Association of Lung Function, Chest Radiographs and Clinical Features in Infants with Cystic Fibrosis

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Abstract

Background—The optimal strategy for monitoring cystic fibrosis (CF) lung disease in infancy remains unclear.

Objective—To describe longitudinal associations between infant pulmonary function tests (iPFTs), chest radiograph (CXR) scores and other characteristics.

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Methods—CF patients 24 months old were enrolled in a 10-center study evaluating iPFTs 4 times over a year. CXRs ~1 year apart were scored with the Wisconsin and Brasfield systems. Associations of iPFT parameters with clinical characteristics were evaluated with mixed effects models.

Results—The 100 participants contributed 246 acceptable flow/volume ($FEV_{0.5}$, FEF_{75}) and 303 acceptable functional residual capacity (FRC) measurements and 171 CXRs. Both Brasfield and Wisconsin CXR scores worsened significantly over the 1 year interval. Worse Wisconsin CXR scores and *S. aureus* were both associated with hyperinflation (significantly increased FRC) but not with diminished $FEV_{0.5}$ or FEF_{75}. Parent-reported cough was associated with significantly diminished FEF_{75} but not with hyperinflation.

Conclusions—In this infant cohort in whom we previously reported worsening in average lung function, CXR scores also worsened over a year. The significant associations detected between both Wisconsin CXR score and *S. aureus* and hyperinflation, as well as between cough and diminished flows, reinforce the ability of iPFTs and CXRs to detect early CF lung disease.

INTRODUCTION

The hallmark features of cystic fibrosis (CF) lung disease include airway infection, inflammation, obstruction and structural lung damage[1-4]. These abnormalities begin in infancy[1-7], often prior to the onset of symptoms[4], and unrecognized early airway damage may progress to irreversible bronchiectasis[3]. Widespread adoption of newborn screening for CF offers the opportunity to intervene in the pre-symptomatic period in order to improve outcomes[8]. Detecting and monitoring early CF lung disease is therefore likely to improve long-term outcomes, but the optimal strategy for monitoring remains unclear.

Infant pulmonary function test (iPFT) measurements by the raised volume rapid thoracoabdominal compression technique (RVRTC) have been shown to be associated with lower airway infection, inflammation and bronchiectasis on computed tomography (CT) of the chest[2,3,6,7,9] and to track into the preschool years[10,11]. While chest CT is the most sensitive means of detecting bronchiectasis in infants with CF[12], concerns remain regarding the attendant risks of anesthesia and radiation exposure. Chest radiographs (CXRs) are recommended in infants as part of routine clinical care[13] and are widely employed. The association of iPFTs and CXR scores in infants has not to our knowledge been evaluated and little is known about the association of iPFTs and other clinical characteristics such as respiratory rate, oximetry or cough. The objective of the current study was to describe cross-sectional and longitudinal associations between iPFTs and clinical characteristics, including CXR scores, in a multicenter cohort of infants with CF[1]. Portions of this work have previously been presented in abstract form[14].

METHODS

Overview and study visits

This was a ten-center, longitudinal, observational study of lung function and associated clinical characteristics in a cohort of infants with CF; details have been previously published[1]. Study visits occurred at enrollment, 6 and 12 months, with an additional visit within a 28 to 35 day window of one of these visits. At each visit, infants participated in sedated lung function testing and clinical data were collected.

Participants

Inclusion criteria included age   24 months at enrollment and confirmed diagnosis of CF[15]. Exclusion criteria included: (1) acute intercurrent respiratory infection, defined as an increase in cough, wheezing, or respiratory rate in the preceding 3 weeks; (2) currently hospitalized for a pulmonary exacerbation; (3) oxyhemoglobin saturation <90% on room air. Additional exclusion criteria were related to contraindications to sedation, as previously published[1]. IRB approval was obtained at each site and informed consent from the parent/guardian of each participant.

Pulmonary function testing

After sedation with 75-125 mg/kg of oral or rectal chloral hydrate (maximum 2 g), plethysmography followed by RVRTC was performed with the nSpire Infant Pulmonary Lab (IPL, nSpire, Inc, Longmont, CO, USA), as previously described[1]. All PFT data were reviewed by an expert panel (SD, RJ, GK) for selection of acceptable measurements[16-18] for analyses. Based on our prior results,[1] the measures analyzed for this manuscript were functional residual capacity (FRC) obtained by plethysmography, forced expiratory volume at 0.5 seconds ($FEV_{0.5}$) and forced expiratory flow at 75% of FVC (FEF_{75}), obtained by RVRTC. Z scores for FRC were derived from the reference equations of Castile, et al[18] and for $FEV_{0.5}$ and FEF_{75} from Jones, et al[19].

Clinical evaluation

At each study visit, data were collected on quiet respiratory rate, oximetry, oropharyngeal cultures, hospitalizations, medications, length, weight and parent-reported cough (0 (none), 1 (rare), 2 (in the morning), 3 (productive cough))[20]. At enrollment, additional data were collected on gender, race, birth history, CF genotype, family history of asthma and environmental allergies, cigarette smoke exposure, and CF diagnosis through newborn screening. CF genotype functional class was categorized according to the method of McKone, et al[21] and Green et al[22]: minimal CFTR function: both alleles with mutations in functional class 1, 2 or 3; residual function: one or both alleles with mutations in CFTR functional class 4 or 5.

CXRs and Scoring

CXRs were obtained within 90 days of the enrollment and month 12 study visits. They were scored centrally by a reviewer (PF) with >20 years' experience in quantitative radiographic assessment of lung disease, blinded to participant identity, age and date. Posterior-anterior and lateral radiographs were scored concurrently by the Wisconsin[23] and Brasfield[24] systems, in batches of 50. Each session began with scoring of six standard calibration films to maximize inter-session consistency. The scorer entered results onto standardized paper report forms. Scores were then entered in duplicate into an Access database. In order to evaluate intra-rater reliability, duplicates of 30 study films were inserted randomly into the set of films to be scored. The scorer was blinded to the presence of these additional films. The Wisconsin score was calculated by the additive method[23]; the possible scores range from 0 (mildest) to 100 (most severe). Possible Brasfield scores range from 25 (mildest) to 0 (most severe)[24].

Statistical Analysis

Participant characteristics were summarized with standard descriptive statistics. Intra-rater reliability of CXR scores was assessed with the intraclass correlation coefficient. When more than one CXR score was available for a film, one score was chosen randomly for all analyses. The correlation between Brasfield and Wisconsin CXR scores at enrollment was assessed using the Spearman correlation coefficient with the confidence interval determined

by bootstrap methods. Because cough is a hallmark clinical characteristic of early CF lung disease[16], we evaluated the association of CXR score and parent-reported cough at the nearest study visit, using generalized linear mixed effects models using a logit link with a random intercept to account for repeated measures. Based on the Wisconsin Neonatal Screening Trial we chose a Wisconsin score of 5 and a Brasfield score of 21 to define the threshold value for transition to potentially irreversible abnormalities[16].

Associations of each lung function parameter with clinical characteristics at the same visit were evaluated using mixed effects models with a random intercept to allow the use of data from all visits and account for repeated measures. Models were adjusted for age, gender and length (time-varying). The effect of baseline clinical characteristics on change from baseline in lung function z-score over the study period was assessed using mixed effects models with random subject and age effects and an interaction between age and the clinical measure. Slope estimates for change in CXR scores with age were derived from a mixed effects model with random intercept. No adjustment was made for multiple comparisons in this hypothesis-generating study. Analyses were conducted using R statistical package version 2.13 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Participants and data collected

One hundred participants from 10 sites were enrolled between 2003 and 2006. Two hundred forty six acceptable RVRTC measurements were obtained from 90 participants and 303 acceptable FRC measurements from 96 participants. One hundred seventy one CXRs were obtained from 98 participants (96 from enrollment, 3 from the 6 month visit and 72 from the 12 month visit). The mean time between CXRs and the corresponding lung function tests was -9.1 (SD 24.9) days; median time was 0 days.

Enrollment characteristics of the study cohort are displayed in Table 1. The mean (SD) age at enrollment was 14 (6.2) months. Most participants (78%) had minimal CFTR function (mutations on both alleles in functional class 1, 2 or 3). Twenty one percent were diagnosed by newborn screening. Average height and weight percentiles were slightly below the general population mean. Almost half of parents reported no cough and 11% reported cigarette smoke exposure *in utero* or after birth. (Because of the observed distribution of parent-reported cough, cough was dichotomized as present/absent in all subsequent analyses.) Mean FEF_{75} z score at enrollment was mildly reduced (-0.47, SD 1.5) and mean FRC z score slightly elevated (1.77, SD 2.5). (Lower FEF_{75} z scores indicate airflow limitation and higher FRC z scores indicate hyperinflation.) CXR scores were in general in the mild range, with mean (SD) Brasfield score 22 (1.5) and mean (SD) Wisconsin score 3.5 (2.7).

CXRs

Based on duplicate scoring of 30 radiographs selected at random, the intraclass correlation coefficient was 0.50 (95% CI 0.17, 0.73) for the Brasfield system and 0.56 (95% CI 0.27, 0.77) for the Wisconsin system. At enrollment, 6 of 96 participants had no abnormalities detected with the Wisconsin system (score = 0) and the same 6 had no abnormalities detected with the Brasfield system (score = 25). The correlation between Wisconsin and Brasfield scores at enrollment was r = -0.75 (95% CI -0.67, -0.81, p<0.001) (Figure 1). Wisconsin and Brasfield CXR scores both worsened significantly with age during the one year study period (Figure 2; Wisconsin mean slope per year 0.86, 95% CI 0.31, 1.41, p=0.005; Brasfield mean slope per year -0.71, 95% CI -1.01, -0.41, p<0.001). Among the 141 CXRs, 40 (23%) had a Wisconsin score 5 and 41 (24%) had a Brasfield score <21,

suggesting a transition to potentially irreversible lung disease[16]. Twenty five CXRs had both a Wisconsin score 5 and a Brasfield score <21. There was no association between either score and presence of parent-reported cough: OR 1.62 (95% CI 0.71, 3.67) for Wisconsin score 5 and OR 1.20 (95% CI 0.53, 2.73) for Brasfield score <21. (An OR >1 indicates that a worse CXR score is associated with the presence of cough.)

Lung function

As previously published[1], mean (95% CI) z scores for all acceptable lung function measures were as follows: FRC 1.92 (1.39, 2.45), $FEV_{0.5}$ 0.06 (-0.15, 0.26), FEF_{75} -0.52 (-0.78, -0.25). In addition, $FEV_{0.5}$ worsened significantly with increasing age (slope -0.6, 95% CI -0.83, -0.37) and there was a trend towards worse FEF_{75} and FRC with increasing age[1].

Associations of lung function and clinical characteristics

The associations of each clinical characteristic with each lung function parameter at the same study visit are displayed in Table 2, from mixed effects models. There was a significant association between Wisconsin CXR score and FRC: a 1 unit higher (worse) CXR score was associated with a mean 4.62 (95% CI 0.66, 8.59) ml higher (worse) FRC. There was also a significant association between the isolation of *S. aureus* from the most recent respiratory culture and FRC: a culture positive for *S. aureus* was associated with a mean 19.3 ml (95% CI 5.1, 33.4) higher FRC. Parent-reported cough was associated with a mean 34.6 ml/s (95% CI 64.2, 5.1) lower FEF_{75}. None of these clinical characteristics was associated with both worse hyperinflation (FRC) and airway obstruction ($FEV_{0.5}$, FEF_{75}). Significant associations were not detected between any lung function parameter and cigarette smoke exposure, *P. aeruginosa* culture status, CF genotype functional class, weight percentile, Brasfield CXR score, respiratory rate or oximetry.

The effect of baseline *P. aeruginosa* culture status, baseline weight percentile, CFTR functional class and cigarette smoke exposure on the change from baseline in lung function z-scores ($FEV_{0.5}$, FEF_{75} and FRC) was assessed by including an interaction between age and the clinical measure in a mixed effects model with random intercept and slope. No significant effect of any baseline characteristic on rate of change of any lung function parameter was detected.

DISCUSSION

In this U.S. multicenter cohort of infants with CF in whom we previously reported a worsening in average lung function[1], we now report that mean Brasfield and Wisconsin CXR scores also worsen significantly over a one-year interval. We also found that worse Wisconsin CXR score and *S. aureus* respiratory infection were significantly associated with hyperinflation (higher FRC), and that parent-reported cough was significantly associated with peripheral airway obstruction (lower FEF_{75}). The reason that we did not observe physiologically consistent effects of these characteristics on both hyperinflation and airway obstruction is unclear.

Chest CTs have been shown to detect bronchiectasis as early as 3 months of age[12], but are expensive and carry risks associated with radiation and anesthesia. In school age children and adolescents with CF, Sanders and colleagues recently showed that CXRs were important predictors of future lung dysfunction, performing as well as CT scans[25], and that Wisconsin and Brasfield CXR scores had excellent sensitivity for detecting abnormal chest CTs[26]. The Wisconsin CF Radiograph Scoring System was specifically developed as an alternative to older scoring systems such as the Brasfield to be sensitive to mild CF lung disease[19], though

neither system was developed to detect the very mild abnormalities now generally seen in infants and toddlers such as those in our cohort.

To our knowledge, ours is the first study to compare Wisconsin and Brasfield CXR scores specifically in infants, evaluate their changes over time in this age range, and to compare CXR scores with iPFTs. Both scoring systems were able to detect abnormalities, though not necessarily in the same participants. Our results do not suggest that one system is superior to the other in this age range. Intra-rater variability was only fair (ICC = 0.5) for both scoring systems in the best possible scenario (single, highly trained scorer). In fact, intra-rater variability for CF-specific CT scoring systems is better (ICC 0.8 – 0.95 in published studies)[27,28]. In addition, variability would likely be greater with less experienced or multiple scorers, reducing the utility of CXR scoring. Our results suggest that, while both Brasfield and Wisconsin scores may be appropriate scoring systems in infants, with similar abilities to detect abnormalities, they may be challenging to implement in a manner that ensures accurate and reproducible results. Of note, both scoring systems evaluate hard-copy films rather than digitized electronic images. It is possible that adapting the scoring systems to digital images could improve intra- and inter-rater variability.

Our finding of an association between lung function (FRC) and recent *S. aureus* infection complements the recent finding by Pillarisetti, et al[2] in a cohort of newborn-screened Australian infants, that $FEV_{0.5}$ z scores declined significantly more rapidly in those infected with *S. aureus*. Both studies suggest a potential adverse effect of *S. aureus* on lung function in infancy. In addition, in the Wisconsin Neonatal Screening Trial, Farrell, et al found an association between Wisconsin CXR score and the occurrence of two respiratory cultures positive for *S. aureus* in the first 2 year of life[16]. In contrast to Pillarisetti, et al, as well as our findings in preschool children with CF[11,29], we did not detect a significant effect of *P. aeruginosa* infection on lung function. This may have been due to the small number of infants who acquired *Pseudomonas* in our cohort, as the observed trends in both airway obstruction (lower $FEV_{0.5}$ and FEF_{75}) and hyperinflation (higher FRC) were in the biologically plausible direction. Our finding of an association between cough and peripheral airway obstruction (FEF_{75}) corroborates that of Kozlowska, et al in the London CF Collaborative infant cohort as well as our own finding in infant and preschool CF children[11].

Strengths of our study include the relatively large size and multicenter nature of our cohort, improving external validity, as well as rigorous quality control and centralized over-reading of all infant PFT data and scoring of all CXRs by a single experienced scorer, minimizing misclassification. Limitations include the short observation period (one year per participant) and lack of more invasive tests such as CT scans or bronchoalveolar lavage. We relied on oropharyngeal cultures for respiratory microbiology, which are known to have limited diagnostic accuracy relative to lower airway cultures[30]. In addition, because the infants in our cohort were enrolled at a relatively "mature" age (mean age at enrollment of 14 months), our results may not be generalizable to newborn infants diagnosed shortly after birth by newborn screening. Lastly, given the multiple statistical tests performed, some of our results could be due to chance and should be corroborated in other cohorts.

In conclusion, our results suggest that both infant PFTs and CXRs may be helpful in monitoring CF lung disease in infants, but also highlight challenges of each of these modalities. Infant lung function tests (plethysmography and RVRTC) require sedation, extensive training and expensive equipment and are not strongly associated with clinical characteristics. Similarly, while CXRs may play a role in detection of early structural airway damage, the expertise required to perform reliable and accurate scoring currently limits their utility. Thus, the "holy grail" of CF infant lung disease monitoring remains elusive. The lung clearance index measured by multiple breath washout holds promise as a sensitive and non-

invasive measure of early heterogeneity of ventilation[4,31-33], but conditions for testing in infants are still undergoing validation and it may not be more sensitive than RVRTC in infants[4,34]. In the future, chest MRI may be used to evaluate aspects of both structure and function without the radiation risks associated with CT, but is still undergoing validation[35]. In fact, monitoring of lung health in infants with CF will likely always require multiple modalities that provide complementary information on lung structure, function and infection and inflammation status. Currently, the risk:benefit ratio of more invasive and more accurate tools such as CT scans, bronchoalveolar lavage and sedated infant PFTs and less invasive but less accurate tools such as CXRs and oropharyngeal cultures must be weighed on an individual basis.

Acknowledgments

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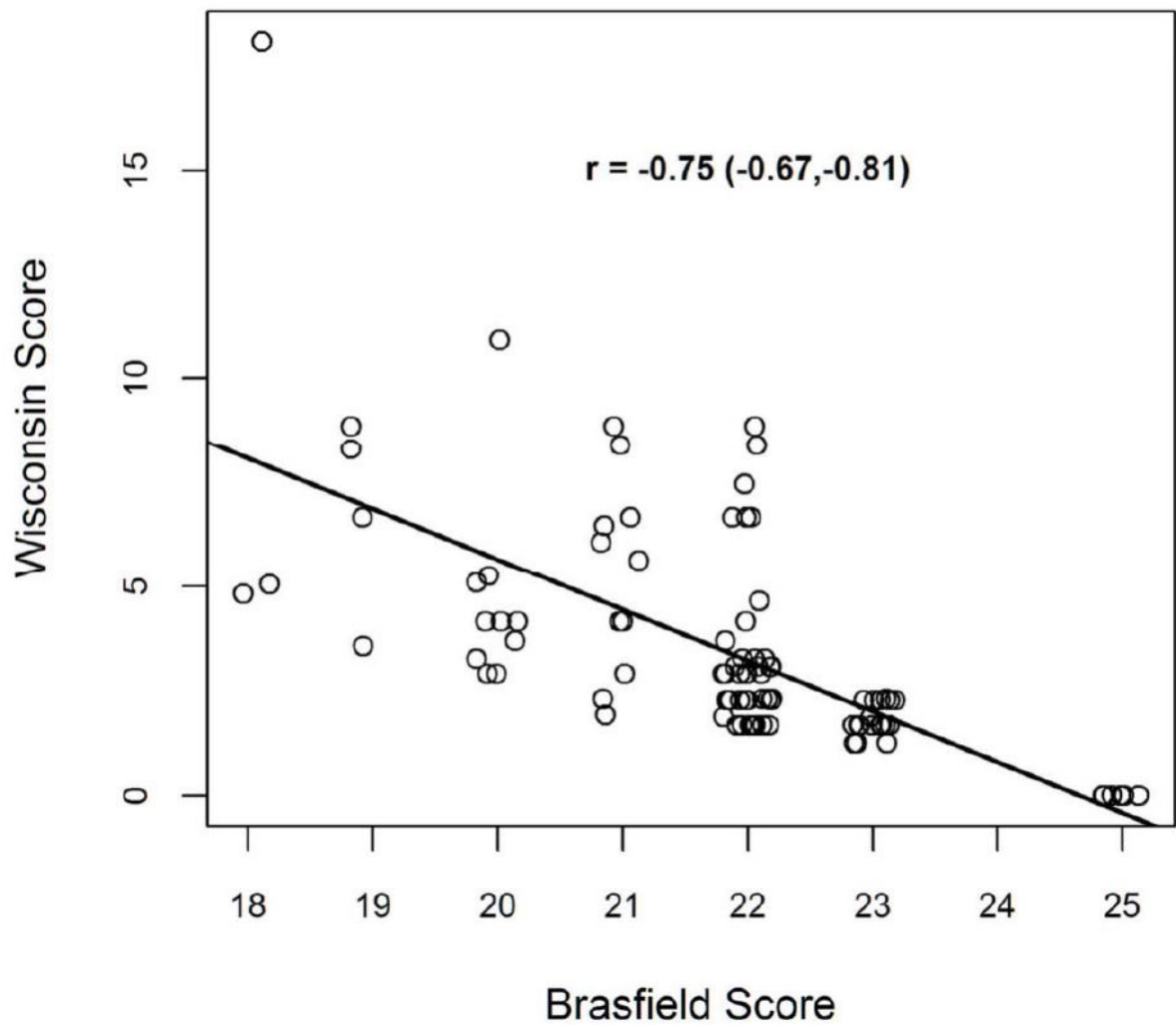
Figure 1. Correlation between Wisconsin and Brasfield chest radiograph scores at enrollment
Wisconsin scores can range from 0 (mildest) to 100 (most severe), and Brasfield scores from
25 (mildest) to 0 (most severe). Brasfield scores are jittered to allow for visibility of all data
points.
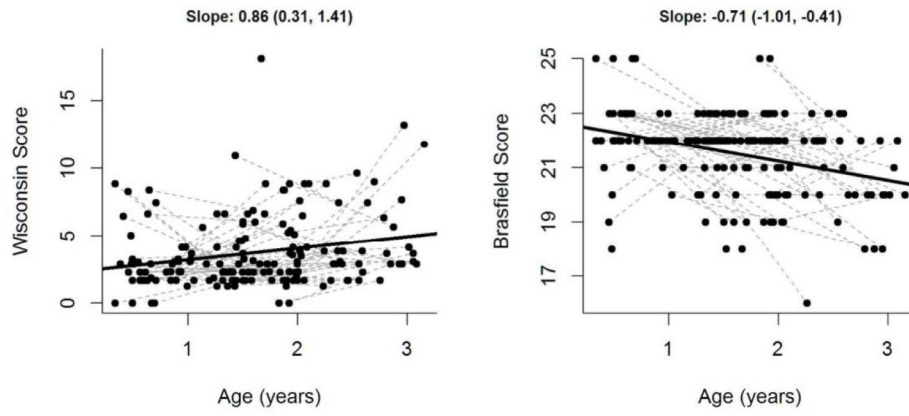
Figure 2. Longitudinal CXR scores by age
Grey dotted lines connect measures within the same subject. Solid line represents the estimated average trend in CXR score with age (slope and 95% CI).

Table 1

Characteristics of the Participants at Enrollment

	N	n (%) or Mean (SD)
Male	100	55 (55)
Age, mo	100	14 (6.2)
CFTR Functional Class[1]	100	
Minimal		78 (78)
Residual		6 (6)
Unclassified		16 (16)
Pancreatic insufficient[2]	100	93 (93)
Diagnosis by newborn screening[3]	100	21 (21)
Height percentile	100	32.7 (26.4)
Weight percentile	100	27.7 (26.3)
P. aeruginosa positive[4]	99	12 (12)
S. aureus positive[4]	99	42 (42)
Parent-reported cough[5]	99	
None		47 (48)
Rare		45 (45)
In morning		6 (6)
Productive		1 (1)
Cigarette smoke exposure[6]	100	11 (11)
FEF_{75}	79	
ml/s		321 (124)
z score		-0.47 (1.5)
$FEV_{0.5}$	79	
ml		330 (92)
Z score		0.10 (1.3)
FRC	93	
ml		258 (84)
Z score		1.77 (2.5)
Brasfield CXR Score[7]	96	22 (1.5)
Wisconsin CXR Score[8]	96	3.5 (2.7)

[1] Minimal, both CFTR mutations in functional class 1, 2 or 3. Residual, one or both mutations in functional class 4 or 5[17, 18]

[2] Reported use of pancreatic enzyme replacement therapy

[3] Newborn screening for CF was being performed at only two of the participating centers at the time of study enrollment, the University of Colorado and Children's Hospital Boston

[4] Based on enrollment oropharyngeal culture

[5] As per reference [20]

[6] Mother smoked during pregnancy or child exposed to smoke after birth, by parent report

[7] Scores can range from 0 to 25. A higher score indicates milder disease.

[8] Scores can range from 0 to 100. A higher score indicates more severe disease.

Table 2

Associations of each lung function measure with clinical characteristics at the same study visit, from a mixed effects model

Clinical Characteristics	Observations (Subjects) N (n)	FEV$_{0.5}$ (ml) Estimate (95% CI)	FEF$_{75}$ (ml/s) Estimate (95% CI)	Observations (Subjects) N (n)	FRC (ml) Estimate (95% CI)
Continuous predictors					
Weight Percentile	246 (90)	0.02 (−0.39, 0.42)	−0.23 (−1.09, 0.63)	303 (96)	−0.15 (−0.50, 0.20)
Brasfield Score	132 (87)	−4.62 (−11.33, 2.09)	−9.49 (−24.67, 5.68)	154 (92)	−5.96 (−12.45, 0.53)
Wisconsin Score	132 (87)	2.81 (−1.85, 7.48)	0.93 (−9.67, 11.53)	154 (92)	**4.62 (0.66, 8.59)**
Respiratory Rate	246 (90)	−0.70 (−1.53, 0.13)	−1.21 (−2.93, 0.52)	303 (96)	0.61 (−0.04, 1.26)
Oximetry	246 (90)	−0.99 (−5.67, 3.70)	−0.17 (−9.96, 9.63)	303 (96)	−0.75 (−1.56, 0.07)
Categorical predictors					
Cigarette smoke exposure[1]	246 (90)	−13.0 (−44.1, 18.1)	−27.4 (−96.2, 41.4)	303 (96)	24.4 (−10.3, 59.0)
P. aeruginosa isolated from most recent culture	194 (89)	−19.2 (−42.2, 3.9)	−37.9 (−85.8, 10.0)	235 (96)	17.3 (−1.3, 36.0)
S. aureus isolated from most recent culture	194 (89)	6.9 (−10.7, 24.5)	4.4 (−32.6, 41.4)	235 (96)	**19.3 (5.1, 33.4)**
Parent-reported cough[2]	245 (90)	−12.6 (−26.8, 1.7)	**−34.6 (−64.2, −5.1)**	302 (96)	−9.4 (−20.6, 1.9)
CFTR functional class[3]	246 (90)			303 (96)	
Residual function		32.8 (−15.6, 81.2)	35.8 (−70.4, 142.0)		14.9 (−34.6, 64.4)
Unclassified		4.7 (−22.5, 31.8)	−15.9 (−76.0, 44.2)		2.0 (−26.6, 30.5)

For continuous measures, estimated mean change in iPFT measure for every one unit change in clinical measure. For categorical measures, estimated mean difference in iPFT measure between categories. Mixed effects models with a random intercept were employed; all models were adjusted for length, age and gender. Significant results are presented in bold.

[1] Collected at baseline visit only

[2] Any cough vs. none

[3] Compared to minimal CFTR function (both alleles in functional class 1, 2 or 3); residual CFTR function, at least one allele in functional class 4 or 5[17,18]