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Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis

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Abstract

Background: It is unknown what proportion of long term lung function decline in cystic fibrosis (CF) is explained by pulmonary exacerbations. The aim of this study was to determine how exacerbations requiring hospitalization contribute to the course of CF lung disease .

Methods: This was a retrospective cohort study. The primary outcome was the rate of decline of forced expiratory volume in 1 second percent predicted (FEV_1% pred).

Results: Of 851 subjects, 415 (48.8%) subjects had $\geq$1 exacerbation. After adjustment for confounders, the annual rate of FEV_1 decline in those without an exacerbation was 1.2%/yr (95% CI: 1.0;-1.5), compared with 2.5%/yr (95% CI: 2.1; 2.8) in those with an exacerbation. The proportion of overall FEV_1 decline associated with $\geq$ 1 exacerbation was 52% (95% CI: 35.0; 68.9). For a given number of exacerbations, the annual rate of FEV_1 decline was greatest in subjects with $\leq$ 6 months between exacerbations.

Conclusions: Half of FEV_1 decline seen in CF patients was associated with pulmonary exacerbations. Time between exacerbations, specifically $\leq$ 6 months between exacerbations, plays an important contribution to overall lung function decline. These findings support using time to next exacerbation as a clinical endpoint for CF trials.

Introduction

Pulmonary exacerbations are significant clinical events in the lives of cystic fibrosis (CF) patients. In 2007, 38% of all CF patients in the US were treated with intravenous (IV) antibiotics for at least one pulmonary exacerbation[1]. Although there is controversy in how to define a pulmonary exacerbation, an increased number of exacerbations is clearly associated with increased morbidity and mortality in CF [2,3]. Several studies have shown that more pulmonary exacerbations are associated with a steeper subsequent decline in lung function, specifically forced expiratory volume in 1 second (FEV_1), particularly among children[4,5,6]. Multiple datasets, including those from the Toronto CF Database, have examined the effect of pulmonary exacerbations, as discrete events, on lung function and have demonstrated that up to a third of CF patients will not recover their baseline FEV_1, with an approximate 3% decrease in FEV_1 following an exacerbation[7,8,9,10]. These studies also identify risk factors for failing to recover lung function following a pulmonary exacerbation, including greater initial drops in FEV_1. However, despite this knowledge, we still do not understand how repeated pulmonary exacerbations affect lung function over the lifetime of a CF patient. This knowledge is crucial in determining how important it is to prevent pulmonary exacerbations, which are often measured as study outcomes in clinical trials in CF. The aim of this study was thus to model FEV_1 decline in a pediatric and adult CF population over a 12 year period and determine the role of pulmonary exacerbations (requiring hospital admission for IV antibiotics) in that decline.

Materials and Methods

Study design and patient population

This was a retrospective cohort study of subjects with CF followed at the Hospital for Sick Children and St Michael's Hospital (Toronto, Canada) from 1997 to 2008. The primary outcome was the annual rate of decline in forced expiratory volume in 1 second percent predicted (FEV_1% predicted).

Subjects were included in the study if they had a confirmed diagnosis of CF based on: a) the presence of clinical features consistent with CF, or b) a positive family history for CF, and either 2 documented sweat chloride values > 60 mEq/L measured by quantitative pilocarpine iontophoresis test, genetic testing showing 2 CF- causing mutations or a nasal potential difference consistent with CF[11]. Subjects were excluded if they were unable to perform reproducible spirometry. There were no subjects in this cohort that were identified by newborn screening. Data were censored at lung transplantation or death.

This study was approved by the Research Ethics Board at the Hospital for Sick Children (1000013759) and St Michael's Hospital (09-087[c]).

Data collection and definitions

The data for this study was extracted from the Toronto Cystic Fibrosis Database housed at the Hospital for Sick Children. This encounter based database prospectively collects information from pediatric and adult CF subjects from every visit including sputum microbiology, medications and pulmonary function testing [12]. Specific information that was unavailable from the database was retrieved through systematic review of hospital health records by one of the study investigators (A.L.).

A pulmonary exacerbation was defined, as previously [10,13], as a hospitalization for respiratory symptoms requiring antibiotics (96% of patients were administered IV antibiotics); hospitalizations for gastrointestinal complications were not included. Consecutive pulmonary exacerbations within 3 weeks of antibiotic treatment were considered as a single event[7]. Exacerbation history was analyzed as ever/never, total number during the study period (grouped as 0, 1, 2-4, ≥5), and as the minimum time between two consecutive exacerbations. FEV_1 values were corrected for height, age and sex and analyzed as percent predicted [14]. Body mass index (BMI) was categorized into normal, underweight and overweight. In children (<18 years of age), BMI was first converted to centiles and categorized into normal, underweight and overweight based on standard cut-offs (<5th centile, 5-85th centile, >85 centile)[15]. In adults, we used standard cut-offs <18, 18-25, >=25 kg/m^2.

Statistical analysis

Baseline characteristics for the cohort were defined based on data from the first year of observation. The overall annual rate of FEV_1 decline was estimated with all recorded measurements using generalized estimating equation (GEE) models, which adjust for the correlated nature of repeated measures in an individual. In the multi-variable models, we adjusted for age (years), gender (male/female), genotype (homozygous ΔF508, heterozygous ΔF508, other, unknown), baseline FEV_1(L/s), year of measurement, age at diagnosis (<1 year, <12 years, ≤18 years, >18 years, unknown), BMI (normal, underweight, overweight) , any previous *Pseudomonas aeruginosa* or *Burkholderia cepacia* complex (BCC) infection, a history of allergic bronchopulmonary aspergillosis (ABPA) (as defined by the treating physician in combination with increased IgE levels) [10], pancreatic insufficiency (defined by enzyme usage) and CF related diabetes (CFRD) (based on oral glucose tolerance test). Age and BMI were

treated as time-varying variables. Socioeconomic status was not available. Furthermore, Medicaid insurance was not investigated since Canada has universal healthcare insurance. Methicillin-resistant *Staphylococcus aureus* (MRSA) was not included due to its low prevalence in the CF population in Canada[16]. Factors which were marginally significant ($p<0.15$) using univariable analysis, or those with strong a priori hypothesis (e.g. sex, age) were entered into a multi-variable model using a step-wise approach. Variables were maintained in the multivariable linear GEE model if they were independently associated with FEV_1 decline, or if they changed the coefficient for the effect of exacerbation on slope on FEV_1. Effect modifications by exacerbations (ever vs. never) and age (>18 vs $\leq$18 years) was evaluated by testing for interactions in the model and conducting stratified analyses where appropriate. In addition, sensitivity analysis were performed excluding subjects >50 years, subjects with a history of BCC infection and subjects with ABPA. The extent to which exacerbations contribute to overall lung function decline over time was estimated using the formula $(\beta_0 - \beta_1)/ \beta_0$, where β_0 is the time co-efficient in the model without the exacerbation covariate and β_1 is the slope in the model which included the exacerbation covariate and potential confounding variables [17].

Results

Study population characteristics

From 1997 to 2008, 851 subjects with CF were followed for a median of 6.7 years (IQR 2.4-9.7). There were 1882 pulmonary exacerbations during the study period. A total of 415 subjects (48.8%) had at least one pulmonary exacerbation requiring hospitalization and antibiotics. The median number of exacerbations per subject was 3 (range 1-19) and the median number of exacerbations per subject per year was 2 (range 1-5). The average time between two consecutive exacerbations was 1 year (range 2 months-6 years).

Compared to subjects who had no pulmonary exacerbations during the study period, subjects with at least one pulmonary exacerbation were followed longer, were younger at baseline, more likely to be female, were diagnosed at a younger age, more likely to be homozygous for delta F508, be pancreatic insufficient, be underweight, have CFRD, have had *P. aeruginosa* or BCC infection have a history of ABPA, and have lower baseline FEV_1 (Table 1).

Factors influencing FEV_1 decline

Using univariable analysis, the overall rate of FEV_1 % predicted decline for the entire study population was 1.6%/yr (95% CI:1.6-1.7). In subjects with at least 1 pulmonary exacerbation, the annual rate of decline was 1.8%/yr (95% CI: 1.8-1.9) compared to 1.1%/yr (95% CI: 1.0-1.1) in subjects without any exacerbations. These rates of FEV_1 decline were similar in children and adults; younger subjects had a higher baseline FEV_1 (Figure 1).

In the multivariable analysis, the annual rate of decline in FEV_1 was modified by exacerbation history (interaction $p<0.0001$) such that the rate of decline was steeper in the exacerbation group. In addition, the rate of FEV_1 decline was proportionally greater in older subjects, those with an earlier study entry, lower baseline FEV_1, underweight subjects and those with a history of BCC infection (Table 2). Although significant in the univariable analysis, *P. aeruginosa* infection, pancreatic insufficiency and CFRD did not contribute to the final multivariable model. After adjusting for potential confounders, the rate of FEV_1 decline in subjects with at least 1 exacerbation was 2.5%/yr (95% CI: 2.1-2.8) compared to 1.2%/yr (95% CI: 1.0-1.5) in subjects without an exacerbation. The proportion of the overall FEV_1 decline (-1.62%/year) associated with pulmonary exacerbations (-2.47%/year) was 52% (95% CI: 35.0-68.9).

Sensitivity analyses

Excluding subjects >50 years of age, those with a history of ABPA or those who subsequently had a transplant did not change the interpretation of the results. When we limited the analysis to those without a history of infection with BCC, the adjusted slope of FEV_1 decline was slightly attenuated (-2.0%/yr, 95% CI: -2.2; -1.7). After adjusting for potential confounders, the annual rate of decline was the same in both children and adults.

The effect of number and timing of pulmonary exacerbations on FEV_1 decline

After adjusting for potential confounders, the total number of exacerbations (grouped as 0, 1, 2-4, ≥ 5 over the study period) was a significant predictor of annual FEV_1 decline. The annual rate of FEV_1 decline for each exacerbation group was compared to the rate of FEV_1 decline in the group with no exacerbations and the relative difference is represented in Figure 2. The rate of FEV_1 decline for the group with only one exacerbation during the study period did not differ significantly from the group with no exacerbations (0.7%; 95% CI: -1.3; 2.5). Relative to the group with no exacerbations, the slope for FEV_1 decline was -5.3% (95% CI: -7.0; -3.5) lower for the group with 2-4 exacerbations -7.9% (95% CI: -9.6; -6.1) lower for those with ≥ 5 exacerbations over the study period.

We subsequently further categorized those patients with more than 2 exacerbations over the study period based on the minimum time between any two consecutive exacerbations (≤ 6 months, > 6 months). Relative to the group with no exacerbations, the greatest FEV_1 decline was observed when the time between two consecutive exacerbations was less than 6 months (Figure 3); this observation was consistent regardless of the total number of exacerbations during the study period. Subjects with the same total number of exacerbations over the 12 years (2-4 exacerbations), but less than 6 months between exacerbations had a greater FEV_1 decline (-6.9% (95% CI: -9.5; -4.2)) compared with the group with more than 6 months between exacerbation (-

4.4% (95% CI: -6.43; -2.40)) (Figure 3A). For subjects with five or more exacerbations and a shorter interval between subsequent exacerbations, the FEV_1 decline was -8.1% (95% CI: -9.9; -6.3) lower compared to the group with no exacerbations, compared with -6.4 (95% CI: -10.5; -2.3) in the group with more than 6 months between exacerbations (Figure 3B).

Discussion

To our knowledge, this is the first study to quantify the effect of pulmonary exacerbations on long term lung function decline in CF and to show that half of FEV_1 decline in CF patients is associated with severe pulmonary exacerbations requiring hospitalization and IV antibiotics. In addition, we confirm that more exacerbations are associated with greater FEV_1 decline, and for the first time demonstrate that time between consecutive exacerbations also plays an important part in long term lung function decline.

Within the spectrum of illness that can be considered a pulmonary exacerbation, severe pulmonary exacerbations requiring intravenous antibiotics has clearly been shown to be associated with lung function decline[4,6], such that a quarter of adult and pediatric CF patients do not recover their baseline FEV_1[7,8]. The annual rate of decline observed in our CF population, is consistent with other studies[18]. However, few studies actually quantify what proportion of FEV_1 decline in CF was associated with such exacerbations over time. Amadori et al. followed the FEV_1 decline of 51 adult CF patients over 5 years and reported an FEV_1 loss of about 30 ml for each exacerbation episode[19]. The study was limited, however, by a small sample size and FEV_1 decline reported in milliliters, which is difficult to interpret since lung function is so strongly related to body size, and therefore commonly interpreted as percent predicted in clinical settings. In comparison, our study followed almost 1,000 CF patients over a 12 year period, the longest reported follow up for FEV_1 decline, and we report that half of FEV_1

decline in CF was associated with pulmonary exacerbations. Although we compared differences in rates of FEV_1 decline, these findings are still clinically relevant as the most severely affected subjects (5 or more exacerbations, $\leq$ 6 months between exacerbations) had double the rate of FEV_1 decline (approximately 2% pred/yr) compared to subjects without any exacerbations during the study period (approx.1% pred/yr). These results further emphasize the important contribution exacerbations have on disease progression in patients with CF.

This study confirmed that an increasing number of pulmonary exacerbations were associated with greater FEV_1 decline. Sanders et al. showed that any exacerbation in children with CF and 3 or more exacerbations in a single year in adults with CF were associated with a significantly increased rate of FEV_1 decline[4] and that those who failed to recover to baseline lung function following an exacerbation were more likely to have a subsequent pulmonary exacerbation in the 3, 6, and 12 months following treatment[7]. De Boer et al. also found that adult CF patients with 3 or more exacerbations per year were at increased risk of a 5% decline in baseline FEV_1, although their definition of an exacerbation included patients who were treated with either oral or intravenous antibiotics [20]. These studies suggest that it is not only the frequency of exacerbations but it is also repetitive, consecutive exacerbations within a short time period that contribute to lung function decline in CF. These findings further support that patients with CF would benefit from close monitoring following an exacerbation. While our study agrees with these observations, in contrast, we do not treat exacerbations as discrete events and therefore describe the contribution of exacerbations to long term lung function decline over a period of 12 years.

In our study we examined the effect of time between exacerbations and show for the first time that two exacerbations within six months contribute towards a faster rate of lung function decline.

This is consistent with previous studies that found 3 exacerbations per year represent a crucial tipping point in terms of CF lung function decline, as the minimum time between exacerbations in this instance has to be within 6 months[4,20]. Although rate of pulmonary exacerbations and time between pulmonary exacerbations are clearly correlated, they are not necessarily equivalent. These data contribute to our understanding of the relevance of consecutive exacerbations and have important implications for clinical research.

Pulmonary exacerbations are frequently used as a study outcome measure in CF trials, and are usually measured as the risk of a pulmonary exacerbation during the study period [21,22],[23]. Our findings suggest that it is not a pulmonary exacerbation *per se*, but consecutive exacerbations within a narrow time period, measured in this case by minimum time between exacerbations, which strongly impact the rate of lung function decline. This has two important implications for CF intervention trials. First, preventing an exacerbation is more important in patients who have recently had an exacerbation than in patients whose prior exacerbation is more remote. Thus history of exacerbation, more specifically, the time since last exacerbation, may be an important inclusion criterion for trials. Secondly, when comparing a treatment and a placebo group in an interventional study, the two groups should be balanced with respect to pulmonary exacerbation history as this may influence the response to therapy and could potentially bias interpretation. For example, in the randomized, double-blind, placebo-controlled trial of high-dose ibuprofen in patients with CF, the treatment group had a significantly slower annual decline in FEV_1 than the placebo groups despite the fact that there was no significant difference between the groups in the number of hospitalizations for pulmonary exacerbations during the study period[24]. If there were more subjects with recent exacerbations prior to study entry in the treatment group than in the placebo group, preventing a pulmonary exacerbation during the study period may have had a

more significant impact on lung function decline in the treated subjects than in the untreated subjects. Thus, although the number of exacerbations was not different between the two groups, the time between exacerbations may have been extended by high-dose ibuprofen therapy. Our findings have implications for future clinical trials that evaluate lung function decline as the primary outcome. Enrolling patients with a history of recent exacerbation may result in a more powerful study design, requiring shorter follow-up time and smaller sample sizes to show therapeutic benefit.

Strengths and Limitations

To our knowledge, this study reports the longest follow-up of lung function decline in both pediatric and adult patients with CF, with over 20,323 observations in 851 subjects over a 12 year period. While this study does not examine the factors associated with lung function decline for each discrete exacerbation as previously done [7,10], it is the first to detail the overall effect of exacerbations on CF lung function decline over time. Another potential limitation is our definition of pulmonary exacerbation. In this study, we defined a pulmonary exacerbation as a hospitalization for respiratory symptoms requiring antibiotics (96% of patients received IV antibiotics). By definition, this includes only the more severe pulmonary exacerbations in the analysis; it is unclear what the role of milder exacerbations is in CF pulmonary deterioration. However, it is a clinically relevant definition. Previous publications have demonstrated that pulmonary exacerbations requiring intravenous antibiotics are associated with significant pulmonary inflammation and it is thus likely that the greatest effect on CF lung function decline would be seen in this patient population[25]. Finally, this study was retrospective which may limit the amount of information that can be obtained about respiratory symptoms at the time of an exacerbation. Even with a prospective study design it is difficult to infer causality, that is, whether

FEV_1 decline occurred prior to the identification of the exacerbation or was a direct result of the exacerbation [4,21,22,26]. Unlike previous studies where exacerbations were treated as discrete events, we examined the contribution of exacerbations on overall lung function decline.

Conclusions

In conclusion, one half of the FEV_1 decline seen in CF patients was associated with severe pulmonary exacerbations requiring hospitalization and antibiotics. In addition, we demonstrate that the time between exacerbations, specifically 6 months or less between exacerbations, is an important predictor of overall lung function decline. These findings support using time to next exacerbation as a clinical endpoint for CF trials.

Contributorship Statement

Dr Waters: contributed to conception and design, acquisition of data, or analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; and final approval of the version to be published. Dr Waters is the guarantor of the paper.

Dr Stanojevic: contributed to conception and design, acquisition of data, or analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; and final approval of the version to be published. Dr Stanojevic is co-first author for this paper.

Mr. Atenafu: contributed to conception and design, acquisition of data, or analysis and interpretation of data; revising it critically for important intellectual content; and final approval of the version to be published.

Ms Lu: contributed to conception and design, acquisition of data, or analysis and interpretation of data; revising it critically for important intellectual content; and final approval of the version to be published.

Dr Yau: contributed to conception and design, acquisition of data, or analysis and interpretation of data; revising it critically for important intellectual content; and final approval of the version to be published.

Dr Tullis: contributed to conception and design, acquisition of data, or analysis and interpretation of data; revising it critically for important intellectual content; and final approval of the version to be published.

Dr Ratjen: contributed to conception and design, acquisition of data, or analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; and final approval of the version to be published.

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Figure Legends

Figure 1. Forced expiratory volume in 1 second percent predicted decline over time in subjects 18 years of age or less without any pulmonary exacerbation (dark broken line), in subjects 18 years of age or less with at least one pulmonary exacerbation during the study period (dark solid line), in subjects older than 18 years of age without any pulmonary exacerbation (light broken line) and in subjects older than 18 years of age with at least one pulmonary exacerbation during the study period (light solid line).

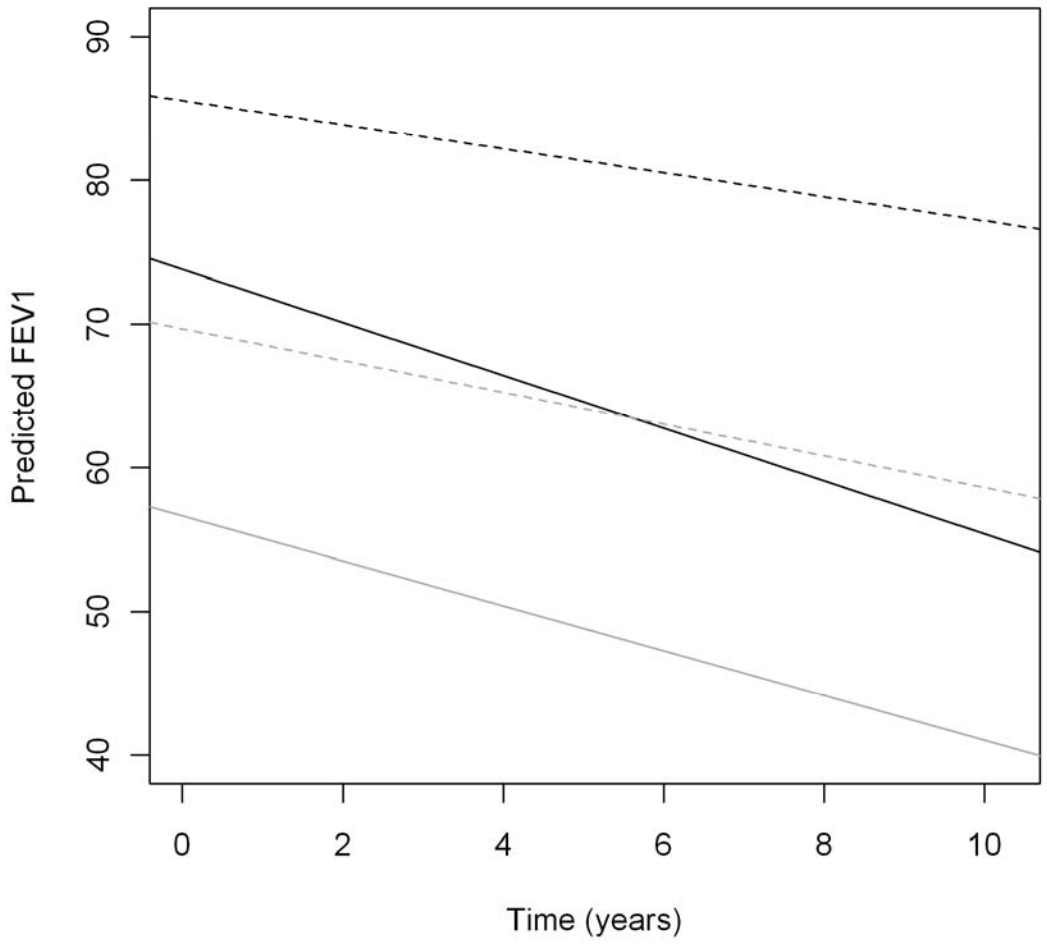

Figure 2. The relative percent difference in the rate of FEV_1 decline (with 95% confidence intervals) for each group according to the number of pulmonary exacerbations during the study period, compared to the group with no pulmonary exacerbations.

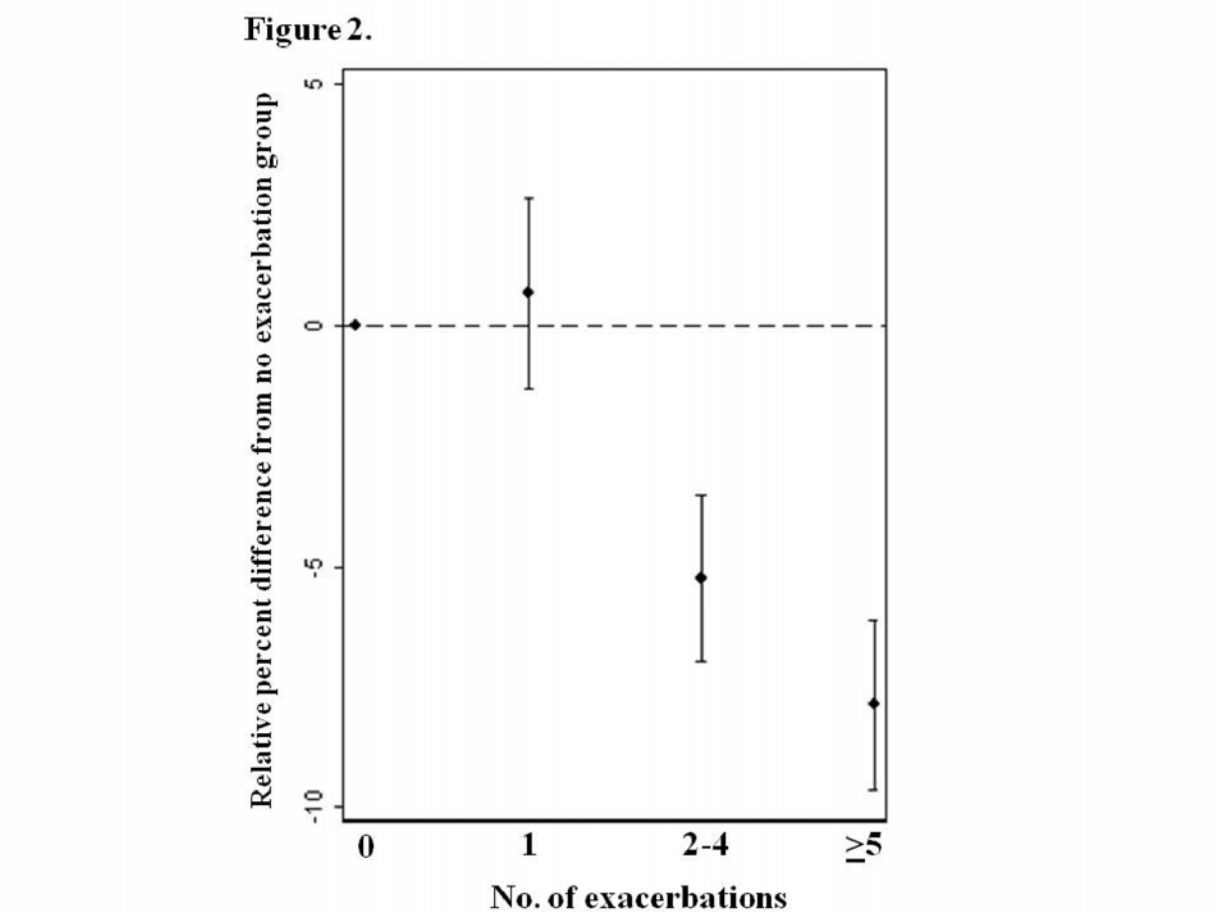

Figure 3. The relative percent difference in the rate of FEV_1 decline (with 95% confidence intervals) compared to the group with no pulmonary exacerbations according to time between exacerbations for subjects with **A)** 2-4 exacerbations during the study period **B)** 5 or more exacerbations during the study period.

Figure 3A.

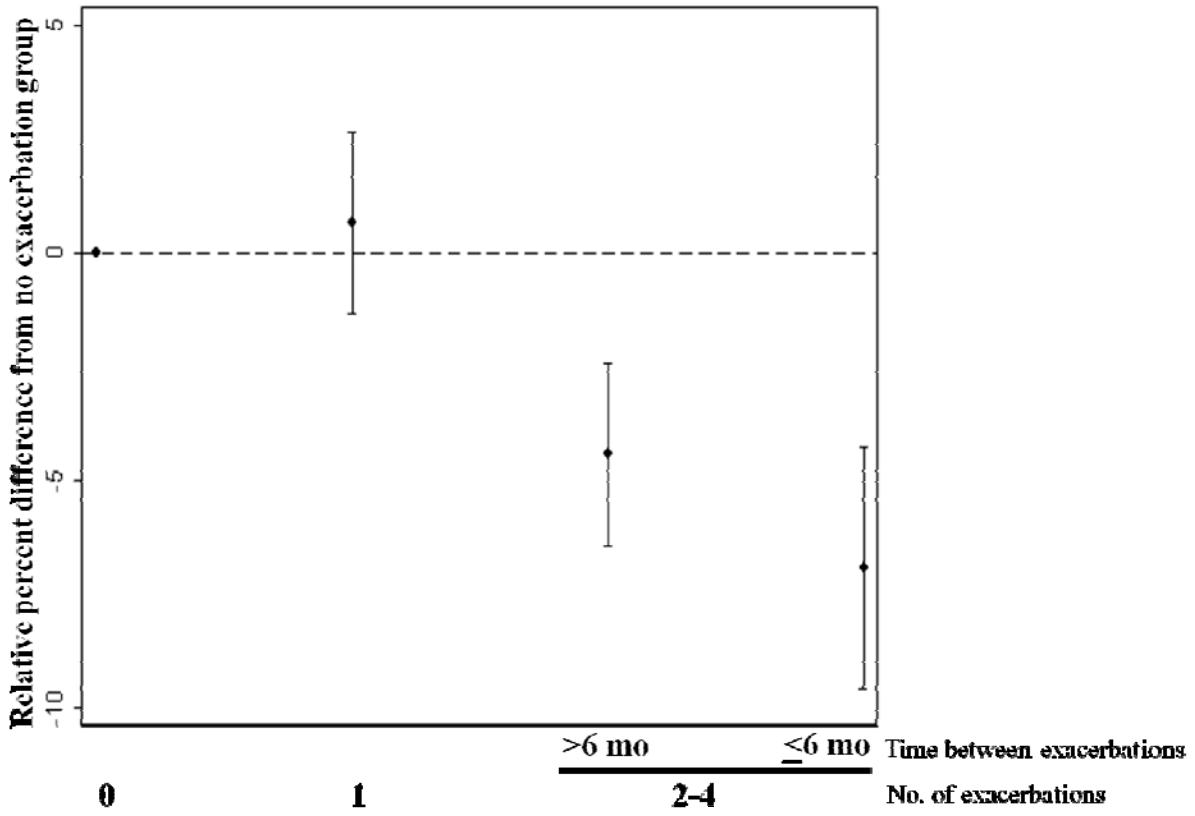
Relative percent difference from no exacerbation group
5
0
-5
-10
>6 mo
≤6 mo
Time between exacerbations
0
1
2-4
No. of exacerbations

Figure 3B.

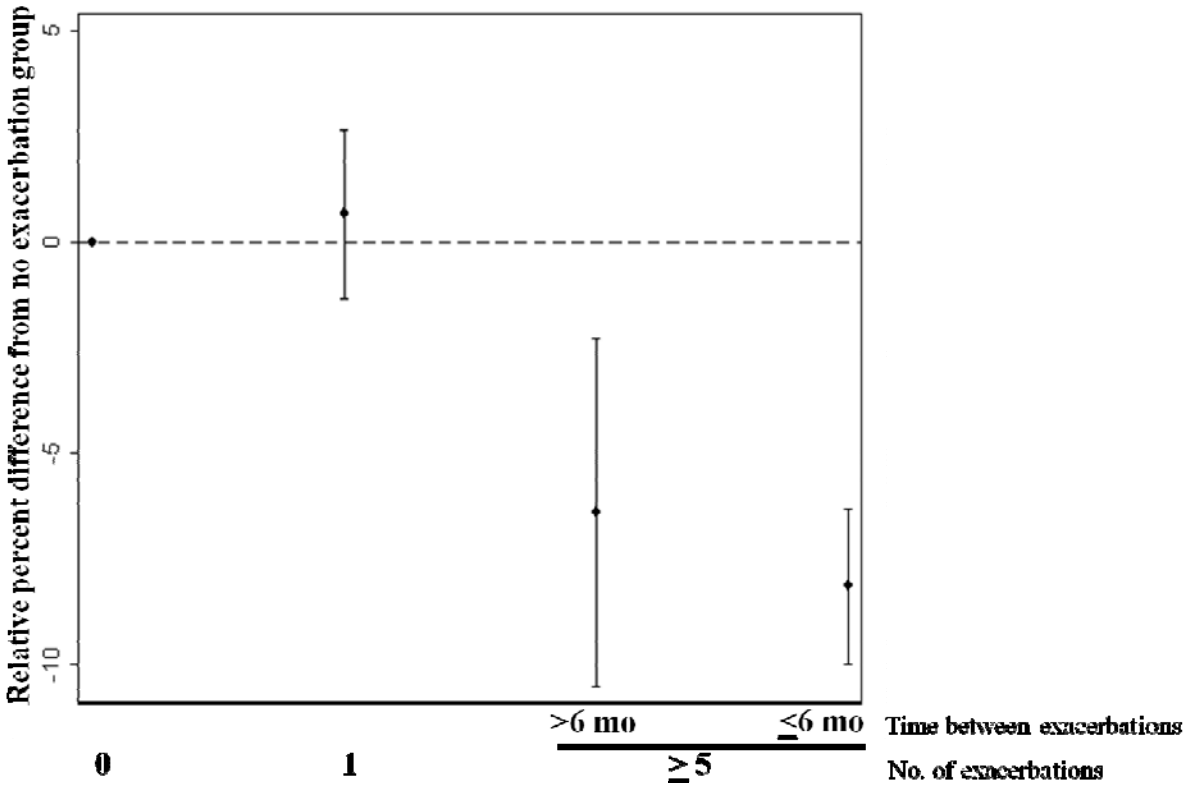
Relative percent difference from no exacerbation group
5
0
-5
-10
>6 mo
≤6 mo
Time between exacerbations
0
1
≥5
No. of exacerbations

Table 1: Study population characteristics at baseline

Variable	No exacerbations (n=436)	≥1 exacerbation (n=415)	Total (n=851)
Follow-up time (yrs), median (IQR)	4.5 (1.6-9.1)	8.2 (3.8-9.9)	6.7 (2.4-9.7)
Female (%)	176 (40.4)	205 (49.4)	381 (44.8)
Age, median (IQR)	19.6 (9.6-31.1)	16.0 (8.5-25.9)	18.0 (8.7-28.5)
Age at diagnosis (%)			
<1 yr	209 (47.9)	247 (60.0)	456 (53.6)
<12 yrs	135 (31.0)	123 (29.6)	258 (30.3)
≤ 18 yrs	22 (5.1)	21 (5.1)	43 (5.1)
> 18 yrs	69 (15.8)	23 (5.5)	92 (10.8)
Unknown	1 (0.2)	1 (0.2)	2 (0.2)
Genotype (%)			
Homozygous ΔF508	160 (36.7)	189 (45.5)	349 (41.0)
Heterozygous ΔF508	159 (36.5)	137 (33.0)	296 (34.8)
Other/Other	40 (9.2)	43 (10.4)	83 (9.8)
Unknown	77 (17.6)	46 (11.1)	123 (14.4)
Pancreatic insufficiency (%)	324 (74.3)	361 (87.0)	685 (80.5)
Body Mass Index (%)			
Underweight	28 (6.4)	42 (10.1)	70 (8.2)
Normal weight	306 (70.3)	332 (80.0)	638 (75.1)
Overweight	101 (23.2)	41 (9.9)	142 (16.7)
CF related diabetes mellitus (%)	30 (6.9)	38 (9.1)	68 (8.0)
***P. aeruginosa* infection (%)**	197 (45.2)	270 (65.1)	467 (54.9)
***B. cepacia* complex infection (%)**	62 (14.2)	71 (17.1)	133 (15.6)
Allergic bronchopulmonary aspergillosis	0 (0)	46 (11.1)	46 (5.4)
Lung Function			
Average no. PFTs/yr/subject, median (IQR)	1 (1-2)	2 (1-3)	1 (1-2)
Baseline FEV_1 % predicted, mean (SD)	74.8 (26.7)	64.0 (24.5)	69.5 (26.2)
Baseline FEV_1 z score, mean (SD)	-2.1 (2.3)	-3.0 (2.1)	-2.5 (2.0)

IQR: interquartile range
PFTs: pulmonary function tests
FEV_1: forced expiratory volume in 1 second
SD: standard deviation

Table 2. Multivariate analysis of variables affecting rate of FEV_1 decline stratified by presence of exacerbation

	No Exacerbations		At least One Exacerbation	
Variable	**Slope (95% CI)**	**P value**	**Slope (95% CI)**	**P value**
Longer duration of follow up (yrs)	-1.21 (-1.48; -0.95)	<0.0001	-2.43 (-2.78; -2.08)	<0.0001
Increasing age (yrs)	-0.19 (-0.26; -0.13)	<0.0001	-0.25 (-0.35; -0.16)	<0.0001
Earlier study entry (calendar yr)	-0.33 (-0.58; 0.08)	0.010	-0.92 (-1.24; 0.60)	<0.0001
Lower baseline FEV_1 (% pred)	-0.81 (-0.84; -0.78)	<0.0001	-0.73 (-0.78; -0.69)	<0.0001
Body mass index				
Normal weight	Ref	Ref	Ref	Ref
Underweight	-3.56 (-4.85; -2.27)	<0.0001	-8.00 (-8.73; -7.26)	<0.0001
Overweight	3.81 (2.90; 4.72)	<0.0001	4.21 (3.35; 5.09)	<0.0001
***B. cepacia* complex infection**	-6.46 (-8.80; -4.12)	<0.0001	-2.78 (-5.53; -0.08)	<0.0001

For example, after adjusting for the other potential confounders, patients in the no exacerbations group with *Burkholderia cepacia* complex infection have an annual rate of FEV_1 decline that is 6.46% greater than the group without *Burkholderia cepacia* complex infection.