Early Life Height Attainment in Cystic Fibrosis is Associated with Pulmonary Function at Age 6 Years

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ABSTRACT

Rationale: In contrast to the well-described association between early-life weight-for-age, body mass index (BMI) and later lung disease in people with cystic fibrosis (CF), the relationship between height-for-age (HFA) percentiles and respiratory morbidity is not as well-studied. We hypothesized that changes in HFA in children with CF in the first 6 years of life would be associated with pulmonary function at ages 6-7 years.

Objective(s): To determine if an association exists between changes in HFA in early life and pulmonary function in school-age children with CF.

Methods: We performed a retrospective longitudinal cohort study of children with CF followed in the CF Foundation Patient Registry (CFFPR), born between 2003 and 2010, diagnosed before age 2 years, and followed through at least age 7 years. Changes in annualized HFA were classified into mutually exclusive categories. Multivariable ANCOVA models were used to test for an association between forced expiratory volume in 1 second (FEV_1) % predicted at age 6-7 years and height trajectory categories.

Results: There were 5,388 eligible children in the CFFPR. The median (IQR) HFA at age 6-7 years was the 39.5^{th} (17.2, 64.9) percentile. The mean (95% CI) FEV_1 % predicted at age 6-7 years was 95.6 (95.1, 96.1). In a multivariable regression model, mean (95% CI) FEV_1 % predicted was higher for children with HFA always above the 50^{th} percentile [97.8 (96.3, 99.4)], compared to children whose height increased ≥10 percentile points, [95.1 (93.7, 96.6)], was stable, [94.3 (92.8, 95.7)], or decreased ≥10 percentile points, [95.7 (94.2, 97.3)]. The association between HFA categories and FEV_1 % predicted was not affected by adding mean annualized BMI percentile at age 6-7 years to the regression model. Among those with HFA that decreased ≥10 percentile points, there was a correlation between the nadir annualized HFA percentile and FEV_1 % predicted at age 6-7 years.

Conclusions: Children with CF with HFA always above the 50th percentile have the highest pulmonary function at age 6-7 years. Maintaining BMI >50th percentile remains an important achievable goal for children with CF, but is not the sole marker that should be examined in evaluating nutrition.

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INTRODUCTION

Cystic fibrosis (CF) is a multisystem autosomal recessive disease that, from early life, leads to deficits in growth and nutrition as well as progressive lung disease.(1, 2) The associations between growth outcomes, particularly weight-for-age (WFA) and body mass index (BMI), and future CF lung disease, have been well-described.(3-6) In order to maximize lung health, the CF Foundation (CFF) has recommended that all children maintain at least the 50th percentile for weight-for-length (WFL) or BMI.(7) However, relying on BMI to determine nutritional status can fail to identify children who may have deficits in growth or poor nutritional status. For example, a child with low WFA may have adequate BMI by having low height for age (HFA). This was demonstrated in an analysis by Konstan et al. which showed that 3% of children with an adequate BMI had WFA below the 10th percentile and 20% had HFA below the 10th percentile. Another 17% of children with a BMI between the 25th and 50th percentile had WFA below the 10th percentile.(8) Furthermore, WFA percentiles may be more strongly associated with future measures of lung disease than BMI percentiles.(3)

Children with CF are at increased risk of low HFA. Children with CF ages 2-19 years have a median height for age (HFA) in the 38th percentile.(9) The primary aim of the recently completed Baby Observational and Nutrition Study (BONUS) study was to examine growth patterns in the first year of life in infants with CF in the era of newborn screening for CF.(1) The BONUS study followed 231 infants and demonstrated that, on average, infants with CF achieve normal weight by 12 months of age, but that linear growth lags behind. Risk factors for low weight or length included respiratory cultures positive for *Pseudomonas aeruginosa* and wheezing.

The relationship between HFA and respiratory morbidity and mortality is not as well-studied as the association between BMI and CF lung disease. Children with CF with short stature have worse lung disease and higher risk for early mortality.(3, 4, 10, 11) In contrast to changes in WFA, changes in HFA between ages 6 and 8 years were not associated with changes in forced expiratory volume in one second (FEV_1) %

predicted over the same time period.(12) VanDevanter et al. attributed improvements in FEV_1 for 6 year old children with CF between 1994 and 2012 to increases in HFA.(13) It is not known if having a BMI greater than the 50^{th} percentile via short stature mitigates the association with respiratory morbidity. Improvements in BMI in early life are associated with better pulmonary function in school-aged children.(5) We hypothesized that changes in HFA in children with CF in the first 6 years of life would be similarly associated with pulmonary function at ages 6-7 years.

METHODS

Objective and Design

Our objective was to determine if an association exists between changes in HFA in early life and pulmonary function in school-age children. To address this objective, we performed a retrospective longitudinal cohort study of children with CF enrolled in the CF Foundation Patient Registry (CFFPR). The Indiana University School of Medicine Institutional Review Board approved the study.

Study Population

People with CF are eligible to be included in the CFFPR if they receive care at one of the CF Foundation's accredited US care centers and they (and/or their legal guardians) provide informed consent. The CFFPR contains data on demographics, CF transmembrane conductance regulator (CFTR) genotype, growth, FEV_1, microbiology, therapies, hospitalizations, and CF-related complications.(14) Data were entered into the CFFPR quarterly from 1994-2002 and at every encounter beginning in 2003. For the current analysis, we obtained data for children with CF born between 2003 and 2010, diagnosed before age 2 years, and followed in the CFFPR through at least age 7 years. We excluded children with a solid organ transplantation or who died before age 7 years.

Variable Definitions

Trajectories of HFA were the main predictor variable. Annualized values for HFA were calculated by averaging the highest HFA value in each quarter of the calendar year. This was done for each year between diagnosis and age 6-7 years based on the Center for Disease Control (CDC) growth charts.(15) Changes in HFA were classified into the following mutually exclusive categories, chosen *a priori*: annualized HFA always above the 50th percentile, or annualized HFA with at least one year below the 50th percentile and: *(1)* increased ≥10 percentile points, *(2)* decreased ≥10 percentile points, or *(3)* was stable (i.e., <10 percentile increase or decrease). These categories were chosen to correspond to a previous analysis,(5) and under the assumptions that *(1)* always having HFA above the 50th percentile is sufficient to maximize

pulmonary function, and *(2)* changes in HFA percentiles would be associated with differences in pulmonary function.

FEV_1 % predicted was the main outcome variable. The mean annualized FEV_1 % predicted was calculated from the average of the best FEV_1 measurement in each quarter of the calendar year using the Global Lung Initiative reference equations (16) in the year they were 7 years of age on December 31.

Statistical Analysis

ANCOVA models were used to test for an association between FEV_1 % predicted at age 6-7 years and height trajectory categories, using Tukey's post-hoc comparison adjustment when there were more than two categories in a main effect. The following potential confounders were included a priori based on a review of the literature for factors that could be associated with growth and/or FEV_1: sex, race, pancreatic enzyme replacement therapy as a surrogate for pancreatic status, infection with *Pseudomonas aeruginosa*, insurance status as a marker of socioeconomic status, and hospitalizations for pulmonary exacerbations.(5, 17-20) All analytic assumptions were verified and all statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

Sensitivity Analyses

To test the robustness of our results, we performed several sensitivity analyses. We tested individually adding *(1)* annualized BMI percentile at age 6-7 years, *(2)* mode of diagnosis, and *(3)* Hispanic ethnicity to our final multivariable regression model. We restricted growth trajectory categories for HFA to changes that occurred after age two years. We restricted the cohort to *(1)* only those with cystic fibrosis transmembrane conductance regulator (CFTR) mutations classes I-III (i.e., those associated with pancreatic insufficiency), and *(2)* those diagnosed before age one year. We used alternative outcome measures: *(1)* annualized forced vital capacity (FVC) at age 6-7 years, and *(2)* annualized FEV_1/FVC ratio at

age 6-7 years. Finally, we compared pulmonary function at age 6-7 years according to changes in HFA for those children with CF whose HFA was always >50th percentile.

RESULTS

There were 5,388 children in the CFFPR born between 2003 and 2010, and followed in the CFFPR through at least age 7 years (**Figure 1**), who also had enough data to determine their height trajectory. Baseline demographic data and clinical status for each category of height growth trajectory are shown in **Table 1**. Among the 69% of children with CF that grew *P. aeruginosa*, the median (IQR) age of acquisition was 1.7 (1.0, 3.1) years. Over half of patients received dornase alfa, inhaled tobramycin, hypertonic saline, H2 blockers, proton pump inhibitors, and supplemental oral feedings (e.g., higher calorie infant formulas, nutritional supplements such as Pediasure, Boost, Scandishakes, Instant Breakfast) at some point by age 6-7 years. The median (IQR) HFA at age 6-7 years was the 39.5th (17.2, 64.9) percentile. The mean (95% CI) FEV_1 % predicted at age 6-7 years for the entire study population was 95.6 (95.1, 96.1).

FEV_1 % predicted and HFA at ages 6-7 years were significantly correlated, rho = 0.16, slightly less than the correlation between FEV_1 % predicted and BMI percentile at ages 6-7 years, rho = 0.22. Only 18.7% always had annualized HFA above the 50th percentile from diagnosis through age 6-7 years (**Table 1**). The group that increased HFA ≥10 percentile points was the largest group, comprising 31.4% of the cohort. The group that was stable, i.e., <10 percentile increase or decrease, made up 28.1% of the cohort, and 21.7% had an HFA that decreased ≥10 percentile points. In comparison with the other growth trajectory categories, the group that always had HFA above the 50th percentile had more children diagnosed after newborn screening and born in 2007-2010, and fewer diagnosed with failure to thrive. This group also had fewer children with CFTR class I-III mutations only, that were ever on Medicaid insurance, pancreatic enzyme replacement therapy, dornase alfa, inhaled tobramycin, or ever had IV-antibiotic treated pulmonary exacerbations, nutritional interventions, or an infection with *P. aeruginosa*. Mean age at acquisition of *P. aeruginosa* was similar among the HFA categories, between 2.1 and 2.3 years of age.

In a multivariable ANCOVA regression model, HFA trajectories in the first 6 years of life were associated with clinically meaningful differences in annualized FEV_1 at age 6-7 years (**Table 2** and **online supplement**

Table E1). In contrast to BMI growth trajectory categories, children with CF with HFA that decreased ≥10 percentile points did not have the lowest pulmonary function at age 6-7 years (**Figure 2**). Tukey's adjustment was used to compare annualized FEV_1 at age 6-7 years between individual HFA categories. Children with CF with HFA always above the 50th percentile had the highest FEV_1 % predicted ($p < 0.05$ when compared to each of the other HFA trajectories individually). Annualized FEV_1 at age 6-7 years was statistically significantly different for each pairwise comparison between HFA trajectories, except for the comparison between the group that increased HFA ≥10 percentile points and the group that decreased ≥10 percentile points ($p = 0.99$).

The magnitude and direction of the association between HFA categories and pulmonary function outcomes at age 6-7 years were similar in sensitivity analyses (**Table 3**). The association between HFA categories and FEV_1 % predicted was not affected by adding mean annualized BMI percentile at age 6-7 years to the final multivariable regression model, indicating that for a given BMI percentile, always having HFA above the 50th percentile was associated with better FEV_1 % predicted at age 6-7 years. Restricting to children with CFTR mutation classes I-III only lowered the estimated mean annualized FEV_1 % predicted at age 6-7 years, as expected. Similarly, restricting to children diagnosed before age 1 year (in the era of newborn screening) increased the annualized FEV_1 % predicted at age 6-7 years. The associations between HFA categories and mean annualized FVC at age 6-7 years was similar to the association with FEV_1 % predicted, as well as the association between BMI categories and annualized FVC at age 6-7 years (see **online supplement Figure E1**). Although the association between HFA categories and FEV_1/FVC was statistically significant, the differences are not clinically meaningful. Similar to the association between pulmonary function and nadir annualized BMI percentile,(5) among those with HFA that decreased ≥10 percentile points, there was a correlation between the nadir annualized HFA percentile and FEV_1 % predicted at age 6-7 years (see **online supplement Table E2**). When we repeated our analysis in those with HFA always above the 50th percentile, those with HFA that decreased by ≥10 percentile points had

the lowest FEV_1 and FVC % predicted at age 6-7 years and those with HFA that was stable had the highest (see **online supplement Figure E2**).

DISCUSSION

As with early life BMI growth trajectories, changes in HFA in the first few years of life are associated with clinically meaningful differences in FEV_1 % predicted at age 6-7 years. Being taller at age 6 years is associated with higher FEV_1 % predicted at age 6-7 years, especially among children who have above average height throughout the first 6 years of life. Further, having above average height throughout early life remained associated with higher FEV_1 % predicted even in sensitivity analysis adjusting for BMI. Notably, FVC % predicted was also higher for children who have above-average height throughout the first 6 years of life, whereas FEV_1/FVC ratio was slightly lower. This suggests that the higher FEV_1 at age 6-7 years is not a result of less airway obstruction, but increases in parenchymal lung growth, i.e., dysanapsis.(21) This would suggest that achieving the CF Foundation's goal of BMI >50th percentile in children with below-average height may not be sufficient to optimize lung growth. This growth pattern – normal BMI, with below average height – occurs commonly in children with CF, who can more easily recover from early low weight for age than experience catch up linear growth.(1) However, children who achieve catch up weight gain by age 2 years are more likely to maintain this catch up weight gain, as well as be taller at school age.(6)

There are several factors that may contribute to deficits in height in children with CF.(22) Growth deficits begin in utero and appear, at least initially, to be unrelated to insulin-like growth factor (IGF)-1 levels.(1, 23) Growth deficits are seen in mouse models of CF, even in the absence of pancreatic insufficiency or malnutrition.(24) This may be because disease-causing mutations in CFTR may have direct impacts on the growth hormone(GH)/IGF-1 axis. IGF-1 is low in the CF pig model by 12 hours of age, as well as in newborns with CF.(25) The GH-IGF-1 axis may be further suppressed through malnutrition and inflammation.(22) Analogously, pubertal delay is common in CF, in part due to malnutrition and inflammation, yet can occur even in the setting of newborn screening and good nutritional status,(26) which could stem from direct effects of CFTR on the hypothalamic-pituitary-gonadal axis.(27) Finally, the stool microbiome in infants

with CF, which contributes to gastrointestinal health, nutrient harvest, and GH signaling, differs between infants with poorer linear growth and infants with CF who attained normal length for age by 12 months of age.(28)

Children whose HFA decreased ≥10 percentiles before age 6 did not have the lowest pulmonary function at age 6-7 years. This was an unexpected finding and in contrast to the association between decreasing BMI in the first 6 years of life and lower pulmonary function at age 6-7 years. We can only speculate that lung growth may be relatively preserved from early life even in the face of slowing linear growth. Although the children in our study largely avoided malnutrition, this lung-sparing growth pattern has been recognized in children without CF who experience malnutrition.(29) However, among children whose HFA decreased before age 6 years, pulmonary function at age 6-7 years is associated with the nadir HFA percentile. This may suggest that, although variations in HFA around the mean are expected, decreases in HFA to lower nadirs may be in part through chronic pathologic processes, e.g., systemic inflammation, malnutrition, suppressed GH-IGF-1 axis.

Prior studies have demonstrated links between short stature and respiratory morbidity and mortality.(3, 4, 10, 11) These studies focused on short stature (height below the 5th or 10th percentile), which is less common in the era of newborn screening and improved lung disease.(13, 30) The introduction of newborn screening has been shown to be associated with improvements in linear growth,(31) but there are relatively few treatment options that can improve height: avoidance of early malnutrition, growth hormone replacement, and, potentially, CFTR modulators.(30, 32, 33) Concerns have been raised that reliance on BMI to determine nutritional status will underestimate children who have potentially poor nutritional status, i.e., low WFA and/or HFA, despite a relatively normal BMI.(8) Our findings would support this hypothesis, and suggest that tracking linear growth in the years before children can perform pulmonary function testing may be helpful in identifying children who may have lower pulmonary function

at age 6-7 years. However, our data also suggest that increasing HFA, at least in early life, may contribute only modestly to improvements in pulmonary function.

There are several limitations to our study. Height measurements may be difficult to obtain in infants and toddlers, which could have increased the variability of HFA percentiles, and consequently, mischaracterize HFA trajectory. However, the standard deviation of annualized HFA measurements did not differ according to age (data not shown). The US CDC recommends recumbent length be measured until a child's 2nd birthday, and standing height thereafter.(15) On average, standing height in the US is 0.8 cm less than recumbent length, which could have increased the proportion of children in our cohort that had decreasing HFA percentiles, however the CDC growth charts account for this difference. The CFFPR does not contain data on potential explanations for height and/or changes in height, including GH levels, markers of inflammation, or fecal microbiome characteristics. Parental height is reported inconsistently and is not routinely measured to ensure accuracy. GH replacement was reported for less than 3% of the cohort. As with all observational studies, the association between HFA >50th percentile and higher pulmonary function does not prove causation. It is possible that early silent lung disease contributes to inflammation, suppresses the GH-IGF-1 axis, and results in lower HFA and pulmonary function. This cohort was heavily treated, both with chronic CF medications, and with nutritional interventions, and it is unknown if growth would have been worse without these treatments. Nearly 1/3rd received lumacaftor/ivacaftor, but likely only for a short time since approval for 2-5-year-olds did not occur until 2018. Results may not be generalizable to other countries where the availability of newborn screening and infant care practices may differ.

In conclusion, children with HFA always >50th percentile between diagnosis of CF and age 6-7 years had the highest pulmonary function at age 6-7 years. Interventions to support this goal are limited, but may be achievable in the future via early initiation of highly effective CFTR modulator therapy.(33) Research into additional potential interventions that promote linear growth are also needed. Maintaining BMI >50th

percentile remains an important achievable goal for children with CF, but the results reported here can serve as a reminder that BMI is not the sole marker that should be examined in evaluating nutrition.

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FIGURE LEGENDS

Figure 1. Diagram of study cohort

Figure 2. Mean (95% CI) annualized FEV_1 % predicted at age 6-7 years associated with (**A**) height trajectory and (**B**) BMI trajectory. P-values indicate differences comparing pairs of trajectory categories connected by lines. Omnibus p-value tests differences among all categories in multivariable ANCOVA regression models.

TABLES

Table 1. Cohort characteristics

	Total	**Height trajectory**			
		Always ≥ 50%ile	**Increased ≥ 10%iles**	**Stable within 10%iles**	**Decreased ≥ 10%iles**
Number of children with CF	5,388	1,010	1,692	1,515	1,171
Female	2,670 (49.6)	534 (52.9)	785 (46.4)	755 (49.8)	596 (50.9)
Birth cohort					
2003-2006	2,486 (46.1)	408 (40.4)	853 (50.4)	742 (49.0)	483 (41.3)
2007-2010	2,902 (53.9)	602 (59.6)	839 (49.6)	773 (51.0)	688 (58.8)
Mode of diagnosis					
Newborn screening	2,553 (47.4)	579 (57.3)	701 (41.4)	619 (40.9)	654 (55.9)
Meconium ileus	1,088 (20.2)	166 (16.4)	374 (22.1)	316 (20.9)	232 (19.8)
Failure to thrive	1,097 (20.4)	76 (7.5)	456 (27.0)	421 (27.8)	144 (12.3)
Other	650 (12.1)	189 (18.7)	161 (9.5)	159 (10.4)	141 (12.0)
CFTR genotype					
Classes I-III only	4,012 (74.5)	665 (65.8)	1325 (78.3)	1154 (76.2)	868 (74.1)
Any Class IV-V	503 (9.3)	159 (15.7)	118 (7.0)	102 (6.7)	124 (10.6)
Other/unknown	873 (16.2)	186 (18.4)	249 (14.7)	259 (17.1)	179 (15.3)
Race					
White	4,802 (89.1)	922 (91.3)	1477 (87.3)	1331 (87.9)	1072 (91.6)

Other	586 (10.9)	88 (8.7)	215 (12.7)	184 (12.2)	99 (8.5)
Hispanic	595 (11.0)	99 (10.4)	152 (9.6)	209 (14.7)	135 (12.2)
Ever Medicaid insurance	3,600 (66.8)	561 (55.5)	1121 (66.3)	1116 (73.7)	802 (68.5)
Pancreatic enzyme replacement therapy	4,983 (92.5)	870 (86.1)	1610 (95.2)	1424 (94.0)	1079 (92.1)
Any IV antibiotic-treated pulmonary exacerbations	2,732 (50.7)	379 (37.5)	902 (53.3)	835 (55.1)	616 (52.6)
Microbiology (ever)					
Pseudomonas aeruginosa	3,738 (69.4)	651 (64.5)	1211 (71.6)	1077 (71.1)	799 (68.2)
Staphylococcus aureus	5,161 (95.8)	954 (94.6)	1626 (96.1)	1456 (96.1)	1125 (96.1)
Methicillin-resistant *S. aureus* (MRSA)	1,970 (36.6)	325 (32.2)	607 (35.9)	602 (39.7)	436 (37.2)
Chronic CF medications (ever)					
Dornase alfa	4,514 (83.8)	779 (77.1)	1438 (85.0)	1301 (85.9)	996 (85.1)
Inhaled tobramycin	3,026 (56.2)	472 (46.7)	989 (58.5)	898 (59.3)	667 (57.0)
Azithromycin	1,162 (21.6)	215 (21.3)	361 (21.3)	327 (21.6)	259 (22.1)
Ivacaftor	152 (2.8)	39 (3.9)	39 (2.3)	37 (2.4)	37 (3.2)
Lumacaftor/ivacaftor	1,697 (31.5)	290 (29.1)	564 (33.6)	480 (32.2)	363 (31.4)
Hypertonic saline	2,735 (50.8)	503 (49.8)	872 (51.5)	755 (49.8)	605 (51.7)
Nutritional interventions (ever)					

H2 blockers	3,173 (58.9)	498 (49.3)	1066 (63.0)	906 (59.8)	703 (60.0)
Proton pump inhibitors	3,932 (73.0)	619 (61.3)	1310 (77.4)	1168 (77.1)	835 (71.3)
Supplemental oral feedings	4,843 (89.9)	830 (82.2)	1553 (91.8)	1379 (91.0)	1081 (92.3)
NG or G- tube feedings	1,110 (20.6)	96 (9.5)	353 (20.9)	424 (28.0)	237 (20.2)
Growth Hormone	155 (2.9)	25 (2.5)	53 (3.1)	43 (2.8)	34 (2.9)

Table 2. Adjusted FEV_1 % predicted at age 6-7 years associated with height trajectory from study entry to age 6-7 years using multivariable ANCOVA regression. P-value tests differences among all categories in multivariable regression models.

	Height trajectory				
	Always ≥ 50%ile	**Increased ≥ 10%iles**	**Stable within 10%iles**	**Decreased ≥ 10%iles**	**P-value**
Number of children with CF	1,010	1,692	1,515	1,171	
FEV_1 % predicted at age 6-7 years					
Adjusted mean (95% CI)	97.8 (96.3, 99.4)	95.1 (93.7, 96.6)	94.3 (92.8, 95.7)	95.7 (94.2, 97.3)	<0.001
Adjusted mean difference (95% CI)	0 (Ref)	2.7 (1.1, 4.3)	3.5 (1.9, 5.2)	2.1 (0.4, 3.8)	<0.001

Table 3. Adjusted pulmonary function at age 6-7 years associated with height trajectory from study entry to age 6-7 years using multivariable ANCOVA regression models. P-value tests differences among all categories in multivariable regression models.

	Height trajectory				
	Always ≥ 50%ile	**Increased ≥ 10%iles**	**Stable within 10%iles**	**Decreased ≥ 10%iles**	**P-value**
Number of children with CF	1,010	1,692	1,515	1,171	
Mean (95% CI) FEV_1 % predicted at age 6-7 years					
Final regression model	97.8 (96.3, 99.4)	95.1 (93.7, 96.6)	94.3 (92.8, 95.7)	95.8 (94.2, 97.3)	<0.001
+BMI percentile at age 6-7 years	96.8 (95.2, 98.2)	94.7 (93.3, 96.1)	94.3 (92.9, 95.7)	95.7 (94.2, 97.2)	0.002
CFTR mutation classes I-III only	93.2 (96.5, 99.8)	90.6 (83.9, 97.2)	89.5 (82.9, 96.1)	90.9 (84.3, 97.5)	<0.001
Children diagnosed <1 year of age	98.8 (96.8, 100.9)	95.9 (94.0, 97.9)	95.4 (93.4, 97.4)	97.0 (95.0, 99.0)	0.003
Ages 2-6 years only	97.6 (96.2, 99.0)	95.3 (93.8, 96.9)	94.4 (93.0, 95.9)	94.5 (92.9, 96.1)	<0.001
+Mode of diagnosis*	96.5 (94.3, 98.7)	94.1 (92.1, 96.1)	93.2 (91.2, 95.3)	94.5 (92.3, 96.6)	<0.001
+Hispanic ethnicity	96.8 (95.1, 98.5)	94.0 (92.5, 95.6)	93.3 (91.7, 94.9)	94.6 (92.9, 96.2)	<0.001

Mean FVC % predicted at age 6-7 years					
Final regression model	102.7 (101.2, 104.3)	99.7 (98.3, 101.1)	98.6 (97.2, 100.1)	100.6 (99.1, 102.1)	<0.001
Mean FEV_1/FVC at age 6-7 years					
Final regression model	0.88 (0.87, 0.89)	0.89 (0.88, 0.89)	0.89 (0.88, 0.90)	0.90 (0.88, 0.90)	<0.001

* Mode of diagnosis categorized as newborn screening, failure to thrive, meconium ileus, or other

FIGURES

Figure 1.

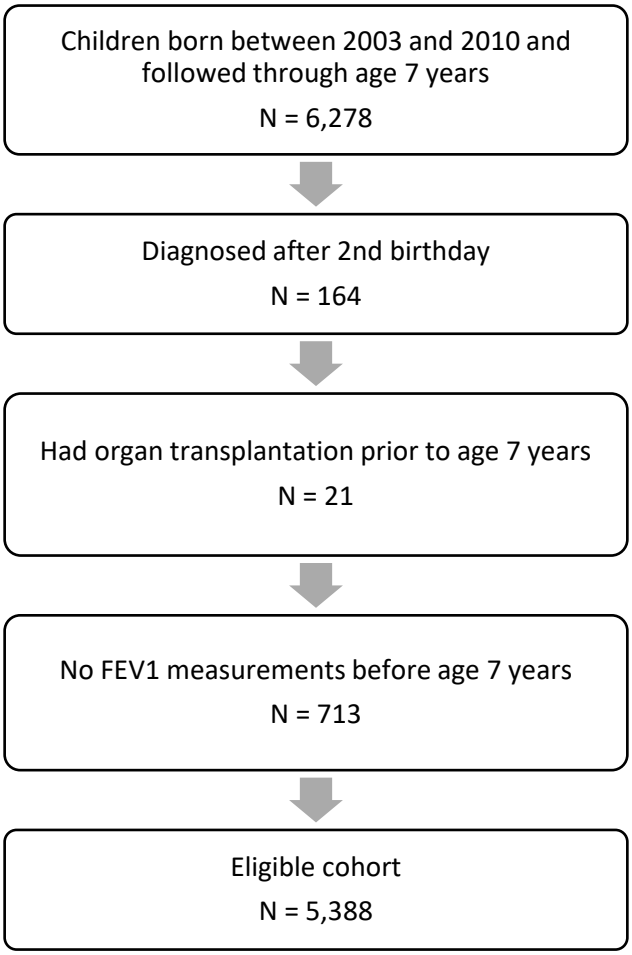
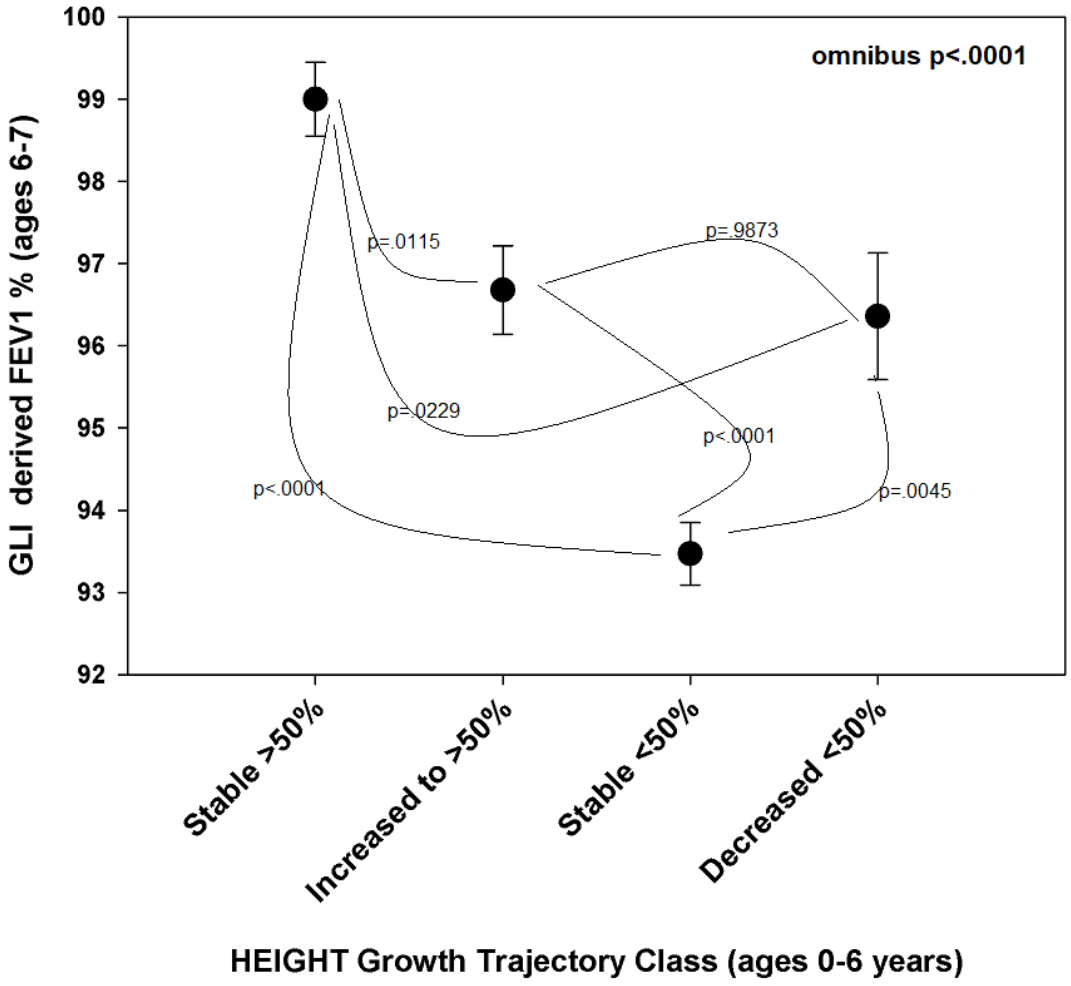
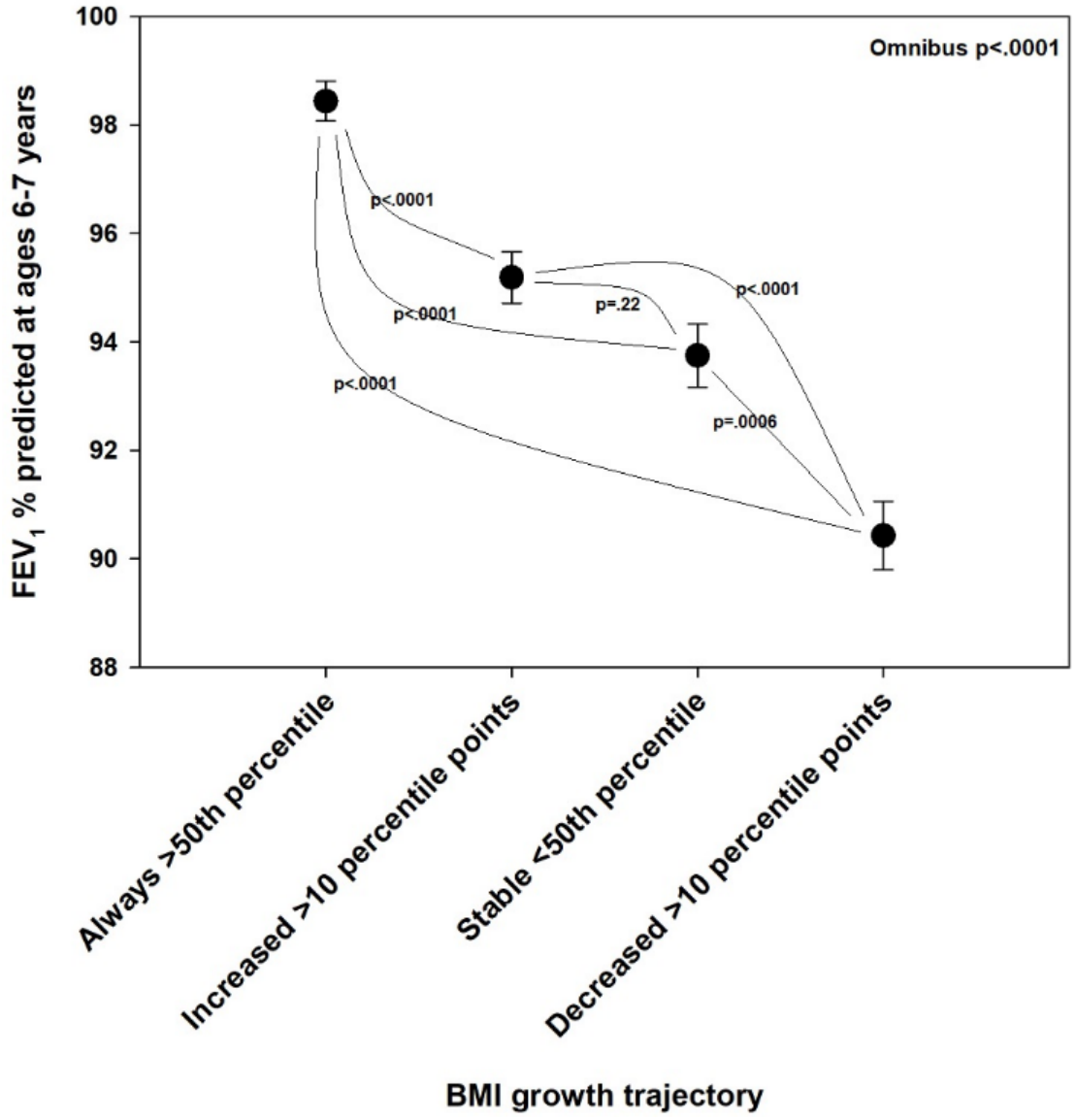


Figure 2.

A


omnibus p<.0001
GLI derived FEV1 % (ages 6-7)
100
99
98
97
96
95
94
93
92
p=.0115
p=.9873
p=.0229
p<.0001
p<.0001
p=.0045
Stable >50%
Increased to >50%
Stable <50%
Decreased <50%
HEIGHT Growth Trajectory Class (ages 0-6 years)

B


Omnibus p<.0001
p<.0001
p<.0001
p=.22
p<.0001
p<.0001
p=.0006
100
98
96
94
92
90
88
FEV1 % predicted at ages 6-7 years
Always >50th percentile
Increased >10 percentile points
Stable <50th percentile
Decreased >10 percentile points
BMI growth trajectory

Early Life Height Attainment in Cystic Fibrosis is Associated with Pulmonary Function at Age 6 Years

Don B. Sanders, James E. Slaven, Karen Maguiness, James F Chmiel, Clement L Ren,

ONLINE SUPPLEMENT

Table E1. Multivariable ANCOVA regression model for mean (95% CI) FEV_1 % predicted at age 6-7 years associated with height trajectory from study entry to age 6-7 years, including estimates of covariates. P-value tests differences among all categories in multivariable regression models.

	Mean (95% CI) estimate for FEV_1 % predicted at age 6-7 years	P-value
Growth trajectory		
Height always >50th percentile	97.8 (96.3, 99.4)	<0.001
Height increased >10%iles	95.1 (93.7, 96.6)	
Height stable	94.3 (92.8, 95.7)	
Height decreased >10%iles	95.7 (94.2, 97.3)	
Sex		
Female	95.6 (94.3, 96.9)	0.47
Male	95.9 (94.6, 97.2)	
Race		
White	94.7 (93.6, 95.8)	0.005
Non-White	96.8 (95.1, 98.6)	
Insurance		
Never Medicaid	97.6 (96.2, 99.0)	<0.001
Ever Medicaid	93.9 (92.6, 95.1)	
Pancreatic status		
Never on pancreatic enzyme replacement therapy	97.8 (95.8, 99.7)	<.001
Ever on pancreatic enzyme replacement therapy	93.7 (92.8, 94.7)	
Pseudomonas status		

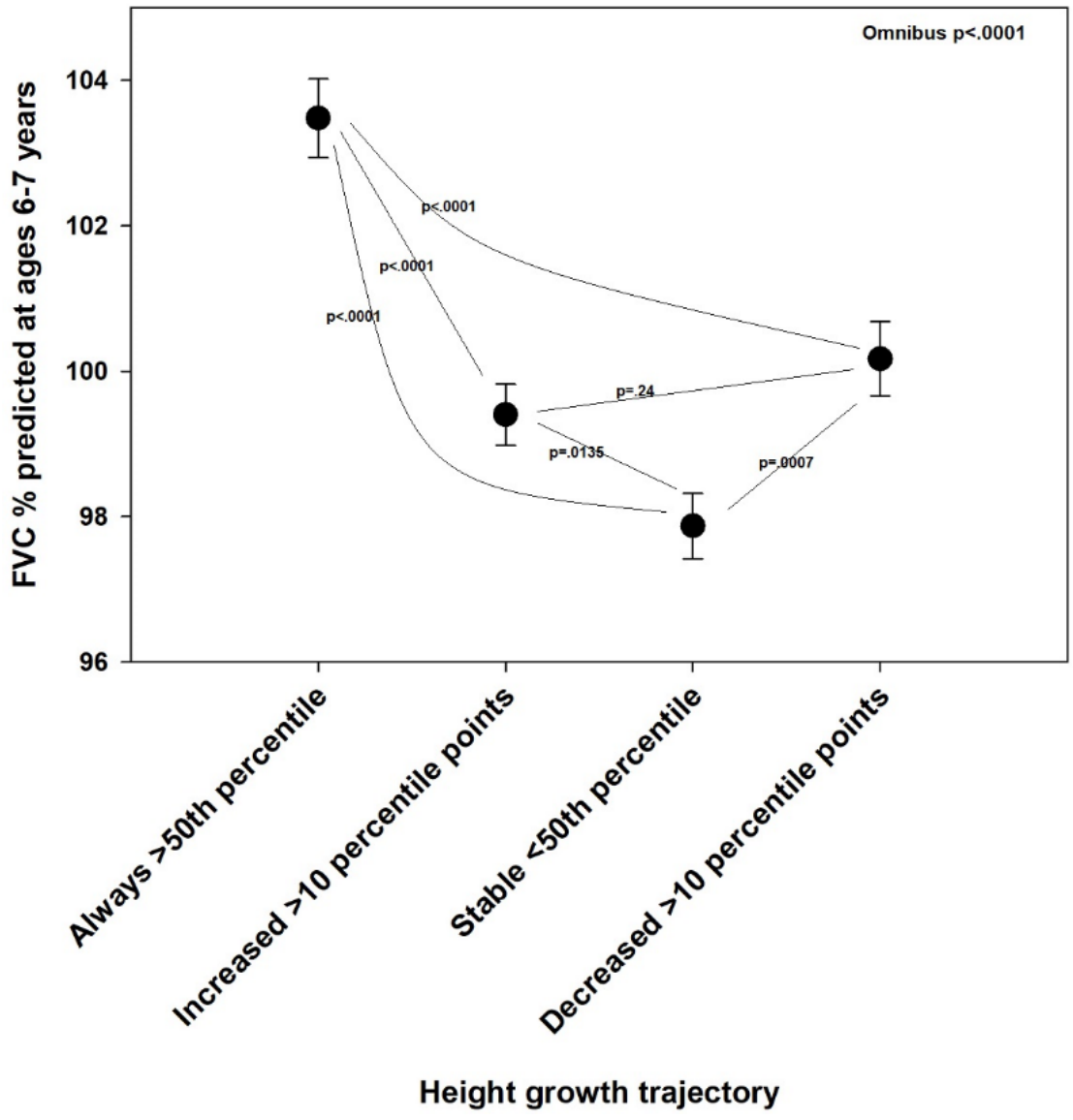
Never infected with *P. aeruginosa*	97.4 (96.0, 98.8)	<0.001
Acquired *P. aeruginosa* before age 3 years	95.6 (94.2, 96.9)	
Acquired *P. aeruginosa* between ages 3 and 6 years	94.2 (92.7, 95.7)	
Number of pulmonary exacerbations treated with IV antibiotics		
<1	100.2 (99.1, 101.3)	<0.001
≥1	91.3 (89.6, 92.9)	

Table E2. Mean (95% CI) pulmonary function at age 6-7 years according to minimum annualized HFA percentile for children with CF with HFA that decreased ≥10 percentile points. P-value tests differences among all categories in multivariable ANCOVA regression models.

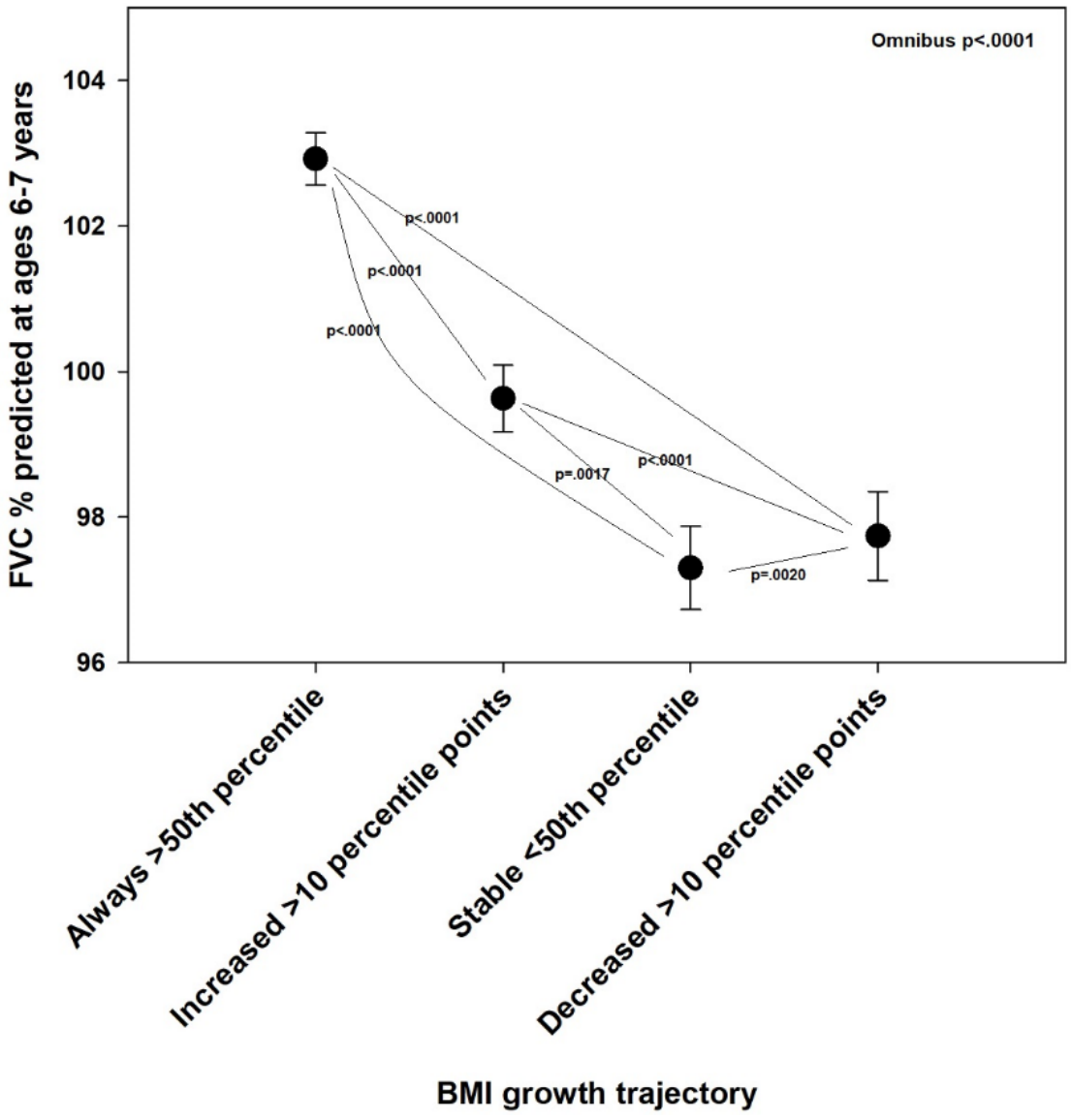
	Minimum Annualized HFA percentile					
	<10th percentile	10th - <20th percentile	20th - <30th percentile	30th - <40th percentile	40th - <50th percentile	P-value
Number of children with CF	264	212	198	162	115	
FVC % predicted	98.1 (95.9, 100.3)	99.2 (97.0, 101.4)	99.3 (97.1, 101.5)	101.9 (99.4, 104.5)	103.9 (101.4, 106.3)	0.011
FEV_1 % predicted	92.5 (90.2, 94.7)	94.9 (92.5, 97.2)	95.3 (93.0, 97.6)	98.0 (95.5, 100.6)	99.4 (96.9, 101.9)	0.001
FEV_1/FVC	0.89 (0.88, 0.90)	0.89 (0.88, 0.90)	0.88 (0.87, 0.89)	0.89 (0.88, 0.90)	0.88 (0.87, 0.90)	0.96

Figure E1. Mean (95% CI) annualized FVC % predicted at age 6-7 years associated with (**A**) height trajectory and (**B**) BMI trajectory. P-values indicate differences comparing pairs of trajectory categories connected by lines. Omnibus p-value tests differences among all categories in multivariable regression models.

A



B


Omnibus p<.0001
FVC % predicted at ages 6-7 years
104
102
100
98
96
p<.0001
p<.0001
p<.0001
p=.0017
p<.0001
p=.0020
Always >50th percentile
Increased >10 percentile points
Stable <50th percentile
Decreased >10 percentile points
BMI growth trajectory