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Acute Exacerbations and Lung Function Loss in Smokers with and without COPD

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ABSTRACT

Background

Acute exacerbations of chronic obstructive pulmonary disease (COPD) increase the risk of death and drive healthcare costs, but whether they accelerate loss of lung function remains controversial. Whether exacerbations in subjects with mild COPD or similar acute respiratory events in smokers without airflow obstruction affect lung function decline is unknown.

Methods

We examined data on the first 2,000 subjects who returned for a second COPDGene visit 5 years after enrolment. Baseline data included demographics, smoking history and CT emphysema. We defined exacerbations (and acute respiratory events in those without established COPD) as acute respiratory symptoms requiring either antibiotics or systemic steroids, and severe events by the need for hospitalization. Throughout the 5-year follow-up period, we collected self-reported acute respiratory event data at six month intervals. We used linear mixed models to fit FEV1 decline based on reported exacerbations or acute respiratory events.

Results

In COPD subjects, exacerbations were associated with excess FEV_1 decline, with the greatest effect in GOLD 1, where each exacerbation was associated with an additional 23mL/year decline(95%CI: 2 to 44; p=0.03), and each severe exacerbation with an additional 87mL/year decline (95%CI: 23 to 151; p= 0.008); statistically significant but smaller effects were observed in GOLD 2 and 3 subjects. In subjects without airflow obstruction, acute respiratory events were not associated with additional FEV_1 decline.

Conclusions

Exacerbations are associated with accelerated lung function loss in subjects with established COPD, particularly those with mild disease. Trials are needed to test existing and novel therapies in subjects with early/mild COPD to potentially reduce the risk of progressing to more advanced lung disease.

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INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (COPD) account for the majority of COPD-related costs [1] and when frequent lead to marked reductions in health-related quality of life [2]. Severe exacerbations requiring hospitalization also portend a poor prognosis, with one- and five-year mortality exceeding 20% and 50% [3-6].Though these impacts have been consistently reported, whether acute exacerbations impact the rate of decline of lung function over time remains uncertain. Although many COPD treatments reduce exacerbation frequency and some studies suggest that inhaled therapies may reduce FEV1 decline,[7,8] there is no information about the association between these two key disease features. Many smokers without COPD also suffer acute respiratory events that appear clinically similar to classic exacerbations in those with established COPD [9,10]. Whether such respiratory events accelerate lung function loss or lead to the development of COPD is unknown.

Previous studies have examined the relationship between acute respiratory illnesses and lung function decline in subjects with established COPD but the findings are not consistent[11-18]. Though some have suggested a significant excess loss of forced expiratory volume in 1-second (FEV_1) for each respiratory event [13], or in those with frequent events [15], others have reported minimal [12] or no relationship [18]. Such disparate results may result from design differences including sample size, study duration, and exacerbation definitions. Most previous studies also focused on more advanced COPD; only the Lung Health Study included subjects with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1 COPD (FEV_1>80% of predicted) and none included those without airflow obstruction (GOLD 0) or with a non-specific or restrictive type spirometric pattern(Preserved Ratio Impaired Spirometry - PRISm) [19,20]. Though the GOLD guidelines include prevention of exacerbations as a major treatment goal in patients with established COPD[3], there are uncertainties about the link between exacerbations and lung function loss, particularly in patients with mild airflow obstruction.[21]

The Genetic Epidemiology of COPD (COPDGene) study enrolled current and former smokers and obtained spirometry and detailed respiratory illness history at the time of enrolment and captured

exacerbations in longitudinal follow-up assessments over 5 years[22]. The study provides a robust dataset to further understand how respiratory events relate to longitudinal FEV_1 decline across a wide range of COPD severity as well as in smokers without COPD. We hypothesized that acute respiratory events would be associated with more rapid FEV_1 decline in all GOLD stages.

METHODS

Study population and assessments

COPDGene (NCT00608764) is a multicenter longitudinal observational cohort study that initially enrolled 10,300participants [22]. Subjects in the current analysis were the first 2,000 subjects who returned for a second COPDGene visit approximately 5 years after their initial visit. To minimize bias related to missing data, we also included baseline data for the 861 subjects who were more than 1 year late for their return visit or declined further participation sometime after their first visit. Written informed consent was obtained from subjects, and the study was approved by the institutional review boards of all 21 participating centers.

COPDGene participants were non-Hispanic white and African-American current and former smokers with at least a 10 pack-year smoking history, with and without COPD[22]. We excluded subjects with known lung diseases other than asthma, such as lung cancer, bronchiectasis and interstitial lung disease. At baseline and at five years after the initial visit, spirometry was performed (ndd Easy-One® spirometer, Andover, MA) before and after administration of 180 mcg of albuterol (via Aerochamber® Activis, Inc, Parsippany, NJ). Bronchodilator reversibility was defined as at least 12% and 200 mL increase in FEV_1or forced vital capacity (FVC) post-bronchodilator [23]. COPD severity was assessed using spirometry criteria outlined by the GOLD guidelines with reference values from the National Health and Nutrition Examination Survey (NHANES) III [24,25]. GOLD 0 refers to current and former smokers without COPD, which although not included in the current GOLD guidelines, was used previously [26]. Subjects with Preserved Ratio Impaired Spirometry (PRISm)are current and former smokers with reduced FEV_1< 80% predicted but normal FEV1/FVC ratio(> 0.70)[19].

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At baseline and follow-up, we performed high resolution computed tomographic (CT) scans at full inspiration. Emphysema was estimated by the percentage of lung volume on the inspiratory CT with attenuation less than -950 Hounsfield Units (HU) (low attenuation area, %LAA950insp) using 3D Slicer software (www.airwayinspector.org) [22].

Exacerbations (and acute respiratory events in those without established COPD) were defined as acute respiratory symptoms that required use of either antibiotics or systemic steroids; severe events were defined by the need for hospitalization[3]. Self-reported acute respiratory event data were collected at 6-month intervals, via an automated telephony system, web-based survey, or phone contact throughout the follow-up period between Visits 1 and 2[27].

Statistical analyses

Linear mixed models were used to fit FEV_1 longitudinally, stratified by GOLD group. Primary predictors included visit (baseline and follow-up), acute respiratory events/exacerbations and their interaction. Covariates included baseline race, sex, percent emphysema and smoking status (continuing, intermittent or former based on longitudinal follow up data) as time-invariant variables, and weight, age, height and bronchodilator response as time-varying variables. Squared terms for age and height were also included in the models. An unstructured covariance structure was used for repeated measures. Total number of exacerbations, number of severe exacerbations, and binary categorization of exacerbations (none versus at least one) were used as predictors in separate models. Data from subjects that either completed both visits (Completers) or only completed Visit 1 and were either overdue by at least one year or requested no further contact (Late) was used to fit models. Subjects with Visit 1 data but who died before Visit 2 (Deceased) were not included in primary analyses. For more details, see the Online Supplement. All statistical analyses were performed in SAS 9.4 (Cary, NC).

RESULTS

For subjects completing both visits, the average time between Visit 1 and Visit 2 was 5.25 years. Clinical characteristics of the primary analytic cohort are shown in Table 1. Subjects in the PRISm and GOLD 0 groups were slightly younger at their baseline visit than those with established airflow obstruction, were more often female and African-American, and exhibited less bronchodilator responsiveness. Current smoking rates declined with increasing severity of COPD while the extent of emphysema and use of inhaled medications was greater in those with more airflow obstruction. As previously published, the use of inhaled medications was as or more common in PRISm subjects than in those with GOLD 0/1 disease [20].

Of the initial 10,300enrolled subjects, 3521were due for Visit 2 at the time of analysis. Of these, 2000 subjects were in the Completer subgroup. There were 861and 660 in the Late and Deceased subgroups, respectively. Subgroups were generally similar except for more former smokers among the Completers in PRISm and GOLD 0-1 groups compared with Late and Deceased, and lower baseline mean FEV1 in GOLD 2-4 for Deceased compared with Completers in GOLD 2-4 (Supplemental Table 1). The proportion of Late subjects was similar across GOLD groups (20% for GOLD 4 and 23%-26% for all other GOLD groups including PRISm).The number of deaths in the GOLD 0 through 4 groups were 115(9%), 27(10%), 127(18%), 151(30%) and 174(57%), respectively, and 66(17%) for PRISm subjects.

Analysis of the exacerbation/acute respiratory event frequency showed that exacerbations were common in all groups (Table 2), with over a third (36.7%) of subjects reporting events during follow up. Both the proportion of subjects who suffered any event and the annualized rates increased with worsening lung function. Severe events requiring hospitalization were common, even in the PRISm and GOLD 0 groups (at least once during follow up in 14% of PRISm, and 8% of GOLD 0), although such events increased markedly in more advanced COPD (at least once during follow up in 10% of GOLD 1, 24% of GOLD 2, 42% of GOLD 3, and 47% of GOLD 4).

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Among subjects without exacerbations/acute respiratory events, we found rates of FEV_1change between +5 and -25 mL/year (Table 3), factoring out expected changes due to aging and other time-varying covariates (height, weight and BDR). The greatest rate of FEV_1decline in absence of exacerbations occurred in those with GOLD 1 and 2, with mean losses of 25 and 19 mL/year, respectively. For GOLD 0 subjects, there was no difference in the rate of FEV_1decline between those who reported significant dyspnea (MRC ≥2) and those that did not (MRC <2); 13 mL/year vs. 9 mL/year, p=0.30. There was also no difference in the relationship between exacerbations and excess decline in FEV_1based on MRC classification (p=0.16 for interaction) among GOLD 0 subjects.

Exacerbations/acute respiratory events of any severity were associated with statistically significant excess FEV_1 decline in GOLD 1, 2, and 3 subjects. The magnitude of effect was largest in GOLD 1 subjects, where each exacerbation was associated with an additional 23mL/year decline in FEV_1.We also found that severe exacerbations were associated with greater declines in $FEV_1$and again the strongest effects were seen in GOLD 1 subjects, where *each* severe exacerbation was associated with an additional 87 mL/year decline in FEV_1 (Table 3 & Figure 1). There was no statistically significant excess decline in FEV_1 for each additional exacerbation/acute respiratory event of any severity in any of the PRISm, GOLD 0 or GOLD 4 groups, although the GOLD 4 data may be impacted by survivor bias as discussed below. Our primary model used Completers and Visit 1 data for Late subjects; additional models were fit for Completers only (see Supplement) as well as for Completers and Visit 1 data for Late and Deceased subjects combined (data not shown) and yielded similar results.

As expected, we found a steeper average decline in FEV_1 among current and intermittent smokers (9ml decline) than among former smokers (2 ml decline; p=0.005 for difference). As smoking cessation slows the rate of FEV_1 decline, we extended models by including smoking status as an effect modifier; models included up to 3-way interaction terms with time, occurrence of severe exacerbations (defined as none versus at least 1)and smoking status (former versus current or intermittent). For GOLD 2 and 3 subjects there was a steeper decline in FEV_1 over time for current/intermittent smokers with a severe

acute exacerbation versus subjects that were either former smokers or did not suffer a severe acute exacerbation or both(57 mL/year versus 18 mL/year ($p<0.0001$) for GOLD 2 and 39mL/year versus 10 mL/year ($p=0.008$) for GOLD 3). Similar results were found when considering exacerbations of any type.

DISCUSSION

The results of this study of more than 2000 well-characterized current and formers smokers followed for five years demonstrate that acute exacerbations are associated with accelerated declines in FEV_1 in those with established COPD, particularly in those with mild (GOLD 1) disease and when the exacerbations are severe. By contrast, although many current and former smokers without airflow obstruction have respiratory impairment and suffer exacerbation-like respiratory events [9,10], we found no evidence that these accelerate lung function loss. Collectively, these findings support the hypothesis that acute exacerbations contribute to COPD progression, particularly in those with disease that is initially mild.

These findings provide novel information in the longstanding debate about the role of bronchitic episodes in the pathogenesis of COPD associated with tobacco products. In the 1970's, the original West London longitudinal spirometry study by Fletcher and Peto[11] demonstrated no relationship between bronchial infections and rate of decline in FEV_1. By contrast, a contemporaneous cohort in the United States did find a relationship between lower respiratory illness frequency and FEV_1 decline among 150 subjects who had COPD at entry [14]. Subsequent longitudinal analysis from the Lung Health Study suggested that in continuous and intermittent smokers, each lower respiratory infection reported was associated with an additional 7 mL/year decline in FEV_1, though no effect was seen in those who had quit smoking [13]. Donaldson et al. found a similar estimate of additional lung function loss (8 mL/year) in subjects with frequent exacerbations (defined as >2.92 exacerbations/year) as compared to those without, though the study was small (n=109) and the exacerbations were based on diary records and thus mild in many cases[15]. Contradictory data came from the 3-year ECLIPSE study, which reported only a 2 mL/year

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greater annual decline in FEV_1 per exacerbation (though no GOLD 1 subjects were included)[12], while the 5-year Hokkaido COPD cohort study found no relationship between exacerbations and FEV_1 decline though the population enrolled was also quite small (n=268)[18]. Our analysis confirms a relationship between exacerbations and lung function loss in subjects with GOLD 2 and 3 disease and adds convincing data that the effect is greatest in subjects with more mild COPD (GOLD 1) and for more severe events.

Our observation that lung function loss related to exacerbations was greatest in those with GOLD 1 disease is novel and has a several potential implications for COPD care. First is the possibility that preventing exacerbations in this subpopulation could reduce the risk of developing severe COPD, an important hypothesis that should motivate randomized trials. The possibility that mild-to-moderate disease may be more amenable to therapy than severe airflow obstruction is supported by the UPLIFT study, which suggested that exacerbations, mortality and perhaps FEV_1 decline were all reduced by tiotropium in subjects with FEV_1> 60% [28]. The link between exacerbations and lung function decline has been questioned, in part because many drugs reduce the risk of exacerbation but none have been definitively shown to reduce FEV_1 loss. This could be explained by the fact that earlier studies mostly excluded GOLD 1 COPD.

An unanticipated finding was the lack of evidence that acute respiratory events impact lung function loss in subjects with GOLD 0 disease or PRISm. Both of these groups have been demonstrated to have significant respiratory symptoms and impairment, in some cases greater than subjects with GOLD 1 COPD, and as we observed, they are also often treated with long-acting bronchodilators and inhaled corticosteroids despite no evidence to support that practice.[9,10,19,29] We can only speculate about why no relationships between acute respiratory events and FEV_1decline were observed in these subjects. One possibility is that whatever mechanisms protect them from the development of COPD, such as enhanced anti-inflammatory or reparative capacity, also protect against lung function loss with episodes of bronchitis. A second possibility that will require additional testing is that acute respiratory events in GOLD 0 subjects are fundamentally different from those in subjects with established COPD, a possibility

supported by the observation that COPD patients but not healthy smokers had significant increases in bacterial colonization after experimental respiratory rhinoviral infection.[30] As shown in COPDGene[9], and recently confirmed in the SPIROMICS cohort[29], the risk of acute respiratory events in symptomatic GOLD 0 current and former smokers often exceeds the risk in patients with established COPD. Additional follow-up of SPIROMICS participants should allow further analyses to either confirm or refute our findings. PRISm subjects have increased emphysema and airway wall thickness, relative to smokers with normal spirometry, but have a number of distinct features compared with those with typical COPD including less bronchodilator responsiveness and greater body mass index [19]. PRISm has also proven to be heterogeneous with a number of phenotypic clusters, each likely the result of different pathophysiological processes [20]. This diversity also likely impacts the nature and impact of acute respiratory events in different PRISm subjects and will require further study.

Though our study was not designed to confirm the pathophysiologic link between exacerbations, their severity, and lung function decline, and we cannot assign directional causality, a number of plausible mechanisms could be proposed. First, exacerbations are associated with significant pulmonary inflammation including activation of matrix metalloproteinases [31] and increased hyaluronidase activity [32], which may trigger a number of permanent changes to the lung parenchyma including airway fibrosis and additional loss of alveolar tissue. Second, some subjects who suffer prolonged exacerbations may not fully recover before the next episode begins leading to a progressive deterioration with each event and faster lung function loss over time [33]. Greater increases in sputum interkeukin-8 (IL-8) and IL-6 from baseline to day 7 of an exacerbation predict a delayed recovery, potentially linking severe exacerbations to more pronounced inflammation and larger lung function decline [34].

Strengths of our study include its large, multi-center sample, longitudinal study design, use of standardized post-bronchodilator spirometry, our careful collection of exacerbation data over a 5-year period and the inclusion of large numbers of GOLD 0 and PRISm subjects. The study is limited by the loss of some subjects to follow up, and as it was observational in nature, we cannot assign causality

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between exacerbations and loss of lung function. Missing data poses issues with many longitudinal studies, and we attempted to account for potential bias in estimates caused by missing data as well as understand differences between completers and 'dropouts' by examining their baseline characteristics. We did find Completers, Late and Deceased subjects to be fairly similar in regards to demographic characteristics and baseline lung function. In addition, our primary analytical approach allowed FEV_1 decline estimates to be adjusted based on Visit 1 data for subjects who were Late for Visit 2. Still, there is the potential that data were *missing not at random* (MNAR). In particular, it is possible that Late subjects had a faster decline in FEV_1 than Completers, and we have no information about progression in the former group as there were only 2 visits requiring spirometry. (See Online Supplement for further discussion.) We do not consider subjects that had COPD-related deaths before they could complete Visit 2 as having missing data, but rather, as having an alternative outcome to an FEV_1 measurement (although subjects that died before Visit 2 may also have had a steeper average FEV_1 decline after Visit 1 than Completers). It is therefore important to consider overall survival as well as FEV_1 decline for living subjects in order to portray a more complete picture of disease progression and note that though the declines in FEV_1 diminished with increasing GOLD stage (and were in fact not significant in GOLD 4), survival also decreased. Though information on final cause of death was unavailable, we anticipate many were directly or indirectly related to COPD.

Our study is also limited by the collection of spirometry at only two time points, approximately five years apart. Although analyses of FEV_1 decline has traditionally relied on more frequent collection of data, we note that in the Lung Health Study, the slopes of FEV_1 decline estimated over five annual tests was not different from that measured with only two time points six years apart[35]. In addition, we did not collect data about how exacerbations were treated (antibiotics, systemic corticosteroids, or both) and thus cannot compare the relative impact of exacerbation treatment on lung function loss.

In summary, we provide novel evidence that exacerbations accelerate lung function loss in subjects with established COPD, particularly when these events are severe and occur in those with mild disease.

These findings emphasize the need for clinical trials in early/mild COPD, to test whether preventing exacerbations could reduce progression to more advanced lung disease.

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Table 1.Baseline characteristics of subjects in the cohort and analysis (Completers or Late).

	PRISm	GOLD 0	GOLD 1	GOLD 2	GOLD 3	GOLD 4
Sample size	318	1223	250	580	357	133
Completers	225	878	185	412	229	71
Late	93	345	65	168	128	62
Age in years, Mean (SD)	58.2 (8.1)	57.6 (8.8)	63.7 (8.8)	63.1 (8.6)	64.3 (8.1)	63.3 (7.5)
Female: number (%)	171 (54)	640 (52)	109 (44)	279 (48)	171 (48)	58 (44)
Race, number (%)						
Non-Hispanic white	173 (54)	775 (63)	203 (81)	440 (76)	286 (80)	110 (83)
Smoking, number (%)						
Current	107 (34)	382 (31)	65 (26)	124 (21)	34 (10)	5 (4)
Former	126 (40)	517 (42)	128 (51)	319 (55)	226 (63)	98 (74)
Intermittent	85 (27)	324 (26)	57 (23)	137 (24)	97 (27)	30 (23)
BMI, Mean (SD)	32.0 (6.9)	28.8 (5.8)	27.2 (5.2)	28.8 (6.0)	28.1 (6.2)	26.7 (5.7)
FEV1 at baseline visit, Mean (SD)						
Liters	2.05 (0.49)	2.84 (0.68)	2.62 (0.65)	1.86 (0.50)	1.13 (0.29)	0.68 (0.18)
% predicted	70.6 (8.0)	97.7 (11.3)	91.4 (9.1)	64.7 (8.5)	40.4 (5.6)	23.4 (4.3)
COPD medications, number (%)						
ICS only	26 (8)	18 (1)	10 (4)	41 (7)	45 (13)	28 (22)
LAMA	26 (8)	28 (2)	23 (9)	158 (28)	184 (52)	88 (67)
ICS and LABA	44 (14)	42 (3)	23 (9)	169 (30)	192 (54)	83 (63)
LABA only	5 (2)	5 (0.4)	2 (1)	34 (6)	29 (8)	23 (18)
Emphysema, Mean (SD)	1.9 (2.9)	2.6 (3.0)	7.2 (6.8)	8.7 (8.2)	18.2 (12.9)	25.3 (12.8)
BDR in liters, Mean (SD)	0.13 (0.34)	0.09 (0.28)	0.25 (0.44)	0.36 (0.48)	0.38 (0.49)	0.28 (0.45)

Abbreviations: GOLD – Global Initiative for Obstructive Lung Disease; PRISm – preserved ratio impaired spirometry; BMI – body mass index; FEV1 – forced expiratory volume; ICS – inhaled corticosteroids; LABA – long-acting beta agonists; LAMA – long-acting anti-muscarinic; BDR – bronchodilator responsiveness. Sample sizes available for analysis for (PRISm, GOLD 0, GOLD 1, GOLD 2, GOLD 3, GOLD 4) were as follows: (312, 1209, 248, 560, 352, 127) for ICS only, (312, 1213, 249, 566, 355, 132) for ICS and LABA, (312, 1211, 248, 566, 354, 131) for LAMA, (309, 1209, 248, 562, 352, 128) for LABA, (299, 1156, 240, 550, 333, 119) for emphysema, and (314, 1205, 248, 576, 355, 132) for BDR. For all other variables, sample sizes are as given in the first row.

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Table 2: Exacerbation distributions and annualized rates for the analytic cohort based on longitudinal follow-up surveys, by GOLD stage.

	PRISm	GOLD 0	GOLD 1	GOLD 2	GOLD 3	GOLD 4
n	282	1111	230	544	339	125
All exacerbations						
≥1 event during follow-up, %	30.5	21.5	27.4	46.5	70.2	69.6
Percentage with average of 1 or more per year	12.8	4.1	7.0	12.5	28.6	35.2
Percentage with average of 2 or more per year	3.9	1.2	1.3	4.4	10.0	12.0
Mean rate, per year	0.30	0.13	0.18	0.36	0.72	0.89
Severe exacerbations						
≥1 event during follow-up, %	13.5	8.1	10.0	24.1	42.2	47.2
Percentage with average of 1 or more per year	4.6	0.9	0.4	2.8	5.6	11.2
Percentage with average of 2 or more per year	1.1	0.4	0.0	0.4	0.9	1.6
Mean rate, per year	0.10	0.04	0.04	0.11	0.20	0.31

Abbreviations: GOLD – Global Initiative for Obstructive Lung Disease; PRISm – preserved ratio impaired spirometry. Longitudinal follow up surveys were available on 1937 of 2000 Completers and 694 of 861 Late subjects in the analytic cohort, combined above.

Table 3: Effect of each exacerbation/acute respiratory event on rate of FEV_1 decline.

	Exacerbations/Acute Respiratory Events of Any Severity		Severe Exacerbations/Acute Respiratory Events	
	Change in FEV_1,mL/year (95% CI)			
Subject Group	Change in those with no exacerbations	Excess change, per exacerbation of any severity	Change in those with no severe exacerbations	Excess change, per severe exacerbation
PRISm	5 (-4, 14)	-6 (-15, 4)	5 (-4, 14)	-17 (-37, 2)
GOLD 0	-9 (-13, -4)	-7 (-15, 2)	-9 (-14, -5)	-7 (-27, 13)
GOLD 1	-25 (-34, -15)	-23 (-44, -2)	-26 (-35, -16)	-87 (-151, -23)
GOLD 2	-19 (-26, -11)	-10 (-20, -1)	-21 (-28, -14)	-20 (-40, 1)
GOLD 3	-8 (-17, 0)	-8 (-15, -1)	-10 (-18, -3)	-20 (-36, -4)
GOLD 4	-4 (-16, 8)	0 (-9, 8)	-2 (-13, 8)	-9 (-29, 12)

Estimates reflect average changes after factoring out expected changes due to time-varying covariates (age, height, weight and BDR).For example, the change in FEV_1 for a GOLD 1 subject with 1,2, or 3 exacerbations over the follow up period can be estimated by adding the excess decline per exacerbation event (-23 mL/year) to the rate in those without events (-25 mL/year) yielding a final annual rate of -48mL/year, -71mL/year, and -94mL/year .

Abbreviations: GOLD – Global Initiative for Obstructive Lung Disease; PRISm – preserved ratio impaired spirometry; FEV1 – forced expiratory volume**;** mL – milliliters; CI – confidence interval.

Number of subjects available for analysis for PRISm, GOLD 0, GOLD 1, GOLD 2, GOLD 3, GOLD 4 groups were 267, 1055, 227, 515, 320 and 113, respectively; number of records available for analysis for the respective groups were 481, 1891, 404, 913, 543 and 183. Some records were not usable due to missing data for BDR, emphysema rate, exacerbations, or some combination of these (see Table 1 and Online Supplement for more details).

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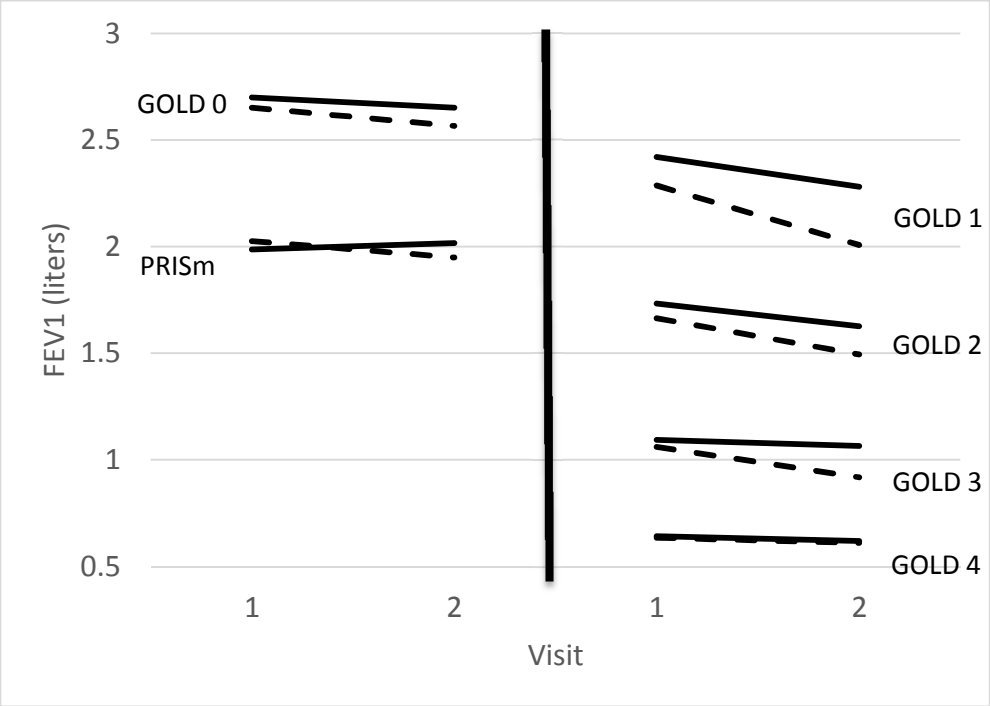
Figure 1. Estimated FEV_1 changes by GOLD group and severe exacerbations status.



Estimates were obtained from linear mixed model fits (see Statistical Analyses section) for the Completerand Late subjects. The plot demonstrates that those with at least one severe exacerbation (dotted lines) had faster declines in FEV1, on average, compared with those that did not (solid lines), for each GOLDgroup.

Online Data Supplement

Acute Exacerbations and Lung Function Loss in Smokers with and without COPD

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Handling missing data and deaths

To minimize the impact of bias on estimates due to loss of follow up, Late subjects were included in the primary analysis along with the Completers. (As defined in the text, the Late subjects included those at least 1 year overdue or those that requested no further contact regardless of their due time for Visit 2.) Since many of the deceased subjects presumably had COPD-related deaths, they were not included in this primary analysis since their death was considered an alternative outcome rather than an event that led to missing data, and in our final results we consider death rates by GOLD group jointly along with FEV_1 progression statistics. However, since cause of death was not available for deceased subjects, we did perform a sensitivity analysis that included deceased subjects, using their Visit 1 data. We also analyzed only complete subjects as an additional sensitivity analysis. Both of these sensitivity analyses yielded results that were fairly similar to the primary analysis. We include the completers-only analysis for comparison, in the *Completers only analysis*section below.

With only 2 visits, addressing missing data is difficult, since we do not have any information about progression of illness for all subjects that missed Visit 2. Still, performing mixed model analyses that include 'partial' subjects allows the opportunity to address bias in estimates as long as data are missing at random (MAR) [32]. This is likely to be an improvement on the 'complete case' analysis that is not guaranteed to yield unbiased estimates unless data are 'missing completely at random' (MCAR), which is a more restrictive type of missing data mechanism, and in fact is a special case of MAR data.

Among the 4861 records for Completer and Late subjects for which lung function data were available, 446 (9%) were dropped from analysis due to missing values for one or more predictors (145 records were dropped for Completers and 301 for Late subjects). Table 3 lists number of subjects and records available for analysis by GOLD group.

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It is possible that data were *missing not at random* (MNAR) to some degree and that this could have affected estimated disease progressions (e.g., subjects missing Visit 2 might have had an average FEV1 decline greater than that of Completers). Although there are methods to account for MNAR data, it requires assumptions difficult or impossible to verify. It is particularly difficult for longitudinal data with only 2 visits. We were somewhat reassured that baseline characteristics of Completers, Late and Deceased subjects were fairly similar, although it doesn't proved that progressions would be similar. We highlight these points in a limitations paragraph in the Discussion section. Since many of the deaths occurring in subjects before Visit 2 could have been due to complications of COPD, we did not view such events as leading to missing values at Visit 2, although certainly many of these subjects could have had rapid declines in FEV1. Instead, we chose to consider survival rates as joint information with COPD declines by GOLD stage. Clearly, although declines were less as GOLD stage increased, survival rates decreased.

Comparing Completer, Deceased and Late subgroups

Supplemental Tables S1a and S1b show characteristics of each subgroup (Completers, Deceased, Late). Variables were compared separately for each GOLD group using Fisher's Exact tests for categorical variables and t-tests for continuous variables. Bolded numbers with asterisks show when $p<0.01$ for differences between the comparison group relative to the Completer group. Tests were performed for FEV_1 % of predicted but not raw FEV_1. Among the 144 tests performed (for the 12 variables x 6 GOLD groups x 2 subgroup comparisons), only 10 were significant at the 0.01 level, 2 for Late versus Completers and 8 for Deceased for Completers. There did not appear to be a strong pattern over variables or GOLD groups, except perhaps for slightly lower mean FEV_1 for Deceased vs. Completers in GOLD 2-4.

Computing visit-specific and change estimates

Estimates of change presented in Tables 3 and S2 used the same values of time-varying covariates at both visits, so that the changes represent the progression in outcomes for subjects not due to expected changes in age, height, weight or BDR. Estimates presented in Figures 1 and S1 used 'least squares means', which means that average values of covariates were used (for class variables this means a straight average over the levels). Thus, differences between visits also factor out expected changes due to the time-varying covariates.

Supplemental Table S1. Baseline characteristics of subjects by group type (Completers, Deceased, Late).

Supplemental Table S1a: counts and percentages for binary demographic variables. Bold and asterisk indicates p<0.01 for given group compared with Completers (within GOLD stage). †Counts and percentages for smoking variable represent current or mixed use (versus former).

	Group	PRISm		GOLD 0		GOLD 1		GOLD 2		GOLD 3		GOLD 4	
Sample size	Completers	225		878		185		412		229		71	
	Deceased	66		115		27		127		151		174	
	Late	93		345		65		168		128		62	
		n	%	n	%	n	%	n	%	n	%	n	%
Female	Completers	120	53	457	52	83	45	190	46	100	44	32	45
	Deceased	35	53	33	**29***	8	30	54	43	62	41	68	39
	Late	51	55	183	53	26	40	89	53	71	55	26	42
Caucasian Race	Completers	123	55	568	65	147	79	314	76	180	79	62	87
	Deceased	37	56	62	54	22	81	98	77	129	85	146	84
	Late	43	46	138	40	9	14	42	25	22	17	14	23
Smoking†	Completers	131	58	486	55	86	46	184	45	93	41	19	27
	Deceased	47	71	86	**75***	17	63	70	55	52	34	41	24
	Late	61	66	220	**64***	36	55	77	46	38	30	16	26
ICS only	Completers	19	9	11	1	4	2	31	8	29	13	13	19
	Deceased	2	3	1	1	2	7	17	14	28	20	39	24
	Late	7	8	7	2	6	9	10	6	16	13	15	25
LABA only	Completers	5	2	4	0.5	1	1	24	6	22	10	10	15
	Deceased	0	0	0	0	1	4	9	7	20	14	27	16
	Late	0	0	1	0.3	1	2	10	6	7	6	13	22
LAMA only	Completers	18	8	20	2	20	11	104	26	108	48	46	65
	Deceased	6	9	1	1	3	12	47	**39***	95	**65***	112	66
	Late	8	9	8	2	3	5	54	33	76	59	42	70
ICS and LABA	Completers	34	15	28	3	16	9	114	28	119	52	48	68
	Deceased	5	8	5	5	2	7	50	41	87	60	112	65
	Late	10	11	14	4	7	11	55	34	73	57	35	57

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Supplemental Table S1b: means and standard deviations for continuous demographic variables. Bold and asterisk indicates p<0.01 for given group compared with Completers (within GOLD stage).

	Group	PRISm		GOLD 0		GOLD 1		GOLD 2		GOLD 3		GOLD 4	
Sample sizes	Completers	225		878		185		412		229		71	
	Deceased	66		115		27		127		151		174	
	Late	93		345		65		168		128		62	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Emphysema, %	Completers	2.1	3.2	2.8	3.1	7.5	7.0	8.7	8.3	17.7	12.7	26.6	13.4
	Deceased	1.5	1.6	2.3	3.1	8.7	7.5	10.2	10.2	20.1	13.2	28.3	14.7
	Late	**1.3***	1.5	2.2	2.9	6.2	6.2	8.8	8.0	19.2	13.3	23.4	11.6
BDR, Liters	Completers	0.15	0.36	0.09	0.28	0.26	0.44	0.36	0.48	0.40	0.49	0.30	0.46
	Deceased	0.20	0.40	0.14	0.34	0.23	0.43	0.33	0.47	0.42	0.49	0.33	0.47
	Late	0.09	0.28	0.10	0.30	0.25	0.43	0.37	0.49	0.34	0.48	0.26	0.44
Age, years	Completers	58.3	8.3	58.0	8.6	64.0	8.2	63.3	8.5	63.8	7.9	63.2	7.7
	Deceased	57.8	9.6	57.6	9.5	67.4	8.3	64.4	9.1	**68.2***	8.3	65.2	7.7
	Late	58.1	7.8	56.7	9.1	62.9	10.3	62.7	8.9	65.4	8.4	63.5	7.3
BMI, kg/m^2	Completers	32.3	6.9	28.9	5.7	27.1	4.8	28.6	5.8	28.2	6.0	26.7	5.5
	Deceased	31.2	8.0	29.1	6.1	25.6	5.3	27.8	6.5	27.1	6.4	25.3	5.7
	Late	31.2	7.0	28.5	6.0	27.5	6.0	29.0	6.3	27.9	6.5	26.7	5.9
FEV_1 at BL, Liters	Completers	2.06	0.49	2.84	0.67	2.60	0.66	1.88	0.49	1.16	0.30	0.69	0.17
	Deceased	2.01	0.56	2.92	0.58	2.62	0.61	1.77	0.56	1.04	0.27	0.61	0.18
	Late	2.04	0.49	2.86	0.68	2.69	0.61	1.81	0.52	1.08	0.27	0.65	0.20
FEV_1 at BL, % pred	Completers	70.5	8.3	97.5	11.3	91.5	9.0	65.0	8.4	40.7	5.8	23.8	4.0
	Deceased	68.7	11.0	95.7	11.1	91.6	10.8	**61.5***	8.3	**38.7***	5.6	**21.6***	5.0
	Late	70.8	7.2	98.2	11.4	91.1	9.2	64.1	8.8	40.0	5.2	23.0	4.7

Abbreviations: GOLD – Global Initiative for Obstructive Lung Disease; PRISm – preserved ratio impaired spirometry; FEV_1 – forced expiratory volume in one second; ICS – inhaled corticosteroid; LABA – long-acting beta agonist; LAMA – long-acting anti-muscarinic; BMI – body mass index; BDR – bronchodilator responsiveness; BL – baseline; SD – standard deviation.

Completers only analysis

The following table and figure are similar to Table 3 and Figure 1 in the main text, but using only subjects that completed both Visit 1 and 2 (Completers).

Supplemental Table S2: Effect of each exacerbation/acute respiratory event on rate of FEV_1 decline, completers only.

	Exacerbations/Acute Respiratory Events of Any Severity		Severe Exacerbations/Acute Respiratory Events	
	Change in FEV_1,mL/year (95% CI)			
Subject Group	Change in those with no exacerbations	Excess change, per exacerbation of any severity	Change in those with no severe exacerbations	Excess change, per severe exacerbation
PRISm	5 (-5, 14)	-6 (-15,4)	5 (-4,14)	-18 (-37,2)
GOLD 0	-7 (-12,-2)	-7 (-16,2)	-8 (-12,-3)	-7 (-27,13)
GOLD 1	-25 (-35,-14)	-21 (-43,0)	-26 (-36,-16)	-75 (-141,-10)
GOLD 2	-19 (-27,-11)	-10 (-20,-1)	-21 (-29,-14)	-20 (-40,1)
GOLD 3	-10 (-19,-2)	-8 (-14,-1)	-12 (-20,-5)	-19 (-35,-3)
GOLD 4	-3 (-16,10)	-1 (-10,8)	-1 (-12,10)	-12 (-33,9)

Abbreviations: GOLD – Global Initiative for Obstructive Lung Disease; PRISM – preserved ratio impaired spirometry; FEV_1 – forced expiratory volume; mL – milliliters; CI – confidence interval. Number of subjects available for analysis for PRISm, GOLD 0, GOLD 1, GOLD 2, GOLD 3, GOLD 4 groups were 216, 846, 179, 400, 225 and 71, respectively; number of records available for analysis for the respective groups were 430, 1682, 356, 798, 448 and 141. Some records were not usable due to missing data for bronchodilator responsiveness, percent emphysema, exacerbations, or some combination of these.

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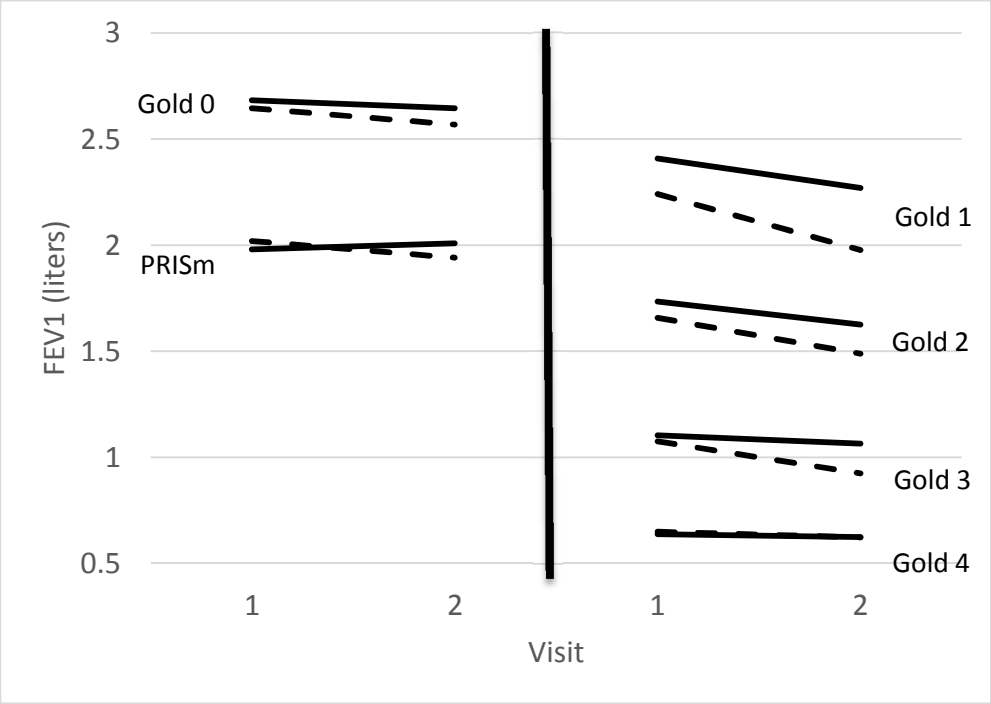
Supplemental Figure S1. Estimated FEV_1 changes by GOLD group and severe exacerbations status (solid line = no severe exacerbation; dashed line = at least one severe exacerbation during follow up), Completers only.



Estimates were obtained from linear mixed model fits (see Statistical Analyses section) for the Completer subjects only.