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Chronic Obstructive Pulmonary Disease as a Risk Factor for Ventricular Arrhythmias Independent of Left Ventricular Function

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Abstract

Background—The association between chronic obstructive pulmonary disease (COPD) and sudden cardiac death has not been fully elucidated.

Objective—Investigate if decreased left ventricular ejection fraction (LVEF) can explain the increased rate of ventricular tachycardias (VT) in COPD.

Methods—In this retrospective study, we included consecutive adult patients who underwent pulmonary function testing (PFT), Holter monitoring, and trans-thoracic echocardiography. COPD was correlated with the frequency of VT in a multivariate analysis which adjusted for known confounders including LVEF. Long term all-cause mortality of patients with COPD and VT was examined.

Results—From 6351 patients who were included in this study (age 66±15 years, 48% woman, 92% Caucasian, LVEF 59±12%), 2800 (44%) had PFT indicative of COPD. VT was nearly twice as likely to occur during the Holter monitoring in COPD patients (13% vs. 23%; $p < 0.001$), and the severity of COPD correlated with the risk of VT (21% vs. 28% vs. 37% for mild-moderate, severe, and very severe COPD; $p < 0.001$). COPD and VT remained independently associated ($p < 0.001$) even after adjusting for LVEF, demographics, and co-morbidities (age, sex, body mass index, hypertension, chronic kidney disease, coronary artery disease, cancer history, diabetes mellitus). COPD was associated with all-cause mortality independently of LVEF ($p < 0.001$).

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Conflicts of Interest:

Dr. Konecny, Mr. Somers, Dr. Park, Dr. John, Dr. Orban, Dr. Asirvatham, Dr. Rihal, and Dr. Brady report no potential conflicts of interest to this work. Dr. Scanlon has been an investigator for clinical trials sponsored by the National Heart Lung and Blood Institute, Dept. of Energy, Altana, Boehringer Ingelheim, Dey L.P. Pharmaceutical, Forest, GlaxoSmithKline, Novartis AG, and Pfizer Inc. Dr. Doshi consulted on research studies for Boston Scientific, St Jude Medical, and Zoll.

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Conclusions—COPD patients are at a higher risk of VT and mortality. This may not be fully attributed to the confounding effect of systolic heart failure measured by LVEF. Further studies are needed to explore the mechanistic interactions between VT and COPD in order to identify if anti-arrhythmic strategies would apply especially to the severe COPD patients.

Keywords

ventricular tachycardia; chronic obstructive pulmonary disease; sudden cardiac death; emphysema; Holter monitoring; pulmonary function test; sudden cardiac death

Introduction

Chronic obstructive pulmonary disease (COPD) ranks as the fourth leading cause of death in the United States, and it remains the only common mortality etiology that continues to rise (COPD deaths increased by 58% between 1990 and 2010).¹ The most frequent causes of death of COPD patients are cardiovascular events,^{2, 3} and emerging evidence suggests that arrhythmias (including ventricular tachycardia [VT])^{4–8} and sudden cardiac death^{9,10} are contributing to these adverse outcomes. COPD is associated with decreased left ventricular ejection fraction (LVEF) due to ischemic cardiomyopathy,¹¹ but whether this confounder fully explains the markedly increased rate of VT among COPD patients remains unknown. This line of investigation is important because severely reduced LVEF according to the current guidelines¹² stipulates implantation of a protective defibrillator, yet it is plausible that myocardium of COPD patients may be uniquely susceptible to an alternative VT mechanism, similar to the well-recognized preponderance for automatic tachycardias in the atrial myocardium of COPD patients (multifocal atrial tachycardia).¹³ We hypothesized that presence and severity of COPD would be associated with the occurrence of VT as documented by electrocardiographic (ECG) Holter monitoring even after adjustment for the LVEF.

Methods

This retrospective study was approved by the Mayo Clinic Institutional Review Board. We identified unique adult patients who completed all of the following between 2000 and 2010: 1) clinically indicated 24-hour ECG Holter monitoring, 2) measurement of resting LVEF from trans-thoracic echocardiography, and 3) pulmonary function testing (PFT) with available measurements of forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Relevant demographic variables, comorbid conditions, and medication use at the time of Holter monitoring were obtained from the electronic medical record, Holter monitor patient log book, and the international classification of diseases codes. Exclusion criteria were: 1) incomplete medical record, 2) restrictive or non-specific pulmonary disease identified on PFT, and 3) patient's preference not to participate in research studies as indicated on the standardized questionnaire routinely administered to all patients.

PFT was performed in the Mayo Clinic PFT Laboratory by a certified technician and the report was then finalized by a board certified pulmonary physician according to the current guidelines.^{14, 15} Severity of COPD was classified in the following manner: 1) mild to moderate COPD defined as $FEV1/FVC < 0.7$ and $FEV1$ percent predicted > 0.5 ; 2) severe

COPD defined as $FEV1/FVC < 0.7$ and $0.3 \leq FEV1 \text{ percent predicted} < 0.5$; 3) very severe COPD defined as $FEV1/FVC < 0.7$ and $FEV1 \text{ percent predicted} < 0.3$. Absence of COPD was defined as $FEV1/FVC \geq 0.7$ and $FEV1 \text{ percent predicted} \geq 0.8$. Patients with restrictive or non-specific pulmonary function test results were excluded.

Portable three-channel Holter monitoring systems (Spacelabs Healthcare, Issaquah, Washington) were used for the 24 hour ECG recording, and the analysis was performed at the Mayo Clinic ECG Laboratory by a certified ECG technician who was supervised by a cardiovascular physician (both blinded to the hypothesis of this study) according to the guidelines.¹⁶ VT was defined as a run of beats arising from the ventricles with duration of at least 3 beats and with cycle length ≤ 600 ms (equivalent to ≤ 100 beats per minute).¹⁷ Frequent VT was defined as >3 separate episodes during the Holter recording. If the patients underwent 48-hour ECG Holter monitoring we used only the first 24-hours of the recording. Left ventricular function was recorded from clinical trans-thoracic echocardiography studies performed at the Mayo Clinic Echocardiographic Laboratory closest to the date of the Holter monitoring. Preference was given to calculated LVEF from M-mode or 2D assessment, but if these were not available visually estimated values of LVEF reported by the interpreting cardiologist were used.

Statistical method included calculation of means and standard deviations for continuous variables, and frequencies for categorical variables. The student's t-test or Wilcoxon test were used for normally distributed or skewed variables, respectively. We performed chi-square test or Fisher exact test to compare the difference between proportions. To determine the relationship between the presence of COPD (dependent variable) and the occurrence of VT as recorded by Holter monitoring (independent variables) we performed multivariate logistic regression analyses which adjusted for LVEF, age, sex, body mass index, hypertension, chronic kidney disease, coronary artery disease, cancer history, diabetes mellitus, and anti-arrhythmic (class I and III) medication use. This wider selection of variable which was aimed at a more comprehensive phenotypic description of the studied cohort as an evaluation of coronary disease type and severity by angiography was not available in most of the patients. Available variables with relevance to all cause survival, risk of coronary disease, or risk of VT were included. Additional multi-variate models were performed with a more focused set of variables (age, sex, and LVEF) showing consistent results with the primary analysis. Other multi-variate logistic regression models evaluated correlation of PFT variables ($FEV1$ percent predicted, FVC percent predicted, diffusing capacity of the lungs for carbon monoxide, and $FEV1/FVC$ ratio) with the occurrence of VT. All models were tested for multi-collinearity and interaction. The data were analyzed using JMP version 12.1.0. $Value < 0.05$ was considered statistically significant.

Survival data were obtained from the Mayo Clinic records, Minnesota Department of Health Database, and from the National Death Index to the time of the primary data collection (2014). Cox proportional hazard models were applied to estimate the effect of COPD on survival after adjusting for potential confounders mentioned above.

Results

We studied 6351 patients (age 66 ± 15 years, 48% woman) with available results of Holter monitoring, LVEF assessment (mean LVEF $59 \pm 12\%$), and PFT (44% indicative of at least mild COPD). As seen in Table 1, there were marked differences in the baseline characteristics between those with and without COPD.

VT occurred more likely in COPD patients, the likelihood of VT occurrence increased with the COPD severity, and COPD patients manifested increased occurrence of other ventricular arrhythmias (Table 2). Non-sustained VTs with duration ≤ 5 beats and ≤ 10 beats were more common among COPD patients. Only 23 patients had sustained (>30 beats) VT during the Holter monitoring period preventing a meaningful statistical comparison of this variable.

In a multi-variate model which adjusted for age, sex, LVEF, body mass index, and relevant comorbidities specified above, COPD remained a significant risk factor for the presence of VT on Holter monitoring ($p=0.0001$, Figure 1A) with the unadjusted odds ratio of 2.11 (95% confidence interval: 1.85–2.41), and adjusted odds ratio of 1.33 (95% confidence interval: 1.15–1.54). The adjusted odds ratio of severe or very severe COPD versus patients without COPD for the prediction of VT was 1.68 (95% confidence interval: 1.41 – 2.05). The estimated parameter effects of COPD and FEV1 (percent predicted) in these models were shown in Figure 1.

Figure 2 depicts a graphical representation of the positive correlation between the COPD severity and the presence of VT after stratification for LVEF at 40% and at 60%. This relationship was most pronounced in patients with relatively preserved LVEF. The patients with very severe COPD and moderately reduced or normal LVEF (40%-60%) were similarly likely to suffer from VT as patients with severely reduced LVEF ($<40\%$) who did not have COPD (37% vs. 39%). Additional multi-variate models evaluated the role of indexed PFT parameters as predictors of VT occurrence on Holter monitoring: the FEV1 (percent predicted), and the ratio of FEV1/FVC were identified as independent risk factors for the VT occurrence (Table 3 and Figure 1B).

Survival analysis data obtained from social security number indices revealed that patients with COPD and VT were at markedly increased risk of death from any cause ($p<0.0001$) after adjustment for LVEF, age, sex, body mass index, hypertension, chronic kidney disease, coronary artery disease, cancer history, diabetes mellitus (Figure 3).

The evaluation of LVEF occurred within 365 days from the PFT date in 69% of studied patients. LVEF was measured within 365 days from the Holter monitoring in 53% of patients, with 59% of LVEF assessments occurring prior to the Holter monitoring. To investigate whether the timing of tests (particularly the sequence of LVEF assessment and Holter monitoring) had an effect on our conclusions we performed 2 additional subgroup analyses. In the first sub-analysis we only included patients in whom LVEF was assessed prior to the Holter monitoring, and in the other we included only those patients who had the LVEF assessed after the Holter monitoring. The association of COPD with VT remained independent of confounders (including LVEF) in both analyses ($p = 0.004$, and $p = 0.005$, respectively).

Discussion

The novel findings of this study were that 1) COPD was associated with increased VT occurrence independently of LVEF and confounding comorbidities, 2) burden of VT in patients with very severe COPD and relatively preserved LVEF was comparable to patients with severely reduced LVEF, and 3) patients with COPD and VT had markedly increased all-cause mortality independent of LVEF, and 4) percent predicted FEV1 correlated with the occurrence of VT after adjusting for LVEF and comorbidities. These data suggest that the propensity of COPD patients for VT may not be fully attributed to the confounding effect of systolic heart failure, and further studies focusing on sustained life-threatening VT in COPD patients are needed given the limitation of the ambulatory 24-hour Holter monitors used in our study.

Existing Literature

Previous studies of COPD patients identified frequent occurrence of cardiovascular events^{2, 3} including arrhythmias.^{5, 6} Pilot studies using continuous ECG monitoring in COPD patients suggested high prevalence of ventricular premature beats and VT but these studies were limited in size (largest N=75)^{18–22} hence limiting their ability to stratify COPD by its objectively documented severity (PFT) or accounting for confounding variables. Shih et al. documented repetitive ventricular arrhythmias in more than 60% of patients with diagnosed COPD, with greater ventricular arrhythmias prevalence in men, patients with edema, and in patients with elevated pCO₂. In this study, a composite of arrhythmias (including VT) could not be associated with worsened survival, possibly due to power limitation (N=69).¹⁸ Recent retrospective study (N=7441) confirmed that the prevalence of VT on Holter monitoring correlated with COPD severity,⁴ but whether this association was merely a reflection of the reduced LVEF caused by ischemic cardiomyopathy commonly seen in COPD patients, or whether mortality could be correlated with VT in this cohort remained unclear.

Underlying Mechanisms

While the pro-arrhythmic substrate of COPD has been recognized in the atrial myocardium in the forms of multifocal atrial tachycardia²³ and atrial fibrillation,^{4, 24} the mechanism surrounding ventricular arrhythmias in COPD is incompletely understood. A deeper understanding of these processes represents a critical opportunity,^{10,25} in part because several of the proposed patho-physiologic mechanisms could be readily treated, including placement of an implantable defibrillator, intra-cardiac ablation, oxygen supplementation, β -adrenergic antagonists, I^f antagonists, avoidance of beta-agonists, or therapies aimed at chronic inflammation and pulmonary hypertension.

Our data indicate that the frequency of isolated ventricular ectopic beats as well as paired premature ventricular beats increased dramatically with the presence and severity of COPD, similarly to the frequency of non-sustained VT. These findings signify increased automaticity and consequently increased number of triggers for VT initiation. However, the average heart rate, minimum heart rate, and maximum heart rate recorded by the Holter monitors remained comparable in the COPD and non-COPD groups. Such findings do not

support the notion that a markedly increased sympathetic tone potentially triggering greater number of automatic VT would be the primary underlying mechanism in our study. Additionally, the cycle length of the VTs in COPD patients was similar to the non-COPD patients. We propose the possibility that a combination of an increased (possibly re-entry) VT substrate together with greater frequency of VT triggers (not dependent only on sympathetic tone) may exist in COPD.

Relationship between COPD, VT, and Sudden Cardiac Death

Our findings suggest that the presence and severity of COPD could represent a variable with an additive value to the currently used estimation of LVEF when identifying patients with the highest risk of VT who could potentially benefit from the implantation of a cardioverter defibrillator. However, the correlation of VT and COPD relied in our study primarily on nonsustained VT as harder endpoints including sustained VT was rarely captured in consecutive ambulatory patients indicated for a 24-hour Holter monitoring. For this reason, a substantial caution has to be exercised when interpreting these data, even though limited evidence showed that non-sustained VT detected in the ambulatory setting carried prognostic value for the occurrence of sudden cardiac death.^{26, 27}

The patients in our study who had COPD on Holter monitor carried an increased risk of all-cause mortality, and this effect was amplified in the presence of VT, making the combination of COPD and VT nearly twice as lethal during the long term follow up. The design of our study did not allow to differentiate which of these deaths were sudden or due to ventricular tachyarrhythmias, and we acknowledge the uncertainty regarding the predictive value of nonsustained VT in the real-life scenario of our study in which the studied ambulatory patients were exposed to all potential confounders related to COPD, including sympathetic activation, hypoxia, electrolytes disturbance, beta-adrenergic stimulants. Further studies need to explore these phenomena.

Confounders of the COPD-Arrhythmia Interactions

COPD and heart disease commonly coexist (COPD affects one quarter of cardiac patients),²⁸ and COPD is markedly under-diagnosed (under-diagnosis reaches staggering 60% to 87% of affected patients)²⁸ likely because dyspnea is commonly attributed to the heart disease alone. The strength of our study is that it focused on a sample of patients in whom lung function has been objectively quantified by PFT in order to minimize classification error. Another common obstacle in investigating the COPD-arrhythmia interactions lies in the potential confounding effect of ischemic cardiomyopathy and coronary artery disease, which have been well recognized as risk factors for VT, and which are known sequelae of long term tobacco smoke inhalation. Decreased LVEF is addressed in current guidelines with appropriate medical and device based treatment recommendations¹² but it is widely recognized that many patients who experience sudden cardiac death lack an implantable defibrillator. Our study incorporated LVEF to remain consistent with current guideline-based algorithms for placement of defibrillator devices, but we readily acknowledge that further delineation of the severity of coronary disease and additional variables regarding the underlying arrhythmogenic substrate would be helpful in identifying the most at-risk cohort in terms of sudden arrhythmic death. We incorporated available variables which are known

contributors to coronary disease into the multivariate models in an attempt to partially mitigate this limitation, and the conclusions remained unchanged.

Limitations

This single center study included objective quantification of lung function, LVEF, and VT from laboratories with high quality-control, but the retrospective database design is subject to its inherent limitations, including unadjusted confounders such as an objectively assessed extent of smoking history, severity of risk factors, extent and location of myocardial scar, extent and treatment of underlying coronary disease, and other differences in medical therapy. In order to obtain sufficient power for a meaningful analysis of the primary hypothesis, we included a convenience sample of patients with continuous ECG testing, PFT, and echocardiography which were performed in the context of clinical care. While a potential selection bias could have been introduced, the demographic and comorbid characteristics of our cohort are similar to those of previously published in large unselected registries of COPD patients,²⁹ and our results are consistent with the growing body of evidence implicating COPD in arrhythmogenesis.^{4, 10, 30} The timing and sequence of the LVEF assessment, Holter monitoring, and PFT can lead to a possible indication bias. The sub-analysis focusing on this issue supports the notion that the conclusions of this study remain similar in patients with echocardiogram performed prior to the Holter monitoring as in those with echocardiogram performed after Holter monitoring, but future prospectively designed studies are needed to fully elucidate this issue.

As discussed above, the 24-hour Holter recordings of ambulatory patients rarely captured sustained VT, and therefore, further studies are needed to identify how our findings translate to the risk of life-threatening ventricular arrhythmias in COPD patients. Our analysis of the all-cause mortality suggests that the combination of COPD and VT recorded on Holter monitoring lead to a particularly increased risk of death.

PFT results even when indexed to age and sex could over-diagnose mild COPD particularly in the elderly population. The magnitude of adjusted risk of the diagnosis of COPD according to currently accepted clinical spirometry cut offs was in our study statistically significant but relatively weak, and it could be potentially attributed to unmeasured confounders (such as severity of coronary disease). Future studies could, however, focus on the subgroup of the most severely affected COPD patients in whom the risk of VT was more pronounced. A standardized and objective assessment of the right ventricular function could not be routinely obtained in this study, and future investigations should address whether right ventricular dysfunction could in part be responsible for the increased number of VT in COPD patients.

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Figure 1.

Multivariate proportional hazard model showing COPD as an independent risk factor for ventricular tachycardia after adjusting for left ventricular ejection fraction, age, female sex, body mass index, hypertension, chronic kidney disease, coronary artery disease, cancer history, diabetes mellitus.

Figure 2.
Positive correlation between VT and COPD after stratification for LVEF.

Figure 3.
Long term survival of patients stratified by the presence of COPD and/or VT.

Table 1

Patient characteristics. Data are presented as mean $\pm$ SD or No. (%). The p-value pertains to the difference between all patients in the “No COPD” group vs. all patients in the “COPD” group.

	No COPD (N=3551)	COPD (N=2800)			p
		Mild/Mod. COPD (N=1982)	Severe COPD (N=652)	Very severe COPD (N=166)	
Age (years)	61 $\pm$ 17	71 $\pm$ 11	72 $\pm$ 11	70 $\pm$ 12	<0.0001
Gender (female)	2011 (57)	752 (38)	216 (33)	47 (28)	<0.0001
Body mass index (kg/m ²)	29 $\pm$ 6	29 $\pm$ 6	29 $\pm$ 6	27 $\pm$ 6	0.0009
FEV1 (percent predicted)	96 $\pm$ 11	71 $\pm$ 14	41 $\pm$ 6	24 $\pm$ 4	<0.0001
FVC (percent predicted)	97 $\pm$ 11	87 $\pm$ 15	62 $\pm$ 13	49 $\pm$ 13	<0.0001
FEV1/FVC	79 $\pm$ 5	63 $\pm$ 6	52 $\pm$ 10	41 $\pm$ 11	<0.0001
Resting peripheral oxygen saturation (%)	96 $\pm$ 2	96 $\pm$ 2	95 $\pm$ 3	94 $\pm$ 4	<0.0001
Coronary artery disease	1707 (48)	1317 (66)	430 (66)	107 (65)	<0.0001
Hypertension	2429 (68)	1581 (80)	504 (77)	124 (74)	<0.0001
Diabetes mellitus	791 (22)	532 (27)	218 (33)	52 (31)	<0.0001
Chronic kidney disease	489 (14)	415 (21)	160 (25)	42 (25)	<0.0001
History of cancer	725 (20)	625 (32)	188 (29)	46 (28)	<0.0001
Left ventricular ejection fraction (%)	60 $\pm$ 11	58 $\pm$ 13	55 $\pm$ 15	53 $\pm$ 14	<0.0001
Beta blocker use	807 (23)	580 (29)	180 (28)	31 (19)	<0.0001
Calcium channel blocker use	223 (6)	158 (8)	63 (10)	23 (14)	0.0002
Anti-arrhythmic medication use (class I and III)	290 (8)	232 (12)	101 (15)	30 (18)	<0.0001
Beta agonist use	391 (11)	437 (22)	311 (48)	110 (66)	<0.0001
Right ventricular dysfunction, elevated pulmonary systolic pressure, or prominent tricuspid valve regurgitation	1277 (36)	925 (47)	289 (44)	68 (41)	<0.0001

FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity

Table 2

Holter monitoring results relevant to ventricular tachyarrhythmias, stratified by the presence and severity of COPD. Data are presented as mean $\pm$ standard deviation or number (%). The p-value pertains to the difference between all patients in the “No COPD” group vs. all patients in the “COPD” group.

	No COPD (N=3551)	COPD (N=2800)			p
		Mild/Mod. COPD (N=1982)	Severe COPD (N=652)	Very severe COPD (N=166)	
Ventricular tachycardia present	445(13)	408(21)	180(28)	62(37)	<0.0001 *0.0001
Frequent ventricular tachycardia (>3 episodes)	161(5)	154(8)	84(13)	24(15)	<0.0001
Ventricular tachycardia duration 5 beats	146(4)	158(8)	71(11)	22(13)	<0.0001 *0.0004
Ventricular tachycardia duration 10 beats	47(1)	53(3)	24(4)	6(4)	<0.0001
Ventricular tachycardia duration 30 beats	13(0)	10(1)	0(0)	1(1)	0.31
Average ventricular tachycardia frequency (beats per minute)	144 $\pm$ 30	143 $\pm$ 30	147 $\pm$ 29	149 $\pm$ 31	0.39
Accelerated idioventricular rhythm present	242(7)	222(11)	109(17)	33(20)	<0.0001
Premature ventricular contractions per hour	65 $\pm$ 216	98 $\pm$ 269	114 $\pm$ 262	140 $\pm$ 283	<0.0001
Paired premature ventricular contractions per hour	1.9 $\pm$ 15.8	4.0 $\pm$ 21.9	4.6 $\pm$ 17.8	5.2 $\pm$ 16.5	<0.0001
Bigeminal premature ventricular contractions per hour	12.2 $\pm$ 87.3	23.5 $\pm$ 132.3	24.0 $\pm$ 148.0	32.3 $\pm$ 155.9	0.0004
Mean heart rate, bpm	74 $\pm$ 12	73 $\pm$ 13	76 $\pm$ 15	79 $\pm$ 15	0.72
Minimum heart rate, bpm	56 $\pm$ 12	56 $\pm$ 13	58 $\pm$ 17	61 $\pm$ 16	0.16
Maximum heart rate, bpm	114 $\pm$ 22	109 $\pm$ 21	108 $\pm$ 21	114 $\pm$ 22	<0.0001
Atrial fibrillation or flutter	432(12)	457(23)	174(27)	49(30)	<0.0001

* adjusted for left ventricular ejection fraction, age, sex, body mass index, hypertension, chronic kidney disease, coronary artery disease, cancer history, diabetes mellitus.

Table 3

Evaluation of pulmonary function parameters as predictors of ventricular tachycardia recorded on Holter monitoring, after adjustment for left ventricular ejection fraction, age, sex, body mass index, hypertension, chronic kidney disease, coronary artery disease, cancer history, diabetes mellitus.

Pulmonary Function Variable (number of patients included in the analysis)	p	β coefficient for the occurrence of ventricular tachycardia per decile increase in the multivariate model (95% confidence interval)
Forced expiratory volume in 1 second –percent predicted (N=6351)	<0.001	–0.050 (–0.076;–0.024)
Forced vital capacity –percent predicted (N=6351)	0.006	–0.036 (–0.062;–0.010)
Ratio of forced expiratory volume in 1 second to forced vital capacity – percent predicted (N=6351)	<0.001	–0.053 (–0.078;–0.028)
Diffusing capacity for carbon monoxide –percent predicted (N=1428)	0.22	–0.033 (–0.087;+0.020)