

Lung Function and Risk of Type 2 Diabetes and Fatal and Nonfatal Major Coronary Heart Disease Events: Possible Associations With Inflammation

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OBJECTIVE — We prospectively examined the relationship between lung function and risk of type-2 diabetes and fatal and nonfatal coronary heart disease (CHD) events and investigated the hypothesis that inflammation may underlie these associations.

RESEARCH DESIGN AND METHODS — A prospective study of 4,434 men aged 40–59 years with no history of cardiovascular disease (CHD or stroke) or diabetes drawn from general practices in 24 British towns and followed up for 20 years.

RESULTS — There were 680 major CHD events (276 fatal, 404 nonfatal) and 256 incident type 2 diabetes during the 20 years follow-up. Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁) but not FEV₁-to-FVC ratio were significantly and inversely associated with incident type 2 diabetes and fatal CHD events (not nonfatal events) after adjustment for age, potential confounders, and metabolic risk factors. The adjusted relative risk (RR) for type 2 diabetes (Quartile 1 vs. Quartile 4) were 1.59 (1.07–2.56) and 1.74 (1.16–2.61) for FVC and FEV₁, respectively ($P = 0.03$ and $P = 0.04$ for trend). The corresponding RR for fatal CHD were 1.48 (1.00–2.21) and 1.81 (1.19–2.76) ($P = 0.002$ and $P = 0.0003$ for trend). Lung function was significantly and inversely associated with C-reactive protein and interleukin-6; the inverse associations with type 2 diabetes for FVC and FEV₁ were attenuated after further adjustment for these factors ($P = 0.14$ and $P = 0.11$ for trend) but remained significant for fatal CHD ($P = 0.03$ and $P = 0.01$, respectively).

CONCLUSIONS — Restrictive rather than obstructive impairment of lung function is associated with incident type 2 diabetes (and fatal CHD) with both associations partially explained by traditional and metabolic risk factors and inflammation.

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The association between impaired lung function and cardiovascular disease (CVD) morbidity and mortality is well established (1,2) although the mechanisms remain unclear. Reduced lung function is also one of the many clinical features associated with type 2 diabetes (3,4). Diabetes has been shown to be associated with impaired pulmonary function in a restrictive pattern (3), and

prospective studies have suggested that reduced lung function may be associated with the development of type 2 diabetes (5–8). It has been suggested that inflammation may be a possible mechanism underlying the association between lung function and incident type 2 diabetes and CVD (6,7,9). Moreover, it has been suggested that lung function is more strongly associated with risk of fatal rather than

nonfatal coronary heart disease (CHD) events and has been implicated in increased fatality following a cardiac event (10). This is of interest given that recent studies have suggested that markers of inflammation, which are associated with lung function (11), may be more strongly associated with risk for fatal than risk for nonfatal vascular events (12,13). While inflammatory markers have been shown to contribute to—but not fully explain—the increased CVD risk associated with reduced lung function (9), the contributing role of inflammation to the associations between lung function and diabetes and fatal and nonfatal CHD events separately has yet to be explored. We have examined the prospective relationship between measures of lung function (including forced vital capacity [FVC], forced expiratory volume in 1 s [FEV₁], and FEV₁-to-FVC ratio) and incident type 2 diabetes as well as with major CHD, fatal CHD, and nonfatal myocardial infarction (MI) separately in middle-aged men and assessed the contributing role of inflammation (C-reactive protein [CRP] and interleukin-6 [IL-6]) to these associations over and above a comprehensive panel of traditional and metabolic risk factors. The findings may also provide further insight into understanding the underlying associations between type 2 diabetes and CHD.

RESEARCH DESIGN AND METHODS

The British Regional Heart Study is a large prospective study of CVD comprising 7,735 men aged 40–59 years and drawn from general practices in each of 24 towns in England, Wales, and Scotland in 1978–1980. The criteria for selecting the town, the general practice, and the subjects, as well as the methods of data collection have been reported (14). Research nurses administered a standard questionnaire that included questions on lifestyle and medical history. Physical measurements including height and weight were made, and venous nonfasting blood samples were obtained to prepare

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serum for the measurement of biochemical and hematological variables. CRP and IL-6 measurements were only available for men in the 7th to 24th towns visited ($n = 4,877$). Details of lifestyle factor classifications, social class, and blood pressure and blood lipid measurements have been reported (14–16). The men were asked to recall a doctor diagnosis of CHD, stroke, diabetes, and a number of other disorders. Men with recall of a doctor's diagnosis of CHD or stroke, known diabetics at screening, and with asymptomatic hyperglycemia ≥ 11.1 mmol/l were excluded ($n = 371$). We also excluded men with missing spirometry function ($n = 72$). After these exclusions, data were available for a group of 4,434 men, who became the subjects of this study.

CRP

In 1,531 men who were included in an earlier case control analysis, CRP was measured using a sensitive enzyme immunoassay (17). In the remainder, CRP was assayed in Glasgow by ultrasensitive nephelometry (Dade Behring, Milton Keynes, U.K.); intraassay and interassay coefficients of variation were 4.7 and 8.3%, respectively. Using the results of a calibration study in 295 subjects whose samples were assayed using both methods, the results of the earlier CRP assays were adjusted to the Glasgow assay, for which the current CRP international standard was used by subtracting -0.128 from the earlier log CRP assay (87.9% of the original value). In a sensitivity analysis, we restricted the analyses to the 3,342 men with CRP assayed by the ultrasensitive nephelometric method. The main findings remained unchanged.

IL-6

IL-6 was assayed using a high-sensitivity ELISA (R & D Systems, Oxford, U.K.). Intraassay and interassay coefficients of variation were 7.5 and 8.7%, respectively. IL-6 data were missing in 183 men.

Lung function

FEV₁ and FVC were measured using a Vitalograph spirometer (model J49-B2) with the subject seated. Two consecutive readings were made 15 s apart and, as per convention, the maximum of these two readings was used. FVC is the maximum volume of air expired during forced expiration and is primarily an indicator of lung volume. FEV₁ is the volume of air expired in the first second of forced expiration and is influenced by lung volume

and airflow obstruction. Cole (18) has shown that dividing by the height² is the most appropriate way of standardizing lung function for stature, and this yielded the best fit to the data (19). FEV₁ and FVC were height standardized to the average height (1.73 m) in the study; thus, height standardization was FEV₁ (FVC) = FEV₁ (FVC) multiplied by $(1.73/\text{height})^2$. The FEV₁-to-FVC ratio, an indicator of airflow obstruction, was defined as the ratio of raw FEV₁ to FVC. While not presented in the main text, we also considered alternative analyses using percentage predicted FEV₁ (raw FEV₁ divided by predicted FEV₁) and percentage predicted FVC (raw FVC divided by predicted FVC). Predicted FEV₁ and FVC were calculated using equations from a reference population of nonsmokers that included age and height as suggested by the European Respiratory Society guidelines (20).

Preexisting undiagnosed CHD and presence of arrhythmia

The World Health Organization (WHO) Rose chest pain questionnaire was administered to all men at the initial examination, and a standard resting 3-lead electrocardiogram (ECG) was recorded at rest (15). A normal rhythm was defined as sinus rhythm, coronary sinus rhythm, or sinus arrhythmia. All other statements of rhythm were treated as an arrhythmia e.g., sinus rhythm with ventricular extrasystoles (15). Preexisting undiagnosed evidence of CHD included evidence of ischemic heart disease on the WHO (Rose) chest pain questionnaire or electrocardiographic evidence of myocardial ischemia or infarction in the absence of a doctor's diagnosis of CHD (15).

Follow-up

All the men have been followed up for all-cause mortality, cardiovascular morbidity, and development of type 2 diabetes from the initial screening in January 1978–July 1980 to June 2008, and follow-up has been achieved for 99% of the cohort (15,16). This analysis is based on a 20-year follow-up from initial screening for each man. Information on deaths was collected through the established “tagging” procedures provided by the National Health Service registers. Fatal CHD events were defined as death with CHD (ICD-9 codes 410–414) as the underlying code. A nonfatal MI was diagnosed according to WHO criteria. Patients who survived a first MI for more than 28 days and who died thereafter during follow-up

were included in the nonfatal group. Case fatality is defined as the proportion of those major CHD events in which death occurred during the 28 days after the first event and in which the death certificate recorded CHD (ICD-9 codes 410–414). Evidence regarding diabetes was obtained by reports from general practitioners and by biennial reviews of the patients' notes (including hospital and clinic correspondence) through to the end of the study period. Cases are based on self-reported diagnoses confirmed by primary care records, an approach which has been validated in the present study.

Statistical methods

The men were divided by quartiles of FVC, FEV₁, and FEV₁-to-FVC ratio. Cox's proportional hazards model was used to assess the multivariate-adjusted relative risk (RR) for each quartile compared with the reference group (lowest quartile). In the adjustment, age, BMI, systolic blood pressure (sBP), HDL cholesterol, triglycerides, total cholesterol, blood glucose, CRP, and γ -glutamyl transferase (GGT) (which has been shown to be a strong predictor of type 2 diabetes) (16) were fitted as continuous variables; all other confounders were fitted as categorical variables. Smoking was fitted as five groups (never, former smokers, 1–19 cigarettes per day, 20–39 cigarettes per day, and 40+ cigarettes per day). Differences for associations between lung function measures and MI/CHD deaths and nonfatal events were evaluated using likelihood ratio tests based on methods of competing risk survival analysis (21). The likelihood ratio tests evaluated the hypothesis that the associations of lung function were the same for MI/CHD deaths and nonfatal MI.

RESULTS — In the 4,434 men with no prevalent diabetes or CHD, there were 256 incident cases of type 2 diabetes and 680 major CHD events (276 fatal, 404 nonfatal) during the 20-year follow-up period.

Table 1 shows baseline characteristics and levels of biological markers according to quartiles of FVC and the FEV₁-to-FVC ratio. FVC was strongly and significantly associated (inversely) with age, current smoking, physical inactivity, manual social class, preexisting evidence of undiagnosed CHD (but not arrhythmias), BMI, sBP, and metabolic risk factors (triglycerides, blood glucose), markers of inflammation (CRP, IL-6, white cell count), and GGT. Similar associations were seen for FEV₁ with the exception of BMI and

Table 1—Characteristics at baseline according to quartiles of FVC and FEV₁-to-FVC ratio

	Quartile				P value
	1	2	3	4	
FVC (l)	<3.97	3.97–	4.43–	4.87–	
Age (years)	53.1	51.4	49.4	47.6	<0.0001
Current smokers (%)	49.6	42.5	36.3	38.2	<0.0001
Inactive (%)	43.8	38.7	34.8	31.4	<0.0001
Heavy drinkers (%)	11.4	10.7	10.6	11.5	0.88
Manual (%)	67.6	62.1	58.3	57.1	<0.0001
Evidence of CHD (undiagnosed) (%)	25.9	22.1	19.4	17.0	<0.0001
Silent MI (ECG) (%)	2.5	3.0	1.3	0.7	0.0002
Arrhythmia (%)	5.9	6.2	6.0	5.4	0.87
BMI (mg/k ²)	25.6	25.5	25.5	25.0	<0.0001
HDL cholesterol (mmol/l)	1.14	1.15	1.15	1.17	0.11
Triglycerides (mmol/l)	1.76	1.72	1.71	1.57	<0.0001
Cholesterol (mmol/l)	6.24	6.28	6.30	6.16	0.12
sBP (mmHg)	148.1	145.6	145.4	143.1	<0.0001
Glucose (mmol/l)	5.53	5.47	5.47	5.42	<0.0001
CRP (mg/l)	1.97	1.31	1.11	0.91	<0.0001
IL-6 (pg/ml)	2.89	2.39	2.14	2.01	<0.0001
WCC (×10 ⁹ /l)	7.17	6.95	6.89	6.82	<0.0001
GGT (IU/l)	16.4	15.2	14.7	13.7	<0.0001
FEV ₁ -to-FVC ratio	<0.71	0.71–	0.77–	0.82–	
Age (years)	52.2	50.8	49.7	48.7	<0.0001
Current smokers (%)	57.9	46.8	37.0	25.2	<0.0001
Inactive (%)	41.1	42.3	33.1	32.2	<0.0001
Heavy drinkers (%)	15.2	12.3	9.4	9.1	<0.0001
Manual (%)	71.2	64.0	56.8	53.0	<0.0001
Evidence of CHD (undiagnosed) (%)	25.0	20.2	18.8	20.5	0.001
Silent MI (ECG) (%)	2.3	1.5	2.0	1.8	0.57
Arrhythmia (%)	6.3	5.5	5.8	5.7	0.87
BMI (kg/m ²)	24.7	25.4	25.5	26.0	<0.0001
HDL cholesterol (mmol/l)	1.17	1.15	1.14	1.14	<0.0001
Triglycerides (mmol/l)	1.60	1.75	1.69	1.72	<0.0001
Cholesterol (mmol/l)	6.09	6.32	6.27	6.31	<0.0001
sBP (mmHg)	146.8	146.3	144.7	144.4	<0.0001
Glucose (mmol/l)	5.42	5.42	5.48	5.53	0.001
CRP (mg/l)	1.68	1.28	1.19	1.03	<0.0001
IL-6 (pg/ml)	2.80	2.32	2.23	2.08	<0.0001
WCC (×10 ⁹ /l)	7.32	7.03	6.89	6.62	<0.0001
GGT (IU/l)	15.0	15.2	14.6	14.9	0.77

Data are means unless otherwise stated. The numbers in bold indicate the range of FVC and FEV₁-to-FVC ratio for the four quartiles. WCC, white cell count.

blood glucose, which showed little association with FEV₁. By contrast, the FEV₁-to-FVC ratio was positively associated with BMI and blood glucose; no association was seen with GGT.

All measures of lung function (FEV₁, FVC, and FEV₁-to-FVC ratio) were strongly (inversely) associated with inflammation markers even after adjustment for age, BMI, evidence of CHD, smoking, physical activity, social class, alcohol intake, blood glucose, triglycerides, sBP, and HDL cholesterol. This was seen in both smokers and nonsmokers (all $P < 0.0001$). The adjusted standardized re-

gression coefficients for CRP for FEV₁, FVC, and FEV₁-to-FVC ratio were -0.21 , -0.27 , and -0.14 for smokers and -0.17 , -0.14 , and -0.04 for nonsmokers, respectively. For IL-6, the corresponding standardized regression coefficients were -0.11 , -0.12 , and -0.06 in smokers and -0.08 , -0.10 , and -0.06 in nonsmokers, respectively.

FVC and FEV₁ were significantly and inversely associated with risk of type 2 diabetes after adjustment for lifestyle characteristics, BMI, sBP, metabolic risk factors (blood glucose, triglycerides, HDL cholesterol), and GGT (Table 2). The in-

verse associations seen with FEV₁ and FVC were attenuated after further adjustment for CRP and IL-6 ($P = 0.14$ and $P = 0.11$ for trend, respectively) although the increased risks in those with low FEV₁ remained significantly increased when compared with high FEV₁ (Table 2). No association was seen between the FEV₁-to-FVC ratio and incident type 2 diabetes.

When examined separately by BMI status (<28 kg/m² and ≥ 28 kg/m²), the increased risk of type 2 diabetes associated with low FVC or low FEV₁ was more apparent in the <28 kg/m² BMI group. The adjusted RRs for FVC (Quartile 1 vs.

Table 2—Lung function and risk of incident type 2 diabetes during 20 years of follow-up

	FVC (l)				P-value trend
	1 (<3.97)	2 (3.97–)	3 (4.43–)	4 (4.87–)	
n	1,095	1,106	1,116	1,117	
Rate/1,000 P-years	4.7	3.2	3.2	2.1	
Model 1	2.54 (1.74–3.70)	1.58 (1.07–2.34)	1.56 (1.06–2.31)	1.00	<0.0001
Model 2	1.94 (1.32–2.86)	1.32 (0.89–1.97)	1.34 (0.90–1.97)	1.00	0.001
Model 3	1.59 (1.07–2.56)	1.14 (0.76–1.71)	1.27 (0.85–1.88)	1.00	0.03
Model 4	1.46 (0.97–2.20)	1.21 (0.81–1.81)	1.03 (0.68–1.55)	1.00	0.14
	FEV ₁ (l)				P-value trend
	1 (<2.95)	2 (2.95–)	3 (3.41–)	4 (3.81–)	
n	1,108	1,107	1,111	1,108	
Rate/1,000 P-years	3.9	3.4	3.5	2.2	
Model 1	2.05 (1.40–3.01)	1.51 (1.03–2.23)	1.56 (1.07–2.26)	1.00	0.005
Model 2	1.92 (1.29–2.86)	1.35 (0.91–1.99)	1.52 (1.04–2.21)	1.00	0.02
Model 3	1.74 (1.16–2.61)	1.36 (0.92–2.03)	1.35 (0.92–1.98)	1.00	0.04
Model 4	1.67 (1.09–2.56)	1.31 (0.87–1.97)	1.40 (0.94–2.08)	1.00	0.11
	FEV ₁ -to-FVC ratio				P-value trend
	1 (<0.71)	2 (0.71–)	3 (0.77–)	4 (0.82–)	
Rate/1,000 P-years	2.5	3.7	3.2	3.6	
Age-adjusted	0.67 (0.46–0.96)	0.87 (0.63–1.21)	0.77 (0.55–1.07)	1.00	0.12

Model 1, age-adjusted; Model 2, Model 1 + adjusted for age, BMI, smoking, physical activity, alcohol intake, social class, evidence of CHD (undiagnosed); Model 3, Model 2 + triglycerides, sBP, HDL cholesterol, blood glucose, and GGT; and Model 4, Model 3 + CRP + IL-6. P-years, person-years.

Quartile 4) were 1.73 (95% CI 1.03–2.93) and 1.14 (0.58–2.22) for the two BMI groups, respectively. The corresponding RRs for FEV₁ were 2.05 (1.17–3.61) and 1.11 (0.56–2.20). However, a formal test for interaction between FEV₁ or FVC and BMI with incident type 2 diabetes was not significant. Although the numbers were small, the increased risk associated with low FEV₁—and to a lesser extent FVC—was also seen in “never smokers” (Quartile 1 vs. Quartile 4: adjusted RR 1.21 [0.53–2.75] and 1.54 [0.63–3.80] for FVC and FEV₁, respectively). No interaction was seen with smoking status.

FVC and FEV₁ were significantly associated with major CHD events largely due to the association with fatal CHD events (Table 3). No association was seen for nonfatal events after adjustment for established risk factors. Comparisons of differing association between fatal and nonfatal events showed significant/marginally significant differences in the relationships between FEV₁ and FVC and fatal CHD and nonfatal MI ($P = 0.04$ and $P = 0.08$, respectively). The inverse association between FVC and FEV₁ with fatal CHD events was attenuated but remained significant after adjustment for CRP and

IL-6 ($P = 0.03$ and $P = 0.01$ for trend) although the increased risk associated with low FVC was no longer significant compared with those with high FVC (Table 3). Exclusion of the men who developed type 2 diabetes during the follow-up period or men with silent MI on ECG (85 men) made little difference to the findings. Although the numbers were small, the inverse association between FVC and FEV₁ and fatal CHD events after adjustment for CRP and IL-6 was seen in “never smokers” (Quartile 1 vs. Quartile 4; adjusted RR 2.86 [95% CI 0.77–10.66] and 2.41 [0.85–6.85] for FVC and FEV₁, respectively). Case fatality decreased with increasing lung function after adjustment for age, and the trend became of marginal significance after adjustment for CRP and preexisting disease. The FEV₁-to-FVC ratio was significantly, but weakly, inversely associated with fatal CHD events after adjustment for age ($P = 0.02$ for trend), but this was attenuated after adjustment for established CV risk factors (adjusted RR for the four quartiles 1.10 [0.76–1.60], 1.13 [0.79–1.63], 0.96 [0.66–1.40] and 1.00).

The percent predicted FVC (FEV₁) was highly correlated with height standardized FVC (FEV₁) ($r = 0.97$), and

models using continuous terms for percent predicted FVC and percent predicted FEV₁ were consistent with the above findings using FVC/height² and FEV₁/height² (data not shown).

CONCLUSIONS— In this study of British middle-aged men without diagnosis of CHD or type 2 diabetes, lung function as measured by FVC and FEV₁ was significantly and inversely associated with risk of incident type 2 diabetes and fatal CHD after adjustment for a wide range of variables including smoking, physical activity, alcohol intake, social class, BMI, preexisting CHD (undiagnosed), blood pressure, total cholesterol, metabolic markers (blood glucose, triglycerides, HDL cholesterol), and hepatic function. Interestingly, inflammatory pathway (i.e., CRP, IL-6) adjustments further attenuated associations between FEV₁ and FVC and type 2 diabetes and fatal CHD. Obstructive airways disease per se (as much as it may be reflected by the first quartile of the FEV₁-to-FVC ratio [<0.71]) was related neither to type 2 diabetes nor independently with CHD events. Our findings confirm previous studies that have reported inverse associations between lung function and type 2 diabetes and

Table 3—Lung function and risk of all major CHD events, fatal and nonfatal MI events, and case fatality during 20 years of follow-up

	FVC (l)				P for trend
	1 (<3.97)	2 (3.97–)	3 (4.43–)	4 (4.87–)	
<i>n</i>	1,095	1,106	1,116	1,117	
Major CHD					
Rate/1,000 P-years	11.9 (225)	9.9 (189)	7.9 (157)	6.1 (123)	
Model 1	1.56 (1.24–1.97)	1.39 (1.11–1.76)	1.19 (0.94–1.51)	1.00	<0.0001
Model 2	1.25 (0.98–1.59)	1.26 (1.00–1.60)	1.09 (0.86–1.39)	1.00	0.007
Model 3	1.14 (0.88–1.47)	1.23 (0.96–1.37)	1.14 (0.88–1.47)	1.00	0.16
Fatal CHD					
Rate/1,000 P-years	5.4 (102)	4.3 (82)	3.0 (59)	1.9 (39)	
Model 1	1.91 (1.30–2.81)	1.70 (1.16–2.51)	1.32 (0.88–1.98)	1.00	<0.0001
Model 2	1.48 (1.00–2.21)	1.50 (1.01–2.22)	1.15 (0.76–1.74)	1.00	0.002
Model 3	1.41 (0.92–2.16)	1.52 (1.00–2.32)	1.28 (0.82–1.98)	1.00	0.03
Nonfatal MI					
Rate/1,000 P-years	6.5 (123)	5.6 (107)	4.9 (98)	4.2 (84)	
Age-adjusted RR	1.39 (1.04–1.86)	1.25 (0.93–1.66)	1.14 (0.85–1.53)	1.00	0.04
Risk factor adjusted #	1.12 (0.82–1.51)	1.15 (0.86–1.53)	1.07 (0.79–1.44)	1.00	0.38
Case fatality (%)	49.1	41.1	36.7	28.7	
Age-adjusted OR	1.40 (0.86–2.27)	1.40 (0.86–2.29)	1.19 (0.72–1.98)	1.00	P = 0.03
+ CRP + preexisting CHD	1.30 (0.80–2.14)	1.36 (0.83–2.22)	1.18 (0.71–1.96)	1.00	P = 0.07
	FEV ₁ (l)				
	1 (<2.95)	2 (2.95–)	3 (3.41–)	4 (3.81–)	
<i>n</i>	1,108	1,107	1,111	1,108	
Major CHD					
Rate/1,000 P-years	12.1 (228)	10.0 (190)	8.2 (161)	5.6 (115)	
Model 1	1.66 (1.31–2.11)	1.44 (1.14–1.83)	1.32 (1.03–1.67)	1.00	<0.0001
Model 2	1.28 (1.00–1.65)	1.18 (0.93–1.51)	1.17 (0.92–1.49)	1.00	0.002
Model 3	1.15 (0.88–1.50)	1.12 (0.87–1.43)	1.20 (0.93–1.55)	1.00	0.12
Fatal CHD					
Rate/1,000 P-years	6.0 (112)	4.1 (78)	3.0 (59)	1.6 (33)	
Model 1	2.41 (1.60–3.63)	1.80 (1.19–2.73)	1.57 (1.02–2.40)	1.00	<0.0001
Model 2	1.81 (1.19–2.76)	1.46 (0.96–2.23)	1.37 (0.89–2.11)	1.00	0.0003
Model 3	1.63 (1.03–2.67)	1.46 (0.93–2.29)	1.42 (0.90–2.25)	1.00	0.01
Nonfatal MI					
Rate/1,000 P-years	6.1 (116)	5.9 (112)	5.2 (102)	4.0 (82)	
Age-adjusted RR	1.32 (0.97–1.79)	1.30 (0.97–1.73)	1.22 (0.91–1.63)	1.00	0.02
Risk factor adjusted #	1.02 (0.74–1.41)	1.04 (0.77–1.40)	1.09 (0.81–1.47)	1.00	0.35
Case fatality (%)	45.3	43.4	37.6	31.7	
Age-adjusted OR	1.77 (1.06–2.95)	1.36 (0.81–2.27)	1.26 (0.74–2.13)	1.00	0.03
+ CRP + preexisting CHD	1.65 (0.97–2.79)	1.31 (0.78–2.21)	1.22 (0.72–2.07)	1.00	0.06

Model 1, age adjusted; Model 2, Model 1 + adjusted for BMI, smoking, physical activity, alcohol intake, social class, preexisting evidence of CHD (undiagnosed), SBP, cholesterol, and HDL cholesterol; and Model 3, Model 2 + CRP + IL-6. OR, odds ratio.

CHD events (1,2,5–8, 22) and extend these findings further by examining the role of inflammation in explaining these associations and differentiating between fatal and nonfatal CHD events.

Lung function and type 2 diabetes

Our results are consistent with other prospective studies that have shown restrictive lung function (reduced FVC and FEV₁) but not obstructive pulmonary function (FEV₁-to-FVC ratio) is associated with the development of type 2 dia-

betes (5–8). Numerous cross-sectional studies have also suggested a restrictive pattern of deterioration in lung function in diabetics (3). Several explanations for the link between lung function and incident type 2 diabetes have been proposed including metabolic pathways, inflammatory processes, and early life influences (6,7). FVC in particular and FEV₁ were associated with metabolic abnormalities and components of the insulin resistance syndrome, which is consistent with several previous studies that have reported

associations between restrictive lung patterns with glucose metabolism and the metabolic syndrome (23). We did not have measures of fasting insulin but simultaneous adjustment for metabolic risk markers closely associated with insulin resistance (BMI, glucose, triglycerides, and HDL cholesterol) and GGT (a correlate of hepatic fat and insulin resistance) (16) did not fully explain the association. We observed a strong association between both restrictive and obstructive lung patterns and inflammatory markers

CRP and IL-6. These factors contributed to the association between reduced lung function—in particular FVC—and type 2 diabetes, although the increased risk associated with low FEV₁ compared with high FEV₁ remained significant. Low birth weight has been linked to both type 2 diabetes and adult lung function (24). Thus, reduced lung function (FEV₁) and risk of type 2 diabetes may also be partially determined by early growth.

Lung function and CHD

Although numerous studies have reported an inverse relationship between lung function (FEV₁ or FVC) and risk of CHD, the independence of the association has been inconsistent (1,2,22); few studies have differentiated between fatal and nonfatal episodes. Our findings, based on a larger number of events, confirmed previous findings that reduced lung function is associated more closely with increased risk of fatal CHD than with nonfatal episodes (10) and predicts increased fatality in the event of a cardiac event (10). The association with fatal events was independent of cardiovascular risk factors and was present in “never smokers.” In most studies, fatal and nonfatal events are combined due to perceptions concerning common etiologies or limited power; this may contribute to the inconsistent findings between studies. The reason for increased incidence of fatal events with poor lung function, in particular FEV₁, appears only partially explained by inflammation (CRP, IL-6). The increased risk of fatal CHD associated with low lung function may potentially be due to ventricular dysrhythmias or silent MIs, which are associated with poor lung function and increased fatality (25), or due to the increased risk of developing diabetes, which also increases case fatality (25). However, exclusion of the 85 men with silent MIs on ECGs or incident diabetics in the study and further adjustment for arrhythmias made little difference to the findings.

Implications for diabetes and excess risk of fatal CHD

The finding from this and other studies suggest that reduced lung function not only preceded the onset of diabetes but also continued at an accelerated pace after the onset of diabetes (4). The increased risk of fatal events and increased case fatality associated with poor lung function suggest that reduced lung function may be another potential factor linking diabe-

tes to increased risk of CHD and increased susceptibility to a fatal episode in the event of a cardiac event (15,25). Speculatively, this association may reflect an impaired respiratory buffering capacity needed in the context of a cardiac event to cope with reduced cardiac output. Further studies are warranted to see if physical training might improve cardiorespiratory function in type 2 diabetics and thus reduce risk of fatal CHD.

Strengths and limitations

The strengths and limitations of the present study require careful consideration. The study is restricted to almost exclusively white European men. However, the study population is socioeconomically representative of middle-aged men in the U.K. and follow-up rates are exceptionally high. Ascertainment of CHD death and MI is based on standard methods. We were able to take into account evidence of CHD (diagnosed and undiagnosed) with factors including ECG evidence of silent MIs and arrhythmias at baseline and a wide range of cardiovascular risk factors. Despite adjusting risk estimates for several potential confounders and mediators, we cannot rule out residual confounding. Although the associations persisted after adjustment for established risk factors, it is possible that this may be due to imprecision due to adjustment for baseline levels only. The current findings based on observational epidemiological data cannot assess causality.

CONCLUSIONS— In this study of middle-aged men free of diagnosed CHD stroke and diabetes, restrictive patterns of lung function (reduced FVC and FEV₁) but not obstructive respiratory patterns (reduced FEV₁-to-FVC ratio) were inversely associated with incident type 2 diabetes and fatal CHD events independent of established risk factors and metabolic risk factors. The association between reduced lung function and fatal CHD and type 2 diabetes in particular was to some extent associated with inflammatory pathways. Further studies are now needed to extend such novel observations. The association between reduced lung function and development of type 2 diabetes and fatal CHD events may provide another possible explanation for the increased risk of fatal CHD in individuals with type 2 diabetes.

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