Lung Clearance Index at 4 Years Predicts Subsequent Lung Function in Children with Cystic Fibrosis

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***Rationale*: The markedly improved life expectancy of children with cystic fibrosis (CF) has created a new challenge, as traditional markers of lung disease are frequently normal in young children. This prevents identification of individuals who may benefit from more aggressive therapy and also obliges large study numbers and prolonged duration for intervention studies. There is an urgent need for alternative surrogates that detect early lung disease and track through early childhood.**

***Objectives*: This study aimed to determine whether multiple-breath washout (MBW) results at preschool age can predict subsequent abnormal lung function.**

***Methods*: Preschool children (3–5 yr) with CF and healthy control subjects underwent spirometry and MBW with testing repeated during early school age (6–10 yr). Primary outcomes were FEV_1 from spirometry and lung clearance index (LCI) from MBW.**

***Measurements and Main Results*: Forty-eight children with CF and 45 healthy children completed testing. Thirty-five (73%) children with CF had abnormal LCI at preschool age, whereas only five had abnormal FEV_1. The positive predictive value of preschool LCI for predicting any abnormal school-age result was 94%, with a negative predictive value of 62%. Only one child with abnormal FEV_1 at school age had had a normal preschool LCI. In contrast, for preschool FEV_1 the positive predictive value was 100%, but negative predictive value was only 25%.**

***Conclusions*: This study demonstrates that an abnormal preschool LCI predicts subsequent lung function abnormalities, whereas a normal preschool LCI usually remains normal. MBW has potential as a clinical and research outcome in young children with CF.**

Keywords: cystic fibrosis; function, respiratory; child; longitudinal study

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Traditional lung function measures are insensitive to early cystic fibrosis (CF) lung disease. Cross-sectional studies suggest that lung clearance index measured from multiple-breath inert gas washout has potential as an alternative, but prospective longitudinal data are lacking.

What This Study Adds to the Field

This is the first prospective, controlled study to demonstrate that lung clearance index measured at preschool age predicts subsequent lung function in children with CF and thus supports its role as a surrogate marker for early lung disease.

Medical care of children and adults with cystic fibrosis (CF) has improved steadily over the last 30 years, with a result that the median life expectancy of infants born with CF today is estimated at greater than 50 years (1). This improved outcome has created new challenges for both clinicians and researchers, particularly with regard to the monitoring and investigation of young children. The aim for this population is to identify and treat those who have early lung disease, ideally at a stage before irreversible lung damage occurs, while protecting individuals without lung disease from the side effects (and expense) of aggressive therapy. The traditional measure of FEV_1 is of little value to clinicians caring for subjects with very early disease, because it is not always feasible in preschool children, is frequently normal, and even when abnormal displays a very slow rate of decline (2–4). For the researcher, the challenge is even greater, as without suitable endpoints that can be applied in early life, trials of early interventions require very large numbers of subjects and prolonged duration. There is an urgent need for alternative surrogate markers that can reliably detect early lung disease before changes become irreversible (2, 5–9).

The two most commonly cited alternative measures are high-resolution computed tomography scans and measures of ventilation distribution (gas mixing) from multiple breath inert gas washout (MBW) tests. At present, there are no published prospective studies comparing the two modalities, but retrospective clinical data suggest that children with evidence of structural damage on high-resolution computed tomography also have abnormal lung clearance index (LCI) (10). There is clear evidence that preschool children, school-age children, and even adults with mild CF lung disease have normal spirometry results but abnormal MBW results (3, 4, 11–13). However, with the exception of one retrospective analysis of longitudinal data that had been collected for clinical indications and did not commence until 6 years of age (4), most of the current data are cross-sectional. The prognostic significance of an abnormal LCI as an early indicator of progressive lung disease in preschool children remains unknown.

The aim of this study was to track spirometry and MBW measurements from preschool to early school age in a cohort of children with CF and a cohort of healthy children, to determine

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*A complete list of members may be found before the beginning of the REFERENCES.

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whether an abnormal gas washout measurement at preschool age predicts abnormal lung function at early school age. Our hypothesis was that preschool LCI would predict early school-age lung function more reliably than preschool FEV_1. Some of the results of this study have been previously reported in the form of an abstract (14).

METHODS

Recruitment

Full details of recruitment and inclusion and exclusion criteria for the London Cystic Fibrosis Collaborative Study (LCFC) have been reported previously (12, 15, 16) and are summarized in the online supplement. The study had full ethical approval, detailed in the online supplement.

Test Procedure

All measurements were performed at the UCL Institute of Child Health. The original test session was performed between the child's third and sixth birthday. All parents first answered a questionnaire about their child's symptoms, and the child was physically examined. The parental questionnaire was supplemented with additional information provided by the child's clinician. All children then performed MBW and spirometry, in that order, following a set protocol (12, 15). MBW was performed with the subjects breathing a dry gas mixture containing 4% sulfur hexafluoride as a tracer gas inhaled through a mask interface via a bias flow apparatus. Primary outcome measure was the LCI (12, 17). Spirometry was performed according to our own laboratory standards, which were identical to those that have subsequently been endorsed by the American Thoracic Society and European Respiratory Society (12, 18, 19). Primary outcome from this measurement was FEV_1, and the secondary outcomes were FVC, forced expired volume in 0.75 s and 0.5 s ($FEV_{0.75}$ and $FEV_{0.5}$), and forced expiratory flow between 25 and 75% of expired volume ($FEF_{25–75}$). From the clinical assessment, the outcomes were presence of cough in the 7 days before testing, the number of additional courses of oral and intravenous antibiotics administered for increased respiratory symptoms in the preceding 12 months, and presence of wheeze or crackles on clinical examination.

Repeat measurement was performed at early school age, between the ages of 6 and 10 years, in the same laboratory. On this occasion MBW was performed using a mouthpiece and nose clip interface, but methodology was otherwise identical (11). Spirometry was performed according to our own laboratory protocols (20), which are based on recommendations for adults and school-age children published by the American Thoracic Society/European Respiratory Society (21). The same outcome measures were calculated.

Analysis

Group means were compared by *t* tests on each test occasion. *Z*-scores for spirometry were calculated from reference equations, with the lower limit of normal defined as -1.96 *z* scores (22). The reference equation for $FEV_{0.5}$ is based on limited data and is currently unpublished but is available at http://www.growinglungs.org.uk. Values of LCI are relatively independent of height, age, and sex in healthy subjects (23), with the upper limit of normal defined as 7.8 (3, 11, 13, 23).

Repeated measures were analyzed by two methods. First, subjects' lung function was classified as normal/abnormal, and the ability of each preschool lung function outcome to predict lung function at early school age was determined by calculating positive (PPV) and negative predictive values (NPV). An abnormal preschool result followed by an abnormal school-age result was classified a true positive; an abnormal preschool result followed by a normal school-age result was classified a false positive; etc. The primary analysis was whether the preschool test predicted any subsequent lung function abnormality; additional analyses were also performed for each early school-age outcome.

Second, longitudinal change was assessed by calculating the 2.5th and 97.5th centiles of within-subject variability of healthy subjects (i.e., the change between the preschool and school-age measurements) and comparing the variability of children with CF to these limits (24). Subjects with CF were considered to have demonstrated significant decline or improvement in lung function if their change in lung function over time was outside the 95% range defined by the 2.5th to 97.5th centiles from the control subjects.

As a secondary analysis, lung function results were compared with the clinical information collected on both test occasions.

The online supplement details ethics approval and power calculation, and contains full descriptions of both test procedure and analysis method, including the CIs for the centiles and the outer limits used in secondary analyses. This latter process allows determination of the sensitivity of the results to the assumption that the control sample provides adequate cut-off centiles.

RESULTS

Forty-five healthy children and 48 children with CF underwent testing on both visits. Preschool testing was performed between March 2001 and May 2005; average interval between tests was 3.7 years (range, 1.3–6.6 yr). Of the children with CF, 18 were male, 32 (67%) were homozygous for the ΔF508 mutation, 11 (23%) were heterozygous for this mutation, and 5 (10%) had two other mutations. Further background information is presented in Table E1 in the online supplement.

Control subjects and index subjects were well matched for age at both visits, but 23 of the healthy control subjects were male, and on both occasions children with CF were significantly shorter and lighter than control subjects (Table 1).

LCI and spirometry outcomes for all subjects on both test occasions are presented in Table 1. A minority of the children were unable to produce all spirometry outcomes at their preschool visit because of rapid exhalation, with only 32 healthy children and 37 children with CF producing an FEV_1. In cross-sectional group comparisons, all lung function results were significantly abnormal in children with CF compared with their healthy control subjects on both test occasions (Table 1). From this initial analysis it appeared that the reference equations for $FEV_{0.5}$ were not reliable at early school age, and further analysis using $zFEV_{0.5}$ was not attempted (*see* online supplement for details).

LCI at preschool was abnormal (greater than 7.8) in 35/48 (73%) children with CF, of whom only 5 (10%) had an abnormal FEV_1 (z score < -1.96). Of those with abnormal LCI at preschool, 33 (94%) had abnormal LCI at early school age (Figure 1A), and 15 (43%) recorded an abnormal FEV_1 by early school age (Figure 1B). Preschool LCI also had high specificity; of the 11 children with normal LCI at early school age, 9 children (82%; 95% confidence interval [CI], 48–97%) had normal preschool LCI, (Figure 1A), whereas of the 32 children with normal $zFEV_1$ at early school age, 12 (38%; 95% CI, 22–56%) had normal LCI at preschool (Figure 1B). The PPV of preschool LCI for predicting any abnormal school-age result was 94% (95% CI, 79–99%), with an NPV of 62% (95% CI, 32–85%) (Table 2). In contrast, for preschool FEV_1 the PPV was 100% (95% CI, 46–100%), and the NPV was only 25% (95% CI, 12–44%). These results are presented graphically in the online supplement (Figure E1A–E1H).

Tracking Longitudinal Changes

LCI remained stable in healthy children over the study period, with a mean (95% CI) within-subject change of 0.0 (-0.2 to 0.2), and 95% range of -1.3 (95% CI, -1.65 to -0.95) and 1.3 (0.95–1.65) (Figure 2A). Of the 48 children with CF, 16 had an increase in LCI greater than 1.3, indicating significant deterioration. Seven had a decrease in LCI greater than 1.3, indicating significant improvement, although LCI remained abnormal in all but two of these children. Twenty-five had no significant change over the study period, in that any change in LCI was within these limits.

TABLE 1. DEMOGRAPHIC INFORMATION AND LUNG FUNCTION RESULTS AT PRESCHOOL AND EARLY SCHOOL AGE, ANALYZED BY PRESENCE OF CYSTIC FIBROSIS

	Healthy Control	CF	Difference (95% CI)	*P* Value
	Preschool			
N	45	48	(CF–HC)	
Age, yr	4.09 (0.7)	4.17 (0.8)	0.08 (0.4 to −0.2)	0.6
zHt	0.32 (1.2)	−0.31 (1.1)	−0.64 (−0.2 to −1.1)	0.001
zWt	0.54 (1.1)	−0.05 (1.1)	−0.60 (−0.2 to −1.0)	0.009
zBMI	0.53 (1.0)	0.23 (1.1)	−0.29 (0.1 to −0.7)	0.2
LCI	6.69 (0.5)	9.47 (2.4)	2.78 (2.1 to 3.5)	<0.001
$zFEV_{0.5}$	0.07 (0.9)	−0.80 (1.3)*	−0.87 (−1.3 to −0.4)	<0.001
$zFEV_{0.75}$	0.22 (0.8)†	−0.85 (1.5)‡	−1.07 (−0.5 to −1.6)	<0.001
$zFEV_1$	0.33 (0.7)§	−0.61 (1.4)†	−0.94 (−0.4 to −1.5)	0.002
zFVC	0.08 (0.8)	−0.47 (1.2)	−0.55 (−0.1 to −0.9)	0.02
$zFEF_{25–75}$	−0.50 (1.0)‖	−1.14 (1.4)¶	−0.64 (−0.1 to −1.2)	0.02
% Predicted $FEV_{0.5}$	101.2 (13.9)	87.5 (21.3)	−13.7 (−21.2 to −6.3)	0.004
% Predicted $FEV_{0.75}$	102.8 (10.9)	88.6 (20.3)	−14.1 (−21.8 to −6.5)	<0.001
% Predicted FEV_1	104.7 (10.4)	90.8 (20.9)	−13.9 (−22.2 to −5.5)	0.002
% Predicted FVC	100.9 (12.3)	92.5 (19.6)	−8.4 (−15.3 to −1.5)	0.018
% Predicted $FEF_{25–75}$	88.9 (24.7)	75.7 (31.6)	−13.2 (−25.8 to −0.7)	0.039
	Early School Age			
N	45	48	(CF–HC)	
Age, yr	7.83 (1.3)	7.83 (1.3)	0.00 (−0.5 to 0.5)	0.9
zHt	0.31 (1.1)	−0.44 (1.1)	−0.74 (−0.3 to −1.2)	0.001
zWt	0.29 (1.0)	−0.26 (1.1)	−0.55 (−0.1 to −1.0)	0.008
zBMI	0.20 (0.9)	−0.04 (1.1)	−0.24 (0.2 to −0.7)	0.25
LCI	6.67 (0.5)	10.26 (2.8)	−3.58 (−2.7 to −4.4)	<0.001
$zFEV_{0.5}$	−0.89 (1.1)	−2.1 (1.6)	−1.21 (−1.8 to −0.6)	<0.001
$zFEV_{0.75}$	−0.31 (1.0)	−1.69 (1.5)	−1.38 (−0.8 to −1.9)	<0.001
$zFEV_1$	−0.11 (0.9)	−1.39 (1.4)	−1.28 (−0.8 to −1.8)	<0.001
zFVC	−0.04 (0.9)	−0.63 (1.3)	−0.55 (−0.1 to −1.1)	0.01
$zFEF_{25–75}$	−0.40 (1.0)	−1.92 (1.5)	−1.52 (−0.9 to −2.0)	<0.001
% Predicted $FEV_{0.5}$	89.5 (13.6)	73.4 (19.1)	−16.1 (−22.9 to −9.2)	<0.001
% Predicted $FEV_{0.75}$	96.2 (12.6)	78.9 (18.7)	−17.3 (−23.9 to −10.7)	<0.001
% Predicted FEV_1	98.8 (12.4)	81.8 (18.4)	−17.0 (−23.5 to −10.5)	<0.001
% Predicted FVC	99.8 (12.2)	91.9 (17.8)	−7.9 (−14.3 to 1.6)	0.014
% Predicted $FEF_{25–75}$	91.9 (24.8)	61.7 (30.0)	−30.1 (−41.2 to −18.7)	<0.001

Definition of abbreviations: CF = cystic fibrosis; CI = confidence interval; $FEF_{25–75}$ = forced expiratory flow between 25 and 75% of expired volume; LCI = lung clearance index. zHt, zWt and zBMI = sex-specific *z*-scores for height, weight, and body mass index, respectively (32).

Results expressed as mean (SD) unless otherwise indicated. *Z*-scores and percent predicted for $FEV_{0.5}$ were derived from sex-specific equations that adjust for age and height. These equations were developed from reference data collected for the Asthma UK Collaborative Spirometry Study, currently unpublished, but available at http://www.growinglungs.org.uk. *Z*-scores and percent predicted for other spirometry outcomes are derived from the same study and have been published (22). It should be noted that the mean $zFEV_{0.5}$ in healthy children at early school age is not zero, indicating that these reference equations may not be reliable at this age (*see* online supplement for further details).

* n = 47.
† n = 37.
‡ n = 41.
§ n = 32.
‖ n = 40.
¶ n = 46.

Of the 16 children that had a significant deterioration in LCI, 5 also had their $zFEV_1$ significantly deteriorate. Of the seven children that had a significant deterioration in $zFEV_1$, five also had significant deterioration in LCI.

The mean (95% CI) change over time for $zFEV_1$ in healthy children was −0.24 (−0.54 to 0.06), 95% range, −1.8 (95% CI, −2.3 to −1.3) to 1.4 (0.9–1.9) (Figure 2B). Of the 37 children with CF with valid measurements on both occasions, FEV_1 fell by more than −1.8 *z* scores in 7 children, none improved, and 30 remained stable.

These changes are presented graphically in the online supplement, along with further analyses related to longitudinal change, taking account of the CIs around the 95% range.

By univariable regression analyses, LCI, $zFEV_1$, $zFEV_{0.75}$, and $zFEF_{25–75}$ at preschool were all significant predictors of early school-age $zFEV_1$. The strength of relationships remained virtually the same after considering the age at baseline, the time between measurements, and *z* score for body mass index at preschool. Further details of the regression analyses are presented in the online supplement (Table E2).

Relationship to Clinical Findings

Twenty-two (46%) of the children with CF had cough in the 7 days before their preschool test, and 32 (67%) in the 7 days before their early school-age test. Fifteen (31%) children had received intravenous antibiotics in the 12 months before their preschool test, and 14 in the 12 months before their early school-age test. The equivalent figures for additional courses of oral antibiotics were 37 and 35, respectively. Only three chil-

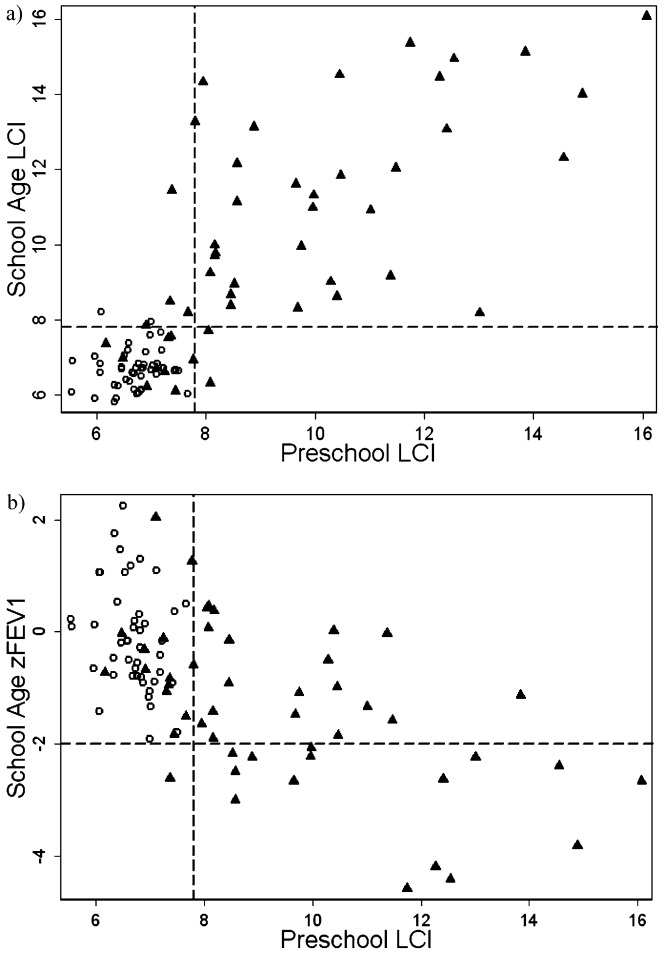

Figure 1. Cross-plots of lung function results obtained at preschool (*horizontal axis*) and early school age (*vertical axis*). Healthy children are displayed as *open circles*; children with CF displayed as *closed triangles*. The *broken lines* represent limits of normality, with children recording a lung clearance index (LCI) greater than 7.8, or a $zFEV_1$ less than −1.96 defined as having abnormal lung function. (*A*) Of the children with cystic fibrosis (CF) with abnormal LCI at preschool age (n = 35, to the right of the vertical line), this remained abnormal at early school age in all but two children (*right lower quadrant*), whose preschool results had been only mildly elevated. Of the 13 children with normal preschool LCI, only 4 developed abnormal early school-age LCI (*upper left quadrant*), and in 3 of these children the value was only just above the normal range. (*B*) Forty-three percent (15/35) of children with CF with abnormal LCI at preschool age had abnormal FEV_1 at early school age (*lower right quadrant*). In contrast, only one of those children with abnormal school-age FEV_1 had a normal preschool LCI (*lower left quadrant*).

dren had evidence of wheeze on each test occasion, and none had crackles. Children with cough in the 7 days before their preschool test tended to have abnormal LCI at that time (P = 0.054), but no other relationships were noted. These results are presented in more detail in the online supplement along with a secondary analysis related to pseudomonas status.

DISCUSSION

This is the first reported study to track lung function results from the preschool years to early school age in children with CF and healthy control subjects. Nearly all children with abnormal LCI at preschool measurement went on to record abnormal lung function at early school age, whereas more than two-thirds of children who recorded normal preschool LCI still had normal lung function at early school age. This suggests that abnormal LCI in young children with CF is a sensitive marker of early lung disease, rather than an epiphenomenon without clinical significance.

Previous Studies

Although the data presented here are the first of their type, five other studies have reported longitudinal measurements of lung function in children with CF through early childhood. An association between reduced forced expired flows and volumes during infancy and those recorded in preschool children was found in two of these studies (15, 25).

The proportion of children with abnormal FEV_1 results at preschool age in the current study is somewhat lower than that detected by either Maristoca and colleagues (25) or Vilozni and colleagues (26) in cross-sectional studies. It should be noted, however, that the average age of children in both these studies was 1 year older than in our preschool group. Furthermore, the proportion of abnormalities detected in any study will depend, among many other things, on whether results are interpreted with respect to a large reference population or local control subjects.

A variety of different methods have been used to monitor longitudinal changes in young children with CF through the early school years (27, 28), including one by Kraemer and colleagues (4) in which LCI was shown to detect abnormality earlier than any other outcome. However, several of these studies did not commence before 5 years and none included a control group, which limits interpretation as to what constitutes a clinically significant change over time.

Strengths and Limitations

The current study was designed to address the methodological limitations of previous studies. First, data collection commenced from 3 years of age. Until recently, the preschool years were described as the "silent period" for lung monitoring, as lung function testing in this age group was considered so difficult (18, 29). Second, identical lung function tests were performed for both the preschool and early school-age test visit after extensive quality control work to ensure that measures at the younger age were valid and repeatable. Third, a prospectively recruited control population was simultaneously tested. Crucially, this allowed correction to be made for the normal variability of the outcome measures over the study period. We suggest that this approach is important in any longitudinal study, but mandatory when studying growing and developing children with lung disease. Our original intention was to complete repeated measurements in 50 subjects in each group. Ultimately we were able to test 48 children with CF and 45 healthy children, and the positive results indicate that our study was adequately powered for the primary outcomes. Although future studies might consider the time differences between measurements, regression to the mean, and the correlation structure of repeated measurements (30), that was not possible in a study of this size, and it should be noted that the reference limits presented here may not apply to other populations.

Caution is required when interpreting longitudinal changes in lung function during early life because of the marked developmental changes that occur during the first 10 years of life (29, 31). For example, younger children have larger airway caliber relative to lung volume and are therefore able to empty

TABLE 2. POSITIVE AND NEGATIVE PREDICTIVE VALUES FOR PRESCHOOL LUNG FUNCTION RESULTS, COUGH, AND PRESCHOOL *PSEUDOMONAS* STATUS AGAINST LUNG FUNCTION RESULTS OBTAINED AT EARLY SCHOOL AGE

		School Age											
		Any Test		LCI		$FEV_{0.75}$		FEV_1		FVC		$FEF_{25–75}$	
		PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV
Preschool	Any test	94	67	94	75	53	92	44	100	14	92	58	83
	LCI	94	62	94	69	51	85	43	92	11	85	57	77
	FEV_1	100	25	100	28	80	56	80	69	20	91	100	53
	$FEV_{0.75}$	100	26	100	29	80	65	80	77	30	90	90	61
	FVC	40	23	100	25	100	64	100	73	25	89	100	57
	$FEF_{25–75}$	93	28	93	31	86	78	79	88	21	91	93	72
	Cough	91	31	91	35	55	69	50	81	23	96	50	54
	PsA	85	50	53	50	45	75	35	75	15	100	53	75

Definition of abbreviations: $FEF_{25–75}$ = forced expiratory flow between 25 and 75% of expired volume; LCI = lung clearance index; NPV = negative predictive value; PPV = positive predictive value; PsA = presence of *Pseudomonas aeruginosa* on airway culture.

Calculation of PPV and NPV is described in the METHODS section. All results are expressed as percentages. The primary analysis was to compare each preschool test against any measure of lung function abnormality at early school age (i.e., first two columns). For completeness, similar analyses are then presented for each individual early school-age test.

their lungs more quickly than older subjects during forced expirations. Not only does this mean that lung emptying may be complete in less than 1 second in many young children (thereby precluding measurement of FEV_1) but also that specific spirometric outcomes may measure different aspects of physiology or pathophysiology at different ages (29, 31). $FEV_{0.75}$ has been proposed as an alternative outcome measure for spirometry in very young children, but analysis of this outcome yielded almost identical results to those obtained using FEV_1. We also recorded $FEF_{25–75}$ as a secondary outcome measure and found little difference in discrimination as compared with FEV_1.

Further caution is required when applying results from our study to CF clinic populations elsewhere. We have provided background demographic data from our CF cohort to aid comparison. At the time the study was performed there were 255 children with CF, aged 6 to 10 years, under the care of LCFC centers. According to center databases, 113 of these children were male, 134 had homozygous ΔF508 genotype, and 159 had grown *Pseudomonas aeruginosa* from a respiratory culture at some stage. Mean FEV_1 for these clinic populations varied by center, in a range of 87 to 92% predicted for four of the LCFC centers and 78% predicted for the fifth center. These data were not collected by standardized methods, and should be interpreted with caution, but indicate that the study cohort was representative of the clinic population from which it was drawn.

In our analysis we calculated positive and negative predictive values to demonstrate how results at preschool testing impacted early school-age results. In this scenario, a "false negative" represents a child who has a normal preschool test and then an abnormal school-age test. These children may well have deteriorated between test occasions, and it is accepted that in this sense the original test was not inaccurate. However, we are using the PPV/NPV analysis here in a specific context, as a simply expressed method of quantifying how well preschool tests predict subsequent abnormality. As long as the context is understood, we suggest that the analysis is of value.

We note that although nearly all children with abnormal LCI at preschool still had abnormal LCI at early school age, many of these children still had normal FEV_1. Previous cross-sectional studies in school-age children with CF have suggested that LCI is more sensitive than FEV_1 for detecting lung disease in this population (3, 11). There is a strong argument for repeating investigation of this cohort in adolescence to determine whether those children currently identified as having persistent mild disease go on to demonstrate reduced spirometry outcomes.

As a secondary analysis, we compared clinical data on both occasions to the lung function results. As previously noted, there was an association between parental reported cough and increased LCI at preschool age. No other relationships were noted, but this study was not designed or powered to specifically detect such relationships.

It is already known that LCI is frequently abnormal in young children with CF, even in the presence of normal spirometry results. This study adds the information that normal preschool LCI usually leads to normal school-age lung function, and abnormal preschool LCI usually leads to abnormal school-age lung function. This potentially allows future researchers planning intervention studies in young children with CF to reduce their sample sizes, as a high NPV and a high PPV would allow selection of a group most likely to exhibit later problems and hence have the greatest potential for treatment effect to occur. Selection of the subgroup with abnormal results at PS would maximize the changes to make the biggest differences, which would require the smallest sample size. The sample size would depend on the variability of the outcome in both study groups and the treatment effect that would be statistically significant. The increase in efficiency by taking this subgroup would also depend on the prevalence of early LCI abnormality.

The data presented in this study should aid future researchers in their sample size calculations.

This study has confirmed that the majority of preschool children with CF have abnormal gas mixing results, even in the presence of normal spirometry. However, for the first time, we have demonstrated that many of the children with these abnormal gas mixing results will go on to have abnormal lung function results at early school age. Furthermore, and crucially, almost two-thirds of those with normal preschool gas mixing results will continue to have normal lung function at follow-up. As the key challenge for both clinicians and researchers in this area is to distinguish children with relatively mild, early lung disease from those who have undetectable or no lung disease, the high NPV of LCI is of great importance. It remains to be demonstrated that LCI responds to intervention in children with mild disease, and that would require a very different study design. However, the results presented here suggest that gas washout studies have

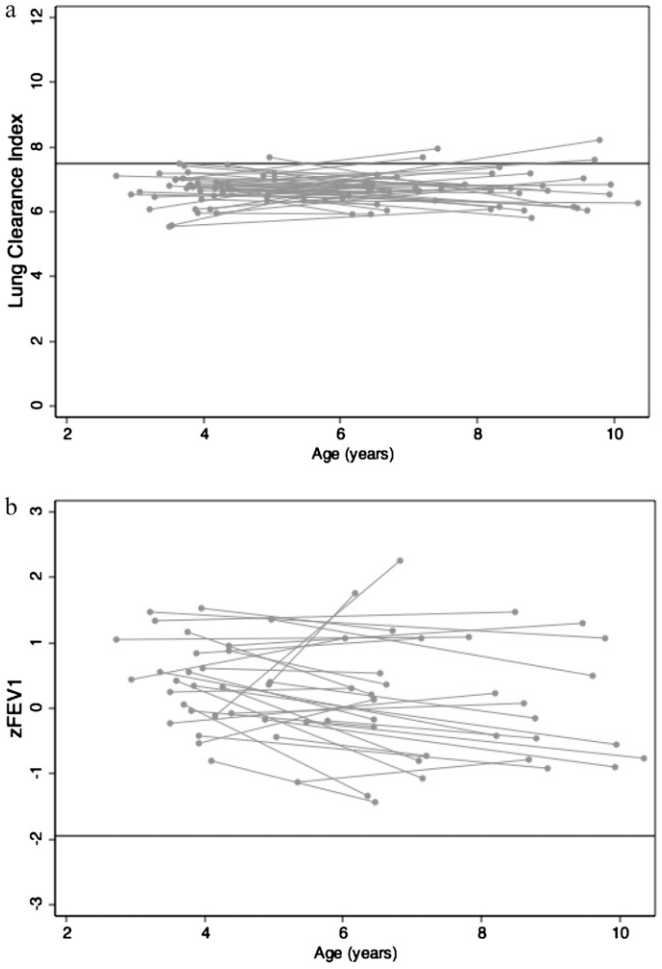

Figure 2. Longitudinal changes in lung clearance index (LCI) and $zFEV_1$ for healthy children. (*A*) LCI remains stable in health with an upper limit of normal of 7.8. The median difference between tests was 0.0, with 95% of control subjects having an LCI at school age that was within ± 1.3 of the value recorded up to 7 years earlier during the preschool years. (*B*) The average change in $zFEV_1$ over time in healthy control subjects was −0.24 (95% limits of agreement ranging from −1.8 to 1.3).

potential for identifying young children with CF who may benefit from more aggressive therapy, as well as providing an objective outcome measure for early intervention studies in infants and preschool children with CF.

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