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Airflow Obstruction, Lung Function, and Incidence of Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Background—Reduced low forced expiratory volume in 1 second (FEV_1) is reportedly associated with an increased risk of atrial fibrillation (AF). Extant reports do not provide separate estimates for never smokers, and for African Americans, who incongruously have lower AF incidence than Caucasians.

Methods and Results—We examined 15,004 middle-aged African Americans and Caucasians enrolled in ARIC cohort study. Standardized spirometry were collected at the baseline examination. Incident AF was identified from the first among the following: ICD codes for AF on hospital discharge records or death certificates or 12-lead ECGs performed during three triennial follow-up visits. Over an average follow-up of 17.5 years, a total of 1,691 (11%) participants developed new onset AF. The rate of incident AF was inversely associated with FEV_1 in each of the four race and gender- groups. After multivariable adjustment for traditional cardiovascular disease risk factors and height, hazard ratios (95% confidence intervals) of AF comparing the lowest with the highest quartile of FEV_1 were 1.37 (1.02,1.83) for white women, 1.49 (1.16,1.91) for white men, 1.63 (1.00,2.66) for black women, and 2.36 (1.30,4.29) for black men. The above associations were observed across all smoking status categories. Moderate/severe airflow obstruction (FEV_1/FVC<0.70 and FEV_1< 80% of predicted value) was also associated with higher AF incidence.

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Conclusions—In this large population-based study with a long term follow-up, reduced FEV_1 and obstructive respiratory disease were inversely - associated with a higher AF incidence after adjusting for measured confounders.

Keywords

lung function; atrial fibrillation; FEV_1; FVC; airflow obstruction; COPD; risk factors

Introduction

Atrial fibrillation (AF), a common arrhythmia, is associated with higher risk of stroke, heart failure (HF), dementia, and mortality [1, 2]. Though borderline or elevated traditional risk factors can explain more than half of the attributable risk of AF [3], studies examining non-traditional risk factors or subclinical disease are limited [4].

AF and chronic obstructive pulmonary disease (COPD), defined by persistent airflow obstruction on spirometry, frequently coexist in clinical settings. Poor lung function, namely low Forced Expiratory Volume in 1 second (FEV_1), and airflow obstruction, are associated with increased risk factors predictive of AF such as coronary heart disease (CHD) [5] and HF [6], and also with stroke, a common complication of AF [7, 8]. Thus, poor lung function and airflow obstruction may potentially lead to an increased risk of AF. However, few studies have examined the association of lung function measures and airflow obstruction with AF[9–12]. Given the potentially strong confounding by smoking, an assessment of such associations among never smokers is particularly important. Lastly, since most studies on the epidemiology of AF were conducted on Caucasians, studies are needed to fill in knowledge gaps about AF in African Americans (AA), a group with paradoxically lower AF incidence despite higher burden of other risk factors [13]. Therefore, we examined whether reduced lung function, as assessed by lower FEV_1, or airflow obstruction assessed by clinical history as well as airflow obstruction detected by spirometry were associated with a higher incidence of AF in the Atherosclerosis Risk in Communities (ARIC) Study, a predominantly biracial cohort of over 15,000 men and women from four US communities. We also explored this association by race, gender, and smoking status.

Method

Study Population

The Atherosclerosis Risk in Communities (ARIC) study is a multi-center population-based prospective study of risk factors for atherosclerosis and the burden of cardiovascular disease. From 1987–1989, 15,792 adults (55.2% women) aged 45–64 years and from four U.S. communities were enrolled, and completed a home interview and clinic visit. Participants were from the following areas: Washington County, Maryland; suburbs of Minneapolis, MN; Jackson, MS; and Forsyth County, North Carolina [14]. Area probability sampling was used at two sites with oversampling of African American at Forsyth County and exclusively African Americans from Jackson. Three follow-up examination visits were conducted, each approximately 3 years apart (the last ending in 1998). In addition, participants received annual follow-up calls since the first visit inquiring about their health and hospitalizations. Details of the ARIC study design have been published [14]. The ARIC study was approved by institutional review boards at each participating center, and written informed consent was obtained from all participants.

In the present study, we excluded the participants who met any of the following hierarchical criteria based on the baseline study visit: a) missing or non-readable ECGs (n=85), or unknown prevalent AF status (n=225); b) prevalent AF or atrial flutter (n=37); c) missing

(n=104) or implausible (n=12) data on lung function value; d) race/ethnicity other than African Americans or Caucasians (n=47); e) missing information on important covariates, including sitting height (n=15), cigarette smoke status (n=14), and cigarette-years of smoking (n=249). After these exclusions, a total of 15,004 of participants (95% of original study cohort) remained for analysis.

Assessment of Atrial Fibrillation

Electrocardiograms (ECGs) and a 2 two-minute rhythm strip from the first visit were examined to identify participants with prevalent AF or atrial flutter. Details for the assessment of AF have been reported previously[15]. AF events were identified from: 1) ECGs performed during follow-up exams; 2) death certificates (ICD-9 code 437.3 or ICD-10 code I48) [16]; 3) hospital discharge records or death certificates through the end of follow up through 2008.

Hospitalizations in ARIC participants were identified through annual follow-up calls and review of local hospital discharges through 2008 [17]. An AF diagnosis was assigned if AF was listed as any cause of death (ICD-9 427.3 or ICD-10 148). AF events identified during hospitalization for cardiac surgery were excluded as these may not relate to the natural history of AF and persistent will be capture in subsequent hospitalization. The validity of hospital discharge diagnoses for AF reported 84% sensitivity and 98% specificity in the ascertainment of AF event among ARIC cohort[15]. The date of incident AF was defined as the first date when ECGs showed AF, hospital discharge coded as AF or death date when AF was listed as a cause of death, whichever occurred first. Most AF incidence cases (87.4%) were identified through hospital discharge codes only. Supplemental Table 1 shows the distribution of AF cases according to the different sources of endpoint ascertainment.

Assessment of Pulmonary function

The main measures of lung function were FEV_1, the volume of gas exhaled in the first second of expiration; and forced vital capacity (FVC), the average maximal volume of gas exhaled after maximal inspiratory effort. Spirometry was conducted at baseline using a water-sealed Collins Survey II volume displacement spirometer (Collins Medical, Inc.) and Pulmo-Screen II software (PDS Healthcare Products, 496 Inc.). At least three acceptable spirograms were obtained from a minimum of five forced expirations. The best single spirograms was identified by a computer and confirmed by a technician. Quality control was carefully conducted throughout the study [18]. All procedures followed the American Thoracic Society guidelines [19].

Assessment of respiratory symptoms was based on self-responses to a standardized questionnaire adapted from the Epidemiology Standardization Project [20]. Airflow obstruction was defined through two means either, a). Self-report of a physician diagnosis of emphysema, bronchitis, or asthma, or b). Spirometry. Post-bronchodilator measurements are required to define COPD optimally, but only pre-bronchodilator measurements were available in this study. Airflow obstruction by spirometry was defined as $FEV_1/FVC<0.70$. We further classified those with airflow obstruction by spirometry into mild ($FEV_1 \geq 80\%$ of predicted value) and moderate plus severe ($FEV_1 < 80\%$ of predicted value) per Global Obstructive Lung Disease (GOLD) criteria[21]. Details of the airflow obstruction assessment in ARIC study have been published [22].

Assessment of Covariates

For the present analysis, we used covariates measured at the first field center visit (1987–89). Anthropometric measures were obtained by trained, certified study personnel following a standardized protocol. Interviewers collected information on age, ethnicity, gender,

smoking, highest education level, medical history, and other factors. For smoking history, participants identified themselves as current, former or never smokers. The average number of cigarette per day and number of years of smoking reported were multiplied to derive cigarette-years of smoking. Education level was classified as did not complete high school (≤ 11 years), high school diploma (12 years), and at least some college (>12 years). Body mass index (BMI) was calculated from measurements of weight to the nearest pound and height to the nearest centimeter, with the participants standing in a scrub suit and without shoes. Sitting height was measured by having the participant sit on a stool approximately 32 inches high in a standard position. Actual sitting height was calculated as the seated participant's height minus the stool height. All sitting height measurements were recorded to the centimeter, rounding down. Participants were asked to bring their current medications at this visit. A medication use history was obtained by self-report of medication intake during last two weeks and by reviewing medication brought by participants to their visit. Each medication was coded by trained and certified interviewers with the use of a computerized medication classification system. Use of medications such as adrenergic beta-agonists, xanthine, and anti-cholinergics was examined as potential confounders. At baseline, inflammatory markers such as white cell count, hemostatic markers such as plasma fibrinogenprotein C, and von Willebrand factor, acute phase and nutrition marker such as albumin, and plasma lipid levels, were measured in central laboratories and using standardized and validated methods as previously described [23]. Prevalent CHD was defined as self-reported physician-diagnosed CHD or the presence of a previous myocardial infarction by ECGs, or self-reported history of coronary bypass or angioplasty of the coronary arteries. Prevalent HF was identified as presence of HF according to Gothenburg criteria [24] or self-reported HF medication use in the past 2 weeks.

Statistical Analysis

FEV1 and FVC vary widely by race and gender, and so does AF rates. Thus, all analyses used either race and gender specific FEV1 groupings or were done separately by race and gender. Initially, we explored the association between measures of lung function and incident AF using restricted cubic spline (Figure 1) [25]. The restricted splines show that the relative HRs decrease sharply as the FEV_1 and FVC were under 2.1 liters for FEV_1 (3.0 for FVC), but was equivalent beyond 3.5 liters for FEV_1 (4.6 for FVC), indicating inflection at those values. Thus, there was a threshold effect around median with most risk seen in the lowest quartile. Based on the shape of splines and to be conservative, FEV_1 and FVC were categorized into race/gender specific quartiles. The median values in each quartile were used as continuous variables for trend estimation. A one standard deviations (SD) difference (race- and gender- specific SD) in the spirometry value was also used for trend estimate.

Cox proportional hazards regression models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CI) of AF by quartiles of FEV_1 and FVC using the highest quartile as reference. Each participant contributed follow-up time from the date of the baseline examination until the earliest of the following dates: AF event, death, lost to follow-up or administrative censoring on 31st December 2008. All models were run by gender-race groups and were adjusted for age, sitting height, and sitting height^2 instead of using % predicted measures which may violate the homogeneity of variance assumptions [26].

The following additional analyses were performed: a) stratified analyses by smoking status (never, former, and current) given its strong potential confounding effect, while adjusting for pack-years of smoking to reduce residual confounding in current or former smokers; b) additional adjustment for obesity (BMI) and pro-inflammatory markers (including white blood cell count, fibrinogen level, albumin level, protein C, and von Willebrand factor) ; c) analyses after excluding those with (or missing information on) HF or CHD, and both to remove potential for confounding due to these conditions; d) analyses after excluding those

without airflow obstruction to remove potential for ascertainment bias; and d) further adjustment for bronchodilators using (beta-agonist, xanthines, and anticholinergic). All analyses were conducted using SAS of version 9.2 (SAS Institute Inc., Cary, North Carolina). A two sided p value of <0.05 for main effects and <0.2 for interactions was considered statistically significant.

Results

A total of 15,004 participants (55.1% female, 26.2% African Americans, average (SD) age at baseline 54 (6) years) were followed for an average of 17.5 (interquartile range 16.6 – 20.6) years. A total of 1,691 (11.3%) participants developed new-onset AF. The selected baseline characteristics of all participants by race- and gender- specific quartiles of FEV_1 are shown in Table 1. In general, having lower FEV_1 was associated with older age, shorter stature, African American race, female gender, smoker, higher BMI, fewer years of formal education, and higher levels of inflammatory markers. In each race- and gender- specific group, participants who developed new-onset AF had lower mean baseline lung function measure (FEV_1 and FVC) than those who remained AF free at the end of study follow up (Table 2).

Pulmonary function test and AF risk

The AF incidence rate decreased monotonically with higher FEV_1 quartiles in each of the four race-gender groups. The average incidence rates of AF per 1000 person years were inversely related to quartiles of FEV_1 and were (lowest to highest quartiles) 6.6, 3.8, 3.5 and 3.2 for white women; 13.7, 8.0, 7.8, and 6.2 for white men; 5.2, 3.2, 2.8, and 2.2 for black women; and 7.5, 5.2, 2.7 and 2.7 for black men, after adjusting for age and sitting height and height square (Table 3). Similar patterns were observed for FVC quartiles (Supplemental Table 2). In analyses restricted to the never smokers group, significant inverse associations between lung function and incident AF were observed (Table 4). The HRs comparing the lowest to highest quartiles of FEV_1 were of greater magnitude in African Americans (who had lower absolute rates) than among Caucasians (p for interaction = 0.15). These HRs were attenuated after additional adjustment for traditional CVD risk factors and systemic markers of inflammation but remained statistically significant. Independent of age, sitting height and smoking status, the hazards of incident AF increased monotonically and inversely by FEV_1 quartiles (Figure 2). Kaplan-Meier survival curves also revealed a monotonic association between FEV_1 and incident AF (Figure 3). In a sub-group analysis restricted to those without HF or/and CHD at baseline visit, the results did not change appreciably (Supplemental Table 3). Further analysis restricted to those without airflow obstruction at baseline showed a similar inverse association between FEV_1 and AF incidence (Supplemental Table 4). Although our primary analyses do not assume linearity, for comparison with previous studies we provide an analysis based on the continuous variable (Supplemental Table 5).

In sub-analyses, similar trend was observed for FVC quartiles; however, the inverse association was not significant after further adjusting for CVD risk factors and systemic markers of inflammation/hemostasis (Supplemental Table 2).

Since the associations between FEV_1 and FVC with incident AF appear to be approximately monotonic, models were fit using continuous lung function measures (Supplemental Table 5). Results are presented for 1 race- and gender- specific SD decreases. The results were consistent with those from the quartile analyses. The cut points for quartile FEV_1/FVC were 0.72, 0.86, and 0.97 for white women; 0.69, 0.74, 0.82 for white men; 0.74, 0.79, and 0.82 for black women; and 0.71, 0.76, and 0.81 for black men. For most race gender groups the boundary of FEV_1 over FVC quartile was around 0.70 and those with value lower than this

had an almost log-linear increase in AF risk (Supplemental Figure 1 and Supplemental Table 2).

Airflow Obstruction and AF

In multivariable adjusted models, those with airflow obstruction ($FEV_1/FVC < 70\%$) had higher AF incidence than those without, hazard ratio were 1.58 (1.29, 1.93) for white women, 1.37 (1.17, 1.60) for white men, 1.10 (0.73, 1.67) for black women, and 1.69 (1.13, 2.55) for black men. Kaplan-Meier survival curves also suggested a monotonic association between airflow obstruction and incident AF (Figure 4). Self-reported physician diagnosis of emphysema or asthma was associated with incident AF among black men but not among any other groups (Table 5). Additional adjustment for use of beta adrenergic agonists, anti-cholinergics, and xanthines didn't change the effect estimates or their confidence interval for the association between FEV1 and AF, or between airflow obstruction and AF (data not shown).

Discussion

In this large population-based, bi-racial, bi-gender cohort, a lower FEV_1 was associated with a higher AF incidence independent of several confounders during an average follow up of 17.5 years.. This inverse association was independent of smoking: it persisted after adjustment for smoking status and cumulative amount smoked and was also seen among never smokers. We found four prospective population-based studies that also evaluated the association of lung function with the risk of AF [9–12]. However, none of these above studies conducted a stratified analysis by smoking status. Our results are consistent with the short term follow up findings from both the Copenhagen City Heart Study [12], and the Cardiovascular Health Study [10]. We extend these results with a longer follow up of a biracial cohort and establishing independence from smoking by examining never smokers separately.

We also observed an association of incident AF with both self-reported physician diagnosis of emphysema and spirometry-defined airflow obstruction. Our findings are consistent with a cross-sectional study [27], where AF prevalence ratios increased with the severity of airflow obstruction. Impaired lung function may increase the risk of AF through several potential mechanisms. Ectopic beats that initiate AF are more likely to originate in the walls of the pulmonary veins where they merge with atria [28]. Though emphysematous changes primarily affect right sided cardiac chambers, few recent studies have shown that moderate emphysema is associated with left ventricular hypertrophy[23], diastolic dysfunction[25, 29], narrower pulmonary vein diameter[30], and structural/electrical abnormalities in pulmonary vein area[30]. Impaired lung function could trigger ectopic beats by deterioration of gas composition and pulmonary hypertension [31], resulting in elevated atrial pressure and alter the electro-physiologic properties of atrial tissues, which in turn trigger AF [32]. Fibrosis of pulmonary veins [33] and stretching of pulmonary veins via increased intra-atrial pressure [34] may also play a role to initiate new-onset AF in individuals with airflow obstruction. The above mechanisms remain speculative and needs further studies using animal models as well among humans. AF ablation registries may help understand the above putative mechanisms.

Other potential pathways involve chronic systemic inflammation and endothelial dysfunction that involves the cardiopulmonary system. The inverse associations between lung function and incident AF were attenuated slightly after additional adjustment for systemic markers of inflammation in our study. Considerable epidemiologic, clinical trial and animal experimental evidence indicate that levels of systemic markers of inflammation are higher in those with low lung volumes. In turn, an involvement of chronic systemic inflammation in the pathogenesis of some chronic respiratory disease [35] and AF [32, 36] has

also been reported. Higher serum concentrations of non-specific markers of inflammation such as C-reactive protein and interleukin-6 have been observed in patients with postoperative AF compared to the controls[36–38]. Recent studies suggested that elevated white blood cell count [32, 39] and C-reactive protein levels [40] were associated with AF in studies with both cross-sectional and longitudinal design. In addition, COPD was associated with higher risk of pneumonia[41], and pneumonia episodes and their severity have been associated with higher AF incidence[42]. Those associations were independent of several CVD risk factors, such as smoking, previous myocardial infarction or HF We observed attenuation of the HR estimates after additional adjustment for baseline levels of inflammatory markers. The present results could not be attributed to either HF or CHD, although some of the potential mechanisms mentioned above may be associated with CHD and HF. It could be argued that participants with HF have some reduction in lung function, which could explain the association between FEV_1 and AF. For instance, HF may predispose to AF through increased atrial filling pressures and atrial dilation [43]; and HF may result in fibrosis and regional conduction abnormalities chronically, which in turn may provide a substrate for AF initiation [30]. Recently, a strong inverse association between reduced lung function and HF has been demonstrated[6]. In our study the inverse association of FEV_1 with incidence of AF remained statistically significant after excluding participants with either HF or CHD at baseline. Lastly, though, medications such as anti-cholinergics, beta agonists, and oral methy-xanthines are potentially arrhythmogenic, their use at baseline visit was low and their adjustment didn't result in any appreciable change in the putative relationship.

Our study has a number of strengths including a relatively large sample size and diverse population, which enabled the estimation of precise incidence rates, stratified by race, gender, and smoking status. In addition, the standardized protocol and the rigorous quality assurance are key strengths. Furthermore, the availability of three decades of longitudinal follow-up permitted complete follow-up (to time of death) on nearly all participants. The prospective design reduces potential bias from recall, while the completeness of follow-up and the annual review of all hospitalization reduce potential for missed or misclassified outcomes.

A few limitations in this study should be considered. Although AF ascertainment in our study was mostly based on hospital discharge codes, previous studies have shown that the validity of AF ascertainment using hospitalizations is acceptable [15, 44], and the incidence of AF in ARIC is similar to those in other studies with a validation of AF [45]. Nevertheless, because participants admitted for comorbid conditions including airflow obstruction may increase propensity of AF detection, this may result in some lead time bias. The definition of new cases of AF in this study could potentially exclude detection of new cases of paroxysmal AF that might not have been detected by ECG or by hospital diagnosis. However, individuals with an index AF event have a high rate of recurrence and conversion to persistent AF [16]. The associations were consistent when AF diagnosis was restricted to diagnosis using study ECG only. Lastly, the possibility of residual confounding cannot be excluded though the extent of potential bias is likely small given our detailed adjustment for known confounders. In addition, as noted, we classified airflow obstruction based on spirometry values without administration of bronchodilator.

Conclusion

Our findings indicate that reduced lung function is associated with a higher incidence of AF, independent of race, gender, smoking, and several other CVD risk factors. Since AF may cause high morbidity from stroke and is associated with increased mortality, our findings suggest that more attention to AF in individuals with impaired lung function and airflow

obstruction is warranted. If these findings are replicated in other cohorts, future studies of the potential mechanisms underlying the observed association may provide other opportunities for AF prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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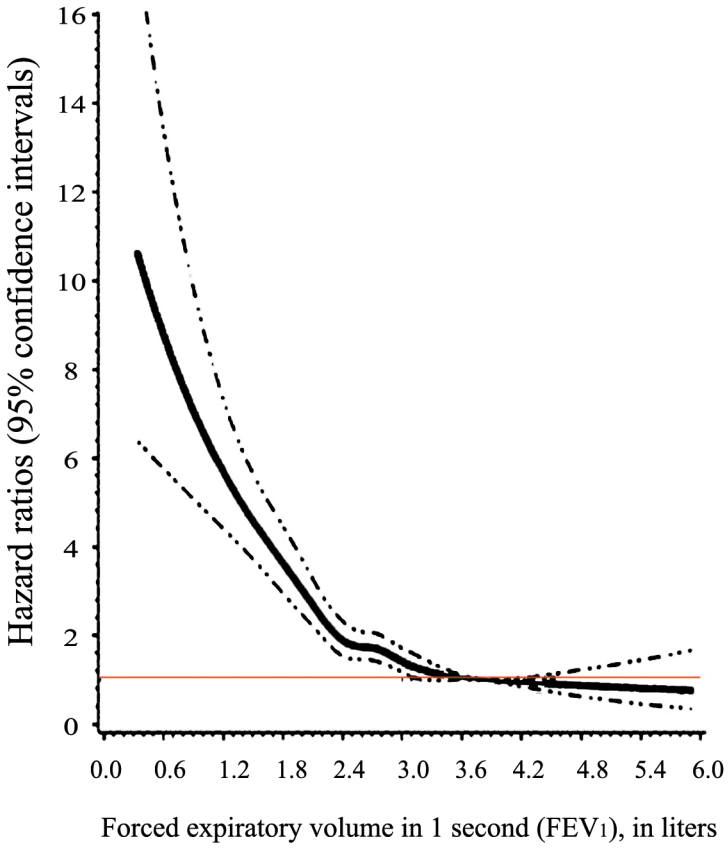

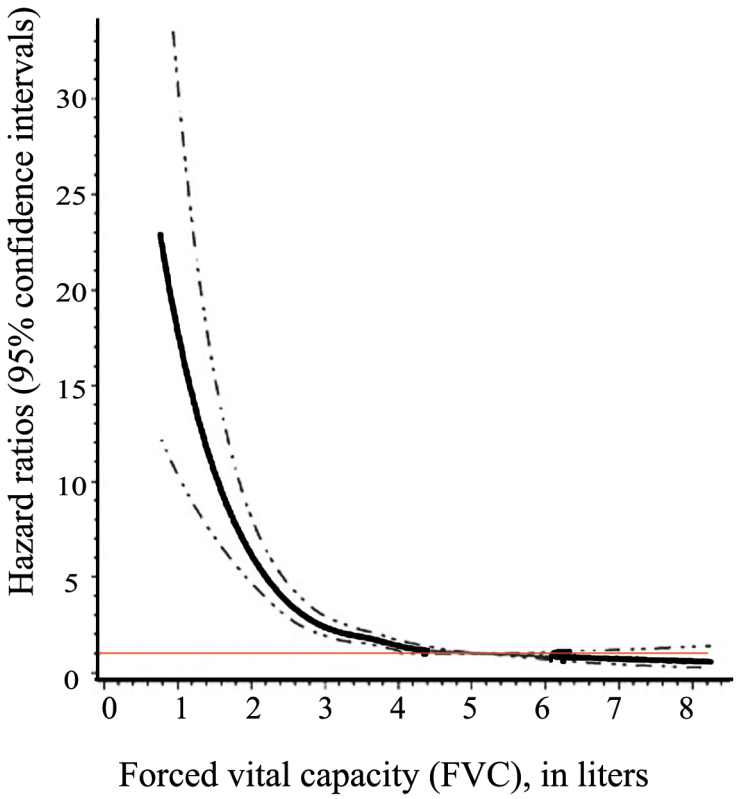

Figure 1.

Hazard ratio (HR, solid line) with 95% confidence intervals (CI, dotted lines)of atrial fibrillation by forced expiratory volume (1s) ($FEV_{1,}$ 1a) and by Forced vital capacity (FVC, 1b), adjusted for sex, race, age (continuous), sitting height, and sitting height^2. The curves are plotted using restricted cubic splines with multiple knots.

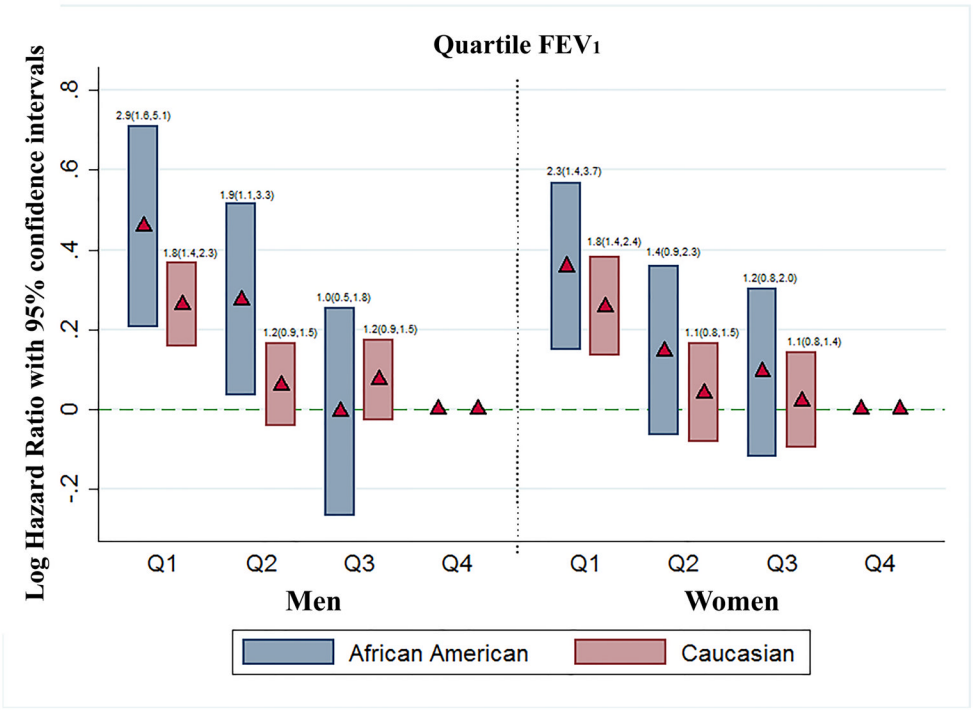

Figure 2.

Estimated Hazard Ratio (95% confidence intervals) of incident atrial fibrillation for the quartiles of forced expiratory volume (1s) for each gender- and race- specific group, adjusted for age (continuous), sitting height, sitting height^2, and smoking. Y axis is plotted on a log scale.

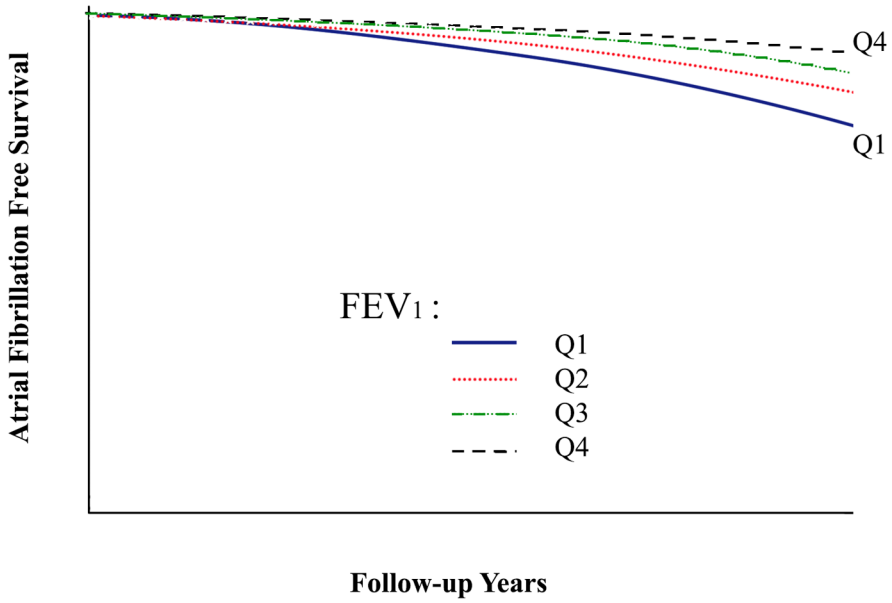

Figure 3.

Kaplan-Meier atrial fibrillation free survival curves by gender and race specific quartiles (Q1 - lowest quartile, Q4 - highest quartile) of forced expiratory volume (1s) i.e., FEV1. Data are from the Atherosclerosis Risk in Communities Study (ARIC) baseline examination (1987–89) in a subsample without prevalent atrial fibrillation and no missing information on important covariates, followed up through 2008.

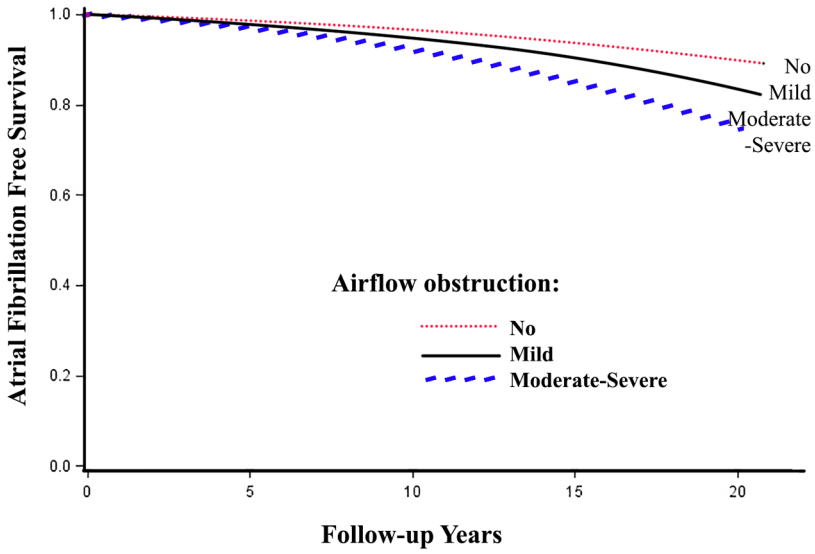

Figure 4.

Kaplan-Meier atrial fibrillation free survival curves by airflow obstruction defined by non-bronchodilator spirometry data using Global Obstructive Lung Disease initiative criteria. Data are from the Atherosclerosis Risk in Communities Study (ARIC) baseline examination (1987–89) in a subsample without prevalent atrial fibrillation and no missing information on important covariates, followed up through 2008.

Table 1

Baseline characteristics of the study population according to race- and gender-specific quartiles of FEV_1, ARIC study, 1987–2008* (n=15,004)

Characteristic	Quartiles of FEV_1 measure				
	1st group (Lowest)	2nd group	3rd group	4th group (highest)	Total
Number in cohort Study Exposures	3,749	3,752	3,753	3,750	15,004
FEV_1 (liters)	2.1 ± 0.5	2.7 ± 0.5	3.0 ± 0.5	3.5 ± 0.7	2.8 ± 0.8
FVC (liters)	3.0 ± 0.8	3.6 ± 0.7	4.0 ± 0.8	4.6 ± 1.0	3.8 ± 1.0
FEV_1/FVC	68 ± 11	75 ± 6	77 ± 6	78 ± 5	74 ± 8
Demographic and AF risk factors					
Age (years)	57 ± 5	55 ± 6	53 ± 5	51 ± 5	54 ± 6
Sitting height (cm)	87 ± 5	88 ± 5	89 ± 4	91 ± 5	89 ± 5
Female (%)	55.1	55.1	55.1	55.1	55.1
Male (%)	44.9	44.9	44.9	44.9	44.9
Caucasians (%)	73.8	73.8	73.8	73.8	50
African American (%)	26.2	26.1	26.2	26.2	26.2
Education					
Less than high school (%)	35.0	26.3	18.6	13.6	23.3
High school (%)	39.8	41.6	42.9	39.6	41.0
Some trade school ± college (%)	25.2	32.1	38.5	46.9	35.7
Smoker					
Current (%)	40.6	26.4	20.4	15.7	25.8
Former (%)	29.6	30.8	33.5	33.5	31.8
Never (%)	29.8	42.8	46.1	50.8	42.4
Cigarette-years of smoking (grams ± week)					
Median	450.0	105.0	36.0	0.0	100.0
IQR‡	0 ~ 840	0 ~ 570	0 ~ 420	0 ~ 280	0 ~ 560
BMI (kg/m^2)	28.1 ± 6.0	28.0 ± 5.4	27.7 ± 5.3	27.1 ± 4.6	27.7 ± 5.4
Heart Failure (%)	9.0	4.5	3.2	1.9	4.7
Coronary heart disease (%)	8.9	5.0	3.4	1.7	4.7
Markers of inflammation					

Characteristic	Quartiles of FEV_1 measure				
	1st group (Lowest)	2nd group	3rd group	4th group (highest)	Total
White blood cell count ($\times 10^3/mm^3$)	6.7 ± 2.1	6.2 ± 1.9	5.9 ± 2.1	5.7 ± 1.7	6.1 ± 2.0
Fibrinogen level (mg/dL)	322.3 ± 72.4	307.2 ± 65.1	296.0 ± 61.2	286.7 ± 55.5	303.0 ± 65.2
Albumin level (g/dL)	3.8 ± 0.3	3.9 ± 0.3	3.9 ± 0.3	3.9 ± 0.3	3.9 ± 0.3
Protein C (mg/L)	3.2 ± 0.6	3.2 ± 0.6	3.2 ± 0.6	3.1 ± 0.6	3.2 ± 0.6
Von Willebrand factor (%)	127.2 ± 52.6	119.1 ± 47.1	115.5 ± 47.5	110.4 ± 43.3	118.0 ± 48.1
Airflow obstruction					
Airflow obstruction (%)	50.4	20.7	11.9	6.0	22.2
Bronchitis (%)	14.7	7.9	5.9	5.3	8.5
Emphysema (%)	4.8	1.0	0.5	0.4	1.7
Asthma (%)	10.4	5.7	4.1	3.1	5.8

ARIC, Atherosclerosis Risk in Communities Study; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; BMI, body mass index

*Values are mean ± SD, or median with IQR for continuous variables, and proportions for categorical variables.

†P-values are for any difference across the quartiles of FEV_1 sing ANOVA, Kruskal-Wallis test, or chi-square test as appropriate.

‡25th–75th percentiles.

Table 2

Adjusted* race- and gender-specific mean values (95% confidence intervals) for FEV_1 and FVC, by the absence or presence of incident atrial fibrillation, ARIC study, 1987–2008 (n=15,004)

Category	FEV_1 (liters)				FVC (liters)			
	Incident AF		No incident AF		Incident AF		No incident AF	
	n	Mean	n	Mean	n	Mean	n	Mean
White Women	572	2.50 (2.47, 2.53)	5,257	2.65 (2.64, 2.67)	572	3.42 (3.39, 3.45)	5,257	3.56 (3.54, 3.57)
White Men	797	3.04 (3.01, 3.07)	4,453	3.20 (3.17. 3.21)	797	4.20 (4.18, 4.24)	4,453	4.35 (4.33, 4.37)
Black Women	186	2.27 (2.24, 2.30)	2,258	2.42 (2.40, 2.44)	186	3.02 (2.99, 3.06)	2,258	3.16 (3.14, 3.19)
Black Men	136	2.81 (2.78, 2.84)	1,345	2.96 (2.94, 2.98)	136	3.82 (3.78, 3.85)	1,345	3.95 (3.93, 3.98)

ARIC, Atherosclerosis Risk in Communities Study; FEV_1:Forced expiratory volume in 1 second; FVC: Forced vital capacity

*Adjustment for age (continuous), sitting height, and sitting height2. Reference values are for someone with age 54 and height of 88.6 cm

Table 3

Race- and gender- specific hazard ratio (95% confidence intervals) of atrial fibrillation according to quartiles of FEV_1, ARIC study, 1987–2008* (n=15,004)

		Caucasians				African American			
		1 (Lowest)	**2**	**3**	**4 (Highest)**	**1 (Lowest)**	**2**	**3**	**4 (Highest)**
Women		(n=1,456)	(n=1,458)	(n=1,458)	(n=1,457)	(n=611)	(n=611)	(n=611)	(n=611)
	Range of FEV_1 (Median)	0.34~2.20 (1.95)	2.20~2.52 (2.37)	2.52~2.83 (2.67)	2.83~4.21 (3.06)	0.51~1.91 (1.68)	1.91~2.21 (2.07)	2.21~2.51 (2.36)	2.51~3.74 (2.72)
	Number of incident AF events	231	133	114	94	74	44	39	29
	Person years (10^3 years)	24.5	26.8	27.6	28.0	9.6	10.7	11.0	11.5
	IR‡(10^3 p-y)	6.6	3.8	3.5	3.2	5.2	3.2	2.8	2.2
	Model 1†	2.21 (1.68, 2.90)	1.21 (0.91, 1.60)	1.10 (0.83, 1.45)	1	2.51 (1.57, 4.03)	1.48 (0.91, 2.41)	1.28 (0.78, 2.07)	1
	Model 2‡	1.81 (1.36, 2.41)	1.10 (0.83, 1.46)	1.05 (0.80, 1.39)	1	2.28 (1.41, 3.69)	1.40 (0.86, 2.29)	1.24 (0.76, 2.01)	1
	Model 3‖	1.37 (1.02, 1.83)	0.93 (0.70, 1.24)	0.97 (0.73, 1.28)	1	1.63 (1.00, 2.66)	1.12 (0.69, 1.84)	1.10 (0.67, 1.80)	1
Men		(n=1,312)	(n=1,313)	(n=1,313)	(n=1,312)	(n=370)	(n=370)	(n=371)	(n=370)
	Range of FEV_1 (Median)	0.47~2.95 (2.59)	2.95~3.45 (3.21)	3.45~3.90 (3.66)	3.90~5.91 (4.21)	0.71~2.58 (2.28)	2.58~2.98 (2.80)	2.98~3.39 (3.17)	3.39~5.22 (3.68)
	Number of incident AF events	298	183	181	135	49	41	22	24
	Person years (10^3 years)	19.6	22.3	23.2	24.4	4.8	6.1	6.5	6.7
	IR‡(10^3 p-y)	13.7	8.0	7.8	6.2	7.5	5.2	2.7	2.7
	Model 1	2.36 (1.88, 2.97)	1.31 (1.03, 1.66)	1.26 (1.00, 1.59)	1	3.17 (1.80, 5.57)	1.96 (1.13, 3.39)	1.01 (0.55, 1.83)	1
	Model 2‡	1.83 (1.44, 2.33)	1.15 (0.91, 1.46)	1.18 (0.94, 1.49)	1	2.87 (1.61, 5.11)	1.88 (1.08, 3.28)	0.99 (0.54, 1.79)	1
	Model 3‖	1.49 (1.16, 1.91)	0.99 (0.78, 1.27)	1.09 (0.86, 1.37)	1	2.36 (1.30, 4.29)	1.53 (0.86, 2.71)	0.81 (0.44, 1.51)	1

ARIC, Atherosclerosis Risk in Communities Study; FEV_1: Forced expiratory volume in 1 second; IR: incidence rate; p-y: person years; HR: hazard ratio; CI: confidence intervals; PYS: person-time at risk

*All models were constructed by the Cox proportional hazards model.

†Model 1: adjustment for age (continuous), sitting height, sitting height^2.

‡Model 2: adjustment for age (continuous), sitting height, sitting height^2, smoking status (never, former, current) and cigarette years of smoking (among current and former smoker).

[||]Model 3: additional adjustment for BMI, education (less than high school, high school, some trade school/college), center, white blood cell count, fibrinogen level, albumin level, protein C, and Von Willebrand factor

P value for all the trends by race and gender group were statistically significant (P<0.01)

Table 4

Race- and gender- specific hazard ratio (95% confidence intervals) of atrial fibrillation according to quartiles of FEV_1, by smoking status, ARIC study, 1987–2008* (n=15,004)

		Caucasians					African American				
		1 (Lowest)	2	3	4 (Highest)	p †	1 (Lowest)	2	3	4 (Highest)	p †
		(n=1,456)	(n=1,458)	(n=1,458)	(n=1,457)		(n=611)	(n=611)	(n=611)	(n=611)	
Women	Current *a*	2.81 (1.35, 5.86)	1.32 (0.61, 2.87)	1.93 (0.90, 4.14)	1	0.001	2.02 (0.77, 5.27)	1.86 (0.75, 4.62)	1.17 (0.44, 3.11)	1	0.107
	Former *b*	1.39 (0.80, 2.44)	0.98 (0.57, 1.69)	0.71 (0.41, 1.23)	1	0.056	2.41 (0.61, 9.48)	1.78 (0.43, 7.42)	2.24 (0.60, 8.40)	1	0.352
	Never *c*	1.83 (1.22, 2.75)	1.23 (0.84, 1.80)	1.10 (0.76, 1.59)	1	0.003	2.51 (1.36, 4.63)	1.10 (0.57, 2.12)	1.07 (0.56, 2.02)	1	0.001
		(n=1,312)	(n=1,313)	(n=1,313)	(n=1,312)		(n=370)	(n=370)	(n=371)	(n=370)	
Men	Current *a*	1.89 (1.11, 3.24)	1.09 (0.63, 1.89)	1.06 (0.60, 1.89)	1	0.001	2.17 (0.95, 4.93)	1.35 (0.59, 3.09)	0.63 (0.23, 1.67)	1	0.025
	Former *b*	1.89 (1.34, 2.66)	1.28 (0.91, 1.80)	1.36 (0.99, 1.86)	1	0.001	2.31 (0.80, 6.63)	1.23 (0.44, 3.40)	0.81 (0.27, 2.46)	1	0.046
	Never *c*	1.70 (1.03, 2.79)	1.06 (0.68, 1.67)	1.04 (0.68, 1.58)	1	0.066	5.04 (1.50, 16.95)	4.28 (1.47, 12.44)	1.82 (0.63, 5.30)	1	0.003

ARIC, Atherosclerosis Risk in Communities Study; FEV_1: Forced expiratory volume in 1 second; IR: incidence rate; p-y: person years; HR: hazard ratio; CI: confidence intervals; PYS: person-time at risk

*All models were constructed by the Cox proportional hazards model.

†Linear test across median values of FEV_1 quartiles.

*a*Current smoker: adjustment for age (continuous), sitting height, sitting height^2, cigarette years of smoking. n=3,868

*b*Former smoker: adjustment for age (continuous), sitting height, sitting height^2, cigarette years of smoking. n=4,777

*c*Never smoke: adjustment for age (continuous), sitting height, sitting height^2. n=6,359

Table 5

Race- and gender- specific incidence rate and hazard ratio (95% confidence intervals) of atrial fibrillation for airflow obstruction, ARIC study, 1987–2008* (n=15,004)

	Caucasians				African American			
	IR† (1000 p-y)	HR (95% CI)			IR† (1000 p-y)	HR (95% CI)		
Women		**Model 1‡**	**Model 2§**	**Model 3‖**		**Model 1‡**	**Model 2§**	**Model 3‖**
No airflow obstruction	4.2	1	1	1	4.0	1	1	1
Airflow obstruction	6.6	1.63 (1.36, 1.95)	1.36 (1.12, 1.65)	1.58 (1.29, 1.93)	5.0	1.30 (0.89, 1.91)	1.15 (0.77, 1.70)	1.10 (0.73, 1.67)
Mild airflow obstruction	4.8	1.14 (0.89, 1.48)	1.04 (0.80, 1.35)	1.28 (0.99, 1.67)	4.2	1.07 (0.61, 1.89)	1.00 (0.56, 1.76)	1.19 (0.67, 2.11)
Moderate/Severe airflow obstruction	9.0	2.37 (1.89, 2.97)	1.87 (1.46, 2.41)	1.98 (1.54, 2.56)	5.6	1.53 (0.94, 2.47)	1.29 (0.78, 2.11)	1.04 (0.61, 1.78)
No Bronchitis	4.4	1	1	1	3.9	1	1	1
Self-reported diagnosis of bronchitis	6.1	1.44 (1.15, 1.80)	1.25 (0.99, 1.57)	1.20 (0.95, 1.52)	5.7	1.50 (0.95, 2.36)	1.32 (0.82, 2.11)	1.14 (0.69, 1.87)
No Emphysema	4.6	1	1	1	4.0	1	1	1
Self-reported diagnosis of emphysema	7.1	1.83 (0.98, 3.43)	1.29 (0.68, 2.43)	1.08 (0.55, 2.13)	12.1	3.18 (1.18, 8.57)	2.44 (0.88, 6.73)	1.69 (0.58, 4.93)
No Asthma	4.6	1	1	1	4.0	1	1	1
Self-reported diagnosis of asthma	6.2	1.39 (1.02, 1.90)	1.33 (0.97, 1.83)	1.24 (0.90, 1.71)	8.7	1.45 (0.88, 2.38)	1.37 (0.83, 2.26)	1.03 (0.61, 1.73)
Men		Model 1‡	Model 2§	Model 3‖		Model 1‡	Model 2§	Model 3‖
No airflow obstruction	6.8	1	1	1	4.9	1	1	1
Airflow obstruction	10.0	1.54 (1.33, 1.77)	1.27 (1.09, 1.48)	1.37 (1.17, 1.60)	8.2	1.77 (1.22, 2.57)	1.57 (1.06, 2.33)	1.69 (1.13, 2.55)
Mild airflow obstruction	7.9	1.17 (0.95, 1.43)	1.06 (0.87, 1.31)	1.20 (0.98, 1.49)	4.0	0.82 (0.41, 1.62)	0.74 (0.37, 1.48)	0.68 (0.31, 1.49)
Moderate/Severe airflow obstruction	12.0	1.88 (1.59, 2.23)	1.47 (1.23, 1.77)	1.52 (1.26, 1.82)	11.5	2.66 (1.77, 4.01)	2.36 (1.54, 3.63)	2.63 (1.68, 4.12)
No Bronchitis	7.5	1	1	1	4.4	1	1	1
Self-reported diagnosis of bronchitis	10.5	1.45 (1.11, 1.89)	1.29 (0.99, 1.69)	1.25 (0.95, 1.64)	9.0	1.84 (0.86, 3.94)	1.76 (0.82, 3.78)	1.59 (0.69, 3.67)
No Emphysema	7.6	1	1	1	5.5	1	1	1
Self-reported diagnosis of emphysema	12.1	1.73 (1.22, 2.44)	1.37 (0.96, 1.94)	1.35 (0.94, 1.93)	17.7	3.98 (1.46, 10.83)	3.94 (1.43, 10.91)	4.73 (1.67, 13.37)
No Asthma	7.6	1	1	1	5.4	1	1	1
Self-reported diagnosis of asthma	5.6	1.15 (0.87, 1.53)	1.18 (0.89, 1.56)	1.16 (0.87, 1.55)	9.8	1.85 (1.00, 3.42)	1.87 (1.00, 3.48)	1.96 (1.04, 3.69)

ARIC, Atherosclerosis Risk in Communities Study; Forced expiratory volume in 1 second; IR: incidence rate; p-y: person years; HR: hazard ratio; CI: confidence intervals

Using spirometry done without bronchodilator, any airflow obstruction was defined as $FEV_1/FVC < 70\%$, mild airflow obstruction was defined $FEV_1/FVC < 70\%$ and $FEV_1 \geq 80\%$ (predicted), moderate/severe airflow obstruction was defined as $FEV_1/FVC < 70\%$ and $FEV_1 < 80\%$ (predicted), and no airflow obstruction as $FEV_1/FVC \geq 70\%$.

*All models were constructed by the Cox proportional hazards model.

†Adjusted for age (continuous).

‡Model 1: adjustment for age (continuous).

§Model 2: additional adjustment for smoking status (never, former, current) and cigarette years of smoking.

||Model 3: additional adjustment for BMI (continuous), education (less than high school, high school, some trade school/college), center, white blood cell count, fibrinogen level, albumin level, protein C, and Von Willebrand factor.