Association between lung function and future risks of diabetes, asthma, myocardial infarction, hypertension and all-cause mortality

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Contribution: ZZ developed the study idea and designed the methodological approach; CS analyzed data and wrote the first draft; RR provided clinical insight; YL provides statistical inputs; all authors contributed to the writing.

Abstract

Background: While forced expiratory volume in 1 second (FEV_1) is a hallmark of disease progression in chronic obstructive lung diseases, little is known about the relationship between baseline FEV_1 and future risks of other medical conditions.

Objective: To study the association between baseline FEV_1 and future risks of diabetes, asthma, myocardial infarction, hypertension and all-cause mortality.

Methods: We used data from the National Health and Nutrition Examination Survey and its Epidemiological Follow-Up Study. Our data provided longitudinal follow-up of the original cohort for up to 12 years. We used two competing risks approaches, the cause-specific hazard model and the Fine-Gray sub-distribution hazard model, to measure the associations between baseline FEV_1 and future risks of the outcomes of interest. All models adjusted for major confounding factors.

Results: The final sample included 3,020 participants (mean baseline age: 44.64 years, standard deviation: 13.44). In the cause-specific hazard model, for every percent increase in the baseline percent predicted FEV_1, the hazard of the event reduced by 2.5% (HR: 0.975 (95% Confidence Interval [CI]: 0.958, 0.994)) for diabetes, 4.3% (HR: 0.957 (95%CI: 0.932, 0.983)) for asthma, and 1.8% (HR: 0.982 (95%CI: 0.971, 0.992)) for all-cause mortality. There was no statistically significant association between baseline percent predicted FEV_1 and future risks of myocardial infarction (HR: 0.987 (95%CI: 0.970, 1.004)) and hypertension (HR: 0.998 (95%CI: 0.992, 1.005)). Consistent results were observed for the Fine-Gray sub-distribution hazard model.

Conclusion: Our data suggests that lower percent predicted FEV_1 values at baseline were significantly associated with higher future risks of diabetes, asthma, and all-cause mortality.

Key words: FEV_1; COPD; competing risk; comorbidities

INTRODUCTION

Pulmonary tests are the mainstay for identification and management of respiratory diseases [1]. Currently, spirometry is the standard test for measuring lung function [2] by quantifying the rate and volume of air flow expired [3]. The forced expiratory volume in 1 second (FEV_1) is a key measure of spirometry [1] and represents the maximal volume of air exhaled in the first second of a forced expiration after a position of full inspiration [4].

While FEV_1 is a hallmark of disease progression among chronic obstructive pulmonary disease (COPD) patients, evidence suggests a linkage between FEV_1 and multiple other chronic conditions and mortality [5]. For instance, previous *ad hoc* studies have found that lung function is inversely associated with the incidence of diabetes [6, 7], heart disease [8, 9], asthma [10], increased blood pressure [11, 12], and mortality [13–17]. Nevertheless, the association between FEV_1 and future events and the competing nature of such events in a unified model has been under-studied.

In this study, we aim to examine possible relationships between baseline FEV_1 and future incidence of four major medical conditions including diabetes, asthma, myocardial infarction, and hypertension, as well as all-cause mortality using a longitudinal observational data. For our analyses, we employ two competing risks frameworks, the cause-specific and the Fine-Gray sub-distribution hazard models.

METHODS

Data: We analyzed data from the publicly available National Health and Nutrition Examination Survey (NHANES I) and its corresponding Epidemiological Follow-Up Study (NHEFS) [18]. NHANES I included baseline information for a representative sample of the United States (US) population aged 25-74 years old and was conducted between 1971 and 1975 [18]. NHEFS was a longitudinal follow-up on NHANES I initiated by the National Centre for Health Statistics and the National Institute on Aging in collaboration with other public health service agencies [19]. The NHEFS longitudinal follow-up was designed to investigate the relationship between clinical, behavioral, and nutritional factors examined in NHANES I and their long-term effects on morbidity, mortality, and hospital utilization. NHANES I's participants aged 25-74 years old, with a complete medical examination in NHANES I, underwent further follow-up investigation on their morbidity, mortality, hospital utilization, changes in risk factors, and functional limitations for the period between their baseline interview and the first follow-up in 1982-84 as a part of the NHEFS [19]. The data files utilized are outlined in *Figure 1*.

Primary outcomes and independent variables: We modeled five medical conditions as our outcomes of interest. The outcomes were diabetes, asthma, myocardial infarction/heart attack, hypertension, and all-cause mortality. We chose these medical conditions for two reasons: first, because they are major events associated with lung function with evidence from prior studies; and second, because we had complete, consistent follow-up data available for these events in NHEFS. The competing events were defined as incident cases over the follow-up period for a maximum of 12 years from the baseline examination until 1982.

Our main independent variables were percent predicted FEV_1 (measured by %) and absolute FEV_1 (measured by liter (L)). The spirometry was carried out using an electronic spirometer (Model '800' electric spirometer manufactured by Ohio Medical Instruments Corporation) [20]. Further information is available elsewhere [20]. The percent predicted FEV_1 was calculated by using the equation provided by Hankinson et al. [21]. In addition, the presence of COPD at baseline was defined based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criterion of having FEV_1/FVC (Forced Vital Capacity) ratio less than 0.7 [5]. Therefore, we utilized the FEV_1/FVC ratio threshold as a covariate in the model.

In line with previous literature [6], we adjusted for other major covariates in the model including age, body mass index (BMI) (kg/m^2), sex, race (black or white), education, smoking status, physical inactivity, marital status, alcohol consumption levels, FEV_1/FVC ratio threshold and Charlson's Comorbidity Index (CCI) score [22, 23]. In addition, to account for the possible 'U-shape' relationship of BMI with mortality, we included BMI-squared as a covariate in the model [24, 25]. All covariates were measured at the baseline period.

Defining incident cases of diabetes, asthma, myocardial infarction, hypertension, and all-cause mortality: We used the 1982-84 NHEFS follow-up file to determine occurrence, and the time of occurrence, of any of the conditions of interest during the follow-up period. In addition to self-reported physician diagnosis, for validation, we used the NHEFS health care services utilization files to determine if individuals had health care facility usage for any of the events of interest in the follow-up period. These files were created based on reports of the respondents and subsequent review of the subjects' medical record that was carried out by contacting the health care facility.

To capture the association of baseline FEV_1 with future incidence of our main conditions/events, we created a cohort of only susceptible ('disease free') individuals at baseline. That is, we included only individuals who were at risk of developing our main events during the follow-up period, and those with a diagnosis before or during the baseline period were excluded. The combination of the medical examination file (using 3-digit International Classification of Diseases (Ninth Revision)-Clinical Modification (ICD9 CM)), the health care needs file, and the medical history file from NHANES I were used to ascertain whether the condition of interest was a prevalent one (defined as a condition that was present at baseline). In particular, for any event of interest, a respondent was considered to have diagnosis for any of the conditions in question at baseline if he/she:

- had the condition at baseline as determined from the health care needs file or the medical history file; or

- had the condition at baseline as determined from the medical examination file; or

- self-reported physician diagnosis of the condition at any time before or during the baseline period.

Individuals with uncertain answers such as those who reported 'didn't know' about their event or reported 'not ascertained' about the onset time of their event during the follow-up period were excluded. The cohort selection process has been illustrated in *Figure 2.*

If a person did not have any events of interest during the follow-up period, he/she was censored in 1982 in our study. In rare situations, if more than one competing event (=n) was

experienced by an individual during a specific year, the same time-to-event was applied to those events with each event having a weight of 1/n.

Statistical model: We developed two competing risks models to study the association of baseline FEV_1 with future risks of our events of interest. First, we used a cause-specific hazard model that quantifies the instantaneous risk of an event of interest at a given time, given that the individual has survived, and has not yet experienced any of the competing events (including the event of interest), up to that time point [26]. Therefore, in this approach, the risk set at a given time includes individuals who are free from any competing events up to that time point.

Second, we used the Fine-Gray sub-distribution hazard model that quantifies the cumulative incidence risk of an event of interest at a given time in the presence of other competing events. This approach models the instantaneous risk of an event at a given time, given that the individual has survived, and has not yet developed the primary event of interest; however the person was allowed to have developed other competing events besides the primary event up to that time point [26–28]. Therefore, the risk set at time t includes those who are free from the event of interest until time t, irrespective of whether or not they have already developed a competing event earlier [26].

All statistical analyses were performed using SAS (version 9.4 SAS Institute Inc., Cary, NC, US).

RESULTS

After excluding individuals with missing information during the follow-up visits (5.8%), the final study sample consisted of 3,020 individuals. When we compared the baseline percent predicted FEV_1 for the individuals with missing information during the follow-up visits against the final sample, the difference was not statistically significant. The final sample had a mean age of 44.64 years (standard deviation (SD)=13.44) at baseline, was predominantly women (54%) and white (93%). The mean BMI was 24.68 kg/m^2 (SD=4.32) and 85% of the sample had a minimum of high school education at baseline. Approximately 15% of the sample had FEV_1/FVC<0.7, the average FEV_1 value was 3.02 L (SD= 0.84 L), and the mean percent predicted FEV_1 was 91.04% (SD= 16.26%) at baseline. Also, 60% of the sample were ever smokers at baseline. The details of other sample characteristics are displayed in **Table 1.**

Cause-specific hazard model

Regression model with percent predicted FEV_1: In the adjusted model, every percent increase in the baseline percent predicted FEV_1 was associated with a reduced future risk of diabetes of 2.5% (hazard ratio (HR): 0.975 (95% Confidence Interval [CI]: 0.958, 0.994)), reduced risk of asthma of 4.3% (HR: 0.957 (95% CI: 0.932, 0.983)), and reduced risk of all-cause mortality of 1.8% (HR: 0.982 (95% CI: 0.971, 0.992)). The association of baseline percent predicted FEV_1 and future risks of myocardial infarction (HR: 0.987 (95% CI: 0.970, 1.004)) and hypertension (HR: 0.998 (95% CI: 0.992, 1.005)) were not statistically significant at a two-tailed p-value of 0.05 (**Table 2**). The effects of the other covariates on future incidence of the events of interest are presented in the **Online Appendix A.**

Regression model with absolute FEV_1*:* Every liter increase in the baseline absolute FEV_1 was associated with a reduced instantaneous future risk of diabetes of 55% (HR: 0.452 (95% CI: 0.270, 0.755)), reduced risk of asthma of 79% (HR: 0.213 (95% CI: 0.096, 0.474)), reduced risk of myocardial infarction of 40% (HR: 0.599 (95% CI: 0.365, 0.984)), and reduced risk of all-cause mortality of 41% (HR: 0.588 (95% CI: 0.426, 0.810)). The association between the baseline FEV_1 and future risk of hypertension was not statistically significant (HR: 0.872 (95% CI: 0.719, 1.057)) (***Table 3***). The effects of the other covariates in the regression on future incidence of the events of interest are presented in the ***Online Appendix B.***

Fine-Gray sub-distribution hazard model

Regression model with percent predicted FEV_1: Every percent increase in the percent predicted FEV_1 at baseline was associated with a 2.3% decrease in the instantaneous risk of diabetes (HR: 0.977 (95% CI: 0.959, 0.996)), 4.1% decrease in the risk of asthma (HR: 0.959 (95% CI: 0.937, 0.982)), and 1.6% decrease in the risk of all-cause mortality (HR: 0.984 (95% CI: 0.974, 0.993)). The associations with myocardial infarction (HR: 0.989 (95% CI: 0.976, 1.002)) and hypertension (HR: 1.000 (95% CI: 0.993, 1.007)) were not statistically significant (***Table 2*** and ***Appendix A***).

Regression model with absolute FEV_1*:* Every liter increase in absolute FEV_1 at baseline was associated with a 53% decrease in the instantaneous risk of diabetes (HR: 0.473 (95% CI: 0.273, 0.821)), 76% decrease in the risk of asthma (HR: 0.235 (95% CI: 0.119, 0.463)), 35% decrease in the risk of myocardial infarction (HR: 0.646 (95% CI: 0.443, 0.942)), and 37% decrease in the risk of all-cause mortality (HR: 0.626 (95% CI: 0.464, 0.845)). The association

with hypertension was not statistically significant (HR: 0.912 (95% CI: 0.756, 1.099)) (see **Table 3** and **Appendix B**).

DISCUSSION

In this study, we examined the possible association of baseline FEV_1 and future risks of four major medical conditions—namely diabetes, asthma, myocardial infarction/heart attack, and hypertension—and all-cause mortality using data from NHANES I and the Epidemiological Follow-Up Study. Our results indicate that FEV_1 may play a key role in the long-term incidence of various medical conditions. We used two competing risks modeling approaches. First, using a cause-specific hazard model, our results showed that every percent decrease in percent predicted FEV_1 at baseline was statistically significantly associated with a 2.5% higher risk of diabetes, 4.3% higher risk of asthma, and 1.8% higher risk of all-cause mortality in the future. Our data did not find statistically significant associations between baseline percent predicted FEV_1 and future risks of myocardial infarction and hypertension at the significance level of 0.05 for the given sample size, although the directions of the point estimates were indicative of a possible association between low baseline FEV_1 and future risks of these conditions.

Second, we used a Fine-Gray sub-distribution hazard model. The results of this model were consistent with those of the cause-specific hazard model indicative of statistically significant higher future risks of diabetes, asthma, and all-cause mortality associated with lower baseline percent predicted FEV_1 values.

The relationship between the baseline FEV_1 and future incidence of diabetes in our study is in the same direction with the previous studies. An earlier population-based Swedish cohort study found that for every additional liter in absolute FEV_1, the odds of diabetes would be reduced by 59% [7]. Despite a different methodology, our estimate was almost similar to the Swedish study (55%). Another study in the US found that every liter increase in FEV_1 (L) was associated with a hazard ratio of 0.698 (p-value<0.001) for diabetes [6]. In our study the corresponding cause-specific hazard ratio was 0.452 (p-value<0.01). The relationship between FEV_1 and diabetes was of particular interest, especially since we adjusted for BMI, a potential confounder, in the regression.

For the association of lung function and future risk of asthma, an earlier study found that reduced lung function at infancy is linked with a greater risk of development of asthma later in life among children [10]. While our results, in an adult population, point towards a similar direction, our estimates cannot be directly compared against those of the previous study; this is because the previous study did not measure lung function by absolute FEV_1.

In addition, for all-cause mortality, our results are in concordance with the previous studies [14, 17, 29, 30]. For example, Schünemann et al. found that the all-cause mortality reduced by 1.5% (HR: 0.985 (95% CI: 0.980, 0.990)), and 1% (HR: 0.990 (95% CI: 0.985,0.995)), for every percent increase in percent predicted FEV_1 among men, and women, respectively [17]. In another study, Leivseth et al. reported that for every 10% decrease in percent predicted FEV_1, the adjusted hazard ratio for all-cause mortality was 1.17 (95% CI 1.09–1.25) in women, and 1.23 (95% CI 1.16–1.30) in men [29]. Similarly, our study found that for every percent

increase in the baseline percent predicted FEV_1, the instantaneous risk of all-cause mortality would reduce by 1.8% (HR: 0.982 (95% CI: 0.971, 0.992)).

Our study has major strengths. First, we conducted our analyses based on a nationally representative dataset with a long follow-up time to quantify the future incidence of the conditions of interest. Second, we looked at the association of the baseline FEV_1 and future risks of multiple conditions in a 'unified' competing risks framework. For our analyses, we used two popular, yet statistically distinct, competing risks methodologies: the cause-specific hazard model and the Fine-Gray sub-distribution hazard model. While our study does not provide evidence on the causal relationships between the outcomes of interest modeled here, it provides evidence on the competing risks nature of these outcomes.

Our analyses faced some limitations as well. For instance, similar to many observational studies, the inability to adjust for packyears among smokers and utilization of medications by participants in our data may lead to certain biases due to unmeasured confounding. Further, patients with lower FEV_1 values may visit their healthcare provider more often than their otherwise healthier counterparts, and this could possibly give them a greater chance of being diagnosed with the conditions of interest. However, for the most part, our results were similar to and consistent with previous studies, including prospective studies. Moreover, given that our study only examined five competing outcomes of interest in a non-institutionalized, relatively healthy US sample, cautions should be exercised in the interpretation of our findings. Also, similar to other observation studies, there could be a possibility of undiagnosed individuals with the diseases of interest being included in our final cohort. Finally, while our long-term follow-up

could be viewed as a strength, it could also lead to potential changes in diagnostic criteria and treatment options over time that might impact outcomes [31].

Our findings in its entirety suggest that taking steps that result in the preservation of lung function can be associated with long-term reductions in the risks of the medical conditions modeled in this study. As such, investments in interventions that preserve lung function can be potentially associated with health and economic benefits well beyond those that have been already quantified in COPD and other respiratory diseases.

CONCLUSION

In our data, lower percent predicted FEV_1 values at baseline were found to be statistically significantly associated with a higher future incidence of diabetes, asthma, and all-cause mortality. Our analyses for absolute FEV_1 yielded similar results for the future incidence of myocardial infarction. Future studies should further investigate these associations and examine other conditions in different patient populations.

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Figure 1. Overview of data files used to create the final analytical file.
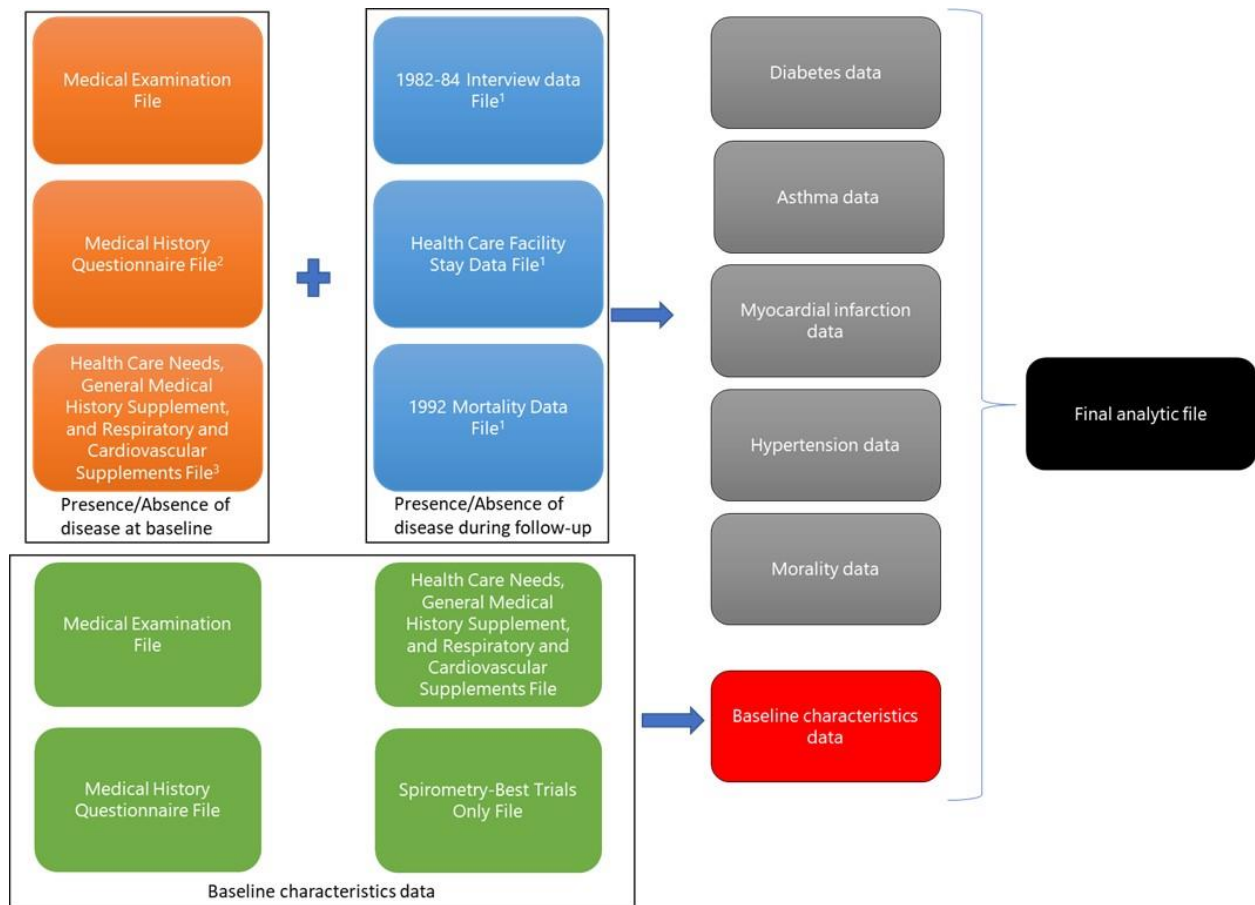
Figure 2. Flow diagram illustrating the cohort selection process.
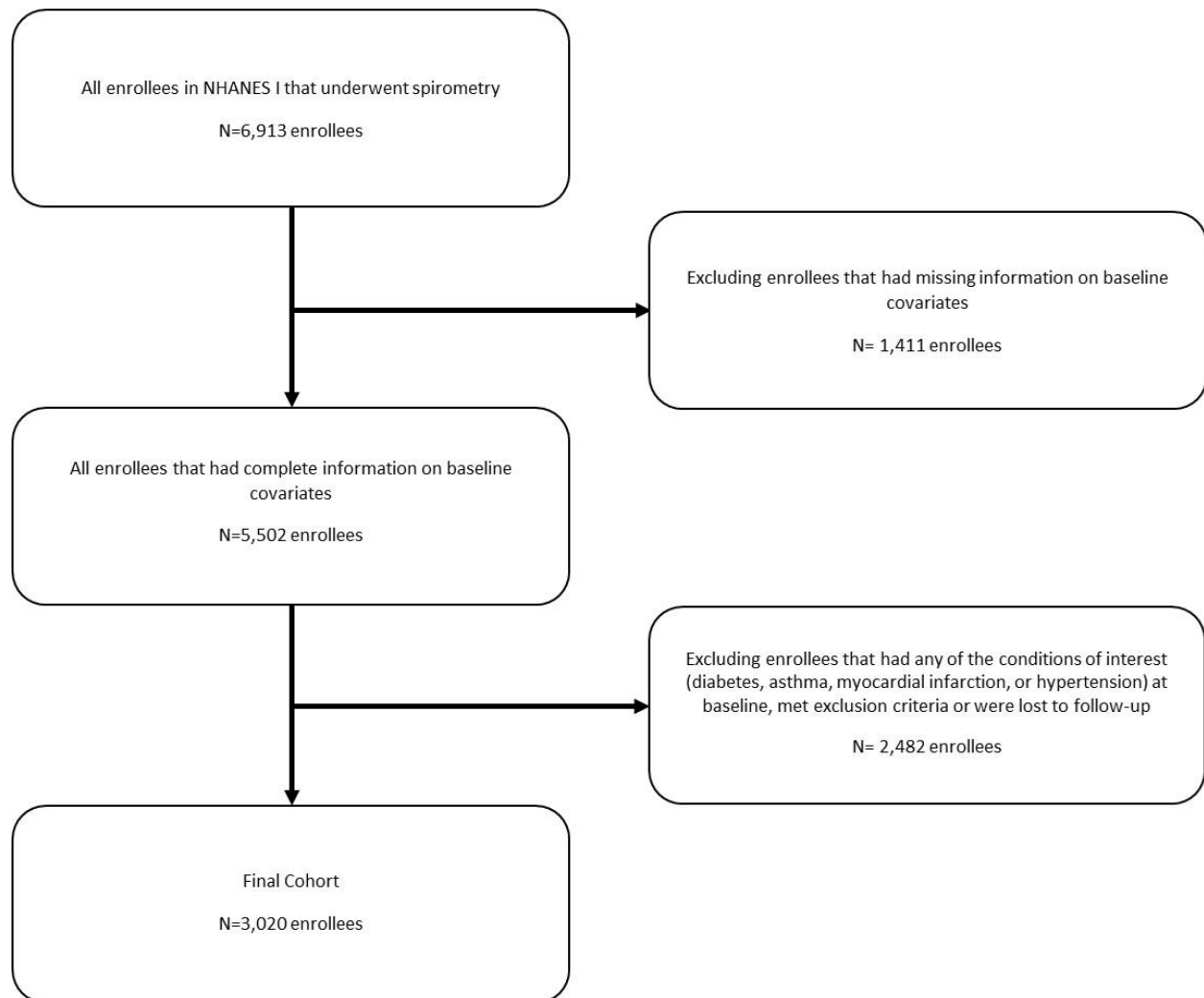
Table 1. Descriptive Characteristics of the study cohort at baseline (Sample size=3,020).

Covariate	Entire cohort	Female	Male
	Mean (SD, Range)	Mean (SD, Range)	Mean (SD, Range)
Age (years)	44.64 (13.44, 25-74)	43.85 (13.04, 25-74)	45.57 (13.85, 25-74)
Body Mass Index (kg/m^2)	24.68 (4.32, 12.59-53.58)	24.15 (4.71, 12.58-53.58)	25.31 (3.71, 14.42-46.95)
Charlson's Comorbidity Index Score [a]	0.06 (0.32, 0-7.00)	0.05 (0.29, 0-6.00)	0.08 (0.35, 0-7.00)
FEV_1	3.02 (0.84, 0.36-6.16)	2.64 (0.58, 0.68-4.97)	3.47 (0.89, 0.36-6.16)
Percent predicted FEV_1	91.04 (16.26, 12.06-195.71)	92.24 (15.72, 31.22-195.71)	89.62 (16.78, 12.06-184.88)
	Frequency (%[1])	Frequency (%[1])	Frequency (%[1])
Baseline FEV_1/FVC<0.7	431 (14.27%)	149 (9.07%)	282 (20.46%)
White race	2803 (92.81%)	1526 (92.94%)	1277 (92.67%)
At least high school education	2569 (85.07%)	1451 (88.37%)	1118 (81.13%)
Ever smoker [b]	1814 (60.07%)	815 (49.63%)	999 (72.50%)
Physically inactive [c]	232 (7.68%)	117 (7.13%)	115 (8.35%)
Currently married	2492 (82.52%)	1308 (79.66%)	1184 (85.92%)
Drinking frequency (alcohol)			
4 or less alcoholic drinks in month	2099 (69.50%)	1298 (79.05%)	801 (58.13%)
Greater than 4 alcoholic drinks in month	921 (30.50%)	344 (20.95%)	577 (41.87%)
Total	3020 (100%)	1642 (100%)	1378 (100%)

[1] Presented as a percentage of the column total.
[a] Conditions (weight) included in the calculation of the Charlson's Comorbidity Index at baseline: Congestive Heart Failure (1), Peripheral Vascular Disease (1), Cerebrovascular Disease (1), Dementia (1), Connective Tissue Disease-Rheumatic Disease (1), Peptic Ulcer Disease (1), Mild Liver disease (1), Paraplegia and Hemiplegia (2), Renal disease (2), Cancer (2), Moderate or Severe Liver Disease (3), Metastatic Carcinoma (6), and HIV/AIDS (6).
[b] Ever smokers are defined as individuals that were current smokers or former smokers at the time of the baseline interview.
[c] Individuals are defined as physically inactive if they responded, 'Quite inactive' to the question 'In your usual day aside from recreation, how active are you?' at the baseline interview.

Table 2. Results of the cause-specific and Fine-Gray sub-distribution hazard models representing hazard ratio for the incidence of the event of interest during the follow-up period for every % increase in percent predicted forced expiratory volume in 1 second at baseline.

	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Cause-specific hazard				
Diabetes	0.975	0.958	0.994	<0.01
Asthma	0.957	0.932	0.983	<0.01
Heart attack/myocardial infarction	0.987	0.970	1.004	0.12
Hypertension	0.998	0.992	1.005	0.66
All-cause mortality	0.982	0.971	0.992	<0.01
Sub-distribution hazard				
Diabetes	0.977	0.959	0.996	0.02
Asthma	0.959	0.937	0.982	<0.01
Heart attack/myocardial infarction	0.989	0.976	1.002	0.10
Hypertension	1.000	0.993	1.007	0.99
All-cause mortality	0.984	0.974	0.993	<0.01

Notes: Covariates adjusted at baseline were age (years), body mass index (BMI) (kg/m^2), BMI^2, FEV_1/FVC<0.7, sex, race (black or white), education, smoking status, physical inactivity, current marital status, alcohol consumption, and percent predicted Forced Expiratory Volume in 1 second (FEV_1) value.

Table 3. Results of the cause-specific and Fine-Gray sub-distribution hazard models representing hazard ratio for the incidence of the event of interest during the follow-up period for every liter increase in absolute forced expiratory volume in 1 second at baseline.

	Hazard Ratio	95% Hazard Ratio Confidence Limits		p-value
Cause-specific hazard				
Diabetes	0.452	0.270	0.755	<0.01
Asthma	0.213	0.096	0.474	<0.01
Heart attack/myocardial infarction	0.599	0.365	0.984	0.04
Hypertension	0.872	0.719	1.057	0.16
All-cause mortality	0.588	0.426	0.810	<0.01
Sub-distribution hazard				
Diabetes	0.473	0.273	0.821	<0.01
Asthma	0.235	0.119	0.463	<0.01
Heart attack/myocardial infarction	0.646	0.443	0.942	0.02
Hypertension	0.912	0.756	1.099	0.33
All-cause mortality	0.626	0.464	0.845	<0.01

Notes: Covariates adjusted at baseline were age (years), body mass index (BMI) (kg/m^2), BMI^2, FEV_1/FVC<0.7, sex, race (black or white), education, smoking status, physical inactivity, current marital status, alcohol consumption, and Forced Expiratory Volume in 1 second (FEV_1) value.

Appendix A. Results of competing risk regression analysis for the effects of covariates.

Table A.1. Results of cause-specific and Fine-Gray sub-distribution hazard models representing hazard ratio of the event of interest for every % increase in percent predicted forced expiratory volume in 1 second.

Parameter	Reference	Diabetes cause-specific hazard				Diabetes sub-distribution hazard			
		Hazard ratio	95% CI		P-value	Hazard ratio	95% CI		P-value
Age: 35-44 years	Age: 25-34 years	1.81	0.61	5.37	0.29	1.79	0.60	5.28	0.29
Age: 45-54 years		2.35	0.85	6.47	0.10	2.24	0.78	6.42	0.14
Age: 55-64 years		4.15	1.53	11.26	<0.01	3.90	1.41	10.79	0.01
Age: 65-74 years		3.53	1.16	10.74	0.03	3.19	0.98	10.31	0.05
Body Mass Index (kg/m^2)		1.46	0.97	2.22	0.07	1.49	1.07	2.07	0.02
(Body Mass Index)^2		1.00	0.99	1.00	0.25	1.00	0.99	1.00	0.09
Percent Predicted Forced Expiratory Volume		0.98	0.96	0.99	<0.01	0.98	0.96	0.99	0.02
Sex: Female	Male	0.47	0.25	0.88	0.02	0.47	0.24	0.91	0.02
Race: White	Race: Black	1.87	0.53	6.67	0.33	1.78	0.48	6.55	0.39
Education: less than high school	Education: at least high school	1.25	0.65	2.41	0.50	1.22	0.62	2.40	0.56
Smoking status: Ever Smoker	Smoking status: Never smoker	0.70	0.38	1.29	0.25	0.70	0.38	1.29	0.26
Physically Inactive	Active	0.23	0.03	1.67	0.15	0.22	0.03	1.68	0.15
Marital status: Currently married	Marital status: Not currently married	1.50	0.63	3.58	0.36	1.46	0.63	3.38	0.38
Alcohol consumption: More than 4 alcoholic drinks in a month	Alcohol consumption: Less than 4 alcoholic drinks in a month	0.96	0.52	1.77	0.89	0.97	0.53	1.76	0.91
FEV1/FVC<0.7		0.73	0.32	1.67	0.45	0.71	0.31	1.66	0.43
Charlson's comorbidity index score		0.77	0.25	2.35	0.65	0.71	0.27	1.86	0.49
		Asthma cause-specific hazard				Asthma sub-distribution hazard			
Parameter	Reference	Hazard ratio	95% CI		P-value	Hazard ratio	95% CI		P-value
Age: 35-44 years	Age: 25-34 years	0.39	0.08	1.94	0.25	0.39	0.07	2.00	0.26
Age: 45-54 years		1.28	0.43	3.83	0.66	1.24	0.47	3.30	0.67
Age: 55-64 years		1.29	0.37	4.43	0.69	1.17	0.39	3.49	0.78
Age: 65-74 years		1.28	0.30	5.39	0.74	1.11	0.26	4.72	0.88
Body Mass Index (kg/m^2)		1.29	0.64	2.59	0.48	1.33	0.75	2.34	0.33
(Body Mass Index)^2		1.00	0.98	1.01	0.56	1.00	0.99	1.01	0.34
Percent Predicted Forced Expiratory Volume		0.96	0.93	0.98	<0.01	0.96	0.94	0.98	<0.01
Sex: Female	Male	2.83	1.11	7.22	0.03	2.94	1.25	6.93	0.01
Race: White	Race: Black	1.55	0.20	12.01	0.67	1.57	0.21	12.05	0.66
Education: less than high school	Education: at least high school	0.35	0.09	1.40	0.14	0.34	0.08	1.42	0.14
Smoking status: Ever Smoker	Smoking status: Never smoker	1.25	0.53	2.96	0.61	1.28	0.59	2.80	0.53
Physically Inactive	Active	2.37	0.76	7.40	0.14	2.24	0.76	6.65	0.15
Marital status: Currently married	Marital status: Not currently married	1.18	0.43	3.25	0.75	1.15	0.44	3.02	0.78
Alcohol consumption: More than 4 alcoholic drinks in a month	Alcohol consumption: Less than 4 alcoholic drinks in a month	0.42	0.14	1.26	0.12	0.42	0.15	1.22	0.11
FEV1/FVC<0.7		1.93	0.71	5.25	0.20	1.92	0.73	5.04	0.18
Charlson's comorbidity index score		1.28	0.43	3.83	0.66	1.17	0.58	2.37	0.66

Table A.1. continued Results of cause-specific and Fine-Gray sub-distribution hazard models representing hazard ratio of the event of interest for every % increase in percent predicted forced expiratory volume in 1 second.

Parameter	Reference	Heart attack/Myocardial Infarction cause-specific hazard				Heart attack/Myocardial Infarction sub-distribution hazard			
		Hazard ratio	95% CI		P-value	Hazard ratio	95% CI		P-value
Age: 35-44 years	Age: 25-34 years	3.84	0.39	37.66	0.25	3.75	0.38	37.39	0.26
Age: 45-54 years		15.41	2.00	118.75	<0.01	14.98	1.92	116.86	<0.01
Age: 55-64 years		36.09	4.78	272.40	<0.01	33.63	4.33	261.44	<0.01
Age: 65-74 years		45.71	5.93	352.43	<0.01	40.84	4.98	335.13	<0.01
Body Mass Index (kg/m^2)		1.17	0.70	1.94	0.56	1.19	0.71	1.99	0.51
(Body Mass Index)^2		1.00	0.99	1.01	0.67	1.00	0.99	1.01	0.59
Percent Predicted Forced Expiratory Volume		0.99	0.97	1.00	0.12	0.99	0.98	1.00	0.10
Sex: Female	Male	0.36	0.18	0.72	<0.01	0.37	0.19	0.71	<0.01
Race: White	Race: Black	2.40	0.54	10.71	0.25	2.33	0.52	10.48	0.27
Education: less than high school	Education: at least high school	1.17	0.63	2.16	0.62	1.15	0.59	2.22	0.68
Smoking status: Ever Smoker	Smoking status: Never smoker	1.80	0.90	3.58	0.10	1.82	0.90	3.66	0.09
Physically Inactive	Active	0.67	0.21	2.19	0.51	0.64	0.20	2.04	0.45
Marital status: Currently married	Marital status: Not currently married	0.71	0.36	1.39	0.31	0.68	0.35	1.31	0.25
Alcohol consumption: More than 4 alcoholic drinks in a month	Alcohol consumption: Less than 4 alcoholic drinks in a month	0.95	0.53	1.72	0.87	0.95	0.52	1.76	0.87
FEV1/FVC<0.7		0.63	0.30	1.33	0.23	0.63	0.32	1.24	0.18
Charlson's comorbidity index score		1.29	0.67	2.47	0.45	1.17	0.63	2.15	0.62
Parameter	Reference	Hypertension cause-specific hazard				Hypertension sub-distribution hazard			
		Hazard ratio	95% CI		P-value	Hazard ratio	95% CI		P-value
Age: 35-44 years	Age: 25-34 years	1.55	1.13	2.14	<0.01	1.54	1.13	2.11	<0.01
Age: 45-54 years		1.85	1.36	2.53	<0.01	1.81	1.33	2.47	<0.01
Age: 55-64 years		1.94	1.38	2.73	<0.01	1.82	1.29	2.57	<0.01
Age: 65-74 years		2.06	1.40	3.03	<0.01	1.86	1.26	2.76	<0.01
Body Mass Index (kg/m^2)		1.20	1.05	1.37	<0.01	1.22	1.07	1.38	<0.01
(Body Mass Index)^2		1.00	1.00	1.00	0.15	1.00	1.00	1.00	0.07
Percent Predicted Forced Expiratory Volume		1.00	0.99	1.01	0.66	1.00	0.99	1.01	0.99
Sex: Female	Male	1.16	0.93	1.45	0.18	1.19	0.95	1.48	0.13
Race: White	Race: Black	0.78	0.55	1.10	0.15	0.76	0.53	1.08	0.13
Education: less than high school	Education: at least high school	1.07	0.82	1.41	0.62	1.04	0.79	1.38	0.78
Smoking status: Ever Smoker	Smoking status: Never smoker	1.08	0.87	1.35	0.50	1.09	0.87	1.36	0.48
Physically Inactive	Active	1.11	0.78	1.60	0.56	1.12	0.78	1.61	0.55
Marital status: Currently married	Marital status: Not currently married	1.09	0.83	1.43	0.56	1.07	0.81	1.40	0.64
Alcohol consumption: More than 4 alcoholic drinks in a month	Alcohol consumption: Less than 4 alcoholic drinks in a month	1.05	0.83	1.32	0.70	1.05	0.84	1.32	0.67
FEV1/FVC<0.7		1.08	0.80	1.48	0.61	1.07	0.79	1.46	0.65
Charlson's comorbidity index score		1.49	1.22	1.83	<0.01	1.37	1.12	1.68	<0.01

Table A.1. continued Results of cause-specific and Fine-Gray sub-distribution hazard models representing hazard ratio of the event of interest for every % increase in percent predicted forced expiratory volume in 1 second.

Parameter	Reference	All-cause mortality cause-specific hazard				All-cause mortality sub-distribution hazard			
		Hazard ratio	95% CI		P-value	Hazard ratio	95% CI		P-value
Age: 35-44 years	Age: 25-34 years	1.36	0.59	3.10	0.47	1.31	0.57	3.03	0.52
Age: 45-54 years		1.74	0.81	3.76	0.16	1.68	0.79	3.56	0.18
Age: 55-64 years		3.74	1.82	7.70	<0.01	3.52	1.73	7.17	<0.01
Age: 65-74 years		11.06	5.51	22.21	<0.01	10.21	5.13	20.34	<0.01
Body Mass Index (kg/m^2)		0.80	0.65	0.99	0.04	0.81	0.62	1.05	0.11
(Body Mass Index)^2		1.00	1.00	1.01	0.02	1.00	1.00	1.01	0.08
Percent Predicted Forced Expiratory Volume		0.98	0.97	0.99	<0.01	0.98	0.97	0.99	<0.01
Sex: Female	Male	0.53	0.35	0.82	<0.01	0.54	0.36	0.82	<0.01
Race: White	Race: Black	2.31	0.94	5.64	0.07	2.20	0.96	5.04	0.06
Education: less than high school	Education: at least high school	1.22	0.81	1.85	0.35	1.23	0.81	1.85	0.34
Smoking status: Ever Smoker	Smoking status: Never smoker	0.74	0.49	1.13	0.16	0.74	0.49	1.12	0.16
Physically Inactive	Active	1.33	0.74	2.39	0.34	1.26	0.71	2.23	0.43
Marital status: Currently married	Marital status: Not currently married	0.89	0.57	1.39	0.60	0.86	0.54	1.38	0.54
Alcohol consumption: More than 4 alcoholic drinks in a month	Alcohol consumption: Less than 4 alcoholic drinks in a month	1.32	0.89	1.94	0.17	1.35	0.91	2.00	0.13
FEV1/FVC<0.7		1.23	0.76	1.98	0.40	1.23	0.74	2.04	0.43
Charlson's comorbidity index score		1.67	1.25	2.22	<0.01	1.55	1.11	2.17	0.01

Appendix B. Results of competing risk regression analysis for the effects of covariates.

Table B.1. Results of cause-specific and Fine-Gray sub-distribution hazard models representing hazard ratio of the event of interest for every liter increase in absolute forced expiratory volume in 1 second.

Parameter	Reference	Diabetes cause-specific hazard				Diabetes sub-distribution hazard			
		Hazard ratio	95% CI		P-value	Hazard ratio	95% CI		P-value
Age: 35-44 years	Age: 25-34 years	1.54	0.51	4.60	0.44	1.53	0.51	4.59	0.45
Age: 45-54 years		1.60	0.56	4.58	0.38	1.55	0.50	4.79	0.45
Age: 55-64 years		2.25	0.76	6.68	0.14	2.18	0.67	7.16	0.20
Age: 65-74 years		1.50	0.43	5.30	0.53	1.42	0.35	5.82	0.63
Body Mass Index (kg/m^2)		1.45	0.95	2.21	0.09	1.46	1.03	2.07	0.03
(Body Mass Index)^2		1.00	0.99	1.00	0.28	1.00	0.99	1.00	0.14
Forced Expiratory Volume in 1 second (FEV1)(liter)		0.45	0.27	0.76	<0.01	0.47	0.27	0.82	<0.01
Sex: Female	Male	0.24	0.11	0.52	<0.01	0.25	0.11	0.56	<0.01
Race: White	Race: Black	2.56	0.72	9.14	0.15	2.38	0.64	8.83	0.20
Education: less than high school	Education: at least high school	1.21	0.63	2.32	0.57	1.19	0.61	2.30	0.61
Smoking status: Ever Smoker	Smoking status: Never smoker	0.71	0.39	1.31	0.28	0.71	0.38	1.32	0.28
Physically Inactive	Active	0.22	0.03	1.62	0.14	0.22	0.03	1.62	0.14
Marital status: Currently married	Marital status: Not currently married	1.51	0.63	3.60	0.35	1.47	0.64	3.42	0.37
Alcohol consumption: More than 4 alcoholic drinks in a month	Alcohol consumption: Less than 4 alcoholic drinks in a month	0.96	0.52	1.77	0.89	0.97	0.53	1.78	0.92
FEV1/FVC<0.7		0.73	0.33	1.65	0.45	0.71	0.30	1.66	0.43
Charlson's comorbidity index score		0.77	0.25	2.36	0.65	0.72	0.28	1.89	0.51
		Asthma cause-specific hazard				Asthma sub-distribution hazard			
Parameter	Reference	Hazard ratio	95% CI		P-value	Hazard ratio	95% CI		P-value
Age: 35-44 years	Age: 25-34 years	0.30	0.06	1.51	0.14	0.30	0.06	1.66	0.17
Age: 45-54 years		0.68	0.21	2.19	0.52	0.69	0.25	1.88	0.46
Age: 55-64 years		0.48	0.12	1.89	0.29	0.46	0.14	1.46	0.19
Age: 65-74 years		0.32	0.06	1.71	0.18	0.30	0.06	1.45	0.14
Body Mass Index (kg/m^2)		1.25	0.62	2.51	0.54	1.28	0.72	2.30	0.40
(Body Mass Index)^2		1.00	0.98	1.01	0.61	1.00	0.99	1.01	0.42
Forced Expiratory Volume in 1 second (FEV1)(liter)		0.21	0.10	0.47	<0.01	0.24	0.12	0.46	<0.01
Sex: Female	Male	0.90	0.31	2.62	0.84	1.00	0.37	2.69	1.00
Race: White	Race: Black	2.66	0.35	20.39	0.35	2.58	0.36	18.53	0.35
Education: less than high school	Education: at least high school	0.33	0.08	1.29	0.11	0.32	0.08	1.31	0.11
Smoking status: Ever Smoker	Smoking status: Never smoker	1.25	0.53	2.97	0.61	1.28	0.58	2.82	0.53
Physically Inactive	Active	2.36	0.76	7.37	0.14	2.21	0.75	6.53	0.15
Marital status: Currently married	Marital status: Not currently married	1.11	0.41	3.06	0.83	1.08	0.42	2.77	0.88
Alcohol consumption: More than 4 alcoholic drinks in a month	Alcohol consumption: Less than 4 alcoholic drinks in a month	0.44	0.15	1.30	0.14	0.44	0.15	1.27	0.13
FEV1/FVC<0.7		1.92	0.71	5.17	0.20	1.90	0.73	4.97	0.19
Charlson's comorbidity index score		1.30	0.42	3.97	0.65	1.20	0.60	2.40	0.61

Table B.1 continued. Results of cause-specific and Fine-Gray sub-distribution hazard models representing hazard ratio of the event of interest for every liter increase in absolute forced expiratory volume in 1 second.

Parameter	Reference	Heart attack/ Myocardial Infarction cause-specific hazard				Heart attack/ Myocardial Infarction sub-distribution hazard			
		Hazard ratio	95% CI		P-value	Hazard ratio	95% CI		P-value
Age: 35-44 years	Age: 25-34 years	3.41	0.35	33.52	0.29	3.38	0.34	33.55	0.30
Age: 45-54 years		11.66	1.48	91.96	0.02	11.78	1.54	89.98	0.02
Age: 55-64 years		23.58	2.97	187.05	<0.01	23.23	3.08	175.34	<0.01
Age: 65-74 years		25.09	2.97	211.66	<0.01	24.26	2.96	198.97	<0.01
Body Mass Index (kg/m^2)		1.16	0.69	1.95	0.57	1.19	0.70	2.02	0.52
(Body Mass Index)^2		1.00	0.99	1.01	0.68	1.00	0.99	1.01	0.60
Forced Expiratory Volume in 1 second (FEV1)(liter)		0.60	0.37	0.98	0.04	0.65	0.44	0.94	0.02
Sex: Female	Male	0.24	0.11	0.54	<0.01	0.26	0.13	0.53	<0.01
Race: White	Race: Black	2.85	0.64	12.75	0.17	2.70	0.59	12.27	0.20
Education: less than high school	Education: at least high school	1.14	0.61	2.11	0.68	1.13	0.59	2.16	0.72
Smoking status: Ever Smoker	Smoking status: Never smoker	1.81	0.91	3.61	0.09	1.82	0.91	3.64	0.09
Physically Inactive	Active	0.65	0.20	2.13	0.48	0.62	0.19	1.97	0.41
Marital status: Currently married	Marital status: Not currently married	0.72	0.37	1.42	0.35	0.69	0.35	1.34	0.27
Alcohol consumption: More than 4 alcoholic drinks in a month	Alcohol consumption: Less than 4 alcoholic drinks in a month	0.95	0.53	1.71	0.86	0.95	0.51	1.75	0.86
FEV1/FVC<0.7		0.61	0.29	1.25	0.18	0.60	0.30	1.20	0.15
Charlson's comorbidity index score		1.28	0.67	2.47	0.45	1.17	0.63	2.16	0.62
		Hypertension cause-specific hazard				Hypertension sub-distribution hazard			
Parameter	Reference	Hazard ratio	95% CI		P-value	Hazard ratio	95% CI		P-value
Age: 35-44 years	Age: 25-34 years	1.50	1.08	2.08	0.01	1.50	1.09	2.07	0.01
Age: 45-54 years		1.72	1.23	2.39	<0.01	1.72	1.24	2.38	<0.01
Age: 55-64 years		1.73	1.18	2.53	<0.01	1.68	1.14	2.47	<0.01
Age: 65-74 years		1.76	1.12	2.75	0.01	1.67	1.06	2.61	0.03
Body Mass Index (kg/m^2)		1.20	1.05	1.37	<0.01	1.21	1.07	1.38	<0.01
(Body Mass Index)^2		1.00	1.00	1.00	0.15	1.00	1.00	1.00	0.08
Forced Expiratory Volume in 1 second (FEV1)(liter)		0.87	0.72	1.06	0.16	0.91	0.76	1.10	0.33
Sex: Female	Male	1.03	0.77	1.36	0.85	1.09	0.82	1.44	0.54
Race: White	Race: Black	0.82	0.58	1.15	0.24	0.78	0.54	1.11	0.17
Education: less than high school	Education: at least high school	1.06	0.81	1.39	0.68	1.03	0.78	1.37	0.83
Smoking status: Ever Smoker	Smoking status: Never smoker	1.07	0.86	1.33	0.56	1.07	0.86	1.34	0.55
Physically Inactive	Active	1.11	0.77	1.59	0.57	1.11	0.77	1.61	0.56
Marital status: Currently married	Marital status: Not currently married	1.09	0.83	1.43	0.53	1.07	0.82	1.41	0.61
Alcohol consumption: More than 4 alcoholic drinks in a month	Alcohol consumption: Less than 4 alcoholic drinks in a month	1.05	0.84	1.32	0.68	1.05	0.84	1.32	0.66
FEV1/FVC<0.7		1.04	0.77	1.41	0.81	1.02	0.75	1.39	0.89
Charlson's comorbidity index score		1.49	1.22	1.83	<0.01	1.37	1.12	1.69	<0.01

Table B.1 continued. Results of cause-specific and Fine-Gray sub-distribution hazard models representing hazard ratio of the event of interest for every liter increase in absolute forced expiratory volume in 1 second.

Parameter	Reference	All-cause mortality cause-specific hazard				All-cause mortality sub-distribution hazard			
		Hazard ratio	95% CI		P-value	Hazard ratio	95% CI		P-value
Age: 35-44 years	Age: 25-34 years	1.21	0.53	2.79	0.65	1.19	0.52	2.74	0.68
Age: 45-54 years		1.34	0.61	2.97	0.47	1.33	0.61	2.89	0.47
Age: 55-64 years		2.52	1.16	5.46	0.02	2.48	1.19	5.17	0.02
Age: 65-74 years		6.18	2.77	13.81	<0.01	6.09	2.85	13.01	<0.01
Body Mass Index (kg/m^2)		0.80	0.64	0.99	0.04	0.80	0.61	1.05	0.11
(Body Mass Index)^2		1.01	1.00	1.01	0.02	1.00	1.00	1.01	0.08
Forced Expiratory Volume in 1 second (FEV1)(liter)		0.59	0.43	0.81	<0.01	0.63	0.46	0.85	<0.01
Sex: Female	Male	0.35	0.22	0.58	<0.01	0.38	0.24	0.59	<0.01
Race: White	Race: Black	2.79	1.14	6.84	0.03	2.62	1.14	6.04	0.02
Education: less than high school	Education: at least high school	1.18	0.78	1.78	0.45	1.19	0.78	1.80	0.42
Smoking status: Ever Smoker	Smoking status: Never smoker	0.75	0.49	1.15	0.19	0.75	0.50	1.14	0.18
Physically Inactive	Active	1.35	0.75	2.42	0.32	1.28	0.73	2.26	0.40
Marital status: Currently married	Marital status: Not currently married	0.90	0.57	1.41	0.64	0.87	0.54	1.40	0.57
Alcohol consumption: More than 4 alcoholic drinks in a month	Alcohol consumption: Less than 4 alcoholic drinks in a month	1.33	0.90	1.96	0.15	1.35	0.91	2.01	0.13
FEV1/FVC<0.7		1.30	0.81	2.08	0.27	1.30	0.79	2.14	0.30
Charlson's comorbidity index score		1.65	1.23	2.21	0.01	1.54	1.10	2.16	0.01