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Lung Function and Incident Coronary Heart Disease

The Atherosclerosis Risk in Communities Study

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The authors examined the association between lung function, as measured by forced expiratory volume in 1 second (FEV_1) and forced vital capacity, and the 10-year incidence of coronary heart disease among 14,480 participants in the Atherosclerosis Risk in Communities Study (1987–1998). Separate proportional hazards models were used for FEV_1 and forced vital capacity, with gender-specific lung function quartiles and lung function × gender interaction terms. An association between lung function and coronary heart disease was observed in both genders and was stronger among women. After adjustment for age, race, study center, height, height squared, smoking, and cardiovascular disease risk factors, the hazard ratios for the first (lowest), second, and third quartiles of FEV_1 were 3.70 (95% confidence interval (CI): 2.19, 6.24), 2.54 (95% CI: 1.49, 4.32), and 2.25 (95% CI: 1.31, 3.87) for women and 1.51 (95% CI: 1.07, 2.13), 1.59 (95% CI: 1.15, 2.20), and 1.52 (95% CI: 1.10, 2.09) for men. After stratification by smoking status, associations were observed in each smoking group for women, while those in men were weaker and less consistent. Similar results were obtained for forced vital capacity. This analysis indicates an association between lung function and incident coronary heart disease that may be stronger in women than in men.

coronary disease; forced expiratory volume; respiratory function tests; smoking; vital capacity

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CHD, coronary heart disease; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second.

A relation between reduced pulmonary function and all-cause mortality, coronary heart disease (CHD) mortality, and cardiovascular disease mortality was initially reported by Higgins and Keller (1) using data from the Tecumseh Community Health Study. There is little if any debate about the plausibility and validity of low pulmonary function as a predictor of all-cause mortality; inverse associations have been reported from many countries and from studies using various spirometric measures (1–18). In contrast, while an association between low spirometric values and subsequent cardiovascular mortality and morbidity has been reported by many investigators (2–6, 17, 19–23), the findings are not consistent (3, 22–24), and questions remain. In particular, some investigators report no such association among men who have never smoked (3, 22, 23). Many studies have not adequately controlled for smoking or have not included women and African Americans. Consequently, questions remain concerning the role of smoking in the observed associations, potential underlying mechanisms, and the applicability of these findings to women and African Americans.

The objective of this study was to determine whether there is a relation between spirometric indices of lung function and

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TABLE 1. Adjusted* gender- and race-specific mean values for forced expiratory volume in 1 second and forced vital capacity, by the absence or presence of incident coronary heart disease (n = 14,480), Atherosclerosis Risk in Communities Study, 1987–1998

Category	Forced expiratory volume in 1 second (liters)						Forced vital capacity (liters)					
	Incident CHD†			No incident CHD			Incident CHD			No incident CHD		
	No.	Mean	95% CI†	No.	Mean	95% CI	No.	Mean	95% CI	No.	Mean	95% CI
Black men	123	2.65	2.54, 2.77	1,331	2.72	2.66, 2.79	123	3.49	3.36, 3.63	1,331	3.58	3.51, 3.66
Black women	117	2.15	2.07, 2.22	2,328	2.30	2.27, 2.33	117	2.83	2.74, 2.92	2,328	3.04	3.00, 3.07
White men	385	3.17	3.10, 3.23	4,429	3.25	3.22, 3.29	385	4.23	4.16, 4.31	4,429	4.35	4.31, 4.39
White women	173	2.57	2.50, 2.63	5,594	2.67	2.65, 2.70	173	3.48	3.41, 3.55	5,594	3.62	3.60, 3.65

* Adjusted for age, smoking status, pack-years of cigarette smoking, height, and height^2.
† CHD, coronary heart disease; CI, confidence interval.

incident CHD, whether this is the case for both genders, and to what degree it is influenced by cigarette smoking in middle-aged Whites and African Americans.

MATERIALS AND METHODS

Study population

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective study of the natural history and etiology of atherosclerotic disease and of cardiovascular disease event rates in four US communities. The study population was selected as a probability sample of 15,792 men and women aged 45–64 years in Forsyth County, North Carolina; Jackson, Mississippi; selected suburbs of Minneapolis, Minnesota; and Washington County, Maryland. The sample from Forsyth County was 12 percent African-American, the sample from Jackson was 100 percent African-American, and the other two samples were predominantly White (25).

The study objectives, design, and cohort examination procedures have been described previously (25). Eligible participants were interviewed at home and invited to undergo a baseline clinical examination. Clinical examinations were conducted from 1987 to 1989, with reexaminations every 3 years until 1998 and continuing follow-up for events.

We excluded persons who met any of the following hierarchical criteria: missing data on pulmonary function (n = 139); prevalent CHD at baseline (n = 744) or CHD status that could not be determined (n = 322); missing or unknown information on smoking status (n = 13); race/ethnicity other than White or African-American (n = 44); and being an African American living in Maryland or Minnesota (n = 50). This left us with a cohort of 14,480 for these analyses.

Baseline measurements

Information on medical history, as well as socioeconomic and lifestyle factors such as smoking and physical activity, was obtained by trained interviewers. Smoking status was characterized as pack-years of smoking and as current, former, or never smoking. Never smokers were defined as persons who had not smoked more than 400 cigarettes in their lifetime. Health status was assessed by the question, "Compared to other people your age, would you say that your health is excellent, good, fair, or poor?" Persons who reported exercising or playing sports were considered physically active.

Prior to their examination at the ARIC study center, participants were asked to fast for 12 hours, refrain from using tobacco, and abstain from vigorous activities. Body mass index (weight (kg)/height (m)^2) was calculated from anthropometric measurements taken with participants standing in scrub suits and without shoes. Sitting blood pressure was measured three times using a random-zero sphygmomanometer, and the average of the last two readings was used. Blood specimens were drawn and processed following a standardized protocol (26).

Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or self-reported use of antihypertensive medication. Diabetes mellitus was defined as a fasting glucose level of ≥126 mg/dl (7.0 mmol/liter), a nonfasting glucose level of ≥200 mg/dl (11.1 mg/dl), a self-reported physician diagnosis, or pharmacologic hypoglycemic treatment.

Assessment of respiratory symptoms was based on responses to a standardized questionnaire adopted from the Epidemiology Standardization Project (27). Chronic bronchitis was defined as chronic cough and phlegm production on most days for at least 3 consecutive months of the year for at least 2 years, wheezing as wheezing for at least 2 years, and dyspnea as shortness of breath and having to stop for breath when walking on level ground with people of the same age. Ascertainment of asthma was based on a self-report of ever having had asthma.

Lung function was measured via the forced vital capacity maneuver, in which the maximal volume of air is exhaled during a forced expiration starting from a position of full inspiration and ending at complete expiration. Forced expiratory volume in 1 second (FEV_1) is the volume of gas exhaled in the first second of expiration, and forced vital capacity (FVC) is the total volume of gas exhaled. Lung function was measured by trained and certified technicians according to the American Thoracic Society criteria, using a standardized protocol (28). Collins Survey II water-seal spirometers (Collins Medical, Inc., Braintree, Massachusetts) driven by IBM PC/XT computers and under the control of Pulmo-Screen software (PDS Healthcare Products, Inc., Louisville, Colorado) were used to assist the tech-

nicians with quality control, calculation of pulmonary function variables, and compilation of results for transmission to the ARIC Pulmonary Function Reading Center. Quality control was carefully monitored throughout the study. Participants performed the FVC maneuver until there were two error-free reproducible maneuvers (FEV_1 and FVC within 5 percent) out of three acceptable maneuvers, with the maneuvers repeated up to eight times if necessary. Technicians were certified annually, with the Director of the Pulmonary Function Reading Center observing each technician test at least two participants. The Pulmonary Function Reading Center analyzed the data weekly for differences between centers and technicians. While there were technician differences across field centers, there were not statistically significant technician differences within centers. While not used extensively in these analyses, percent predicted FEV_1 and FVC were computed using gender- and race-specific prediction equations that included height and age.

Ascertainment of CHD events

Incident CHD events were identified in the ARIC Study from telephone contacts with study participants or relatives of decedents to identify hospitalizations and deaths, surveys of local hospital discharge lists and death certificates, and reviews of 12-lead electrocardiograms performed at the triennial ARIC clinic visits to detect unrecognized myocardial infarction (25, 29). Trained abstractors reviewed the hospital charts for hospitalized participants and recorded the signs and symptoms present at admission, including chest pain, cardiac enzyme levels, and the results of up to three electrocardiograms taken during the hospitalization. Trained staff coded the electrocardiograms using the Minnesota Diagnostic Code (30). Out-of-hospital deaths were ascertained by means of death certificates, interviews with next of kin, and questionnaires completed by the patient's physician. When available, coroner reports and autopsy reports were used for validation.

CHD was defined as a validated definite or probable hospitalized myocardial infarction, CHD death, or unrecognized myocardial infarction that was detected at a follow-up examination. An unrecognized myocardial infarction was defined by the appearance between the first and subsequent ARIC examinations of a major Q wave or a minor Q wave with ischemic ST-T changes, or a myocardial infarction by computerized NOVACODE criteria (31), confirmed by side-by-side visual electrocardiogram comparison. All potential clinical CHD events were reviewed, and disagreements were adjudicated if necessary by the ARIC Morbidity and Mortality Classification Committee using published criteria (25, 29). Follow-up continued until the date of death, the date of last contact (if lost), or December 31, 1998.

Prevalent CHD was defined as a self-reported history of myocardial infarction or cardiac revascularization (coronary bypass surgery or coronary angioplasty) at baseline or evidence of a myocardial infarction on the baseline electrocardiogram. The 322 persons whose baseline CHD status could not be determined because of inconsistent or incomplete responses were excluded from the analysis.

Statistical analysis

Age-adjusted mean values or proportions for CHD risk factors were computed by gender-specific quartiles of FEV_1 or FVC, using a continuous age variable and standardizing the distributions to the mean age of the entire cohort. The first quartile included persons with the lowest lung function. Age-adjusted means or proportions were also computed by incident CHD status.

To examine the relation between lung function and incident CHD, we fitted Kaplan-Meier survival curves by gender and lung function quartile (32). Proportional hazards models were fitted following several steps (32). Model 1 included age, gender, race, study center, height, and height squared ($height^2$). Model 2 additionally contained smoking status and pack-years of smoking. Major cardiovascular disease risk factors (hypertension, diabetes, low density lipoprotein cholesterol, high density lipoprotein cholesterol, body mass index, and ethanol consumption) were added in model 3. For all of the proportional hazards models, 797 persons with missing values for any of the aforementioned covariates were excluded.

We also fitted models that contained self-reported health status (a four-level ordinal variable) and physical activity, hemostasis markers (fibrinogen level, albumin level, white blood cell count, and Factor VIII percentage), or respiratory symptoms (chronic bronchitis, dyspnea, wheezing, and asthma). The numbers of persons with missing values for these three groups of variables were 6, 121, and 0, respectively.

We assessed a possible interaction between gender and lung function by including lung function × gender interaction terms for each quartile of lung function in the models. Because a statistically significant ($p < 0.05$) interaction of large magnitude was found, only models containing the lung function × gender interaction terms are presented. While models stratified by gender were considered, the small number of events in some gender × smoking groups resulted in extremely imprecise estimates.

We carried out analyses for each category of smoking (current, former, and never) to investigate possible variation by smoking status and to more completely control for any residual confounding. For the current and former smoking categories, we included pack-years of smoking in models 2 and 3 to adjust for residual confounding. We also examined the association between continuous lung function variables and CHD incidence. We plotted the log(-log) survival curves by quartile of lung function and found no obvious violations of the proportional hazards assumption. We also examined alternative exposure definitions such as percent predicted FEV_1, percent predicted FVC, FEV_1/height, or $FEV_1/height^2$ in models that did not contain separate height and $height^2$ terms. We conducted the analyses using SAS, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Of the 14,480 persons included in the analyses, 6,268 (43 percent) were male and 8,212 (57 percent) were female. The mean age was 54.4 for males and 53.7 for females. The

TABLE 2. Age-adjusted mean values or proportions for baseline characteristics among women, by quartile of forced expiratory volume in 1 second and the absence or presence of incident coronary heart disease (*n* = 8,212), Atherosclerosis Risk in Communities Study, 1987–1998

Variable	Quartile of FEV_1*				Incident CHD*	
	1 (lowest) (*n* = 2,052)	2 (*n* = 2,054)	3 (*n* = 2,053)	4 (highest) (*n* = 2,053)	Yes (*n* = 290)	No (*n* = 7,922)
Lung function						
FEV_1 (liters)	1.79	2.27	2.58	3.02	2.17	2.42
Forced vital capacity (liters)	2.50	3.01	3.38	3.90	2.90	3.20
Demographic factors and CHD risk factors						
Age (years)	56.27	54.50	53.09	51.12	55.96	53.66
Height (cm)	159.76	161.21	162.82	165.47	162.43	162.30
Body mass index†	29.38	28.29	27.40	26.24	29.56	27.78
LDL* cholesterol level (mg/dl)	137.37	137.95	136.01	133.49	149.47	135.72
HDL* cholesterol level (mg/dl)	55.03	56.61	58.72	60.49	49.54	58.00
Alcohol consumption (g/week)	18.10	17.32	20.76	23.31	12.11	20.13
Race (African-American)	0.50	0.34	0.23	0.10	0.42	0.29
Education						
Less than high school	0.37	0.26	0.19	0.12	0.39	0.23
High school	0.32	0.37	0.39	0.39	0.33	0.37
Some trade school/college	0.31	0.38	0.42	0.48	0.27	0.40
Smoking						
Current smoker	0.40	0.26	0.19	0.12	0.47	0.24
Former smoker	0.19	0.20	0.24	0.27	0.15	0.22
Never smoker	0.42	0.53	0.57	0.61	0.39	0.54
Health						
Excellent	0.21	0.31	0.36	0.46	0.19	0.34
Good	0.47	0.48	0.50	0.46	0.44	0.48
Fair	0.26	0.19	0.12	0.08	0.31	0.16
Poor	0.06	0.03	0.02	0.01	0.08	0.03
Physically active	0.48	0.57	0.65	0.70	0.49	0.61
Hypertension	0.47	0.37	0.32	0.23	0.63	0.34
Diabetes mellitus	0.19	0.12	0.09	0.06	0.33	0.11
Respiratory symptoms						
Chronic bronchitis	0.08	0.03	0.03	0.03	0.09	0.04
Wheezing	0.14	0.07	0.05	0.04	0.11	0.07
Dyspnea	0.06	0.03	0.02	0.01	0.07	0.03
Asthma	0.12	0.05	0.04	0.03	0.10	0.06
Markers of inflammation and coagulation						
White blood cell count (1,000/mm^3)	6.53	6.11	5.80	5.52	6.92	5.96
Fibrinogen level (mg/dl)	329.56	311.24	299.56	289.99	340.83	306.43
Albumin level (g/dl)	3.79	3.82	3.84	3.86	3.74	3.83
Factor VIII (%)	142.51	137.17	130.81	127.66	150.35	133.98
Von Willebrand factor (%)	127.21	121.59	115.11	110.02	132.73	117.99

* FEV_1, forced expiratory volume in 1 second; CHD, coronary heart disease; LDL, low density lipoprotein; HDL, high density lipoprotein.
† Weight (kg)/height $(m)^2$.

average length of follow-up was 9.8 years, with a minimum and maximum of 0.01 and 12.1 years and an interquartile range of 9.4–10.9 years. There were 508 CHD events in men and 290 in women. Table 1 provides gender- and race-specific mean values for FEV_1 and FVC in relation to incident CHD. In all race-gender groups, persons who developed incident CHD had lower adjusted mean baseline lung function than those who remained disease-free. Higher lung

TABLE 3. Age-adjusted means or proportions for baseline characteristics among men, by quartile of forced expiratory volume in 1 second and the absence or presence of incident coronary heart disease (*n* = 6,268), Atherosclerosis Risk in Communities Study, 1987–1998

Variable	Quartile of FEV_1*				Incident CHD*	
	1 (lowest) (*n* = 1,567)	2 (*n* = 1,567)	3 (*n* = 1,567)	4 (highest) (*n* = 1,567)	Yes (*n* = 508)	No (*n* = 5,760)
Lung function						
FEV_1 (liters)	2.41	3.14	3.59	4.23	3.21	3.37
Forced vital capacity (liters)	3.63	4.27	4.78	5.54	4.41	4.58
Demographic factors and CHD risk factors						
Age (years)	57.07	55.09	53.80	51.54	55.88	54.24
Height (cm)	173.43	174.63	176.64	180.04	176.10	176.25
Body mass index†	27.50	27.80	27.46	27.05	27.74	27.42
LDL* cholesterol level (mg/dl)	136.59	139.98	140.72	137.22	148.21	137.82
HDL* cholesterol level (mg/dl)	46.13	44.48	44.08	44.71	41.23	45.15
Alcohol consumption (g/week)	83.51	73.57	65.06	64.18	68.40	71.67
Race (African-American)	0.44	0.29	0.16	0.06	0.25	0.23
Education						
Less than high school	0.35	0.26	0.18	0.10	0.28	0.22
High school	0.27	0.28	0.28	0.25	0.29	0.27
Some trade school/college	0.37	0.46	0.54	0.65	0.42	0.51
Smoking						
Current smoker	0.50	0.30	0.21	0.12	0.38	0.27
Former smoker	0.35	0.41	0.46	0.51	0.39	0.43
Never smoker	0.16	0.29	0.32	0.39	0.23	0.30
Health						
Excellent	0.22	0.33	0.40	0.50	0.27	0.37
Good	0.45	0.50	0.48	0.44	0.48	0.47
Fair	0.26	0.15	0.11	0.06	0.20	0.14
Poor	0.06	0.02	0.02	0.00	0.04	0.02
Physically active	0.55	0.62	0.68	0.76	0.58	0.66
Hypertension	0.43	0.36	0.29	0.22	0.47	0.31
Diabetes mellitus	0.15	0.12	0.10	0.06	0.24	0.10
Respiratory symptoms						
Chronic bronchitis	0.13	0.05	0.04	0.03	0.09	0.06
Wheezing	0.18	0.09	0.05	0.04	0.10	0.09
Dyspnea	0.04	0.01	0.00	0.00	0.02	0.01
Asthma	0.10	0.06	0.04	0.03	0.06	0.06
Markers of inflammation and coagulation						
White blood cell count (1,000/mm^3)	6.68	6.31	6.06	5.84	6.75	6.17
Fibrinogen level (mg/dl)	312.56	299.98	290.95	280.10	318.93	293.53
Albumin level (g/dl)	3.88	3.92	3.94	3.97	3.89	3.93
Factor VIII (%)	133.00	127.91	124.41	121.27	132.03	126.05
Von Willebrand factor (%)	124.40	117.52	114.08	109.97	126.06	115.50

* FEV_1, forced expiratory volume in 1 second; CHD, coronary heart disease; LDL, low density lipoprotein; HDL, high density lipoprotein.
† Weight (kg)/height $(m)^2$.

function was found among men compared with women and among Whites compared with African Americans. While the absolute gender difference in mean FEV_1 and FVC was greater among African Americans than among Whites, the proportional difference was the same.

Tables 2 (women) and 3 (men) provide age-adjusted gender-specific data on baseline characteristics by quartile of FEV_1. The upper cutpoints for the FEV_1 quartiles were 2.10 liters, 2.43 liters, and 2.76 liters for women and 2.88 liters, 3.36 liters, and 3.83 liters for men. Clear trends were

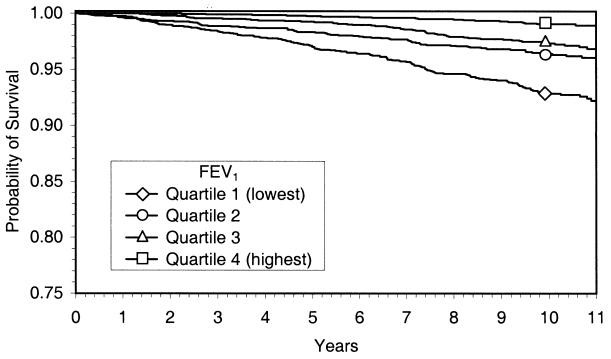

FIGURE 1. Kaplan-Meier survival curves for incident coronary heart disease among women, by quartile of forced expiratory volume in 1 second (FEV_1), Atherosclerosis Risk in Communities Study, 1987–1998.

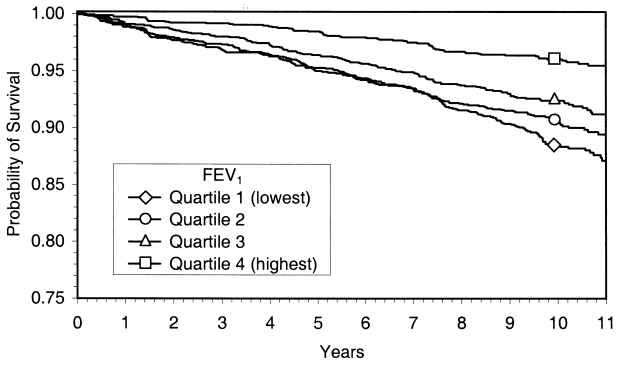

FIGURE 2. Kaplan-Meier survival curves for incident coronary heart disease among men, by quartile of forced expiratory volume in 1 second (FEV_1), Atherosclerosis Risk in Communities Study, 1987–1998.

observed across quartiles of FEV_1 for most of the covariates considered. Lung function increased with height in both genders. Among women, lower FEV_1 was associated with increased age, a greater proportion of African Americans, and fewer years of formal education. Being a current smoker, reporting poor health, being physically inactive, or having respiratory symptoms, hypertension, or diabetes was inversely associated with FEV_1. Low density lipoprotein cholesterol level was inversely associated with FEV_1, while high density lipoprotein cholesterol level and alcohol consumption were directly associated. Levels of white blood cells, fibrinogen, albumin, Factor VIII, and von Willebrand factor were indicative of greater levels of inflammation and coagulation activity among women with lower FEV_1. These trends were also seen when women who developed incident CHD were compared with women who did not. Similar trends were seen in men, with some exceptions. There were no consistent differences in body mass index or low density lipoprotein cholesterol level, and high density lipoprotein cholesterol level and alcohol consumption were inversely associated with FEV_1. Men who developed incident CHD consumed less alcohol and had higher low density lipoprotein cholesterol levels and body mass indexes than those who did not.

The upper cutpoints for the FVC quartiles were 2.79 liters, 3.20 liters, and 3.61 liters for women and 3.97 liters, 4.53 liters, and 5.13 liters for men. Similar trends were seen for FVC and FEV_1, except that among men body mass index was inversely associated with FVC, and no consistent trend was seen for alcohol consumption (data not shown).

The Kaplan-Meier plots revealed a monotonic relation between FEV_1 and incident CHD, with loss of the gradient for the two lowest quartiles of FEV_1 in men and higher incidence rates among men than among women (see figures 1 and 2). Tables 4–6 show the results of proportional hazards analyses with gender interaction terms. Table 4 shows results for quartiles of FEV_1, table 5 for quartiles of FVC, and table 6 for continuous FEV_1 and FVC variables. While a strong monotonic inverse relation between quartiles of FEV_1 and FVC and incident CHD was observed among women after adjustment for height, height^2, age, race, study center, and smoking, the relation was weaker among men (upper portions of tables 4 and 5). Further adjustment for cardiovascular disease risk factors attenuated the hazard ratios for FEV_1 and FVC among men and women, but inverse relations were still evident.

Because of the complex relation between smoking, lung function, and CHD, we repeated the analysis after stratification by smoking status (lower portions of tables 4 and 5). This greatly increased the imprecision of the estimates, and some of the findings do not show a dose-response effect. Overall, however, the results are consistent with an inverse relation between lung function and CHD. In each smoking group, the relation was stronger among women than among men. These associations were attenuated in each smoking category after adjustment for additional covariates, but they remained strong among women. High hazard ratios were observed for FEV_1 among women who were current or former smokers and for FVC among women who were former smokers.

A global test of the lung function × gender interaction terms was highly statistically significant ($p < 0.05$) in all models for the entire cohort. In the analyses stratified by smoking status, most of the global tests for the interaction terms had p values above 0.20. However, examination of these hazard ratios also lends support for effect-measure modification of the lung function-CHD relation by gender. When sample size permitted fitting separate models for men and women, similar results were obtained.

Additional adjustment for physical activity and self-reported overall health status or for respiratory symptoms had negligible effects on the hazard ratios (data not shown). This may have been due, in part, to the crude nature of these measurements. Additional adjustment for hemostasis markers did not meaningfully change the hazard ratios, although the percent changes from the model 3 estimates were as high as 14 percent (data not shown).

Because the relation between FEV_1 and FVC and incident CHD appears to be approximately monotonic, at least for women, models were fitted using continuous lung function

TABLE 4. Adjusted hazard ratios for incident coronary heart disease according to quartile of forced expiratory volume in 1 second, with gender interaction terms, by smoking status (n = 13,683), Atherosclerosis Risk in Communities Study, 1987–1998

Quartile* of FEV_1†	Women							Men						
	No. of events	Model 1‡		Model 2§		Model 3¶		No. of events	Model 1‡		Model 2§		Model 3¶	
		HR†	95% CI†	HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI	HR	95% CI
Total														
1 (lowest)	130	7.11	4.25, 11.90	5.32	3.17, 8.94	3.70	2.19, 6.24	154	2.50	1.80, 3.46	1.72	1.22, 2.42	1.51	1.07, 2.13
2	69	3.74	2.20, 6.34	3.17	1.87, 5.39	2.54	1.49, 4.32	139	2.19	1.59, 3.02	1.79	1.29, 2.48	1.59	1.15, 2.20
3	52	2.81	1.64, 4.81	2.57	1.50, 4.41	2.25	1.31, 3.87	117	1.85	1.35, 2.54	1.65	1.20, 2.27	1.52	1.10, 2.09
4 (highest)	18	1.00		1.00		1.00		61	1.00		1.00		1.00	
Smoking status														
Current smokers														
1 (lowest)	64	7.28	2.24, 23.65	6.68	2.05, 21.74	5.20	1.59, 17.00	72	2.30	1.09, 4.85	2.08	0.98, 4.41	1.81	0.86, 3.83
2	34	5.64	1.72, 18.55	5.43	1.65, 17.85	4.79	1.46, 15.79	56	2.86	1.37, 5.96	2.74	1.31, 5.70	2.49	1.20, 5.19
3	22	4.74	1.41, 15.89	4.70	1.40, 15.76	4.08	1.22, 13.68	34	2.35	1.11, 4.97	2.27	1.07, 4.81	2.09	0.99, 4.41
4 (highest)	3	1.00		1.00		1.00		9	1.00		1.00		1.00	
Former smokers														
1 (lowest)	19	8.96	2.56, 31.37	8.31	2.37, 29.20	5.45	1.55, 19.18	60	2.14	1.32, 3.46	1.92	1.17, 3.16	1.68	1.02, 2.77
2	11	4.73	1.30, 17.23	4.51	1.24, 16.45	3.24	0.88, 11.88	50	1.55	0.97, 2.49	1.46	0.90, 2.35	1.22	0.75, 1.97
3	10	3.73	1.02, 13.63	3.65	1.00, 13.35	3.13	0.85, 11.43	50	1.44	0.92, 2.25	1.39	0.89, 2.18	1.28	0.82, 2.01
4 (highest)	3	1.00		1.00		1.00		35	1.00		1.00		1.00	
Never smokers														
1 (lowest)	47	3.69	1.82, 7.46	3.69	1.82, 7.46	2.54	1.24, 5.22	22	2.08	1.03, 4.19	2.08	1.03, 4.19	1.79	0.88, 3.63
2	24	1.72	0.84, 3.53	1.72	0.84, 3.53	1.39	0.67, 2.89	33	1.89	1.01, 3.56	1.89	1.01, 3.56	1.79	0.94, 3.39
3	20	1.48	0.72, 3.06	1.48	0.72, 3.06	1.38	0.66, 2.85	33	1.89	1.03, 3.44	1.89	1.03, 3.44	1.65	0.90, 3.03
4 (highest)	12	1.00		1.00		1.00		17	1.00		1.00		1.00	

* The highest quartile (quartile 4) is the reference category in each comparison.

† FEV_1, forced expiratory volume in 1 second; HR, hazard ratio; CI, confidence interval.

‡ Model 1: Results were adjusted for age, race, study center, height, and height^2. The models included $FEV_1 \times$ gender interaction terms for each quartile of FEV_1.

§ Model 2: Results were adjusted for the model 1 covariates and for smoking status (in full cohort) and pack-years of smoking (in full cohort, current smokers, and former smokers).

¶ Model 3: Results were adjusted for the model 2 covariates and for hypertension, diabetes mellitus, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and body mass index.

variables (table 6). Results are presented for interquartile-range decreases in FEV_1 (1.02 liters) and FVC (1.36 liters). The results were consistent with those from the quartile analyses, and the interaction term was statistically significant for all models in the entire cohort and in each stratified analysis.

Given the close agreement between FEV_1 and FVC (r = 0.83), it is not surprising that these two measures had similar associations with incident CHD. Models using quartiles or continuous terms for percent predicted FEV_1, percent predicted FVC, FEV_1/height, and FEV_1/ height^2 were consistent with the above findings (data not shown). In contrast, there was no observed association between FEV_1/FVC and incident CHD among women or men (data not shown). Using race- and gender-specific quartiles did not substantially change these results.

Modifying the CHD endpoint to include coronary revascularization events decreased the strength of all of the above associations in women and essentially eliminated the association among men (data not shown). The number of incident events added when revascularization procedures were included was much greater among men (n = 233) than among women (n = 73).

DISCUSSION

For decades, attention has focused on the identification of precursors for CHD. In addition to traditional risk factors such as smoking, hypertension, and diabetes, studies have examined the contribution of lung function to the risk of CHD morbidity and mortality. We found a strong association between lung function and incident CHD among women and a weaker association among men, both in the full cohort and in never smokers. Some investigators have reported significant associations between lung function and cardiovascular disease or CHD mortality in both men and women (3, 5, 8, 9), while others have reported significant associations in all-male cohorts (2, 19–21). However, the Honolulu Heart Study did not find an association between cardiovascular disease morbidity and mortality and lung function among nonsmokers in an all-male cohort (22, 23). Similarly, researchers in the Busselton Health Study reported no significant association between lung function and CHD mortality among nonsmoking men after minimal adjustment or among nonsmoking women after further adjustment for cardiovascular disease risk factors (3). Inconsistencies in the literature

TABLE 5. Adjusted hazard ratios for incident coronary heart disease according to quartile of forced vital capacity, with gender interaction terms, by smoking status (*n* = 13,683), Atherosclerosis Risk in Communities Study, 1987–1998

Quartile* of FVC†	Women							Men						
	No. of events	Model 1‡		Model 2§		Model 3¶		No. of events	Model 1‡		Model 2§		Model 3¶	
		HR†	95% CI†	HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI	HR	95% CI
Total														
1 (lowest)	130	6.88	4.17, 11.35	5.61	3.40, 9.25	3.54	2.13, 5.88	142	2.19	1.57, 3.05	1.67	1.19, 2.33	1.36	0.97, 1.90
2	65	3.24	1.94, 5.41	2.85	1.71, 4.76	2.19	1.31, 3.67	149	2.15	1.58, 2.93	1.83	1.34, 2.50	1.53	1.12, 2.09
3	54	2.69	1.60, 4.51	2.52	1.50, 4.22	2.21	1.32, 3.71	111	1.60	1.17, 2.18	1.47	1.08, 2.00	1.36	0.99, 1.85
4 (highest)	20	1.00		1.00		1.00		69	1.00		1.00		1.00	
Smoking status														
Current smokers														
1 (lowest)	60	4.17	1.92, 9.04	3.89	1.79, 8.46	2.77	1.26, 6.10	58	1.23	0.70, 2.17	1.15	0.65, 2.03	0.94	0.53, 1.67
2	27	2.17	0.97, 4.86	2.09	0.94, 4.67	1.73	0.77, 3.88	58	1.63	0.96, 2.76	1.56	0.92, 2.65	1.36	0.80, 2.32
3	28	2.78	1.26, 6.13	2.73	1.24, 6.02	2.36	1.07, 5.22	34	1.24	0.71, 2.17	1.20	0.69, 2.11	1.12	0.64, 1.95
4 (highest)	8	1.00		1.00		1.00		21	1.00		1.00		1.00	
Former smokers														
1 (lowest)	19	8.36	2.71, 25.79	7.87	2.55, 24.31	4.73	1.51, 14.78	53	2.14	1.29, 3.54	1.96	1.17, 3.26	1.59	0.94, 2.68
2	13	4.80	1.53, 15.02	4.59	1.47, 14.37	3.25	1.03, 10.21	61	1.83	1.16, 2.88	1.73	1.10, 2.73	1.38	0.87, 2.18
3	7	2.10	0.61, 7.21	2.05	0.60, 7.04	1.62	0.47, 5.59	44	1.23	0.78, 1.94	1.19	0.76, 1.87	1.08	0.69, 1.69
4 (highest)	4	1.00		1.00		1.00		38	1.00		1.00		1.00	
Never smokers														
1 (lowest)	51	5.58	2.46, 12.63	5.58	2.46, 12.63	3.55	1.55, 8.13	31	3.45	1.56, 7.63	3.45	1.56, 7.63	2.87	1.29, 6.36
2	25	2.63	1.15, 5.98	2.63	1.15, 5.98	2.08	0.91, 4.76	31	3.17	1.49, 6.73	3.17	1.49, 6.73	2.75	1.28, 5.89
3	19	2.13	0.93, 4.91	2.13	0.93, 4.91	2.09	0.91, 4.81	33	3.16	1.53, 6.54	3.16	1.53, 6.54	3.01	1.45, 6.23
4 (highest)	8	1.00		1.00		1.00		10	1.00		1.00		1.00	

* The highest quartile (quartile 4) is the reference category in each comparison.

† FVC, forced vital capacity; HR, hazard ratio; CI, confidence interval.

‡ Model 1: Results were adjusted for age, race, study center, height, and height^2. The models included FVC × gender interaction terms for each quartile of FVC.

§ Model 2: Results were adjusted for the model 1 covariates and for smoking status (in full cohort) and pack-years of smoking (in full cohort, current smokers, and former smokers).

¶ Model 3: Results were adjusted for the model 2 covariates and for hypertension, diabetes mellitus, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and body mass index.

can perhaps be explained by differing methods of adjusting lung function measures for height and gender, the use of differing techniques to adjust for smoking status, and differing endpoints.

Lung function is strongly correlated with height and gender. While most investigators have used percent predicted FEV_1, Vollmer et al. (33) discourage its use because of potential violations of the homogeneity of variance assumptions that underlie regression models. Vollmer et al. reported little difference in the performance of other adjustment methods, including FEV_1/height, FEV_1/height^2, and adjustment for age and height (33). These different adjustment strategies have implications for the nature of the relation being modeled, and we agree with Vollmer et al., who recommend using FEV_1 and adjusting for age and height (33). Our analyses using percent predicted FEV_1, FEV_1/height, and FEV_1/ height^2 yielded essentially the same results.

Smoking has profound detrimental effects on the pulmonary and cardiovascular systems. Most previous studies included smoking status as a covariate in multivariate modeling (3–6, 8, 9, 13, 15, 16, 18, 20, 22, 23) or stratified the data by smoking status and/or restricted analysis to never smokers (3, 8, 12, 17, 18, 20, 23). Because of measurement error in the ascertainment of smoking history and the relatively crude categorization of the exposure to smoking and its effects, it is unlikely that merely including indicator variables for never, former, and current smoking in a model will adequately control for confounding. Furthermore, any potential effect modification will be obscured. Even the inclusion of pack-years may result in considerable residual confounding. Consequently, stratification by smoking status or restriction to never smokers seems to be preferable, despite the resulting reduction in statistical power.

The most common endpoints in this literature have been CHD mortality (3, 5, 8, 9, 12, 20, 24) and cardiovascular disease mortality (2, 4, 12, 15, 18). Other endpoints have included myocardial infarction (16, 17), angina pectoris (16), sudden death (17), congestive heart failure, and cardiovascular disease morbidity (18). Some studies have addressed CHD morbidity and mortality, although definitions and case ascertainment methods have differed (19, 23, 24).

We used an endpoint consisting of validated "hard" events: CHD death, hospitalized myocardial infarction, or

TABLE 6. Adjusted hazard ratios for incident coronary heart disease according to continuous lung function variables, with gender interaction terms, by smoking status (*n* = 13,683), Atherosclerosis Risk in Communities Study, 1987–1998

Lung function variable	Women						Men					
	Model 1*		Model 2†		Model 3‡		Model 1*		Model 2†		Model 3‡	
	HR§	95% CI§	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Forced expiratory volume in 1 second (1.02 liters)¶												
Total	3.30	2.59, 4.21	2.62	2.04, 3.38	2.18	1.67, 2.84	1.47	1.28, 1.68	1.22	1.05, 1.42	1.17	1.00, 1.36
Smoking status												
Current smoker	2.06	1.42, 2.99	1.93	1.32, 2.82	1.74	1.17, 2.58	1.24	0.98, 1.58	1.18	0.93, 1.50	1.11	0.87, 1.41
Former smoker	3.18	1.82, 5.58	3.01	1.71, 5.30	2.61	1.40, 4.85	1.38	1.11, 1.72	1.30	1.04, 1.64	1.27	1.00, 1.62
Never smoker	3.18	1.97, 5.14	3.18	1.97, 5.14	2.38	1.44, 3.92	1.41	0.99, 2.02	1.41	0.99, 2.02	1.35	0.94, 1.94
Forced vital capacity (1.36 liters)#												
Total	4.28	3.17, 5.79	3.54	2.62, 4.80	2.42	1.76, 3.33	1.61	1.35, 1.92	1.35	1.13, 1.62	1.15	0.96, 1.39
Smoking status												
Current smoker	2.68	1.71, 4.21	2.51	1.59, 3.94	1.95	1.21, 3.13	1.14	0.85, 1.53	1.09	0.81, 1.47	0.94	0.70, 1.27
Former smoker	4.28	2.11, 8.68	4.04	1.99, 8.21	2.72	1.28, 5.77	1.62	1.22, 2.15	1.54	1.15, 2.05	1.31	0.97, 1.77
Never smoker	4.48	2.62, 7.64	4.48	2.62, 7.64	2.79	1.60, 4.87	1.89	1.27, 2.82	1.89	1.27, 2.82	1.55	1.03, 2.34

* Model 1: Results were adjusted for age, race, study center, height, and height^2. The models also included a lung function × gender interaction term.

† Model 2: Results were adjusted for the model 1 covariates and for smoking status (in full cohort) and pack-years of smoking (in full cohort, current smokers, and former smokers).

‡ Model 3: Results were adjusted for the model 2 covariates and for hypertension, diabetes mellitus, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and body mass index.

§ HR, hazard ratio; CI, confidence interval.

¶ Hazard ratio for a decrease equal to the interquartile range (1.02 liters) for forced expiratory volume in 1 second.

Hazard ratio for a decrease equal to the interquartile range (1.36 liters) for forced vital capacity.

unrecognized myocardial infarction. Inclusion of "soft" events (coronary artery bypass surgery or angioplasty) decreased the strength of the lung function-incident CHD association in women and essentially eliminated the association among men. In this combined endpoint, the proportion of events reflecting cardiac procedures was greater among men (44 percent of events) than among women (34 percent of events), while the proportion of myocardial infarctions was smaller among men (34 percent) than among women (43 percent). Consequently, if lung function is associated with myocardial infarction and CHD death but is not associated with cardiac procedures, incomplete detection and/or misclassification could explain our inability to detect an association between lung function and CHD in men when using the combined endpoint.

Because the ascertainment and validity of endpoints defined as revascularization procedures may be more influenced by access to care and treatment practices than myocardial infarction and CHD death, we place confidence in our findings obtained using "hard" events only. Exclusion of revascularization procedures misses an unknown number of persons who would have proceeded to develop a "hard" CHD event had they not had a cardiac procedure. However, the variability by gender (and probably by race) in this type of misclassification argues against the inclusion of cardiac procedures in these analyses.

While reduced pulmonary function may merely serve as an overall marker of poor health, the associations displayed in tables 2 and 3 are consistent with various mechanisms putatively linking impaired lung function with cardiovascular mortality and incident atherothrombotic coronary events. Several such mechanisms have been posited to explain the increased CHD risk among persons with poor lung function, such as the role of the lungs in the capture and elimination of external toxic agents (34, 35) and a ventilation/perfusion mismatch associated with impaired lung function (36, 37) (M. Tockman, University of South Florida, personal communication, 1993).

Our findings of higher levels of inflammatory markers among persons with lower lung function, both in the entire cohort and in nonsmokers (data not shown), are consistent with another potential mechanism (21). Key factors contributing to impaired lung function can initiate a systemic inflammation response, as would be the case for exposure to cigarette smoke and gaseous or small particulate matter pollutants, among others. A proinflammatory environment, in turn, may increase the risk of atherosclerosis and thrombosis and thus increase the risk for CHD. Interestingly, adjustment for markers of systemic inflammation only slightly decreased the hazard ratios, although this does not rule out systemic inflammation as a mechanism linking lung function and CHD risk. Although several of these proposed mechanisms are plausible, to our knowledge systematic empirical validation in their support is still lacking.

The stronger lung function-CHD association for women than for men is dependent on the use of multiplicative models. A comparison of risk ratios and risk differences reveals that risk differences are greater for men—reflecting their greater baseline risk of CHD—while the risk ratios are greater for women, as can be seen in figures 1 and 2. Within

the proportional hazards framework, our findings suggest that lung function has a greater proportional effect on the hazard of developing CHD among women than among men. Important gender differences in the anatomy and physiology of the respiratory tree have been described (38) and may explain the more harmful effect that cigarette smoke appears to have on the female respiratory system (38, 39), the reported differential pulmonary deposition of particulate matter by gender (40, 41), and our observed gender difference in the lung function-CHD association.

This study had several important strengths. Its large, biracial, population-based cohort permitted stratification of data by smoking status, with further adjustment for pack-years of smoking. The large number of events allowed assessment of effect modification by gender. Lung function was measured using a standardized protocol, with strict quality control procedures. We used several different methods to adjust for height and examined several measures of lung function. There was also thorough ascertainment and validation of incident events.

This study also had several important weaknesses. Lung function is notoriously difficult to measure, and its quantification can be effort-dependent. While technicians were thoroughly trained and certified, followed a standardized protocol, and were monitored for quality control purposes, some measurement error in the ascertainment of lung function undoubtedly remained. Despite the large size of the cohort, small numbers of events in some gender × smoking groups prevented us from stratifying the data by gender and from fully exploring potential effect modification by race. Finally, the possibility of some misclassification of events cannot be ruled out.

Our findings suggest that the observed association between lung function and incident CHD is not entirely due to confounding from smoking, as demonstrated by consistent findings among never, current, and former smokers. Consideration of baseline inflammatory markers decreased the hazard ratios by only a small amount. We found that, on the multiplicative scale, the association between lung function and incident CHD is stronger among women than among men. To our knowledge, this gender difference has not been previously reported. It is not known whether this represents an artifact, the consequence of residual confounding, a chance finding, or biologic differences between men and women. The biologic pathways linking impaired lung function and cardiovascular disease are still unknown and warrant further study.

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