Published in final edited form as:

Pediatr Pulmonol. 2011 January ; 46(1): 31–35. doi:10.1002/ppul.21322.

The Effects of an Intensive Behavior and Nutrition Intervention Compared to Standard of Care on Weight Outcomes in CF

Lori J. Stark, PhD^{1,*}, Lisa Opiari-Arrigan, PhD¹, Alexandra L. Quittner, PhD², Judy Bean, PhD¹, and Scott W. Powers, PhD¹

¹Cincinnati Children's Hospital Medical Center/University of Cincinnati College of Medicine, Cincinnati, Ohio

²University of Miami, Coral Gables, Florida

Summary

Inadequate intake and suboptimal growth are common problems for patients with CF and a critical target for intervention. The purpose of this study was to compare the growth outcomes of children with CF who participated in a randomized clinical trial to improve energy intake and weight to children with CF receiving standard of care during the same time period. Our primary outcome was change in body mass index z-score (BMI z-score) over 2 years. An exploratory outcome was forced expiratory volume at 1-sec (FEV₁) over 2 years. Participants were children ages 4–12 with CF, who participated in a randomized clinical trial of behavior plus nutrition intervention versus nutrition education alone, and a matched Comparison Sample receiving standard of care drawn from the Cystic Fibrosis Foundation (CFF) Registry. Children in the Clinical Trial Group (N = 67) participated in a 9-week, nutrition intervention and were followed at regular intervals (3, 6, 12, 18, and 24 months) for 2 years post-treatment to obtain anthropometric and pulmonary function data. For each child in the Comparison Sample (N = 346), these measures were obtained from the CFF Registry at matching intervals for the 27-month period corresponding to the clinical trial. Over 27 months, children in the Clinical Trial Group (the combined sample of the behavior plus nutrition and the nutrition alone) demonstrated significantly less decline in BMI z-score, -0.05 (SD = 0.68, CI = -0.23 to 0.13), as compared to children in the Comparison Sample, -0.21 (SD = 0.67, CI = -0.31 to -0.11). No statistically significant differences were found for decline in FEV₁ between children in the Clinical Trial Group and the Comparison Sample. The key implication of these findings is that intensive behavioral and nutritional intervention is effective and needs to be adapted so that it can be broadly disseminated into clinical practice.

Keywords

cystic fibrosis; nutrition status; behavior therapy; nutrition education

INTRODUCTION

Better growth and nutritional status is strongly associated with better pulmonary function¹⁻³ and is an independent predictor of survival in patients with CF.⁴ Despite this evidence, less than one half of the children with CF in the United States meet the CF Foundations recommendations for a BMI 50th percentile.⁵ Not only do patients with CF require significantly higher caloric intake than healthy children due to a disease-related energy imbalance, but they also experience symptoms that interfere with adequate intake, such as chronic poor appetite, infection-related anorexia, gastro-esophageal reflux, and abdominal pain.⁶ Thus, inadequate intake and suboptimal growth are common problems for patients with CF and a critical area for intervention.

For growth deficits in children ages 1 – 12 years, the CF Foundation currently recommends intensive treatment with behavioral intervention in conjunction with nutrition counseling.⁵ Across multiple studies, behavioral intervention combined with nutrition education has consistently demonstrated clinically and statistically significant increases in daily energy intake and weight over the course of a 2- to 3-month intervention period.^{5,7-11} Recently, results from the first randomized clinical trial comparing a behavioral plus nutrition education intervention to nutrition education alone, with equivalent number and duration of treatment contacts across conditions, demonstrated that over the short-term (9-week intervention period) the behavioral plus nutrition education intervention led to greater improvements in daily energy intake and weight.¹² However, 2 years following treatment, children in both treatments successfully maintained daily energy intakes of ~120% of the healthy population and 20% above baseline, and showed equivalent improvement in body mass index *z*-score (BMI *z*-score). This trial did not have a standard of care control group and therefore limits our understanding of the importance of these findings in the context of usual care for nutritional management. The goals of nutrition management at the time of the study were to support normal growth and nutrition for patients at all ages through assessment of nutritional status at every visit (3–4 months) and nutritional education with active dietary intervention by a dietitian initiated when a patient declined below their established weight curve or fell below the 89% of ideal weight for height.¹³ Active management included assessment of energy intake and fat absorption, education to increase energy needs, and behavioral assessment and counseling.¹³

The purpose of this study was to compare the growth outcomes of children who participated in the clinical trial to children with CF receiving standard of care during the same time period to determine whether the improvements in BMI *z*-score from baseline to 2 years post-treatment were a function of the experimental interventions or improvements in CF care in general. Our primary outcome was change in BMI *z*-score over 2 years. An exploratory outcome was forced expiratory volume at 1-sec (FEV₁) over 2 years. We hypothesized that children with CF who participated in the clinical trial would have significantly less decline in BMI *z*-score from pretreatment through the 2-year follow-up as compared to children receiving standard of care.

MATERIALS AND METHODS

Participants

Children with CF who participated in a randomized clinical trial of behavior plus nutrition intervention and nutrition education alone and a matched sample of comparison children receiving standard of care drawn from the Cystic Fibrosis Foundation (CFF) Registry data as described below.

Clinical Trial Group—Subjects in the randomized clinical trial comparing a behavior plus nutrition education intervention (Be-In-CHARGE!; manual online at www.oup.com/us/pediatricpsych) to a nutrition education intervention alone were recruited from five CF Centers located in the US. The study was approved by the institutional review committee at each medical center, consent and assent was obtained. Inclusion criteria were ages 4–12 years, diagnosis of CF by sweat test, pancreatic insufficient, and 40th percentile weight for age and sex or weight for height at the time of the chart review. Exclusion criteria included insulin-dependent diabetes; FEV₁ <40% predicted, significant developmental delays or impairments, such as autism, cerebral palsy, or mental retardation; positive sputum culture for *B. cepacia* Complex; or receiving supplemental enteral or parenteral nutrition. As there were no group differences on BMI *z*-score or FEV₁ for children in the two conditions at baseline or at 2 years post-intervention¹² the subjects were combined into one group, subsequently referred to as the Clinical Trial Group.

Comparison Sample—Children with CF, at a targeted ratio of five patients for every child in the clinical trial, who were the same age, seen during the recruitment period of the trial, 1996–1999, and met the inclusion/exclusion criteria used in the clinical trial were randomly drawn from the CFF Registry. The CFF Registry is a national database comprised of 23,000 individuals with CF who receive care at CF Foundation-accredited care centers.¹⁴ Data on height, weight, and pulmonary function tests (among other variables) are collected at each patient visit, at each center, and entered into a centralized database. Centers similar to the clinical trial centers in terms of geographic region, academic affiliation, and center size were identified.

Procedures

Participants in the clinical trial attended seven, 90-min intervention sessions over the course of 9 weeks. The two interventions were equivalent in terms of amount of time and contact during treatment, and only varied in the content. The details of each intervention protocol, the clinical trial procedures, and study results have been previously reported.^{12,15}

Participants completed a baseline evaluation and follow-up assessments in clinic scheduled at post-treatment (9 weeks), and 3, 6, 12, 18, and 24 months after the conclusion of treatment to obtain anthropometric data, following the guidelines established by Cameron¹⁶ and pulmonary function data assessed by FEV₁, using equations from Wang et al.¹⁷

For each child in the Comparison Sample, clinically collected anthropometric and lung function data assessed by FEV₁ using equations from Wang et al.¹⁷ was obtained from the CFF Registry for a 27-month period corresponding to the time frame of the clinical trial

(baseline through 2 years post-treatment). Not all children were old enough to reliably complete FEV₁ (< 6 years), therefore there are data on 36 children in the Clinical Trial Group and 173 in the Comparison Sample for this outcome.

Statistical Analysis

Data were analyzed using SAS version 9.1 statistical software (SAS Institute, Inc., Cary, NC). Demographic variables were compared using *t*-tests for continuous variables and chi-square tests for categorical variables.

Linear modeling was used to compare children in the Clinical Trial Group with the Comparison Sample drawn from the CFF Registry. Our primary outcome, change in BMI *z*-score from baseline to 2 years post-treatment (27 months), was analyzed as a difference score calculated from baseline for each of the seven follow-up assessment points (post-treatment, 3, 6, 12, 18, and 24 months post-treatment). The independent variables were fixed effects for group (Clinical Trial Group vs. Comparison Sample), time point, and the interaction of the two. Our exploratory outcome was FEV₁. As FEV₁ is not typically examined as a difference score, our dependent variable was the FEV₁ score at each assessment point. The independent variables were group, time, and the group by time interaction. Because difference over time between the groups was of primary interest, the interaction of group and time, indicating slope differences, was examined.

RESULTS

Study Population

Clinical Trial—A total of 79 children with CF and their families were randomized to treatment across five sites, 39 to behavior plus nutrition education, and 40 to nutrition education only. Six families in each intervention condition dropped out prior to receiving active treatment, yielding a total of 67 participants (35 boys and 32 girls). Children in the trial ranged in age from 4 to 12 years with a mean age of 7.64 years.

Comparison Sample—A targeted ratio of five patients for every child in the clinical trial were matched on age and gender from the CFF Registry, from CF Centers of comparable size and geographical region yielding a final Comparison Sample of 355 children with a total of 1,701 observations. All observations spanning the 27-month time period which matched the intervention child's participation in the clinical trial were obtained. Only observations taken during the same time frame as the intervention child's observations were used, ± 1 month for each time period (i.e., baseline, post-treatment, 3-, 6-, 12-, 18-, and 24-month follow-up). If a child had both an observation at -1 month and $+1$ month corresponding to a specific time period, one clinic visit was chosen at random. After this matching procedure, five children had only a baseline observation and they were eliminated from the data set. An additional five observation points were eliminated because they were either clearly mistakes (i.e., weight at one observation was 2.5 kg and one child's baseline height was greater than all subsequent heights) or they were extreme outliers (> 6 SD from the mean). This yielded a total of 1,691 observations from 346 children for the Comparison Sample. There were 160 girls and 186 boys with a mean age of 7.44 years.

Demographic Comparison

As seen in Table 1, there were no differences in age, gender, race, baseline BMI z -score, percentage of patients with a baseline BMI z -score ≥ 0 , or FEV₁ between the Clinical Trial Group and Comparison Sample (p s = ns).

BMI z -Score

Children in the Clinical Trial Group demonstrated significantly less decline in BMI z -score over 27 months than children in the Comparison Sample ($F(6,2101) = 6.41, P < 0.0001$). Over 2 years post-treatment, children in the Clinical Trial Group experienced an average decline in BMI z -score of -0.05 ($SD = 0.68, CI = -0.23$ to 0.13) while children in the Comparison Sample had a decline of -0.21 ($SD = 0.67, CI = -0.31$ to -0.11).

FEV₁

Children in the Clinical Trial Group had a mean baseline FEV₁ of 89.95% ($n = 36$), which declined to 88.74% ($n = 36$) after 27 months, yielding a decrease of 1.21%. Children in the Comparison Sample had a mean baseline FEV₁ 87.71% ($n = 173$) which declined to 84.45% ($n = 129$) 27 months later, for a decrease of 3.25%. When examined in a longitudinal statistical analysis, no statistically significant differences were found for decline in FEV₁ between children in the Clinical Trial Group and the Comparison Sample.

DISCUSSION

To our knowledge, this is the first study to compare the growth and pulmonary status of children with CF who participated in a short-term (9-week) nutrition intervention clinical trial to those receiving standard of care over 2 years (27 months). By utilizing the CFF Registry to obtain a Comparison Sample, we demonstrated that providing a short-term intensive intervention aimed at nutrition, whether focused on behavior plus nutrition education or just nutrition education alone, was more efficacious than standard of care for children 4–12 years. Children who participated in the clinical trial experienced an average decline of 0.05 in their BMI z -score over 27 months, whereas the Comparison Sample declined four times as much during the same period. While there is no corresponding CFF Registry data on caloric intake, numerous studies have reported that the typical intake of children with CF is about 100% of the recommended energy for children^{18–21} rather than the 120–150% recommended for CF^{22,23} and achieved by children who received the intensive intervention provided in the clinical trial.¹² Thus, our data suggests that standard of care, as it was being delivered during the time of the study was not achieving optimal growth outcomes in comparison to what could be achieved with more intensive and structured interventions.

In an exploratory analysis, no significant difference was found in FEV₁ over 27 months between children who participated in the clinical trial and those in the Comparison Sample. While the difference in FEV₁ decline of 2.04% predicted between the children in the clinical trial and those in the Comparison Sample, was not significant, it should be noted that this difference is similar to differences found between treatment and control groups in studies of pulmonary medications.²⁴ The current sample size was not powered for this outcome and

the clinical significance of this difference is not known; however, reports from the CFF Registry show individuals with better nutritional status (BMI percentile) have better pulmonary functioning as measured by FEV₁.⁵

The findings from this study add to our growing understanding that standard care nutrition support for children with CF may not be sufficient to optimize growth and nutritional status. Results from our previous clinical trial¹² demonstrated improvements in expected energy intake from baseline to 27 months later and maintenance from post-treatment of 120% of the estimated energy requirement (EER), which is in line with CF Foundation nutrition guidelines. While these results were compelling, without a comparison of growth in patients receiving standard of care during the same time period, the question of whether to attribute the improvements in BMI z-scores observed in the clinical trial to effects of the intervention or changes in standard care remained. Data from this study addresses this question and suggests that additional intensive and structured nutritional intervention, focused on increasing caloric intake, is beneficial for achieving better nutritional status for children with CF. These data would further compel health care providers to be more innovative in how more intensive intervention for nutrition can be delivered. As many face to face treatments for children with other health conditions are being evaluated for delivery over the internet²⁵⁻²⁷ this may be one modality worth exploring for families of children with CF whose primary barrier to receiving more intensive intervention is distance to the CF Center and the disruption frequent visits cause to parents' work and children's school schedules.

While compelling, our conclusions should be tempered by the limitations of the design: specifically, the use of a Comparison Sample drawn from the CFF Registry and not a randomized standard of care control group. Therefore, while we know the recommendations for nutrition treatment at the time of the clinical trial¹³ we do not know how or whether these were implemented and it is likely "standard of care" was not uniform across CF Centers. Also, while we attempted to match our Comparison Sample to our study sample on relevant characteristics, it would have been more rigorous to have a randomized control for these comparisons. Use of data from a national database is less standardized in terms of collection of anthropometric and lung function measures, and provides fewer opportunities to correct data errors which may occur. We minimized these issues by selecting a larger sample from the database and carefully cleaning the data for obvious errors.

This study adds to the literature by demonstrating, through direct comparison with a matched sample from the CFF Registry, that short-term, intensive nutrition intervention is more efficacious than standard of care for preventing decline in growth. Given the importance of weight and nutritional status for long-term health in CF;^{1,2,21} this study offers further support for the CF Foundations recommendation that children between 1 and 12 years of age with growth deficits receive intensive treatment with behavioral intervention in conjunction with nutrition counseling to promote weight gain.⁵ The key implication of these findings is the importance of modifying this intensive behavioral and nutritional intervention so that it that can be more widely disseminated across patients with CF.

ACKNOWLEDGMENTS

This study was supported by grants R01 DK50092 and D24 DK 059492 from the National Institutes of Health (L.J.S.). Additional support was provided by grant M01 RR0808 from the National Center for Research Resources of the NIH. The funders had no role in the design nor conduct of the study, in the collection, analysis, nor interpretation of the data, nor in the decision to publish, the preparation, review, nor approval of the manuscript. No honorarium or other form of payment was given to anyone to produce the manuscript. We also gratefully acknowledge the Cystic Fibrosis Foundation for use of the CFF Patient Registry.

Funding source: National Institutes of Health, Number R01 DK50092, Number D24 DK 059492; National Center for Research Resources of the NIH, Number M01 RR 0808.

REFERENCES

- Peterson ML, Jacobs DR, Milla CE. Longitudinal changes in growth parameters are correlated with changes in pulmonary functioning in children with cystic fibrosis. *Pediatrics*. 2003; 112:588–592. [PubMed: 12949289]
- Konstan MW, Butler SM, Wohl ME, Stoddard M, Matousek R, Wagener JS, et al. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *J Pediatr*. 2003; 142:624–630. [PubMed: 12838189]
- Konstan MW, Butler SM, Wohl ME, Stoddard M, Matousek R, Wagener JS, Johnson CA, Morgan WJ. Investigators and coordinators of the epidemiologic study of cystic fibrosis. *Am J Clin Nutr*. 2004; 80:1201–1206. [PubMed: 15531666]
- Sharma R, Florea VG, Bolger AP, Doehner W, Florea ND, Coats AJ, et al. Wasting as an independent predictor of mortality in patients with cystic fibrosis. *Thorax*. 2001; 56:746–750. [PubMed: 11562511]
- Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton HB. 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; 108:832–839. [PubMed: 18442507]
- Morton AM. Symposium 6: young people, artificial nutrition and transitional care. The nutritional challenges of the young adult with cystic fibrosis: transition. *Proc Nutr Soc*. 2009; 68:430–440. [PubMed: 19698200]
- 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; 116:1442–1450. [PubMed: 16322169]
- Stark LJ, Bowen AM, Tyc VL, Evans S, Passero MA. A behavioral approach to increasing calorie consumption in children with cystic fibrosis. *J Pediatr Psychol*. 1990; 15:309–326. [PubMed: 2380876]
- Stark LJ, Knapp L, Bowen AM, Powers SW, Jelalian E, Evans S, et al. Increasing calorie consumption in children with cystic fibrosis: replication with two year follow-up. *J Appl Behav Anal*. 1993; 26:435–450. [PubMed: 8307828]
- Stark LJ, Mulvihill MM, Powers SW, Jelalian E, Keating K, Creveling S, Byrnes-Collins B, Harwood I, Passero MA, Light M, Miller DL, Hovell MF. Behavioral intervention to improve calorie intake of children with cystic fibrosis: treatment vs. wait-list controls. *J Pediatr Gastroenterol Nutr*. 1996; 22:240–253. [PubMed: 8708877]
- Stark LJ, Opipari LC, Spieth LE, Jelalian E, Quittner AL, Higgins L, Mackner L, Byars K, Lapey A, Stallings VA, Duggan C. Contribution of behavior therapy to dietary treatment in cystic fibrosis: a randomized controlled study with two-year follow-up. *Behav Ther*. 2003; 34:237–258.
- Stark LJ, Quittner AL, Powers SW, Opipari-Arrigan L, Bean JA, Duggan C, Stallings VA. Randomized clinical trial of behavioral intervention and nutrition education to improve caloric intake and weight in children with cystic fibrosis. *Arch Pediatr Adolesc Med*. 2009; 163:915–921. [PubMed: 19805710]
- Ramsey B, Farrell P, Pencharz P. Nutritional assessment and management in cystic fibrosis: consensus conference. *Am J Clin Nutr*. 1992; 55:108–116. [PubMed: 1728810]

14. Cystic Fibrosis Foundation. Patient Registry Data 2008 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation; 2009.
15. Opiari-Arrigan L, Powers SW, Quittner AL, Stark LJ. Mealtime problems predict outcome in clinical trial to improve nutrition in children with CF. *Pediatr Pulmonol*. 2010; 45:78–82. [PubMed: 19953660]
16. Cameron, N. The methods of auxological anthropometry. In: Falkner, F.; Tanner, J., editors. *Human growth*. New York: Plenum Press; 1986. p. 3–43.
17. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BGJ. Pulmonary functioning between 6 and 18 years of age. *Pediatr Pulmonol*. 1993; 15:75–88. [PubMed: 8474788]
18. Anthony H, Bihs J, Phelan P, Paxton S. Relation between dietary intake and nutritional status in cystic fibrosis. *Arch Dis Child*. 1998; 78:443–447. [PubMed: 9659091]
19. Stark LJ, Jelalian E, Mulvihill MM, Powers SW, Bowen AM, Spieth LE, Keating K, Evans S, Creveling S, Harwood I, Passero MA, Hovell MF. Eating in preschool children with cystic fibrosis and healthy peers: behavioral analysis. *Pediatrics*. 1995; 95:210–215. [PubMed: 7838637]
20. Stark LJ, Mulvihill MM, Jelalian E, Bowen AM, Powers SW, Tao S, Creveling S, Passero MA, Harwood I, Light M, Lapey A, Hovell MF. Descriptive analysis of eating behavior in school-age children with cystic fibrosis and healthy control children. *Pediatrics*. 1997; 99:665–671. [PubMed: 9113942]
21. Zemel BS, Jawad AF, Fitzsimmons S, Stallings VA. Longitudinal relationship among growth, nutritional status, and pulmonary function in children with cystic fibrosis: analysis of the Cystic Fibrosis Foundation National CF Patient Registry. *J Pediatr*. 2000; 137:374–380. [PubMed: 10969263]
22. Dodge JA. Nutritional requirements in cystic fibrosis: a review. *J Pediatr Gastroenterol Nutr*. 1988; 7:S8–S11. [PubMed: 3042941]
23. Hubbard VS. Nutritional considerations in cystic fibrosis. *Semin Respir Med*. 1985; 6:308–313.
24. Konstan MW, Schluchter MD, Xue W, Davis PB. Clinical use of Ibuprofen is associated with slower FEV1 decline in children with cystic fibrosis. *Am J Respir Crit Care Med*. 2007; 176:1084–1089. [PubMed: 17872492]
25. Lelieveld OT, Armbrust W, Geertzen JH, de Graaf I, van Leeuwen MA, Sauer PJ, et al. Promoting physical activity in children with juvenile idiopathic arthritis through an internet-based program: results of a pilot randomized controlled trial. *Arthritis Care Res*. 2010; 62:697–703.
26. Palermo TM, Wilson AC, Peters M, Lewandowski A, Somhegyi H. Randomized controlled trial of an Internet-delivered family cognitive-behavioral therapy intervention for children and adolescents with chronic pain. *Pain*. 2009; 146:205–213. [PubMed: 19695776]
27. Ritterband LM, Ardalan K, Thorndike FP, Magee JC, Saylor DK, Cox DJ, Sutphen JL, Borowitz SM. Real world use of an Internet intervention for pediatric encopresis. *J Med Internet Res*. 2008; 10:e16. [PubMed: 18653440]

TABLE 1

Characteristics (Mean (SD)) of Children in the Clinical Trial and the CFF Registry Comparison Sample

	Clinical Trial Group (N = 67)	Comparison Sample (N = 346)
Age (months)	91.20 (33.17)	89.03 (32.92)
Gender	52% male (n = 35)	54% male (n = 186)
Race	97% white (n = 65)	97% white (n = 336)
Baseline BMI z-score	-0.63 (0.94)	-0.47 (0.85)
Baseline BMI z-score ≥ 0	22.4% (n = 15)	30.9% (n = 107)
Baseline FEV ₁ percent predicted	89.95 (17.79) (n = 36)	87.71 (20.16) (n = 173)