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Why does lung function predict mortality? Results from the Whitehall II Cohort Study

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Abstract

The authors examined the extent to which socioeconomic position, behavior-related factors, cardiovascular risk factors, inflammatory markers and chronic diseases explain the association between poor lung function and mortality in 4,817 participants from the Whitehall II study (69.9% men, aged on average 60.8 years (Standard Deviation=5.9)). Forced expiratory volume in one second (FEV_1) was used to measure lung function in 2002–2004. 139 participants died during the mean follow-up of 6.4 years (SD=0.8). In a model adjusted for age and sex, being in the lower tertile of FEV_1 /height^2 was associated with a 1.92-fold (95% confidence interval: 1.35–2.73) increased risk of mortality compared to being in the top two tertiles. Once age, sex and smoking history were taken into account, the most important explanatory factors for this association were inflammatory markers (percentage reduction of the FEV_1 /height^2 -mortality association=21.3%), coronary heart disease, stroke and diabetes (percentage reduction=11.7%) and alcohol consumption, diet, physical activity and BMI (percentage reduction=9.8%). The contribution of socio-economic position and cardiovascular risk factors was small (percentage reduction ≤3.5%). Taken together, these factors explained 32.5% of the association. Multiple pathways link lung function to mortality; our results show inflammatory markers to be particularly important.

MESH Keywords Adult ; Aged ; Biological Markers ; blood ; Cardiovascular Diseases ; metabolism ; mortality ; psychology ; Chronic Disease ; Cohort Studies ; Female ; Great Britain ; Health Behavior ; Humans ; Inflammation ; blood ; Lung ; physiopathology ; Male ; Middle Aged ; Predictive Value of Tests ; Respiratory Function Tests ; Retrospective Studies ; Risk Factors ; Socioeconomic Factors ; Survival Rate

Author Keywords lung function ; FEV1 ; mortality ; inflammation ; middle aged

Poor lung function, often characterized by low forced expiratory volume in one second (FEV_1), is a well-established predictor of mortality with early work in this domain dating from 1970 [1] . This association is seen across the continuum of the FEV_1 distribution [2 –5] and over short and long follow-ups [2 –7] , with the longest follow-up period being over 40 years [2 , 8] Several mechanisms have been proposed to explain these associations [5 , 9 –11] including smoking, age-related chronic conditions, and inflammation. However, the relative importance of different mechanisms remains unclear as few studies have been able to use a comprehensive range of explanatory risk factors within a single methodological set up. The objective of the present study is therefore to examine the extent to which socioeconomic factors, health behaviors, cardiovascular risk factors and diseases, and inflammatory markers explain the association between lung function and all-cause mortality.

MATERIALS AND METHODS

Study population

Data are drawn from the Whitehall II study established in 1985 as a longitudinal study on 10,308 civil servants (6,895 men and 3,413 women) [12] . All civil servants aged 35–55 years in 20 London based departments were invited to participate by letter, 73% agreed. The baseline examination (Phase 1) took place during 1985–1988 and involved a clinical examination and a self-administered questionnaire including sections on lifestyle factors. Subsequent phases of data collection have alternated between postal questionnaire alone (Phases 2 (1988–1990), 4 (1995–1996), 6 (2001) and 8 (2006)) and postal questionnaire accompanied by a clinical examination (Phases 3 (1991–1993), 5 (1997–1999), 7 (2002–2004) and 9 (2007–2009)). Participants gave written consent to participate in the study and the University College London ethics committee approved the study. Measures of lung function were introduced to the study in 2002–2004 (Phase 7) when the mean age of participants was 60.8 years, SD=5.9, range=50.5–73.7 years.

Lung function

Lung function was measured using a portable flow spirometer (MicroPlus Spirometer, Micro Medical Ltd, Kent, UK), administered by a trained nurse. Participants with the following conditions were allowed to opt out of lung function tests: recently been coughing up blood of unknown origin, ever had a pneumothorax, severe angina requiring hospitalization in the previous 6 months, ever had a heart attack or stroke, ever had a pulmonary embolism or an aneurysm, recent ear or eye surgery, recent stomach or chest surgery, ever suffered with a perforated ear drum or hernia, and blood pressure higher than 180/96 mmHg on the day. Thus, 4,832 (74.5%) of the 6,483 participants who came for the clinical examination between 2002 and 2004 undertook spirometry. We assessed Forced Vital Capacity (FVC) and FEV_1 . FVC measures the volume of air that can forcibly be blown out after full inspiration, measured in litres. FEV_1 measures the volume of air expelled in the first second during the FVC manoeuvre, again measured in litres 13 . The largest FVC and FEV_1 values from three manoeuvres (Pairwise correlations between 0.91 and 0.93 for the three measures of FEV_1 and between 0.94–0.96 for FVC) were used in the analysis.

Mortality

A total of 10,297 respondents (99.9%) were successfully traced for mortality through the national mortality register kept by the National Health Services Central Registry using the National Health Service identification number assigned to each British citizen. In our analysis, mortality follow-up began at the measurement of lung function during the medical examination (2002–2004, Phase 7) and ended on the 31st January 2010.

Covariates

Socio-demographic variables used were age, sex, and socioeconomic position (6-level civil service employment grade). Employment grade in the Whitehall II study is a comprehensive marker of socioeconomic circumstances and is related to salary, social status and level of responsibility 12 .

Health behaviors were drawn from questionnaires at Phases 1, 3, 5, and 7. Smoking history was assessed using questions on smoking status and current amount of tobacco smoked categorized as “current smoker at Phase 7”, “recent ex-smoker” (those who stopped smoking between Phases 1 and 7), “long-term ex-smoker” (those who stopped smoking before Phase 1), and “never smoker”. The “current smoker” category was further divided into three groups according to the number of cigarettes smoked per day: less than 10, between 10 and 20, and more than 20. Alcohol consumption was assessed via questions on the number of alcoholic drinks (“measures” of spirits, “glasses” of wine, and “pints” of beer) consumed in the last seven days. This was converted to number of units (1 unit=8 grams) of alcohol. The frequency of fruit and vegetable consumption was assessed on an 8-point scale, ranging from “seldom or never” to “two or more times a day”. The number of hours of moderate and vigorous physical activity per week was calculated from a question on the number of hours of physical activity at different levels at Phases 1 and 3, and from a 20-item questionnaire on the frequency and duration of participation in walking, cycling, sports, gardening, housework, and home maintenance, at Phases 5 and 7 14 . Summary measures of these health behaviors over the four phases were used in the present analysis; smoking history as defined above, and for the other health behavior measurements mean values over the four phases.

Body mass index (BMI) at Phase 7 was calculated as weight divided by height squared (kg/m^2). Weight was measured in underwear to the nearest 0.1 kg using an electronic Soehnle scale with a digital readout (Leifheit AS, Nassau, Germany). Height was measured in bare feet to the nearest millimetre using a stadiometer with the participant standing completely erect with the head in the Frankfort plane. BMI was categorized as: BMI<20, BMI 20.0–24.9, BMI 25–29.9, and BMI ≥30.

Cardiovascular risk factors included in the analysis were serum cholesterol, systolic and diastolic blood pressure, and were measured during the clinical examination at Phases 1, 3, 5, and 7. Blood pressure was measured twice with the participant sitting after a 5-minute rest using the Hawksley random-zero sphygmomanometer. The average of two readings was taken to be the measured blood pressure. Serum cholesterol was measured within 72 hours in serum stored at 4°C using enzymatic colorimetric methods. As for the health behaviors, the mean of these measures over the four phases of data collection (Phases 1, 3, 5 and 7) was used to reflect history of these risk factors in the analysis.

Chronic conditions included prevalence of coronary heart disease (CHD), stroke, and diabetes. CHD prevalence was based on clinically verified events and included myocardial infarction and definite angina 15 . Stroke was assessed using a self-reported measure of physician diagnosis. Diabetes was defined by a fasting glucose ≥7.0 mmol/L or a 2-hour postload glucose ≥11.1 mmol/L or reported doctor diagnosed diabetes, or use of diabetes medication 16 .

Inflammatory markers included interleukin-6 (IL-6) and C-reactive protein (CRP), assessed at Phases 3 and 7. During the clinical examination fasting serum was collected and was stored at −70°C until analysis. Samples from both phases were analysed at the same

time. CRP was measured using a high-sensitivity immunonephelometric assay in a BN ProSpec nephelometer (Dade Behring, Milton Keynes, UK). IL-6 was measured using a high-sensitivity ELISA assay (R & D Systems, Oxford, UK) 17 . As the distributions of CRP and IL-6 were skewed, they were log-transformed for the analysis. The mean of the Phases 3 and 7 measures was used in the analysis.

Statistical analysis

FEV_1 divided by height squared was used in the analysis as it adjusts the lung function measure for body size and has been shown to be a good predictor of mortality 4 , 6 . We also examined the associations with FVC/height^2 and FEV_1 percent of the predicted value (FEV_1 % pred) and report these results briefly. As the distribution of the lung function differs by sex, we used sex-specific tertiles of the lung function measures in the analyses.

We first assessed the differences in all covariates between those who were alive and those who had died at the end of the follow-up period using t-tests for continuous variables and chi-square tests for categorical variables. We also investigated the association between sex-specfic tertiles of FEV_1 /height^2 and covariates using linear regression for continuous variables and logistic regression for dichotomous variables.

In order to examine the relationship between lung function and mortality graphically over the follow-up period, unadjusted and fully adjusted survival curves were plotted for tertiles of FEV_1 /height^2 , 18 . Subsequently, Cox regression with age as time-scale was used to estimate Hazard Ratios (HR) and their 95 percent confidence intervals (CI) for the association between the tertiles of lung function and mortality. The proportional hazards assumption for the Cox model was confirmed formally by the Shoenfeld's tests.

As no difference of risk was found between the two upper tertles of FEV_1 /height^2 , the results show the HR of mortality associated with being in the lower FEV_1 /height^2 compared to that in the upper two tertles of FEV_1 /height^2 . We first examined the extent to which this association was explained by smoking history. In order to do this, we added smoking history to the model including age and sex (model 1). The reduction in model 1 attributed to smoking history was calculated using the formula "$100 \times (\beta_{\text{Model 1}} - \beta_{\text{Model 1+smoking history}})/(\beta_{\text{Model 1}})$". Subsequently, the extent to which this association was attenuated was examined by adding socioeconomic position, other health behaviors and BMI, cardiovascular risk factors, chronic diseases, and inflammatory markers, sequentially and then all covariates simultaneously to the model adjusted for age, sex and smoking history (model 2). The reduction in model 2 attributed to the group of covariates under consideration was calculated using the formula "$100 \times (\beta_{\text{Model 2}} - \beta_{\text{Model 2+covariates}})/(\beta_{\text{Model 2}})$". All analyses were repeated using FVC/height^2 instead of FEV_1 /height^2 as the measure of lung function. We also undertook analysis using FEV_1 % pred, computed based on reference values from Quanjer and colleagues 19 .

The main analysis was performed using the statistical software STATA 10, StataCorp LP, Texas, USA. Adjusted survival curves were calculated using the statistical software SAS 9 and the macro proposed by Cole and colleagues.18

RESULTS

Sample description

A total of 4,817 participants with complete data on lung function and all covariates were included in the analysis; 139 died during a mean follow-up period of 6.4 years (SD=0.8). Compared to the 1,666 participants who came to the clinical examination at Phase 7 (2002–2004) but did not participate in the spirometry test, the 4817 individuals on whom the analysis is based had a lower rate of all-cause mortality (2.9% vs. 6.1%, P <0.001), particularly that from respiratory diseases (0.2% vs. 0.3%, p <0.001), cardiovascular diseases (0.6% vs. 1.5%, P <0.001), and cancer (1.4% vs. 2.1%, P <0.001) although not lung cancer (3 cases in study participants vs. 0 case in others). This group was also younger (60.8 vs. 61.9 years, P <0.001), composed of fewer current smokers (7.3% vs 9.2%, P <0.001) but showed no difference in self-reported history of asthma (9.9% vs. 10.0%, P =0.96).

Table 1 presents characteristics of the study participants as a function of the vital status at the end of follow-up. Table 2 shows that there was a linear association between all the covariates and the sex-specific tertiles of FEV_1 /height^2 (P ≤0.005). 721 (15.0%) of the 4,817 participants of the present study had a FEV_1 /FVC ratio lower than 70%; their inclusion in the analysis did not change the results much so all analyses are based on all 4817 individuals. There was no gender difference in the association between FEV_1 /height^2 and mortality (P for interaction = 0.79) leading us to combine men and women in the analysis.

Association between lung function and mortality

In analysis adjusted for age and sex, compared to the top tertile of FEV/height^2 , there was no higher risk of mortality in the second tertile (HR=0.96; 95% CI: 0.57–1.60), whereas participants in the lower tertile showed higher risk (HR=1.88; 95% CI: 1.19–2.97). As a result, we combined the top two tertiles in subsequent analyses. Figure 1 shows unadjusted and fully adjusted survival curves using

sex-specific tertiles of FEV_1 /height^2 . As is clear from the figure, a difference in probability of survival between these two groups started to appear after approximately 18 months of follow-up and persisted over the rest of the follow-up. The dotted line in the figure shows the attenuation in the association with the addition of covariates to the model.

Table 3 presents the adjustment for covariates in greater detail. In model 1, adjusted for age and sex, being in the lower tertile of FEV_1 /height^2 was associated with a 1.92-fold (95% CI: 1.35–2.73) increased risk of mortality compared to being the top two tertiles. When smoking history was entered in the model, this association was reduced by 4.9% (HR=1.86; 95% CI: 1.31–2.66; model 2). The inclusion of socioeconomic position (model 3) and cardiovascular risk factors (model 5) to this model did not substantially change the association (percentage reduction ≤3.5%). When physical activity, diet, alcohol consumption and BMI were entered in model 2, the association was reduced by 9.8%. When these behaviors were introduced separately, physical activity made the greatest attenuation (8.0% for physical activity, and less than 4% for the other health behaviors and BMI). The percentage reduction related to chronic diseases was 11.7%. Adding inflammatory markers to model 2 reduced the association between FEV_1 /height^2 and mortality by 21.3%. All these covariates taken together explained 32.5% of the association in addition to the 4.9% explained by smoking history.

When we replaced FEV_1 /height^2 by FVC/height^2 as the measure of lung function, the HR for mortality for the lower tertile compared to the top two tertiles was 1.83 (95% CI: 1.68) in the model adjusted for age and sex. All the covariates taken together explained 52.3% of this association in addition to the 3.7% explained by smoking history, with inflammatory markers leading to the greatest attenuation in the association (28.0%). The analysis using FEV_1 % pred (online supplement Web Table 1) showed being in the lowest tertile to be associated with a 1.55-fold (95% CI: 1.11–2.17) higher risk of mortality compared to the top two tertiles. Here again, inflammation markers explained the greater part of the association (33.9%).

We also undertook analyses using cause-specific mortality but due to the small number of deaths these analyses are restricted to cardiovascular (N=35) and cancer (N=68) mortality. Those in the lowest FEV/height^2 tertile had greater risk of cardiovascular (HR=1.90; 95% CI: 0.94–3.85) and cancer mortality (HR=2.08; 95% CI: 1.25–3.43), although the first association did not reach statistical significance at conventional level. Inflammatory markers explained the greater part of the association with cardiovascular (33.5% in addition to the 5.0 % explained by smoking history) and cancer mortality (12.5% in addition to the 10.9% explained by smoking history). All the covariates together explained 70.1% of the association with cardiovascular and 13.3% of that with cancer mortality in addition to smoking history.

Sensitivity analysis

We performed further analyses in several subgroups in order to ascertain the robustness of our findings. The analyses were repeated among never smokers (N=2,422, Web Table 2), those without a self-reported history of asthma (N=4,336, Web Table 3), in groups with FEV/FVC<70% (N=721, Table S4) and ≥70% (N=4096, Web Table 4). Also, analyses excluding participants in the lowest tertile of the fat-free-mass distribution (N=2,842, Web Table 5) and separately on those with BMI<30kg/m^2 (N=3976, Web Table 6) and ≥30kg/m^2 (N= 841, Web Table 6) yielded results largely similar to those in the main analysis. Further analyses (Web Table 7) excluding deaths from respiratory diseases (N=2) and lung cancer (N=1) in the first two years of follow-up also support our main findings. Finally, we examined the role of the explanatory variables by excluding participants with CRP level greater than 10 mg/L (Web Table 8) to rule out the influence of infection on the day of the examination 20 . Here again, the results were similar to those reported in the full sample.

DISCUSSION

Data from a large British cohort show that poor lung function, characterised by low FEV_1 /height^2 , is associated with higher risk of all-cause mortality in late midlife. Similar results were found for FVC/height^2 and FEV_1 % pred. Socioeconomic position, health behaviors and BMI, cardiovascular risk factors, cardiovascular diseases, and inflammatory markers were used to explain this association and our results show inflammatory markers, and to a lesser extent behavior-related factors and chronic diseases to explain the greater part of the association between lung function and mortality. Taken together, these factors explained a third (FEV_1 /height^2) to half (FVC/height^2 & FEV_1 % pred) of the associations.

It is well established that lung function predicts mortality 2 , 4 , 5 , 21 even though the mechanisms underlying this association remain unclear 5 , 9 –11 . Studies have examined changes in this association after adjusting for the effects of smoking, cardiovascular risk factors or diseases 4 , 5 , 11 but to our knowledge no study has attempted to quantify the impact of a wide range of different explanatory factors on the association. Lung function was once thought to reflect only smoking status which was hypothesized to explain its association with mortality. However, several studies, including our study, have shown lung function also to be related to mortality in never-smokers. 3 , 6 , 11 , 22 , 23 Clearly, smoking is not the only explanation of this association. Physical activity 24 –26 and healthier diet 27 –29 have also been found to be associated with better lung function and obesity to reduced lung function 30 . Our results show health behaviors and BMI to explain approximately 10% of the association between lung function and mortality, with the effect driven mainly by smoking and physical activity.

Other plausible explanatory factors are chronic comorbidities. This hypothesis is supported by the fact that patients with chronic obstructive pulmonary disease (COPD) die mainly from causes other than respiratory diseases 31 ; arguing for the “common cause” hypothesis. Ageing is accompanied by an increase in multiple chronic diseases resulting in high comorbidity at older ages, including COPD 10 . Thus lung function might simply be a proxy for general health, explaining its association with mortality 5 , 32 . Another possibility is that impaired lung function allows excessive quantity of inhaled environmental deleterious agents to enter the body that then lead to disease and death 33 . In the present study, chronic diseases, such as coronary heart disease, stroke and diabetes, explained 12% of the association between FEV_1 /height^2 and mortality. However, our data did not allow us to distinguish between the two proposed pathways: lung function as a proxy for general health and chronic diseases as mediating the association between lung function and mortality.

More recently, the inflammatory hypothesis has been proposed as a potential explanatory factor of the relationship between lung function and other comorbidities leading to death 9 , 10 . Indeed, higher levels of inflammatory markers have been found among persons with impaired lung function 34 , 35 . However, it is still debated whether it is inflammation that leads to lung function deterioration or the inverse. 10 , 34 , 36 , 37 Inflammation is associated with several chronic conditions 10 , such as osteoporosis, diabetes, and atherosclerosis, that are all risk factors for mortality. Thus, there are some arguments in favour of a possible role of inflammatory markers in the association between lung function and mortality and our results support this hypothesis.

Nevertheless, the importance of inflammatory markers in this association may also be due to residual confounding of smoking as higher levels of inflammation are found in smokers. Furthermore, it has been suggested that inflammation leads to muscle wasting 10 , 38 that is itself linked to lower lung functioning 36 , 39 . Our analysis based on never smokers and excluding those in the lowest tertile of the fat-free-mass distribution showed inflammation to continue to play a role in mediating the association between lung function and mortality.

Strengths and weaknesses

The primary strength of this study is the large number of factors investigated to explain the association between lung function and mortality. Indeed, data on health behaviors and cardiovascular risk factors were available over a 15 year-period preceding the assessment of lung function. Moreover, to our knowledge, this is the first study to assess the role of inflammatory markers. A further strength of the study is the use of adjusted survival curves that allow us to summarize the data by avoiding potential weaknesses of the multiplicative model 40 .

Three limitations of this study must also be noted. First, although the sample covered a wide socioeconomic range, with annual full-time salaries ranging from £4,995 to £150,000, data are from white-collar civil servants and cannot be assumed to be representative of the general population. Second, the inflammatory markers considered in our study are general markers of inflammation, included in the Whitehall II study, to assess outcomes such as cardiovascular disease and do not constitute ideal “lung function” markers. Third, our results must be interpreted with caution as the study design does not allow us to rule out the reverse causation between lung function and other covariates. Finally, these results are based on the healthier Whitehall participants, that is, those who were still alive and took part in the screening at Phase 7 of the study and who reported no contraindicative conditions against participation in the lung function tests. Nevertheless, lower lung function still predicts mortality in this selected population and our results are likely to underestimate the true association.

Conclusions

This study is the first to investigate several potential explanations underlying the well-established association between lung function and mortality. The main finding emphasises the importance of inflammatory markers for this association. The other important explanatory factors were health behaviors and chronic diseases, such as coronary heart disease, stroke and diabetes. These results show that multiple processes are likely to link lung function and mortality.

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Figure 1

Unadjusted and Adjusted Survival Curves for Categories of Lung Function, Whitehall II study, United Kingdom, 2002–2010 (N=4817)[a] [a] See Table 4 for number of participants at risk of mortality.

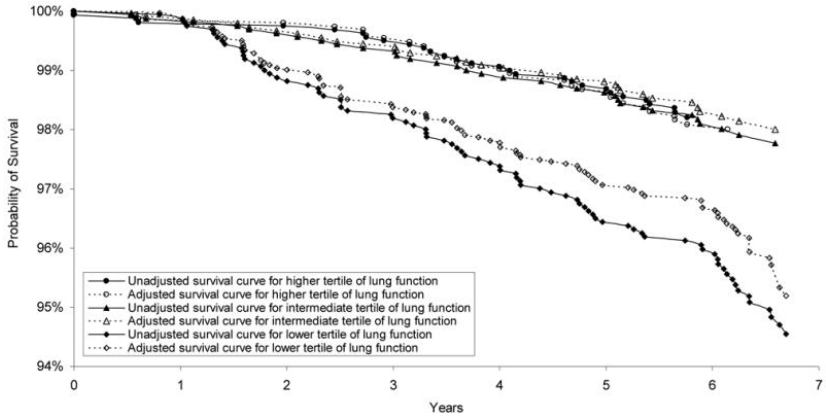

Table 1

Characteristics of Study Population as a Function of Vital Status at the end of Follow-up[a] , Whitehall II study, United Kingdom, 2002–2010 (N=4817)

		Alive at the end of follow-up	Dead at the end of follow-up	p
N (%)		4678 (97.1)	139 (2.9)	
Socio-demographic factors				
Age	M (SD)	60.7 (5.9)	63.7 (6.1)	<0.001
Women	N (%)	1448 (30.9)	51 (36.7)	0.15
Low employment grade	N (%)	500 (10.7)	23 (16.6)	0.03
Health behaviors				
Current smokers	N (%)	354 (7.6)	19 (13.7)	0.008
Units of alcohol/week	M (SD)	11.4 (11.4)	13.1 (16.0)	0.10
Frequency of fruit & vegetable consumption/week	M (SD)	8.1 (3.3)	7.8 (3.5)	0.24
Hours of moderate & vigorous physical activity/week	M (SD)	3.7 (2.7)	3.0 (2.6)	0.003
BMI (kg/m^2)	M (SD)	26.5 (4.3)	28.3 (5.3)	<0.001
Cardiovascular risk factors				
Systolic blood pressure (mmHg)	M (SD)	122.6 (12.0)	125.6 (12.3)	0.004
Diastolic blood pressure (mmHg)	M (SD)	76.3 (7.7)	77.5 (8.2)	0.07
Total blood cholesterol (mmol/L)	M (SD)	6.0 (0.9)	6.0 (0.9)	0.94
Chronic diseases				
Diabetes	N (%)	406 (8.7)	26 (18.7)	<0.001
Coronary heart disease	N (%)	298 (6.4)	19 (13.7)	0.001
Stroke	N (%)	61 (1.3)	6 (4.3)	0.003
Inflammatory markers				
CRP (log transformed)	M (SD)	0.04 (1.00)	0.49 (1.08)	<0.001
IL6 (log transformed)	M (SD)	0.50 (0.54)	0.80 (0.61)	<0.001
Lung function				
FEV_1 (L)	M (SD)	2.9 (0.8)	2.5 (0.8)	<0.001
FEV_1 /$height^2$ (L/m^2)	M (SD)	1.0 (0.2)	0.9 (0.2)	<0.001
FVC (L)	M (SD)	3.9 (1.0)	3.4 (0.9)	<0.001
FVC/$height^2$ (L/m^2)	M (SD)	1.3 (0.3)	1.2 (0.3)	<0.001

Abbreviations: M, mean; SD, standard deviation; FEV1, forced expiratory volume; FVC, forced vital capacity.

a End of follow-up was defined as 31st of January, 2010 or date of censoring, whichever occurred first.

Table 2

Characteristics of the Study Population as a Function of Tertiles of FEV_1 /height^2 , Whitehall II study, United Kingdom, 2002–2010 (N=4817)

		Sex-specific tertiles of FEV_1 /height^2			
		Higher	**Intermediate**	**Lower**	**p for trend** [a]
N (%)		1,605 (33.3)	1,606 (33.3)	1,606 (33.3)	
Socio-demographic factors					
Age	M (SD)	58.2 (4.9)	60.8 (5.7)	63.3 (5.9)	<0.001
Women	N (%)	498 (31.0)	479 (29.8)	522 (32.5)	0.37
Low employment grade	N (%)	107 (6.7)	155 (9.7)	261 (16.3)	<0.001
Health behaviors					
Smoking history[b]					<0.001
Current smokers	N (%)	80 (5.0)	128 (8.0)	165 (10.3)	
Recent ex-smokers	N (%)	171 (10.7)	184 (11.5)	180 (11.2)	
Long-term ex-smokers	N (%)	521 (32.5)	510 (31.8)	456 (28.4)	
Never smokers	N (%)	833 (51.9)	784 (48.8)	805 (50.1)	
Units of alcohol/week	M (SD)	12.0 (11.4)	11.8 (11.6)	10.6 (11.8)	<0.001
Frequency of fruit & vegetable consumption/week	M (SD)	8.4 (3.3)	8.2 (3.3)	7.7 (3.2)	<0.001
Hours of moderate & vigorous physical activity/week	M (SD)	3.8 (2.7)	3.7 (2.6)	3.4 (2.7)	<0.001
BMI					<0.001
<20 kg/m^2	N (%)	52 (3.2)	45 (2.8)	46 (2.9)	
20–25 kg/m^2	N (%)	614 (38.3)	539 (33.6)	523 (32.6)	
25–30 kg/m^2	N (%)	715 (44.6)	715 (44.5)	727 (45.3)	
≥30 kg/m^2	N (%)	224 (14.0)	307 (19.1)	310 (19.3)	
Cardiovascular risk factors					
Systolic blood pressure (mmHg)	M (SD)	120.6 (11.2)	122.8 (12.0)	124.7 (12.4)	<0.001
Diastolic blood pressure (mmHg)	M (SD)	75.3 (7.7)	76.5 (7.7)	77.2 (7.6)	<0.001
Total blood cholesterol (mmol/L)	M (SD)	5.9 (0.9)	6.0 (0.9)	6.0 (0.9)	<0.001
Chronic diseases					
Diabetes	N (%)	88 (5.5)	129 (8.0)	215 (13.4)	<0.001
Coronary heart disease	N (%)	50 (3.1)	97 (6.0)	170 (10.6)	<0.001
Stroke	N (%)	12 (0.8)	24 (1.5)	31 (1.9)	0.005
Inflammatory markers					
CRP (log transformed)	M (SD)	−0.21 (0.99)	0.06 (0.96)	0.30 (1.00)	<0.001
IL6 (log transformed)	M (SD)	0.36 (0.48)	0.51 (0.52)	0.67 (0.57)	<0.001

Number of deaths	N (%)	28 (1.7)	33 (2.1)	78 (4.9)	<0.001

Abbreviations: FEV1, forced expiratory volume; M, mean; SD, standard deviation; BMI, body mass index; IL-6, interleukin-6; CRP, C-reactive protein.

a calculated from a linear regression for continuous variables and from a logistic regression for dichotomous variables.

b "Recent ex-smokers" defined participants who stopped smoking between Phases 1 (1988–1990) and 7 (2002–2004) and "long-term ex-smokers" participants who stopped smoking before Phase 1 (1988–1990).

Table 3

Mechanisms to Explain the Association Between Lung Function and Mortality, Whitehall II study, United Kingdom, 2002–2010 (N=4817)

Adjustment	HR[a]	95% CI	p	% reduction[b]
Model 1: adjusted for age and sex	1.92	1.35–2.73	<.001	
Model 2: Model 1 + smoking histor[c]	1.86	1.31–2.66	0.001	4.9
Model 3: Model 2 + socioeconomic position	1.84	1.29–2.63	0.001	1.7
Model 4: Model 2 + other health behaviors[d] + BMI	1.75	1.23–2.50	0.002	9.8
Model 5: Model 2 + blood cholesterol, systolic and diastolic blood pressure	1.82	1.27–2.59	0.001	3.5
Model 6: Model 2 + chronic diseases[e]	1.73	1.21–2.48	0.003	11.7
Model 7: Model 2 + inflammatory markers[f]	1.63	1.14–2.33	0.008	21.3
Model 8: fully-adjusted	1.52	1.05–2.19	0.03	32.5

a HR comparing participants in the lower sex-specific tertile of forced expiratory volume/height^2 to those in the top two tertiles.

b % reduction comparing Model 2 to Model 1 and then Models 3 to 8 to Model 2

c Smoking history constituted using smoking status measured from 1985/88 to 2002/04 and current amount of tobacco smoked in 2002/04.

d Alcohol consumption, physical activity, fruit and vegetable consumption.

e Diabetes, Coronary Heart Disease and self-reported stroke.

f Interleukin-6 and C-reactive protein, log-transformed.

Table 4

Number of participants at risk of mortality along the follow-up period, Whitehall II study, United Kingdom, 2002–2010 (N=4817)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
No. at risk							
Higher tetile of FEV_1 /height^2	1605	1596	1591	1586	1579	1571	1166
Intermediate tertile of FEV_1 /height^2	1606	1603	1598	1593	1586	1581	1199
Lower tertile of FEV_1 /height^2	1606	1602	1585	1570	1557	1538	1209