Title: Lung clearance index and structural lung disease on computed tomography in early cystic fibrosis

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At a Glance Commentary

Scientific Knowledge on the Subject:

The lung clearance index has been suggested as a surrogate for chest computed tomography to detect structural lung abnormalities in individuals with cystic fibrosis, however the associations between lung clearance index and early structural lung disease are unclear.

What This Study Adds to the Field:

This study is the first to examine the associations between lung clearance index and structural lung disease detected on chest computed tomography across the entire paediatric age range. Our data indicates that the lung clearance index is sensitive to the presence and extent of structural lung disease in preschool and school-aged children with CF, but is not sensitive to mild structural abnormalities in infancy. The lung clearance index may be a useful tool to monitor structural disease progression, and an important outcome measure in clinical trials in young children with cystic fibrosis. However, our data indicate that lung clearance index should not be used as a surrogate to chest imaging to screen for bronchiectasis in children with cystic fibrosis.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

Abstract

Rationale: The lung clearance index is a measure of ventilation distribution from the multiple breath washout technique. Lung clearance index has been suggested as a surrogate for chest computed tomography to detect structural lung abnormalities in individuals with cystic fibrosis, however the associations between lung clearance index and early structural lung disease are unclear.

Objective: We assessed the ability of lung clearance index to reflect structural lung disease on chest computed tomography across the entire paediatric age range.

Methods: Lung clearance index was assessed in 42 infants (0-2y), 39 preschool (3-6y), and 38 school-aged (7-16y) children with cystic fibrosis prior to chest computed tomography, and 72 healthy controls. Scans were evaluated for CF-related structural lung disease using the PRAGMA quantitative outcome measure.

Measurements and Main Results: In infants with cystic fibrosis, lung clearance index is insensitive to structural disease (Kappa -0.03 (-0.05, 0.16)). In preschool children with cystic fibrosis, lung clearance index correlates with total disease extent. In school-aged children lung clearance index correlates with extent of total disease, bronchiectasis, and air trapping. In preschool and school aged children, lung clearance index has a good positive (83-86%), but poor negative (50-55%), predictive value to detect the presence of bronchiectasis.

Conclusions: These data suggest lung clearance index may be a useful surveillance tool to monitor structural lung disease in preschool and school age children with cystic fibrosis. However, lung clearance index cannot replace chest imaging using computed tomography to screen for bronchiectasis in this population.

Abstract word count: 247

Keywords: Multiple breath washout, infant, child, imaging, cystic fibrosis.

Introduction

Structural lung abnormalities develop early in individuals with cystic fibrosis (CF) and progress rapidly into irreversible structural disease (1-3). To delay the onset and progression of lung disease interventions should ideally commence early in life. However, effective and personalised interventions require accurate and simple means to monitor disease severity (4). As such there is a clear imperative for the development of minimally invasive and sensitive markers of structural lung disease that can be applied routinely in the clinical setting.

Chest computed tomography (CT) is the gold standard for assessing the presence and extent of CF-related structural lung disease (1, 3), and outcome measures appropriate for infants and young children with mild disease have recently been developed (5). However, despite ongoing improvements in technology resulting in lower doses (6, 7), the use of ionising radiation limits the frequency at which CT can be performed. Alternative techniques, such as lung function measurements, may allow the assessment of lung disease at more frequent intervals, reduce the number of CT scans required for the monitoring of structural lung disease progression in early life, and serve as endpoints for clinical trials.

Spirometry, particularly forced expiratory volume in 1 second (FEV_1), is the most widely used method of monitoring CF lung disease.. However FEV_1 is insensitive to detect the onset and progression of early CF lung disease (8), and difficult to obtain reliably in infants and young children (9, 10).

Lung clearance index (LCI) is a marker of global ventilation distribution derived from the multiple breath washout technique (MBW). LCI is elevated in a small proportion of infants (11, 12), and the majority of preschool (13, 14) and school aged (8, 15) children with CF. In

older children with CF, LCI has been shown to be more sensitive than FEV₁ to detect the presence of structural lung disease (8, 16, 17). However, there are only weak correlations between LCI and structural lung disease in infants with CF (18) and there are no data on the ability of LCI to indicate the presence or severity of structural lung disease in preschool children aged three to six years. This is arguably the most important age group due to the rapid progression of structural disease during this period (3). For LCI to be considered as a routine clinical investigation or outcome measure for intervention trials, further evidence regarding the ability of LCI to accurately reflect structural lung damage in infants and children with CF of all ages is required. The aim of this study was to assess the associations between MBW outcomes and CF-related structural lung disease across the entire paediatric age range. We hypothesized that the associations between MBW outcomes and structural lung disease would be age dependent, with stronger associations seen in older children with more established CF-related lung disease. Some of the results of these studies have been previously reported in the form of abstracts (19, 20).

Methods

Study population

Infants and children with CF undergoing annual surveillance or clinically indicated chest CT scan at Princess Margaret Hospital in Perth and the Royal Children's Hospital in Melbourne, Australia were eligible to take part in this study (detailed methods are provided in the online data supplement). Healthy children without CF over the age of two years were recruited from the local population in Perth to undertake lung function measurements. The ethics committee of each institution approved the study, and parents gave written informed consent to each aspect of the study separately.

Multiple Breath Washout

The Exhalyzer D system was used for MBW data collection (Ecomedics AG, **Duernten**, Switzerland). Infant MBW (3 months to two years) was performed in the supine position using 4% sulphur-hexafluoride (SF₆) while asleep following chloral hydrate sedation (18, 21). In children over two years, MBW was performed using 100% oxygen to washout resident nitrogen gas from the lungs (22). Functional residual capacity (FRC), LCI, the first (M1/M0) and second (M2/M0) moment ratios were derived from visits with at least two acceptable measurements with no evidence of leak or irregular breathing pattern (23). The lung clearance index was considered the primary outcome from MBW testing in this study.

Chest Computed Tomography

Chest CT was only obtained in patients with CF. CT scans in infants and preschool children were performed prior to bronchoalveolar lavage collection under intravenous general anaesthetic. Volumetric inspiratory scans were obtained at a positive airway opening pressure of 25 cmH₂O, and volumetric or limited slice expiratory scans obtained at an airway opening pressure of 0 cmH₂O (i.e. relaxed end expiratory volume) (3, 24). In school-aged children, spirometry-assisted volumetric chest CT scans were obtained, whereby inspiratory scans were obtained at total lung capacity and expiratory scans were collected at residual volume (25).

To assess CT-determined structural lung disease, the quantitative PRAGMA-CF scoring method was used (5). Briefly, a grid overlaid on ten equidistant axial slices is annotated for the presence of bronchiectasis (outer edge bronchus-artery cross-sectional area ratio > 1), mucus plugging (high density airway occlusion or tree-in-bud appearance), bronchial wall thickening (assessed subjectively as airway walls that are thicker or have increased signal

density relative to normal airways) on inspiratory scans, and trapped air (geographic low density regions) on expiratory scans (5). The extents (represented as volume proportions of the lung) of total airways disease (% disease), bronchiectasis (% bronchiectasis) and trapped air (% air trapping) were calculated and considered the primary outcome from chest CT. Chest CT scans were also scored for the presence and extent of bronchiectasis, mucus plugging, bronchial wall thickening and air trapping using a simplified CF-CT scoring method as described previously (2, 3).

Statistical analysis

The upper limit of normal for MBW indices were calculated from a prospective healthy control population of preschool and school aged children (n = 72) and published reference equations for infants (LCI only as there are no reference data are available for moment ratios in infants) (26). The agreement between MBW indices and the presence of bronchiectasis and air trapping was assessed using the Kappa coefficient of agreement and receiver operating characteristic (ROC) curves. Sensitivity, specificity, positive and negative predictive values were calculated together with 95% exact binomial confidence intervals. Associations between MBW indices and the extent of structural lung disease were assessed using linear mixed effects models with random intercepts for repeated visits to account for clustering. The coefficients of the fixed effects of the linear mixed models, with 95% confidence intervals and p-values are presented. All analyses were performed using Stata 13.0 (Stata Corp. 2013, College Station, TX).

Results

Study population

Matched MBW and chest CT data were available for 49 visits in 42 infants (3 months to two years), 52 visits in 39 preschool children (three to six years) and 48 visits in 38 school-aged children (seven to 16 years) with CF (Table 1). In addition, MBW data were available on a prospective healthy control population of 72 preschool and school aged children (three to 15 years) with no history of respiratory disease (Table E1 in the online data supplement). In the control population LCI, M1/M0 and M2/M0 were found to be independent of height or age (Figure 1). We found that 22% of infants, 58% of preschool and 58% of school-aged children with CF had an LCI above the upper limit of normal (Table 2).

Agreement between MBW indices and the presence of bronchiectasis

The agreement between LCI and the presence of bronchiectasis on chest CT is shown in Table 2. An abnormal LCI and detectable bronchiectasis was uncommon in infants with CF resulting in a low sensitivity and low positive predicted value. The majority of preschool and school aged children with CF had an LCI above the upper limit of normal (58%) and had bronchiectasis detected on CT (69%), resulting in a high concordance between the two measures (~70%). In these older age groups LCI had a sensitivity and specificity of ~70% to detect bronchiectasis. The positive predictive value for LCI was high indicating that in over 80% of visits when LCI is abnormally elevated bronchiectasis can be detected on chest CT. However, the negative predictive value of LCI was low (50-55%) indicating that in half of the visits where LCI is within the normal range bronchiectasis was still detected on CT. The results for the moment ratios were similar to that of LCI and are presented in Table E2 in the online data supplement. In addition, we performed an ROC analysis for LCI and the presence of bronchiectasis (Table E3 in the online data supplement). We determined the optimal LCI value (calculated to maximise sensitivity and specificity) to detect bronchiectasis, to be 7.8 lung turnovers for each age group.

Agreement between MBW indices and the presence of air trapping

The agreement between LCI and the presence of air trapping on chest CT is shown in Table 3. The prevalence of air trapping increased with age from 58% in infants, 85% in preschool children, and 94% in school-age children. There was significant agreement between LCI and the presence of air trapping on CT in infants with CF. However the sensitivity of LCI to detect air trapping on CT was only 38%. There was no agreement between LCI and air trapping presence in preschool and school-aged children with CF. In preschool children, LCI had a lower positive (73%) and negative (41%) predictive value to detect air trapping presence than in infants. In school-aged children, LCI had a high positive (93%), but almost negligible negative (5%) predictive value to detect air trapping. The results for the moment ratios were similar to that of LCI and are presented Table E4 in the online data supplement.

Associations between MBW outcomes and extent of structural disease

We examined the association between MBW outcomes and the extent of structural disease abnormalities on chest CT using PRAGMA-CF scores (Table 4; Figure 2). In infants with CF, LCI and M1/M0 did not correlate with any structural disease extent scores. There was, however, a significant association between M2/M0 and the extent of bronchiectasis and air trapping. In preschool children with CF, LCI positively correlated with total structural disease extent but not the extent of bronchiectasis or air trapping. Both M1/M0 and M2/M0 in preschool children correlated with total structural disease and bronchiectasis extent, but not air trapping. In school-aged children with CF, LCI and M2/M0 positively correlated with total disease, bronchiectasis, and air trapping extent. M1/M0 did not correlate with any disease extent scores in school-aged children. We found similar associations between MBW outcomes and structural disease extent scores using the simplified CF-CT scoring method (Table E5 in the online data supplement).

Discussion

The objective of this study was to determine the ability of MBW measures of ventilation distribution to act as a minimally invasive surrogate for structural lung disease in children with CF. We compared MBW outcomes against chest CT, the current gold standard method to detect structural lung disease in CF. We found that LCI is relatively insensitive to the presence and extent of early structural abnormalities in infants with CF. In preschool and school-aged children, LCI had good agreement and correlation with the presence and extent of structural abnormalities on CT. However, the low negative predictive value of LCI for the presence of bronchiectasis and air trapping in infants and children with CF suggests that LCI should not be used as a surrogate for chest CT to indicate the presence of structural disease. Despite the limitations of LCI to identify lung damage, LCI could be a useful tool for monitoring early lung disease in CF, and therefore longitudinal assessments of LCI in relation to other clinical outcomes including inflammation, infection and structural lung disease trajectory are needed.

We found that LCI was relatively insensitive to the presence and extent of structural lung disease in infants with CF. This supports data from a previous study by our group, that examined associations between LCI, moment ratios and structural lung disease on limited slice chest CT scans scored using a CF-CT scoring method modified for use in children (18). This study found a weak correlation between LCI, moment ratios and the extent of air trapping on CT (18). Our current study utilised volumetric chest CT scans, that have been shown to be more sensitive to detect early structural lung disease, and the PRAGMA-CF scoring method that quantifies early structural disease (5). We found that LCI was relatively insensitive to detect the presence of bronchiectasis and air trapping on chest CT, and did not correlate with any structural disease extent parameter in infants with CF. There was,

however, a correlation between M2/M0 and bronchiectasis and air trapping extent, suggesting that moment ratio analysis may be more sensitive to the extent of early disease than LCI. Structural lung disease in the first two years of life in infants with CF following newborn screening and treatment in a specialist centre is mild; only 20% of infants in our study had detectable bronchiectasis and the mean percentage of the lung affected by bronchiectasis was 0.2%. The prevalence of bronchiectasis in this study is higher than that previously reported by our group (3), which is likely due to the greater sensitivity to detect bronchiectasis in volumetric scans compared with the 3-slice technique used previously. While the extent of structural disease in infants with CF is low, we have previously shown that disease extent is associated with more rapid progression of lung disease over the subsequent two years in infants with CF, and thus is likely to be clinically relevant (5). The LCI may be more useful as a tool to reflect potentially reversible changes in the lungs associated with inflammation and infection in this age group (11, 27), but the results from our current study indicate that MBW indices are not sufficiently sensitive to be used as a surrogate for the detection and monitoring of early structural lung disease in infants with CF.

This study is the most comprehensive examination of the relationships between LCI and structural lung disease in infants and preschool children with CF. This developmental period is associated with increasing prevalence and extent of structural lung disease along with worsening ventilation inhomogeneity (increased LCI) (1, 13, 14). The prevalence of bronchiectasis in our population was 69% in preschool children, compared with only 20% in infants with CF. Given the rapid increase in the prevalence of bronchiectasis in the preschool years, this period arguably represents a window of opportunity for interventions aimed at preventing or slowing the development of irreversible structural disease. In the present study MBW outcomes, LCI and moment ratios had good agreement, sensitivity and specificity to

detect the presence of bronchiectasis on chest CT. We also found positive correlations between MBW outcomes and the extent of structural lung disease. These data suggest that MBW outcomes could be used as a surveillance tool for the monitoring of established structural disease in children with CF. However, we advise caution regarding the use of LCI as a screening tool or surrogate for chest CT to detect the presence of structural lung disease. While we found that the majority of children with an abnormal LCI had bronchiectasis detected on their CT (positive predictive value = 83%), we found that only half of the children with an LCI within the normal range did not have bronchiectasis detected on CT (negative predictive value = 50%). This means that a significant portion of children would be misdiagnosed as not having bronchiectasis if LCI was used as the sole screening/detection tool. We believe that the LCI would be ideally suited as a non-invasive monitoring tool for preschool children with CF that could be applied regularly in the clinical setting in conjunction with imaging techniques for the detection and monitoring of structural disease.

These data support previous studies regarding the ability of LCI to reflect structural disease in school-aged children with CF. We found that LCI and moment ratios correlated with the presence and extent of structural lung disease in school-aged children with CF, as has been reported previously (8, 16, 17). We found that over 85% of children with an abnormal LCI had bronchiectasis detected on chest CT. However, the negative predictive value of LCI was again low (55%) indicating that in half of the visits where LCI was normal, bronchiectasis was still detected on CT. In a study of individuals with CF aged five to 19 years, LCI had a lower positive (71%) and higher negative predictive (69%) to detect the presence of bronchiectasis on CT compared with the present study (8). In individuals with CF aged six to 26 years with a normal FEV₁ (>80% predicted), LCI had a positive predictive value of 88% and negative predictive value of 63% to detect an abnormal chest CT (16). Similarly, in a

younger cohort of school-aged children (6 – 10 years) LCI had a positive predictive value of 88% and negative predictive value of 44% to reflect an abnormal chest CT (17). It is important to note that positive and negative predictive values are dependent on the prevalence of structural lung disease in the population and may not be generalizable to a population with a different prevalence. Together these data support the notion that an abnormal LCI is highly predictive of the presence of structural lung disease, however, an LCI within the normal range does not rule out structural lung disease detected on chest CT.

Strengths of the present study include the use of a prospective healthy control cohort for the calculation of upper limits of normal for LCI and moment ratios in preschool and school-aged children. In infants with CF, the second moment ratio was more strongly correlated with the extent of structural lung disease than LCI, possibly because moment ratios can detect more peripheral ventilation inhomogeneity at the latter portion of the washout compared with LCI. As a result moment ratios may be most valuable to calculate in early life where the disease is dominated by small changes to the peripheral airways. We also utilised the novel PRAGMA-CF quantitative CT scoring method, aimed specifically at quantifying the extent of early structural abnormalities in early CF lung disease (5). While we did not see any appreciable difference in the structure-function extent relationships between PRAGMA and CF-CT scores, we believe that the PRAGMA-CF is the most appropriate method for assessing CT scans in young children with CF. Limitations of the current study include the differences in the MBW testing in infancy (sedated, supine, SF₆ gas) compared with children (awake, seated, 100% oxygen to washout resident nitrogen gas). Sedation during lung function may have caused atelectasis or air trapping. It is also possible that the use of an exogenous tracer gas (SF₆) for MBW testing in infancy could underestimate ventilation inhomogeneity due to the SF₆ gas not penetrating occluded lung units. In addition there were difference in chest CT

scanning techniques in infants and preschool (anaesthetised, expiratory scan at functional residual capacity) and school-age (awake, spirometry-assisted, expiratory scan at residual volume). Our study aimed to determine if LCI could be used as a surrogate for chest CT to detect structural disease, and thus was not designed to examine the effect of clinical variables, such as pulmonary infection status, inflammation, or exacerbations on the associations between MBW and CT outcomes. All the children in our study, including the three adolescent patients who underwent clinically indicated chest CT scans, were clinically stable at the time of CT and MBW testing. Current studies that have examined relations between LCI and structural lung disease have been cross-sectional in nature, and thus we are not yet able to determine whether LCI can track the development and progression of structural lung disease over time.

Treatment and monitoring of lung disease should commence early in life in individuals with CF in order to prevent the onset and/or slow the progression of lung disease. The LCI is a promising lung function outcome that can be measured across the entire paediatric age range. The results from this study suggest that the LCI is sensitive to detect the presence and extent of structural lung disease detected by chest CT in preschool and school-aged children with CF, but is not sensitive to detect mild structural abnormalities in infancy. While LCI may be a useful surveillance tool in CF and potentially a feasible clinical trial outcome, our data indicate that LCI should not be used as a surrogate to chest imaging for the detection of bronchiectasis in children with CF.

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Figure legends

Figure 1: Lung clearance index plotted against age for healthy control children (circles) and children with cystic fibrosis (triangles). LCI = lung clearance index. Horizontal lines indicate the upper (7.7) and lower (5.7) limits of normal for LCI.

Figure 2: Scatter plots of LCI plotted against % disease, % bronchiectasis, and % air trapping scores in infants (A – red markers), preschool (B – green markers) and school-aged (C – blue markers) children with CF. LCI = lung clearance index.

Tables

Characteristics	Infants	Preschool	School-age
Number of children	42	39	38
Number of visits	49	52	48
Age (y)	0.94 (0.57)	5.42 (1.05)	9.77 (2.48)
Sex [male: female]	16 : 26	16 : 23	21 : 17
Height z-score (95% CI)	0.03 (-0.20, 0.28)	0.08 (-0.20, 0.34)	-0.20 (-0.44, 0.04)
Weight z-score (95% CI)	-0.12 (-0.33, 0.53)	0.19 (-0.13, 0.51)	0.26 (-0.04, 0.55)
FEV1 L (95% CI)			1.80 (1.65, 1.95)
FEV1 z-score (95% CI)			-0.13 (-0.51, 0.26)
FVC L (95% CI)			2.19 (2.03, 2.34)
FVC z-score (95% CI)			0.23 (-0.12, 0.57)
Phe508del/Phe508del	58% (25/42)	62% (25/39)	54% (21/38)
Phe508del/other	36% (16/42)	30% (12/39)	35% (14/38)
Severe genotype	88% (38/42)	91% (35/39)	88% (34/38)
Multiple Breath Washout			
Functional residual capacity	0.19 (0.08)	0.91 (0.19)	1.51 (0.77)
Lung clearance index	7.81 (0.80)	8.17 (1.22)	8.35 (1.78)
First moment ratio	2.30 (0.28)	1.78 (0.24)	1.95 (0.91)
Second moment ratio	11.02 (4.16)	8.80 (2.05)	7.19 (3.41)
PRAGMA-CF scores			
Bronchiectasis present	20% (10/49)	69% (36/52)	69% (33/48)
Air trapping present	58% (29/49)	85% (44/52)	94% (45/48)
Bronchiectasis extent (%)	0.18 (0.34)	1.88 (3.38)	2.05 (3.21)
Air trapping extent (%)	1.35 (2.73)	6.37 (12.02)	20.8 (21.34)
Disease extent (%)	1.35 (1.05)	4.26 (4.29)	4.86 (5.13)

Table 1: Demographics of study population Data is presented as mean (standard deviation) or % (proportion) unless otherwise stated. 95% CI = 95% confidence interval. Height, weight and BMI z-scores were calculated using WHO growth standards (28, 29)

	Infant	Preschool	School-age
LCI ULN	Derived from Lum <i>et al.</i> 2013	7.7	7.7
Abnormal LCI (%)	22% (11/49)	58% (30/52)	58% (28/48)
Bronchiectasis present	20% (10/49)	69% (36/52)	69% (33/48)
Concordance (%)	65% (32/49)	69% (36/52)	73% (35/48)
Kappa coefficient	-0.03 (-0.05, 0.16)	0.35 (0.10, 0.60) #	0.42 (0.20, 0.64) #
Sensitivity	20% (2.5, 56)	69% (52, 84)	73% (55, 87)
Specificity	77% (61, 89)	69% (41, 89)	73% (45, 92)
Positive predictive value	18% (2.3, 52)	83% (65, 94)	86% (67, 96)
Negative predictive value	79% (63, 90)	50% (28, 72)	55% (32, 77)

Table 2: Agreement between LCI and the presence of bronchiectasis on chest CT using PRAGMA-CF scores. Brackets contain n values or 95% confidence interval. LCI = lung clearance index; ULN = upper limit of normal. Upper limit of normal for LCI in infants was derived from the equation in Lum *et al.* 2013. The upper limit of normal for LCI in preschool and school-age children was derived from our prospective healthy population (Table E1 in the online data supplement). * $p < 0.05$; # $p < 0.01$; Φ $p < 0.001$.

	Infant	Preschool	School-age
LCI ULN	Derived from Lum <i>et al.</i> 2013	7.7	7.7
Abnormal LCI (%)	22% (11/49)	58% (30/52)	58% (28/48)
Air trapping present	58% (29/49)	85% (44/52)	94% (45/48)
Concordance (%)	65% (32/49)	60% (31/52)	56% (27/48)
Kappa coefficient	0.30 (0.06, 0.54) Φ	0.15 (-0.13, 0.43)	-0.02 (-0.16, 0.14)
Sensitivity	38% (19, 59)	63% (45, 79)	58% (42, 72)
Specificity	92% (74, 99)	53% (28, 77)	33% (0.84, 91)
Positive predictive value	82% (48, 98)	73% (54, 88)	93% (77, 99)
Negative predictive value	61% (43, 76)	41% (21, 64)	5% (0.13, 25)

Table 3: Agreement between LCI and the presence of air trapping on chest CT using PRAGMA-CF scores. Brackets contain n values or 95% confidence interval. LCI = lung clearance index; ULN = upper limit of normal. Upper limit of normal for LCI in infants was derived from the equation in Lum *et al.* 2013. The upper limit of normal for LCI in preschool and school-age children was derived from a prospective healthy population (Table E1 in the online data supplement). $p < 0.05$; # $p < 0.01$; Φ $p < 0.001$.

	LCI	M/M0	M2/M0
Infants			
% Disease	0.03 (-0.14, 0.20)	0.00 (-0.01, 0.01)	0.02 (0.04, 0.16)
% Bronchiectasis	-0.33 (-0.82, 0.16)	0.01 (-0.02, 0.04)	0.31 (0.18, 0.45) Φ
% Air trapping	0.04 (-0.04, 0.12)	0.00 (-0.00, 0.01)	0.05 (0.03, 0.08) Φ
Preschool			
% Disease	0.10 (0.02, 0.19) *	0.02 (0.00, 0.04) *	0.17 (0.03, 0.31) *
% Bronchiectasis	0.11 (0.00, 0.22)	0.02 (0.00, 0.05) *	0.20 (0.01, 0.39) *
% Air trapping	0.02 (-0.01, 0.05)	0.00 (0.00, 0.01)	0.02 (-0.03, 0.07)
School-age			
% Disease	0.18 (0.10, 0.27) Φ	0.03 (-0.02, 0.08)	0.36 (0.19, 0.53) Φ
% Bronchiectasis	0.29 (0.14, 0.43) Φ	0.04 (-0.05, 0.13)	0.55 (0.28, 0.83) Φ
% Air trapping	0.06 (0.04, 0.07) Φ	0.01 (-0.01, 0.02)	0.10 (0.06, 0.14) Φ

Table 4: Association between MBW outcomes and the extent of structural disease on CT using PRAGMA-CF scores. Brackets contain 95% confidence interval. LCI = lung clearance index; M1/M0 = first moment ratio; M2/M0 = second moment ratio. Coefficients indicate the increase in MBW outcomes for each unit increase in CT outcomes. * $p < 0.05$; # $p < 0.01$; Φ $p < 0.001$.

Figures

Figure 1: Lung clearance index plotted against age for healthy control children (circles) and children with cystic fibrosis (triangles). LCI = lung clearance index. Horizontal lines indicate the upper (7.7) and lower (5.7) limits of normal for LCI.

Figure 2: Scatter plots of LCI plotted against % disease, % bronchiectasis, and % air trapping scores in infants (A – red markers), preschool (B – green markers) and school-aged (C – blue markers) children with CF. LCI = lung clearance index.