Behavioral and Nutritional Treatment for Preschool-Aged Children With Cystic Fibrosis
A Randomized Clinical Trial

Scott W. Powers, PhD, ABPP; Lori J. Stark, PhD; Leigh A. Chamberlin, RD, MED; Stephanie S. Filigno, PhD; Stephanie M. Sullivan, BS; Kathleen L. Lemanek, PhD; Jennifer L. Butcher, PhD; Kimberly A. Driscoll, PhD; Cori L. Daines, MD; Alan S. Brody, MD; Teresa Schindler, MS, RDN; Michael W. Konstan, MD; Karen S. McCoy, MD; Samya Z. Nasr, MD, CPI; Robert G. Castile, MD, MS; James D. Acton, MD; Jamie L. Wooldridge, MD; Babette S. Zemel, PhD; John P. Clancy, MD

IMPORTANCE Evidence-based treatments that achieve optimal energy intake and improve growth in preschool-aged children with cystic fibrosis (CF) are a critical need.

OBJECTIVE To test whether behavioral and nutritional treatment (intervention) was superior to an education and attention control treatment in increasing energy intake, weight z (WAZ) score, and height z (HAZ) score.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial included 78 children aged 2 to 6 years (mean age, 3.8 years) with CF and pancreatic insufficiency (intervention, n = 36 and control, n = 42). The study was conducted at 7 CF centers between January 2006 and November 2012; all 78 participants who met intent-to-treat criteria completed through follow-up.

INTERVENTIONS Behavioral intervention combined individualized nutritional counseling targeting increased energy intake and training in behavioral child management skills. The control arm provided education and served as a behavioral placebo controlling for attention and contact frequency. Both treatments were delivered in person or telehealth (via telephone). Sessions occurred weekly for 8 weeks then monthly for 4 months (6 months). Participants then returned to standard care for 1 year, with 12-month follow-up thereafter.

MAIN OUTCOMES AND MEASURES Changes in energy intake and WAZ score were examined from pretreatment to posttreatment (6 months) and change in HAZ score was assessed pretreatment to follow-up (18 months). Covariates included sex, Pseudomonas aeruginosa status at baseline, and treatment modality (in person vs telehealth).

RESULTS At baseline, mean (SD) energy intake was 1462 (329) kcals/d, WAZ score was −0.44 (0.81), and HAZ score was −0.55 (0.84). From pretreatment to posttreatment, the intervention increased daily energy intake by 485 calories vs 58 calories for the control group (adjusted difference, 431 calories; 95% CI, 282 to 581; \( P < .001 \)) and increased the WAZ score by 0.12 units vs 0.06 for the control (adjusted difference, 0.09; 95% CI, −0.06 to 0.24; \( P = .25 \)). From pretreatment to follow-up, the intervention increased the HAZ score by 0.09 units vs −0.02 for the control (adjusted difference, 0.14 units; 95% CI, 0.001 to 0.27; \( P = .049 \)). Measured treatment integrity and credibility were high for both groups.

CONCLUSIONS AND RELEVANCE Behavioral and nutritional intervention improved energy intake and HAZ score outcomes but not WAZ score outcomes. Our results provide evidence that behavioral and nutritional treatment may be efficacious as a nutritional intervention for preschoolers aged 2 to 6 years with CF and pancreatic insufficiency.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Scott W. Powers, PhD, ABPP, Division of Behavioral Medicine and Clinical Psychology, Center for Child Behavior and Nutrition Research and Training, 3333 Burnet Ave, MLC 3015, Cincinnati, OH 45229-3039 (scott.powers@cchmc.org).
Early childhood is a critical time for optimizing growth in patients with cystic fibrosis (CF). A prospective observational study using the US Cystic Fibrosis Foundation (CFF) Patient Registry demonstrated that attainment of higher weight-for-age percentiles and height-for-age percentiles at age 4 years was associated with improved survival through age 18 years. The CFF is finalizing new guidelines for the care of preschool-aged children (ages 2-5 years). One of the 3 focal areas is nutrition and a major recommendation is the critical need for evidence from randomized clinical trials to inform CF care in this age group.

Meeting CFF care guidelines is challenging for families of toddlers and preschool-aged children. Specifically, parents find it difficult to meet the increased energy intake goals for children with CF. Meal-time behaviors in early childhood can impede attainment of the increased energy intake. Behavioral and nutritional treatment sets energy intake goals and addresses meal-time behaviors and has shown efficacy in school-aged children with CF in a multicenter clinical trial. Pilot single-center clinical investigations have suggested that this approach could help toddlers and preschool-aged children with CF to achieve energy intake goals. To advance care during this critical period of child development, a multicenter randomized clinical trial is needed that evaluates an early intervention that targets eating behaviors and helps to improve weight-for-age and height-for-age status in preschool-aged children with CF.

The objective of this randomized clinical trial was to test whether behavioral and nutritional treatment (BEH) was superior to an education and attention control treatment (control) in children aged 2 to 6 years diagnosed as having CF and pancreatic insufficiency (PI). It was hypothesized a priori that compared with the control intervention, BEH treatment would lead to (1) greater energy intake, (2) improvement in weight z (WAZ) score from pretreatment to posttreatment (a 6-month period), and (3) improvement in height z (HAZ) score from pretreatment to follow-up assessment (an 18-month period). Energy intake and WAZ score were also examined between groups in a post hoc fashion from pretreatment to follow-up.

Methods

Participants

Between January 2006 and November 2012, children with CF and PI aged 2 to 6 years participated in this multicenter clinical trial from 7 accredited CF centers. The study, titled Families Understanding Nutrition (The FUN Study), was approved by the institutional review board at each site and parents/guardians provided written informed consent. Inclusion criteria included CF diagnosis based on meeting 2 of the following criteria: sweat chloride by quantitative pilocarpine electroforephoresis of 60 mEq/L or greater, 2 clinical features consistent with CF, or genetic testing demonstrating mutations associated with CF; confirmation of PI based on fecal elastase of less than 100 μg per gram of stool (Kaleida Health Women and Children’s Hospital Laboratory, Buffalo, New York); at least 6 months post-CF diagnosis; and no restrictions in consuming a high-fat diet. Exclusion criteria included WAZ score greater than 1.0 (age and sex adjusted) determined using the Centers for Disease Control and Prevention Anthropic Software Program (2000 data, Division of Nutrition, Centers for Disease Control and Prevention); current use of supplemental nutrition through enteral or parenteral feeding; diagnosis of other conditions or use of current medication known to affect growth; diagnosis of developmental delay; genetic potential for height as acceptable according to the 2002 consensus conference guidelines; and dietary intake exceeding 140% of the average estimated energy requirement (EER; based on sex, age, and active physical activity level; and intake assessed using 3-day diet recall).

Recruitment and Randomization

Children were identified from a clinical database and medical record review at each CF center. Families who agreed to participate provided informed written consent and were screened for eligibility. Eligible participants were randomized into 1 of 2 treatment groups: BEH or control using a permuted block design for assignment using 2 strata (WAZ score ≤ −1.0 or −1.0 < WAZ score ≤ 1.0). Randomization was based on a computer-generated predetermined schedule produced by a biostatistician and concealed from study personnel until baseline assessment measures were complete. Randomization assignment was supplied via secure email to the study therapist when the participant had met eligibility criteria. Families were aware that there were 2 different behavioral/educational treatments but were unaware of the differences of the specific components of each treatment.

Study Design and Treatments

The BEH and control treatments were provided as in-person or telehealth (telephone) delivery. After completing the weekly and monthly interventions, participants returned to standard care and a 12-month follow-up assessment was conducted (18 total months from baseline assessment to follow-up assessment).

At a Glance

- Preschool-aged children with cystic fibrosis need treatments to achieve optimal energy intake and improve growth.
- This multicenter randomized clinical trial tested the impact of behavioral and nutritional treatment on improving energy intake and growth in young children with cystic fibrosis and pancreatic insufficiency.
- The behavioral and nutritional treatment improved energy intake by 485 calories per day and met the target of 140% of dietary recommended intake for an active preschool-aged child.
- The behavioral and nutritional treatment improved height z score by 0.09 units over 18 months.
- Change in weight was not superior to the control treatment (behavior = 0.12-unit and control = 0.06-unit increase over 6 months).
- Evidence from clinical trials is needed to inform practice, particularly in this age group of children with cystic fibrosis.
was unable to consistently record the child’s daily intake, areg-
diet diary throughout the weekly sessions and for 7 days prior
result in energy intake increases targeted at 140% EER.
their behavior and nutrition curriculum (eg, regular self-
be calculated based on CFF care guidelines by the CF center team
during the 6 months of trial intervention.
were followed by 4 monthly treatment sessions focused on
maintenance of treatment gains.

Table 1. Session-by-Session Content Summary for BEH Treatment and Education and Attention Control Treatment

<table>
<thead>
<tr>
<th>Session</th>
<th>BEH Treatment</th>
<th>Education and Attention Control Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weekly Sessions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Rationale for using BEH to meet CFF EER nutrition recommendations for this age group; CF physiology: increased energy needs; how to keep a food record</td>
<td>Setting a routine meal and snack schedule; dosage and timing of enzymes to maximize absorption; and managing sick days</td>
</tr>
<tr>
<td>2</td>
<td>Focus on increasing calories at snacks; setting snack calorie goal and teaching parents to use differential attention (praise and ignoring) to encourage eating</td>
<td>Energy needs and CF; carbohydrate, fat, and protein: food sources and how each are used by the body; and food guide pyramid</td>
</tr>
<tr>
<td>3</td>
<td>Setting breakfast goal; review of differential attention and how to use at breakfast, introducing a 20-min meal time and how to use contingency management (if, then rule) to reward meeting the calorie goal</td>
<td>Respiratory and infection control: how germs are spread, proper hand washing, and the spread of infection between individuals with CF; Pseudomonas aeruginosa; burkholderia cepacia</td>
</tr>
<tr>
<td>4</td>
<td>Practice meal: providing coaching to parents in use of differential attention and limit setting during a practice meal with their child; review symptoms of enzyme inadequacy. This session was delivered in person to telehealth participants</td>
<td>Fat and water-soluble vitamins and minerals: sources and uses in the body; essential fatty acid deficiency</td>
</tr>
<tr>
<td>5</td>
<td>Lunch: setting lunch calorie goal and applying behavioral child-management skills across all meals; problem solving of specific ongoing behavioral concerns at meals individualized for each family (eg, pace of eating, food refusal, stalling, leaving the table, and tantrums at the table)</td>
<td>Methods of cleaning and maintaining respiratory equipment</td>
</tr>
<tr>
<td>6</td>
<td>Dinner: setting dinner calorie goal, bringing all the skills together, and using behavioral skills to encourage child to try new foods; neophobia</td>
<td>Review of current medical regimen/prescribed treatment plan: enzymes, vitamins, steroids, antibiotics, airway clearance, and nutrition</td>
</tr>
<tr>
<td>Monthly Sessions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Maintaining caloric intake at each meal; behavioral management skills with any new/ongoing meal-time problems; managing sick days to support weight gain; and managing snack intake when away from home</td>
<td>Language, social, and emotional development</td>
</tr>
<tr>
<td>9</td>
<td>Maintaining caloric intake at each meal; behavioral management skills with any new/ongoing meal-time problems; managing sick days to support weight gain; and managing snack intake when away from home</td>
<td>Vehicle and bicycle safety: use of bicycle helmets and car seats</td>
</tr>
<tr>
<td>10</td>
<td>Maintaining caloric intake at each meal; behavioral management skills with any new/ongoing meal-time problems; managing sick days to support weight gain; and managing snack intake when away from home</td>
<td>Home and outdoor safety: burn prevention, water safety, playground safety, and firearm safety</td>
</tr>
<tr>
<td>11</td>
<td>Maintaining caloric intake at each meal; behavioral management skills with any new/ongoing meal-time problems; managing sick days to support weight gain; and managing snack intake when away from home</td>
<td>Review of current medical regimen/prescribed treatment plan: enzymes and nutritional guidelines for toddlers to preschool-aged children</td>
</tr>
</tbody>
</table>

The BEH treatment combined individualized nutritional counseling that targeted increasing energy and fat intake and parent training in behavioral child-management skills based on social learning theory to improve meal-time behaviors. The appropriate dosage and timing of pancreatic enzyme replacement therapy plus regular meal schedule were monitored. Calorie and fat intake goals were set to meet the minimum 140% EER, with 40% of calories derived from fat. Parent management skills were taught to address common meal-time behavioral challenges of toddlers and preschool-aged children (Table 1). The rationale was that weekly BEH intervention would result in energy intake increases targeted at 140% EER. Thereafter, BEH intervention once per month would support the child and family to continue at this level of intake throughout the remainder of the 6-month treatment. Parents kept 7-day diet diaries throughout the weekly sessions and for 7 days prior to each monthly session. In unique situations when a family was unable to consistently record the child’s daily intake, a registered diettian contacted the family by telephone to collect the information through 3 24-hour food recalls (2 weekdays and 1 weekend day).22,23

The education and attention control treatment provided education and served as a behavioral placebo in terms of controlling for attention and contact frequency provided in the BEH treatment group. Families were provided with information including general nutrition, enzyme therapy, respiratory infection control, and typical child development anticipatory guidance and safety for preschool-aged children. While general nutritional information consistent with the CFF Consensus Conference Guidelines was included in the control treatment, specific techniques that were central components of our behavior and nutrition curriculum (eg, regular self-monitoring via diet diary completion: setting specific meal-by-meal energy intake goals and providing graphical feedback on progress; and integrating behavioral techniques to reach energy intake and food choice goals) were not compo-
nents of the control treatment. Families kept 7-day diet diaries following the baseline visit and the week before assessment at month 6 (posttreatment) and month 18 (follow-up) visits. At each session, a 24-hour dietary recall was conducted. Content for each control session is summarized in Table 1.

Outcome Measures
Energy intake was assessed using 7-day diet diaries recorded by parents. All families received kitchen measuring tools including an electronic food scale, and they received 60-minute training on how to keep a weighed food record including how to measure food and complete the diet diary via written instructions, modeling, and active practice. Families were instructed to record information on the diet diaries after each snack and meal. All diet diaries were reviewed for completeness and accuracy by a registered dietitian, who also completed clarifications when needed. The data were analyzed by a blinded, independent pediatric research registered dietitian using Nutrition Data System for Research software versions 2006 through 2011 developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis. Final calculations were completed using Nutrition Data System for Research version 2011. The Nutrition Data System for Research time-related database updates analytic data while maintaining nutrient profiles true to the version used for data collection. Data were examined as average kilocalories per day over a 7-day period at study end points, as well as the percentage estimated energy expenditure (based on sex, age, and an active physical activity level).

Weight and height were assessed by staff trained by an expert in anthropology in children using standardized procedures and blinded to the child’s treatment group assignment. Children were measured in minimal clothing and without shoes to obtain height and weight. The child’s weight in kilograms, measured to the nearest 100 g, was obtained using a digital scale (Scaletronix Inc). The child’s height was obtained using a stadiometer (Holtain) and measured to the nearest millimeter. Height was obtained standing unless the child was unwilling to stand, then a supine measurement was obtained (n = 1 at baseline; 2 at posttreatment; and 0 at follow-up). All measurements were obtained in triplicate and the mean used for analyses. The WAZ and HAZ scores were calculated using the mean measurement and the Centers for Disease Control and Prevention Anthropometric Software Program.

Other Measures
Treatment Integrity
Postdoctoral psychology fellows conducted the BEH sessions using a structured treatment manual. Fellows were trained and supervised by a licensed clinical psychologist with specialized experience in behavioral management. The control sessions were conducted using a structured treatment manual by a protocol-trained professional (eg, registered dietitian, psychology postdoctoral fellow, or clinical research professional) under the supervision of a registered dietitian. Treatment integrity and accuracy were evaluated by independent evaluators using session video or audi-tapes and specific checklists to obtain a percentage accuracy score. Therapist drift was addressed by reinstruction of staff if quarterly review showed less than 80% accuracy for any given session.

Treatment Credibility
Parents completed an 8-item measure of treatment credibility at the conclusion of the pretreatment session (baseline), posttreatment, and at follow-up to document whether each of the treatment groups had equivalent credibility. Each item was scored on a scale of 0 (not confident/not relevant at all) to 8 (very confident/relevant) regarding whether the nutritional and CF care information provided was useful in helping to attain nutritional goals.

Detection of Pseudomonas aeruginosa at baseline was assessed by obtaining an oropharyngeal culture and analyzed by a central laboratory (Cincinnati Children’s Hospital Medical Center, Cincinnati, Ohio) to ensure consistency.

Statistical Analysis
Analyses of WAZ and HAZ change scores were carried out within the PROC GLM procedure (SAS Institute Inc) using an analysis of covariance model with sex, P aeruginosa status at baseline, treatment modality, and baseline value of the corresponding outcome variable as covariates. Some data were missing for energy intake (n = 3 baseline; 13 posttreatment; and 14 at follow-up), and thus the PROC MIXED procedure (SAS) with maximum likelihood estimation was used to analyze this outcome with time as a repeated measures factor; no group main effect at baseline for energy intake; and sex, baseline P aeruginosa status, and treatment modality as covariates in the statistical model (see the eAppendix in Supplement 2 for a more complete description of the statistical analysis plan).

Results
Participant Flow and Baseline Characteristics
The flow of the participants through the trial appears in the Figure. Of the 78 participants who met intent-to-treat criteria (defined as attending the first treatment session), 36 were randomly assigned to the BEH and 42 to the control interventions. This represents 48% of families assessed for eligibility and approached to participate and 76% of those who consented to participate.

At baseline, there were no statistically significant differences between the groups on demographics(Table 2).

Energy Intake Change From Baseline to Posttreatment
At posttreatment, the BEH group was consuming a mean (SD) of 1947 (459) kcal/d and the control group’s energy intake was 1529 (387) kcal/d. The group mean difference in change scores was 431 (P < .001) (Table 3).

WAZ Score Change From Baseline to Posttreatment
At posttreatment, the BEH group had a mean (SD) WAZ score of −0.24 (0.76) and the control group average WAZ score was −0.45 (0.77). The group mean difference in change scores for WAZ was 0.09 (P = .25) (Table 3).
HAZ Score Change From Baseline to Follow-up
At follow-up, the BEH group had a mean (SD) HAZ score of $-0.30 (0.88)$ and the control group average HAZ score was $-0.71 (0.86)$. The group mean difference in change scores for HAZ was $0.14 (P = .049)$ (Table 3).

Post Hoc Analyses
Energy Intake Change From Baseline to Follow-up
At follow-up, the BEH group was consuming a mean (SD) of $1960 (440)$ kcal/d and the control group's energy intake was $1739 (416)$ kcal/d. The group mean difference in changes scores was $239 (P = .02)$ (Table 3).

WAZ Score Change From Baseline to Follow-up
At follow-up, the BEH group had a mean (SD) WAZ score of $-0.22 (0.83)$ and the control group average WAZ score was $-0.40 (0.96)$. The group mean difference in change scores for WAZ was $0.07 (P = .61)$ (Table 3).

Treatment Integrity/Fidelity
The BEH and control treatments were delivered as planned. Independent assessment of fidelity to the treatment manuals demonstrated 93% accuracy and there was no evidence of contamination across the study groups (ie, control did not receive any BEH content).

Treatment Credibility/Satisfaction
With a score of 8 representing the highest level of credibility/satisfaction, the BEH and control interventions were viewed as highly credible throughout the trial. At baseline, both groups were considered equally credible (BEH, 7.5 and control, 7.3). After treatment, credibility remained high in both groups; however, a separation was seen, with the BEH group showing more credibility and satisfaction at post-treatment (BEH, 7.6 and control, 6.4). Credibility was maintained at a high level at follow-up (BEH, 6.8 and control, 6.5), with both groups considered equally credible at this point.

Safety
The BEH and control treatments were well tolerated. There were no serious adverse events related to the study treatments. Adverse events were generally expected given the disease of CF (eg, pulmonary exacerbations) (Table 4).
Discussion

To our knowledge, this is the first multicenter randomized clinical trial that tested the impact of a BEH treatment on improving energy intake and growth in young children with CF and PI (ages 2-6 years). Our BEH intervention was designed to be applied as early growth failure prevention (e.g., including patients with $z$ scores greater than 0 and up to $+1.0$), as well as a treatment for preschool-aged children who had clinically significant growth faltering (e.g., $z$ scores of $≤−0.3$). A comparison group that received education and

Table 2. Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (N = 78)</th>
<th>Education and Attention Control Treatment (n = 42)</th>
<th>Behavioral and Nutritional Treatment (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>3.8 (1.3)</td>
<td>3.7 (1.3)</td>
<td>3.8 (1.2)</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>43 (55)</td>
<td>23 (55)</td>
<td>20 (56)</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>77 (99)</td>
<td>42 (100)</td>
<td>35 (97)</td>
</tr>
<tr>
<td>Ethnicity (% non-Hispanic)</td>
<td>75 (96)</td>
<td>40 (95)</td>
<td>35 (97)</td>
</tr>
<tr>
<td>Maternal education $^c$</td>
<td>Less than high school</td>
<td>2 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td></td>
<td>High school graduate or obtained general educational development diploma</td>
<td>21 (28)</td>
<td>10 (26)</td>
</tr>
<tr>
<td></td>
<td>Some college or junior college</td>
<td>26 (35)</td>
<td>14 (36)</td>
</tr>
<tr>
<td></td>
<td>College graduate</td>
<td>25 (34)</td>
<td>14 (36)</td>
</tr>
<tr>
<td>Paternal education $^d$</td>
<td>Less than high school</td>
<td>3 (4)</td>
<td>2 (5)</td>
</tr>
<tr>
<td></td>
<td>High school graduate or obtained general educational development diploma</td>
<td>22 (30)</td>
<td>9 (23)</td>
</tr>
<tr>
<td></td>
<td>Some college or junior college</td>
<td>22 (30)</td>
<td>14 (36)</td>
</tr>
<tr>
<td></td>
<td>College graduate</td>
<td>26 (36)</td>
<td>14 (36)</td>
</tr>
<tr>
<td>Household income $^e$</td>
<td>6.4 (2.0)</td>
<td>6.5 (2.1)</td>
<td>6.4 (1.9)</td>
</tr>
<tr>
<td>Detection of Pseudomonas aeruginosa at baseline</td>
<td>4 (5)</td>
<td>1 (2)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Treatment modality (% in person)</td>
<td>41 (53)</td>
<td>22 (52)</td>
<td>19 (53)</td>
</tr>
</tbody>
</table>

Abbreviations: HAZ, height $z$; WAZ, weight $z$.

$^a$P > .22 for all baseline group comparisons.

$^b$Seventy-eight met intent to treat, defined as having completed visits beyond baseline.

$^c$For maternal education, overall, n = 74; control, n = 39; and behavioral and nutritional treatment, n = 35.

$^d$For paternal education, overall, n = 73; control, n = 39, and behavioral and nutritional treatment, n = 34.

$^e$Income was divided into 9 categories (6 = $35 000-$49 999/year, 7 = $50 000 to $74 999/year).

Table 3. Changes in Energy Intake, Weight Z Score, and Height Z Score $^a$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Behavioral and Nutrition Treatment (n = 36)</th>
<th>Education and Attention Control Treatment (n = 42)</th>
<th>Group Mean Difference in Change (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake, kcal/db $^c$</td>
<td>1462 (330)</td>
<td>1947 (459)</td>
<td>485 (355)</td>
<td>1461 (332)</td>
</tr>
<tr>
<td>Weight $z$ score</td>
<td>$−0.36 (0.75)$</td>
<td>$−0.24 (0.76)$</td>
<td>$0.12 (0.40)$</td>
<td>$0.51 (0.85)$</td>
</tr>
<tr>
<td>Height $z$ score</td>
<td>$−0.39 (0.85)$</td>
<td>$−0.30 (0.88)$</td>
<td>$0.09 (0.26)$</td>
<td>$−0.69 (0.82)$</td>
</tr>
<tr>
<td>Energy intake, kcal/db $^c$</td>
<td>1462 (330)</td>
<td>1960 (440)</td>
<td>545 (304)</td>
<td>1461 (332)</td>
</tr>
<tr>
<td>Weight $z$ score</td>
<td>$−0.36 (0.75)$</td>
<td>$−0.22 (0.83)$</td>
<td>$0.15 (0.48)$</td>
<td>$−0.51 (0.85)$</td>
</tr>
</tbody>
</table>

$^a$All change variables are calculated as change from baseline. All group mean differences in change account for missing data using maximum likelihood estimation, when necessary, and are model based, which yields an adjusted difference, controlling for covariates. Least-square estimation was used when no missing data were present (this approach is equivalent to maximum likelihood for our models in this special case).

$^b$Tests were post hoc exploratory comparisons.
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Table 4. Frequency of Participants Reporting Any Adverse Events by Treatment Group and Body System*

<table>
<thead>
<tr>
<th>Body System</th>
<th>Education and Attention Control Treatment (n = 42)</th>
<th>Behavioral and Nutrition Treatment (n = 36)</th>
<th>P Value for χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive*</td>
<td>21 (50)</td>
<td>29 (81)</td>
<td>.05*</td>
</tr>
<tr>
<td>Immune</td>
<td>19 (45)</td>
<td>12 (33)</td>
<td>.28</td>
</tr>
<tr>
<td>Respiratory</td>
<td>29 (69)</td>
<td>23 (64)</td>
<td>.63</td>
</tr>
<tr>
<td>Head, ears, eyes, nose, and throat</td>
<td>34 (81)</td>
<td>24 (67)</td>
<td>.15</td>
</tr>
<tr>
<td>Other</td>
<td>11 (26)</td>
<td>13 (36)</td>
<td>.34</td>
</tr>
</tbody>
</table>

*Based on self-report; only body systems with 5 or more adverse events were reported.

**Symptoms assessed using questionnaires at each treatment session and typically reported as abdominal pain or stool issue. Clinical adjustment of enzyme replacement therapy is part of the protocol and implemented by a blinded member of the cystic fibrosis care team.

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controlled for therapist attention, as well as number and time of contacts, was used. As predicted, BEH treatment delivered either in person or via telehealth led to increased energy intake and improvement in height. Change in weight was not statistically different from the control treatment. Measured fidelity to treatment indicated that both interventions were delivered as intended. Treatment credibility assessments demonstrated both the BEH and control interventions were viewed favorably by the families. Adverse event monitoring indicated that BEH treatment was safe and well tolerated.

Improvement in height z score in young children with CF has the potential to impact clinical outcomes and survival. Beker et al39 demonstrated in a longitudinal study using data from the CFF Patient Registry that stature, more than weight, was a significant prognostic indicator of survival. Their findings suggested that height for age be used as an effective screening assessment and called for clinicians, families, and patients to work together to maximize linear growth through medical and nutritional intervention. Yen et al3 specifically examined the relation between nutritional status early in life and later lung function, complications of CF, and survival. Using a sample of 3142 patients from the CFF Patient Registry from 1989 to 1992, they found that greater weight for age at 4 years was associated with greater height for age, better pulmonary function, fewer complications (i.e., acute pulmonary exacerbations and days in hospital), and better survival through age 18 years. When stature was examined as a predictor of outcomes at age 18 years, children at age 4 years with higher height-for-age percentiles had fewer pulmonary exacerbations, spent fewer days in the hospital, and had better survival at age 18 years. They concluded that a survival advantage appears to emerge in the first decade of life for children achieving better height status. This highlights the potential impact of our results for BEH treatment when provided to children aged 2 to 6 years.

Cystic fibrosis is a systemic disorder, with early-life nutritional, gastrointestinal, and respiratory manifestations. There are numerous complex interactions that contribute to the disease course in CF, including cystic fibrosis transmembrane regulator genotype, airway infection, the care environment, modifying genes, and the application of evidence-based interventions (CFF pulmonary guidelines and CFF nutritional guidelines).34-35 Optimizing growth is a key goal in the preschool population, and indeed early diagnosis and nutritional intervention through newborn screening has improved growth throughout childhood.34,35 The results of the current trial are significant because they present a successful intervention that improves caloric intake and enhances growth in a CF preschool-age population reflecting the diversity of growth parameters commonly encountered in the clinic. The BEH intervention is broadly applicable to patients with and without growth failure, and the multicenter design portends its generalizability and portability. As the CF community seeks to determine the role of novel respiratory and systemic interventions in the young CF population (clinicaltrials.gov Identifier: NCT01705145 and the study by Rosenfeld et al36), the results reported here provide data supporting an additional intervention to positively influence the growth outcomes associated with survival.

A limitation of our trial may be the broad range of participants’ nutritional status allowed by the inclusion criterion. The multicenter randomized trial conducted by Stark et al15 enrolled children with CF aged 4 to 12 years and limited participants to those who were below the 40th percentile weight for age. We expanded the weight range to include up to a +1.0 WAZ score because our focus was on early intervention to maximize nutritional status in younger children. However, this design may have impacted the magnitude of change possible at a group mean level on change in WAZ score endpoint.

Of the families who were approached about participation (excluding participants who consented but were found to not meet inclusion criteria), about 60% were randomized. This participation rate may limit generalizability of the treatment effects to those who are willing and able to engage in weekly treatment.

Conclusions

When compared with a control group that included education and equal therapist attention, BEH treatment focused on preschool-aged children with CF and PI resulted in significantly improved energy intake and HAZ scores but not WAZ scores. Given the clinical impact of optimal nutritional status in young children with CF and the clear implications for better health over time, the results of this multicenter trial provide support to include this treatment as part of evidence-based care to ensure optimal nutritional and growth status in preschool-aged children with CF.
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