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

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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 years and body mass index (BMI) percentiles between ages 2 and 6 years. The association between growth trajectories before age 6 and forced expiratory volume in 1 second (FEV_1)% predicted at age 6-7 years was evaluated using multivariable linear regression.

Results A total of 6805 subjects met inclusion criteria. Children with annualized WFL-BMI always >50th percentile (N = 1323 [19%]) had the highest adjusted mean (95% CI) FEV_1 at 6-7 years (101.8 [100.1, 103.5]). FEV_1 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 FEV_1 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 FEV_1 at 6-7 years.

Conclusions Within-patient changes in nutritional status in the first 6 years of life are significantly associated with FEV_1 at age 6-7 years. The establishment of a clear relationship between early childhood growth measurements and later lung function suggests that early nutritional interventions may impact on eventual lung health. *(J Pediatr 2015;167:1081-8)*.

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 (FEV_1) 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 is limited to support an association between longitudinal changes in growth early in life and later lung health for individual patients. Konstan et al[3] described an association between growth indices at age 3 years and FEV_1 at age 6 years, even after adjusting for the severity of lung disease at age 3 years. Yen et al[4] extended this analysis and described an association between patients with higher weight-for-age percentile at age 4 years and better FEV_1 from 6 to 18 years of age, fewer pulmonary exacerbations, and better survival.

Together these 2 studies suggest the need to optimize nutrition early in life. However, their assessments of growth were taken at only 1 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 years 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

BMI	Body mass index
CF	Cystic fibrosis
CFF	CF Foundation
CFFPR	CFF Patient Registry
CFTR	CF transmembrane conductance regulator
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
NBS	Newborn screening
WFL	Weight-for-length

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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 FEV_1 at age 6 years 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 FEV_1 at age 6-7 years, and determine if the timing of changes affects the relationship between growth trajectories and FEV_1 at age 6-7 years.

Methods

The CFFPR contains data on demographics, CF transmembrane conductance regulator (CFTR) genotype, growth, FEV_1 microbiology, therapies, hospitalizations, and complications.[6] 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 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 years. Age was defined as the age on December 31. We compared mean FEV_1% 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). FEV_1% predicted was calculated as the average of the maximum FEV_1 value for each quarter in the year that each child was age 7 years on December 31 using the Global Lung Initiative 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 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 (ie, 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 (ie, <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 3 categories, at least 1 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 1 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 1 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). The Seattle Children's Hospital Institutional Review Board approved the study.

Statistical Analyses

The χ^2 and t tests were used to compare proportions and means. Bivariate analyses were conducted using t tests and ANOVA 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 FEV_1% 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 FEV_1: sex, race (White compared with non-White), insurance status (ever a Medicaid recipient compared with 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 (ie, 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 CFTR mutations (ie, 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 compared with other modes); and (3) evaluated for effect modification by mode of diagnosis (NBS compared with 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 FEV_1% 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 FEV_1% predicted at