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Exacerbations and lung function decline in COPD: New insights in current and ex-smokers

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Summary
Aim: To investigate whether there is a significant relationship between an increased frequency of exacerbations and the rate of forced expiratory volume in 1 s (FEV_1) decline in COPD patients.
Methods–measurements: About 102 COPD patients (44 smokers, 58 ex-smokers) participated in a 3-year prospective study. Exacerbations were identified as worsening of patient's respiratory symptoms as recorded on diary cards. Spirometry was performed every 6 months. The effect of frequent exacerbations on lung function was investigated using random effects models.
Results: The median (mean(95% CI)) annual exacerbation rate was 2.85 (3.1 (2.7–3.6)). Patients with an annual exacerbation rate over the median rate had significantly lower baseline post-bronchodilation FEV_1(%pred), higher MRC dyspnoea score and chronic cough compared to patients who had an annual exacerbation rate less than the median. The average annual rate of FEV_1(%pred), adjusted for smoking decline (ΔFEV_1), was found significantly increased in frequent compared to infrequent exacerbators ($P = 0.017$). The highest ΔFEV_1 was observed in smokers frequent exacerbators and a significant interaction between exacerbation frequency and ΔFEV_1 was also observed in ex-smokers.
Conclusions: Our findings suggest that an increased frequency of exacerbations is significantly associated with FEV_1 decline even in ex-smokers. Thus, smoking and frequent exacerbations may have both negative impact on lung function. Smoking cessation and prevention of exacerbations should be a major target in COPD.

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Introduction

In COPD, exacerbations caused mainly by infections of the tracheobronchial tree or inhalation of toxic gases,[1] are an important characteristic of the disease. During an exacerbation a remarkable worsening of a patient's baseline symptoms is observed. COPD exacerbations are the major cause of physician visits and hospital admissions associated with acute respiratory failure, causing premature mortality as well as a worsening of the quality of life.[1] Furthermore, the number of past exacerbations has been related both to the risk of future recurrent exacerbations and to relapse following treatment.[2] Thus, frequent exacerbations followed by incomplete recovery may be an important risk factor of lung function decline.[3] However, the influence of exacerbations on the progression of the COPD has not been well established.[4–6]

The British Hypothesis, proposed in the 1960s, was that repetitive chest infections or chronic airway infection might be the cause of airway obstruction. This hypothesis was tested in two longitudinal studies, the conclusions of which were that exacerbations had no effect on the annual rate of change of FEV_1.[4,5] However, the landmark study of Fletcher and Peto[4] was performed only in patients with mild COPD. Other studies on lung function decline have come to the opposite conclusion. Kanner et al.[7] found an accelerated rate of FEV_1 decline due to lower respiratory illnesses in smokers with mild COPD. Donaldson et al.[8] reported a relation between exacerbations and lung function decline in 32 COPD patients. The same group also reported an incomplete recovery of lung function in 7% of COPD patients.[3] In this setting, questions still remain due to small number of carefully designed studies of appropriate patients with varying disease severity.

Our primary aim in this study is to investigate whether an increased frequency of exacerbations is associated with an accelerated rate of FEV_1 decline in both smokers and ex-smokers with COPD.

Methods

Patients

This investigation was a 3-year prospective study, incorporating a run-in period and outpatient clinic visits, scheduled every 3 months. Consecutive sampling was used to recruit patients with a diagnosis of COPD according to the GOLD definition,[9,10] who attended the respiratory outpatient clinic at Chania General Hospital on the island of Crete, Greece, between June 2002 and October 2002. A history of bronchial asthma or other respiratory disease and continuous use of systemic steroids more than 30 days in the previous year were used as exclusion criteria. One hundred and six patients agreed to participate. Seventy-three patients were continuously being taken care of at the clinic and of 33 patients referred to the clinic for first time during the recruitment period and fulfilled inclusion criteria. The study was approved by the ethics committee of the local health authority and the patients provided their consent.

At recruitment participants provided responses to questions related to smoking history, respiratory symptoms and signs, MRC (4-point scale) and current medication use.[11,12] Smoking status was verified by exhaled CO at each visit.[13] A run-in period of 4 weeks following recruitment was used to ensure that all patients had been free of an acute exacerbation and had not received antibiotics or short courses of systemic corticosteroids over the same period. Four subjects were withdrawn during the run-in period. The remaining 102 patients were reviewed for a total follow-up of 3 years.

Spirometry

Every 6 months post-bronchodilation spirometry was performed following premedication with 200 μg salbutamol via metred-dose inhaler, according to standardized guidelines guidelines,[14] using a computerised system (Lab, 2.12; Jaeger; Wuerzburg, Germany). Attention was taken on the day that the spirometry was performed, the subject was free of an exacerbation; otherwise the test was postponed until recovery.

Definition of COPD exacerbation

The definition of an exacerbation was based on criteria described previously by Anthonisen et al.[15] requiring either, increase of at least two major respiratory symptoms (dyspnoea, sputum amount, and sputum purulence) or, increase of one major symptom in addition to at least one minor symptom (wheeze, cough, fever, nasal discharge, sore throat), for at least two consecutive days. The first day with increased symptoms was taken as the onset of the exacerbation. Following an exacerbation, patients were required to have a 2-week period (recovery period) with the same or less symptoms as those present before the start of an exacerbation before another exacerbation was studied.

Monitoring of exacerbation

A patient directed diary card and hospital-outpatient clinic data were used to identify exacerbations.

Diary card: The development of the diary card was based in previously used diary card[16] following accepted principles.[15] Accordingly, all patients were instructed to record, at the end of each day, any increase in major and minor symptoms with regard to the last 24 h. Patients recorded changes in their symptoms using a binary coded system. For each symptom, two options were available on the diary card: either increased perception/new onset or not. Consequently, they were instructed to mark the corresponding area on the diary card, when they perceived an increase over their normal, stable condition in chronic symptoms or symptoms of new onset, otherwise they had to mark the area of ''no increase perception/no new onset''.

Patients were seen and diary cards were collected in scheduled outpatient clinic visits every 3 months. Patients were also instructed to call three members (D.M., A.D., E.N.) of the medical team and to attend unscheduled visits whenever they noticed deterioration in symptoms. In these cases, patients were assessed within 48. Their symptoms were validated and exacerbations were diagnosed according to Anthonisen's criteria and termed as ''reported

exacerbations''. A standard protocol based on GOLD statement[9] was used for individual exacerbation treatment.

The diary symptom card was checked for repeatability and accuracy. Briefly, a member of the medical team (AD)—blinded to patient's progress—visited 25 patients, randomly selected, thrice in each year and administered a symptoms-questionnaire identical to diary cards, with regard to the last 24 h. Consequently, the correlation between questionnaire and diary card was evaluated for all items. Significant correlations were found in all items; the lowest correlation was found in nasal discharge item ($\rho = 0.74$, $P = 0.001$). Additionally, 25 patients randomly selected, were especially instructed to notify the medical centre when they had increased symptoms. These patients were seen on the same day and consequently on the 7th, 14th, 21st, 30th day by a member of the medical team (EN) who administered the above-mentioned questionnaire. This procedure was repeated until 75 cases of exacerbation were available for assessment. The agreement between questionnaire and diary card as to whether an exacerbation was ended or not, was 88%.

Medical records: Exacerbations where no diary card symptoms were recorded were identified by questioning the patients about their symptoms when at the clinic visits or, or by reviewing the outpatient clinic and admissions medical records every 6 months.

Exacerbation rate

The total number of exacerbations was obtained by adding the number of exacerbations recorded in the diary cards to the number of exacerbations identified in the medical records that were not recorded in the cards (Fig. 1). The annual rate for each patient was calculated by dividing the total number of exacerbations by the number of days participated in the study and multiplying by 365.

Classifications

Patients were grouped into two categories according to the annual rate of total number of exacerbations experienced. Those experiencing more than the median annual exacerbation rate were termed ''frequent exacerbators'' whereas these with fewer than the median were considered ''infrequent exacerbators''. This classification scheme was used in previous studies of similar design.[8] Each of the two above categories were then classified into two subgroups, current or ex-smoker.

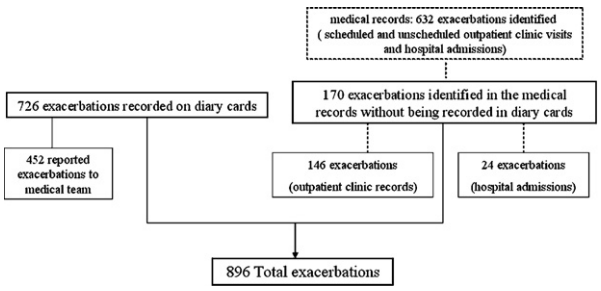

Figure 1 Registration characteristics of exacerbations in this study.

Statistical analysis

Random effects modelling (REM or the multilevel model for change) was used to investigate the possible relationship between exacerbation frequency and lung function decline. REM is the most suitable method for estimating rates of change, with allowance for the correlation structure of repeated measurements.[17] In analysis, the dependant variable was change in post-bronchodilation forced expiratory volume in 1 s (FEV_1) expressed either as a percentage of the predicted value or in millilitres (ml) logarithmically transformed, adjusting for age, height, sex and baseline lung function. Initially, unconditional growth models were fitted in order to describe net variation in slope and intercept between individuals. Subsequently, conditional analyses were undertaken in which systematic inter-individual differences in intercept and slope were examined as a function of the binary fixed effect representing frequent/infrequent exacerbations, adjusting for smoking status. Power analysis based on sample size gave a power of over 80% to detect a difference of 1 percentage unit between two groups, based on 5 repeated measurements, variance 500 and a correlation of about 0.9 between respective measurements.

Smokers and ex-smokers were also considered as separate groups. Full maximum likelihood estimation was used in all models and improvement in model fit was assessed using Akaike's information criterion (AIC). Fixed effects were tested for statistical significance using *t*-statistics. Model fit was assessed using plots of levels 1 and 2 standardized residuals against fitted values. The *lme* function in the *nlme* package in the *R* environment (*R* versus 1.7) was used.[18]

Analysis was repeated stratifying the patients into two groups according either to the median rates of reported exacerbations or, of medical records identified exacerbations. Similar results were obtained and therefore are not presented in detail.

Results

Baseline characteristics of participants are presented in Table 1. According to the GOLD severity of COPD 22(21.5%) patients were stages 0–I, 33(32.5%) were stage II, 29(28.5%) were stage III, 18(17.5%) were stage IV. Six subjects were lost to follow up and 13 died during the 3-year study period. These subjects were at baseline of similar age, FEV_1 (%pred), and smoking status to those who completed more than five spirometric assessments ($P > 0.05$). The participants recorded their symptoms on the diary cards for median(IQR) 720(720–1080) days. There was no significant difference in compliance rates of the diary cards between frequent and infrequent exacerbators (Mann–Whitney *U*-test, $P = 0.83$).

There were available 597 spirometric assessments for analysis which are less than scheduled because of patient withdrawals, missing assessments or, exacerbations. Frequent exacerbators performed mean(95% CI) 5.2(5.6–5.9) spirometric tests and infrequent exacerbators 4.5(5.1–6) ($P = 0.12$).

Table 1 Baseline characteristics of 102 COPD patients, overall and by smoking status.

	Overall $n = 102$	Ex-smokers $n = 58$	Current smokers $n = 44$	P-value**
Age (years)	65 (1.0)	68.5 (1.0)	62 (1.6)	0.002
Male/female	86/16	51/7	35/9	NS
FEV_1 (%pred)*	56.4 (2.2)	52.4 (2.9)	61.8 (3.2)	0.047
Pack-years	52.7 (2.3)	55 (3.4)	49 (2.9)	NS
FEV_1/FVC (%)	55 (1.5)	54 (2.1)	57.9 (2.2)	NS
MRC score	1 (0–4)	2 (0–4)	1 (0–3)	NS
Chronic cough, *n* (%)	68 (66.6)	38 (65)	30 (68)	NS
Chronic sputum, *n* (%)	48 (47)	28 (49)	20 (45.5)	NS
Chronic wheeze, *n* (%)	33 (32)	19 (33)	14 (32)	NS
Inhaled steroids, *n* (%)	38 (37)	22 (38)	16 (36)	NS
Inhaled LABAs, *n* (%)	39 (38)	23 (40)	16 (36)	NS

Continuous data are expressed as mean (SE), MRC score are presented as median (min–max) unless otherwise indicated. NS = non-significant ($P > 0.05$), MRC = Medical Research Council, LABAs = long acting beta 2 agonists.
*Post-bronchodilation value.
**Current and ex-smokers characteristics were compared using the Mann–Whitney test (for continuous variables) or χ^2 test (for categorical data), as appropriate.

Exacerbations

Ninety-five (93%) patients experienced at least one exacerbation over the 3-year study period. The overall median (mean(95%CI)) annual exacerbation rate was 2.85 (3.1 (2.7–3.6)). The exacerbation rates were 3 (3.3 (3–3.9)), 3 (2.8 (2.5–3.2)) and 2 (2.3 (1.8–2.8)) for the first, second and third year, respectively. About 81% of total exacerbations were recorded on the diary cards; 19% of total exacerbations were not recorded on the cards and were identified from the medical records (outpatient clinics and admissions).

There were no significant differences in the exacerbation rate between smokers and ex-smokers (Fig. 2). Baseline characteristics of COPD patients according to exacerbation status are presented in Table 2. Frequent exacerbators had significantly lower baseline FEV_1% compared to infrequent exacerbators (51.8% versus 60.2%, Mann–Whitney *U*-test, $P = 0.048$), although no differences in the main treatment modalities (long acting beta-2 agonists and/or inhaled corticosteroids) used in frequent and infrequent exacerbators (χ^2, $P > 0.05$) were observed. The GOLD severity scale of the disease was associated with the number of exacerbations and the number of admissions to hospital (Kruskal–Wallis, *P*-values 0.007 and 0.0005, respectively).

Additionally, the annual hospital-admission rate due to severe exacerbations was 0.35 (0.27–0.42). The number of admissions was correlated with the number of exacerbations of each patient ($\rho = 0.6$, $P = 0.001$). The duration of hospitalisation (days) was longer in frequent than in infrequent exacerbators 7.3(6.1–8.5) versus 4.3(3.5–5.1), respectively, $P = 0.045$).

Lung function decline

The mean annual rate of FEV_1 (%pred) decline (ΔFEV_1,%pred/year) of the entire group was 2.6 (95% CI 2.2, 3.0, $t = -7.33$, $P < 0.0001$) corresponding to an absolute value of 74 ml/year. REM analysis revealed that the annual rate of decline was significantly higher in smokers compared to ex-smokers and the estimated effect of smoking, adjusting for exacerbation status, added to the 3-year average decline in FEV_1 (%pred) −1.8 (−2.1, −1.5) percentage units per year ($P = 0.004$).

There was a significant interaction between FEV_1 decline and exacerbation frequency (Fig. 3). REM analysis revealed that ΔFEV_1, %pred/year was significantly higher in frequent exacerbators than in infrequent exacerbators, controlling for smoking status. The estimated effect of frequent exacerbations added to ΔFEV_1, %pred/year −1.4 (−1.05, −1.75) percentage units ($P = 0.017$).

When REM was applied for frequent and infrequent exacerbators in each smoking category, a statistically significant decrease in FEV_1 over the 3-year period was seen in each category, but not in ex-smokers infrequent exacerbators (Table 3).

The analyses were repeated using the log-transformed FEV_1 values (ml). The results were very similar to the above and therefore are not presented in detail.

Discussion

In this investigation, we evaluated the interaction between FEV_1 and COPD exacerbations in a population consisting of 102 patients with COPD of varying severity for a total of 3-year follow-up period. The main findings of this study are (i) COPD patients with frequent exacerbations showed a higher rate of decline in FEV_1 compared to patients with infrequent exacerbations, (ii) the highest rate of decline in FEV_1 was demonstrated in smokers who are frequent exacerbators, and (iii) although the data of this study suggest that smoking is a major determinant of the lung function decline in COPD, the novel point is the considerable interaction between exacerbation frequency and lung function decline in COPD even in ex-smokers. These findings support previous studies reporting that increased frequency

Table 2 Baseline characteristics of frequent (⩾median annual exacerbation rate) and infrequent exacerbators (<median annual rate).

	Frequent exacerbations $n = 51$	Infrequent exacerbations $n = 46$	P-value*
Age (years)	67 (3)	63 (2.5)	NS
Male/female	42/9	39/7	NS
Current smokers/ex-smokers	22/29	19/27	NS
Pack-years	55 (3)	49 (4)	NS
FEV_1 (%pred)†	51.8 (3)	60.2 (3)	0.048
FEV_1/FVC (%)	52.5 (2)	58.5 (2)	NS
MRC score, median (min–max)	2 (1–4)	1 (0–3)	0.005
Chronic cough, *n* (%)	40(78)	24(52)	0.005
Chronic sputum, *n* (%)	26(51)	19 (41)	NS
Chronic wheeze, *n* (%)	18(35)	12(26)	NS
Respiratory symptoms at baseline‡	39 (76)	23 (50)	0.005
Inhaled steroids, *n* (%)	16 (31)	21 (45)	NS
Inhaled LABAs, *n* (%)	15 (29)	22 (47)	NS

Continuous data are expressed as mean (SER) unless otherwise indicated. NS = non-significant ($P > 0.05$), MRC = Medical Research Council, LABAs = long acting beta 2 agonists.

*Current and ex-smokers characteristics were compared using the Mann–Whitney test (for continuous variables) or χ^2 test (for categorical data), as appropriate.

†Post-bronchodilation value.

‡At least two out of the following four symptoms were present: cough, sputum, MRC dyspnea score ⩾2, wheezing.

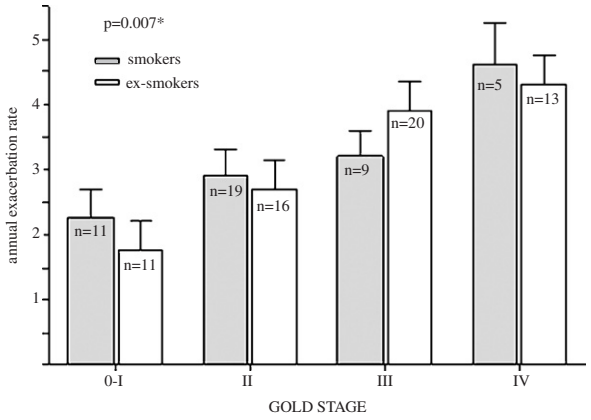

Figure 2 COPD exacerbations during the 3-year study period according to GOLD stages. *Difference between GOLD stage of disease severity.

of exacerbations is significantly associated with FEV_1 decline.[7,8]

This study has limitations. First, the definition of COPD exacerbation is still under discussion and no consensus exists for the identification of exacerbations.[3,7,19,20] However, we used the generally accepted definition of Anthonisen's et al.[15] and on baseline, we evaluated baseline patients' status using previously validated questionnaires.[11,12] Second, it is known that COPD patients have a low perception of dyspnoea and underreport exacerbations to physicians.[21] In order to increase the accuracy of the diagnosis of an exacerbation, we used daily records data of respiratory symptoms. This is an accepted methodology for the assessment of COPD exacerbations in terms of symptoms.[8,21] Despite the fact that collecting daily prospective data on symptom changes is rather difficult to be applied widely in the everyday clinical practice, it offers the advantage that episodes when patients experience an exacerbation and record their symptoms but do not consult their physician can be analysed. In this way, we found a median annual exacerbation rate of 2.85 (mean 3.1) which is similar to previously reported rates where diary cards were used[8] and higher than the reported rates when symptoms questioning alone was used.[7,20] Some might argue that the criteria used in this study for definition, onset and resolution of exacerbations are subjective, not "solid" and therefore of low clinical importance because they depend on patients reports of symptoms. However, these criteria are applied widely in medical practice and previous studies used similar methodology.[8,15,22,23]

The main endpoints of this study were assessed at 3- and 6-month intervals, during the 3-year follow-up period. Despite that a 3-year period is a relatively short time period in the course of the disease, it is a sufficient period for statistical evaluation. In addition, the primary aim of the lung function modelling procedures presented here was to assess the rate of change in FEV_1 with time rather than focus on absolute FEV_1 values. Furthermore, the use of daily cards for the diagnosis of exacerbations requires patient's compliance that may decrease with time. Thus, we believe that the 3-year follow-up period of this study was a reasonable duration for balancing diagnostic accuracy and compliance.

It might be implying that although we are seeing high rates of decline in frequent exacerbators, this may be because they have lower baseline values and not because they are frequent exacerbators. We believe that this was not the case in the present study. In order to control further

Table 3 Average annual FEV_1 decline (%pred)* over the 3-year-study period obtained using random effects modelling, for all COPD patients, smokers and ex-smokers separately, by exacerbation status.

Exacerbation status	Smokers				Ex-smokers			
	n	Mean	95% CI		*n*	Mean	95% CI	
Frequent exacerbations (⩾median annual rate)	22	−4.10	(−4.40, −3.80)	$P<0.0001$	29	−2.80	(−3.1, −2.5)	$P<0.0001$
Infrequent exacerbations (<median annual rate)	19	−3.15	(−3.55, −2.75)	$P=0.002$	27	−0.85	(−1.1, −0.5)	$P=0.3$

*Adjusted for sex, age, smoking status, baseline FEV_1 (%pred).

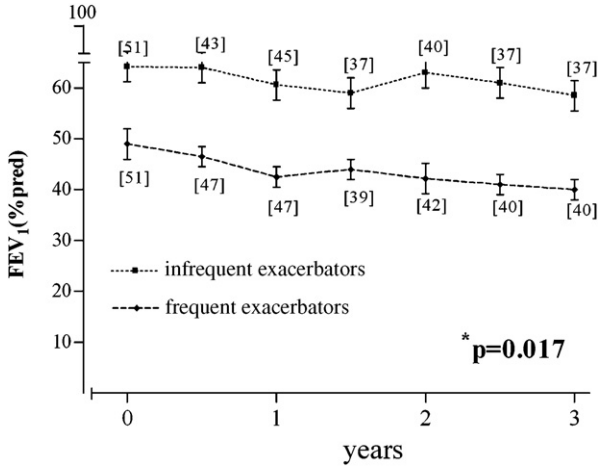

Figure 3 FEV_1(%pred) change from baseline over the 3-year study period by total exacerbation status. Values are means with bars representing SE and numbers in brackets reflect patients with valid readings at each time point. *Difference in average annual decline rate in FEV_1(%pred) between frequent and infrequent exacerbators, obtained by REM.

for the "horse-racing effect", we have modelled the complete FEV_1 growth trajectory (intercept and rate of change) of each individual and have assessed differences in rates of change over time, whilst also accounting for possible differences in baseline values between groups. Furthermore, to ensure that baseline FEV_1 are not too different between groups we classified the study population into relatively homogeneous groups (GOLD) and then applying the REM.

The progressive decline of lung function reported in our COPD patients is greater than that reported in the general population.[4] However, there is considerable intersubject variation in the rate of FEV_1 decline, depending on the population studied. For example, Simmons et al.[24] reported rates of 60–100 ml/year among smokers with mild-to-moderate COPD while the ISOLDE study reported 50 and 59 ml/year decline in FEV_1 in fluticasone treated and placebo groups, respectively.[25] In the present study, the estimated overall mean FEV_1 decline was 74 ml/year but our sample may be more homogenous in terms of race-ethnicity since all patients were white Greeks living in the island of Crete and in their vast majority male. In addition our population represented mainly COPD patients followed at a specialist hospital clinic. In this respect, it is reasonable to consider that less symptomatic patients were probably not referred to the clinic.[26] This could be also a plausible explanation for the fact that ex-smokers had similar cough, sputum production and use of medication as the continuous smokers in this study. On the other hand this population is probably more heterogeneous than those of other studies with respect to baseline disease severity, smoking status and particularly treatment modalities; for instance a total of 38% of our patients were treated with inhaled steroids. Therefore, the conclusions drawn in the present investigation should be rather applied to male COPD patients with increased respiratory symptoms than to the general COPD population.

The present study shows that frequent exacerbations are associated with an accelerated loss of FEV_1 compared to infrequent exacerbations. Our findings is in accordance with previous studies,[7,8,27] although their design was different from our study in terms of the population studied and outcome assessment. Donaldson et al.[8] prospectively followed 109 COPD patients for 4 years based on diary cards, but the assessment of FEV_1 decline was made on a subgroup of 32 patients of their cohort. Kanner et al.[7] found an accelerated FEV_1 decline only in smokers with frequent exacerbations. However, they assessed exacerbation only by questioning their participants annually, and their group comprised relatively young individuals with early COPD. These reasons could explain the low reported exacerbation rate (0.24 $year^{-1}$) in the latter study. Dowson et al.[27] found a significant interaction between exacerbation frequency and lung function decline in terms of vital capacity and diffusing capacity of the lung for carbon monoxide but not with FEV_1. However, their data derived exclusively from patients with a_1-antitrypsin-deficiency and exacerbation data were mainly collected at 6-month assessment.

In agreement with other studies,[7,28] the smokers in this study had a more rapid FEV_1 decline, particularly those with frequent exacerbators. Smoking is known to be associated with both increased airway inflammation and accelerated rate of FEV_1 decline.[4,29] However, the inflammatory manifestation of current smoking may mask the underlying ongoing inflammatory process characterizing COPD.[30] Previous studies have shown that airway inflammation induced by smoke may persist independently from smoking.[29,31]

A notable observation of our study is that COPD ex-smokers with frequent exacerbations exhibited a significantly increased rate of FEV_1 decline. In contrast, ex-smokers infrequent exacerbators exhibited no significant loss of lung function. This is of importance because the course of the disease in patients with advanced COPD is not well defined, particularly in patients quitting smoking.[32] In a previous study, Kanner and colleagues[7] found no significant interaction between exacerbations and FEV_1 in subjects who quitted smoking. However, their data were derived from a population with early COPD (mean FEV_1 78.2%pred) and low exacerbation frequency. Thus, we believe that in our cohort of COPD patients with advanced disease, a higher frequency of exacerbations was significantly associated with a negative impact on FEV_1 decline even in ex-smokers.

It should be underlined here that this significant association between exacerbations and FEV_1 decline does not prove a causal relationship. Increased frequency of exacerbations may directly accelerate loss of FEV_1, but the opposite could be also possible: loss of lung function may lead to increased exacerbation frequency. In this respect, a randomized longitudinal clinical intervention study is necessary to assess definitively whether or not frequent exacerbations are the cause of an accelerated rate of lung function decline. However, our findings still suggest a positive feedback involving frequency of exacerbations and FEV_1 decline and that a common pathway for both these two important parameters is possible. Furthermore, the positive association between lung function decline and exacerbation frequency suggests a considerable negative impact of exacerbations on health status and costs. Especially, if one considers that patients with impaired lung function experience also more severe exacerbations.[33]

In summary, although the data suggest that continuing smoking is the major determinant of accelerating loss of lung function, an increased frequency of exacerbations appears also to be associated with an accelerate rate of lung function decline. Thus, therapies that have an impact upon exacerbation frequency may modify chronic obstructive pulmonary disease progression in terms of lung function and overall health status. Physicians in charge of patients with COPD should encourage early reporting of all exacerbations in this patient group and they should be alert to offer them prompt therapy. In COPD, not only smoking cessation but also a decrease frequency of exacerbations should be a major target of management.

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