This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Corresponding author. UIHC – Internal Medicine, 200 Hawkins Drive – C33 GH, Iowa City, IA, 52242, USA. spyridon-fortis@uiowa.edu (S. Fortis).

CRediT authorship contribution statement

Spyridon Fortis: Formal analysis, Conceptualization, Funding acquisition, Writing - original draft, has full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, Study concept and design.

Emily S. Wan: Funding acquisition, Formal analysis, Writing - original draft. Ken Kunisaki: Funding acquisition, Formal analysis, Writing - original draft. Patrick Tel Eyck: Funding acquisition, Formal analysis, Writing - original draft. Zuhair K. Ballas: Funding acquisition, Formal analysis, Writing - original draft. Emily S. Wan: Funding acquisition, Formal analysis, Writing - original draft. Ken Kunisaki: Funding acquisition, Formal analysis, Writing - original draft. James D. Crapo: Funding acquisition, Formal analysis, Writing - original draft. Russell P. Bowler: Funding acquisition, Formal analysis, Writing - original draft. John E. Hokanson: Funding acquisition, Formal analysis, Writing - original draft. Chris Wendt: Funding acquisition, Formal analysis, Writing - original draft. Edwin K. Silverman: Funding acquisition, Formal analysis, Writing - original draft. Alejandro P. Comellas: Conceptualization, Funding acquisition, Formal analysis, Writing - original draft. Study concept and design. Funding acquisition, Formal analysis, Writing - original draft, Acquisition, analysis, or interpretation of data: All authors., Drafting of the manuscript: All authors, Critical revision of the manuscript for important intellectual content: All authors.

Declaration of competing interest

SF has received grants from the American Thoracic Society and Fisher &Paykel. RPB has received consulting fees from Boehringer Ingelheim, AstraZeneca, and GlaxoSmithKline. In the past three years, EKS received honoraria from Novartis for Continuing Medical Education Seminars and grant and travel support from GlaxoSmithKline. The rest of authors declare no competing interests.

Ethics approval

Clinical Center | Institution Title | Protocol Number
---|---|---
National Jewish Health | National Jewish IRB | HS-1883a
Brigham and Women’s Hospital | Partners Human Research Committee | 2007-P-000554/2; BWH
Baylor College of Medicine | Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals | H-22209
Michael E. DeBakey VAMC | Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals | H-22202
Columbia University Medical Center | Columbia University Medical Center IRB | IRB-AAAC9324
Duke University Medical Center | The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB) | Pro00004464
Johns Hopkins University | Johns Hopkins Medicine Institutional Review Boards (JHM IRB) | NA_00011524
Los Angeles Biomedical Research Institute | The John F. Wolf, MD Human Subjects Committee of Harbor-UCLA Medical Center | 12756-01
Morehouse School of Medicine | Morehouse School of Medicine Institutional Review Board | 07–1029
Temple University | Temple University Office for Human Subjects Protections Institutional Review Board | 11369
University of Alabama at Birmingham | The University of Alabama at Birmingham Institutional Review Board for Human Use | FO70712014
University of California, San Diego | University of California, San Diego Human Research Protections Program | 070876
University of Iowa | The University of Iowa Human Subjects Office | 200710717
Ann Arbor VA | VA Ann Arbor Healthcare System IRB | PCC 2008-110732
University of Minnesota | University of Minnesota Research Subjects’ Protection Programs (RSPP) | 0801M24949
University of Pittsburgh | University of Pittsburgh Institutional Review Board | P0007132059
University of Texas Health Sciences Center at San Antonio | UT Health Science Center San Antonio Institutional Review Board | HSC20070644H
Health Partners Research Foundation | Health Partners Research Foundation Institutional Review | 07–127
University of Michigan | Medical School Institutional Review Board (IRBMED) | HUM0001973
Increased mortality associated with frequent exacerbations in COPD patients with mild-to-moderate lung function impairment, and smokers with normal spirometry

Spyridon Fortis\textsuperscript{a,b,*}, Emily S. Wan\textsuperscript{c,d}, Ken Kunisaki\textsuperscript{e,f}, Patrick Tel Eyck\textsuperscript{g}, Zuhair K. Ballas\textsuperscript{h}, Russell P. Bowler\textsuperscript{i}, James D. Crapo\textsuperscript{i}, John E. Hokanson\textsuperscript{j}, Chris Wendt\textsuperscript{e,f}, Edwin K. Silverman\textsuperscript{c}, Alejandro P. Comellas\textsuperscript{b}

\textsuperscript{a}Center for Access & Delivery Research & Evaluation (CADRE), Iowa City VA Health Care System, Iowa City, IA, USA

\textsuperscript{b}Division of Pulmonary, Critical Care and Occupational Medicine, University of Iowa Hospital and Clinics, Iowa City, IA, USA

\textsuperscript{c}Channing Division of Network Medicine, Brigham and Women’s Hospital, Boston, MA, USA

\textsuperscript{d}VA Boston Healthcare System, Jamaica Plain, MA, USA

\textsuperscript{e}Minneapolis Veterans Affairs Health Care System, Minneapolis, MN, USA

\textsuperscript{f}University of Minnesota, Minneapolis, MN, USA

\textsuperscript{g}Biostatistics and Research Design, Institute for Clinical and Translational Science, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

\textsuperscript{h}Division of Immunology, Department of Internal Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

\textsuperscript{i}Department of Medicine, National Jewish Health, Denver, CO, USA

\textsuperscript{j}Department of Epidemiology, Colorado School of Public Health, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Abstract

\textbf{Background:} The burden of frequent respiratory exacerbations in COPD patients with mild-to-moderate spirometric impairment and smokers with preserved lung function is unknown.

\textbf{Methods:} We categorized COPD participants in COPDGene with post-bronchodilator FEV1% predicted $\geq$ 50\% by the annual exacerbation frequency into three groups: i) frequent exacerbators (top 5\%; $n = 109$), ii) exacerbators (>0 but less than frequent exacerbators; $n = 1,009$), and iii) No exacerbation ($n = 981$). Exacerbations were defined as respiratory episodes requiring
antibiotics and/or systemic steroids. We performed a Cox proportional hazards regression analysis to examine the association with mortality. We repeated the same process in current/former smokers with preserved spirometry (FEV1 ≥80%predicted and FEV1/FVC ≥0.7).

Results: Among 2,099 COPD participants, frequent exacerbators had ≥1.8 exacerbations/year and were responsible for 34.3% of the total exacerbations. There were 102 (10.4%) deaths in the group with no exacerbations, 119 (11.8%) in the exacerbator group, and 24 (22%) in the frequent exacerbators. Adjusted mortality in frequent exacerbators was higher relative to individuals with no exacerbations (hazard ratio (HR) = 1.98; 95%CI = 1.25–3.13). An increase in frequency of exacerbations by one exacerbation/year was associated with increased mortality (HR = 1.40, 95%CI = 1.21–1.62). Among 3,143 participants with preserved spirometry, frequent exacerbators had ≥0.8 exacerbations/year and were responsible for more than half of the exacerbations. There were 93 (4.2%) deaths in the group with no exacerbations, 28 (3.8%) in the exacerbator group, and 14 (7.6%) in the frequent exacerbators. The adjusted mortality was increased in frequent exacerbators with preserved spirometry relative to those with no exacerbations (HR = 2.25; 95%CI = 1.26–4.01).

Conclusions: In COPD participants with mild-to-moderate spirometric impairment and smokers with preserved spirometry, the frequent exacerbator phenotype is responsible for a large proportion of total exacerbations and associated with high mortality.

Keywords
Chronic obstructive pulmonary disease; Exacerbations; Mortality

1. Introduction
Chronic obstructive pulmonary disease (COPD) patients experience exacerbations of the disease, defined as acute worsening of respiratory symptoms, that typically become more frequent as the disease progresses [1]. A major component of the burden of COPD is related to COPD exacerbations. Moderate and severe exacerbations are associated with a decline in lung function and health status, and substantial healthcare cost [2-5]. Severe COPD exacerbations require hospitalization and are responsible for more than 70% of the direct health-care cost of the disease [4,6]. In a cohort of COPD patients with moderate-to-severe lung function impairment, 13.6% of them were frequent exacerbators, defined as patients with at least 2 exacerbations every year [7], and were responsible for 50.6% of all hospitalizations [8]. Therefore, identifying COPD patients with frequent exacerbations is of major importance [9].

COPD-related hospitalizations are associated with increased short and long-term mortality [10-14]. As the frequency of COPD-related hospitalizations increases, the long-term mortality increases [15,16]. In a multicenter study using administrative data, COPD patients with at least 2 hospitalizations a year had increased mortality relative to those with no hospitalizations [17]. The long-term mortality among those with frequent exacerbations, not requiring hospitalizations, is under-studied. More recently, it has also been recognized that symptomatic smokers with normal spirometry also have respiratory exacerbations [18,19]. The burden of respiratory exacerbation including health-care utilization and mortality among
frequent exacerbators has predominantly been studied in COPD patients with significant lung function impairment [8,16] while the burden of the disease in patients with mild lung function impairment or preserved lung function remains unstudied. We hypothesized that the burden of disease in COPD with mild-to-moderate lung impairment, and smokers with preserved spirometry, with frequent exacerbations is high. To investigate our hypothesis we used data of COPD participants with post-bronchodilator FEV1% predicted ≥50% predicted and smokers with normal spirometry from the COPDGene study with at least 3 years follow-up. We defined frequent exacerbators as those individuals at the top 5% in exacerbation frequency within their spirometric group. We assessed the burden of disease associated with frequent exacerbations, including mortality, and we identified factors associated with frequent exacerbators.

2. Methods

2.1. Data collection

We analyzed data from COPDGene, an ongoing study conducted at multiple clinical centers throughout the United States (http://www.copdgene.org/). Subjects were current and former smokers with ≥10 pack-years of smoking who self-identified as non-Hispanic whites (NHW) or African Americans (AA) and were between the ages of 45–80 years at enrollment. The institutional review boards at each participating center approved the study protocol, and written informed consent was obtained from all participants. Details of the study protocol have been published previously [20]. Briefly, participants completed a modified American Thoracic Society Respiratory Epidemiology questionnaire. Dyspnea was assessed using the modified Medical Research Council (mMRC) scale. Subjects performed pre- and post-bronchodilator spirometry according to American Thoracic Society–European Respiratory Society (ATS-ERS) guidelines [21] and a 6-min walk test (6-MWT) at the enrollment visit. Volumetric chest CT scans were obtained at total lung volume (TLV) (maximal inspiration) and at functional residual capacity (FRC) (end-tidal expiration) [20]. Percent emphysema and gas trapping were quantified using 3D Slicer software (www.airwayinspector.org) [20].

We included COPD participants with post-bronchodilator FEV1% predicted ≥50% and participants with normal spirometry. Individuals with lung transplant or lung volume reduction surgery, and those with less than 3 years follow-up data were excluded. Respiratory exacerbation data were collected prospectively after enrollment. Subjects were contacted every 6 months after enrollment and completed a standardized questionnaire regarding respiratory exacerbations through the Longitudinal Follow-Up program. Vital status was also ascertained using information from the social security death index and the Longitudinal Follow-up program.

2.2. Definitions and outcomes

COPD was defined as post-bronchodilator FEV1/FVC <0.7. Preserved spirometry was defined as post-bronchodilator FEV1/FVC ≥0.7 and FEV1% predicted ≥80%. Exacerbations were defined as episodes of worsening respiratory symptoms requiring use of antibiotics and/or systemic steroids. Severe exacerbations were defined as those requiring
hospitalizations or emergency room visits. Other variable definitions have been previously described [20]. We defined frequent exacerbators as those at the top 5% in the average exacerbation frequency. Since the frequent exacerbator phenotype has not been investigated in COPD patients with mild-to-moderate lung function impairment and smokers with preserved spirometry, we did not use the typical 2 exacerbations/year definition [7]. In a sensitivity analysis, we defined frequent exacerbators as those with ≥2 exacerbations per year.

History of acute bronchitis or pneumonia was defined as self-reported history of bronchitis or pneumonia at study enrollment. Similarly, history of asthma, and obstructive sleep apnea were also self-reported. History of cancer was defined as self-reported history of lung, breast, prostate, colon, and/or bladder cancer. Bronchodilator response was defined as an increase in prebronchodilator FEV1 and/or FVC greater than or equal to 12% and greater than or equal to 200 ml after bronchodilator administration [22]. TLV was measured from volumetric inspiratory chest CT scans and is a surrogate of plethysmographic total lung capacity. TLV% predicted was calculated based on MESA predicted values [23]. Percent emphysema and gas trapping was calculated as previously [20].

2.3. Statistical analysis

We stratified COPD participants into 3 groups based on their annual rate of respiratory exacerbations: i) No-exacerbation, ii) exacerbators (>0 but less than frequent exacerbators), and iii) frequent exacerbators (top 5% in the rate of respiratory exacerbations). We compared the characteristics of participants between groups using ANOVA for continuous variables and chi-squared or fisher exact test for categorical variables.

In a univariate analysis, we identified variables associated with the frequent exacerbator group (frequent exacerbator vs the rest). Variables associated with the frequent exacerbator group with univariate p value < 0.10 were considered for a multivariable logistic regression model. Medication use and current smoking status were not considered for the model as participants with frequent exacerbations used more medications and were less likely to be current smokers (confounding by indication). Variables were selected for the final model using a stepwise backward variable elimination process to minimize the Akaike information criterion (AIC) [24]. We assessed for variable multicollinearity using correlation matrices and variance inflation factors [25]. We repeated the multivariable analysis after multiple imputations (5 datasets) by chained equations (MICE) to account for missing variables. We used the Multivariate Imputation by Chained Equations (MICE) package R software [26,27].

We used Cox proportional hazard regression models to examine the association between the groups with all-cause mortality (time-to-death analysis). We also used Cox proportional hazard regression models to examine the association between exacerbation frequency (exacerbation/year) and all-cause mortality. Models included the following covariates: age, gender, race, current smoking status, smoking pack-years, BMI, post-bronchodilator FEV1% predicted at enrollment, and history of obstructive sleep apnea. In a sensitivity analysis, we defined frequent exacerbators as those with 2 or more exacerbations per year, and we assessed the association of frequent exacerbations with mortality.
Similarly, we stratified current or former smokers with normal spirometry based on their annual rate of respiratory exacerbations, and we performed the same analysis as above. All statistical analyses were conducted using R statistical software (http://www.r-project.org/) using the following R software packages: ‘car’, ‘dunn.test’, ‘ggplot2’, ‘survminer’, ‘tableone’, ‘mice’, ‘pscl’, ‘MASS’, ‘AER’, ‘survival’, and ‘DescTools’.

3. Results

Of 10,194 participants in COPDGene with at least 10 pack-years history of smoking, 2,713 have COPD with post-bronchodilator FEV1%predicted ≥50% and 4,368 have normal spirometry (Supplement Fig. 1). Of 2,713 participants with COPD and post-bronchodilator FEV1%predicted ≥50%, we excluded 1 that had lung transplant/lung volume reduction and 613 for whom we did not have exacerbation data for at least 3 years. Of 4,386 current or former smokers with preserved spirometry, we excluded one that had lung transplant/lung volume reduction and 1,242 for whom we did not have exacerbation data for at least 3 years. We analyzed data of 2,099 COPD participants with post-bronchodilator FEV1%predicted ≥50% and 3,143 current or former smokers with preserved spirometry.

3.1. COPD participants with mild-to-moderate lung function impairment (n = 2,099)

In COPD participants with post-bronchodilator FEV1%predicted ≥50%, the median duration of follow-up was 8 years (interquartile range = 6.6–8.9). The top 5% in exacerbation frequency (n = 109) had 1.8 or more exacerbations per year (frequent exacerbators), 1,009 had >0 exacerbation/year but less than 1.8 exacerbation a year (exacerbators), and 981 had no exacerbations. Table 1 shows the characteristics of the 3 groups. The count of respiratory exacerbations was 5,913 for all COPD participants, 3,886 (65.7%) for the exacerbators, and 2027 (34.3%) for the frequent exacerbators. The count of severe respiratory exacerbations was 1,919 for all COPD participants, 1,308 (68.2%) for the exacerbators, and 611 (31.8%) for the frequent exacerbators.

In frequent exacerbators during a median follow-up time of 7.4 years (interquartile range = 5.7–8.8), the median count of exacerbations was 18 with a range of 6–36 (interquartile range = 13–22) and median count of severe exacerbations was 4 with a range of 0–28 (interquartile range = 1–8).

Lung function (every 10% increase in FEV1%predicted with an odds ratio (OR) = 0.82; 95%CI = 0.68–0.99), 6-min walk distance (every 100 ft increase; OR = 0.94; 95%CI = 0.88–1.00), %emphysema (every 1%; OR = 1.05; 95%CI = 1.02–1.07), dyspnea (OR = 2.35; 95%CI = 1.41–4.00), chronic bronchitis (OR = 1.85; 95%CI = 1.17–2.90), history of asthma (OR = 2.13; 95%CI = 1.35–3.34), history of acute bronchitis and/or pneumonia (OR = 2.04; 95%CI = 1.17–3.77), and history of cancer (OR = 1.95; 95%CI = 1.05–3.45) were associated with the frequent exacerbator group (Supplement Table 1). Analysis after multiple imputations for missing values showed almost identical findings.

In the mortality analysis, there were 102 (10.4%) deaths in the group with no exacerbations, 119 (11.8%) in the exacerbator group, and 24 (22%) in the frequent exacerbator group (Fig. 1). After adjusting for age, sex, race, smoking pack-years, current smoking status, body...
mass index, lung function, and history of obstructive sleep apnea, the frequent exacerbator phenotype was associated with increased mortality (hazard ratio (HR) = 1.98; 95% CI = 1.25–3.13, p = 0.004) (Table 2). When we defined frequent exacerbator phenotype as ≥2 exacerbation/years, we observed similar findings (Supplement Table 2). After adjusting for age, sex, race, smoking pack-years, current smoking status, body mass index, lung function, and history of obstructive sleep apnea, an increase in frequency of exacerbations by one exacerbation/year was associated with increased mortality (HR = 1.40, 95% CI = 1.21–1.62, p < 0.001).

### 3.2. Current or former smokers with normal spirometry (n = 3,143)

In current or former smokers with normal spirometry, the median duration of follow-up was 8.1 years (interquartile range = 6.9–8.9). The top 5% in exacerbation frequency (n = 185) had 0.8 or more exacerbations per year (frequent exacerbators), 743 had >0 exacerbations but less than 0.8 exacerbation a year (exacerbators), and 2,215 had no exacerbations. Table 3 shows the characteristics of the 3 groups. The count of total respiratory exacerbations was 3,548 for all participants with normal spirometry, 1620 (45.7%) for the exacerbators, and 1928 (54.3%) for the frequent exacerbators. The count of severe respiratory exacerbations was 1,086 for all participants with normal spirometry, 519 (44.8%) for the exacerbators, and 567 (55.2%) for the frequent exacerbators.

In frequent exacerbators during a median follow-up time of 8 years (interquartile range = 6.9–8.8), the median count of exacerbations was 8 with a range of 3–48 (interquartile range = 7–11) and median count of severe exacerbations was 2 with a range of 0–18 (interquartile range = 0–5).

Pack-years (every 10 with OR = 1.13; 95% CI = 1.05–1.21), dyspnea (OR = 2.10; 95% CI = 1.44–3.05), history of asthma (OR = 3.63; 95% CI = 2.52–5.20), history of acute bronchitis and/or pneumonia (OR = 2.16; 95% CI = 1.50–3.16), and history of obstructive sleep apnea (OR = 1.58; 95% CI = 1.04–2.34) were associated with the frequent exacerbator group (Supplement Table 3). We performed an additional analysis after multiple imputations accounting for missing values with almost identical findings.

In the mortality analysis, there were 93 (4.2%) deaths in the group with no exacerbations, 28 (3.8%) in the exacerbator group, and 14 (7.6%) in the frequent exacerbator group. After adjusting for age, sex, race, smoking pack-years, current smoking status, body mass index, lung function, and history of obstructive sleep apnea, the frequent exacerbator group was associated with increased mortality compared to that with no exacerbations (HR = 2.25; 95% CI = 1.26–4.01, p = 0.006) (Table 4). When we defined frequent exacerbator phenotype as ≥2 exacerbation/years, we observed similar findings (Supplement Table 4). After adjusting for age, sex, race, smoking pack-years, current smoking status, body mass index, lung function, and history of obstructive sleep apnea, an increase in frequency of exacerbations by one exacerbation/year was associated with increased mortality (HR = 1.66, 95% CI = 1.24–2.22, p < 0.001).
4. Discussion

Among COPD participants with mild-to-moderate spirometric impairment, we showed that the top 5% of patients with the most exacerbations (frequent exacerbators) are responsible for 34.3% and 31.8% of total and severe exacerbations, respectively. The mortality of COPD patients with frequent exacerbators is approximately double the mortality of the rest of the mild-to-moderate COPD participants in the study. Furthermore, in current or former smokers with normal spirometry, the frequent exacerbators are responsible for more than half of the total and severe exacerbations, respectively, and also have increased adjusted mortality relative to those with no exacerbations. An increase in frequency of exacerbations in COPD and current or former smokers with normal spirometry by one exacerbation a year was associated with increased mortality.

COPD patients with 2 or more exacerbations every year were defined as “frequent exacerbators” based on the landmark ECLIPSE study [7]. Since then, this cut-off has been used to identify high-risk COPD patients where escalation of treatment may be needed [1]. Using a hypothesis-free approach, Le Rouzic and colleagues found that frequent exacerbators have an average of 2.89 exacerbations/year as opposed to “infrequent exacerbators” who have an average of 0.71 exacerbations/year [28]. Two exacerbations in a given year is not a highly stable COPD exacerbation phenotype as exacerbations tend to occur in clusters. However, a patient with ≥2 exacerbations/year in the previous year has more than 46% chance to have at least 2 exacerbations in the subsequent year [29]. As the number of exacerbations increase, the probability of a subsequent exacerbation increases and the frequent exacerbator phenotype becomes more “stable” [17]. Suissa et al. showed that the median time to subsequent hospitalization is 5.4 years after the first hospitalization, 1.6 years after the second one, and 0.3 years after the seventh one [12]. In the current study, we found that the top 5% in exacerbation frequency among COPD patients with mild-to-moderate lung function impairment has ≥1.8 exacerbations/year which indicates that 2 exacerbation/year is likely the appropriate cut-off even among COPD patients with mild-to-moderate lung function impairment. Our findings also suggest that in current or former smokers with preserved spirometry, one exacerbation a year may indicate a “high-risk phenotype”.

In the ECLIPSE study, which included COPD participants with moderate or severe lung function impairment and an average FEV1% predicted of 48%, every year about a quarter of them had at least 2 exacerbations but they were not always the same individuals. Twelve percent of the entire cohort consistently had ≥2 exacerbations every year [7]. In the SPIROMICs cohort that includes COPD subjects across a wide spectrum of lung function with an average of FEV1% predicted of 63%, Han et al. found that every year 10–15% of the participants had 2 or more exacerbations but only 2.1% of them consistently had ≥2 exacerbations/year for 3 consecutive years [29]. The frequent exacerbator phenotype is relatively uncommon [30,31].

Nonetheless, the frequent exacerbator phenotype is associated with a high burden of disease. In a cohort of COPD patients with post-bronchodilator FEV1% predicted below 70%, Beeh et al. demonstrated that 13.6% of COPD participants classified as frequent exacerbators...
were responsible for 50% of total hospitalizations [8]. Similarly, we found that among COPD participants with mild-to-moderate lung impairment, the top 5% in exacerbation frequency is responsible for approximately one third of all exacerbations. Moreover, we showed that the top 5% in exacerbation frequency among former or current smokers with normal spirometry is responsible for more than half of exacerbations.

COPD-related hospitalizations are associated with increased mortality [12,16,32] which increases further with each hospitalization [15]. In our study, frequent exacerbators (not necessarily with hospitalizations) have increased mortality after adjustment for demographics, smoking exposure, body mass index (BMI), and lung function relative to the mortality in individuals with no exacerbations. This association remains even when we defined frequent exacerbators as those with 2 or more exacerbations a year. An increase in frequency of exacerbations in COPD patients with mild-to-moderate lung impairment by one exacerbation a year is associated with 41% increase in mortality. This is the first study showing that frequent exacerbator phenotype is associated with increased mortality even among current or former smokers with preserved spirometry. An increase in frequency of exacerbations in smokers with normal spirometry by one exacerbation a year is associated with 62% increase in mortality.

History of asthma, gastroesophageal reflux disease, prior exacerbations, increased respiratory symptoms, poor health status, worsening lung function, increased fibrinogen and white blood cells, certain cytokines, and evidence of small airway disease in the chest CT have been reported as risk factors for frequent exacerbators [7,29,33]. Poor lung function and prior exacerbations are the most consistent risk factors. Chronic bronchitis is also associated with high risk for exacerbations [34] but the association between chronic bronchitis with frequent exacerbations is inconsistent [7]. In our analysis, poor lung function, poor exercise capacity, increased radiographic emphysema, dyspnea, chronic bronchitis, history of asthma, history of prior exacerbations and pneumonia, and history of cancer were risk factors for frequent exacerbators among COPD participants. Cancer may be related with immunodeficiencies [35], a known risk factor for COPD exacerbations [36]. Among current or former smokers with normal spirometry, smoking pack-years, dyspnea, history of asthma, history of prior exacerbation and pneumonia, and obstructive sleep apnea were associated with frequent exacerbations. Obstructive sleep apnea may be confounded by obesity hypoventilation syndrome [37]. Patients with obesity hypoventilation syndrome may be frequently hospitalized with acute respiratory failure and misdiagnosed with COPD [38]. For that reason, in the mortality analysis obstructive sleep apnea was included in the models as a co-variate.

Our study has several limitations. First, we examined the average of exacerbations per year in a study period with a duration ≥3 years as opposed to annual exacerbations. Nevertheless, the definition of frequent exacerbation as 2 exacerbations a year for several consecutive years has limited clinical value as health care providers do not have the luxury of longitudinal data to decide the appropriate treatment plan. Secondly, our mortality analysis in the participants with preserved spirometry is limited by the low death rates and the relatively small sample size. Third, our mortality analysis is inherently biased as we selected patients with ≥3 years follow-up and therefore all the participants were alive for at
least 3 years. Another limitation is the variable participation in the Longitudinal Follow-Up program (exacerbations). In addition, we did not have data regarding plasma eosinophilic counts and carbon dioxide in arterial blood gases that may provide additional information regarding the exacerbation risk. Racial minorities other than black individuals did not participate in the study. The above do not undermine the strength of our study which are the wealth of our demographic and medical history data, and the stringent quality control of our questionnaires, spirometry and radiographic measurements. Moreover, the large number of women and black individuals in our study makes our findings more externally applicable.

The frequent exacerbator phenotype is potentially a clinically relevant phenotype as it may indicate specialized COPD treatments. e.g. COPD patients with chronic hypercapnic respiratory failure have a median of 5 exacerbations per year and one-year mortality of 33% [39,40] and benefit from domiciliary nocturnal non-invasive ventilation. Non-invasive ventilation in those patients can reduce exacerbations and mortality by one third. Another example is COPD patients with antibody deficiency syndrome that have a median rate of 4 exacerbations a year and their exacerbation rate drops to a median of 0.75 a year after treatment with immunoglobin replacement treatment and/or prophylactic antibiotics [36].

In conclusion, the top 5% with the most exacerbations in COPD participants with mild-to-moderate lung impairment is responsible for approximately one third of all exacerbations. Among current or former smokers with preserved spirometry, the top 5% of those with the most exacerbations is responsible for more than half of the exacerbations in the cohort. COPD participants and current or former individuals with preserved spirometry have increased mortality compared to those with no exacerbations. These findings demonstrate for the first time that even in the absence of severe lung function impairment, the frequent exacerbator phenotype is associated with increased mortality. An increase in frequency of exacerbations by one exacerbation a year is associated with increased mortality. Future studies should investigate disease mechanisms associated with frequent exacerbations with the goal to develop interventions with great impact on disease burden.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgements**

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States Government.

**Funding**

The project described was supported by Award Number U01 HL089897 and Award Number U01 HL089856 from the National Heart, Lung, and Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, and Blood Institute or the National Institutes of Health. COPDGene is also supported by the COPD Foundation through contributions made to an Industry Advisory Board comprised of AstraZeneca, Boehringer-Ingelheim, Genentech, GlaxoSmithKline, Novartis, Pfizer, Siemens, and Sunovion. SF was supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Rural Health, Veterans Rural Health Resource Center (Award # 14380), and the Health Services Research and development (HSR&D) Service through the Comprehensive Access and Delivery Research and Evaluation (CADRE) Center (CIN 13–412), and has received grants from the American Thoracic Society and Fisher &Paykel.
References

[1]. Disease Gifcol, Global Strategy for The Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2020 Report), 2020.

[2]. Miravitlles M, Ferrer M, Pont A, Zalacain R, Alvarez-Sala JL, Masa F, Verea H, Murio C, Ros F, Vidal R, et al., Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study, Thorax 59 (5) (2004) 387–395. [PubMed: 15115864]

[3]. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA, Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease, Thorax 57 (10) (2002) 847–852. [PubMed: 12324669]

[4]. Darnell K, Dwivedi AK, Weng Z, Panos RJ, Disproportionate utilization of healthcare resources among veterans with COPD: a retrospective analysis of factors associated with COPD healthcare cost, Cost Eff. Resour. Allocation 11 (2013) 13.

[5]. Dransfield MT, Kunisaki KM, Strand MJ, Anzueto A, Bhatt SP, Bowler RP, Criner GJ, Curtis JL, Hanania NA, Nath H, et al., Acute exacerbations and lung function loss in smokers with and without chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med 195 (3) (2017) 324–330. [PubMed: 27556408]

[6]. Sullivan SD, Ramsey SD, Lee TA, The economic burden of COPD, Chest 117 (2 Suppl) (2000) 5S–9S. [PubMed: 10673466]

[7]. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, Miller B, Lomas DA, Agusti A, Macnee W, et al., Susceptibility to exacerbation in chronic obstructive pulmonary disease, N. Engl. J. Med 363 (12) (2010) 1128–1138. [PubMed: 20843247]

[8]. Beeh KM, Glaab T, Stowasser S, Schmidt H, Fabbri LM, Vogelmeier CF, Characterisation of exacerbation risk and exacerbator phenotypes in the POET-COPD trial, Respir. Res 14 (2013) 116. [PubMed: 24168767]

[9]. Silverman EK, Exacerbations in chronic obstructive pulmonary disease: do they contribute to disease progression? Proc. Am. Thorac. Soc 4 (8) (2007) 586–590. [PubMed: 18073387]

[10]. McGhan R, Radcliff T, Fish R, Sutherland ER, Welsh C, Make B, Predictors of rehospitalization and death after a severe exacerbation of COPD, Chest 132 (6) (2007) 1748–1755. [PubMed: 17890477]

[11]. Nannini LJ, Hospitalization due to COPD exacerbation, Chest 142 (6) (2012) 1697. [PubMed: 23208363]

[12]. Groenewegen KH, Schols AM, Wouters EF, Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD, Chest 124 (2) (2003) 459–467. [PubMed: 12907529]

[13]. Ai-Ping C, Lee KH, Lim TK, In-hospital and 5-year mortality of patients treated in the ICU for acute exacerbation of COPD: a retrospective study, Chest 128 (2) (2005) 518–524. [PubMed: 16100133]

[14]. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA, Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease, JAMA 274 (23) (1995) 1852–1857. [PubMed: 7500534]

[15]. Suissa S, Dell’Aniello S, Ernst P, Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality, Thorax 67 (11) (2012) 957–963. [PubMed: 22684094]

[16]. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, Salcedo E, Navarro M, Ochando R, Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease, Thorax 60 (11) (2005) 925–931. [PubMed: 16055622]

[17]. Blagev DP, Collingridge DS, Rea S, Press VG, Churpek MM, Carey K, Mularski RA, Zeng S, Arjomandi M, Stability of frequency of severe chronic obstructive pulmonary disease exacerbations and health care utilization in clinical populations, Chronic. Obstr. Pulm. Dis 5 (3) (2018) 208–220. [PubMed: 30584584]

Respir Med X: Author manuscript; available in PMC 2022 July 28.
[18]. Bowler RP, Kim V, Regan E, Williams AAA, Santorico SA, Make BJ, Lynch DA, Hokanson JE, Washko GR, Berez P, et al. Prediction of acute respiratory disease in current and former smokers with and without COPD, Chest 146 (4) (2014) 941–950. [PubMed: 24945159]

[19]. Woodruff PG, Barr RG, Bleecker E, Christenson SA, Couper D, Curtis JL, Gouskova NA, Hansel NN, Hoffman EA, Kanner RE, et al., Clinical significance of symptoms in smokers with preserved pulmonary function, N. Engl. J. Med 374 (19) (2016) 1811–1821. [PubMed: 27168432]

[20]. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beatty TH, Curran-Everett D, Silverman EK, Crapo JD, Genetic epidemiology of COPD (COPDGene) study design, COPD 7 (1) (2010) 32–43. [PubMed: 20214461]

[21]. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, et al., Standardisation of spirometry, Eur. Respir. J 26 (2) (2005) 319–338. [PubMed: 16055882]

[22]. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gutafsson P, Hansen J, et al., Interpretative strategies for lung function tests, Eur. Respir. J 26 (5) (2005) 948–968. [PubMed: 16264058]

[23]. Hoffman EA, Ahmed FS, Baumhauer H, Budoff M, Carr JJ, Kronmal R, Reddy S, Barr RG, Variation in the percent of emphysema-like lung in a healthy, nonsmoking multiethnic sample. The MESA lung study, Ann. Am. Thorac. Soc 11 (6) (2014) 898–907. [PubMed: 24983825]

[24]. Burns RJ, Deschenes SS, Schmitz N, Associations between depressive symptoms and social support in adults with diabetes: comparing directionality hypotheses with a longitudinal cohort, Ann. Behav. Med 50 (3) (2016) 348–357. [PubMed: 26631086]

[25]. Brethel L, Gainey J, Penwell A, Nathaniel TI, Predictors of thrombolysis in the telestroke and non telestroke settings for hypertensive acute ischemic stroke patients, BMC Neurol. 18 (1) (2018) 215. [PubMed: 30577762]

[26]. Zhang Z, Multiple imputation with multivariate imputation by chained equation (MICE) package, Ann. Transl. Med 4 (2) (2016) 30. [PubMed: 26889483]

[27]. Fortis S, O’Shea AMJ, Beck Mae BF, Nair R, Schmidt GA, Kaboli PJ, Perencevich EN, Reisinger HS, Sarrazin MV, A simplified critical illness severity scoring system (CISSS): development and internal validation, J. Crit. Care 61 (2020) 21–28. [PubMed: 33049489]

[28]. Le Rouzic O, Roche N, Cortot AB, Tillie-Leblond I, Masure F, Perez T, Boucot I, Hamouti L, Ostinelli J, Prili B, et al., Defining the “frequent exacerbator” phenotype in COPD: a hypothesis-free approach, Chest 153 (5) (2018) 1106–1115. [PubMed: 29054347]

[29]. Han MK, Quibrera PM, Carretta EE, Barr RG, Bleecker ER, Bowler RP, Cooper CB, Comellas A, Couper DJ, Curtis JL, et al., Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort, Lancet. Res. Med 5 (8) (2017) 619–626.

[30]. Labaki WW, Martinez FJ, Time to understand the infrequency of the frequent exacerbator phenotype in COPD, Chest 153 (5) (2018) 1087–1088. [PubMed: 29731034]

[31]. Nachef Z, Mador MJ, COPD exacerbator phenotype: time for reassessment? Lancet. Res. Med 5 (8) (2017) 600–601.

[32]. Almagro P, Calbo E, Ochoa de Echague A, Barreiro B, Quintana S, Heredia JL, Garau J, Mortality after hospitalization for COPD, Chest 121 (5) (2002) 1441–1448. [PubMed: 12006426]

[33]. Wan ES, DeMeo DL, Hersh CP, Shapiro SD, Sama SR, Fuhlbrigge AL, Foreman MG, Silverman EK, Clinical predictors of frequent exacerbations in subjects with severe chronic obstructive pulmonary disease (COPD), Respir. Med 105 (4) (2011) 588–594. [PubMed: 21145719]

[34]. Kim V, Criner GJ, Chronic bronchitis and chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med 187 (3) (2013) 228–237. [PubMed: 23204254]

[35]. Mortaz E, Tabarsi P, Mansouri D, Khosravi A, Garssen J, Velayati A, Adcock IM, Cancers related to immunodeficiencies: update and perspectives, Front. Immunol 7 (2016) 365. [PubMed: 27703456]
[36]. McCullagh BN, Comellas AP, Ballas ZK, Newell JD Jr., Zimmerman MB, Azar AE, Antibody deficiency in patients with frequent exacerbations of chronic obstructive pulmonary disease (COPD), PloS One 12 (2) (2017), e0172437. [PubMed: 28212436]

[37]. Mokhlesi B, Tulaimat A, Faibussowitsch I, Wang Y, Evans AT, Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea, Sleep Breath. 11 (2) (2007) 117–124. [PubMed: 17187265]

[38]. Marik PE, Chen C, The clinical characteristics and hospital and post-hospital survival of patients with the obesity hypoventilation syndrome: analysis of a large cohort, Obes. Sci. Pra 2 (1) (2016) 40–47.

[39]. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, Dowson L, Duffy N, Gibson GJ, Hughes PD, et al., Effect of home noninvasive ventilation with oxygen therapy vs oxygen therapy alone on hospital readmission or death after an acute COPD exacerbation: a randomized clinical trial, J. Am. Med. Assoc 317 (21) (2017) 2177–2186.

[40]. Kohnlein T, Windisch W, Kohler D, Drabik A, Geiseler J, Hartl S, Karg O, Laier-Groeneveld G, Nava S, Schonhofer B, et al., Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial, Lancet. Res. Med 2 (9) (2014) 698–705.
Fig. 1.
Crude survival in COPD participants with post-bronchodilator FEV1% predicted ≥50% (n = 2,099) stratified by exacerbation group: i) No exacerbations (No exacerbation), ii) Exacerbations/year > 0 and < 1.8 (Exacerbators), and iii) Exacerbation/year ≥ 1.8 (Frequent Exacerbators).
| Clinical Center             | Institution Title                                                                 | Protocol Number       |
|----------------------------|-----------------------------------------------------------------------------------|-----------------------|
| National Jewish Health     | National Jewish IRB                                                               | HS-1883a              |
| Brigham and Women’s Hospital | Partners Human Research Committee                                                 | 2007-P-000554/2; BWH |
| Baylor College of Medicine | Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals | H-22209               |
| Michael E. DeBakey VAMC    | Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals | H-22202               |
| Columbia University Medical Center | Columbia University Medical Center IRB                                           | IRB-AAAC9324         |
| Duke University Medical Center | The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB) | Pro00004464         |
| Johns Hopkins University   | Johns Hopkins Medicine Institutional Review Boards (JHM IRB)                     | NA_00011524          |
| Los Angeles Biomedical Research Institute | The John F. Wolf, MD Human Subjects Committee of Harbor-UCLA Medical Center | 12756–01             |
| Morehouse School of Medicine | Morehouse School of Medicine Institutional Review Board                          | 07–1029              |
| Temple University         | Temple University Office for Human Subjects Protection Institutional Review Board | 11369                |
| University of Alabama at Birmingham | The University of Alabama at Birmingham Institutional Review Board for Human Use | FO70712014           |
| University of California, San Diego | University of California, San Diego Human Research Protections Program | 070876                |
| University of Iowa        | The University of Iowa Human Subjects Office                                      | 200710717            |
| Ann Arbor VA              | VA Ann Arbor Healthcare System IRB                                               | PCC 2008-110732      |
| University of Minnesota   | University of Minnesota Research Subjects’ Protection Programs (RSPP)            | 0801M24949           |
| University of Pittsburgh  | University of Pittsburgh Institutional Review Board                             | PRO07120059          |
| University of Texas Health Sciences Center at San Antonio | UT Health Science Center San Antonio Institutional Review | HSC20070644H         |
| Health Partners Research Foundation | Health Partners Research Foundation Institutional Review | 07–127               |
| University of Michigan    | Medical School Institutional Review Board (IRBMED)                                | HUM00014973          |
| Minneapolis VA Medical Center | Minneapolis VAMC IRB                                                           | 4128-A               |
| Fallon Clinic             | Institutional Review Board/Research Review Committee Saint Vincent Hospital – Fallon Clinic – Fallon Community Health Plan | 1143                 |

*Respir Med X. Author manuscript; available in PMC 2022 July 28.*
Table 1
Characteristics of COPD participants with post-bronchodilator FEV1%predicted ≥50% and at least 3 years follow up (n = 2,099).

| No Exacerbation | Exacerbators | Frequent exacerbators | P value* |
|-----------------|--------------|-----------------------|----------|
| Exacerbations per year | 0 | >0 and <1.8 | ≥1.8 |
| n | 981 | 1009 | 109 |
| Follow-up duration, y (IQR) | 7.9 (6–8.8) | 8.1 (7.1–9) | 7.4 (5.7–8.8) | <0.001 |
| Age, y ± SD | 63.40 ± 8.47 | 63.47 ± 8.67 | 62.32 ± 8.62 | 0.411 |
| Female, n (%) | 399 (40.7%) | 544 (53.9%) | 56 (51.4%) | <0.001 |
| African American, n (%) | 199 (20.3%) | 190 (18.8%) | 17 (15.6%) | 0.43 |
| Active smokers, n (%) | 460 (46.9%) | 435 (43.1%) | 35 (32.1%) | 0.007 |
| Pack-years smoking ± SD | 48.21 ± 25.70 | 49.27 ± 25.41 | 55.58 ± 29.73 | 0.20 |
| Body mass index, kg/m2 ± SD | 27.76 ± 5.23 | 28.97 ± 6.34 | 29.02 ± 5.94 | <0.001 |
| History of Asthma, n (%) | 147 (15.0%) | 250 (24.8%) | 40 (36.7%) | <0.001 |
| History of acute bronchitis, n (%) | 334 (34.0%) | 588 (58.3%) | 79 (72.5%) | <0.001 |
| History of pneumonia, n (%) | 324 (33.0%) | 476 (47.2%) | 74 (67.9%) | <0.001 |
| Obstructive Sleep Apnea, n (%) | 118 (12.0%) | 199 (19.7%) | 28 (25.7%) | <0.001 |
| Gastroesophageal Reflux, n (%) | 230 (23.5%) | 354 (35.1%) | 48 (44.0%) | <0.001 |
| Diabetes Mellitus, n (%) | 104 (10.6%) | 117 (11.6%) | 12 (11.0%) | 0.78 |
| History of Cancer, n (%) | 72 (7.3%) | 104 (10.3%) | 19 (17.4%) | <0.001 |
| Chronic bronchitis, n (%) | 163 (16.6%) | 258 (25.6%) | 42 (38.5%) | <0.001 |
| mMRC>2, n (%) | 281 (28.7%) | 463 (46.1%) | 81 (74.3%) | <0.001 |
| Post-FEV1% predicted ± SD | 75.37 ± 14.77 | 70.63 ± 13.79 | 64.35 ± 11.65 | <0.001 |
| Post-FVC% predicted ± SD | 93.58 ± 15.64 | 90.98 ± 15.93 | 88.67 ± 15.63 | <0.001 |
| Bronchodilator response, n (%) | 281 (28.9%) | 351 (34.9%) | 46 (43.0%) | <0.001 |
| 6-min-walk-test distance, ft ± SD | 1437.25 ± 357.68 | 1357.60 ± 352.82 | 1197.26 ± 339.28 | <0.001 |
| ICS/LABA, n (%) | 141 (14.4%) | 275 (27.3%) | 61 (56.0%) | <0.001 |
| LAMA, n (%) | 115 (10.7%) | 259 (25.7%) | 50 (45.9%) | <0.001 |
| ICS, n (%) | 44 (4.5%) | 84 (8.3%) | 15 (13.8%) | <0.001 |
| LABA, n (%) | 32 (3.3%) | 42 (4.2%) | 8 (7.3%) | 0.10 |
| Total exacerbations per year ± SD | 0.00 ± 0.00 | 0.50 ± 0.42 | 2.66 ± 0.80 | <0.001 |
| Severe exacerbations per year ± SD | 0.00 ± 0.00 | 0.17 ± 0.24 | 0.81 ± 0.83 | <0.001 |
| Total exacerbations ± SD | 0.00 ± 0.00 | 3.85 ± 3.27 | 18.60 ± 7.30 | <0.001 |
| Severe exacerbations ± SD | 0.00 ± 0.00 | 1.30 ± 1.79 | 5.61 ± 5.77 | <0.001 |
| Emphysema, % ± SD | 6.47 ± 6.70 | 7.37 ± 7.73 | 11.31 ± 10.23 | <0.001 |
| Gas trapping, % ± SD | 23.44 ± 14.03 | 26.61 ± 14.48 | 33.94 ± 15.75 | <0.001 |
| TLY, L ± SD | 5.95 ± 1.42 | 5.74 ± 1.33 | 5.92 ± 1.46 | 0.00401 |
| TLY% predicted ± SD | 109.14 ± 16.16 | 110.74 ± 17.08 | 113.10 ± 18.45 | 0.0176 |
| Pi10, mm ± SD | 3.65 ± 0.13 | 3.68 ± 0.13 | 3.69 ± 0.14 | <0.001 |

* ANOVA for continuous and chi square of fisher exact test for categorical variables

Respir Med X. Author manuscript; available in PMC 2022 July 28.
Data regarding gastroesophageal reflex, mMRC, bronchodilator response, 6-min-walk-test distance, TLV, Pi10, gas trapping and emphysema were missing in 1, 2, 6, 11, 21, 103, 119, 333, and 103 participants, respectively.

ICS = inhaled glucocorticosteroids; IQR = interquartile range; LABA = long acting beta-agonist; LAMA = long acting muscarinic antagonist; mMRC = modified Medical Research Council scale, post-FEV1% predicted = post-bronchodilator forced expiratory volume in 1 s %predicted; post-FVC% predicted = post-bronchodilator forced vital capacity %predicted; Pi10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; TLV = total lung volume at maximum inspiratory volumes measure by chest CT.
Table 2

Association of exacerbation group with mortality in COPD participants with post-bronchodilator FEV1% predicted ≥50% with at least 3 years follow up (n = 2,099).

|                | HR (95% CI)     | P value |
|----------------|-----------------|---------|
| No Exacerbation (n = 981) | ref             | ref     |
| Exacerbators (n = 1,009)    | 0.91 (0.70, 1.20) | 0.52    |
| Frequent exacerbators (n = 109) | 1.98 (1.25, 3.13) | 0.004   |

Cox Proportional Hazards regression models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index (BMI), post-bronchodilator FEV1% predicted, and history of obstructive sleep apnea.

HR = hazard ratio.
Table 3

Characteristics of current and former smokers with normal spirometry with at least 3 years follow up (n = 3,143).

|                      | No Exacerbation | Exacerbators | Frequent exacerbators | P value |
|----------------------|-----------------|--------------|-----------------------|---------|
| Exacerbations per year| 0               | >0 and <0.8  | >0.8                  |         |
| Follow-up duration, y (IQR) | 8 (6.5–8.8)    | 8.4 (7.5–9.1) | 8 (6.9–8.8)          | <0.001  |
| Age, y ± SD          | 58.07 ± 8.60    | 58.38 ± 8.60 | 57.12 ± 8.45         | 0.2     |
| Female, n (%)        | 1049 (47.4%)    | 463 (62.3%)  | 123 (66.5%)          | <0.001  |
| African American, n  | 699 (31.6%)     | 212 (28.5%)  | 67 (36.2%)           | 0.09    |
| Active smokers, n (%)| 1103 (49.8%)    | 349 (47.0%)  | 92 (49.7%)           | 0.41    |
| Pack-years smoking ± SD | 36.98 ± 20.57  | 35.72 ± 18.55 | 43.78 ± 25.54      | <0.001  |
| Body mass index, kg/m² ± SD | 28.70 ± 5.55   | 30.01 ± 6.09  | 30.91 ± 6.59         | <0.001  |
| History of Asthma, n (%) | 179 (8.1%)     | 123 (16.6%)  | 73 (39.5%)           | <0.001  |
| History of acute bronchitis, n (%) | 634 (28.6%)     | 364 (49.0%)  | 114 (61.6%)          | <0.001  |
| History of pneumonia, n (%) | 565 (25.5%)      | 268 (36.1%)  | 88 (47.6%)           | <0.001  |
| Obstructive Sleep Apnea, n (%) | 244 (11.0%)     | 126 (17.0%)  | 43 (23.2%)           | <0.001  |
| Gastroesophageal Reflux, n (%) | 428 (19.3%)      | 236 (31.8%)  | 71 (38.4%)           | <0.001  |
| Diabetes Mellitus, n (%) | 224 (10.1%)    | 102 (13.7%)  | 29 (15.7%)           | 0.004   |
| History of Cancer, n (%) | 115 (5.2%)      | 49 (6.6%)    | 12 (6.5%)            | 0.31    |
| Chronic bronchitis, n (%) | 197 (8.9%)      | 118 (15.9%)  | 42 (22.7%)           | <0.001  |
| mMRC>2, n (%)         | 374 (16.9%)     | 190 (25.6%)  | 88 (47.6%)           | <0.001  |
| Post-FEV1% predicted ± SD | 97.76 ± 11.37   | 96.72 ± 11.60  | 94.38 ± 10.66       | <0.001  |
| Post-FVC% predicted ± SD | 96.56 ± 11.56   | 95.58 ± 12.06  | 94.69 ± 10.85       | 0.026   |
| Bronchodilator response, n (%) | 214 (9.8%)     | 61 (8.4%)    | 25 (13.5%)           | 0.11    |
| 6-min-walk-test distance, ft ± SD | 1534.40 ± 352.08 | 1484.22 ± 353.94  | 1366.52 ± 332.02   | <0.001  |
| ICS/LABA, n (%)       | 45 (2.0%)       | 49 (6.6%)    | 39 (21.1%)           | <0.001  |
| LAMA, n (%)           | 31 (1.4%)       | 19 (2.6%)    | 22 (11.9%)           | <0.001  |
| ICS, n (%)            | 23 (1.0%)       | 16 (2.2%)    | 15 (8.1%)            | <0.001  |
| LABA, n (%)           | 2 (0.1%)        | 5 (0.7%)     | 4 (2.2%)             | <0.001  |
| Total exacerbations per year ± SD | 0.00 ± 0.00     | 0.27 ± 0.19  | 1.37 ± 0.76          | <0.001  |
| Severe exacerbations per year ± SD | 0.00 ± 0.00     | 0.09 ± 0.14  | 0.41 ± 0.50          | <0.001  |
| Moderate-to-severe exacerbations, n (%) | 0.00 ± 0.00     | 2.18 ± 1.50  | 10.42 ± 6.73         | <0.001  |
| Severe exacerbations, n (%) | 0.00 ± 0.00     | 0.70 ± 1.10  | 3.06 ± 3.70          | <0.001  |
| Emphysema, % ± SD     | 2.36 ± 2.77     | 2.50 ± 3.13  | 2.36 ± 2.87          | 0.56    |
| Gas trapping, % ± SD  | 10.72 ± 8.67    | 10.29 ± 8.05 | 10.58 ± 8.53         | 0.54    |
| TLV, L ± SD           | 5.46 ± 1.32     | 5.20 ± 1.22  | 5.10 ± 1.18          | <0.001  |
| TLV% predicted ± SD   | 102.95 ± 15.56  | 103.06 ± 14.94 | 104.06 ± 14.54     | 0.66    |
| Pi10, mm ± SD         | 3.63 ± 0.11     | 3.65 ± 0.11  | 3.67 ± 0.12          | <0.001  |

Data regarding bronchodilator response, 6-min-walk-test distance, TLV, Pi10, gas trapping and emphysema were missing in 40,10,184,199,582, and 184 participants, respectively.
ICS = inhaled glucocorticosteroids; LABA = long acting beta-agonist; LAMA = long acting muscarinic antagonist; mMRC = modified Medical Research Council scale, post-FEV1% predicted = post-bronchodilator forced expiratory volume in 1 s %predicted; post-FVC% predicted = post-bronchodilator forced vital capacity %predicted, Pt10 = square root of wall area for a hypothetical airway with an internal perimeter of 10 mm; TLV = total lung volume at maximum inspiratory volumes measured by chest CT.

^d ANOVA for continuous and chi square of fisher exact test for categorical variables.
Table 4

Association of exacerbation group with mortality in current and former smokers with normal spirometry with at least 3 years of follow-up (n = 3,143).

|                        | HR (95% CI)     | P value |
|------------------------|-----------------|---------|
| No Exacerbation (n = 2,215) | ref             | ref     |
| Exacerbators (n = 743)   | 1.02 (0.67, 1.57) | 0.92    |
| Frequent Exacerbators (n = 185) | 2.25 (1.26, 4.01) | 0.006   |

Cox Proportional Hazards regression models for mortality included the following co-variates: age, sex, race, smoking status, smoking pack-years, body mass index (BMI), post-bronchodilator FEV1% predicted, and history of obstructive sleep apnea.

95%CI = 95% Confidence interval; HR = hazard ratio.