Relationship between lung function impairment and incidence or recurrence of cardiovascular events in a middle-aged cohort

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ABSTRACT

Introduction: Lung function impairment may be a risk factor for cardiovascular disease (CVD) events.
Objective: To determine the relationship between the severity of airflow obstruction based on modified Global Initiative on Obstructive Lung Disease (GOLD) criteria and the prevalence, and incidence or recurrence of CVD in a cohort of U.S. adults ages 45-64 years from 1987 through 2001.
Methods: We analyzed data from 14,681 adults using logistic regression to determine the cross-sectional association between lung function impairment and prevalent CVD at baseline and Cox regression to examine the prospective association of lung function impairment at baseline with CVD over 15 years of follow-up. Models were adjusted for age, sex, race, smoking, comorbid hypertension and diabetes, cholesterol levels, and fibrinogen level.
Results: At baseline, the crude prevalence of CVD was higher among subjects with GOLD 2 (odds ratio [OR] 2.9, 95% confidence interval [CI] 2.0, 4.5) and GOLD 3 or 4 COPD (OR 3.0, 95% CI 0.8, 2.1), compared to normal subjects. These relative risks were greatly reduced after adjusting for covariates (OR 1.4, 95% CI 1.2, 1.8 for GOLD 2 and OR 1.3, 95% CI 0.8, 2.1 for GOLD 3 or 4). Similarly, the association between COPD and risk of incident or recurrent CVD was much stronger in the unadjusted models (hazard ratio [HR] 2.4, 95% CI 2.4, 2.7 for GOLD 2 and 2.9, 95% CI 2.2, 3.9 for GOLD 3 or 4) than in the adjusted ones (HR 1.2, 95% CI 1.03, 1.4 for GOLD 2 and 1.5, 95% CI 1.1, 2.0 for GOLD 3 or 4).
Conclusion: We observed a crude association between lung function impairment and prevalent and incident or recurrent CVD that was greatly reduced after adjusting for covariates including age, sex, race, smoking, comorbid hypertension and diabetes, cholesterol levels, and fibrinogen level. These data suggest that this association may be, in part, mediated through established CVD risk factors included in our adjusted models.

Keywords: Lung function, COPD, GOLD classification, cardiovascular disease, stroke, inflammation, restrictive lung disease

INTRODUCTION

Ischemic heart disease and cerebrovascular disease are currently the top two leading causes of death worldwide, responsible for more than one fifth of all deaths, and are projected to remain so through 2020[1;2]. Chronic obstructive pulmonary disease (COPD) is expected to be the third leading cause of worldwide mortality by 2020 and the fifth leading cause of disability-adjusted life years lost[2]. This triad of cardiac disease, stroke, and COPD have an enormous economic, medical, and social burden on US adults [3-10]. Processes that result in restriction on spirometry, which comprise both interstitial lung diseases, diabetes mellitus, congestive heart failure and other causes of small lung volumes, also impart significant morbidity and mortality in the US [6;7]. The role of systemic inflammation and systemic inflammatory markers such as C reactive protein, fibrinogen, and tumor necrosis factor-alpha may be important in all of these disease processes[11-15].

Cardiovascular mortality has been shown to be up to two-fold higher in COPD patients than in a matched population without COPD[5;16]. Previous studies have linked lung function impairment with the risk of developing cardiovascular disease and stroke even after adjusting for factors such as body mass index (BMI), physical activity, hypertension, diabetes, and smoking status[5;17-23]. However, lung function impairment in these studies has been classified by quartiles of FEV_1 or mean FEV_1 which are not routinely used clinically to assess the severity of impairment[18;20;21].

In 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was formed to improve investigation and management of this complex disease and treatment strategies have been recommended based on GOLD staging[24]. Our goal was to examine the prevalence, incidence, and recurrence of cardiac events and stroke in the Atherosclerosis Risk in Communities (ARIC) cohort of adults age 45-64 and followed from 1987 to 2001 using a modification of the GOLD classification of lung function impairment.

METHODS

Study Population

The ARIC study was initiated in 1987 as a longitudinal, population-based study of the etiology and clinical sequelae of atherosclerosis. Study protocols were approved for protection of human subjects. Participants were selected from the entire population by probability sampling from four US communities: Forsyth County, NC; Minneapolis, MN; Washington County, MD; and Jackson, MS (where only African Americans were sampled). Specific details of the ARIC study are published elsewhere[25]. Our analysis was limited to ARIC participants aged 45-64 years old at baseline, who provided information on respiratory symptoms and diagnoses, cardiovascular events or stroke, and medical history, had lipid profiles available, and who underwent adequate pulmonary function testing at the baseline examination. Only those participants for whom follow-up data were available were analyzed (n = 14,681).

Pulmonary function data

Spirometry was conducted using contemporary American Thoracic Society guidelines[26;27]. We developed sex- and race-specific internal prediction equations for FEV_1 and FVC following standard methods previously described[28]. We defined a subject as having a respiratory symptom if they reported cough, phlegm, dyspnea, or wheeze.

A modification of the GOLD criteria was used to classify subjects according to their stage of COPD[24;29]: GOLD 3 or 4 (FEV_1/FVC <0.70 and FEV1<50% predicted), GOLD 2 (FEV_1/FVC <0.70 and FEV_1 $\geq$50 to <80% predicted), GOLD 1 (FEV_1/FVC <0.70 and FEV_1 $\geq$80% predicted), restricted (FEV_1/FVC $\geq$70% and FVC <80% predicted, GOLD 0 (presence of

respiratory symptoms in the absence of any lung function abnormality), and no lung disease (Table 1).

Table 1: Definitions of prevalent, incident, and recurrent cardiovascular disease and lung function impairment using a modification of the Global Initiative for Lung Disease (GOLD) criteria for chronic obstructive pulmonary disease.

Cardiovascular Disease at Baseline
Self-reported myocardial infarction
Coronary artery bypass graft
Angioplasty
Self-reported hospitalized for a myocardial infarction
Myocardial infarction on electrocardiogram
Self-reported prior stroke
Cardiovascular Disease – Incident or Recurrent
New changes on electrocardiogram consistent with myocardial infarction
Definite or probable hospitalization for myocardial infarction (validated)
Definite or probable ischemic stroke
Coronary heart disease death
Modified GOLD stages of lung disease
GOLD 3 or 4 - $FEV_1/FVC^* < 0.70$ and $FEV_1 < 50\%$ predicted
GOLD 2 - $FEV_1/FVC < 0.70$ and $FEV_1 >= 50$ to $< 80\%$ predicted
GOLD 1 - $FEV_1/FVC < 0.70$ and $FEV_1 >= 80\%$
GOLD 0 - presence of respiratory symptoms with no lung function abnormality
Restricted - $FEV_1/FVC >= 0.70$ and $FVC < 80\%$ predicted), and no lung disease
Normal – Not in any of the above categories

*FEV_1 is the forced expiratory volume in one second and FVC is the forced vital capacity.

Bronchodilator response was not evaluated so classification is based on "prebronchodilator" level. Only the baseline pulmonary function data was used to stratify participants, and they remained in these groups for interpretation of prevalent risk and incident or recurrent events.

Ascertainment of baseline cardiovascular status and incident or recurrent events

Cardiovascular disease (CVD) events included cardiac disease and stroke. CVD was considered present at baseline if the subject self-reported a myocardial infarction, coronary artery bypass graft, angioplasty, had been hospitalized for a myocardial infarction, had evidence on the electrocardiogram of a myocardial infarction, or had a self-reported stroke at the baseline exam[25].(Table 1) Incident cardiac events were defined as a definite or probable hospitalized myocardial infarction, coronary heart disease death, or myocardial infarction that was detected at follow-up by electrocardiogram changes (major Q wave or a minor Q wave with ischemic ST-T changes or a myocardial infarction by computerized NOVACODE criteria[30], confirmed by side-to-side electrocardiogram comparison) who did not meet this criteria at baseline[31;32]. CVD recurrence was defined as a definite or probable hospitalized myocardial infarction, coronary heart disease death, or myocardial infarction that was detected at follow-up by electrocardiogram changes (major Q wave or a minor Q wave with ischemic ST-T changes or a myocardial infarction by computerized NOVACODE criteria, confirmed by side-to-side electrocardiogram comparison) in those participants identified as having baseline cardiovascular disease. Stroke was defined according to published criteria related to the occurrence and duration of neurological signs and symptoms, the results of neuroimaging and diagnostic procedures, and treatments provided[10;33]. The analysis was restricted to definite or probable ischemic stroke only.

Variable Definitions

Participants were classified as "former smokers" or "current smokers" based on positive responses to "Have you ever smoked cigarettes?" and "Do you now smoke cigarettes?", respectively. Pipe or cigar smokers were considered as "smokers", i.e. subjects who denied current cigarette smoking but reported current or former pipe or cigar smoking were considered current or former smokers, respectively. Never smokers were defined as persons who had not smoked more than 400 cigarettes in their lifetime and had never smoked pipes or cigars. Diabetes mellitus was defined as a baseline glucose level >= 126 mg/dl or use of a medication for diabetes or high blood sugar. Subjects were classified as having hypertension if they either reported a physician diagnosis of hypertension, were on treatment for hypertension, or had evidence of hypertension at the examination (either a diastolic blood pressure >= 90 mm hg or a systolic blood pressure >= 140, based on three measurements). Body mass index was calculated as weight divided by height squared (kg/m2), measured at the baseline examination. Education level was categorized as less than high school, completion of high school, or more than high school. High density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and fibrinogen levels were measured in serum samples [34].

Analysis

All analyses were conducted with SAS version 9.1 (SAS Institute, Cary, NC), SUDAAN version 9.0 (RTI, Research Triangle Park, NC) and SPSS version 10 (SPSS Inc, Chicago, IL, USA).

Our primary outcome of interest was incidence or recurrence of cardiac events or stroke that occurred during the study period. Secondary outcomes were the relationship between prevalent CVD and lung function impairment at the baseline examination and the relationship between lung function impairment and CVD in the study population stratified by gender, age, race, and smoking status. For CVD events, censoring occurred on either the first CVD-related hospitalization or event, death, or the date the person was last known to be alive. We developed Cox proportional hazards models using the procedure SURVIVAL in SUDAAN. Plots of the log–log survival curves for each covariate were produced to ensure that the proportional hazards assumptions were satisfied. Age, sex, race, smoking status, pack-years of smoking, BMI, education level, HDL-C, LDL-C, fibrinogen, diabetes mellitus and hypertension at baseline were included in the adjusted models. Analyses were also performed on subsets of subjects stratified by sex, race, smoking status, and age category, and interactions were evaluated between these variables and our modified GOLD categories.

RESULTS

Our analysis included 14,681 of the initial 15,732 ARIC cohort participants. Excluded subjects did not differ significantly with regard to age, sex, or smoking status ($p > 0.05$ for all) from included subjects, but were more likely to be of black race ($p < 0.01$). The demographic distribution of the analysis cohort is included in Table 2. Baseline 5-year age groups were evenly distributed from 45 to 64 years. The cohort was 55.2% female and 74.2% white. Diabetes was present in 11.2%, hypertension in 34.0%, overweight (BMI 25-29) in 39.4%, and obesity (BMI >= 30) in 27.1%. The mean HDL-C level was 52.0 (standard error [SE] 0.1) mg/dL, the mean LDL-C was137.7 (SE 0.3) mg/dL, and the mean fibrinogen level was 303.3 (SE 0.5) mg/dL.

Table 2: Demographic distribution of study participants, proportion with prevalent cardiovascular disease (CVD) at baseline, and results from univariate and multivariable logistic regression models. From the Atherosclerosis Risk in Communities Study 1987-1989 and follow-up through 2001

	Number (%)	With prevalent CVD at baseline (%)*	Univariate Risk of CVD at baseline Odds Ratio (95% CI)	Multivariate Risk of CVD at baseline Odds Ratio (95% CI) †
Age				
45-49	3,913 (26.7)	105 (2.7)	1.0	1.0
50-54	3,806 (25.9)	172 (4.5)	1.7 (1.3, 2.2)	1.4 (1.1, 1.8)
55-59	3,591 (24.5)	264 (7.4)	2.9 (2.3, 3.6)	1.9 (1.5, 2.4)
60-64	3,026 (22.9)	345 (10.2)	4.1 (3.3, 5.2)	2.3 (1.8, 3.0)
Sex				
Female	8,104 (55.2)	253 (3.1)	1.0	1.0
Male	6,577 (44.8)	633 (9.6)	3.3 (2.9, 3.8)	2.3 (1.9, 2.7).
Race				
White	10,887 (74.2)	659 (6.1)	1.0	1.0
Black	3,794 (25.8)	227 (6.0)	1.0 (0.9, 1.2)	1.0 (0.8, 1.2)
Smoking status				
Current smoker	4,170 (28.4)	291 (7.0)	2.3 (1.9, 2.7)	0.9 (0.6, 1.4)
Former smoker	4,751 (32.4)	410 (8.6)	2.9 (2.4, 3.4)	1.4 (0.9, 2.2)
Never smoker	5,760 (39.2)	185 (3.2)	1.0	1.0
Pack-years				
60 or more	711 (4.8)	126 (17.7)	6.1 (4.8, 7.7)	2.5 (1.6, 4.2)
40-59	1,262 (8.6)	157 (12.4)	4.0 (3.2, 5.0)	2.1 (1.3, 3.3)
20-39	2,843 (19.4)	226 (8.0)	2.5 (2.0, 3.0)	1.5 (0.99, 2.4)
1-19	3,434 (23.4)	145 (4.2)	1.3 (1.01, 1.6)	0.9 (0.6, 1.5)
Unknown	240 (1.6)	21 (8.8)	2.7 (1.7, 4.3)	1.7 (0.9, 3.3)
0	6,191 (42.2)	211 (3.4)	1.0	1.0
Diabetes Mellitus				
Yes	1,642 (11.2)	215 (13.1)	2.8 (2.4, 3.3)	1.8 (1.5, 2.2)
No	13,039 (88.8)	671 (5.2)	1.0	1.0
Hypertension				
Yes	4,992 (34.0)	485 (9.7)	2.5 (2.2, 2.9)	1.9 (1.7, 2.3)
No	9,689 (66.0)	401 (4.1)	1.0	1.0
Body Mass Index				
< 20	477 (3.3)	24 (5.0)	1.1 (0.7, 1.7)	1.5 (0.96, 2.5)
20-24	4,446 (30.3)	209 (4.7)	1.0	1.0
25-29	5,778 (39.4)	366 (6.3)	1.4 (1.2, 1.6)	0.9 (0.7, 1.03)
30 and higher	3,980 (27.1)	287 (7.2)	1.6 (1.3, 1.9)	0.8 (0.7, 1.01)
Education (years)				
< 12	3,423 (23.3)	321 (9.4)	2.1 (1.8, 2.5)	1.5 (1.2, 1.8)
12	4,764 (32.5)	260 (5.5)	1.2 (0.99, 1.4)	1.2 (0.96, 1.4)
> 12	6,494 (44.2)	305 (4.7)	1.0	1.0
HDL-C mg/dL**		52.0 (0.1)	0.67 (0.63, 0.71)	0.81 (0.76, 0.87)
LDL-C mg/dL**		137.7 (0.3)	1.07 (1.05, 1.08)	1.05 (1.03, 1.06)
Fibrinogen mg/dL**		303.2 (0.5)	1.05 (1.04, 1.05)	1.02 (1.01, 1.03)
GOLD Status*				

GOLD 3 or 4	262 (1.8)	29 (11.1)	3.0 (2.0, 4.5)	1.3 (0.8, 2.1)
GOLD 2	1,388 (9.5)	150 (10.8)	2.9 (2.4, 3.6)	1.4 (1.1, 1.8)
GOLD 1	1,612 (11.0)	99 (6.1)	1.6 (1.2, 2.0)	1.0 (0.8, 1.3)
GOLD 0	2,039 (13.9)	132 (6.5)	1.7 (1.4, 2.0)	1.4 (1.1, 1.8)
Restricted	1,187 (8.1)	148 (12.5)	3.4 (2.8, 4.2)	2.3 (1.9, 2.9)
Normal	8,193 (55.8)	328 (4.0)	1.0	1.0
Total	14,681	886 (6.0)		

*Baseline CVD criteria and modified Global Initiative on Obstructive Lung Disease (GOLD) criteria defined in Table 1
† Adjusted for age, sex, race, smoking status, pack years of cigarettes, diabetes mellitus, body mass index, education level, hypertension, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), fibrinogen, and GOLD status.
**Third column displays mean value and standard error in parentheses. Risks are displayed per 10 mg/dL increase

The baseline prevalence of CVD was 6.0% and higher among those with advanced age, male sex, presence of diabetes and hypertension, higher BMI, and lower education level (Table 2). The prevalence was also increased among current or former smokers and related to the number of pack-years. In the unadjusted model, the prevalence of CVD was significantly higher in those with GOLD 2 (Odds Ratio [OR] 2.9, 95% confidence interval [CI] 2.4, 3.6) and GOLD 3 or 4 COPD (OR 3.0, 95% CI 2.0, 4.5), compared to normal subjects. Adjustment for covariates decreased the relative risk for prevalent disease compared to the unadjusted model (OR 1.4, 95% CI 1.1, 1.8 for GOLD 2 and OR 1.3, 95% CI 0.8, 2.1 for GOLD 3 or 4). The highest overall multivariate association between baseline CVD and lung function impairment was observed for those classified as restricted (OR 2.3, 95% CI 1.9, 2.9).

The association between lung function impairment and risk of incident and recurrent CVD events over 15 years are shown in Table 3. Subjects with baseline CVD were more likely to have a CVD event (41.8 events vs. 8.1 events per 1000 person years) and to die (34.9 deaths vs. 8.8 deaths per 1000 person years) than those without baseline CVD. Subjects with GOLD 2 (hazard ratio [HR] 2.4, 95% CI, 2.1, 2.7) and GOLD 3 or 4 COPD (HR 2.9, 95% CI 2.2, 3.9) had the highest univariate risk of CVD events. This finding was decreased in the adjusted models (HR 1.2, 95% CI 1.03, 1.4 for GOLD 2 and 1.5, 95% CI 1.1, 2.0 for GOLD 3 or 4 COPD).

Table 3: Incident or recurrent cardiovascular events to 15 years of follow-up among subjects A) free of cardiovascular disease or stroke at baseline B) with cardiovascular disease or stroke at baseline and C) all subjects stratified by GOLD stage*. From the Atherosclerosis Risk in Communities Study 1987-1989 and follow-up through 2001

	N	Incident or recurrent cardiovascular events per 1000 person years*	Deaths per 1000 person years	Univariate risk of a cardiovascular event from Cox Proportional Hazards Model Hazard Ratio (95% CI)	Multivariate risk of cardiovascular event from Cox Proportional Hazards Model Hazard Ratio (95% CI) †
A. No Cardiovascular disease (CVD) at baseline					

GOLD 3 or 4	233	16.8	46.4	2.2 (1.6, 4.0)	2.0 (1.03, 3.9)
GOLD 2	1,238	13.5	18.0	1.7 (1.3, 2.3)	1.3 (0.96, 1.9)
GOLD 1	1,513	8.4	9.7	1.4 (0.9, 2.0)	1.3 (0.9, 1.8)
GOLD 0	1,907	9.0	8.7	1.3 (0.96, 1.9)	1.2 (0.9, 1.7)
Restricted	1,039	12.3	13.1	1.6 (1.2, 2.2)	1.4 (1.02, 1.9)
Normal	7,865	6.4	5.9	1.0	1.0
Total	13,795	8.1	8.8		
B CVD at baseline					
GOLD 3 or 4	29	66.7	98.9	2.8 (2.0, 3.8)	1.3 (0.9, 1.9)
GOLD 2	150	54.4	39.1	2.1 (1.8, 2.5)	1.2 (0.98, 1.4)
GOLD 1	99	43.0	38.4	1.3 (1.1, 1.6)	1.0 (0.9, 1.2)
GOLD 0	132	41.9	37.2	1.4 (1.2, 1.7)	1.1 (0.9, 1.3)
Restricted	148	50.9	39.2	2.0 (1.6, 2.3)	1.2 (0.98, 1.4)
Normal	328	31.4	25.7	1.0	1.0
Total	886	41.8	34.9		
C All subjects					
GOLD 3 or 4	262	20.4	50.8	2.9 (2.2, 3.9)	1.5 (1.1, 2.0)
GOLD 2	1,388	16.9	20.1	2.4 (2.1, 2.7)	1.2 (1.03, 1.4)
GOLD 1	1,612	10.1	11.2	1.4 (1.2, 1.7)	1.1 (0.9, 1.3)
GOLD 0	2,039	10.7	10.2	1.5 (1.3, 1.7)	1.1 (0.98, 1.3)
Restricted	1,187	16.1	16.0	2.3 (2.0, 2.6)	1.2 (1.1, 1.5)
Normal	8,193	7.2	6.6	1.0	1.0
Total	14,681	9.7	10.2		

* Modified Global Initiative on Obstructive Lung Disease (GOLD criteria and incident or recurrent cardiovascular disease (CVD) criteria are defined in Table 1.

† Adjusted for age, sex, race, smoking status, pack years of cigarettes, diabetes mellitus, body mass index, education level, hypertension, high density lipoprotein of cholesterol (HDL-C), low density lipoprotein of cholesterol (LDL-C), fibrinogen, GOLD status and, among all subjects, prevalent CVD.

We did not find any significant interaction between the GOLD category and smoking status, age category, race, or sex ($p > 0.10$ for each) for our primary outcome of time to CVD event. When the cohort was stratified by smoking status, the rate of CVD events and deaths was higher among current-smokers (14.6 CVD events and 16.7 deaths per 1,000 person years) than among former- (10.0 CVD events and 9.8 deaths per 1,000 person years) or never-smokers (6.2 CVD events and 6.1 deaths per 1,000 person years, Table 4). In the stratified analyses, the relation between lung function impairment, in the adjusted models, was weakest among the current smokers, but there was a large degree of overlap between all three smoking categories (Table 4). The tables examining the relationship between CVD events and lung function impairment stratified by gender, age, and race are available in an online supplement (supplemental tables 1-3). Men had twice the rate of CVD events than women (13.9 vs. 6.5 per 1,000 person years), older subjects (age 55-64) had twice the rate of events than younger subjects (13.4 vs. 6.5 per 1,000 person years), and blacks had a slightly higher rate of events than whites (12.1 vs. 8.9 per 1,000 person years).

Table 4: Incident or recurrent cardiovascular events* and death to 15 years of follow-up among A) never- B) former- and C) current-smokers stratified by GOLD stage*. From the Atherosclerosis Risk in Communities Study 1987-1989 and follow-up through 2001

	N	Incident or recurrent	Deaths per 1000 person	Univariate risk of a cardiovascular	Multivariate risk of cardiovascular

		cardiovascular events per 1000 person years*	years	event from Cox Proportional Hazards Model Hazard Ratio (95% CI)	event from Cox Proportional Hazards Model Hazard Ratio (95% CI) †
A. Never-smokers					
GOLD* 3 or 4	19	13.2	17.0	2.6 (0.9, 7.8)	1.9 (0.7, 5.6)
GOLD 2	185	9.4	9.5	1.8 (1.2, 291	1.5 (0.96, 2.3)
GOLD 1	431	4.0	6.1	0.8 (0.5, 1.2)	0.8 (0.5, 1.3)
GOLD 0	761	8.0	6.9	1.5 (1.2, 2.0)	1.2 (0.9, 1.6)
Restricted	469	12.2	12.8	2.4 (1.8, 3.1)	1.5 (1.1, 1.9)
Normal	3,895	5.3	4.9	1.0	1.0
Total	5,760	6.2	6.1		
B. Former-smokers					
GOLD 3 or 4	88	24.5	49.7	3.3 (2.1, 5.2)	2.3 (1.5, 3.6)
GOLD 2	422	16.3	17.4	2.1 (1.7, 2.8)	1.3 (1.02, 1.8)
GOLD 1	564	10.2	9.2	1.3 (1.03, 1.7)	1.1 (0.9, 1.5)
GOLD 0	510	10.2	9.6	1.3 (1.01, 1.8)	1.2 (0.9, 1.5)
Restricted	315	20.8	19.4	2.7 (2.1, 3.6)	1.4 (1.1, 1.9)
Normal	2,852	7.7	7.0	1.0	1.0
Total	4,751	10.0	9.8		
C. Current-smokers					
GOLD 3 or 4	155	19.3	56.5	1.7 (1.1, 2.5)	1.1 (0.7, 1.6)
GOLD 2	781	19.2	24.3	1.7 (1.3, 2.0)	1.1 (0.9, 1.4)
GOLD 1	617	14.6	17.0	1.3 (0.99, 1.6)	1.1 (0.8, 1.4)
GOLD 0	768	13.9	14.2	1.2 (0.9, 1.5)	1.0 (0.8, 1.3)
Restricted	403	17.3	17.0	1.5 (1.1, 1.9)	0.9 (0.7, 1.2)
Normal	1,446	11.7	10.7	1.0	1.0
Total	4,170	14.6	16.7		

*Modified Global Initiative on Obstructive Lung Disease (GOLD criteria and incident or recurrent cardiovascular disease (CVD) criteria are defined in Table 1.

† Adjusted for age, race, smoking status, diabetes mellitus, body mass index, education level, hypertension, high density lipoprotein of cholesterol (HDL-C), low density lipoprotein of cholesterol (LDL-C), fibrinogen, GOLD status and prevalent CVD.

Figure 1 depicts the Kaplan-Meier curve of the relation between lung function impairment and incident or recurrent CVD, while figure 2 depicts the fully adjusted Cox proportional hazards model curves.

DISCUSSION

In this analysis of a large, prospective population-based cohort, lung function impairment was associated with an increased risk of having or developing CVD in adults; the highest risks were observed among those with GOLD 2 (moderate) and GOLD 3 or 4 (severe/very severe) COPD. After adjusting for multiple covariates including age, sex, race, smoking status, diabetes, hypertension, cholesterol levels, and fibrinogen levels, the relation between lung function impairment and CVD was reduced, suggesting that some of this relation may be mediated through these other factors.

Previous research suggests that systemic inflammation present in COPD leads to the increased CVD risk, and that treatment aimed at decreasing inflammation in those with COPD may decrease the development of cardiovascular disease or reduce event recurrence. Vascular

inflammation may also contribute to impaired airway vascular smooth muscle relaxation in COPD. Treatment with agents that affect systemic inflammation or vascular disease such as corticosteroids, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers have been shown to alter the prognosis of COPD patients [35-39] and one retrospective meta-analysis has suggested a reduction in all-cause mortality in COPD patients treated with inhaled corticosteroids[40]. Our finding that the risk of CVD was greatly reduced in the models that adjusted for HDL-C, LDL-C, fibrinogen and comorbid disease suggests that part of the CVD risk seen in COPD is medicated by these other factors that may be responsive to intervention.

Although low-grade chronic systemic inflammation likely contributes to the association between lung function impairment and CVD, factors such as the role of the lungs in the capture and elimination of external toxic agents may also be important[20].

Previous research has shown a relationship between lung function impairment based on quartile of FEV_1 percent predicted or diagnosed COPD and incident cardiac disease or ischemic stroke, with an increased risk primarily noted within population subsets, such as whites [18], women [20;41], and younger populations [23]. These analyses, however, were not able to make a distinction between those with mild, moderate or severe impairment in lung function or separate out those with restrictive impairment. Our study, however, used the clinically relevant GOLD staging to classify COPD, which does make this distinction.

An interesting finding in our study is the association between restriction on spirometry and CVD risk. As shown in Table 2, restriction was a stronger risk factor for CVD than either GOLD 2 or GOLD 3 or 4 COPD, the risk for incident or recurrent CVD in those with restriction was similar to that seen in GOLD 2 COPD. Neither the degree nor causes of restricted lung disease were examined in this analysis, but future studies may be undertaken to further investigate the relationship between CVD and restriction on spirometry.

Strengths of this study include the large cohort of patients, length of follow-up, and well-defined outcome events. Even though this was a very large sample, though, certain subgroups had small numbers. For example, the number of subjects with prevalent CVD was 150 for GOLD 2 and 29 for GOLD 3 or 4. Also, subjects were classified based on initial PFTs which may not have represented a true baseline, and the restriction category was categorized based on a decreased FVC with a normal FEV_1/FVC ratio rather than the gold standard, total lung capacity measurements. The effect of lung function impairment on CVD outcomes was decreased in the fully adjusted models suggesting that additional confounders that were not included in the analysis might explain these findings. Conversely, it is also possible that our models "over-adjusted". For example, if the effect of lung function impairment on CVD is mediated through inflammation or comorbid disease then adjusting for these factors might mask the true association between lung function impairment and CVD.

CONCLUSION

We observed an association between lung function impairment and risk of prevalent, and incident or recurrent CVD in a large population-based cohort. This association was reduced in models that adjusted for age, sex, race, smoking status, diabetes mellitus, hypertension, cholesterol levels, and fibrinogen levels, suggesting that these effects may be mediated in part though these other factors. The implications of these findings are that clinicians should consider spirometry in their patients with CVD or follow markers of systemic inflammation, such as CRP, in COPD patients to help assess or manage their CVD risk. Future studies may be directed towards better identifying reasons for the linkage between lung function impairment and CVD risk and determining if interventions can improve outcomes.

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FIGURE LEGENDS

Figure 1: Kaplan-Meier curves of incident or recurrent cardiovascular events* among all subjects by GOLD* Stage. From the Atherosclerosis Risk in Communities Study 1987-1989 and follow-up through 2001.

* Modified Global Initiative on Obstructive Lung Disease (GOLD) criteria and incident or recurrent cardiovascular disease (CVD) criteria are defined in Table 1.

Figure 2: Multivariate risk* of incident and recurrent cardiovascular events† by GOLD† Stage. From the Atherosclerosis Risk in Communities Study 1987-1989 and follow-up through 2001.

* Adjusted for age, sex, race, smoking status, pack years of cigarettes, diabetes mellitus, body mass index, education level, hypertension, high density lipoprotein cholesterol (HDL-C),low density lipoprotein cholesterol (LDL-C), fibrinogen, GOLD status and, prevalent CVD.
† Modified Global Initiative on Obstructive Lung Disease (GOLD criteria and incident or recurrent cardiovascular disease (CVD) criteria are defined in Table 1.

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Supplemental Table 1: Incident or recurrent cardiovascular events* and death to 15 years of follow-up among A) men and B) women stratified by GOLD stage*. From the Atherosclerosis Risk in Communities Study 1987-1989 and follow-up through 2001

	N	Incident or recurrent cardiovascular events per 1000 person years*	Deaths per 1000 person years	Univariate risk of a cardiovascular event from Cox Proportional Hazards Model (95% CI)	Multivariate risk of cardiovascular event from Cox Proportional Hazards Model (95% CI) †
A. Men					
GOLD 3 or 4	145	26.9	54.5	2.7 (1.9, 3.8)	1.7 (1.2, 2.4)
GOLD 2	788	20.7	23.9	2.0 (1.7, 2.4)	1.2 (0.98, 1.5)
GOLD 1	921	13.9	14.1	1.3 (1.1, 1.6)	1.1 (0.94, 1.4)
GOLD 0	814	16.4	14.2	1.6 (1.3, 1.9)	1.2 (1.01, 1.5)
Restricted	466	23.6	21.4	2.3 (1.9, 2.8)	1.3 (1.1, 1.6)
Normal	3,443	10.4	8.5	1.0	1.0
Total	6,577	13.9	13.4		
B. Women					
GOLD 3 or 4	117	13.4	46.5	2.8 (1.7, 4.6)	1.2 (0.7, 2.0)
GOLD 2	600	12.2	15.2	2.5 (2.0, 3.2)	1.3 (0.98, 1.7)
GOLD 1	691	5.3	7.5	1.1 (0.8, 1.5)	0.9 (0.7, 1.3)
GOLD 0	1,225	7.2	7.7	1.5 (1.2, 1.8)	1.0 (0.8, 1.3)
Restricted	721	11.7	12.6	2.4 (1.9, 3.0)	1.1(0.9, 1.4)
Normal	4,750	5.0	5.3	1.0	1.0
Total	8,104	6.5	7.7		

* Modified Global Initiative on Obstructive Lung Disease (GOLD criteria and incident or recurrent cardiovascular disease (CVD) criteria are defined in Table 1.
† Adjusted for age, race, smoking status, diabetes mellitus, body mass index, education level, hypertension, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), fibrinogen, GOLD status and prevalent CVD.

Supplemental Table 2: Incident or recurrent cardiovascular events* and death to 15 years of follow-up among A) people 45-54 years old and B) 55-64 years old stratified by GOLD stage*. From the Atherosclerosis Risk in Communities Study 1987-1989 and follow-up through 2001

	N	Incident or recurrent cardiovascular events per 1000 person years*	Deaths per 1000 person years	Univariate risk of a cardiovascular event from Cox Proportional Hazards Model (95% CI)	Multivariate risk of cardiovascular event from Cox Proportional Hazards Model (95% CI) †
A. 45-54 years old					
GOLD 3 or 4	68	7.8	26.3	1.6 (0.7, 3.6)	0.8 (0.3, 1.9)
GOLD 2	512	13.2	11.8	2.7 (2.1, 3.5)	1.3 (1.00, 1.8)
GOLD 1	634	7.3	5.7	1.5 (1.1, 2.0)	1.2 (0.9, 1.6)
GOLD 0	1,143	7.7	5.8	1.6 (1.3, 2.0)	1.0 (0.8, 1.3)
Restricted	614	11.4	9.4	2.4 (1.8, 3.0)	1.1 (0.8, 1.4)
Normal	4,748	4.9	4.1	1.0	1.0
Total	7,719	6.5	5.6		
B. 55-64 years old					
GOLD 3 or 4	194	26.1	61.2	2.6 (1.9, 3.5)	1.7 (1.2, 2.4)
GOLD 2	876	19.3	25.3	1.9 (1.6, 2.2)	1.2 (0.98, 1.5)
GOLD 1	978	12.0	15.0	1.2 (0.9, 1.7)	1.0 (0.9, 1.3)
GOLD 0	896	14.8	16.2	1.4 (1.2, 1.7)	1.2 (0.97, 1.4)
Restricted	573	21.7	23.6	2.1 (1.7, 2.5)	1.3 (1.1, 1.6)
Normal	3,445	10.5	10.2	1.0	1.0
Total	6,962	13.4	15.6		

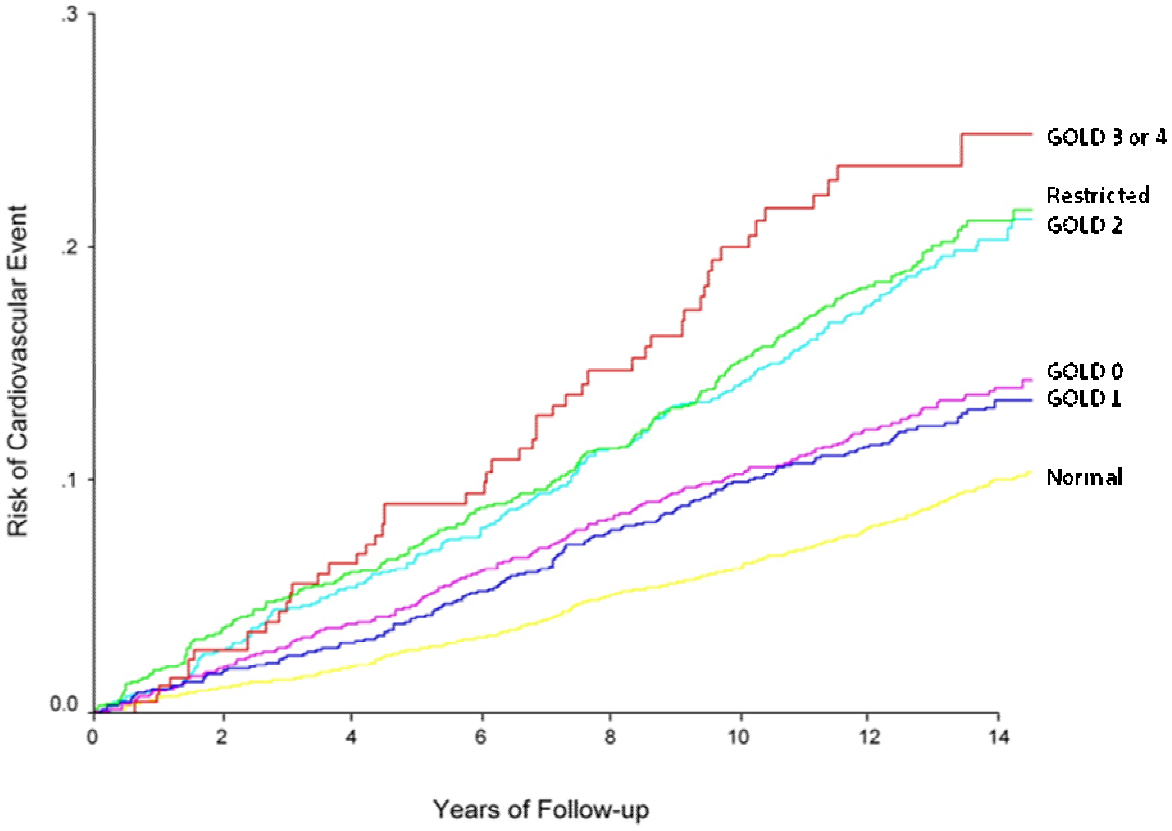
* Modified Global Initiative on Obstructive Lung Disease (GOLD criteria and incident or recurrent cardiovascular disease (CVD) criteria are defined in Table 1.
† Adjusted for age, sex, smoking status, diabetes mellitus, body mass index, education level, hypertension, high density lipoprotein cholesterol (HDL-C),low density lipoprotein cholesterol (LDL-C), fibrinogen, GOLD status and prevalent CVD.

Supplemental Table 3: Incident or recurrent cardiovascular events* and death to 15 years of follow-up among A) whites and B) blacks stratified by GOLD stage*. From the Atherosclerosis Risk in Communities Study 1987-1989 and follow-up through 2001

	N	Incident or recurrent cardiovascular events per 1000 person years*	Deaths per 1000 person years	Univariate risk of a cardiovascular event from Cox Proportional Hazards Model (95% CI)	Multivariate risk of cardiovascular event from Cox Proportional Hazards Model (95% CI) †
A. Whites					
GOLD 3 or 4	205	21.8	46.6	3.5 (2.6, 4.8)	1.7 (1.2, 2.4)
GOLD 2	1,114	16.0	17.1	2.5 (2.2, 3.0)	1.2 (1.00, 1.5)
GOLD 1	1,323	9.4	10.1	1.5 (1.2, 1.8)	1.1 (0.9, 1.3)
GOLD 0	1,488	9.7	8.3	1.5 (1.3, 1.8)	1.2 (0.98, 1.4)
Restricted	762	14.8	14.1	2.4 (1.9, 2.9)	1.2 (0.96, 1.5)
Normal	5,995	6.3	5.6	1.0	1.0
Total	10,887	8.9	8.8		
B. Blacks					
GOLD 3 or 4	57	14.6	68.1	1.6 (0.7, 3.4)	0.9 (0.4, 1.8)
GOLD 2	274	21.1	33.5	2.2 (1.7, 3.0)	1.2 (0.9, 1.6)
GOLD 1	289	13.3	16.5	1.4 (1.01, 1.8)	1.1 (0.8, 1.5)
GOLD 0	551	13.5	15.8	1.4 (1.1, 1.8)	1.0 (0.8, 1.4)
Restricted	425	18.5	19.4	2.0 (1.5, 2.5)	1.3 (1.04, 1.7)
Normal	2,198	9.5	9.6	1.0	1.0
Total	3,794	12.1	14.3		

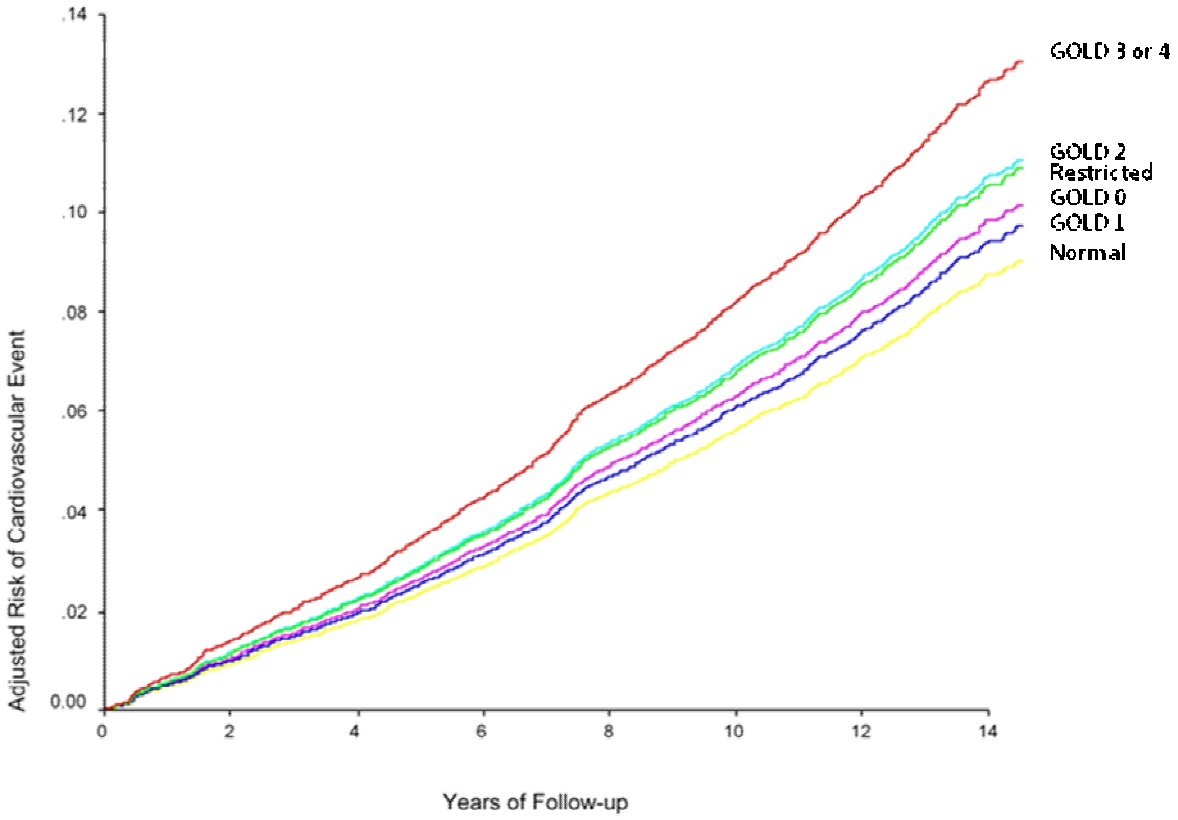
* Modified Global Initiative on Obstructive Lung Disease (GOLD criteria and incident or recurrent cardiovascular disease (CVD) criteria are defined in Table 1.
† Adjusted for age, sex, smoking status, diabetes mellitus, body mass index, education level, hypertension, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), fibrinogen, GOLD status and prevalent CVD.

Figure 1: Kaplan-Meier curves of incident or recurrent cardiovascular events* among all subjects by GOLD* Stage. From the Atherosclerosis Risk in Communities Study 1987-1989 and follow-up through 2001



[#] Modified Global Initiative on Obstructive Lung Disease (GOLD) criteria and incident or recurrent cardiovascular disease (CVD) criteria are defined in Table 1.

Figure 2: Multivariate risk* of incident and recurrent cardiovascular events† by GOLD† Stage. From the Atherosclerosis Risk in Communities Study 1987-1989 and follow-up through 2001



* Modified Global Initiative on Obstructive Lung Disease (GOLD criteria and incident or recurrent cardiovascular disease (CVD) criteria are defined in Table 1.

† Adjusted for age, sex, race, smoking status, pack years of cigarettes, diabetes mellitus, body mass index, education level, hypertension, high density lipoprotein cholesterol (HDL-C),low density lipoprotein cholesterol (LDL-C), fibrinogen, GOLD status and, prevalent CVD.