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Association of Chronic Cough and Pulmonary Function with 6-Minute Walk Test Performance in HIV Infection

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Abstract

Objective—Chronic lung disease has been associated with greater impairment in self-reported physical function in HIV patients. We sought to study this association using objective measures of physical or pulmonary function.

Design—Baseline data from the Examinations of HIV Associated Lung Emphysema (EXHALE) study, a multicenter observational cohort of HIV-infected and uninfected Veterans.

Methods—We assessed the association between clinical, laboratory, and pulmonary function measures on six-minute walk test (6-MWT). Multivariable linear regression models were generated to identify factors associated with 6-MWT performance.

Results—340 participants completed 6-MWT (mean age 55 years), with 68% black race, 94% men and 62% current smokers. Overall, 180 (53%) were HIV-infected and 63 (19%) had spirometry-defined COPD. In a multivariable model, age, current smoking, and obesity (BMI>30) were independently associated with lower 6-MWT performance, but HIV infection was not; there

was a significant interaction between HIV and chronic cough, such that distance walked among HIV-infected participants with chronic cough was 51.76 meters less (p=0.04) compared to those without cough or HIV. Among HIV-infected participants, the forced expiratory volume in one second (FEV_1, % predicted), to a greater extent than total lung capacity or diffusion capacity, attenuated the association with chronic cough; decreased FEV_1 was independently associated with lower 6-MWT performance in those with HIV.

Conclusion—Older age, current smoking and airflow limitation were important determinants of 6-MWT performance in the HIV-infected participants. These findings suggest potential interventions to improve physical function may include early management of respiratory symptoms and airflow limitation.

Keywords

Respiratory measurement; Immunodeficiency; Clinical epidemiology; 6-MWT; airflow limitation

Introduction

Physical function is composed of multiple physiologic factors, including endurance, strength, flexibility and balance, and is an important component to health-related quality of life. Determinants of physical function performance are cardiovascular, function, ventilatory capacity and muscle strength[1, 2]. Prior studies suggest that HIV-infected patients have greater limitations in physical function compared to HIV-uninfected patients of the same age[3-5]. The Six-Minute Walk Test (6-MWT) is a commonly used functional measure that reflects the ability to perform activities of daily living in addition to estimate ambulatory capacity. Performance in the 6-MWT is associated with health related quality of life and mortality in patients with congestive heart failure[6, 7], chronic obstructive pulmonary disease (COPD)[8, 9] and interstitial lung disease (ILD)[10-13].

A prior study has shown that 6-MWT can be safely used to assess fitness in HIV-infected adults and correlates with objective measures of fitness such as aerobic capacity[14]. An association between chronic lung disease and HIV has been associated with greater impairment in self-reported physical function[3, 15]. These studies, however, did not include an objective measure of physical function, and did not objectively assess for the presence of lung disease by measurement of pulmonary function. As HIV-infected patients are aging on effective antiretroviral therapy (ART), pulmonary function abnormalities and chronic lung diseases are increasing in prevalence[16], and could contribute to impaired physical function observed in HIV-infected populations. The goal of this report was to determine risk factors for decreased performance on 6-MWT among HIV-infected patients when compared to HIV-uninfected patients, with a specific focus on measures of pulmonary function.

Methods

Study Description

The cohort consisted of HIV-infected and uninfected participants enrolled in the Examinations of HIV Associated Lung Emphysema (EXHALE), a pulmonary substudy of the Veterans Aging Cohort Study (VACS)[17]. EXHALE is an ongoing observational,

longitudinal multicenter study conducted at four of the eight Veterans Affairs (VA) Medical Centers (VAMC) participating in VACS, namely the Atlanta, Bronx, Houston and Los Angeles VAMC. Potential participants were approached for enrollment in EXHALE from the General Medicine and Infectious Diseases outpatient clinics; enrollment was stratified by HIV and current smoking status to obtain a similar proportion of current smokers amongst the HIV-uninfected participants as found in the HIV-infected participants. Those individuals with a history of lung diseases other than COPD or asthma were excluded, as were patients with acute respiratory infections or illness in the four weeks prior to the baseline measurements. Enrollment began in 2009 and is ongoing. Results presented here represent the cross-sectional analysis of baseline data from 180 HIV-infected and 160 HIV-uninfected participants who were enrolled from 2009 through 2012. Institutional Review Boards at all locations approved this study, and participants provided written informed consent.

Data Collection

Baseline study procedures for EXHALE that were included in these analyses consisted of a questionnaire, pulmonary function testing (PFT) and measure of distance covered during 6-MWT. At study entry, all participants self-completed a questionnaire that consisted of a standardized assessment of smoking, drug use, history of lung diseases and respiratory symptoms[18]. Based on survey data, presence of chronic cough symptoms was defined as those who reported cough on most days for three consecutive months or more during the year for more than 1 year.

Demographic and pharmacy data, laboratory values and diagnostic codes (ICD-9) for existent medical conditions were obtained via the VA national electronic medical records. Variables included age, gender, race, and antiretroviral therapy (ART). Labs including hemoglobin, CD4 cell count, and plasma HIV RNA level were obtained within 6 months of enrollment. Cardiovascular disease was defined by ICD-9 codes as the composite of coronary artery disease, congestive heart failure and peripheral vascular disease (all ICD-9 code groupings for medical conditions provided on *www.vacohort.org*).

Pulmonary function testing (PFT)

Spirometry pre- and post-bronchodilator was performed according to American Thoracic Society criteria[19, 20]. Static lung volumes were measured by plethysmography. Diffusing capacity was measured by transfer of carbon monoxide (DLCO) by single breath method[21]. PFTs were obtained by certified, trained respiratory technicians or research personnel. PFTS were obtained in the clinical pulmonary function laboratories at the associated medical center. Site pulmonologists or study investigators reviewed PFT results for quality control; results that were not interpretable and did not meet ATS criteria for acceptability and reproducibility were not included in these analyses. Fixed airflow obstruction consistent with COPD was defined primarily as a ratio of the post-bronchodilator forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) below 70%. Predicted normal values for spirometry were determined using Hankinson formulas, and for DLCO using Neas formulas[22, 23]. Both of these formulas include adjustments for age, gender, race/ethnicity, and height; percent predicted DLCO is

also corrected for hemoglobin concentration. PFT were interpreted blinded to HIV status, following the ERS/ATS 2005 recommendations[24].

Six-Minute Walk Testing

A standardized 6-minute walk test was performed by 340 participants in accordance with ATS guidelines[25]. Participants were coached to walk at their fastest comfortable pace on an even surface for 6 minutes, and the total distance covered was measured; the same protocol was followed for HIV-infected and uninfected participants. We referred to this total distance as the result of 6-MWT. Predicted values were calculated using equations published by Enright and Sherrill[26], which are based on age, gender, and measured BMI.

Statistical Methods

We compared demographic and clinical characteristics, as well as the results of the 6-MWT, between HIV infected and uninfected patients using chi-squared, Wilcoxon Rank Sum Tests, and Student's t-test as appropriate. Given the increased burden of respiratory symptoms[3, 27, 28] and the interaction between self-reported lung disease and decreased physical function among HIV-infected individuals reported previously, we included an interaction term for HIV and chronic cough in a multivariable linear regression model adjusted for demographic and exposure predictors (patient age, sex, race/ethnicity, BMI category [<25, 25-30 and >30], smoking status and injection drug use). To test whether the association between chronic cough and poor 6-MWT performance was explained by pulmonary function, we tested a series of nested models, including individual measures of pulmonary function adjusting for demographic and exposure predictors. For our final model, predictors of poor performance on 6-MWT were chosen *a priori* based on published studies, or if they demonstrated a significant association ($p<0.10$) in unadjusted analyses. These included patient age, race, BMI category, smoking status, injection drug use, hemoglobin, cardiovascular disease, and FEV_1% predicted. Age and all PFT coefficients are presented in 10 units increment. Tests of statistical significance (p values) and 95% confidence intervals for the measure of association were calculated; a p-value of <0.05 was considered significant. All analyses were performed using a statistical software package (Stata version 11; StataCorp, College Station, TX).

Results

The analytic cohort consisted of 340 participants who completed the 6-MWT, 53% of whom were HIV-infected. Complete PFT and survey data were available for 323 participants. HIV-infected participants were on average 3 years older than HIV- uninfected participants. Compared to the HIV-uninfected participants, those with HIV were more likely to be male (98% vs. 88%; $p<0.001$) and to have a BMI < 25 (38% vs. 18%; $p<0.01$) (Table 1). Prevalence of current cigarette smoking, number of pack-years, injection drugs are presented in Table 1. The HIV-infected group had a median CD4 cell count of 431 cells/μl. Overall, 35% of the HIV-infected patients had a CD4 count below 350 and 14% a CD4 count below than 200; 43% had CD4 nadir less than 200, determined by review of all available laboratory records in the VA system. The majority (89%) of the HIV-infected patients were on ART in the 6 months prior to enrollment.

HIV-infected patients were more likely to report symptoms consistent with chronic cough and compatible symptoms of chronic phlegm and dyspnea. The prevalence of chronic cough was 25% in HIV-infected and 16% in HIV-uninfected participants (p=0.04). The prevalence of chronic phlegm was 33% and 16% for HIV-infected and HIV-uninfected respectively and the prevalence of wheeze was 51% for both groups (Table 1). The mean Medical Research Council (MRC) dyspnea score (range 1-5) for the HIV-infected was 1.91 (SD 1.3), and was not significantly different from the mean MRC dyspnea score for HIV-uninfected 1.75 (SD 1.2). Cardiovascular disease, liver failure and renal insufficiency were equally present in both groups.

Overall, the median distance walked by both groups was 426 meters (m). The median value of the 6-MWT was not statistically different between the HIV-infected and uninfected participants (426m vs. 421m respectively; p=0.60). Notably, both groups walked less than 576m, which is the median distance walked by healthy adult men, with ages between 43 and 77 described in the literature[26].

PFT results were generally within the normal range, with the exception of DLCO, which was lower than predicted normal in HIV-infected and uninfected participants. The FEV_1, and TLC % predicted, and the FEV_1/FVC ratio were similar in HIV-infected and uninfected participants (Table 1). Spirometry-defined COPD was found in 30 (19%) of the HIV-infected subjects and in 36 (20%) of the HIV-uninfected subjects. This difference was not statistically significant. The FVC % predicted, however, was higher and the DLCO % predicted was significantly lower among the HIV-infected compared to uninfected participants. Approximately 25% of the patients with chronic cough had fixed airflow obstruction, consistent with spirometry-defined COPD.

Predictors of 6-MWT among HIV-infected and HIV-uninfected Participants

In order to investigate whether respiratory symptoms influence 6-MWT performance and whether this association differs by HIV status, we determined predictors of 6-MWT performance in a multivariable model. The β coefficient for a predictor estimated by these models describes the difference in meters walked in the 6MWT for a one unit change in that predictor, adjusted for other variables in the model. We found that the effect of chronic cough on 6-MWT was modified by HIV infection when adjusting for age, sex, race/ethnicity, BMI, smoking status and injection drug use, such that an interaction term between HIV infection and chronic cough was significant (β -51.76 p=0.04) (Table 2). In this model age, expressed per 10-year increments, (β -19.39, p<0.01), BMI >30 (β -36.75, p<0.01), and current smoking (β -46.34, p<0.01) were also independently associated with poor performance on 6-MWT.

Predictors of 6-MWT among HIV-infected Participants

Given the effect modification of HIV infection on the association of chronic cough and 6-MWT performance, we stratified subsequent models by HIV status. Among HIV-infected participants, older age (β -32.86, p<0.001 per 10-year increments), current smoking (β -49.46, p<0.01) and injection drug use (β -30.39 p=0.02), were significantly associated with poor performance on the 6-MWT on bivariate analyses. Of HIV-specific factors, those with

detectable HIV viral load walked on average 27 meters less compared to those with undetectable viral load (p=0.04), whereas CD4 cell count and use of ART were not significant. Symptoms of chronic cough were also associated with 6-MWT performance (β -41.52, p=0.003) in bivariate analysis. On objective assessment of pulmonary function, FEV_1 % predicted (β 12.47, p<0.001), FVC % predicted (β 13.21, p=0.001), and DLCO % predicted (β 8.0, p=0.04) were all significantly associated with 6-MWT. In contrast, among the HIV-uninfected participants, injection drug use, hemoglobin, symptoms of chronic bronchitis, FEV_1 % predicted and FVC % predicted were not significantly associated with 6-MWT (data not otherwise shown).

To understand the association between chronic cough symptoms and 6-MWT among the HIV-infected participants, we generated a series of models. When adjusting for age, gender, race, BMI, injection drug use and smoking status, chronic cough was independently associated with performance of 6-MWT (β-31.18, p=0.03), without inclusion of pulmonary function measures. Then in a series of nested models, we examined whether the association with chronic cough was attenuated when including individual measures of pulmonary function. Because FEV_1 and FVC co-varied, only FEV_1 was used in models. We found that FEV_1 % predicted (β 10.17, p=0.002) attenuated the association of chronic cough symptoms with 6-MWT in HIV-infected patients (β-22.79, p=0.12), whereas TLC % predicted (β 9.16, p=0.02) or DLCO % predicted (β 4.73 p=0.24) did not attenuate the association with chronic cough (β -37.58, p=0.01 and β -36.54, p=0.02 respectively) (Table 3).

Finally, we generated a complete multivariable linear regression model including FEV_1 stratified by HIV-status. We found that age (β -24.14, p=0.01), and FEV_1 % predicted (β 10.18, p<0.01) were statistically significant independent predictors of 6-MWT performance when adjusting for age, sex, race/ethnicity, BMI, smoking status, and cardiovascular disease (Table 4) among HIV-infected participants. Detectable HIV viral load and CD4 cell number did not retain significance and were not included in the final model. Current smoking status was a strong independent predictor of poor performance in 6-MWT for both HIV-infected and uninfected groups.

Discussion

Six-minute walk testing has features that make it ideal for testing functional performance in both outpatient and inpatient settings. In this cross-sectional study we compared the 6-MWT in HIV-infected patients to uninfected patients with similar clinical characteristics. Consistent with prior studies, we found that older age, current smoking and obesity were significantly associated with poor performance on 6-MWT. Among HIV-infected but not HIV-uninfected participants, symptoms of chronic cough were significantly associated with decreased 6-MWT performance. Airflow limitation (as defined by FEV_1% predicted) appeared to explain this association, and the FEV_1 was an independent predictor of 6-MWT in the HIV-infected patients in multivariable models.

These data highlight the significant role that airflow limitation, as reflected by symptoms of chronic cough and decreased FEV_1, plays in the physical performance of HIV-infected individuals. These factors appear to play a stronger role in 6-MWT performance in HIV-

infected patients compared to those without HIV. Reasons for this difference are uncertain, but we have previously demonstrated that HIV-infected patients may experience a greater degree of respiratory symptoms for a similar limitation in lung function when compared to HIV-uninfected patients[29]. Whether greater inflammation systemically or within the airways of HIV-infected patients plays a role in this relationship requires further investigation.

Clinically, chronic cough symptoms are an easy-to-elicit marker that may signal an increased risk for poor 6-MWT performance among HIV-infected patients, and can serve as a prompt for clinicians to consider evaluation of physical function as well as pulmonary function. Not unique to the Veteran population, chronic cough and other respiratory symptoms are prevalent in other studies of HIV-infected patients as well[27, 28]. These data further raise the possibility that appropriate treatment of respiratory symptoms and airway obstruction in HIV-infected individuals could have an impact on physical function and as a result could also confer improvement in health-related quality of life[30].

In healthy individuals, the most important predictor of 6-MWT has been described as age, evident in patients older than 60 years[31], followed by sex[26, 31]. In COPD patients, multiple predictors have been shown to independently influence 6-MWT performance, including degree of airflow limitation, sex, race, age and BMI[32]. Our data suggest, when comparing coefficients in models stratified by HIV status, that age may play a stronger role in decline in 6-MWT in HIV-infected participants than in HIV-uninfected. These data underscore the need to better understand the decrements in physical function associated with aging in HIV.

Our study adds to the knowledge of factors that influence physical function in HIV-infected patients. Previous reports have shown that HIV-infected patients on ART have preserved capacity to perform activities of daily life but are limited in vigorous activities[15, 33]. Several studies support that HIV infection is associated with limitations in self-reported[34] and measured physical function[35]. Our results suggest that risk factors for poor 6-MWT performance vary by HIV status, although HIV infection itself and variables related to HIV disease control were not independent predictors of 6-MWT performance.

Novel findings in our work are that HIV-infected participants with chronic cough walk on average 42 meters less than HIV-infected patients without chronic cough in unadjusted analyses, and further that there was a significant interaction between HIV and chronic cough, such that distance walked among HIV-infected participants with chronic cough was nearly 52 meters less compared to those without HIV or chronic cough in multivariable analysis. This association between chronic cough and 6-MWT performance is mostly explained by airflow limitation (FEV_1) rather than by restrictive disease (TLC) or gas exchange impairment (DLCO) in the HIV-infected participants. These findings are notable, despite the fact that the majority of patients with chronic cough did not meet spirometric criteria for COPD, based on the most recent GOLD criteria guidelines[36], yet had demonstrable decreases in 6-MW distance that approach the clinically meaningful difference of 50 meters. Our data also underscore the significant impact of current smoking as a strong predictor of low 6-MWT in both HIV-infected and uninfected patients, in concordance with

previous reports in the literature[5, 37, 38], and highlight the need for improved smoking cessation in this population.

Some of the limitations in this study include the predominantly male Veteran population, the relatively young age of the participants, and the lack of an objective measure for cardiovascular disease. Future studies incorporating longitudinal analysis and objective measurements of cardiovascular disease with 6-MWT performance are needed. Nonetheless, to our knowledge, this is the first report on quantification and characterization of the impact of chronic lung disease on physical function as measured by 6-MWT in HIV-infected patients.

In conclusion, we found that airflow limitation, as reflected by symptoms of chronic cough and as objectively measured by decreased FEV_1 % predicted, are independently associated with poor performance on 6-MWT among HIV-infected patients. Early detection as well as preventative measures, such as smoking cessation and management of airflow limitation may decrease the impact of chronic lung disease on physical function in HIV.

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Table 1

Demographic and Clinical Characteristics of EXHALE Cohort Participants by HIV Status

	HIV-Infected	HIV-Uninfected	p value
N	180	160	
Age, years	55 (49-58)	52(48-58)	0.14
Sex, male	177 (98)	141 (88)	<0.001
Race/Ethnicity			0.05
Black	130 (72)	100 (63)	
White	22 (12)	35 (22)	
Hispanic / Other	28 (16)	25 (16)	
BMI			<0.01
<25	67 (38)	28 (18)	
25-30	67 (38)	53 (33)	
≥30	42 (24)	77 (49)	
Exposures			
Smoking status			0.44
Current	116 (65)	93 (58)	
Former	37 (21)	38 (24)	
Never	25 (14)	28 (17)	
Pack-year history	24 (12, 41)	20 (8, 37)	0.14
IDU ever	55 (31)	27 (17)	0.004
Laboratory Data			
Hemoglobin, g/dL	14 (13, 15)	14 (13, 15)	0.22
CD4 cell count, cells/μl	431 (298, 607)	-	
CD4 less than 350	60 (35)	-	
CD4 less than 200	24 (14)	-	
CD4 nadir	142 (50, 259)	-	
Log plasma HIV viral level, copies/ml	1.68 (1.7, 2.3)	-	
HAART use in prior 6 months	160 (89)	-	
Respiratory Symptoms			
Chronic cough	43 (25)	24 (16)	0.04
Chronic phlegm	50 (30)	24 (16)	0.004
Wheeze	82 (46)	67 (42)	0.47
Dyspnea (MRC score), mean (SD)	1.91 (1.3)	1.75 (1.2)	0.23
Chronic Conditions			
Cardiovascular disease	21 (12)	24 (15)	0.37
Liver failure	7 (4)	3 (2)	0.27
Renal Insufficiency	14 (8)	7 (4)	0.19
6-Minute Walk Distance (6-MWD)			
6-MWD, meters	426 (375, 472)	421 (379, 488)	0.60
6-MWD % predicted (Enright's)	70 (61, 79)	71 (63, 81)	0.29
Pulmonary Function Tests			

	HIV-Infected	HIV-Uninfected	p value
FEV_1 %	92 (82, 105)	91 (78,100)	0.18
FVC %	96 (87, 106)	93 (84, 102)	0.04
FEV_1/FVC	78 (71, 82)	79 (74, 83)	0.35
TLC %	89 (79, 105)	90 (80, 101)	0.62
DLCO %	64 (54, 76)	68 (59, 78)	0.02

Values presented as n (%) or median (IQR) unless indicated otherwise. BMI, body mass index; pack-years, number of packs smoked per day × years smoked; IDU, injection drug use; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; DLCO, diffusing capacity.

Table 2

Multivariable Regression Model Evaluating the Predictors of 6-MW Distance Among HIV-infected and HIV-uninfected in the EXHALE Cohort

	β Coefficient	95% CI	p-value
HIV-infected*Chronic cough	−51.76	−99.8, −3.71	0.04
Age/per 10 years	−19.39	−32.6, −6.2	<0.01
Male	15.71	−25.4, 56.9	0.45
Race			
Black	Ref		
White	31.41	4.1, 58.8	0.03
Hispanic	−20.19	−47.7, 7.3	0.15
BMI			
<25	Ref		
25-30	10.55	−13.7, 34.8	0.40
>30	−36.75	−62.6, −10.9	<0.01
Smoking Status			
Never	Ref		
Current	−46.34	−74.3, −18.4	<0.01
Former	−19.73	−52, 12.5	0.23
Injection Drug Use	−0.73	−24.1, 26.6	0.95

β Coefficient: Six minute walk (6-MW) distance in meters. BMI, body mass index.

Model also adjusted for HIV and chronic cough in addition to their interaction.

Table 3

Association of Chronic Cough with PFTs in HIV-infected Participants

	Model 1		Model 2		Model 3		Model 4	
	β Coef	p-value	β Coef	p-value	β Coef	p-value	β Coef	p-value
Chronic Cough	−31.18	0.03	−22.79	0.12	−37.58	0.01	−36.54	0.02
Age	−26.92	<0.01	−22.59	0.01	−24.37	<0.01	−22.52	0.02
Gender	19.80	0.66	17.97	0.68	19.66	0.66	16.87	0.71
Race								
White	25.15	0.19	25.43	0.17	4.90	0.82	26.82	0.19
Hispanic	−2.24	0.90	7.78	0.67	−8.37	0.64	−3.31	0.85
BMI								
25-30	11.22	0.43	5.84	0.67	10.93	0.45	4.09	0.78
>30	−22.78	0.16	−19.82	0.22	−23.99	0.15	−29.48	0.08
Smoking Status								
Current	−31.58	0.09	−39.52	0.04	−46.59	0.02	−36.37	0.07
Former	−14.30	0.51	−18.18	0.41	−24.09	0.30	−19.50	0.41
Injection Drug Use	−15.45	0.27	−12.76	0.37	−15.66	0.28		
FEV1%*			10.17	0.002				
TLC%*					9.16	0.02		
DLCO%*							4.73	0.24

Model 1: 6MWD, chronic bronchitis, age, gender, race, BMI, smoking status, injection drug use

Model 2: 6MWD, chronic bronchitis, age, gender, race, BMI, smoking status, injection drug use, FEV1%

Model 3: 6MWD, chronic bronchitis, age, gender, race, BMI, smoking status, injection drug use, TLC%

Model 4: 6MWD, chronic bronchitis, age, gender, race, BMI, smoking status, injection drug use, DLCO%

BMI, body mass index; FEV_1, forced expiratory volume in 1 second; TLC, total lung capacity; DLCO, diffusing capacity.

* per 10 unit change

Table 4

Multivariable Regression Model Evaluating Predictors of 6-MWD by HIV Status

	HIV-Infected			HIV-Uninfected		
	β Coefficient	**95% CI**	**p-value**	**β Coefficient**	**95% CI**	**p-value**
Age	−24.14	−41.4, −6.8	0.01	−6.35	−29.0, 16.3	0.58
Male	2.71	−87.1, 92.5	0.95	21.78	−31.4, 74.9	0.42
Race/Ethnicity						
Black	Ref					
White	16.22	−19.7, 52.2	0.37	34.05	−6.7, 74.7	0.10
Hispanic / Other	6.60	−28.5, 41.7	0.71	−42.73	−88.2, 2.69	0.07
BMI						
≤25	Ref					
25-30	4.59	−22.7, 31.9	0.74	−0.83	−47.2, 45.5	0.97
≥30	−28.13	−59.8, 3.6	0.08	−51.68	−98.4, −4.9	0.03
Smoking Status						
Never	Ref					
Current	−38.72	−74.2, −3.3	0.03	−62.49	−105.9, −18.9	<0.01
Former	−11.18	−53.3, 30.9	0.60	−19.13	−68.7, 30.5	0.45
Cardiovascular Disease	0.22	−36.8, 37.3	0.99	−39.53	−83.8, 4.8	0.08
Hemoglobin	6.96	−1.70, 15.6	0.11	−1.26	−13.9, 11.5	0.85
$FEV_1\%$*	10.18	3.8, 16.6	<0.01	1.25	−8.9, 11.5	0.81

* per 10 unit change