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Examining the Effects of Age on Health Outcomes of Chronic Obstructive Pulmonary Disease: Results From the Genetic Epidemiology of Chronic Obstructive Pulmonary Disease Study and Evaluation of Chronic Obstructive Pulmonary Disease Longitudinally to Identify Predictive Surrogate Endpoints Cohorts

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Abstract

Rationale—The prevalence of chronic obstructive pulmonary disease (COPD) and its associated comorbidities increase with age. However, little is understood about differences in the disease in patients over 65 years of age compared with younger patients.

Objectives—To determine disease characteristics of COPD and its impact in older patients compared with younger patients.

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Methods—We examined baseline characteristics of patients with COPD (global obstructive lung disease stage II–IV) in 2 large cohorts: Genetic Epidemiology of COPD Study (COPDGene) and Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE). We compared demographics, indices of disease severity, prevalence of comorbidities, exacerbation frequency, and quality of life scores in patients ≥65 years of age vs patients <65 years of age. We also tested for associations of age with disease characteristics and health outcomes.

Results—In the COPDGene cohort, older patients (n = 1663) had more severe disease as measured by forced expiratory volume in 1 second (1.22 vs 1.52 L, $P < .001$), use of long-term oxygen therapy (35% vs 22%, $P < .001$), 6-minute walk distance (355 vs 375 m, $P < .001$), and radiographic evidence of emphysema (14% vs 8%, $P < .001$) and air trapping (47% vs 36%, $P < .001$) and were more likely to have comorbidities compared with younger patients (n = 2027). Similarly, in the ECLIPSE cohort, older patients (n = 1030) had lower forced expiratory volume in 1 second (1.22 vs 1.34 L, $P < .001$), greater use of long-term oxygen therapy (7% vs 5%, $P = .02$), shorter 6-minute walk distance (360 vs 389 m, $P < .001$), and more radiographic evidence of emphysema (17% vs 14%, $P = .009$) than younger patients (n = 1131). In adjusted analyses of both cohorts, older age was associated with decreased frequency of exacerbations [odds ratio = 0.52, 95% confidence interval (CI) 0.43-0.64 in COPDGene, odds ratio 0.79, 95% CI = 0.64-0.99 in ECLIPSE] and a better quality of life = (lower St. Georges respiratory questionnaire = score) ($\beta = -8.7$, 95% CI = −10.0 to −7.4 in COPDGene, $\beta = -4.4$, 95% CI = −6.1 to 3.2 in ECLIPSE).

Conclusions—Despite greater severity of illness, older patients with COPD had better quality of life and reported fewer exacerbations than younger patients. Although this observation needs to be explored further, it may be related to the fact that older patients change their expectations and learn to adapt to their disease.

Keywords

Elderly; quality of life; 6-minute walk distance; comorbidities

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The population of older people is growing by 2% per year, a rate which is faster than the growth of the total world population.[1] By 2030, it is estimated that 20% of the population of the United States with be over the age of 65 years.[2] Although morbidity and mortality from many diseases have either declined or been stable over time, morbidity and mortality from lung diseases have increased with the increasing age of the population.[3] Aging leads to a decline of the structure and function of organs, including the airways and lungs. One mechanism by which this may occur is through loss of adaptive immunity and increase in nonspecific tissue inflammation.[4] Chronic disease such as chronic obstructive pulmonary disease (COPD) may accelerate the aging process. COPD is a progressive respiratory condition characterized by difficulty breathing and airflow limitation. It is currently the third leading cause of death worldwide.[1] The prevalence of COPD exponentially increases with age. While the estimated cumulative prevalence of COPD is 3.1% in people less than 40 years of age and 8.2% in people 40-64 years of age, it is 14.2% in people over 65 years of age.[5]

In 2010, the Global Burden of Disease estimates found that 23.1% of total disease burden was attributable to disorders in people ages 60 years and older, and COPD accounted for

43.3 million disability-adjusted life years in older people.[6] Comorbidities, which are part of the definition of the disease,[7] are a significant contributor to the burden of disease, particularly in older people, since multimorbidity increases with age. Analysis of Medicare data from 2008 found that 67% of people aged 65 years and older had multiple chronic conditions, and the prevalence of multiple comorbid conditions increased with age.[8] Multimorbidity in the elderly leads to increased functional impairment, poor quality of life (QOL), inpatient hospitalizations, and high health-care utilization and costs.[9,10]

Despite the strong associations between COPD, comorbidities, and aging, little is understood about the impact of age in the COPD population. Many studies have investigated physiologic parameters, functional capacity, and QOL in middle-aged COPD patients[11–15]; however, limited data exist detailing COPD patients over the age of 65 years.[16–19] We hypothesized that age is a significant contributor to measures of COPD impact, even after controlling for severity of disease. Using subject-level data from the well-characterized Genetic Epidemiology of COPD study (COPDGene),[20] we examined baseline characteristics of older patients (age ≥65 years) and younger patients (age 45-64 years) with COPD. To further validate our findings, we replicated the analysis using data from another large COPD cohort study, the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study.[21]

Methods

Study Participants

COPDGene cohort—Full details of the COPDGene study design, methods, and inclusion and exclusion criteria are described elsewhere.[20] COPDGene is a multicenter, prospective cohort study of the genetic epidemiology of smoking-related lung disease. Participants were enrolled at 21 clinical centers located in the United States from November 2007 until July 2012. A total of 10,364 patients were enrolled. Participants were recruited by various methods, including screening at primary care or pulmonary office visits and public advertising. Participants were eligible if they were between 45 and 80 years of age and had at least a 10 pack-year history of smoking. In addition, participants had to be able to perform spirometry and could not have been under treatment for an exacerbation in the 30 days before enrollment. In this analysis, we included participants with a postbronchodilator forced expiratory volume in 1 second (FEV_1) ≤80% of predicted and a postbronchodilator FEV_1 to forced vital capacity (FVC) ratio ≤0.7. A total of 3690 participants with global obstructive lung disease (GOLD) grade II–IV COPD were included in this analysis. All participants provided written, informed consent. The research protocol was approved by the institutional review boards at participating centers.

ECLIPSE cohort—Full details of the ECLIPSE study design, methods, and inclusion and exclusion criteria are described elsewhere.[21] ECLIPSE was a 3-year, multicenter, longitudinal prospective study conducted at 46 centers in 12 countries. Participants were eligible if they had a clinical diagnosis of COPD, were between 40 and 75 years of age, and had at least a 10 pack-year smoking history. In addition, they had a postbronchodilator FEV_1 ≤80% of predicted and a postbronchodilator FEV_1 to FVC ratio ≤0.7. A total of 2161

participants with GOLD grade II–IV COPD were included in the analysis. All participants provided written, informed consent. The research protocol was approved by the ethics and review boards of the participating centers.

Study Procedures

In both studies, questionnaires were used to record demographics, medical history, smoking history, and comorbidities. Participants completed assessments of dyspnea using the modified Medical Research Council dyspnea scale and health status using the St. George's Respiratory Questionnaire (SGRQ) in the COPDGene cohort and the SGRQ for COPD patients (SGRQ-C) in the ECLIPSE cohort. The body mass index (BMI), airflow obstruction, dyspnea, and exercise (BODE) index was calculated as previously described.[22]

In the COPDGene study, exacerbations were defined by use of an antibiotic and/or steroid or admission to the hospital for a respiratory "flare-up" on the American Thoracic Society Respiratory Disease questionnaire.[23] Severe exacerbations were defined as those requiring assessment in the emergency department or hospital admission. In the ECLIPSE study, a functional definition of exacerbation was used and was based on the decision by a patient's primary clinician or by study personnel to prescribe antibiotics and/or systemic corticosteroids.[24] A severe exacerbation was defined as one requiring hospitalization.

All participants underwent standardized spirometry before and after the administration of 180 mg of inhaled albuterol and a standardized 6-minute walk test. Chest computerized tomography (CT) was performed at baseline. Percent emphysema and percent gas trapping were determined from chest CT scans by percent low attention areas at Hounsfield unit thresholds of 950 and 856, respectively.[25]

We used an age cut-off of 65 years to stratify participants from both cohorts into 2 strata.

Statistical Analysis

Summary statistics are presented as proportions [with 95% confidence intervals (CI)] or medians [with interquartile ranges (IQR)]. Bivariate associations, Student *t* tests, Mann-Whitney U tests, and χ^2 tests were examined, as appropriate. To adjust for baseline subject characteristics that may have confounded the relationship between subject age and clinical outcomes, multivariable logistic (for severe exacerbation) and linear (for QOL scores, 6-min walk distance, percent emphysema and percent gas trapping) regression modeling was performed. Model variables were selected a priori by investigators or based on the review of medical literature. All odds ratios (ORs) and beta-coefficients are presented with 95% CIs. All analyses were performed using Stata 12.0 software (StataCorp, College Station, TX) and SAS v 9.3 (SAS, Cary, NC). All *P* values are 2-sided, with *P* values of < .05 considered statistically significant.

Results

Baseline Characteristics

Of the 3690 participants with COPD in the COPDGene cohort, 2027 were <65 and 1663 were ≥65 years of age. Participant characteristics by group are summarized in Table 1.

Median age was 58 years in the younger group and 71 years in the older group ($P < .001$). There were more male participants in the older group compared with the younger group (58% vs 53%, $P = .004$). There was no difference in median BMI between the groups. Older participants were less likely to be current smokers (20% vs 58%, $P < .001$) but had smoked a greater median number of pack-years (52 vs 43 pack-years, $P < .001$).

Elderly participants had a longer mean duration of disease (8 vs 5 years, $P < .001$), were more likely to require long-term oxygen therapy (35% vs 22%, $P < .001$), had worse lung function as measured by FEV_1 in liters (1.22 vs 1.52 L, $P < .001$), and had worse exercise tolerance as measured by 6-minute walk distance (355 vs 375 m, $P < .001$). However, GOLD lung function classification, BODE index, and modified Medical Research Council dyspnea score did not differ between the groups. Older participants also had more emphysema (14% vs 8%, $P < .001$) and more gas trapping on CT (47% vs 36%, $P < .001$). Despite worse lung function and more severe disease by CT, older participants had lower total SGRQ scores (37 vs 44, $P < .001$) compared with younger participants, indicating better QOL. These findings are summarized in Table 1.

The ECLIPSE cohort had similar characteristics. Of the 2161 participants with COPD in the ECLIPSE cohort, 1131 were <65 and 1030 were ≥65 years of age. Subject characteristics per group are summarized in Table 1. Median age was 59 years in the younger group and 69 years in the elderly group. There were more males in the elderly group compared with the younger group (70% vs 61%, $P < .001$). There was no difference in median BMI between the groups. Elderly participants had a longer duration of disease (7 vs 6 years, $P < .001$), were more likely to require long-term oxygen therapy (7% vs 5%, $P .02$), had worse lung function as measured by FEV_1 in liters (1.22 vs =1.34 L, $P < .001$), and worse exercise tolerance as measured by 6-minute walk distance (360 vs 389 m, $P < .001$). BODE score did not differ between the groups. Elderly participants had better quality life as measured by lower SGRQ-C scores (47 vs 50, $P = .002$).

Exacerbations

Table 2 shows frequent exacerbations, defined as ≥2 exacerbations in the year prior, did not differ by age group ($P = .57$ for COPDGene, $P = .30$ for ECLIPSE). Severe exacerbations were less common in the older group in the COPDGene cohort (18% in 65-year-old group vs 26% in <65-year-old group, $P < .001$), but trended toward being more common in the ECLIPSE cohort (17% in ≥65-year-old group vs. 14% in <65-year-old group, $P = .052$).

Comorbidities

Older participants had a higher prevalence of comorbidities in both cohorts as shown in Table 3. In the COPDGene cohort, this included coronary artery disease, congestive heart failure, hypertension, diabetes, and gastroesophageal reflux disease. In the ECLIPSE cohort, this included hypertension, congestive heart failure, and diabetes. In both groups, asthma was more common in the younger groups.

Effect of Age on Clinical Variables in Adjusted Analysis

After adjustment for baseline variables (sex, race, BMI, pack-years of smoking, current smoking, FEV_1 in liters, ever physician-diagnosed asthma, diabetes, hypertension, and gastroesophageal reflux disease in both cohorts and coronary artery disease for the COPDGene cohort), when compared with younger participants, the older population in the COPDGene cohort had a significantly decreased risk of severe exacerbation (OR = 0.51, 95% CI 0.43-0.62) as well as a significantly decreased risk of frequent exacerbation (OR = 0.52, 95% CI 0.43-0.64). In the ECLIPSE study, older participants had a significantly decreased risk of frequent exacerbation (OR = 0.79, 95% CI 0.64-0.99), but age did not affect the risk of severe exacerbation (OR = 1.08, 95% CI 0.84-1.39). In both studies, the adjusted analysis demonstrated that older age was associated with a better quality of life, shorter 6-minute walk distance, and less emphysema by CT scan as shown in Table 4. In the COPDGene study, older age was also associated with less gas trapping by CT scan.

Discussion

The purpose of this study was to determine the association of age with COPD disease characteristics and health outcomes from 2 large COPD cohort studies. Our results from both COPDGene and ECLIPSE cohorts demonstrate that older patients with COPD had worse disease as evidenced by lower lung function, and worse exercise tolerance than younger patients. In addition, older patients were more likely to have increased number of common comorbidities compared with younger patients. Frequent and severe exacerbations were more common in younger patients in the COPDGene cohort. Frequent, but not severe, exacerbations were more common in younger patients in the ECLIPSE cohort. Despite worse disease and greater comorbidities, quality of life was significantly better in older patients in both cohorts.

Elderly COPD participants in both the COPDGene and the ECLIPSE cohorts were characterized by a greater proportion of men and fewer active smokers but a greater smoking history. In the United States, the prevalence of COPD diagnosed by spirometry is increasing in women but decreasing in men. Death rates from COPD are also declining in men, but remain unchanged in women.[26] Thus, the lower proportion of women in the older population of people with COPD may be a reflection of the changing epidemiology of COPD in men vs women. Radiographic evidence of emphysema was also greater in the older group compared with the younger group in this study. CT imaging is a validated method for assessing emphysema.[27] Because percent low attenuation area increases with increasing age and number of pack-years smoked and is also higher in ex-smokers,[28] this finding is not surprising. Because progression of emphysema over time is highly variable,[29] it is unclear if the greater percent low attenuation areas in older patients is a result of rapid increase in radiographic emphysema with age or a gradual decline over time. However, the finding of greater radiographic emphysema in older patients parallels the other evidence of more severe disease in this group, including lower lung function, decreased exertional tolerance, and greater need for oxygen. Although age became a negative predictor of CT emphysema and air trapping in the adjusted model, this may be a result of the presence of other strong

predictors or unobserved confounding factors. The rationale behind why this is might be unclear. Thus, further study is needed in longitudinal follow-up.

Acute exacerbations of COPD have a significant impact on the disease and its progression. They are associated with decline in lung function,[30] poorer QOL,[31] and increased risk of death.[32] In this study, frequent exacerbations were more common in younger participants in both the COPDGene and ECLIPSE cohorts. Furthermore, severe exacerbations were more common in older participants in the COPDGene cohort. However, this was not replicated in the ECLIPSE cohort. Although both frequency and severity of exacerbations have been associated with severity of the disease,[24,33] we found that frequent exacerbations occurred 20%-50% less frequently in elderly patients after adjustment for severity of disease including FEV_1. There are several possible explanations for these findings. A prior history of exacerbations is the most reliable predictor of frequent exacerbations, and exacerbation frequency seems to be fairly stable over time.[24] Because of the morbidity and mortality associated with exacerbations, those patients without exacerbations may have been more likely to survive to older age. Older patients may also be more reluctant to seek help when experiencing an exacerbation. Underreporting of exacerbations is common in patients with COPD, with studies showing that 50%-68% of exacerbations are not reported.[31,34,35] Age is 1 factor associated with the likelihood of reporting exacerbation, with older patients less likely to report exacerbations.[35] Physical limitation and emotional response, including fear, are major reasons leading patients to identify exacerbations and contact healthcare professionals.[36] Because older patients may limit their activities or have co-existing cognitive impairment, they may be less likely to recognize an exacerbation and therefore less likely to seek help. Finally, patients with frequent exacerbations may represent a unique phenotype un-related to severity of disease. This phenotype may be related to increased systemic inflammation.[37] The conflicting findings in the 2 cohorts in regard to severe exacerbations may also be related to the differing definitions of severe exacerbations.

We found that elderly patients had significantly better QOL as measured by the SGRQ or SGRQ-C compared with younger patients. This finding persisted even after taking into account objective measures of physiologic impairment, comorbidities, and other potential confounders. These results are consistent with those of a recent study of patients in the Lung Tissue Research Consortium, the majority of which had a diagnosis of COPD. Older patients (age ≥65 years) had significantly lower total SGRQ scores than younger patients (age <65 years), indicating better health status.[38] However, older adults in the Lung Tissue Research Consortium had better lung function as measured by FEV_1, FVC, and diffusing capacity of the lungs for carbon monoxide and similar 6-minute walk distance compared with younger adults, whereas older patients in the current study had worse lung function and decreased exertional tolerance. Similarly, results from the Subpopulations and Intermediate Outcome Measures in COPD Study demonstrated that patients over age 65 years had better quality of life compared with patients age 50-64 years.[39] In addition, dyspnea was more strongly associated with QOL in the middle-aged patients. In assessing QOL in older people, there is not a clear relationship between disability, disease severity, and QOL.[40] QOL depends on other factors such as the type of physical activity, psychological factors, wealth and the strategies employed to manage difficulties.[41] In addition, older people are generally more optimistic and have a more favorable perception of their health than might be expected based

objectively on their functional status.[42] Older people may also have a more positive perception of their health status than younger people[43] because they use different reference points to judge satisfaction. Furthermore, over time, older people may adapt to the aging process and having chronic illnesses.[40,44,45] Older patients with COPD may compensate for functional imitations by maximizing reserves, anticipating problems, and avoiding difficulties. They may also continue to participate in recreational activities by planning ahead and taking rests.[41] In this cross-sectional analysis, advancing age seems to exert a small but significant "protective" effect on quality of life in COPD patients,[19] but its clinical significance is worthy of investigation.

The main strength of this analysis is the use of 2 separate, large cohorts of well characterized of patients with COPD, use of valid outcome measures with generally consistent findings across the 2 cohorts. However, the study has some limitations. Medication use, which is a potential confounder, was not analyzed. Adherence to pharmacologic therapy in patients with COPD is low, with up to 60% of COPD patients being nonadherent.[46] It is possible that older patients may be more likely to be nonadherent because more severely ill patients may experience greater difficulty with inhaler technique and, therefore, may not be using medications correctly[47,48] and presence of mild cognitive impairment.[49] Furthermore, caution is required in interpretation of our findings as our analysis did not include patients without COPD or GOLD grade 1 disease, obstructive sleep apnea, bronchiectasis, and depression, which may have deleterious impact on quality of life. This study was also cross-sectional, uncontrolled and used age of 65 years as a somewhat arbitrary cut-off to define older patients because it is close to retirement age. Thus, longitudinal studies are needed to better understand the natural progression of COPD as people age.

In summary, despite the fact that older patients with COPD have evidence of more severe disease, they report less frequent exacerbations and have a better quality of life. This may result from the fact that older patients change their expectations and learn to adapt to the disease. Because exacerbations and health-related quality of life are common endpoints for clinical trials in COPD, age-related differences in these outcomes should be considered. Further studies are needed to better understand the impact of the disease over time as people age.

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Table 1

Characteristics of Participants With COPD in COPDGene and ECLIPSE Cohorts in Participants ≥65 Years of Age Compared With <65 Years of Age

	COPDGene			ECLIPSE		
	<65 Y n = 2027	**≥65 Y n = 1663**	***P* Value**	**<65 Y n = 1131**	**≥65 Y n = 1030**	***P* Value**
Demographics						
Age, y	58 (53-62)	71 (68-74)	<.001	59 (55-62)	69 (67-72)	<.001
Male, %	53	58	.004	61	70	<.001
African American, %	31	13		2	1	.03
BMI, kg/m^2	27 (23-32)	27 (24-31)	.53	26 (22-30)	26 (23-30)	.46
Smoking history						
Current smoking, %	58	20	<.001	44	27	<.001
Pack-y smoked	43 (33-61)	52 (39-75)	<.001	42 (30-56)	46 (32-60) *	<.001
Disease Characteristics						
Duration of COPD, years GOLD stage, %	5 (3-10)	8 (4-14)	<.001	6 (4-11)	7 (4-13)	<.001
II	55	48		44	44	
III	29	35		41	43	
IV	16	17	.59	15	12	.15
BODE index	3 (1-4)	3 (1-5)	.14	3 (2-4)	3 (2-5)	.10
Oxygen use, %	22	35	<.001	5	7	.02
FEV_1, L	1.52 (1.05-2.03)	1.22 (0.87-1.66)	<.001	1.34 (0.98-1.75)	1.22 (0.92-1.57)	<.001
FEV_1, % predicted	54 (37-68)	49 (35-63)	<.001	47 (35-61)	47 (37-61)	.25
6MWD, m	375 (296-454)	355 (270-426)	<.001	389 (307-463)	360 (280-420)	<.001
mMRC dyspnea score	2 (1-3)	2 (1-3)	.11	2 (1-2)	2 (1-2)	.03
SGRQ total score *	44 (25-61)	37 (23-53)	<.001	50 (36-64)	47 (34-61)	.002
Emphysema by CT, %	8 (3-23)	14 (5-24)	<.001	14 (7-25)	17 (9-26)	<.001
Gas trapping by CT, %	36 (20-57)	47 (31-60)	<.001	NC	NC	

6MWD, 6-minute walk distance; mMRC, modified Medical Research Council; NC, not collected.

Data expressed as median (interquartile range).

* COPDGene study used the SGRQ. ECLIPSE study used the SGRQ-C questionnaire to calculate SGRQ total score.

Table 2

Comparison of Exacerbation History in Prior Year in the COPDGene and ECLIPSE Cohorts in Participants ≥65 Years of Age and <65 Years of Age

Exacerbations in Prior Year	COPDGene			ECLIPSE		
	<65 Y n = 1962	≥65 Y n = 2522	*P* Value	<65 Y n = 1131	≥65 Y n = 1030	*P* Value
0	60	62		53	53	
1	20	22		24	27	
≥2	20	16	.57*	23	20	.30*
Severe	26	18	<.001	14	17	.052

*Overall χ^2 analysis for number of exacerbations between age groups (0,1, ≥2).

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Table 3

Comparison of Comorbidities in the COPDGene and ECLIPSE Cohorts in Participants ≥65 Years of Age Compared With <65 Years of Age

	COPDGene			ECLIPSE		
	<65 Y n = 1962	**≥65 Y n = 2522**	***P* Value**	**<65 Y n = 1131**	**≥65 Y n = 1030**	***P* Value**
Hypertension, %	45	58	<.001	37	44	<.001
Coronary artery disease, %	5	14	<.001			
Congestive heart failure, %	5	6	.04	5	8	.002
Diabetes, %	11	15	<.001	9	12	.01
GERD, %	29	32	.04	25	27	.33
Asthma, %	28	20	<.001	25	20	.005

GERD, gastroesophageal reflux disease.

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Table 4

Multivariable Associations Between Age Group and Clinical Outcomes in Participants With COPD

	COPDGene				ECLIPSE			
	OR	**β**	**95% CI**	***P* Value**	**OR**	**β**	**95% CI**	***P* Value**
Severe exacerbation	0.51		0.43, 0.62	<.001	1.08		0.84, 1.39	.53
Frequent Exacerbation (>2)	0.52		0.43, 0.64	<.001	0.79		0.64, 0.99	.04
SGRQ score		−8.7	−10.0, −7.4	<.001		−4.4	−6.1, −3.2	<.001
6-minute walk distance		−16	−48, 16	.32		−17	−27, −7	<.001
% emphysema on CT		−2.7	−3.6, −1.8	<.001		−1.6	−2.6, −0.7	.001
% gas trapping on CT		−2.2	−3.4, −0.9	.001				

Age <65 years was the referent group.

Analyses were adjusted for sex, race, BMI, pack-years of smoking, current smoking, FEV_1 in liters, ever physician-diagnosed asthma, coronary artery disease, diabetes, hypertension, and GERD in the COPDGene cohort. The same adjustments were made for the ECLIPSE study, except coronary artery disease was not included.