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# Comorbidities of COPD Have a Major Impact on Clinical Outcomes, Particularly in African Americans

**Nirupama Putcha, MD,[1] Meilan K. Han, MD,[2] Carlos H. Martinez, MD,[2] Marilyn G. Foreman, MD,[3] Antonio R. Anzueto, MD[4], Richard Casaburi, MD,[5] Michael H. Cho, MD,[6] Nicola A. Hanania, MD,[7] Craig P. Hersh, MD,[6] Gregory L. Kinney, PhD,[8] Barry J. Make, MD,[9] Robert M. Steiner, MD,[10] Sharon M. Lutz, PhD,[8] Byron M. Thomashow, MD,[11] Andre A. Williams, PhD,[12] Surya P. Bhatt, MD,[13] Terri H. Beaty, PhD,[14] Russell P. Bowler, MD,[9] Joe W. Ramsdell, MD,[15] Jeffrey L. Curtis, MD,[2] Douglas Everett, PhD,[12] John E. Hokanson, PhD,[8] David A. Lynch, MB,[16] E. Rand Sutherland, MD,[9] Edwin K. Silverman, MD,[6] James D. Crapo, MD,[9] Robert A. Wise, MD,[1] Elizabeth A. Regan, MD,*[17] Nadia N. Hansel, MD,*[1] and the COPDGene® Investigators**

***indicates two senior authors for this manuscript**

## Abstract

### Background

COPD patients have a great burden of comorbidity. However, it is not well established whether this is due to shared risk factors such as smoking, if the comorbidities impact patients' exercise capacity and quality of life, or whether there are racial disparities in their impact on COPD.

### Methods

We analyzed data from 10,192 current and ex-smokers with (cases) and without COPD (controls) from the Genetic Epidemiology of COPD (COPDGene®) study cohort to establish risk for COPD comorbidities adjusted for pertinent covariates. In adjusted models, we examined comorbidity prevalence and impact in African-Americans (AA) and non-Hispanic whites (NHW).

### Results

Comorbidities are more common in individuals with COPD compared to those with normal spirometry (controls), and the risk persists after adjustments for covariates including pack-years smoked. After adjustment for confounders, 8 conditions were independently associated with worse exercise capacity, quality of life and dyspnea. There were racial disparities in the impact of comorbidities on exercise capacity, dyspnea and quality of life, with the presence of osteoarthritis and gastroesophageal reflux disease having a greater negative impact on all three outcomes in AAs than NHWs ($p<0.05$ for all interaction terms).

### Conclusions

Individuals with COPD have a higher risk for comorbidities than controls, an important finding shown for the first time comprehensively after accounting for confounders. Individual comorbidities are associated with worse exercise capacity, quality of life, and dyspnea, in AAs compared with NHWs.

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**Abbreviations:** COPD Genetic Epidemiology study, **COPD Gene®**;African Americans, **AA**; non-Hispanic whites, **NHWs**; congestive heart failure, **CHF**; chronic kidney disease, **CKD**; obstructive sleep apnea, **OSA**; gastroesophageal reflux disease, **GERD**; coronary heart disease, **CHD**; Global Initiative for chronic Obstructive Lung Disease, **GOLD**; body mass index, **BMI**; 6-minute walk distance, **6MWD**; St. George's Respiratory Questionaire, **SGRQ**; modified Medical Research Council dyspnea questionnaire, **MMRC**;forced expiratory volume in 1 second, **FEV1**;odds ratio, **OR**; confidence level, **CL**; peripheral vascular disease, **PVD**; Evaluation of COPD Longitudinally to Indentify Predictive Surrogate Endpoints, **ECLIPSE**

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**Address correspondence to:**

Nirupama Putcha, MD, MHS
5501 Hopkins Bayview Circle
JHAAC 4B.74
Baltimore, MD 21224
nputcha1@jhmi.edu
410-550-0545

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1 Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD

2 Division of Pulmonary and Critical Care Medicine, University of Michigan, Ann Arbor

3 Divison of Pulmonary and Critical Care Medicine, Morehouse School of Medicine, Atlanta, GA

4 Pulmonary Section, Department of Medicine, University of Texas Health Science Center, and South Texas Veterans Health Care System, San Antonio

5 Rehabilitation Clinical Trials Center, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA

6 Channing Division of Network Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

7 Section of Pulmonary, Critical Care and Sleep Medicine, Baylor College of Medicine, Houston, TX

8 Colorado School of Public Health, Aurora, CO

9 Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, CO

10 Department of Radiology, Temple University School of Medicine, Philadelphia, PA

11 Division of Pulmonary, Allergy and Critical Care Medicine, Columbia University, New York, NY

12 Division of Biostatistics and Bioinformatics, National Jewish Health, Denver, CO

13 Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama, Birmingham

14 Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

15 Department of Medicine, University of California San Diego, San Diego

16 Division of Radiology, National Jewish Health, Denver, CO

17 Department of Medicine, National Jewish Health, Denver, CO

## Introduction

The prevalence of comorbidities is higher in COPD patients than the general population.[1-8] Comorbidities, including congestive heart failure (CHF), chronic kidney disease (CKD), diabetes, and obstructive sleep apnea (OSA) have been linked to mortality in COPD.[8-16] Specific comorbidities including gastroesophageal reflux disease (GERD),[17] CHF,[10] diabetes,[8,18] obesity,[19,20] asthma[21,22] and coronary heart disease (CHD)[23,24] have also been associated with worse quality of life, exercise capacity, exacerbation risk and dyspnea. However, these findings have been shown for individual comorbidities, without regard to multimorbidity of the COPD population.

African-Americans (AAs) with COPD have an increased risk of mortality,[25] and experience worse quality of life than non-Hispanic whites (NHWs).[26] In general cohorts, AAs have also been shown to have increased prevalence [27] of and mortality[27-35] from chronic conditions, such as cardiovascular disease, CKD, diabetes and stroke. However, it is unknown whether there are racial disparities in the impact of comorbidities on clinical outcomes in COPD.

There were 3 important hypotheses for this paper. First, we hypothesized that individuals with COPD would have higher risk for developing comorbidities compared to smokers without COPD after accounting for important confounding factors. Second, we hypothesized that comorbidities would play an important role in determining clinical outcomes in COPD, even after controlling for confounding variables and other comorbid conditions given that multiple comorbidities co-exist in individuals with COPD. Finally, we hypothesized there are racial differences between AAs and NHWs on the impact of comorbidities in COPD outcomes. To test these hypotheses, we conducted a comprehensive assessment of comorbidity in the Genetic Epidemiology of COPD (COPDGene®) study. Because it is a well-characterized population including a large number of AAs, the COPDGene® study provides an ideal opportunity to understand how comorbidities contribute to the clinical heterogeneity of COPD which has become increasingly recognized in recent COPD clinical research.

## Methods

### *COPDGene® Study Design*

The COPDGene® is an observational study in 21 American centers. The design and goals of this study have been previously described.[36] The study recruited 10,192 current and former smokers (January 2008 through April 2011) with and without COPD to provide adequate power to detect genetic differences in the group. To be included, individuals had to be either NHW or AA between ages 45-80 years old with a minimum 10 pack-year smoking history. We analyzed cases of individuals falling within the Global Initiative for chronic Obstructive Lung Disease(GOLD) guidelines' severity of airflow limitations levels 2-4 [37](n=3690) and current or former smokers without COPD having normal spirometry (controls) (n=4388). The study was approved by institutional review boards at each center (e-Table 1 in the online supplementary material) and all participants provided informed consent.

### *Comorbidity Assessment*

Comorbidities were ascertained by self-report of physician diagnosis, except obesity which was based on each individual's body mass index (BMI) (e-Table 2 in online supplementary material). We included comorbid chronic diseases and also risk factors for diseases, such as high cholesterol, obesity and hypertension.

### *Clinical Outcomes*

Exercise capacity was measured using 6-minute walk distance (6MWD), expressed in feet using a standardized protocol.[38] Quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ)[39] which measures disease impact specific to respiratory disease with higher numbers (range 0-100) representing worse quality of life (more impairment). Dyspnea was measured using the modified Medical Research Council (MMRC) dsypnea questionnaire scale[40] with higher numbers (range 0-4) indicating worse dyspnea. All outcomes were assessed as part of the main COPDGene® study.

### *Statistical Analysis*

All analyses were performed using Stata 12 statistical software.[41] Using a test of proportions, we compared prevalence of comorbidities in cases vs. controls as well as between AAs and NHWs COPD cases. To determine differences in comorbidity prevalence between cases and controls, logistic regression models were fit with comorbidities as outcomes, case status as exposure of interest, and adjusted for age, gender, race, education level (less than high school, high school and some college, college or more) and pack-years of smoking history. An interaction term between race and COPD status was added to the logistic regression models to determine if race modified the impact of COPD status on the risk for specific comorbidities.

Among those within the GOLD 2-4 COPD levels, we assessed whether comorbidities were associated with clinical outcomes (6MWD, SGRQ, and MMRC). We performed adjusted multivariable regression models (linear or logistic regression models based upon the outcome of interest) including all covariates (age, gender, race, absolute post-bronchodilator forced expiratory volume in 1 second (FEV1), pack-years of smoking, education level and current smoking status) and all comorbidities simultaneously to assess which conditions are independently associated with the outcomes. We added interaction terms between comorbidities and race (both separately included in models as well) to determine if the impact of comorbidities upon patient-reported outcomes was modified by race. We also calculated variance inflation factors for the linear regression models in order to determine if significant collinearity existed between the individual comorbidities in the multivariable models.

**Table 1: Baseline Demographics and Clinical Characteristics of the Cohort, Comparing GOLD 2-4 cases With Controls.**

| | Gold 2-4 Cases (N=3690) | Controls (current and former smokers) (N=4388) | p-value |
|---|---|---|---|
| Age, years | 63.4 (8.5) | 56.7 (8.4) | <0.001 |
| Female, n(%) | 1,638 (44) | 2,068 (47) | 0.014 |
| African American, n(%) | 836 (23) | 1,807 (41) | <0.001 |
| FEV1 percent predicted | 50.2 (18.0) | 97.5 (11.5) | <0.001 |
| FEV1/FVC ratio | 49.5 (13.1) | 78.7 (5.2) | <0.001 |
| Pack-years smoked | 53.0 (27.5) | 37.2 (20.2) | <0.001 |
| Current smoker, n(%) | 1,501 (41) | 2,619 (60) | <0.001 |
| BMI, kg/m$^2$ | 28.1 (6.3) | 28.9 (5.8) | <0.001 |
| 6 minute walk distance, feet | 1174.8 (397.0) | 1491.5 (350.7) | <0.001 |
| SGRQ score, total | 40.9 (21.9) | 17.0 (18.0) | <0.001 |
| MMRC dyspnea score | 2.1 (1.4) | 0.8 (1.2) | <0.001 |
| Education attained, n(%) | | | 0.001 |
| Some high school | 532 (14) | 551 (13) | |
| High school or some college | 2,022 (55) | 2,324 (53) | |
| College graduate and beyond | 1,135 (31) | 1,513 (34) | |
| Number of comorbidities | 3.3 (2.3) | 2.4 (2.0) | <0.001 |

All values are mean (SD) unless otherwise indicated. P-values were calculated with t-tests for continuous variables and chi-squared tests for categorical.

## Results

### *Comorbidity Prevalence in Cases and Controls*

Baseline demographics and clinical characteristics of the cohort in COPD cases (N=3,690) and controls (N=4,388) are displayed in Table 1 and have been previously described.[42,43] COPD cases had worse lung function and more cumulative smoking history (but fewer current smokers) compared to controls. Most comorbidities were more prevalent in those with COPD, with the exception of obesity, which was less prevalent in COPD, and hay fever which was not statistically different between groups (e-Table 3 in the online supplementary material). COPD cases had a higher comorbidity burden compared to controls (3.3 conditions in cases vs. 2.4 in controls, p<0.001). After adjustment for confounders, risk for most comorbidities continued to be higher in COPD cases compared to controls (Figure 1). The highest risks were for CHF (odds ratio [OR] 3.36, 95% confidence level [CI] 2.37-4.49) and osteoporosis (OR 1.66, 95% CI 1.43-1.94). Individuals with COPD had a lower risk for high cholesterol (OR 0.84, 95% CI 0.75-0.93) and obesity (OR 0.87, 95% CI 0.79-0.97).

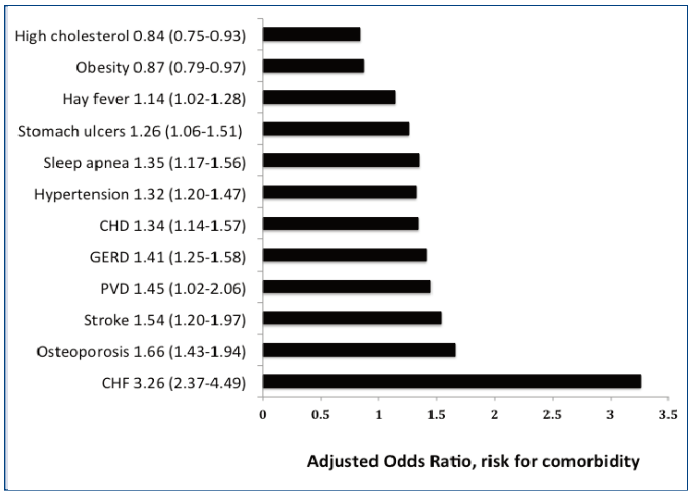


**Figure 1: Odds Ratios With 95% Confidence Intervals (in parentheses) for Risk of Specific Comorbidities Based on COPD Case Status.** Adjusted for age at enrollment, gender, race, pack years smoked and education level. For all conditions pictured, COPD case status was significantly associated with increased risk for the condition with the exception of obesity and high cholesterol, in which case status was significantly associated with decreased risk. Conditions in which case status was not associated with increased risk were cancer, diabetes, and osteoarthritis (not pictured).

**Table 2: Specific Comorbidity Prevalence Comparing African-Americans Versus Non-Hispanic Whites Among GOLD 2-4 Participants.**

| Comorbidity | Non- Hispanic whites (N=2853) | African-Americans (N=836) | p-value |
|---|---|---|---|
| Diabetes | 343 (12) | 139 (17) | <0.001 |
| Hypertension | 1400 (49) | 468 (56) | <0.001 |
| Stomach ulcers | 305 (11) | 67 (8) | 0.024 |
| Sleep apnea | 507 (18) | 124 (15) | 0.048 |
| CHD | 516 (18) | 92 (11) | <0.001 |
| PVD | 109 (4) | 17 (2) | 0.012 |
| High cholesterol | 1266 (44) | 263 (32) | <0.001 |
| Cancer | 215 (8) | 35 (4) | <0.001 |
| Osteoarthritis | 645 (23) | 119 (14) | <0.001 |
| Osteoporosis | 570 (20) | 70 (8) | <0.001 |
| GERD | 951 (33) | 165 (20) | <0.001 |

All values displayed as N(%). Unadjusted prevalence of comorbidities in non-Hispanic whites compared to African-Americans. Shaded cells indicate conditions significantly more pre valent in non-Hispanic whites , non-shaded cells indicate conditions more prevalent in African Americans. Conditions without significant difference between groups not shown.

Among participants with COPD, diabetes (17% vs. 12% prevalence in AA vs. NHW, p<0.001) and hypertension (56% vs. 49%, p<0.001) were more common in AAs (Table 2). However, after adjusting for confounders, there were no significant statistical interactions between race and case status in risk for individual comorbidities.

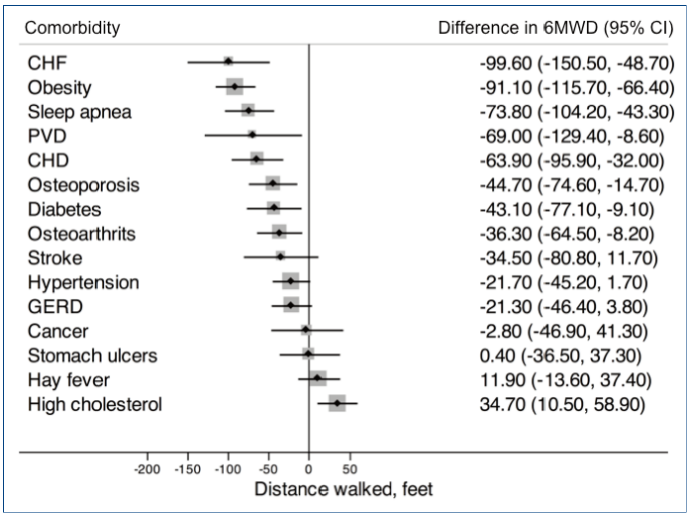


**Figure 2a: Adjusted Associations Between Comorbidities and Exercise Capacity Measured by 6MWD Among GOLD 2-4 Cases.** All listed conditions were included in one model along with age at enrollment, gender, race, FEV1 (post-bronchodilator), pack years of smoking, education level and current smoking status. Associations reported as difference in 6MWD with 95% confidence intervals.

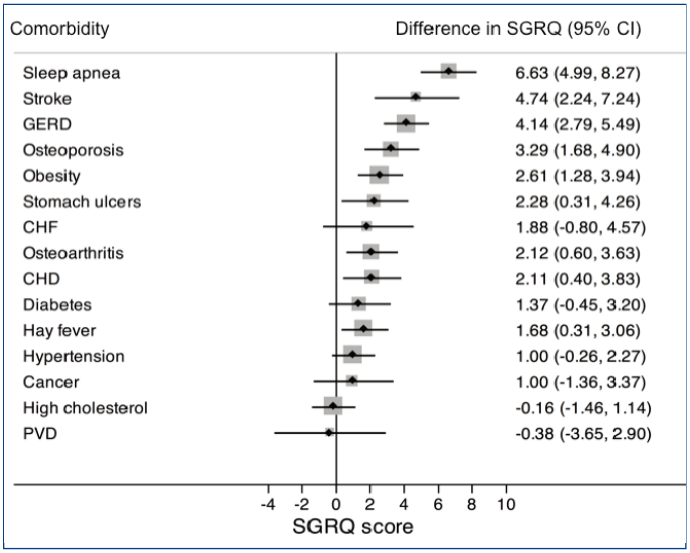


**Figure 2b: Adjusted Associations Between Comorbidities and Quality of Life Measured by the SGRQ Among GOLD 2-4 Cases.** All listed conditions were included in a single model along with age at enrollment, gender, race, FEV1 (post-bronchodilator), pack years of smoking, education level and current smoking status. Associations reported as difference in SGRQ with 95% confidence intervals.

## *Impact of Comorbidities on Clinical Outcomes*

### 6MWD

After adjusting for all other comorbidities in addition to potential confounders (Figure 2a), CHF (99.6 fewer feet walked, 95% CI -150.5,-48.7), obesity (91.1 fewer feet walked, 95% CI -115.7, -66.4) and OSA (73.8 fewer feet walked, 95% CI -104.2, -43.3) had the strongest independent associations with exercise capacity. Peripheral vascular disease (PVD), CHD, diabetes, osteoporosis and osteoarthritis were also significantly associated with shorter distance walked in 6 minutes. Addition of height to the above models did not appreciably change our results. For models including all comorbidities simultaneously, checking the variance inflation factors indicated that collinearity was not a significant issue.

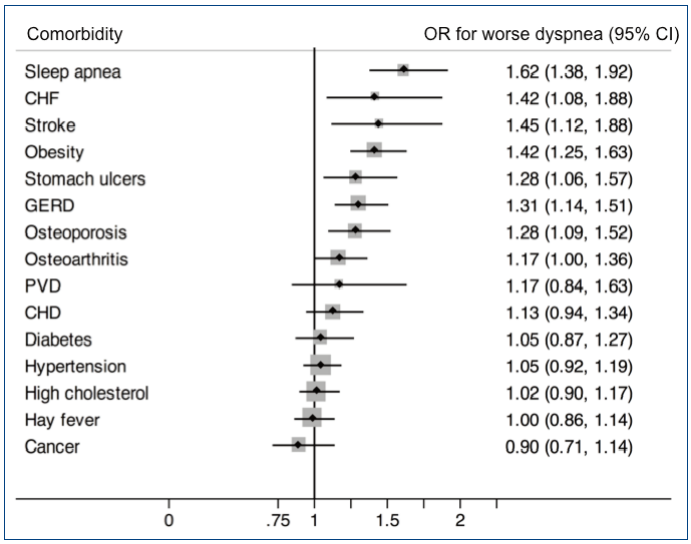


**Figure 2c: Adjusted Associations Between Comorbidities and Dyspnea Measured by MMRC Among GOLD 2-4 Cases.** All listed conditions were included in one model along with age at enrollment, gender, race, FEV1 (post-bronchodilator), pack years of smoking, education level and current smoking status. Associations reported as OR for worse MMRC score with 95% confidence intervals.

### SGRQ

After adjusting for all comorbidities simultaneously, 9 conditions were independently associated with higher SGRQ (Figure 2b), most remarkably OSA (higher SGRQ score by 6.6 points; 95% CI 4.9-8.3), stroke (4.7; 95% CI 2.2-7.2) and GERD (4.1; 95%CI 2.8-5.5).

### Dyspnea

After controlling for all comorbidities, (Figure 2c) 8 conditions including OSA (OR for worse dyspnea 1.62, 95% CI 1.38-1.92), CHF (OR 1.42; 95% CI 1.08-1.88), and stroke (OR 1.45; 95% CI 1.12-1.88) were independently associated with worse dyspnea.

## *Racial Differences in Impact of Comorbidities on Clinical Outcomes in COPD*

Despite having younger age, less smoking history, better lung function and fewer comorbidities, AAs had worse dyspnea, exercise capacity and health status in unadjusted calculations (Table 3).

There were racial disparities in the impact of comorbidities on outcomes (Table 4). Osteoarthritis and GERD had a greater impact on AAs than NHWs. The presence

**Table 3: Baseline Demographics and Clinical Characteristics of the Cohort, Comparing African-Americans to Non-Hispanic Whites, GOLD 2-4 Cases.**

| | African-Americans (N=836) | Non-Hispanic Whites (N=82,854) | p-value |
|---|---|---|---|
| Age, years | 59.0 (8.2) | 64.7 (8.2) | <0.001 |
| Female, n(%) | 377 (45) | 1,261 (44) | 0.641 |
| FEV1 percent predicted | 52.2 (17.8) | 49.6 (18.0) | <0.001 |
| Pack years smoked | 42.4 (23.0) | 56.1 (28.0) | <0.001 |
| Current smoker, n(%) | 509 (61) | 992 (35) | <0.001 |
| BMI, kg/m$^2$ | 28.0 (6.8) | 28.1 (6.1) | 0.671 |
| 6 minute walk distance, feet | 1050.6 (395.6) | 1211.7 (389.9) | <0.001 |
| SGRQ score, total | 44.0 (23.3) | 40.0 (21.4) | <0.001 |
| MMRC dyspnea score | 2.3 (1.4) | 2.1 (1.4) | <0.001 |
| Education attained, n(%) | | | <0.001 |
| Some high school | 224 (27) | 308 (11) | |
| High school or some college | 497 (59) | 1,525 (53) | |
| College graduate and beyond | 115 (14) | 1,020 (36) | |
| Number of comorbidities | 3.1 (2.2) | 3.4 (2.3) | <0.001 |

All values are mean (SD) unless otherwise indicated.

of GERD was associated with 109.1 (95% CI-170.4, -47.9) fewer feet walked in six minutes, 9.1 (95% CI 5.5, 12.7) points higher on the SGRQ scale, and OR 1.93 (95% CI 1.40, 2.66) for worse dyspnea score in AAs compared to 38.5 (95% CI -65.1, -12.0) fewer feet walked, 5.8 (95% CI 4.4, 7.2) points higher on the SGRQ and OR 1.49 (95% CI 1.29, 1.72) for worse dyspnea in NHWs. Osteoarthritis was associated with 132.6 (95% CI -202.8, -62.3) fewer feet walked in 6 minutes, 6.7 (95%CI 2.5, 10.8) points higher on the SGRQ scale and OR 2.05 (95% CI 1.43, 2.96) for worse dyspnea score in AAs compared to 64.2 (95% CI -94.2, -34.2) fewer feet walked, 4.5 (95% CI 2.9, 6.1) points higher on the SGRQ and OR 1.37 (95% CI 1.16, 1.61) for worse dyspnea in NHWs. Only obesity was less detrimental in AAs compared to NHWs in its contribution to decreased exercise capacity. The cardiovascular risk factors of hypertension and high cholesterol also had worse effects on quality of life and dyspnea among AAs as compared to NHWs. Sensitivity analyses were performed including use of inhaled corticosteroids in all of the above models, with minimal change in our results (data not shown).

## Discussion

Using the large multi-center COPDGene® study, we confirmed that most comorbidities are significantly more prevalent among individuals with COPD than in controls. Further, among individuals with COPD, most comorbidities were independently and strongly associated with lower exercise capacity, worse respiratory-specific quality of life and dyspnea. Importantly, several common comorbidities, particularly GERD and osteoarthritis, had a greater impact on clinical outcomes in AAs with COPD than in NHWs.

Our results support those of previous studies showing an increased comorbidity burden among individuals with COPD compared to general populations.[2-4,8,44] Though in some cases these studies did control for confounding,[3,4,44] there has not yet been a comprehensive accounting of comorbidity risk in individuals with COPD while also accounting for confounders. A recently published study displayed not only a higher prevalence of comorbidity in patients with COPD to compared smoking controls, it also demonstrated that the risk for comorbidity is higher in smokers with and without COPD compared to nonsmoking controls.[45] One study described clusters of comorbidities in individuals with COPD to define clinical subgroups with regards to inflammation and outcomes.[46] Our approach differs in that we attempt to understand the contribution of each comorbidity within the framework of coexisting conditions. Specifically, we found that risk for cardiovascular conditions is substantially increased in individuals with COPD compared to controls after adjustment for smoking. These findings challenge us to understand the mechanism for this increased risk, particularly for cardiovascular conditions, among individuals with COPD. Some have hypothesized that systemic inflammation leading to or resulting from COPD puts the individual at heightened risk for cardiovascular disease.[47] The finding that a subgroup with COPD and higher levels of inflammatory biomarkers have a higher risk for heart disease and diabetes[46,48] lends some weight to this theory. Other explanations include increased susceptibility or increased exposure to the toxic effects of smoke in COPD.[49]

A majority of comorbidities studied were independently associated with worse exercise capacity, respiratory-specific quality of life, and dyspnea. Though a study from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) cohort did not show a significant association between cardiovascular disease and exercise capacity[50] other studies have shown associations of cardiovascular diseases[8,10,23,24] and diabetes [8,18] with exercise capacity, poor quality of life, exacerbation risk, dyspnea and mortality. Our findings extend those of previous studies in that we were able to control for the presence of other conditions, confirming the independence of these associations in some cases. Our results show that CHF, OSA and obesity were

strongly linked to worse exercise capacity. Given that the results are based on associations noted in this observational study, we cannot conclude causality, and it is possible that individuals have worse cardiovascular disease as a result of poor exercise capacity. Regardless, such a finding is important in its suggestion that programs for improving exercise capacity such as pulmonary rehabilitation could be particularly beneficial in patients with concomitant cardiovascular disease. Finally, the finding that OSA is strongly associated with poor exercise capacity, quality of life and worse dyspnea in individuals with COPD challenges us to better understand this overlap syndrome and suggests that more aggressive diagnosis and treatment of this disease could improve clinical outcomes in COPD. One could speculate that the mechanism for the impact of OSA, particularly untreated or undertreated OSA, on clinical outcomes in COPD would be through worsening of pulmonary vascular disease, which would in turn impact clinical endpoints such as exercise capacity and dyspnea.

We found that most comorbidities were less prevalent in AA COPD cases compared with NHWs, but when present, these comorbidities were associated with higher risk for worse outcomes among AAs with COPD. Among cases, both GERD and osteoarthritis were associated with a higher risk for worse clinical outcomes in all measured domains in AAs compared to NHWs. In addition, other comorbidities such as osteoporosis (for quality of life), high cholesterol and hypertension (both for quality of life and dyspnea) also had greater impact on health outcomes in AAs compared to NHWs. The etiology for GERD and osteoarthritis being important comorbidities which impact AAs more than NHWs is unclear, however it is possible that AAs are more susceptible to dietary influences or exercise habits which predispose individuals to developing these diseases and subsequent poor health outcomes. Previous investigations have also suggested that other clinical factors, such as exacerbations and total percent emphysema measured on quantitative CT, are more strongly linked to poor health outcomes, such as quality of life and exercise capacity, among AAs as compared to NHWs. [26,50] In addition, cardiovascular disease and CKD have been associated with heightened mortality risk for AAs in general population studies,[28-35,52,53] supporting our findings that chronic diseases may have disparate health impacts on AAs. Though it is possible that the differences found by race could be related to confounding factors such as access to care and medication use, the comprehensive data available on our study population allowed us to control for these important

**Table 4: Stratified Analyses by Race for Association With COPD Outcomes Based Upon Presence of Comorbidites.**

| | Non-Hispanic Whites | | African-Americans | |
|---|---|---|---|---|
| **6MWD** | **Coeff** | **95% CI** | **Coeff** | **95% CI** |
| Osteoarthritis | -64.2 | (-94.2, -34.2) | -132.6 | (-202.8, -62.3) |
| Obesity | -139.4 | (-165.7, -113.2) | -65.9 | (-117.8, -14.0) |
| GERD | -38.5 | (-65.1, -12.0) | -109.1 | (-170.4, -47.9) |
| **SGRQ** | **Coeff** | **95% CI** | **Coeff** | **95% CI** |
| Osteoarthritis | 4.5 | (2.9, 6.1) | 6.7 | (2.5, 10.8) |
| Osteoporosis | 4.0 | (2.4, 5.7) | 6.8 | (1.6, 12.1) |
| Hypertension | 1.9 | (0.6, 3.2) | 7.3 | (4.3, 10.4) |
| High cholesterol | 1.4 | (0.1, 2.8) | 5.0 | (1.8, 8.2) |
| GERD | 5.8 | (4.4, 7.2) | 9.1 | (5.5, 12.7) |
| **MMRC** | **OR** | **95% CI** | **OR** | **95% CI** |
| Osteoarthritis | 1.37 | (1.16, 1.61) | 2.05 | (1.43, 2.96) |
| Hypertension | 1.19 | (1.04, 1.36) | 1.57 | (1.20, 2.04) |
| High cholesterol | 1.14 | (0.99, 1.31) | 1.58 | (1.20, 2.08) |
| GERD | 1.49 | (1.29, 1.72) | 1.93 | (1.40, 2.66) |

Coefficients and 95% CIs represent adjusted difference in exercise capacity (6 minute walk distance) or quality of life (SGRQ score) based upon presence of comorbidities (reference group those without comorbid condition listed). Odds ratios and 95% CIs represent adjusted risk for worse dyspnea (measured 1 point worse on MMRC score scale) based upon presence of comorbidities (reference group those without comorbid condition listed). Stratified analyses also adjusted for pack-years smoked, age at enrollment, current smoking status, education level and gender. Stratified analyses displayed for those comorbidities with statistically significant interaction terms between race and comorbidities in full models ($p<0.05$ for all interaction terms).

parameters in our analyses. It is also possible that certain conditions are associated with worse clinical outcomes in AAs because of a higher severity of illness in AAs compared to NHWs, given that data on severity of illness for comorbidities was not available in this study.

Our study is subject to some limitations. The data are cross-sectional, thus inferences about causality are limited. Comorbid conditions were defined by self-report of physician diagnosis ("Have you ever been told by a physician that you have..."), without regards to severity of the disease or treatment status. Validity of self-report for defining chronic diseases appears to vary based upon characteristics of the study population, the disease in question, and whether the disease is prevalent or incident. Self-report for diseases such as diabetes or osteoarthritis[54-56] is likely more valid than that of CHD or stroke,[56-58] though this validity is much more variable in the case of malignancy.[57-59] Comparing the prevalence of comorbid conditions in our study to another population in which conditions were identified with objective data such as laboratory values, anthropometrics and validated instruments,[46] we find that with some comorbidities such as hypertension the prevalence is comparable (51% in our study, 48% in the Vanfleteren, et al, study), while in other comorbidities the prevalence is disparate, as in osteoporosis (17% in our study, 31% in the VanFleteren, et al study). Comparing to Divo, et al,[9] which also used medication and objective data to confirm the presence of conditions when available, our study showed a lower prevalence of congestive heart failure (5% vs. 15.7%) and coronary heart disease (17% vs. 30.2%) but a comparable prevalence of gastric ulcers (10% vs.11.5%). Though some of these differences in prevalence could potentially be attributed to the difference between self-report and objective measures of comorbidity, it is also possible that different prevalence of disease exists between European and American populations. In this study, individuals with active cancer undergoing treatment or with suspected lung cancer were excluded, a possible reason for the insignificant findings for the association of cancer with outcomes. Further, the group with cancer reported cancers of bladder, breast, colon or prostate, representing a heterogeneous spectrum of disease burden. Additionally, COPDGene® did not gather data on the presence of depression or anxiety (shown in previous studies to be prevalent with COPD[8] and when present, associated with poor outcomes, [50] nor was data available on anemia in the population. We also did not have data on the severity of comorbidities or the current treatment status of conditions, which would potentially impact the association with outcomes. Finally, we used education level as a surrogate measure for socioeconomic status. This has been shown to be an appropriate and relevant measure of socioeconomic status in previous studies.[60,61]

In conclusion, this study shows a high prevalence of comorbidities and a large impact by these conditions on functional status in individuals with COPD. In particular, certain comorbidities were more predictive of poor functional status in African-Americans compared to non-Hispanic whites. Currently, it is unknown if targeting therapies for specific comorbidities will improve functional status in COPD. A better understanding of how comorbidities contribute to the heterogeneity of COPD is important. Ultimately, developing such an understanding can determine whether screening for and treating comorbidities can improve quality of life, symptoms and exercise capacity of patients with COPD.

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**Declaration of Interest:**

All authors declare that they have no special interests related to or impacting the work included in this manuscript with the following exceptions: RC, BMT, RAW, CPH, BJM, EKS, MKH report monies paid to them for consultancy; RC, RAW, BJM and EKS report monies paid to their institutions; RC, BJM, EKS and MKS report monies paid for lectures; BMT, RAW, BJM, and MKH report being on advisory boards; BJM and MKH report royalties paid to them for previous work, and BJM reports paid educational presentations as well as paid manuscript preparation.

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