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Characterization Of Age-Associated Copd Progression In The Copd Gene Cohort

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CHARACTERIZATION OF AGE-ASSOCIATED COPD PROGRESSION IN THE COPD GENE COHORT

by

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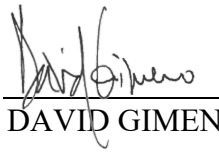

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CHARACTERIZATION OF AGE-ASSOCIATED COPD PROGRESSION IN THE COPD GENE COHORT

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Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating lung disease affecting primarily older adults. Incidence, morbidity and mortality from COPD are increasing worldwide. The purpose of this study was to determine the associations between age at baseline and markers of disease progression in COPD patients using data generated by the Genetic Epidemiology of COPD (COPD Gene) study. Participants with COPD were stratified by age (younger: age <65 years, elderly: age ≥ 65 years) and disease characteristics (lung function, exercise tolerance, exacerbation history, and comorbidity burden) at baseline and five-year follow up were compared between groups. Associations between age group and changes in these measures were also assessed. Disease characteristics differed significantly between elderly and younger COPD patients at both study visits. Elderly COPD patients had worse lung function and more comorbidities than younger COPD patients, while younger COPD patients reported more dyspnea and more frequent and severe exacerbations than elderly COPD patients. Following covariate adjustment, elderly participants were less likely than younger participants to develop new frequent exacerbations over the study period (relative risk ratio (95% confidence interval): 0.42 (0.20, 0.87)). There were no other

significant associations between age group and markers of disease progression. These results suggest that although elderly COPD patients exhibit evidence of more severe lung function impairment than younger COPD patients, the rate of disease progression is similar between elderly and younger patients. However, further exploration is needed to understand the possible contribution of survivorship bias to this finding. Nevertheless, this study supports the importance of early detection and early intervention to slow disease progression and maximize both life expectancy and quality of life for COPD patients.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating lung disease characterized by obstructive airflow patterns and abnormal inflammatory response to noxious stimuli.[1] The risk for developing COPD is believed to emerge from complex interactions between a susceptible genome and exposure to environmental and/or lifestyle factors. By far the greatest risk factor for COPD is smoking; however, only about 20% of smokers will develop COPD.[2] In addition, 15-20% of COPD cases have been attributed to workplace exposures.[2] Exposure to air pollution, including industrial emissions and biomass burning, childhood infections, and malnutrition are also emerging as important risk factors for COPD.[2,3] The debilitating effects of COPD arise as a result of the increasing lung function impairment that accompanies disease progression, resulting in the hallmark symptoms of COPD: dyspnea, cough, and increased sputum production.[4] These symptoms are important drivers of the overall burden of COPD and are associated with significant reductions in quality of life, including disruption of daily activities, increased anxiety and depression levels, sleep disturbances, and increased risk of exacerbations.[4] COPD exacerbations are acute periods of increased symptom severity from a patient's normal state that often result in increased medication use, emergency room visits and hospitalizations.[5] Frequency of exacerbations is an important determinant of health-related quality of life in COPD patients and is also linked to the rate of lung function decline, morbidities, and mortality risk.[5] In addition to exacerbations, COPD is also linked with increased risk for

several comorbid diseases that compound the morbidity, resource use, and mortality risk associated with COPD. These include lung cancer, cardiovascular diseases (coronary heart disease, heart failure, arrhythmias, peripheral artery disease, and hypertension), diabetes mellitus, osteoporosis, and gastroesophageal reflux disease (GERD).[6–9]

Pathology

Several distinct disease processes contribute to airflow limitation in COPD including small airway disease, emphysema, and chronic obstructive asthma.[9] The relative contribution of each process to the disease phenotype varies between individuals, creating a spectrum of COPD manifestations. Small airway disease is a disease process affecting the bronchi and bronchioles and consists of two main components, first: acute inflammation and mucus plugging of the small airways, and second: fibrosis, narrowing, and destruction of the small airways.[10] The first process is at least partially reversible, whereas the second is irreversible.[10] Emphysema is a pathological term describing a gradual process of destruction of the lung parenchyma, including the alveoli.[11] This process is irreversible and eventually results in hyperinflation, loss of elastic recoil, loss of surface area for gas exchange, and airflow limitation.[11] There are two predominant phenotypes of emphysema: centrilobular and panlobular. Centrilobular emphysema affects predominantly the upper lobes of the lung and the apices of the upper and lower lobes.[12] In contrast, panlobular emphysema is spread diffusely throughout the lung and is frequently associated with Alpha-1 antitrypsin deficiency.[12] Finally, asthma is a disorder of the airways characterized by chronic inflammation and hyper-responsiveness that contribute to recurrent episodes of wheezing,

breathlessness, coughing, and tightness of the chest.[13] Asthma patients whose airflow obstruction is not completely reversible are also considered to have COPD, though the etiology of their disease is likely to be distinct from individuals with COPD related to small airway disease and/or emphysema.[13]

Disease Classification and Assessment of Lung Function

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) was initiated by the National Heart, Lung and Blood Institute (NLHBI) and the World Health Organization (WHO) in 1998 to generate and communicate consensus recommendations for the management of COPD. [9] These recommendations are published as the *Global Strategy for Diagnosis, Management and Prevention of COPD*, also called the GOLD report. The evidence-based recommendations laid out in the GOLD report include the GOLD spirometry grades for severity of airflow limitation. Spirometry is a technique for assessing lung function via measurements of the volume and/or speed of air that can be inhaled and exhaled. The two most important spirometry measurements in COPD are the forced expiratory volume in one second (FEV1) and the forced vital capacity (FVC).[9] Despite the utility of spirometry measurements for diagnosing and quantifying airflow limitation in COPD patients, these measurements do not correlate well with patient functional status, quality of life, or mortality.[14] Therefore, several additional assessments are commonly used in evaluating COPD patients. These assessments include the Modified Medical Research Council Dyspnea Scale (MMRC) for evaluation of dyspnea and the six-minute walk test for assessment of functional status in COPD patients.[14] The six-minute walk test has been shown to associate

well with quality of life, lung function, and mortality risk, with shorter distances being associated with worse outcomes.[15,16] One final assessment technique used with COPD patients that is of particular interest to researchers is the use of computed tomography (CT) scans to visualize and quantify gas trapping and emphysema.[17,18] Research in this field has led to increased understanding of the heterogeneity that characterizes the patterns of lung damage seen in COPD patients and has allowed identification of specific subgroups of patients that may be more or less likely to benefit from therapeutic trials.

Aging and COPD

COPD is primarily a disease of the elderly (age ≥ 60-65 years) and both incidence and prevalence increase with age.[2,19,20] In particular, the incidence of COPD has been estimated to increase almost ten-fold with aging, increasing from 0.78 cases per 1000 person-years at age 40-44 years to 6.82 cases per 1000 person-years at age 75-79 years.[21] Similarly, the prevalence of COPD is about 3% among individuals less than 40 years of age and increases to about 8% in individuals between 40 and 64 years of age. In individuals greater than 65 years of age, COPD prevalence further increases to 14-20%.[2,19] The observation that incidence (and prevalence) of COPD increases with age suggests a role for the aging process in COPD pathogenesis.[1,3] Aging is a biological process involving a gradual reduction in homeostasis and increasing risk of disease and death.[22] In the lung, aging is accompanied by structural and physiological changes that share features with the pathological changes seen in COPD, including emphysematous changes, fibrosis, and chronic inflammation.[22]

Significant dysregulation of the immune system and tissue repair processes are also believed to be key features in the pathology of both aging and COPD.[1,22] Changes in tissue repair processes known to occur with aging, including increases in markers of cellular senescence, imbalances of extracellular matrix proteins and gene expression, mitochondrial dysfunction, telomere shortening, and stem cell exhaustion have been observed in COPD lungs and experimental models of COPD.[20,22,23] Immunosenescence is the term used to describe the characteristic changes in the immune system observed with aging.[1] Over time, the ability of the immune system to respond adaptively to antigens diminishes.[1] To compensate for the loss of adaptive immunity, the innate immune system becomes chronically activated, resulting in a persistently pro-inflammatory state.[1,23] Similar changes are also observed in individuals with COPD; in particular, an impaired ability to suppress pro-inflammatory immune responses.[22–24] Both aging and COPD are also associated with accumulation of senescent cells, which exhibit a senescence-associated secretory phenotype (SASP) characterized by secretion of proinflammatory cytokines, chemokines, and matrix metalloproteinases.[23] This combination of cellular mediators results in both autocrine effects and paracrine effects that serve to amplify and spread senescence to surrounding cells.[23] Interactions between the SASP and a dysfunctional immune system result in inflammaging, accelerated aging and development of age-associated diseases, such as COPD.[23]

Despite evidence of anatomical and molecular similarities between the aging lung and the lung affected by COPD, as well as associations between aging and COPD development, relatively little is understood about whether or how COPD progression, in particular lung

function decline, exacerbations, and comorbidity burden, differs between age groups. Previous research in two separate cohorts of COPD patients (the Genetic Epidemiology of COPD or COPDGene study and the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints or ECLIPSE study) has demonstrated differences in disease characteristics between older (age ≥65 years old) and younger (age <65 years old) individuals with COPD.[4,6,13] Older individuals tended to experience worse lung function as indicated by lower FEV1 (COPDGene: 30% lower, $p<0.001$; ECLIPSE: 12% lower, $p<0.001$). Older COPD patients also had a greater percentage of emphysema (COPDGene: 6% greater, $p<0.001$; ECLIPSE: 3% greater, $p<0.001$) and gas trapping (COPDGene: 11% greater, $p<0.001$) on computed tomography scans.[4] Finally, elderly individuals with COPD also tended to have a greater number of comorbidities, including hypertension, coronary artery disease, congestive heart failure, diabetes, and gastroesophageal reflux disease compared to younger individuals.[4] However, these results are cross-sectional, and therefore do not provide information on disease progression. To understand the effects of aging on COPD progression, examination of longitudinal data is needed to determine the differences in disease progression between elderly and younger COPD patients.

Innovation

To date, the literature provides relatively little information on how progression of COPD differs between older and younger COPD patients. This information is important, as it will allow clinicians to tailor treatment strategies to the potentially unique demands of elderly versus younger patients. Research has demonstrated the importance of effective disease

management for reducing exacerbations and improving quality of life for COPD patients.[25] This study will utilize data generated by the Genetic Epidemiology of COPD (COPDGene) study.[26] The COPDGene study was undertaken to identify genetic factors associated with COPD, to describe disease phenotype subgroups, and to assess the relationships between genetic factors and disease phenotypes.[26] This dataset includes baseline and five-year follow up data on current and former smokers (at least 10 pack-year history of smoking) with and without COPD. The data collected includes demographics, self-reported symptom scoring, pre- and post- bronchodilator spirometry, and computed tomography scans. This longitudinal data will allow for the assessment of disease progression from year 1 to year 5 and the exploration of the effects of age on this progression.

Public Health Significance

The importance of COPD as a major public health issue is becoming increasingly apparent as morbidity and mortality from COPD continue to increase worldwide.[27] In the last 30 years, mortality from COPD has increased by approximately 163% and COPD is now the third leading cause of death worldwide.[2,27] However, it is widely accepted that COPD is significantly under-diagnosed, both in the early stages of disease and in advanced stages; thus the true burden of disease is likely to be much higher.[3,27] COPD is also one of the few chronic diseases for which mortality is increasing.[21] Currently, the global annual death rate attributed to COPD is estimated to be about three million people.[9] Over the next 40 years, this number is expected to increase to over five million COPD-related deaths a year.[9]

In the United States alone, an estimated 12-24 million people are living with COPD, many of whom are undiagnosed.[25] In addition to considerable reductions in quality of life, COPD imposes a significant economic burden on society, costing approximately $4000 per patient per year in the US.[25] In 2010, this amounted to just over $50 billion: $32 billion in direct, health-care related costs, and $20.4 billion in indirect costs related to the disabling effects of COPD including lost wages of patients and their family caregivers, sick-leave, and impaired work performance.[25,28] An estimated 45%-75% of the direct costs of COPD are attributed to physician and emergency room visits, hospitalizations, and increased medication use due to COPD exacerbations.[28] GOLD stage, number of comorbidities, and level of dyspnea have also been identified as significant drivers of health care-related costs of COPD.[29,30]

As a result of its chronicity, individuals with COPD often suffer its effects for many years before dying prematurely due to disease complications. This results in significant loss of productivity and life-years. The Global Burden of Disease Study estimates that chronic respiratory diseases account for about 4.5% of global disability-adjusted life years (DALYs), with COPD responsible for approximately 3.24% of global DALYs.[31] COPD also accounts for approximately 3.64% of global years lived with disability and 3.1% of global years of life lost.[31]

The results of this study are expected contribute to an improved understanding of disease progression in COPD. Ultimately, these results are expected to have a positive impact by

reducing the burden of COPD through contributing to efforts to improve the quality of life experienced by individuals with COPD.

Hypothesis and Specific Aims

The long-term goal of this research is to contribute to the understanding of COPD disease pathogenesis and improve the quality of life for COPD affected individuals. The immediate objective of the proposed research is to characterize the patterns of disease progression (lung function decline, exacerbation history, and comorbidity status) in elderly (age greater than 65 years) compared to younger (age between 45 and 64 years) COPD patients and to assess the associations between age and changes in lung function and exacerbation history among COPD patients.

The specific aim of this study was to determine the associations between age at baseline and markers of disease progression (lung function decline, exacerbation history, and comorbidity status) at follow up in COPD patients. The hypothesis for this aim was that elderly (older than 65 years at baseline) COPD patients would exhibit accelerated patterns of disease progression when compared to younger (age between 45 and 64 years at baseline) COPD patients.

METHODS

Study Design

This study utilized data collected as part of the COPDGene study (www.copdgene.org), a multicenter observational study of 10,198 non-Hispanic white and African-American individuals aged 45-80 years old with at least a 10 pack-year history of smoking with (n=3,695) or without COPD (n=6437).[26] Participants were initially enrolled between November 2007 and July 2012, at which time baseline data was collected. Participants then returned for a follow up visit (n=6,284) approximately five years after the initial visit and data collection was repeated to allow assessment of disease progression.[26]

Study Sample

Participants included in this analysis were those with COPD (diagnosed via spirometry as described below) classified as GOLD Stage 2 – GOLD stage 4 (defined as described below). Participants also must have had data available for both visit 1 and visit 2. Of the 10,198 participants in the full cohort, 3,695 had COPD and 1,566 of these individuals had data for both visits. Of these, 899 were less than 65 years of age and 667 were aged 65 or older. Baseline characteristics of participants with COPD that were subsequently lost to follow up compared to individuals with COPD who completed the study are summarized in Table 1. Individuals lost to follow up were similar to study completers with respect to demographics and smoking history. Although non-completers were significantly older on average than individuals who completed the study (mean ± SD: 63.6 ± 8.8 vs 62.9 ± 8.1 years, p=0.02, respectively, Table 1), the actual magnitude of this difference was quite small.

Similarly, individuals lost to follow up had greater pack year histories of smoking compared to study completers (mean ± SD: 54.0 ± 29.3 vs 51.5 ± 24.8 pack years, $p<0.001$, respectively, Table 1), but again, the magnitude of the difference was small. Across disease characteristics examined, non-completers had significantly worse values compared to study completers (longer duration of disease, lower FEV1 and FEV1 % of predicted, shorter 6-minute walk distance, greater percent of emphysema and percent of gas trapping on CT scans, greater proportions of individuals with higher GOLD and MMRC scores, greater proportions of individuals with frequent and severe exacerbations, and lower BMI; Table 1). Finally, completers and non-completers had similar frequencies of CAD, Diabetes, and Asthma, but non-completers had greater frequencies of hypertension, CHF, and GERD (Table 1).

Table 1. Demographic and disease characteristics of study completers vs those lost to follow up.

	Completers (N = 1566)	Lost to follow up (N = 2129)	p-value*
Demographics			
Age (years)	62.9 (8.1)	63.6 (8.8)	.02
Gender (male)	860 (54.9%)	1193 (56.0%)	0.50
Race (non-Hispanic white)	1219 (77.8%)	1636 (76.8%)	0.47
Smoking History			
ATS Pack Years	51.5 (24.8)	54.0 (29.3)	<0.001
Smoking Status (current smoker)	649 (41.4%)	855 (40.2%)	0.43
Disease Characteristics			
Duration of COPD (years)	7.1 (7.1)	9.9 (9.1)	0.005
FEV1 (L)	1.53 (0.58)	1.38 (0.66)	<0.001
FEV1 (%predicted)	53.1 (15.5)	48.2 (19.4)	<0.001
6 Minute Walk Distance (meters)	386.6 (109.2)	336.0 (124.9)	<0.001
% Emphysema on CT	12.3 (11.4)	14.2 (13.9)	<0.001
% Gas Trapping on CT	37.6 (18.4)	39.4 (21.9)	0.02
Final GOLD Score			<0.001
2	898 (57.3%)	1027 (48.2%)	
3	544 (34.7%)	620 (29.1%)	
4	124 (8.0%)	482 (22.6%)	
MMRC Score			0.001
0	366 (23.5%)	385 (18.1%)	
1	244 (15.7%)	237 (11.2%)	
2	321 (20.6%)	337 (15.9%)	
3	433 (27.8%)	651 (30.7%)	
4	195 (12.5%)	513 (24.2%)	
Frequent Exacerbations (yes)	227 (14.5%)	442 (20.8%)	<0.001
Severe Exacerbations (yes)	288 (18.4%)	550 (25.8%)	<0.001
BMI	28.4 (6.1)	27.8 (6.4)	0.003
Comorbidity Status			
Hypertension (yes)	758 (48.4%)	1114 (52.3%)	0.02
CAD (yes)	148 (9.5%)	194 (9.1%)	0.73
CHF (yes)	61 (3.9%)	137 (6.4%)	0.001
Diabetes (yes)	192 (12.3%)	291 (13.7%)	0.21

GERD (yes)	504 (32.2%)	612 (28.7%)	0.02
Asthma (yes)	432 (31.0%)	566 (29.6%)	0.51

*, p-value based on independent samples T-test (continuous data) or Chi-squared test (categorical data). ATS: American Thoracic Society, FEV1: forced expiratory volume in 1 second, CT: computerized tomography scan, GOLD: Global Initiative for Obstructive Lung Disease, MMRC: Modified Medical Research Council Scale for dyspnea, BMI: body mass index, CAD: coronary artery disease, CHF: congestive heart failure, GERD: gastroesophageal reflux disease.

Ethical Considerations

As part of the original COPDGene study, written informed consent was obtained from all study participants at the time of enrollment. All study procedures were approved by the institutional review boards at the participating study centers. The current research was approved by the Office of the Institutional Review Board at The University of Texas Health Science Center at San Antonio (UT Health San Antonio) and the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston (UTHealth).

Measurements

To determine the associations between age at baseline and markers of disease progression (lung function decline, exacerbation history, and comorbidity status) at follow up in COPD patients, several measures of disease progression between baseline and five-year follow up were compared between elderly versus younger COPD patients. All model variables were chosen a priori by the investigators and based on review of the literature.

Measures of disease progression

As part of the original study, spirometry measurements were performed according to American Thoracic Society Guidelines[26,32]. Spirometry measurements were performed pre and post bronchodilator administration to assess the reversibility of any present airflow limitation. Airflow limitation indicative of COPD was defined according to GOLD guidelines as a postbronchodilator FEV1/FVC ratio of less than 0.7.[33] The severity of airflow

limitation was determined by the FEV1 percent predicted value (FEV1 % predicted, calculated based on NHANES reference equations[34]). The GOLD grading scale was then used to assign severity grades, from least to most severe, as follows: FEV1 % predicted ≥ 80 = GOLD 1, 50 ≤ FEV1 % predicted < 80 = GOLD 2, 30 ≤ FEV1 % predicted < 50 = GOLD 3, and FEV1 % predicted < 30 = GOLD 4.[33]

To analyze the extent of emphysema and gas trapping on lung CT scans, the density mask technique was used. The density mask technique is based on the differences in CT attenuation between normal lung tissue, emphysematous tissue, and areas of non-emphysematous gas trapping.[17,18,26] CT scans were obtained during full inspiration and full expiration and the percent of low attenuation areas was calculated. For quantification of emphysema, a Hounsfield unit (HU) threshold of -950 HU on inspiratory CT was used. For quantification of gas trapping a HU threshold of -856 HU on expiratory CT was used.[12,17,18,26] Eight measures of disease progression in COPD were included in the analysis: FEV1 (clinically measured as previously described), GOLD score (assigned as previously described), presence of severe exacerbations (self-reported yes or no to being hospitalized for an exacerbation in the previous year), frequency of exacerbations in the previous year (self-reported frequency of exacerbations in the last year, categorized into: 0: 1 or fewer exacerbations in the previous year or 1: ≥2 exacerbations in the previous year), Modified Medical Research Council Dyspnea Scale (MMRC) score, 6-minute walk distance (clinically measured according to the American Thoracic Society official guidelines [35]), percent of emphysema on CT scan (clinically measured as previously described), and percent of gas

trapping on CT scan (clinically measured as previously described). The change in these measures was calculated as the difference from visit 1 to visit 2 (change = visit 2 – visit 1). The changes in MMRC Dyspnea score and GOLD score were further classified as follows: negative change (visit 1 > visit 2) = improved, zero change (visit 1 = visit 2) = stable, and positive change (visit 1 < visit 2) = declined.

Covariates

The following covariates were also examined: gender (male or female), race (non-Hispanic white, black/African American), body mass index (BMI, clinically measured), American Thoracic Society pack-years of smoking (ATS pack-years, calculated based on self-reported smoking history), smoking status (self-reported as: currently smoking, or not currently smoking), duration of COPD (calculated based on self-reported age at physician diagnosed COPD), and comorbidity status (self-reported yes or no for physician diagnosis of: hypertension, coronary artery disease (CAD), congestive heart failure (CHF), diabetes, gastroesophageal reflux disease (GERD), and self-reported asthma status (yes or no to question: “have you ever had asthma?”)). The change in ATS pack-years, smoking status, duration of COPD, and comorbidity status were also calculated as previously described. The change in comorbidity status was then further classified as follows: negative change (visit 1 > visit 2) = resolved, zero change (visit 1 = visit 2) = stable, and positive change (visit 1 < visit 2) = new diagnosis.

Statistical Analyses

Descriptive statistics (frequency and percentage, or mean and standard deviation, as appropriate) were used to summarize the distribution of each variable in the study sample stratified by age (age between 45 and 65 versus age 65 or greater), at each visit. Age groups were compared at each visit using independent samples T-test for continuous data or Chi-squared test for categorical data. Paired samples analyses (paired samples T-test for continuous data or Stuart-Maxwell test for categorical data) were then used to summarize the unadjusted change from visit 1 to visit 2 in each variable for each age group. To examine the relationship between age group and disease progression, the change in each measure of disease progression was regressed against age group using multinomial logistic (for categorical variables) and multivariable linear (for continuous variables) regression analysis techniques. Each model was adjusted for age at baseline and for the baseline values of the previously described covariates. Variables not different between age groups at baseline or follow up were excluded from the final models (BMI, CHF, diabetes, and GERD). For the multinomial logistic regression models, the independence of irrelevant alternatives assumption was assessed using the seemingly unrelated estimation (suest)-based Hausman test. For the linear regression models, the normalcy of residuals assumption was assessed using a normal quantile-quantile plot of the residuals, homoskedasticity of the residuals was assessed by plotting the studentized residuals against the predicted values of Y, absence of multicollinearity of the predictors was assessed using the variance inflation factor with a cut-off value of 5, and influential observations were assessed using Cook's distance with a cut-off value of 1. All analyses were performed using Stata version 16[36].

Study Power

Based on the results of Parulekar et al [4], given a median difference in FEV1 of 0.3 L between elderly and younger COPD patients, an estimated un-pooled standard deviation of 0.88, a sample size of 1566 with an alpha of 0.05 provided a power of 1.0 to detect a difference in FEV1 between elderly and younger COPD patients.

RESULTS

Demographic and disease characteristics by age group

The demographic and disease characteristics of participants less than 65 years of age at baseline compared to participants 65 years of age or older at baseline (visit 1) and at 5-year follow up (visit 2) are summarized in Table 2.

At baseline, the average age of participants in the age less than 65 years group (younger) was 57.2 years (SD: 5.1 years) and the average age of participants in the age 65 years or greater (elderly) group was 70.7 years (SD: 3.9 years) ($p<0.001$, Table 2). The elderly group contained a greater proportion of males and non-Hispanic whites compared to the younger group (% males: 59.4% vs 51.6%, $p=0.002$; and % non-Hispanic white: 88.6% vs 69.9%, $p<0.001$, respectively, Table 2). Elderly COPD patients had a greater pack year history of smoking compared to younger COPD patients (mean ± SD: 56.1 ± 27.0 vs 48.1 ± 22.6, respectively, $p<0.001$, Table 2), but were less likely than younger COPD patients to be current smokers (20.7% vs 56.8%, respectively, $p<0.001$, Table 2). Elderly COPD patients had greater duration of COPD compared to younger COPD patients (mean ± SD: 9.9 ± 9.1 vs 7.1 ± 7.1 years, respectively, $p<0.001$, Table 2).

Elderly COPD patients tended to have worse lung function metrics compared to younger COPD patients, however this trend did not hold for all lung function measures studied. Elderly COPD patients had significantly lower FEV1 compared to younger COPD

patients (mean ± SD: 1.42 ± 0.52 L vs 1.62 ± 0.61 L, respectively, p<0.001, Table 2), but had similar FEV1 % of predicted (mean ± SD: 52.5 ± 15.0 vs 53.5 ± 15.8, elderly vs younger, p=0.18) and six minute walk distance (mean ± SD: 386.2 ± 103.6 m vs 386.9 ± 113.2 m, elderly vs younger, p=0.9) compared to younger COPD patients. Similarly, elderly COPD patients had greater percentage of emphysema (mean ± SD: 14.1 ± 11.1 % vs 10.8 ± 11.4 %, elderly vs younger, p<0.001) and gas trapping (mean ± SD: 41.61 ± 17.4 % vs 34.45 ± 18.6 %, elderly vs younger, p<0.001) on CT scan compared to younger patients, but had similar GOLD scores (score 2: 55.8% vs 58.5%, score 3: 36.4% vs 33.5%, score 4: 7.8% vs 8.0%, elderly vs younger, respectively, p=0.477) to younger COPD patients. In contrast, elderly COPD patients had a smaller proportion of individuals with high (3 or 4) MMRC scores (score 3: 25.9% vs 29.2%, score 4: 9.2% vs 15.0%, p<0.001, elderly vs younger, respectively p=0.001), and were less likely to experience frequent and/ or severe exacerbations (frequent exacerbations: 12.0 % vs 16.4%, elderly vs younger, p=0.02; severe exacerbations: 13.6% vs 21.9%, elderly vs younger, p<0.001) compared to younger COPD patients. Finally, elderly and younger COPD patients had similar BMIs (mean ± SD: 28.4 ± 5.5 vs 28.4 ± 6.5, elderly vs younger, p=0.72).

With respect to comorbidities, greater proportions of elderly COPD patients had hypertension (56.1% vs 42.8%, elderly vs younger, p<0.001) and CAD (14.5% vs 4.2%, elderly vs younger, p<0.001), but fewer elderly participants had asthma (25.7% vs 34.9%, elderly vs younger, p<0.001) compared to younger COPD patients. The proportions of patients with CHF (3.4% vs 4.2%, elderly vs younger, p=0.43), diabetes (13.8% vs 11.1%,

elderly vs younger, p=0.11), and GERD (33.6% vs 31.2%, elderly vs younger, p=0.31) were similar between elderly and younger COPD patients.

At five-year follow up, similar differences between the age groups were observed for demographic variables, smoking history, and comorbidity status (Table 2). Differences between age groups in disease characteristics, including duration of COPD, FEV1, % emphysema, % gas trapping, MMRC score, exacerbation history, and BMI were also similar at five-year follow up to the differences between age groups seen at baseline (Table 2). In contrast, FEV1 % predicted was higher in elderly participants compared to younger participants at visit 2 (mean ± SD: 49.6 ± 15.9 vs 47.6 ± 16.7, elderly vs younger, p=0.02), whereas FEV1 % predicted had been similar between groups at baseline. Similarly, whereas six-minute walk distance was similar between age groups at baseline, by visit 2, six-minute walk distance was lower in elderly participants compared to younger participants (mean ± SD: 319.0 ± 130.2 m vs 334.3 ± 132.4 m, elderly vs younger, p=0.03). Finally, at visit 2, elderly participants had slightly better GOLD scores compared to younger participants (score 2: 49.2% vs 47.7%, score 3: 38.5% vs 34.1%, score 4: 12.3% vs 18.1%, elderly vs younger, respectively, p=0.005), whereas GOLD scores had been similar between age groups at baseline.

Table 2. Demographic and disease characteristics of each age group at baseline and follow-up.

	Visit 1			Visit 2		
	less than 65	65 or older		less than 65	65 or older	
	(N = 899)	(N = 667)	p-value*	(N = 899)	(N = 667)	p-value*
Demographics						
Age (years)	57.2 (5.1)	70.7 (3.9)	<0.001	62.7 (5.1)	76.1 (4.0)	<0.001
Gender (male)	464 (51.6%)	396 (59.4%)	0.002	464 (51.6%)	396 (59.4%)	0.002
Race (non-Hispanic white)	628 (69.9%)	591 (88.6%)	<0.001	628 (69.9%)	591 (88.6%)	<0.001
Smoking History						
ATS Pack Years	48.1 (22.6)	56.1 (27.0)	<0.001	50.0 (23.2)	56.8 (27.4)	<0.001
Smoking Status (current smoker)	511 (56.8%)	138 (20.7%)	<0.001	378 (42.0%)	89 (13.3%)	<0.001
Disease Characteristics						
Duration of COPD (years)	7.1 (7.1)	9.9 (9.1)	<0.001	12.6 (7.2)	15.3 (9.1)	<0.001
FEV1 (L)	1.62 (0.61)	1.42 (0.52)	<0.001	1.35 (0.57)	1.23 (0.49)	<0.001
FEV1 (%predicted)	53.5 (15.8)	52.5 (15.0)	0.18	47.6 (16.7)	49.6 (15.9)	0.018
6 Minute Walk Distance (meters)	386.9 (113.2)	386.2 (103.6)	0.90	334.3 (132.4)	319.0 (130.2)	0.026
% Emphysema on CT	10.8 (11.4)	14.1 (11.1)	<0.001	13.0 (13.1)	15.2 (12.6)	0.002
% Gas Trapping on CT	34.45 (18.6)	41.61 (17.4)	<0.001	39.4 (20.2)	43.5 (18.9)	<0.001
Final GOLD Score			0.477			0.005
2	526 (58.5%)	372 (55.8%)		429 (47.7%)	328 (49.2%)	
3	301 (33.5%)	243 (36.4%)		307 (34.1%)	257 (38.5%)	
4	72 (8.0%)	52 (7.8%)		163 (18.1%)	82 (12.3%)	
MMRC Score			0.001			<0.001
0	197 (22.0%)	169 (25.4%)		176 (19.6%)	135 (20.2%)	
1	122 (13.6%)	122 (18.3%)		101 (11.2%)	113 (16.9%)	
2	180 (20.1%)	141 (21.2%)		170 (18.9%)	109 (16.3%)	
3	261 (29.2%)	172 (25.9%)		283 (31.4%)	229 (34.3%)	
4	134 (15.0%)	61 (9.2%)		169 (18.8%)	81 (12.1%)	
Frequent Exacerbations (yes)	147 (16.4%)	80 (12.0%)	0.02	174 (19.4%)	80 (12.0%)	<0.001

Severe Exacerbations (yes)	197 (21.9%)	91 (13.6%)	<0.001	200 (22.2%)	112 (16.8%)	0.008
BMI	28.5 (6.5)	28.4 (5.5)	0.721	28.2 (6.9)	27.9 (5.9)	0.28
Comorbidity Status						
Hypertension (yes)	384 (42.8%)	374 (56.1%)	<0.001	471 (52.4%)	417 (62.5%)	<0.001
CAD (yes)	51 (5.7%)	97 (14.5%)	<0.001	74 (8.2%)	115 (17.2%)	<0.001
CHF (yes)	38 (4.2%)	23 (3.4%)	0.431	54 (6.0%)	47 (7.0%)	0.41
Diabetes (yes)	100 (11.1%)	92 (13.8%)	0.111	154 (17.1%)	119 (17.8%)	0.71
GERD (yes)	280 (31.2%)	224 (33.6%)	0.314	323 (35.9%)	234 (35.1%)	0.73
Asthma (yes)	279 (34.9%)	153 (25.7%)	<0.001	279 (34.9%)	153 (25.7%)	<0.001

*, p-value based on independent samples T-test (continuous data) or Chi-squared test (categorical data). ATS: American Thoracic Society, FEV1: forced expiratory volume in 1 second, CT: computerized tomography scan, GOLD: Global Initiative for Obstructive Lung Disease, MMRC: Modified Medical Research Council Scale for dyspnea, BMI: body mass index, CAD: coronary artery disease, CHF: congestive heart failure, GERD: gastroesophageal reflux disease.

Unadjusted change within each age group

The average change in demographic and disease characteristics within each age group from baseline to follow up are summarized in Table 3. The time elapsed between study visits was similar between age groups and no changes in the gender or race distributions of the groups occurred (Table 3). Pack year history of smoking increased ($p<0.001$) for both elderly (mean ± SD: 0.7 ± 1.9 years) and younger (2.0 ± 2.6 years) COPD patients. Changes in smoking status also occurred in both age groups. In the younger age group, 16.9% of participants quit smoking between visit 1 and visit 2 and 2.1% of participants restarted smoking between visit 1 and visit 2. Similarly, in the elderly age group, 8.8% of participants quit smoking between visit 1 and visit 2 and 1.5% of participants restarted smoking between visit 1 and visit 2.

Both age groups experienced declines ($p<0.001$) in FEV1 and FEV1 % of predicted between study visits (FEV1 mean ± SD: -0.27 ± 0.31 L in the younger age group and -0.20 ± 0.24 L in the elderly age group; FEV1 % of predicted mean ± SD: -6.0 ± 10.2 % in the younger age group and -2.9 ± 8.8 % in the elderly age group), as well as significant ($p<0.001$) decreases in six-minute walk distances (mean ±SD, younger group: -51.8 ± 124.6 m and in the elderly group: -66.8 ± 95.5 m). Between study visits, increases in the percentage of emphysema and gas trapping on CT scans also occurred in both age groups (% emphysema mean ± SD: 2.3 ± 0.2% in the younger age group and 1.3 ± 5.7% in the elderly age group; % gas trapping mean ± SD: 5.9 ± 10.8% in the younger age group and 2.2 ± 9.0% in the elderly age group, all $p<0.001$). Changes in participant GOLD scores between visits

occurred in both age groups. In the younger age group, 5.1% of participants had an improved (lower) GOLD score at visit 2 compared to visit 1 and 24.4% of participants had a worse (higher) GOLD score at visit 2 compared to visit 1. In the elderly age group, 6.9% of participants had an improved GOLD score at visit 2 compared to visit 1 and 17.8% of participants had a worse GOLD score at visit 2 compared to visit 1. Similarly, 25.2% of younger participants had an improved MMRC score at visit 2 compared to visit 1 and 34.1% had a worse MMRC score at visit 1 compared to visit 2 ($p=0.03$, Table 3). In elderly participants, 21.2% had improved and 36.5% had worse MMRC scores at visit 2 compared to visit 1 ($p<0.001$., Table 3).

Changes in exacerbation frequency and severity tended to differ for younger vs elderly participants. In the younger age group, 14.1% of participants began experiencing frequent exacerbations and 11.1% of participants who previously experienced frequent exacerbations ceased to experience these ($p=0.07$, Table 3). In contrast, in elderly participants, 6.4% of participants began experiencing and 6.4% of participants ceased to experience frequent exacerbations ($p=1.0$, Table 3). The reverse tended to be true for severe exacerbations: in younger participants, 13.9% began to experience severe exacerbations and 13.6% ceased to experience severe exacerbations ($p=0.85$, Table 3). In elderly participants, 12.6% developed severe exacerbations and 9.4% ceased to experience severe exacerbations ($p=0.08$, Table 3). In both age groups, BMI decreased ($p<0.001$) between visit 1and visit 2 (mean ± SD, younger group: -0.2 ± 3.4 and in the elderly group: -0.5 ± 2.8).

Finally, with the exception of asthma (which did not change), significant changes in comorbidity status occurred for both age groups (Table 3). In the younger age group, 13.8% of participants received a new diagnosis of hypertension and 1.3% of participants' hypertension resolved between visit 1 and visit 2 ($p<0.001$, Table 3). Likewise, in the elderly group, 11.4% of participants received a new diagnosis of hypertension and 4.9% of participants' hypertension resolved between visit 1 and visit 2 ($p<0.001$, Table 3). 3.9% of younger and 5.7% of elderly participants received a new diagnosis of CAD and 1.3% of younger and 3.0% of elderly participants' CAD resolved between visit 1 and visit 2 ($p<0.001$ and $p=0.02$ for younger and elderly groups, respectively, Table 3). Similar patterns occurred for CHF: 3.1% of younger and 5.1% of elderly participants received a new diagnosis of CHF and 1.3% of younger and 1.5% of elderly participants' CHF resolved between visit 1 and visit 2 ($p=0.01$ and $p<0.001$ for younger and elderly groups, respectively, Table 3). Changes in diabetes status between visit 1 and visit 2 also occurred in both age groups. In the younger age group, 8.1% of participants received a new diagnosis of diabetes and 2.1% of younger participants' diabetes resolved between visit 1 and visit 2 ($p<0.001$). In the elderly age group, these numbers were 0.7% and 4.8%, respectively. Finally, GERD status did not change for elderly participants ($p=0.37$, Table 3), but did change for younger participants ($p=0.002$, Table 3). 13.6% of younger participants received a new diagnosis of GERD, and 8.8% of younger participants' GERD resolved between visit 1 and visit 2.

Table 3. Average change in demographic and disease characteristics from baseline to follow up within each age group

	less than 65		65 or older	
	(N = 899)	p-value[†]	(N = 667)	p-value[†]
Demographics				
Age (years)	5.6 (0.8)	<0.001	5.4 (0.6)	<0.001
Gender (male)	no change	1.00	no change	1.00
Race (non-Hispanic white)	no change	1.00	no change	1.00
Smoking History				
ATS Pack Years	2.0 (2.6)	<0.001	0.7 (1.9)	<0.001
Smoking Status		<0.001		<0.001
no change	728 (81.0%)		598 (89.7%)	
quit smoking	152 (16.9%)		59 (8.8%)	
restarted smoking	19 (2.1%)		10 (1.5%)	
Disease Characteristics				
Duration of COPD (years)	5.5 (0.8)	<0.001	5.4 (0.6)	<0.001
FEV1	-0.27 (0.31)	<0.001	-0.20 (0.24)	<0.001
FEV1 (%predicted)	-6.0 (10.2)	<0.001	-2.9 (8.8)	<0.001
6 Minute Walk Distance (meters)	-51.8 (124.6)	<0.001	-66.8 (95.5)	<0.001
% Emphysema on CT	2.3 (0.2)	<0.001	1.3 (5.7)	<0.001
% Gas Trapping on CT	5.9 (10.8)	<0.001	2.2 (9.0)	<0.001
Final GOLD Score		<0.001		<0.001
improved	46 (5.1%)		46 (6.9%)	
stable	634 (70.5%)		502 (75.3%)	
declined	219 (24.4%)		119 (17.8%)	
MMRC Dyspnea Score		0.03		<0.001
improved	225 (25.2%)		141 (21.2%)	
stable	364 (40.7%)		281 (42.3%)	
declined	305 (34.1%)		243 (36.5%)	
Frequent Exacerbations		0.07		1.00
ceased to experience	100 (11.1%)		43 (6.4%)	
no change	672 (74.7%)		581 (87.1%)	
began to experience	127 (14.1%)		43 (6.4%)	
Severe Exacerbations		0.85		0.08
ceased to experience	122 (13.6%)		63 (9.4%)	

no change	652 (72.5%)		520 (78.0%)	
began to experience	125 (13.9%)		84 (12.6%)	
BMI	-0.24 (3.43)	<0.001	-0.48 (2.76)	<0.001
Comorbidity Status				
Hypertension		<0.001		<0.001
new diagnosis	124 (13.8%)		76 (11.4%)	
no change	737 (82.1%)		558 (83.7%)	
resolved	37 (4.1%)		33 (4.9%)	
CAD		<0.001		0.02
new diagnosis	35 (3.9%)		38 (5.7%)	
no change	852 (94.8%)		609 (91.3%)	
resolved	12 (1.3%)		20 (3.0%)	
CHF		0.01		<0.001
new diagnosis	28 (3.1%)		34 (5.1%)	
no change	859 (95.6%)		623 (93.4%)	
resolved	12 (1.3%)		10 (1.5%)	
Diabetes		<0.001		<0.001
new diagnosis	73 (8.1%)		5 (0.7%)	
no change	807 (89.8%)		630 (94.5%)	
resolved	19 (2.1%)		32 (4.8%)	
GERD		0.002		0.37
new diagnosis	122 (13.6%)		68 (10.2%)	
no change	697 (77.6%)		541 (81.1%)	
resolved	79 (8.8%)		58 (8.7%)	
Asthma		1.00		1.00
new diagnosis	0 (0%)		0 (0%)	
no change	799 (100.0%)		595 (100.0%)	
resolved	0 (0%)		0 (0%)	

Ŧ, p-value based on paired samples T-test (continuous data) or Stuart-Maxwell test (categorical data). ATS: American Thoracic Society, FEV1: forced expiratory volume in 1 second, CT: computerized tomography scan, GOLD: Global Initiative for Obstructive Lung Disease, MMRC: Modified Medical Research Council Scale for dyspnea, BMI: body mass index, CAD: coronary artery disease, CHF: congestive heart failure, GERD: gastroesophageal reflux disease.

Associations between age group and disease progression

The associations between age group and disease progression are summarized in Table 4. All models were adjusted for age at baseline, gender, race, American Thoracic Society pack-years of smoking at baseline, smoking status at baseline, duration of COPD at baseline, and for the presence of hypertension, coronary artery disease, and/or asthma at baseline. All model assumptions were determined to be within acceptable limits. The younger age group was used as the reference group for all models.

Being in the elderly age group versus the younger age group did not have an impact on either the development of severe exacerbations (relative risk ratio (95% confidence interval): 1.17 (0.59, 2.31)) nor on the resolution of existing severe exacerbations (0.83 (0.44, 1.58)) between visit 1 and visit 2. There was also no effect of age group on the resolution of existing frequent exacerbations (relative risk ratio (95% confidence interval): 0.56 (0.27, 1.16)), but elderly participants were less likely than younger participants to develop new frequent exacerbations (0.42 (0.20, 0.87)). Age group did not have a significant effect on decline in GOLD score (relative risk ratio (95% confidence interval): 0.86 (0.35, 2.08)), nor on improvement in GOLD score (relative risk ratio (95% confidence interval): 0.89 (0.52, 1.55)). There was also no association between age group and changes in MMRC scores from baseline to follow up (overall model: p=0.57, relative risk ratio (95% confidence interval) for improved MMRC score: 0.83 (0.46, 1.49) and for worse score: 0.93 (0.54, 1.60)). Similarly, there was no effect of age group on decline in six-minute walk distance (overall model: p=0.08; β-coefficient (95% confidence interval): -0.67 (-28.42, 27.08) meters) or on the

increase in percent of emphysema on CT scan (overall model: p=0.22; β-coefficient (95% confidence interval): -0.62 (-2.10, 0.86)) between visits. Finally, age group had no effect on the increase in percent of gas trapping on CT scan from baseline to follow up (β-coefficient (95% confidence interval): -2.34 (-5.09, 0.41)), or on the decline in FEV1 from baseline to follow up (β-coefficient (95% confidence interval): -22.50 (-85.87, 40.86) ml).

Table 4: Multivariable associations between age group and disease progression in the study population.

	Relative Risk Ratio	β-coefficient	95% CI
Severe exacerbations			
improved	1.17	-	0.59, 2.31
declined	0.83	-	0.44, 1.58
Frequent exacerbations			
improved	0.56	-	0.27, 1.16
declined	0.42	-	0.20, 0.87
MMRC score			
improved	0.83	-	0.46, 1.49
declined	0.93	-	0.54, 1.60
GOLD score			
improved	0.86	-	0.35, 2.08
declined	0.89	-	0.52, 1.55
Six-minute walk distance (meters)	-	-0.67	-28.42, 27.08
%Emphysema	-	-0.62	-2.10, 0.86
%Gas trapping	-	-2.34	-5.09, 0.41
FEV1 (ml)	-	-22.50	-85.87, 40.86

FEV1: forced expiratory volume in 1 second, GOLD: Global Initiative for Chronic Lung Disease score, MMRC: Modified Medical Research Council Scale for dyspnea. All models adjusted for age at baseline, gender, race, American Thoracic Society pack-years of smoking at baseline, smoking status at baseline, duration of COPD at baseline, presence of hypertension, coronary artery disease, and asthma. The younger age group is the reference group for all models.

DISCUSSION

The purpose of this study was to examine the relationship between aging and progression of COPD in the longitudinal COPDGene cohort. The results suggest that elderly individuals with COPD had worse lung function compared to younger individuals with COPD as evidenced by lower FEV1, higher percent of emphysema, and greater percent of gas trapping at both baseline and 5-year follow up. Although exercise tolerance was similar between elderly and younger individuals at baseline, at 5-year follow up, exercise tolerance was lower in elderly COPD patients compared to younger COPD patients. Elderly patients also had greater frequencies of comorbidities including hypertension and coronary artery disease than younger patients. These results are consistent with those of previous studies that have suggested elderly COPD patients experience worse lung function, increased exertional intolerance, and greater frequencies of comorbidities.[19]

Despite this cross-sectional evidence of worse lung function, elderly individuals were less likely to experience severe and/or frequent exacerbations compared to younger individuals and reported less dyspnea (lower MMRC scores) than younger individuals with COPD. This apparently contradictory result may be explained by differences in individual perceptions of dyspnea between older and younger COPD patients. Dyspnea, by definition, is a subjective experience that is unique to every individual.[37] Current understanding of the mechanisms of dyspnea and perception of dyspnea remains limited, but includes cortical integration of complex sensory information from multiple sensory mechanisms within the respiratory system.[37] Previous research has suggested that perception of dyspnea is dampened

in elderly individuals, which may be related to lower nerve conduction velocity or other impairments in axon structure and function.[38] Research has further suggested individuals with decreased perception of breathlessness also tend to report fewer and less severe exacerbations compared to individuals with greater sensitivity to breathlessness.[39] Together, these results may help explain why elderly participants in this study reported less dyspnea and fewer and milder exacerbations compared to younger participants.

Over the follow up period, both elderly and younger COPD patients experienced clinically significant declines in lung function and exercise tolerance as well as increases in the frequencies of comorbidities. These findings are consistent with the understanding of COPD as a progressively debilitating disease.[1] Changes in variables from visit 1 to visit 2 were predominantly consistent between younger and elderly COPD patients – if a variable increased significantly in one age group, it tended to do the same in the other age group. The main difference in disease progression within age groups was the magnitude of the change, which tended to be larger in the younger group and smaller in the elderly group. One possible explanation for this observation is that because the elderly group started out worse than the younger group, there was relatively less opportunity for further decline in the elderly group such that their condition remained compatible with continued participation in the study or survival. Indeed, previous studies have suggested that lung function decline is faster early in the disease course of COPD and slows in the more advanced stages of disease. [40] Furthermore, rapid decline in lung function, particularly in FEV1, has been associated with increased risk of mortality, even in individuals with otherwise normal lung function. [41]

There were relatively few differences in the rates of change in lung function parameters between elderly and younger COPD patients. Consistent with the previous result that elderly individuals tended to experience less change over time than the younger age group, individuals in the elderly age group were less likely to develop frequent exacerbations compared to participants in the younger age group. Again, this finding is consistent with a requirement for preserving a level of functioning compatible with continued study participation and/or life. There were no other significant associations between age group and measures of COPD progression. These results suggest that the biological process of aging, *per se*, is not a major driver of lung function decline, exacerbation status, and/or development of comorbidities during the course of COPD progression. Instead, it seems likely that another distinct factor, with a role in both aging and lung pathology, such as integrity of the immune system, may play a critical role in programming host susceptibility to COPD progression.

This research has to be interpreted in the context of several potential limitations. First, the data captured as part of the COPDGene study relies on many self-reported measures, which are subject to recall bias and other errors of memory. This is particularly an issue for the analysis of comorbidities, many of which seem unlikely to resolve over the study period (e.g. CHF, CAD, diabetes), but were nevertheless reported as such by some study participants. Additionally, we could not examine associations between age and lung function decline in individuals with COPD who never smoked, as this data was not available in the dataset. Also, the racial/ethnic composition of the study population was limited to non-

Hispanic Whites and African Americans in order to ensure sufficient power for the original analysis. Therefore, the results of the current analysis cannot be applied to non-smokers and individuals of other racial/ethnic backgrounds. Finally, survivorship bias may be affecting our results. Analysis of individuals lost to follow up suggests that indeed individuals lost to follow up may have been experiencing more severe illness compared to the individuals that completed the study. Therefore, it is possible that our sample consisted of relatively less affected individuals who were able to attend both study visits and who may not be fully representative of the entire population of COPD patients.

This study also has several important strengths. First, the metrics used to assess disease progression, including the six-minute walk distance, MMRC scores, GOLD scores, and spirometry measurements, are well-validated and well-standardized techniques often used for these types of studies.[9,26] Further, COPDGene coordinators put into place detailed study protocols and quality assurance protocols to ensure study measurements were implemented consistently and results were comparable across study sites. Finally, the COPDGene study included a large cohort of participants with meticulously collected and curated data, with relatively little missing data, allowing the present study to be adequately powered, without the need to make imputations for missing data.

In conclusion, this study suggests that while elderly individuals with COPD exhibit evidence of more severe lung function impairment, they tend to report less dyspnea and fewer and less severe exacerbations compared to younger individuals with COPD. This

pattern persists over time, although younger individuals tend to experience a greater magnitude of decline in lung function measurements compared to elderly individuals. Despite these findings, the data did not provide strong support for a role of aging in the pathogenesis of COPD. However, the contribution of survivorship bias to these findings remains unclear. Nevertheless, this study emphasizes the importance of early diagnosis and early intervention to slow the progression of disease in order to preserve maximum life expectancy and quality of life for individuals affected by COPD. Further research into what other host factors, such as immune system integrity, may explain varying patterns of disease progression in COPD patients is warranted.

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