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Early Life Growth Trajectories in Cystic Fibrosis are Associated with Pulmonary Function at Age 6 Years

Don B. Sanders, MD, MS¹, Aliza Fink, DSc², Nicole Mayer- Hamblett, PhD^{3,4}, Michael S. Schechter, MD, MPH⁵, Gregory S. Sawicki, MD, MPH⁶, Margaret Rosenfeld, MD, MPH⁴, Patrick A. Flume, MD⁷, and Wayne J. Morgan, MD⁸

¹Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI

²Cystic Fibrosis Foundation, Bethesda, MD

³Department of Biostatistics, University of Washington, Seattle, WA

⁴Department of Pediatrics, University of Washington, Seattle, WA

⁵Department of Pediatrics, Virginia Commonwealth University, Richmond, VA

⁶Department of Pediatrics, Boston Children's Hospital, Boston, MA

⁷Departments of Medicine and Pediatrics, Medical University of South Carolina, Charleston, SC

⁸Department of Pediatrics, University of Arizona, Tucson, AZ

Abstract

Objective—To determine whether severity of lung disease at age 6 years is associated with changes in nutritional status before age 6 within individual children with cystic fibrosis (CF).

Study Design—Children with CF born between 1994 and 2005 and followed in the CF Foundation Patient Registry from age 2 through 7 years were assessed according to changes in annualized weight-for-length (WFL) percentiles between ages 0 and 2 and body mass index (BMI) percentiles between ages 2 and 6. The association between growth trajectories before age 6 and forced expiratory volume in one second (FEV₁) % predicted at age 6-7 years was evaluated using multivariable linear regression.

Results—A total of 6,805 subjects met inclusion criteria. Children with annualized WFL-BMI always >50th percentile [N=1,323 (19%)] had the highest adjusted mean [95% Confidence Interval (CI)] FEV₁ at 6-7 years [101.8 (100.1, 103.5)]. FEV₁ at 6-7 years for children whose WFL-BMI increased >10 percentile points by age 6 years was 98.3 (96.6, 100.0). This was statistically significantly higher than FEV₁ for children whose WFL-BMI was stable [94.4 (92.6, 96.2)] or decreased >10 percentile points [92.9 (91.1, 94.8)]. Among children whose WFL-BMI increased >10 percentile points, achieving and maintaining WFL-BMI >50th percentile at younger ages was associated with significantly higher FEV₁ at 6-7 years.

Conclusions—Within-patient changes in nutritional status in the first 6 years of life are significantly associated with FEV₁ at age 6-7 years, suggesting that interventions that improve nutrition in early life may lead to improvements in later lung function.

Keywords

CF; FEV₁; Forced expiratory volume in 1 second; Weight; BMI; Newborn screening

INTRODUCTION

Cystic fibrosis (CF) is a multisystem genetic condition that leads to deficits in growth and nutrition as well as progressive lung disease.(1) Strong cross-sectional correlations between growth indices and forced expiratory volume in 1 second (FEV₁) have led the CF Foundation (CFF) to recommend that all children maintain at least the 50th percentile for weight-for-length (WFL) or body mass index (BMI).(2) With the widespread adoption of newborn screening (NBS) for CF, clinicians have the opportunity to encourage early weight gain, but the evidence to support an association between longitudinal changes in growth early in life and later lung health for individual patients is limited. Konstan *et al.* described an association between growth indices at age 3 and FEV₁ at age 6, even after adjusting for the severity of lung disease at age 3.(3) Yen *et al.* extended this analysis and described an association between patients with higher weight-for-age percentile at age 4 years and better FEV₁ from 6 to 18 years of age, fewer pulmonary exacerbations, and better survival.(4) Together these two studies suggest the need to optimize nutrition in early in life. However, their assessments of growth were taken at only one time point and measures of lung disease are limited in early childhood. Therefore, it is not known if improvements in growth in early life can minimize later lung disease, or whether the timing of these changes is important. Lai *et al.* (5) demonstrated that children with CF whose WFL decreased in the first 2 years of life had worse lung disease at age 6 than children whose WFL increased or remained stable in the first 2 years of life, but small numbers precluded the ability to assess changes in growth at other time points.

To maximize the potential benefits of NBS, it is necessary to understand if efforts to achieve and maintain the CFF goal of WFL and BMI >50th percentile in early life are associated with later lung health. The CFF Patient Registry (CFFPR) is a unique database with data on over 45,000 people with CF in the US, enabling longitudinal assessments of growth trajectories in individual patients. We hypothesized that increases in growth indices in early life in individual patients would be associated with higher FEV₁ at age 6 than growth indices that were stable or decreasing. Our objectives for this analysis were to: characterize early life growth trajectories in children with CF, determine if these trajectories are associated with FEV₁ at age 6-7 years, and determine if the timing of changes affects the relationship between growth trajectories and FEV₁ at age 6-7 years.

METHODS

The CFFPR contains data on demographics, cystic fibrosis transmembrane conductance regulator (CFTR) genotype, growth, FEV₁, microbiology, therapies, hospitalizations, and

complications.(6) Data were entered into the CFFPR quarterly from 1994 to 2002 and at every encounter beginning in 2003. For the current analysis, we obtained data for children with CF born between 1994 and 2005, diagnosed before age 2 years, and followed in the CFFPR through at least age 7 years. Subjects were excluded if they had a solid organ transplantation prior to age 7. Age was defined as the age on December 31st. We compared mean FEV₁ % predicted at 6-7 years of age with changes in growth indices (WFL for ages 0- 2 years and BMI for ages 2-6 years). FEV₁ % predicted was calculated as the average of the maximum FEV₁ value for each quarter in the year that each child was age 7 on December 31st using the Global Lung Initiative (GLI) reference equations.(7) Quarters that did not have data were not included in the average.

Annualized values for WFL and BMI were calculated for each year between ages 0 and 6 years from the average of the maximum WFL and BMI percentiles from each quarter. Changes in annualized WFL and BMI percentiles were calculated based on the Center for Disease Control (CDC) growth charts (8) between ages 0 and 6 years. The median within-patient difference between WFL percentiles at age 2 years and BMI percentiles at age 2 years was only 0.2 percentile, so WFL and BMI percentiles were considered to be a continuous variable (WFL-BMI). Growth before age 6 years was classified into the following mutually exclusive categories: annualized WFL-BMI always above the 50th percentile, i.e., always meeting the CFF goal; annualized WFL-BMI that increased >10 percentile points from the first year in the study to age 6 years; annualized WFL-BMI that was stable, i.e., <10 percentile increase or decrease from the first year in the study to age 6 years; or annualized WFL-BMI that decreased >10 percentile points from the first year in the study to age 6 years. For subjects in the last three categories, at least one annualized measurement of WFL-BMI fell below the 50th percentile. Subjects with annualized WFL-BMI always >50th percentile could have increases or decreases in WFL-BMI, as long as the annualized measurements of WFL-BMI always remained above the 50th percentile. In contrast, a subject would be included in the increased >10 percentile points category if their initial WFL was above the 50th percentile, followed by at least one year with WFL-BMI below the 50th percentile, as long as the final BMI was at least 10 percentile points higher than the initial WFL percentile. A missing category was also created for those with only one year with a recorded WFL or BMI. These categories were chosen to represent growth patterns that clinicians may seek to encourage (WFL-BMI always >50th percentile, increasing, or stable) or avoid (decreasing WFL-BMI).

Chi squared and t-tests were used to compare proportions and means. Bivariate analyses were conducted using t-tests and analysis of variance to assess the statistical significance of the observed differences in means. Multivariable linear regression was used to test for an association between the categories of growth trajectories and FEV₁ % predicted at age 6-7 years. The following potential confounders were included *a priori* based on a review of the literature for factors associated with growth and/or FEV₁: gender, race (white as compared to non-white), insurance status (ever a Medicaid recipient as compared to never), pancreatic enzyme replacement therapy as a surrogate for pancreatic status (patients were categorized as pancreatic insufficient if they were prescribed pancreatic enzyme replacement therapy before age 6 years), and age of first reported *Pseudomonas aeruginosa* infection (0-2 years, 3-6 years, and never infected).(9-14)

To test the robustness of our results, we performed several sensitivity analyses. We tested the effect of adding the following variables individually to our final multivariable linear regression model: (1) height percentile at age 6 years, (2) CF center (i.e., clustering by site), and (3) the mean annual frequency of pulmonary exacerbations between study entry and age 6 years. In addition, we tested replacing Medicaid insurance with maternal education and White/non-White with Hispanic/non-Hispanic. To address changes in the pattern of diagnosis after the gradual introduction of NBS during this time period (which may identify more subjects with pancreatic sufficiency), we (1) repeated our analysis, restricted to subjects with class I-III cystic fibrosis transmembrane conductance regulator (CFTR) mutations (i.e., those associated with pancreatic insufficiency) or those who entered the study during the first year of life, (2) compared the categories of growth trajectories according to mode of diagnosis (NBS as compared to other modes), and (3) evaluated for effect modification by mode of diagnosis (NBS as compared to other modes). To examine the effect of obesity, we added a category for WFL-BMI always >85th percentile. For subjects whose WFL-BMI increased >10 percentile points, we examined FEV₁ % predicted at age 6-7 years according to the age at which they first reached and maintained a WFL or BMI >50th percentile. For subjects whose WFL-BMI decreased >10 percentile points, we examined the FEV₁ % predicted at age 6-7 years according to the lowest annual WFL or BMI percentile. Using the same growth trajectory categories, we tested for an association with mean FEV₁ % predicted at ages 6-7 years with alternative predictors, including (1) annualized weight for age percentile, (2) annualized length/height for age percentile, (3) annualized BMI for age percentile only (i.e., excluding ages 0-1), and (4) annualized WFL for age only (i.e., excluding ages 3-6 years). Finally, we tested for an association between the categories of growth trajectories and alternative outcomes, including: (1) mean forced vital capacity (FVC) % predicted at ages 6-7 years and (2) best FEV₁ % predicted at ages 6-7 years. Statistical analyses were performed using SAS 9.3 (SAS Institute, Inc, Cary, North Carolina). *P* values of <0.05 were considered significant. No adjustments were made for multiple comparisons. The Seattle Children's Hospital Institutional Review Board approved the study.

RESULTS

Cohort characteristics

There were 10,916 children in the CFFPR born between 1994 and 2005 that were diagnosed with CF (Figure 1). Of these, there were 2,765 who were diagnosed after their second birthday, 593 not tracked in the CFFPR at age 7 years, 139 who died before age 7 years, 3 who received an organ transplant prior to age 7 years, and 2,479 who did not have measurements of FEV₁ by age 7 years. Thus, there were 6,805 total eligible subjects for this study. Baseline demographic data and clinical status for each category of growth trajectory are shown in Table 1. There were 120 (1.8%) children who met inclusion criteria but only had WFL or BMI available in one year and thus did not have a defined growth trajectory. NBS was not widespread in the US until after 2004. Because we restricted our analysis to children diagnosed before age 2 years, the percent of patients with meconium ileus is higher than in the general CF population. In comparison to the other growth trajectory categories, the group with annualized WFL-BMI always >50th percentile had more children who were

male, diagnosed after the first 3 months of life, born in 2002-2005, diagnosed after “other” presenting symptoms, and no infection with *Pseudomonas aeruginosa* before age 6 years. This group also had fewer children born in 1994-1997 or diagnosed after meconium ileus or failure to thrive. Figure 2 (available at www.jpeds.com) illustrates the mean WFL-BMI percentile for each category of growth trajectory between 0 and 6 years of age. The mean (SD) FEV₁ % predicted at age 6-7 years for the entire study population was diminished at 92.2 (17.8).

Association of growth trajectories with lung function at age 6-7 years

In a multivariable linear regression model, subjects with WFL-BMI always >50th percentile had the highest FEV₁ % predicted at age 6-7 years (Table 2). Among subjects with at least one annualized WFL-BMI percentile <50th percentile, FEV₁ % predicted for subjects whose WFL-BMI increased >10 percentile points was significantly lower than for subjects with annualized WFL-BMI always >50th percentile, but significantly higher than for subjects with WFL-BMI that was stable or decreased >10 percentile points. Subjects with WFL-BMI that decreased >10 percentile points had the lowest FEV₁ % predicted; this difference was statistically significant in comparison to subjects with WFL-BMI always >50th percentile and WFL-BMI that increased >10 percentile points. The statistical significance and effect size of the differences between categories of growth trajectories were similar in the unadjusted linear regression model.

Sensitivity analyses

The magnitude and direction of the association between WFL-BMI and FEV₁ % predicted at age 6-7 years were similar when we (1) individually added height percentile at age 6 years, CF Center, and the mean annual frequency of pulmonary exacerbations to our final multivariable regression model (Table 3A; available at www.jpeds.com); (2) replaced White/non-White race with Hispanic/non-Hispanic ethnicity or replaced Medicaid insurance status with maternal education; or (3) restricted our analysis to only patients with CFTR class I-III mutations or those who entered the study during the first year of life. FEV₁ % predicted at age 6-7 years was higher for children diagnosed via NBS, 100.6 (98.8, 102.3)% predicted than for children diagnosed with meconium ileus, 96.6 (94.8, 98.3)% predicted, or FTT, 94.3 (92.6, 96.1)% predicted in a model with mode of diagnosis added to the final multivariable regression model. However, the interaction between mode of diagnosis and categories of growth trajectories was not significant (p value=0.36).

Of the 1,323 subjects with WFL-BMI always >50th percentile, 98 (7.4%) maintained a WFL-BMI >85th percentile. In the final multivariable regression model, children with WFL-BMI always >85th percentile had an adjusted mean (95% CI) FEV₁ % predicted at age 6-7 of 103.6 (99.9, 107.2). This was similar to children who maintained WFL-BMI between the 50th and 85th percentiles [101.7 (99.8, 103.4)].

Among the subjects whose WFL-BMI increased >10 percentile points, we compared FEV₁ at age 6-7 years according to the age at which they first achieved and maintained WFL-BMI >50th percentile (Figure 3A). The FEV₁ at age 6-7 years was higher for subjects who achieved this goal at younger ages. This difference was statistically significant between

subjects who maintained WFL-BMI >50th percentile from age 1 year, as compared to subjects who intermittently or never reached this goal, or reached it only at age 6 years. In subjects whose WFL-BMI decreased >10 percentile points, FEV₁ % predicted at age 6-7 years was associated with the lowest annual WFL-BMI percentile reached before age 6 years (Figure 3B). Among subjects whose lowest WFL-BMI was between the 0 and 9th percentiles, the mean age was 3.6 years at this nadir; for subjects who had their lowest WFL-BMI between the 40th and 49th percentiles, the mean age was 4.5 years.

Using the same growth trajectory categories, the magnitude and direction of the association with mean FEV₁ % predicted at ages 6-7 years was similar when we used annualized weight for age percentile, annualized length/height for age percentile, annualized BMI for age percentile only (i.e., excluding ages 0-1), or annualized WFL for age only (i.e., excluding ages 3-6 years) as predictors (Table 3B). Finally, results were similar between the categories of growth trajectories and mean forced vital capacity (FVC) % predicted at ages 6-7 years and the best FEV₁ % predicted at ages 6-7 years (Table 3C).

DISCUSSION

This study demonstrates that individual growth trajectories in the first few years of life in children with CF are associated with clinically meaningful differences in FEV₁ % predicted at age 6 years. Our results support the CFF goal of maintaining WFL-BMI >50th percentile throughout childhood, as children who met this goal through age 6 had the best FEV₁ % predicted at age 6-7. For children who did not maintain the CFF goal throughout the first 6 years, it is encouraging that those who had increases in WFL-BMI had higher FEV₁ % predicted at age 6-7 than children who had stable or worsening WFL-BMI. Furthermore, among children who had increases in WFL-BMI, FEV₁ % predicted at age 6-7 was higher the younger the children were when they reached and maintained the CFF goal, and among children who had worsening WFL-BMI, FEV₁ % predicted at age 6-7 was lower according to the lowest WFL-BMI reached before age 6. These results suggest that interventions that result in improved nutrition in the first few years of life may have important effects on severity of lung disease later in life.

Previous studies have identified a correlation between nutrition measures at ages 2, 3, and 4 years with better pulmonary function test results later in life, and less morbidity and mortality.(3-5, 15) A recent study that analyzed secular trends in growth and pulmonary function in children with CF born between 1994 and 2012 and tracked in the CFFPR demonstrated increases in mean height-for-age percentiles and FEV₁ z-scores in children born more recently.(16) FEV₁/FVC ratios did not increase over this time period, leading the authors to speculate that the improvements in FEV₁ may be a result of improved lung growth due to increased attention to nutrition in early life. Our study supports this hypothesis by demonstrating that improvements in nutrition within a given child are associated with higher FEV₁ % predicted at age 6-7 years, even when adjusting for gender, race, socioeconomic status, pancreatic status, and infection with *P. aeruginosa*. Our sensitivity analysis also demonstrated an association between improvements in nutrition and FVC % predicted at age 6-7 years and that within a given growth trajectory category, taller children had better FEV₁ % predicted. Differences in FEV₁ % predicted at age 6 years are

likely to affect life-long outcomes, as higher FEV₁ % predicted at age 6 years is associated with later pulmonary outcomes.(17) These results should encourage providers and families that efforts to achieve improvements in nutrition early in life are associated with later improvements in lung health.

There are several important aspects to consider in nutritional interventions in young children with CF. Problematic feeding behaviors, which can occur more frequently in children with CF and may make gaining weight difficult, may need to be addressed.(18-20) A recent study that made use of CFFPR data demonstrated that CF Centers in the highest quartile for mean BMI percentiles prescribed significantly higher enzyme doses, and had more patients using acid blockers and nasogastric or gastrostomy tube feeds than CF Centers in the lowest quartiles for mean BMI percentiles.(21) These results indicate that more aggressive nutritional interventions may be important in improving nutritional outcomes. More broadly, systematic approaches to improving nutritional status have been demonstrated to be sustainable over time in different CF Centers.(22) This is especially pertinent as nearly half of US CF Centers have a median WFL-BMI in the first 6 years of life below the 50th percentile.(6)

Our study confirmed and extends prior findings by demonstrating that subjects whose WFL or BMI was >50th percentile had the best FEV₁ at age 6-7 years.(3, 4) These findings support the CFF guidelines that all children maintain BMI >50th percentile.(2, 23) The importance of avoiding growth faltering early in life is highlighted by the comparison of subjects who entered the study with a WFL <50th percentile, but who eventually achieved a WFL-BMI >50th percentile: children who reached this goal before age 2 years had the highest FEV₁ at age 6 years. These results suggest the importance of early growth in establishing a life course of progression of lung disease. Lai *et al.* showed that subjects who had early growth faltering and malnutrition but who recovered birth weight z-scores by age 2 years had better FEV₁ at age 6 years, regardless of growth patterns at ages 2-6 years.(5) A more recent analysis of CFFPR data showed that low weight and length at age 4 months was the best predictor of poor growth at 24 months.(24) The CF Foundation recommends frequent evaluation in CF clinics for all infants with CF. This frequent monitoring provides a significant opportunity to intervene and avoid malnutrition and growth faltering that may be present as early as the first 2 weeks of life for children with CF.(25) In a comparison of infant care practices between CF clinics with the highest and lowest mean FEV₁ in 1994-1999, centers who had the highest mean FEV₁ evaluated infants more often, both for routine and sick visits, obtained more respiratory cultures, and used more oral and IV therapies.(26)

Another key finding of our study that should be emphasized is that children whose WFL-BMI was stable but below the 50th percentile had lower FEV₁ % predicted at age 6 years than children who had increasing WFL-BMI. Even though not all children with CF can achieve WFL and BMI >50th percentile due to genetic [e.g., familial growth patterns or insulin-like growth factor (IGF)-1 deficiency (27)] and/or environmental factors [e.g., in utero or early life tobacco smoke exposure (28, 29)] that may limit potential growth, our findings suggest that there may be risks (i.e., lower future lung function) associated with

settling for stable nutrition rather than increasing WFL-BMI and/or achieving WFL-BMI >50th percentile.

There are several limitations to our study. First, we would point out that spirometry is the only measure of lung disease included in the CFFPR. Recent studies have made clear that even the children with normal FEV₁ in this analysis are likely to show evidence of lung disease if evaluated by more sensitive measures such as the lung clearance index (LCI) and chest CT, even in the presence of a normal FEV₁.(30, 31) Second, as with all observational studies, we must be careful to point out that the association we found between early childhood growth trajectories and lung function does not prove causation. It is possible that early silent underlying lung disease may impact nutritional parameters. Furthermore, our study does not demonstrate whether different growth trajectories occur because of direct nutritional or pulmonary interventions, or due to underlying factors contributing to both nutritional status and lung health, such as gene modifiers. Ongoing prospective studies that closely monitor growth, nutrition, and pulmonary status may provide stronger evidence of causation, as would clinical intervention trials.

The subjects in the current study were born before widespread NBS, and before many current standard CF therapies were available, limiting its generalizability to more recent birth cohorts. We should also point out that our study does not address the appropriateness of alternative nutrition goals, i.e., other than a WFL or BMI >50th percentile, although these have been chosen because of previous research showing that patients who maintain these levels of nutrition have the best pulmonary outcomes.(2) In our sensitivity analysis, we compared mean FEV₁ % predicted at age 6-7 years by height at age 6 and found that increased height was significantly associated with higher FEV₁ % predicted. Additionally, even within each growth trajectory category, taller children had higher mean FEV₁ % predicted than shorter children. Finally, the CFFPR has limited data to address the genetic potential of subjects, such as birth weights and parental data, so we could not consider this in our analysis.

In conclusion, children with WFL-BMI always >50th percentile between the diagnosis of CF and 6 years, in keeping with current CFF guidelines, had the highest mean FEV₁ % predicted at age 6-7 years. Among those with WFL-BMI <50th percentile in at least one year before age 6, those children whose WFL-BMI increased >10 percentile points by age 6 years had higher FEV₁ at age 6-7 years in comparison to subjects whose WFL-BMI was stable or decreased >10 percentile points. These results suggest that interventions to improve growth in the first few years of life within an individual patient with CF may result in improved lung health. These early life interventions may have life-long effects and should encourage providers to promote optimal nutrition frequently and consistently.

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Abbreviations

BMI	Body Mass Index
CF	Cystic Fibrosis
CFF	Cystic Fibrosis Foundation
CFFPR	Cystic Fibrosis Foundation Patient Registry
CI	Confident Interval
FEV₁	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
NBS	Newborn Screening
WFL	Weight For Length

REFERENCES

1. Gibson R, Burns J, Ramsey B. Pathophysiology and management of pulmonary infections in cystic fibrosis. *Am J Respir Crit Care Med*. 2003; 168:918–51. [PubMed: 14555458]
2. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H, Clinical Practice Guidelines on Growth and Nutrition Subcommittee Ad Hoc Working Group. et al. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc*. 2008; 108:832–9. [PubMed: 18442507]
3. Konstan M, Butler S, Wohl M, Stoddard M, Matousek R, Wagener J, et al. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *J Pediatr*. 2003; 142:624–30. [PubMed: 12838189]
4. Yen EH, Quinton H, Borowitz D. Better nutritional status in early childhood is associated with improved clinical outcomes and survival in patients with cystic fibrosis. *J Pediatr*. 2013; 162:530–5.e1. [PubMed: 23062247]
5. Lai H, Shoff S, Farrell P, Wisconsin Cystic Fibrosis Neonatal Screening Group. Recovery of birth weight z score within 2 years of diagnosis is positively associated with pulmonary status at 6 years of age in children with cystic fibrosis. *Pediatrics*. 2009; 123:714–22. [PubMed: 19171643]
6. CF Foundation. 2012 Patient Registry Annual Data Report. 2013.
7. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012; 40:1324–43. [PubMed: 22743675]
8. Kuczmarski R, Ogden C, Grummer-Strawn L, Flegal K, Guo S, Wei R, et al. CDC growth charts: United States. *Adv Data*. 2000;1–27. [PubMed: 11183293]
9. Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. *J Pediatr*. 1997; 131:809–14. [PubMed: 9427882]

10. Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson R. *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol*. 2002; 34:91–100. [PubMed: 12112774]
11. Braun AT, Farrell PM, Ferec C, Audrezet MP, Laxova A, Li Z, et al. Cystic fibrosis mutations and genotype-pulmonary phenotype analysis. *Journal of Cystic Fibrosis*. 2006; 5:33–41. [PubMed: 16275171]
12. Quittner AL, Schechter MS, Rasouliyan L, Haselkorn T, Pasta DJ, Wagener JS. Impact of socioeconomic status, race, and ethnicity on quality of life in patients with cystic fibrosis in the United States. *Chest*. 2010; 137:642–50. [PubMed: 19820076]
13. Hamosh A, FitzSimmons SC, Macek M, Knowles MR, Rosenstein BJ, Cutting GR. Comparison of the clinical manifestations of cystic fibrosis in black and white patients. *J Pediatr*. 1998; 132:255–9. [PubMed: 9506637]
14. Schechter M, Shelton B, Margolis P, Fitzsimmons S. The association of socioeconomic status with outcomes in cystic fibrosis patients in the United States. *Am J Respir Crit Care Med*. 2001; 163:1331–7. [PubMed: 11371397]
15. VanDevanter DR, Wagener JS, Pasta DJ, Elkin E, Jacobs JR, Morgan WJ, et al. Pulmonary outcome prediction (POP) tools for cystic fibrosis patients. *Pediatr Pulmonol*. 2010; 45:1156–66. [PubMed: 20717915]
16. VanDevanter DR, Pasta DJ, Konstan MW. Improvements in Lung Function and Height among Cohorts of 6-Year-Olds with Cystic Fibrosis from 1994 to 2012. *J Pediatr*. 2014; 165:1091–7.e2. [PubMed: 25134852]
17. Taylor-Robinson D, Whitehead M, Diderichsen F, Olesen HV, Pressler T, Smyth RL, et al. Understanding the natural progression in %FEV1 decline in patients with cystic fibrosis: a longitudinal study. *Thorax*. 2012; 67:860–6. [PubMed: 22555277]
18. Powers SW, Patton SR, Byars KC, Mitchell MJ, Jelalian E, Mulvihill MM, et al. Caloric intake and eating behavior in infants and toddlers with cystic fibrosis. *Pediatrics*. 2002; 109:E75–5. [PubMed: 11986481]
19. Powers SW, Mitchell MJ, Patton SR, Byars KC, Jelalian E, Mulvihill MM, et al. Mealtime behaviors in families of infants and toddlers with cystic fibrosis. *J Cyst Fibros*. 2005; 4:175–82. [PubMed: 15982934]
20. Powers SW, Jones JS, Ferguson KS, Piazza-Waggoner C, Daines C, Acton JD. Randomized clinical trial of behavioral and nutrition treatment to improve energy intake and growth in toddlers and preschoolers with cystic fibrosis. *Pediatrics*. 2005; 116:1442–50. [PubMed: 16322169]
21. Haupt ME, Kwasny MJ, Schechter MS, McColley SA. Pancreatic enzyme replacement therapy dosing and nutritional outcomes in children with cystic fibrosis. *J Pediatr*. 2014; 164:1110–5.e1. [PubMed: 24560182]
22. Savant AP, Britton LJ, Petren K, McColley SA, Gutierrez HH. Sustained improvement in nutritional outcomes at two paediatric cystic fibrosis centres after quality improvement collaboratives. *BMJ quality & safety*. 2014; 23(Suppl 1):i81–9.
23. Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, Spear SL, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr*. 2009; 155:S73–93. [PubMed: 19914445]
24. Heltshe SL, Borowitz DS, Leung DH, Ramsey B, Mayer-Hamblett N. Early attained weight and length predict growth faltering better than velocity measures in infants with CF. *J Cyst Fibros*. 2014; 13:723–9. [PubMed: 24917114]
25. Marcus M, Sondel S, Farrell P, Laxova A, Carey P, Langhough R, et al. Nutritional status of infants with cystic fibrosis associated with early diagnosis and intervention. *Am J Clin Nutr*. 1991; 54:578–85. [PubMed: 1877513]
26. Padman R, McColley SA, Miller DP, Konstan MW, Morgan WJ, Schechter MS, et al. Infant care patterns at epidemiologic study of cystic fibrosis sites that achieve superior childhood lung function. *Pediatrics*. 2007; 119:e531–7. [PubMed: 17332172]
27. Sermet-Gaudelus I, Souberbielle JC, Azhar I, Ruiz JC, Magnine P, Colomb V, et al. Insulin-like growth factor I correlates with lean body mass in cystic fibrosis patients. *Arch Dis Child*. 2003; 88:956–61. [PubMed: 14612353]

28. Rosenfeld M, Emerson J, McNamara S, Joubran K, Retsch-Bogart G, Graff GR, et al. Baseline characteristics and factors associated with nutritional and pulmonary status at enrollment in the cystic fibrosis EPIC observational cohort. *Pediatr Pulmonol*. 2010; 45:934–44. [PubMed: 20597081]
29. Rubin BK. Exposure of children with cystic fibrosis to environmental tobacco smoke. *N Engl J Med*. 1990; 323:782–8. [PubMed: 2392132]
30. Gustafsson P, De Jong P, Tiddens H, Lindblad A. Multiple-breath inert gas washout and spirometry versus structural lung disease in cystic fibrosis. *Thorax*. 2008; 63:129–34. [PubMed: 17675316]
31. de Jong P, Lindblad A, Rubin L, Hop W, de Jongste J, Brink M, et al. Progression of lung disease on computed tomography and pulmonary function tests in children and adults with cystic fibrosis. *Thorax*. 2006; 61:80–5. [PubMed: 16244089]

Figure 1.
Diagram of study cohort

Figure 2.

Mean WFL-BMI percentile by age for each category of growth trajectories. There were 1,323 children with annualized WFL-BMI always >50th percentile through 6 years. Among children with at least one annualized WFL-BMI <50th percentile, WFL-BMI increased >10 percentile points for 3,205, remained stable for 1,184, and decreased >10 percentile points for 973.

Figure 3.

Mean FEV₁ % predicted at ages 6-7 years associated with (A) age at which subjects whose WFL-BMI increased >10 percentile points first reached and maintained WFL-BMI >50th percentile and (B) the lowest annualized WFL-BMI percentile for subjects whose WFL-BMI decreased >10 percentile points. The vertical bars represent the 95% confidence intervals.

Table 1

Demographics and clinical characteristics of study cohort.

Characteristic	Total	WFL-BMI growth trajectory				
		Always >50 th percentile	Increased >10 percentile points	Stable	Decreased >10 percentile points	Missing
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	6805	1323 (19.4)	3205 (47.1)	1184 (17.4)	973 (14.3)	120 (1.8)
Male	3424 (50.3)	744 (56.2)	1559 (48.6)	578 (48.8)	476 (48.9)	67 (55.8)
Age at Diagnosis						
<3 months	3831 (56.3)	650 (49.1)	1863 (58.1)	664 (56.1)	595 (61.2)	59 (49.2)
3 to <6 months	1286 (18.9)	250 (18.9)	598 (18.7)	227 (19.2)	179 (18.4)	32 (26.7)
6 months to <1 year	939 (13.8)	208 (15.7)	446 (13.9)	156 (13.2)	113 (11.6)	16 (13.3)
1 to <2 years	749 (11.0)	215 (16.2)	298 (9.3)	137 (11.6)	86 (8.8)	13 (10.8)
Birth cohort						
1994-1997	2256 (33.2)	362 (27.4)	1118 (34.9)	413 (34.9)	313 (32.2)	50 (41.7)
1998-2001	2261 (33.2)	419 (31.7)	1148 (35.8)	374 (31.6)	291 (29.9)	29 (24.2)
2002-2005	2288 (33.6)	542 (41.0)	939 (29.3)	397 (33.5)	369 (37.9)	41 (34.2)
Race/ethnicity*						
Caucasian	6412 (94.2)	1253 (94.7)	3037 (94.8)	1108 (93.6)	905 (93.0)	109 (90.8)
Black	321 (4.7)	45 (3.4)	157 (4.9)	59 (5.0)	56 (5.8)	4 (3.3)
Hispanic	587 (8.9)	112 (8.8)	281 (9.0)	105 (9.2)	65 (7.0)	24 (20.0)
Mode of diagnosis						
Meconium Ileus	1867 (27.4)	271 (20.5)	970 (30.3)	328 (27.7)	275 (28.3)	23 (19.2)
Newborn screening	1035 (15.2)	216 (16.3)	444 (13.8)	190 (16.0)	174 (17.9)	11 (9.2)
Failure to Thrive	2253 (33.1)	359 (27.1)	1140 (35.6)	422 (35.6)	292 (30.0)	40 (33.3)
Other	1650 (24.2)	477 (36.0)	651 (20.3)	244 (20.6)	232 (23.8)	46 (38.3)
CFTR genotype						
Classes I – III	5273 (77.5)	965 (72.9)	2514 (78.4)	955 (80.6)	761 (78.2)	78 (65.0)
Classes IV, V	325 (4.8)	98 (7.4)	125 (3.9)	50 (4.2)	40 (4.1)	12 (10.0)

Characteristic	Total	WFL-BMI growth trajectory				
		Always >50 th percentile	Increased >10 percentile points	Stable	Decreased >10 percentile points	Missing
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Other/unknown	1048 (15.4)	235 (17.8)	481 (15.0)	156 (13.2)	154 (15.8)	22 (18.3)
Not genotyped	159 (2.3)	25 (1.9)	85 (2.7)	23 (1.9)	18 (1.8)	8 (6.7)
Insurance status						
Medicaid/state program**	4449 (65.4)	831 (62.8)	2174 (67.8)	762 (64.4)	642 (66.0)	40 (33.3)
Age at first infection with <i>Pseudomonas aeruginosa</i>						
0-2 years	3166 (46.5)	526 (39.8)	1630 (50.9)	536 (45.3)	469 (48.2)	5 (4.2)
3-6 years	1690 (24.8)	343 (25.9)	760 (23.7)	318 (26.9)	250 (25.7)	19 (15.8)
No Infection	1949 (28.6)	454 (34.3)	815 (25.4)	330 (27.9)	254 (26.1)	96 (80.0)
Chronic CF medications**						
Domase alfa	4650 (68.3)	924 (69.8)	2219 (69.2)	786 (66.4)	678 (69.7)	43 (35.8)
Inhaled tobramycin	4384 (64.4)	804 (60.8)	2132 (66.5)	762 (64.4)	656 (67.4)	30 (25.0)
Azithromycin	652 (9.6)	141 (10.7)	299 (9.3)	107 (9.0)	101 (10.4)	4 (3.3)
Pancreatic enzyme replacement therapy	6589 (96.8)	1255 (94.9)	3158 (98.5)	1158 (97.8)	952 (97.8)	66 (55.0)
Nutritional Interventions**						
H2 blockers	1798 (26.4)	357 (27.0)	839 (26.2)	302 (25.5)	295 (30.2)	5 (4.2)
Proton pump inhibitors	2221 (32.6)	431 (32.6)	1064 (33.2)	368 (31.1)	351 (36.1)	6 (5.0)
Supplemental oral feedings	3951 (58.1)	780 (59.0)	1838 (57.4)	701 (59.2)	604 (62.1)	28 (23.3)
Nasogastric or gastrostomy tube supplemental feedings	1354 (19.9)	111 (8.4)	731 (22.8)	282 (23.8)	224 (23.0)	6 (5.0)

* not mutually exclusive

** Ever from study entry to age 6 years

Multivariable linear regression model for FEV₁ % predicted at ages 6-7 years associated with growth trajectory from study entry to age 6 years. Total N = 6,805 subjects.

Table 2

	Mean (95% CI) Estimate for FEV ₁ % predicted at age 6-7 years*	Mean (95% CI) Difference in FEV ₁ % predicted at age 6-7 years*
Growth trajectory		
WFL-BMI always >50 th percentile	101.8 (100.1, 103.5)	Reference
WFL-BMI increased >10 percentile points	98.3 (96.6, 100.0)	-3.5 (-4.6, -2.4)
WFL-BMI stable	94.4 (92.6, 96.2)	-7.4 (-8.8, -6.0)
WFL-BMI decreased >10 percentile points	92.9 (91.1, 94.8)	-8.9 (-10.3, -7.4)
Male	94.6 (93.1, 96.0)	Reference
Female	94.3 (92.8, 95.8)	-0.4 (-1.2, 0.4)
White	93.2 (92.0, 94.4)	Reference
Non-White	95.6 (93.6, 97.7)	2.2 (0.5, 4.0)
Ever Medicaid**	91.7 (90.2, 93.2)	Reference
Never Medicaid**	97.1 (95.6, 98.6)	5.5 (4.6, 6.4)
Ever on pancreatic enzyme replacement therapy**	92.1 (91.1, 93.2)	Reference
Never on pancreatic enzyme replacement therapy**	96.7 (94.2, 99.2)	6.6 (3.9, 9.3)
Never infected with <i>P. aeruginosa</i>	96.6 (95.1, 98.1)	Reference
Acquired <i>P. aeruginosa</i> ages 0-2 years	93.1 (91.5, 94.6)	-3.5 (-4.5, -2.5)
Acquired <i>P. aeruginosa</i> ages 3-6 years	93.6 (91.9, 95.2)	-3.2 (-4.3, -2.0)

* Adjusted for all covariates listed

** Ever from study entry to age 6 years

Table 3

Estimates of mean (95% CI) pulmonary function at ages 6-7 years from multivariable linear regression models including sensitivity analyses with additional variables added individually to the final multivariable regression model, alternative predictors used in the final multivariable regression model, and alternative outcomes.

	Growth trajectory			
	Always >50 th percentile	Increased >10 percentile points	Stable	Decreased >10 percentile points
Final regression model	101.8 (100.1, 103.5)	98.3 (96.6, 100.0)	94.4 (92.6, 96.2)	92.9 (91.1, 94.8)
+ height at age 6 years	99.7 (97.9, 101.4)	96.6 (94.9, 98.2)	92.8 (91.0, 94.6)	91.4 (89.5, 93.2)
+ CF center	98.6 (96.7, 100.4)	95.3 (93.5, 97.0)	91.9 (90.0, 93.8)	90.3 (88.3, 92.3)
+ mean annual pulmonary exacerbation frequency	97.0 (95.4, 98.5)	94.6 (93.1, 96.1)	91.4 (89.7, 93.0)	89.8 (88.1, 91.5)
Replace White/non-White with Hispanic/non-Hispanic ethnicity	99.3 (97.6, 101.0)	95.8 (94.2, 97.4)	91.9 (90.2, 93.7)	90.3 (88.5, 92.1)
Replace Medicaid with maternal education	99.9 (97.8, 102.0)	96.7 (94.7, 98.7)	92.7 (90.5, 94.9)	92.0 (89.7, 94.3)
Restricted to CFTR mutation classes I-III only	98.8 (97.3, 100.3)	94.9 (93.6, 96.2)	91.1 (89.6, 92.7)	89.4 (87.8, 91.0)
Restricted to children entering during first year	98.7 (97.4, 100.1)	95.1 (94.0, 96.2)	91.3 (89.9, 92.7)	89.9 (88.4, 91.3)
Alternative predictors				
Weight for age percentile	102.8 (100.8, 104.7)	99.1 (97.4, 100.7)	93.9 (92.2, 95.6)	94.7 (92.6, 96.7)
Length/height for age percentile	101.7 (99.8, 103.6)	98.4 (96.7, 100.1)	95.7 (94.0, 97.4)	96.5 (94.7, 98.3)
BMI percentile for age only (ages 2-6 years)	101.3 (99.7, 102.9)	97.2 (95.5, 98.8)	95.1 (93.3, 96.8)	92.5 (90.8, 94.)
WFL percentile for age only (ages 0-1 years)	100.8 (98.3, 103.3)	97.2 (94.7, 99.7)	95.4 (92.8, 98.1)	94.7 (91.9, 97.4)
Alternative outcomes				
Mean FVC % predicted at ages 6-7 years	106.1 (104.5, 107.7)	102.5 (100.9, 104.1)	98.6 (96.9, 100.2)	97.7 (96.0, 99.5)
Best FEV ₁ % predicted at ages 6-7 years	111.6 (109.9, 113.3)	108.4 (106.8, 110.0)	104.5 (102.8, 106.3)	103.0 (101.2, 104.8)