)	Adjusted HR† (95% CI)	No. events (%)	Adjusted HR† (95% CI)
FVC% pred				
Lowest (Q1)				
High CRP	16.4	2.5 (1.9–3.3)	8.5	2.4 (1.5–3.7)
Low CRP	13.3	1.9 (1.5–2.4)	7.1	2.0 (1.4–2.7)
Highest (Q4)				
High CRP	10.5	0.9 (0.7–1.3)	4.9	0.9 (0.6–1.2)
Low CRP	7.7	Reference	4.2	Reference
FEV_1% pred				
Lowest (Q1)				
High CRP	15.8	2.2 (1.8–2.8)	7.9	2.3 (1.6–3.3)
Low CRP	13.5	1.7 (1.4–2.2)	7.5	1.9 (1.4–2.6)
Highest (Q1)				
High CRP	11.9	1.3 (1.0–1.6)	6.4	1.2 (0.9–1.8)
Low CRP	7.9	Reference	4.3	Reference

†Adjusted for age, sex, race/ethnicity, education, smoking, history of disease (hypertension, dyslipidemia, diabetes, asthma, or chronic obstructive pulmonary disease), height, BMI, and TC. High CRP, >0.22 mg/dl; low CRP, ≤0.22 mg/dl. Abbreviations as in Tables 1,2.

expected, participants with normal lung function had the lowest prevalence of mortality. Regarding the mortality from CVD and CAD, the participants with low FVC and low FEV_1 had the highest prevalence of mortality (21.5% and 11.6%, respectively), followed by those with low FVC and normal FEV_1 (18.8% and 10.6%, respectively). Adjusted HR for CVD and CAD mortality were significantly increased in individuals who had low FVC and normal FEV_1 (CVD: HR, 2.8; 95% CI: 1.5–5.2; CAD: HR, 3.8; 95% CI: 1.9–7.8) or who had low FVC and FEV_1 (CVD: HR, 2.1; 95% CI: 1.5–2.8; CAD: HR, 2.1; 95% CI: 1.3–3.2) compared with those with normal lung function. Subjects with normal FVC and low FEV_1, however, were not associated with that mortality risk.

We further investigated the association between lung function and cardiovascular mortality by assessing CRP level. **Figure** presents the cumulative mortality from CVD and CAD in the extreme quartiles of FVC% pred and FEV_1% pred, by classifying individuals based on whether they had high (>0.22 mg/dl) or low (≤0.22 mg/dl) CRP. Participants with the lowest spirometric volume and high CRP had the highest cumulative risk, and the risk was nearly 15% and 7–8% for CVD and CAD, respectively.

Table 4 lists the HR for mortality in the extreme quartiles of lung volume in relation to CRP level, after adjusting for potential risk factors. When participants with the highest spirometric parameters (Q4) and low CRP were defined as the reference group, the adjusted HR for cardiovascular mortality significantly increased in individuals with the lowest FVC% pred or FEV_1% pred (Q1), and the risk was prominent in subjects with high CRP. A similar pattern was observed for CAD mortality. Individuals who had the lowest spirometric parameters (Q1) and >0.22 mg/dl CRP simultaneously had the highest HR for FVC% pred and for FEV_1% pred: HR, 2.4 (95% CI: 1.5–3.7), and HR, 2.3 (95% CI: 1.6–3.3), respectively.

Discussion

In this prospective cohort study of a representative sample of the US population, we found that reduced lung function was significantly associated with cardiovascular mortality in adults. The participants with the lowest FVC% pred or FEV_1% pred (Q1) at baseline had a nearly 2-fold increased risk of CVD and CAD mortality compared with individuals with the highest baseline FVC% pred or FEV_1% pred (Q4). After adjusting for cardiovascular risk factors (ie, smoking, hypertension, diabetes, and systemic inflammatory markers), the HR remained significant and was dose responsive ($P<0.05$ for trend; **Table 4**). Subgroup analyses based on ever smoking (former and current smokers), age (<65 years and ≥65 years), and sex also indicated a robust association between lung function and mortality risk. In addition, the cardiovascular risk differed when the CRP was stratified as low (≤0.22 mg/dl) or high (>0.22 mg/dl). CRP level increased cardiovascular mortality risk, and the risk increases were prominent among the subjects with the lowest spirometric data.

The present findings reinforce existing evidence of an association between lung function and cardiovascular mortality. Many studies, from epidemiologic studies to systematic reviews, have shown that reduced lung function, even a relatively modest reduction, significantly predicts cardiovascular mortality over short- and long-term follow-up periods.[4–7,9] The current study also showed significant trends of increasing risk with diminishing spirometric volumes. Compared with the highest spirometric volumes (Q4), participants in the lowest quartile (Q1) had an increased risk of CVD (HR, 2.1; 95% CI: 1.7–2.6) for FVC% pred; HR, 1.7, 95% CI: 1.4–2.1 for FEV_1% pred). The increased risks were present not only in the participants with the worst spirometric parameters but also in those individuals with a moderate reduction. A significant increase in CAD mortality was of particular interest. Few studies have focused on reduced lung function as a predictor of CAD or death.[3,4,6,7,20] From a longitudinal study of the Renfrew and Paisley survey, Hole et al found that subjects with the lowest FEV_1% pred had a nearly 2-fold increased risk of ischemic heart disease mortality.[7] Schünemann et al examined whether lung function remained a significant predictor of mortality over 25 years using data from the Buffalo Health Study.[4] For the entire follow-up period, the adjusted HR for ischemic heart disease were 2.11 (95% CI: 1.20–3.71) for men and 1.96 (95% CI: 0.99–3.88) for women. These observations were similar to

the present risk estimate, with an approximately 2-fold increased risk, and suggested that the increased risk was apparent even for a slight reduction of FEV_1% pred.[4,7] In the Atherosclerosis Risk in Communities study, Schroeder et al found a strong association between lung function and the incidence of CAD among women but a weaker association among men, both in the full cohort and among never smokers.[3] More interestingly, a recent study showed that the addition of FVC to Framingham risk score, which is a global risk algorithm for estimating cardiovascular event risk, provided a significant benefit in predicting mortality (area under the curve, 0.64 vs. 0.56; $P<0.05$) in intermediate-risk individuals.[11]

Although lung function effectively predicts CVD and CAD mortality, the mechanism underlying this association is still unclear. Several potential explanations for the association have been proposed. First, smoking may be responsible for this relationship because smoking affects both lung function and CVD and death.[21,22] This association, however, is independent of smoking status and is present in never smokers.[3,7,9,23,24] Sabia et al found that the contribution of smoking history (current smoking, recent ex-smoker, long-term ex-smoker, and never smoker) to lung function and cardiovascular risk association might not be very large, implying that smoking is not the only explanation for this phenomenon.[10] Second, lung function could be an indicator of general health, thus associating poor lung function with mortality risk in general.[4] Third, the lung is a primary defense organ against external exotic agents, such as air pollution and diesel exhaust fumes, and could result in increased tolerance to toxic substances, which then leads to disease and death.[25–27] In addition, a potential central player in the association is low-grade systemic inflammation. Systemic inflammatory markers have been inversely associated with spirometric indices and have been suspected of being involved in lung function-related cardiovascular events.[28–32] Recent data emphasized the importance of inflammatory markers, which explain more of the association between lung function and mortality than other variables, including socioeconomic position, health behaviors, cardiovascular risk factors, and disease.[10]

Considerable attention has been focused on CRP in relation to the association between lung function and cardiovascular mortality.[9,29,30,33] CRP level has been used as a consistent measure of underlying low-grade systemic inflammation and as an important marker linked to the development of cardiovascular events.[33–35] Circulating CRP level is associated with increased mortality in both the general population and COPD patients.[5,33] Although an association between lung function, inflammation, and CVD and death has been suggested, few studies have evaluated the potential relationship. Engstrom et al investigated whether FVC was associated with high inflammation-sensitive plasma proteins (ISP) including 1-antitrypsin, ceruloplasmin, fibrinogen, haptoglobin, and orosomucoid, and whether inflammatory markers contributed to increased cardiovascular events among men with reduced FVC.[1] They found that low FVC was associated with high ISP and with an increased risk of myocardial infarction and cardiovascular death. Notably, among men with low FVC, the relative risk of myocardial infarction was 2.5 (95% CI: 1.7–3.6) for individuals with high protein levels and 1.7 (95% CI: 1.1–2.4) for men with low protein levels. Sin and Man reported that subjects with moderate and severe airflow obstruction had an increased risk of ischemic changes on electrocardiogram.[5] In particular, individuals with elevated CRP (>0.22 mg/dl) had a nearly 2-fold (relative odds, 2.2; 95% CI: 1.5–3.3) increased risk of cardiac injury. The present observations are similar to these results. We found that cumulative mortality from CVD and CAD increased as lung function decreased and that CRP was elevated. High CRP significantly increased HR among subjects with the lowest FVC% pred or FEV_1% pred (**Table 4**). These findings suggest an important role for systemic inflammation in the link between poor lung function and cardiovascular risk.

Establishing whether reduced lung function elicits systemic inflammation or whether increased systemic inflammation leads to a decline in lung function is difficult. The present results suggest that reduced lung function is responsible for systemic inflammation. An experimental study by Suwa et al provided evidence supporting this hypothesis.[36] The inhalation of fine particulate matter in hyperlipidemic rabbits provoked a low-grade pulmonary inflammatory response, a release of potentially harmful cytokines, and changes in blood coagulability. That study suggested that particle-induced airway inflammation leads to the propagation of systemic inflammation, which may in turn increase the risk of acute cardiovascular events and the potential for accelerated atherosclerosis and CVD.[37] Future studies are needed to clarify the mechanistic pathway related to systemic inflammation in the association between lung function and cardiovascular risk.

The lung function test is a non-invasive method used in clinical settings to provide additional prognostic information on CVD that may help to better predict the risk for future cardiovascular events. In addition, previous studies suggested that there are associations between impaired lung function and inflammation markers as well as prospective cardiovascular events. Clinicians who manage patients with possible respiratory inflammation, such as an occupational history or exposure to dust and particles, could evaluate both the cardiovascular and respiratory systems. By exploring emerging data that indicate a link between lung function, inflammation and CVD, new management strategies to produce better outcomes in patients who have impaired lung function and CVD may be discovered.

The limitations of this study included the use of a single spirometric measurement at baseline and a long interval between measurement and follow-up. We acknowledge that lung function certainly changed over the follow-up period, and that the influence of changes in lung function on the risk of death was not addressed. In addition, because spirometric testing is effort-dependent, a degree of measurement error in the ascertainment of lung function can exist, despite a standardized protocol and strict quality control. The NHANES III Linked Mortality File ascertained mortality from death certificates, but this approach may overestimate the burden of cardiovascular events as the cause of death, especially at older ages,[38] and misclassification bias is possible. Finally, we adjusted for cardiovascular risk factors and disease in the statistical model; due to the observational nature of this investigation, we cannot rule out the possibility of residual confounding effects by unmeasured confounders.

Conclusions

Lung function decline is associated with an increased mortality risk from CVD and CAD in the general population. We have also provided evidence of the significant association between spirometric lung volume, CRP, and cardiovascular mortality. The present study confirms the findings of previous reports and indicates that the association between reduced lung function and cardiovascular risk is mediated by low-grade systemic inflammation. This suggests that lung function measures are beneficial for targeting individuals who are at high

risk of cardiovascular mortality.

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Disclosures

All authors have no conflict of interest to declare.

References

1. Engstrom G, Lind P, Hedblad B, Wollmer P, Stavenow L, Janzon L, et al. Lung function and cardiovascular risk: Relationship with inflammation-sensitive plasma proteins. *Circulation* 2002; **106:** 2555–2560.
2. Kato J, Koike A, Hoshimoto-Iwamoto M, Nagayama O, Sakurada K, Sato A, et al. Relation between oscillatory breathing and cardiopulmonary function during exercise in cardiac patients. *Circ J* 2013; **77:** 661–666.
3. Schroeder EB, Welch VL, Couper D, Nieto FJ, Liao D, Rosamond WD, et al. Lung function and incident coronary heart disease: The Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2003; **158:** 1171–1181.
4. Schunemann HJ, Dorn J, Grant BJ, Winkelstein W Jr, Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. *Chest* 2000; **118:** 656–664.
5. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003; **107:** 1514–1519.
6. Wannamethee SG, Shaper AG, Rumley A, Sattar N, Whincup PH, Thomas MC, et al. Lung function and risk of type 2 diabetes and fatal and nonfatal major coronary heart disease events: Possible associations with inflammation. *Diabetes Care* 2010; **33:** 1990–1996.
7. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: Findings from the Renfrew and Paisley prospective population study. *BMJ* 1996; **313:** 711–715; discussion 715–716.
8. Hata J, Kiyohara Y. Epidemiology of stroke and coronary artery disease in Asia. *Circ J* 2013; **77:** 1923–1932.
9. Sin DD, Wu L, Man SF. The relationship between reduced lung function and cardiovascular mortality: A population-based study and a systematic review of the literature. *Chest* 2005; **127:** 1952–1959.
10. Sabia S, Shipley M, Elbaz A, Marmot M, Kivimaki M, Kauffmann F, et al. Why does lung function predict mortality? Results from the Whitehall II Cohort Study. *Am J Epidemiol* 2010; **172:** 1415–1423.
11. Lee HM, Le H, Lee BT, Lopez VA, Wong ND. Forced vital capacity paired with Framingham Risk Score for prediction of all-cause mortality. *Eur Respir J* 2010; **36:** 1002–1006.
12. Dahl M, Tybjaerg-Hansen A, Vestbo J, Lange P, Nordestgaard BG. Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; **164:** 1008–1011.
13. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: A systematic review and a meta-analysis. *Thorax* 2004; **59:** 574–580.
14. Centers for Disease Control and Prevention. Plan and Operation of the Third National Health and Nutrition Examination Survey, 1988–94. *Vital Health Stat* 1994; **1**(32). http://www.cdc.gov/nchs/data/series/sr_01/sr01_032.pdf (accessed June 2, 2013).
15. National Center for Health S. NHANES III Linked Mortality File. 2006. http://www.cdc.gov/nchs/data_access/data_linkage/mortality/nhanes3_linkage.htm (accessed October 30, 2012).
16. Anderson RN, Minino AM, Hoyert DL, Rosenberg HM. Comparability of cause of death between ICD-9 and ICD-10: Preliminary estimates. *Natl Vital Stat Rep* 2001; **49:** 1–32.
17. American Thoracic Society. Standardization of spirometry: 1987 update: Statement of the American Thoracic Society. *Am Rev Respir Dis* 1987; **136:** 1285–1298.
18. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; **159:** 179–187.
19. National Center for Health Statistics. NHANES III Reference Manuals and Reports. CD ROM No. 6-0178 (1096). Hyattsville, MD: Data Dissemination Branch, 1996.
20. Knuiman MW, James AL, Divitini ML, Ryan G, Bartholomew HC, Musk AW. Lung function, respiratory symptoms, and mortality: Results from the Busselton Health Study. *Ann Epidemiol* 1999; **9:** 297–306.
21. Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF. Systemic effects of smoking. *Chest* 2007; **131:** 1557–1566.
22. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: An update. *J Am Coll Cardiol* 2004; **43:** 1731–1737.
23. Batty GD, Gunnell D, Langenberg C, Smith GD, Marmot MG, Shipley MJ. Adult height and lung function as markers of life course exposures: Associations with risk factors and cause-specific mortality. *Eur J Epidemiol* 2006; **21:** 795–801.
24. Chinn S, Gislason T, Aspelund T, Gudnason V. Optimum expression of adult lung function based on all-cause mortality: Results from the Reykjavik study. *Respir Med* 2007; **101:** 601–609.
25. Jerrett M, Burnett RT, Pope CA 3rd, Ito K, Thurston G, Krewski D, et al. Long-term ozone exposure and mortality. *N Engl J Med* 2009; **360:** 1085–1095.
26. Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med* 2007; **356:** 447–458.
27. Mills NL, Tornqvist H, Gonzalez MC, Vink E, Robinson SD, Soderberg S, et al. Ischemic and thrombotic effects of dilute diesel-exhaust inhalation in men with coronary heart disease. *N Engl J Med* 2007; **357:** 1075–1082.
28. Fogarty AW, Jones S, Britton JR, Lewis SA, McKeever TM. Systemic inflammation and decline in lung function in a general population: A prospective study. *Thorax* 2007; **62:** 515–520.
29. Hancox RJ, Poulton R, Greene JM, Filsell S, McLachlan CR, Rasmussen F, et al. Systemic inflammation and lung function in young adults. *Thorax* 2007; **62:** 1064–1068.
30. Jiang R, Burke GL, Enright PL, Newman AB, Margolis HG, Cushman M, et al. Inflammatory markers and longitudinal lung function decline in the elderly. *Am J Epidemiol* 2008; **168:** 602–610.
31. Shaaban R, Kony S, Driss F, Leynaert B, Soussan D, Pin I, et al. Change in C-reactive protein levels and FEV1 decline: A longitudinal population-based study. *Respir Med* 2006; **100:** 2112–2120.
32. Thyagarajan B, Jacobs DR, Apostol GG, Smith LJ, Lewis CE, Williams OD. Plasma fibrinogen and lung function: The CARDIA Study. *Int J Epidemiol* 2006; **35:** 1001–1008.
33. Man SF, Connett JE, Anthonisen NR, Wise RA, Tashkin DP, Sin DD. C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. *Thorax* 2006; **61:** 849–853.
34. Clearfield MB. C-reactive protein: A new risk assessment tool for cardiovascular disease. *J Am Osteopath Assoc* 2005; **105:** 409–416.
35. Rifai N, Ridker PM. High-sensitivity C-reactive protein: A novel and promising marker of coronary heart disease. *Clin Chem* 2001; **47:** 403–411.
36. Suwa T, Hogg JC, Quinlan KB, Ohgami A, Vincent R, van Eeden SF. Particulate air pollution induces progression of atherosclerosis. *J Am Coll Cardiol* 2002; **39:** 935–942.
37. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; **105:** 1135–1143.
38. Lloyd-Jones DM, Martin DO, Larson MG, Levy D. Accuracy of death certificates for coding coronary heart disease as the cause of death. *Ann Intern Med* 1998; **129:** 1020–1026.

Supplementary Files

Supplementary File 1

Table S1. Subject characteristics vs. mortality

Table S2. Baseline mortality for ever smokers (former or current)

Table S3. Mortality according to FVC% pred, FEV_1% pred and age

Table S4. Mortality according to FVC% pred, FEV_1% pred and gender

Please find supplementary file(s);
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