Lung clearance index to track acute respiratory events in school-age children with cystic fibrosis

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Abstract

Objective:

The lung clearance index (LCI) is responsive to acute respiratory events in preschool children with cystic fibrosis (CF) but its' utility to identify and manage these events in school-age children with CF is not well defined.

Methods:

In a multisite prospective observational study, LCI and forced expiratory volume in 1 second (FEV_1) were measured quarterly and during acute respiratory events. Linear regression was used to compare relative changes in LCI and FEV_1 % predicted at acute respiratory events. Logistic regression was used to compare the odds of a significant worsening in LCI and FEV_1 % predicted at acute respiratory events. Generalized estimating equation models were used to account for repeated events in the same subject.

Results:

A total of 98 children with CF were followed for two years. There were 265 acute respiratory events. Relative to a stable baseline measure, LCI (+8.9%; 95% CI 6.5 to 11.3) and FEV_1% predicted (-6.6%; 95% CI -8.3 to -5.0) worsened with acute respiratory events. A greater proportion of events had a worsening in LCI compared to a decline in FEV_1% predicted (41.7% vs 30.0%; p=0.012); 53.9% events were associated with worsening in LCI or FEV_1. Neither LCI nor FEV_1 recovered to baseline values at the next follow-up visit.

Conclusions:

In school-age children with CF, LCI is a sensitive measure to assess lung function worsening with acute respiratory events and incomplete recovery at follow-up. LCI and FEV_1 in combination capture a higher proportion of events with functional impairment.

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Keywords: cystic fibrosis**,** pulmonary exacerbations, acute respiratory events, lung clearance index, multiple breath washout test, children

At A Glance

Scientific knowledge:

The lung clearance index (LCI) has been shown to worsen with acute respiratory symptoms and to detect treatment effects in preschool children with CF. However, it is unclear whether there is any benefit to using LCI to monitor acute respiratory events in school-age children with CF.

What this study adds to the field:

This prospective observational study shows that LCI is responsive to the spectrum of acute respiratory events in school-age children with CF and is more sensitive than FEV_1 to identify the events with the mildest clinical phenotype. LCI is sensitive to detect incomplete lung function recovery at follow-up. LCI captures functional abnormalities in more acute respiratory events than FEV1 but the results are discordant, which suggests that using both outcome measures together is superior to using either measure alone.

Introduction

Cystic fibrosis (CF) is characterized by progressive obstructive lung disease which is the major cause of disease-related morbidity and mortality (1). Pulmonary exacerbations, episodes of acute worsening of respiratory symptoms, directly contribute to disease progression (2–5). The clinical impact of severe exacerbations on disease progression is well described in the CF literature (5–8). In children, severe exacerbations are relatively rare and the majority of respiratory events are treated with oral antibiotics on an outpatient basis (8–10). However, there is also evidence that these milder events are important in affecting long term outcomes (4, 10).

Respiratory events in children present with a wide spectrum of clinical symptoms and there is no established definition of a mild pulmonary exacerbation (11–13). Distinguishing self-resolving viral infections from more serious lower respiratory tract respiratory events can be difficult and physicians typically have a low threshold to prescribe antibiotics. This results in highly variable management strategies among providers and CF centers (14).

Spirometry is currently the only objective physiological measure to guide treatment decisions in school-age children. Acute changes in FEV_1 usually trigger antibiotic treatment but the majority of mild respiratory events do not have significant spirometry changes (11).

The Lung Clearance Index (LCI), the primary outcome of the multiple breath washout (MBW) test, measures ventilation inhomogeneity. LCI, an established outcome measure in interventional trials (15–17) correlates with bronchiectasis on chest computed tomography scans and with measures of inflammation on bronchoalveolar lavage samples (18–20). We have recently shown that LCI worsens during acute respiratory events and detects treatment effects in preschool CF

children (21). However, it is unclear whether there is any additional benefit to using LCI to monitor changes in lung function with acute respiratory symptoms in school-age children. In this prospective longitudinal observational study, we aimed to describe changes in LCI with acute respiratory events in school-age children with CF.

Some of the results of this study have been previously reported in the form of abstracts (22, 23).

Methods:

Study Design

This was a prospective longitudinal study in school-age children with CF at the Hospital for Sick Children, Toronto and Riley Hospital for Children, Indianapolis. The ethics committee of each institution approved the study and parents gave written informed consent to participant. Further details of the eligibility criteria are presented in the online supplement.

Participants attended a study visit at enrolment and every 3-months subsequently for two years in keeping with routine clinical follow-up. Participants notified the research team if they experienced new or worsening respiratory symptoms and were invited to attend an additional symptomatic study visit. At each study visit, a clinical history and physical exam were obtained by a CF physician. The visit was classified as stable if the participant was judged to be at their baseline clinically or as symptomatic if increased symptoms and/or signs were present.

Categorization of acute respiratory events

The term acute respiratory event refers to any symptomatic visit regardless of whether treatment was administered. The categorization of acute respiratory events is outlined in Table 1. Given the lack of a standardized definition of acute respiratory events in clinical practice, they were categorized based on treatment status so that we could evaluate the LCI treatment response at follow-up. Acute respiratory events treated with antibiotics were called pulmonary exacerbations. Pre-treatment with antibiotics could have impacted the magnitude of LCI change, therefore, if antibiotics were initiated before the clinic visit the pulmonary exacerbation was categorized as "already treated". In addition, we defined unobserved pulmonary exacerbations as acute respiratory events that were treated with antibiotics, usually over the phone, and symptoms were resolved before the next study visit.

Acute respiratory events that were not treated with antibiotics were categorized as increased cough events. The term 'persistent symptoms' was used for participants with a subacute onset of respiratory symptoms or symptoms that lingered for at least two weeks after completing a course of antibiotics.

Baseline was defined as the most recent stable visit prior to an acute respiratory event (further details in the OLS). The term "enrolment" was used to describe the status of the subject at study entry. Follow-up was defined as the next study visit.

At the end of the data collection period, all symptomatic visits were categorized by one investigator (LP) and reviewed by a second reviewer (FR); disagreements were discussed, and

consensus was achieved in all cases. All clinical and research documentation was reviewed when categorizing study visits and LCI measurements were not considered during the process.

Study Outcomes

Nitrogen MBW was performed using the Exhalyzer D (Ecomedics, Duernten, Switzerland) device in accordance with standardized protocols based on the American Thoracic and European Respiratory Societies (ATS/ERS) consensus statement (24). Spirometry was performed according to ATS/ERS guidelines (25). Percent-predicted values were calculated using the Global Lung Function Initiative reference equations (26). Physicians used spirometric measurements to inform treatment decisions but were blinded to the LCI results.

The Cystic Fibrosis Questionnaire-Revised (CFQ-R) (Respiratory Domain only) was completed by the participant (versions 6 to 13 years or ≥14 years) or the parent (for children ≤13 years) at each visit.

Statistical Analysis

All statistical analysis was performed in Stata V.14 (StataCorp, College Station, TX, USA). Descriptive statistics were used to summarize demographic and clinical features. Univariate logistic regression within a generalized estimating equation (GEE) model was used to investigate clinical factors associated with the odds of antibiotic treatment.

All the analysis was based on $LCI_{2·5}$, which represents the number of lung volume turnovers required to reduce the tracer gas concentration to 2·5% of its initial concentration. The relative change in LCI and FEV_1 was calculated for each acute respiratory event compared to a

participants' baseline (i.e. the most recent stable visit within the last six months). The correlation between relative changes in LCI and FEV_1% predicted at each acute respiratory event was calculated using a Pearson correlation. Relative changes in LCI (and FEV_1% predicted) from baseline were compared between the categorized events using a linear regression within a GEE model, where the relative change between two stable visits was the reference group. We performed a sensitivity analysis limiting the analysis to include only the first acute respiratory event per participant.

LCI can change by approximately 15% between visits in health (29–31), and FEV_1 has a similar degree of variability (30, 32). Given that a 10% drop in FEV_1% predicted is generally considered meaningful in clinical practice (33, 34), we compared LCI and FEV_1% predicted using a 10% threshold. As a sensitivity analysis, we compared LCI and FEV_1% predicted at a 15% threshold. Logistic regression within a GEE model was used to compare the odds of a 10% worsening in either outcome measure. Logistic regression within a GEE model was also used to compare the odds of 90% recovery of LCI and FEV1% predicted to baseline at the first stable visit following an acute respiratory event.

Results

Patient characteristics

Eight hundred and sixty-four visits, which included 529 stable visits, from 98 participants with CF were included in this study (Figure 1). Of the 265 acute respiratory events in the study, 180 events had a stable baseline LCI and FEV_1 measurement. 161 acute respiratory events had both a stable baseline *and* at least one follow-up study visit after the event. The demographic

characteristics at enrollment are shown in Table 2. The mean age of the study population at enrollment was 9.6 years (range 5 to 16.8 years) and approximately half were diagnosed by newborn screening (Table 2). FEV_1 was in the normal range, greater than the age-specific lower limit of normal, for the majority of participants (90.8%), whereas 66.3% had an abnormal enrolment LCI (>7.91 units)(26, 35). Participants were followed for a median (IQR) of 2 years (1.9 to 2.0) and attended a median (IQR) of 9 (8 to 10) study visits over the 2-year follow-up. We captured a median (IQR) of 3 (2 to 4) symptomatic and 6 (4 to 7) stable visits per participant. 90 (91.8%) of participants had at least one captured acute respiratory event during the study period. In addition to the captured pulmonary exacerbations, there were 136 unobserved pulmonary exacerbations.

Characteristics of acute respiratory events

The median (IQR) acute respiratory event rate was 2.0 events per year (1.4 to 3.1). Overall, 62.2% (n=165) of acute respiratory events were treated with antibiotics. The median (IQR) pulmonary exacerbation rate, including all observed and unobserved acute respiratory events that were treated with antibiotics, was 1.5 events per year (0.64 to 2.5). The median increased cough event rate was lower at 0.48 events per year (0 to 0.52).

There was a similar proportion of captured pulmonary exacerbations in Toronto and Indianapolis (61.3% versus 72.9%; p=0.11) but there were more unobserved pulmonary exacerbations in Indianapolis (28.2% versus 35.8% versus; p=0.045). Overall, the median rate of acute respiratory events was similar for the Toronto and Indianapolis sites (2.0 versus 2.4 events per year; p=0.66).

Clinical features observed with acute respiratory events are displayed in Table 3. Features of severe exacerbations, such as hemoptysis (2.3%), losing ≥5% of body weight (2.3%) and new lobar infiltrates on chest radiograph (1.5%) were rare. Compared to the untreated acute respiratory events, pulmonary exacerbations had worse respiratory symptoms as reflected in the changes in the CFQ-R Respiratory score and CRISS scores from baseline (Table 3). Pulmonary exacerbations also had a higher frequency of increased chest congestion or change in sputum (62.2%), an acute drop in FEV_1 (41.4%), adventitious sounds on auscultation (29.0%) and increased work of breathing (11.5) associated with the acute respiratory event.

Acute respiratory events with a reported FEV_1% decline ≥10% (OR 4.3 95% CI 2.1 to 8.7), increased chest congestion or change in sputum production (OR 3.1 95% CI 1.9 to 5.2) or new or increased adventitious sounds on examination (OR 4.6 95% CI 1.9 to 11.2) were more likely to be treated with antibiotics. Participants were less likely to be treated if there was clinical evidence of upper respiratory tract symptoms (e.g. nasal congestion, sore throat, fever) (OR 0.47 95% CI 0.29 to 0.78).

Lung function changes from baseline to symptomatic visit

Baseline measurements from the most recent stable study visit were taken a median (IQR) of 98 days (84 to 130) before an acute respiratory event visit (see table E1 in the online supplement). Including all acute respiratory events, LCI increased by 8.9% (95% CI 6.5 to 11.3) or 0.87 units (95% CI 0.64 to 1.1) and FEV_1% predicted decreased by 6.6% (95% CI -8.3 to -5.0) from baseline to the symptomatic visit. Adjustment for age, LCI and FEV_1 at enrolment or BMI centile did not attenuate the association (see Supplementary table Table E2). There was also no significant association between positive respiratory cultures for the main CF pathogens including

Pseudomonas aeruginosa, Staphylococcus aureus, methicillin resistant *Staphylococcus aureus or Haemophilus influenza* and the magnitude of LCI or FEV_1 change (supplemental Table E2).

When analyzed as acute respiratory event sub-categories, the LCI changes with pulmonary exacerbations (9.9%; 95% CI 6.7 to 13.5 or 0.99 units; 95% CI 0.69 to 1.3), already treated pulmonary exacerbations (8.6%; 95% CI 3.7 to 11.4% or 0.82 units; 95% CI 0.69 to 1.3) and persistent symptoms (9.1%; 95% CI 1.1 to 17.0 or 0.96 units; 95% CI 0.21 to 1.7) were similar in magnitude to each other, but the LCI change with increased cough events (7.5%; 95% CI 3.6 to 11.4 or 0.68 units; 95% CI 0.31 to 1.1) was less pronounced (Figure 2a and Table E3 in the online supplement).

FEV_1 worsened by 9.8% (95% CI -11.9 to -7.8) from baseline with pulmonary exacerbations, -6.9% (95% CI -10.1 to -3.6) with already treated exacerbations but did not change with increased cough events (-2.5%; 95% CI -4.9 to 0.005) or with persistent symptoms (-2.6%; 95% CI -8.1 to 2.9) (Figure 2b and Table E3 in the online supplement).

Relationship between LCI and FEV_1% predicted

A weak correlation between LCI and FEV_1% predicted was observed with acute respiratory events ($r=0.34$; 95% CI -0.47 to -0.21; $p<0.001$; Figure 3). The relationship between LCI and FEV_1% predicted was weaker for increased cough events ($r=-0.27$ 95% CI -0.50 to -0.006, $p=0.05$) than for pulmonary exacerbations ($r=-0.45$; 95% CI -0.60 to -0.26, $p<0.001$).

On an individual level, 53.9% (n=97) of events were associated with a 10% worsening in either LCI or FEV_1% predicted. A greater proportion of acute respiratory events had a 10% increase (worsening) in LCI compared to a 10% decline in FEV_1% predicted (41.7% (n=75) vs 30.0% (n=54); p=0.012) (Figure 4). A similar proportion of pulmonary exacerbations were associated with a significant worsening in LCI and FEV_1% predicted but fewer increased cough events were associated with a significant worsening in FEV_1 (Table 4). A similar pattern was observed when a threshold of 15 % was used (Table 4).

With a 10% change cut off, there were 115 (63.9%) concordant and 65 (36.1%) discordant acute respiratory events as illustrated in Figure 3. There were twice as many discordant events with a 10% increase in LCI and a stable FEV1 compared to a 10% drop in FEV1 and a stable LCI (66.2% versus 33.9%). In a logistic regression analysis to investigate factors associated with discordant acute respiratory events, lower FEV_1% predicted at enrolment was the only characteristic associated with discordant events (see Supplementary Table E4 OLS).

Lung function changes from baseline to follow-up

Including all acute respiratory events with a stable baseline and at least one follow-up visit, both LCI and FEV_1% predicted improved from the symptomatic visit, but on a group level, neither measure recovered to baseline at the consecutive follow-up visit (Figure 2).

We also investigated whether lung function recovered to baseline values once symptoms had resolved (i.e. at the first *stable* visit following an acute respiratory event). Including all acute respiratory events, LCI was significantly higher (mean difference 3.0%; 95% CI 0.45 to 5.7) at

the first stable follow-up visit compared with baseline. In contrast, FEV_1% predicted was not significantly different from baseline (mean difference -1.3%; 95% CI -3.0 to 0.33) (Figure 4a). The percentage of acute respiratory events in which lung function was ≥90% of baseline at the next stable follow-up visit is illustrated in Figure 4b; a lower proportion of acute respiratory events recovered ≥90% of baseline LCI compared to FEV_1 (75% versus 86%; p=0.006).

Measurement Feasibility

Overall, MBW was successfully performed at 96.0% (n=829) of study visits (Figure 1). MBW measurements were obtained at a similar proportion of stable (96.5%; n=529) and symptomatic (94.3%; n=265) study visits (p=0.26).

Sensitivity analyses

When the analysis of lung function changes with acute respiratory events was limited to the first symptomatic visit per participant, the changes in LCI and FEV_1 were similar to the main analysis (see table E5 in the online supplement). We also included symptomatic follow-up visits as separate events in the analysis, but this did not meaningfully change the results (see OLS for further details).

We regrouped symptomatic visits based on the duration of respiratory symptoms. The magnitude of FEV_1 change was similar for acute respiratory events regardless of the duration of respiratory symptoms while there was a higher LCI associated with events with longer symptom duration. (Supplemental Table E6).

Discussion

In this prospective observational study of school-age children with CF, we describe the clinical phenotypes of acute respiratory events and their impact on lung function. All acute respiratory event phenotypes were associated with a significant worsening of LCI. On an individual level, LCI was more sensitive than FEV_1 to detect functional changes with acute respiratory events. While LCI captured abnormalities in more acute respiratory events compared with FEV_1, the results were discordant, suggesting that using both outcome measures combined is superior to using one measure alone for clinical monitoring of children with CF.

Compared with FEV_1, LCI detected more lung function abnormalities with untreated increased cough events. By opting not to treat with antibiotics, physicians categorized these acute respiratory events as less severe and this was reflected in their milder clinical phenotype and the lesser magnitude of lung function worsening. However, nearly a quarter of participants did not return to baseline levels at follow-up, highlighting that these symptomatic but untreated acute respiratory events may be more clinically meaningful than perceived by either the physician or the patient themselves.

The discordance between LCI and FEV_1 with acute respiratory events could be explained by the physiological differences between the outcome measures (19, 36). The MBW test quantifies the efficiency of gas mixing in the peripheral airways while spirometry measures airflow resistance and is relatively insensitive to small airway disease. Novel chest imaging techniques such as functional and structural magnetic resonance imaging (MRI) have been shown to correlate with ventilation inhomogeneity in stable (37, 38) and exacerbating CF patients (39, 40). Future studies

could further elucidate the physiology of these events by performing chest imaging in cases with discordant LCI and FEV_1. Regardless of the underlying mechanism, the fact that LCI and FEV_1 respond differently to events would suggest that combining both outcome measures increases the detection of functionally relevant disease.

The Australasian CF Bronchoalveolar Lavage trial prospectively investigated acute respiratory events in young children and included all events regardless of treatment status. They reported that the rate of respiratory events in the first two years was associated with reduced FEV_1 z scores at 5 years of age (3). In the current study, the degree of FEV_1 recovery after pulmonary exacerbations (16%) was similar to a previous registry-based study which included orally treated exacerbations in adults and children (18%) (4). By comparison, LCI detected more residual lung function deficit with 25% of pulmonary exacerbations failing to recover 90% of baseline LCI once symptoms were resolved. A similar proportion of untreated increased cough events did not recover to baseline LCI values. These results support previous work demonstrating that even mild respiratory events contribute to the progression of CF lung disease (3, 4, 10). Identifying more events with lung function abnormalities could change thresholds for treatment and augment lung function recovery. A randomized controlled trial would be the ideal way to investigate whether lung function recovery can be improved by interventions such as antibiotics in patients with a measured deterioration in LCI.

While LCI is responsive to acute respiratory events overall, what defines a clinically meaningful change in LCI on an individual level remains unclear. As reported by several studies, the intrinsic variability of the LCI is approximately 15% (3, 4, 41, 42). The variability of FEV_1 is

similar to LCI, despite a drop of 10% being considered clinically meaningful (30, 32, 43). We compared changes in LCI and FEV1 at a 10% threshold to reflect clinical practice even though this is within the variability of both tests. However, our interpretations were similar when we applied a 15% threshold. In clinical practice, when a patient presents with new respiratory symptoms and a high pretest probability of a pulmonary exacerbation, antibiotics are often prescribed even when changes in lung function are within the intrinsic variability of the test. Observational studies that included pulmonary exacerbations treated with oral (4) and intravenous antibiotics (12) showed that in over half of events, there is either no change in FEV_1 or a worsening of less than 10%. The current study demonstrates that LCI can help identify additional events with lung function abnormalities which could potentially help to guide treatment decisions in clinical care.

A subgroup of this cohort was previously enrolled in a one-year observational study during the preschool years (3,4). Analysis of the preschool and school-age cohorts independently demonstrated that LCI worsened at visits with increased respiratory symptoms. However, the magnitude of LCI increase with treated and untreated acute respiratory events was higher in the preschool study (3). At follow-up, there was also a greater treatment effect with antibiotics in the preschool cohort. These differences could be explained in several ways. The current school-age cohort study included a much broader age range of participants. The preschool study reported a negative relationship between LCI at enrolment and the relative increase in LCI, so milder lung disease in the preschool group could account for some of the observed differences. Both studies provide evidence to support the clinical utility of the LCI in children with CF and increased respiratory symptoms.

There are some methodological limitations to be considered. Firstly, some events had incomplete baseline and/or follow-up data and were not included in all the analyses. For example, some participants with frequent symptomatic visits did not have a stable follow-up visit and this may have overestimated the magnitude of lung function recovery. Some participants with consecutive respiratory events had their first stable visit more than 6 months after the event, therefore the observed changes in lung function may have represented the cumulative impact of multiple respiratory events rather than the effect of one isolated event.

Secondly, our aim was to reflect clinical practice and capture the spectrum of acute respiratory illnesses encountered in children with CF, but we were limited by the lack of a standardized definition of a pulmonary exacerbation or a grading scale of severity. We categorized acute respiratory events based on treatment status, and while this strategy enabled us to evaluate the LCI response to antibiotic treatment at follow-up, treatment decisions can be subjective and vary between physicians. In a sensitivity analysis we recategorized acute respiratory events based on the duration of symptoms rather than antibiotic treatment. We found that worse LCI, but not FEV_1, was associated with events with more chronic symptoms. It is possible that LCI could be used to identify those events that could benefit from intensified treatment.

Thirdly, we attempted to capture all respiratory illnesses during the study but, in keeping with usual clinical practice, many events were treated with antibiotics over the phone. Furthermore, there were differences in the management of acute respiratory events between the two study sites with more unobserved pulmonary exacerbations at one site. Given that the overall rate of acute

respiratory events was similar across the two sites, these differences were unlikely to confound the results.

Fourthly, because the study design reflected usual clinical care, the time intervals between visits varied between participants and this may have impacted the observed changes. Although, when the time from baseline was added as a covariate in the linear regression model it had no impact on the magnitude of LCI or FEV_1 change.

Finally, we compared LCI and FEV_1 changes with treated and untreated acute respiratory events, but physicians were only aware of the FEV_1 result. The fact that FEV_1 was used to guide treatment decisions introduces a bias to the comparison of the acute respiratory event phenotypes.

This study provides new evidence to support the clinical utility of the LCI in children with CF but there are other factors to consider before it can be incorporated routinely into clinical practice. Although MBW is feasible to perform, the test requires trained operators and technically acceptable tests to ensure correct interpretation. MBW testing can be time-consuming and challenging to incorporate into routine evaluations. Future work should focus on adapting the test and quality control procedures for enhanced feasibility and efficiency. Furthermore, to clarify the role of LCI in disease management, further studies should demonstrate that its use translates to improved patient outcomes.

In conclusion, LCI worsened with all respiratory event phenotypes and was more sensitive than FEV_1 to untreated respiratory events. Lung function recovery, as measured by both LCI and FEV_1, was incomplete at follow-up, which demonstrates that even events with milder clinical presentations contribute to the progression of lung disease. Incorporating LCI into clinical care

as an additional outcome measure could help standardize treatment strategies and optimize functional outcomes.

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Figure Legends

Figure 1: Flow diagram of participants

¥Patients had residual symptoms from a captured respiratory event, these events were not analysed as separate events

*These patients were treated for a drop-in lung function but did not have increased respiratory symptoms. They were not included in the analysis.

Figure 2: Relative change in a) LCI and b) FEV_1% predicted from baseline to pulmonary exacerbations (n=76) and untreated increased cough events (n=47) and from baseline to the next consecutive follow-up visit. Data presented as estimated mean values, error bars represent 95% confidence intervals as determined by linear regression using GEE models to account for multiple measurements in the same participant. The between stable visit changes in LCI and FEV_1% predicted were used as the reference group in each analysis.

Figure 3: Comparison of relative changes in LCI and FEV_1% predicted from baseline to the symptomatic study visit. Complete data for both LCI *and* FEV1 to calculate a relative change from baseline were available for 180 acute respiratory events. Vertical line represents 10% worsening in FEV_1% predicted, and horizontal line represents 10% worsening in LCI.

Figure 4:

a) Relative changes in LCI and FEV_1 percent predicted from baseline to the first stable visit after acute respiratory events for events, all pulmonary exacerbations and increased cough events. Data presented as estimated mean values, error bars represent 95% confidence intervals as

determined by linear regression using GEE models to account for multiple measurements in the same participant. The reference group is the between stable visit changes

b) Proportion of events with recovery of FEV1% predicted and LCI recovery to 90% of baseline values at the next stable visit. For example, 75% of events with recovery to 90% of baseline LCI after an acute respiratory event.

Tables

Table 1: Classification of acute respiratory events

Visit type	Stable	Pulmonary exacerbation	Already Treated Pulmonary exacerbation	Increased cough event	Persistent Symptoms
Respiratory symptoms	None or stable	New or acute worsening	New or acute worsening	New or acute worsening	Ongoing
Treatment with antibiotics (oral/IV)	No	Yes	Yes	No	No
Timing of antibiotics		Start date on or after study visit	Start date before study visit		

Table 2: Demographics of study population at enrolment

Demographics	**N=98**
Age at enrolment, years, mean (range)	**9.6 (5 – 16.8)**
Diagnosed by newborn screening, n (%)	**53 (54)**
Male sex, n (%)	**45 (46)**
Genotype functional class n(%)	
Class 1-III	**93 (95)**
Class IV-V	**5 (5)**
LCI, units, mean (SD) ¥	**9.2 (2.1)**
LCI above upper limit of normal (35) **, n (%)**	**65 (66)**
FEV_1 percent predicted, mean (SD) ¥	**96.6% (11.6)**
FEV_1 percent predicted below lower limit of normal (26)**, n(%)**	**10 (10)**
BMI centile, mean (SD)	**45.6 (23.6)**

Medication use at enrolment, n (%)	
Hypertonic saline	**46 (47)**
Dornase alfa	**49 (50)**
CFTR modulator	**27 (28)**
Chronic inhaled antibiotic	**8 (8)**

¥ values taken from the first stable study visit of the study

Table 3: Clinical characteristics of acute respiratory events present at the symptomatic study visit.

Variable	**Pulmonary exacerbation** **N=124**	**Already Treated Pulmonary exacerbation** **N=41**	**Increased cough event** **N=80**	**Persistent symptoms** **N=20**
Route of Treatment, n (%)				
Oral	94 (75.8)	37 (90.2)	-	-
Inhaled	15 (12.0)	0 (0)	-	-
Intravenous	15 (12.0)	4 (8.7)	-	-
Symptom scores Mean (95% CI)				
ʌCFQ-R (parent)	-23.9 (-26.7 to -21.2)	-25.7 (-30.2 to -21.1)	-14.0 (-17.3 to -10.7)	-9.4 (-19.2 to 0.37)
ʌCFQ-R (self)	-11.3 (-13.7 to -8.8)	-11.3 (-15.3 to -7.4)	-4.0 (-7.1 to -1.1)	-10.6 (-17.2 to -3.9)
ʌCRISS	15.8 (13.2 to 18.4)	9.9 (5.7 to 14.1)	12.8 (9.6 to 15.9)	9.1 (2.1 to 16.1)
Clinical Features, n (%)				
Increased cough	131 (98.5)	44 (95.7)	81 (100)	15 (75.0)

Increased chest congestion or change in sputum	88 (66.2)	18 (39.1)	26 (32.7)	7 (26.8)
Decrease in FEV_1% predicted by 10% or more	55 (41.4)	7 (15.2)	8 (9.9)	2 (10.5)
New or increased adventitial sounds on lung exam	38 (29.0)	2 (4.4)	6 (7.3)	1 (4.2)
Oxygen saturation < 90% on room air of ≥5% decline from previous baseline	2 (1.5)	0	0	0
New lobar infiltrate(s) or atelectasis on chest radiograph	2 (1.5)	1 (2.2)	0	0
Increased work of breathing or respiratory rate	15 (11.5)	0	1 (1.2)	0
Hemoptysis †	3 (2.3)	0	0	0
Weight loss ≥5% body weight	3 (2.3)	0	0	0
Symptoms or signs of viral upper respiratory infection β	43 (39.5)	12 (29.3)	48 (58.5)	1 (12.5)
Symptom duration, days, median (IQR)	7 (4 to 15)	24.5 (14.5 to 36)	6 (3 to 12)	62 (17 to 89.5)

*Weight loss ≥5% body weight or decreased across 1 major percentile in past 6 months

†Hemoptysis defined as more than streaks on more than one occasion in past week

β Symptoms or signs of a viral upper respiratory tract infection included nasal congestion, sore throat, fever and rash

ʌ change in symptom score from a recent stable baseline to the symptomatic visit. Data presented as mean difference (95% confidence interval), calculated using linear regression within a generalized estimating equation model.

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire- Revised Respiratory score; CRISS, Chronic Respiratory Infection Symptom Score

Table 4: Proportion of acute respiratory events with ≥10% or ≥15% worsening in lung function relative to baseline, as measured by either LCI or FEV_1% predicted.

Event type	**≥10% worsening relative to baseline**			**≥15% worsening relative to baseline**		
	LCI n (%)	FEV1 n (%)	LCI or FEV1 n (%)	LCI n (%)	FEV1 n (%)	LCI or FEV1 n (%)
All events n=180	75 (41.7)	54 (30.0)	97 (53.9)	58 (32.2)	29 (16.1)	108 (40.0)
Pulmonary exacerbation n=86	37 (43.0)	39 (45.3)	55 (64.0)	29 (33.7)	21 (24.4)	39 (45.3)
Already treated pulmonary exacerbation n=30	13 (43.3)	8 (26.7)	16 (53.3)	9 (30.0)	5 (16.7)	12 (40.0)
Increased cough events n=54	20 (37)	7 (13.0)	21 (38.9)	16 (29.6)	3 (5.6)	17 (31.5)
Persistent symptoms n=10	5 (50.0)	0	5 (50)	4 (40.0)	0	4 (40)

Figure 1

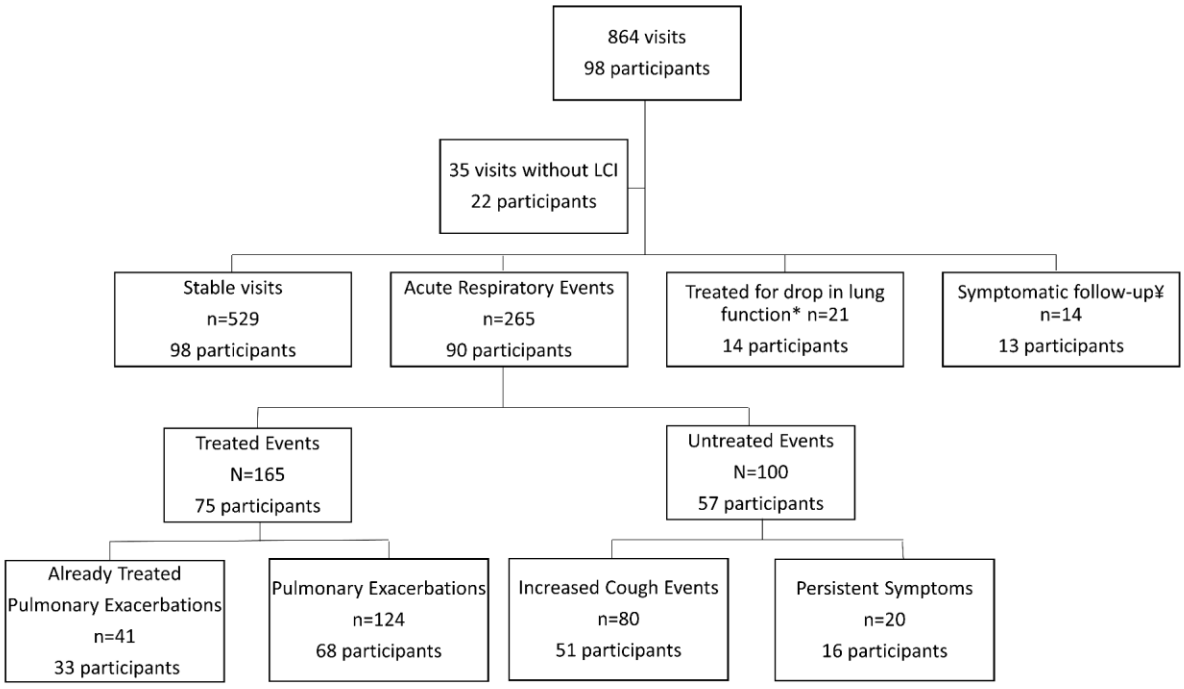

864 visits
98 participants
35 visits without LCI
22 participants
Stable visits
n=529
98 participants
Acute Respiratory Events
n=265
90 participants
Treated for drop in lung function* n=21
14 participants
Symptomatic follow-up¥
n=14
13 participants
Treated Events
N=165
75 participants
Untreated Events
N=100
57 participants
Already Treated Pulmonary Exacerbations
n=41
33 participants
Pulmonary Exacerbations
n=124
68 participants
Increased Cough Events
n=80
51 participants
Persistent Symptoms
n=20
16 participants

Figure 2:

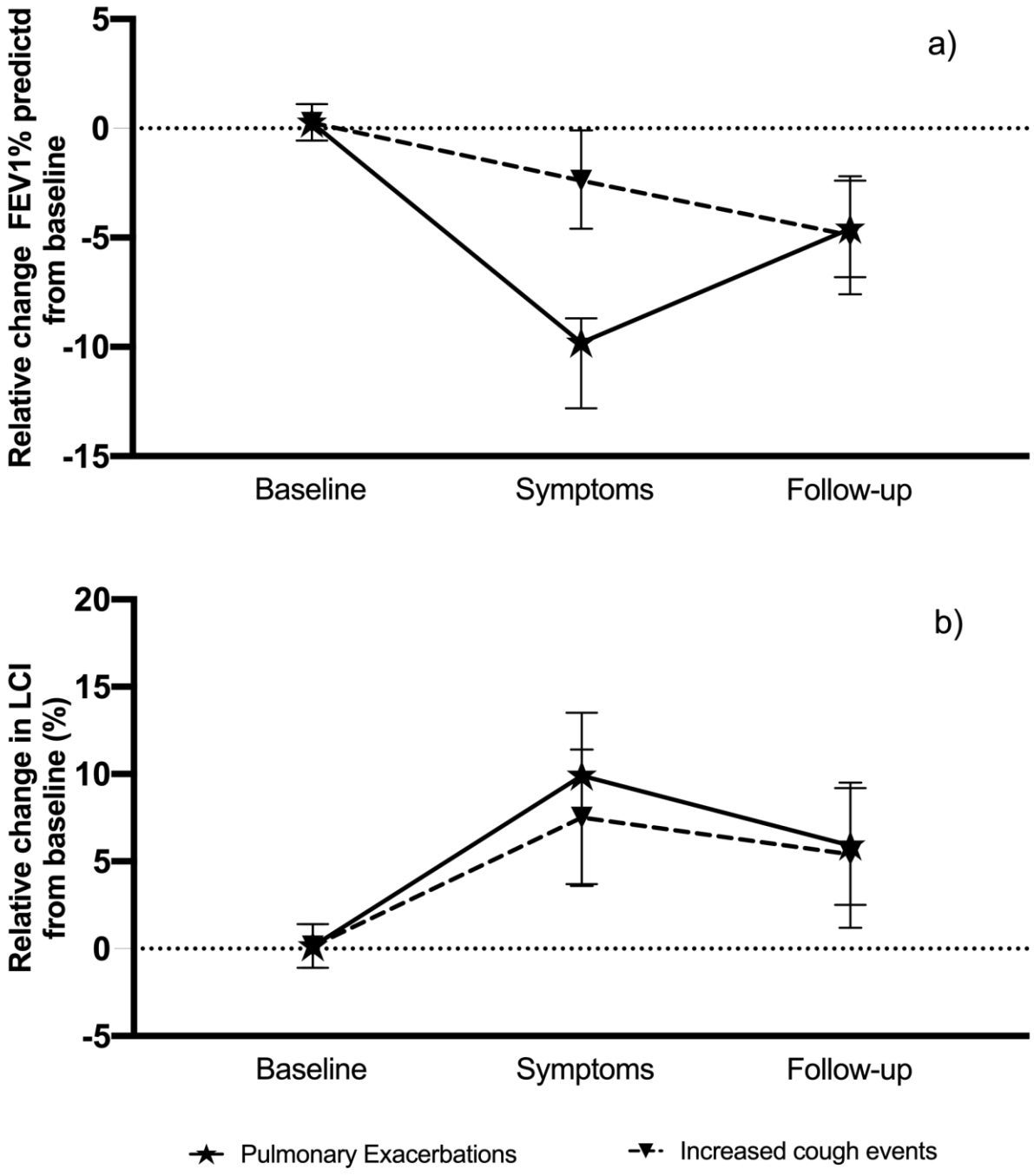

a)
Relative change FEV1% predictd from baseline
5
0
-5
-10
-15
Baseline
Symptoms
Follow-up
b)
Relative change in LCI from baseline (%)
20
15
10
5
0
-5
Baseline
Symptoms
Follow-up
Pulmonary Exacerbations
Increased cough events

Figure 3:

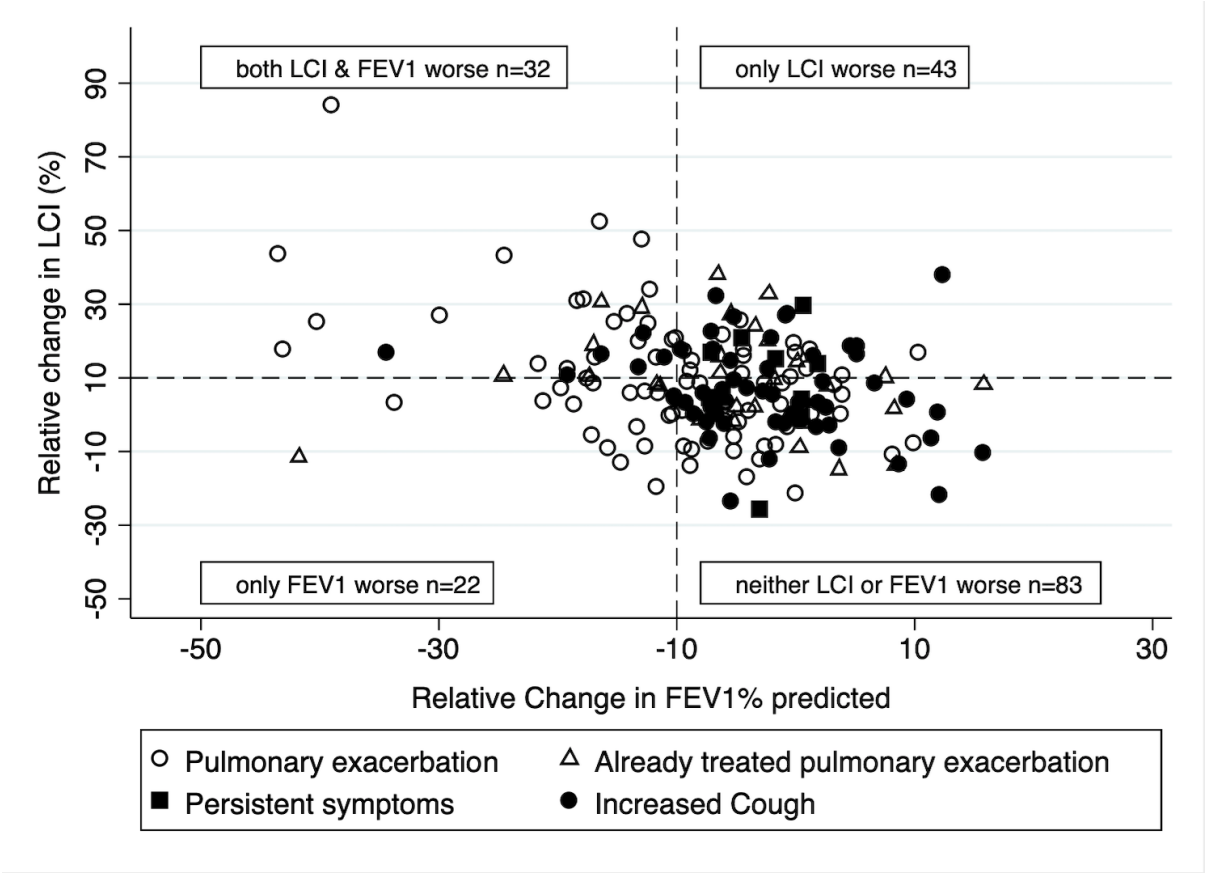
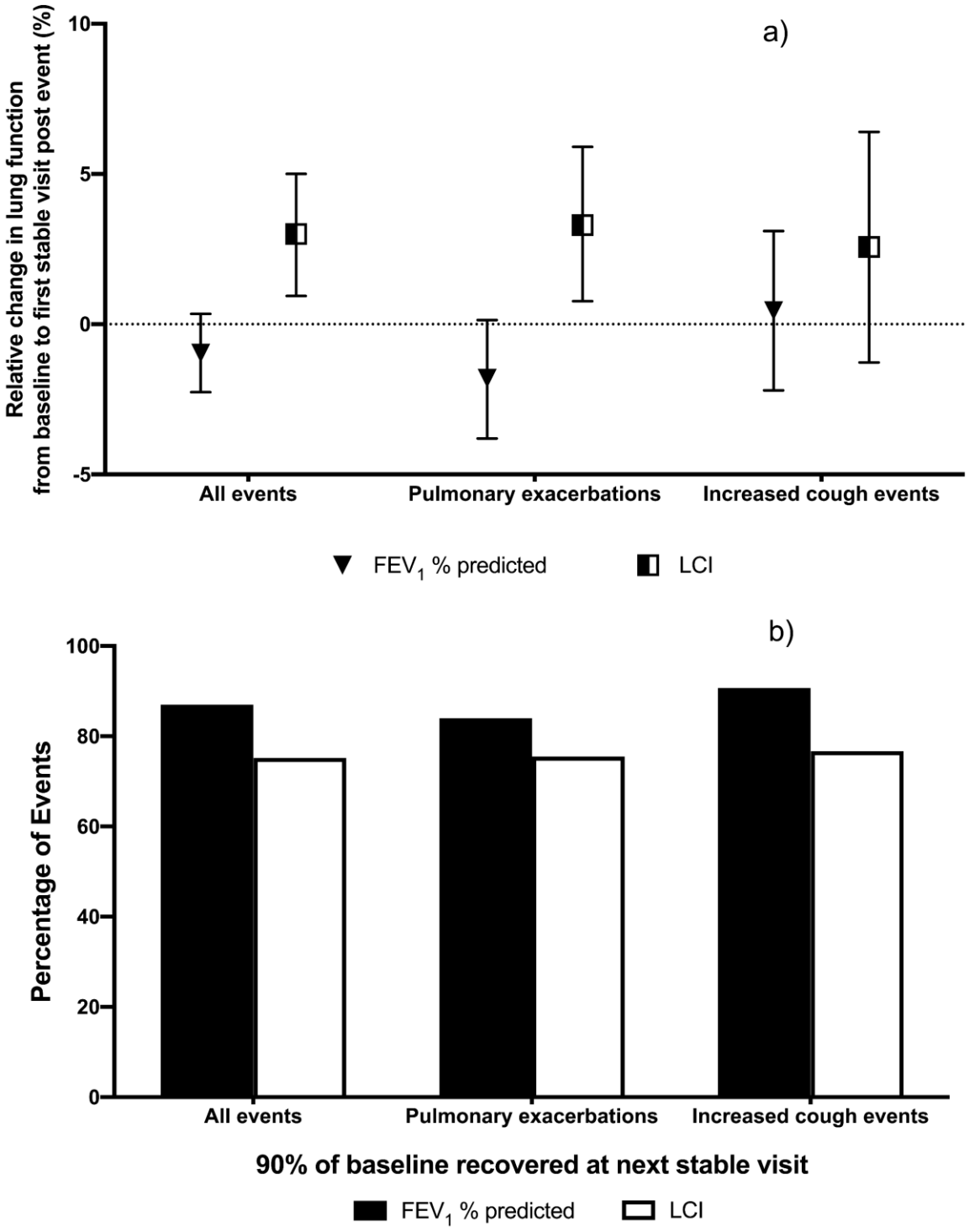

both LCI & FEV1 worse n=32
only LCI worse n=43
only FEV1 worse n=22
neither LCI or FEV1 worse n=83
Relative change in LCI (%)
90
70
50
30
10
-10
-30
-50
-50
-30
-10
10
30
Relative Change in FEV1% predicted
Pulmonary exacerbation
Already treated pulmonary exacerbation
Persistent symptoms
Increased Cough

Figure 4:


a)
Relative change in lung function from baseline to first stable visit post event (%)
10
5
0
-5
All events
Pulmonary exacerbations
Increased cough events
FEV1 % predicted
LCI
b)
Percentage of Events
100
80
60
40
20
0
All events
Pulmonary exacerbations
Increased cough events
90% of baseline recovered at next stable visit
FEV1 % predicted
LCI