A Lipid-Based Nutrient Supplement but Not Corn-Soy Blend Modestly Increases Weight Gain among 6- to 18-Month-Old Moderately Underweight Children in Rural Malawi

Chrissie Thakwalakwa, Per Ashorn, John Phuka, Yin Bun Cheung, André Briend, Taneli Puulamainen, and Kenneth Maleta

1Department of International Health, University of Tampere Medical School, Tampere 33014, Finland; 2College of Medicine, University of Malawi, Blantyre P/Bag 360, Malawi; 3Singapore Clinical Research Institute, 138669, Singapore; 4Department of Paediatrics, Tampere University Hospital, Tampere 33014, Finland; and 5National Public Health Institute, Helsinki 30, Finland

Abstract

Although widely used, there is little information concerning the efficacy of corn-soy blend (CSB) supplementation in the treatment of moderate underweight in African children. Lipid-based nutrient supplements (LNS), which have proven to be beneficial treatment for severely wasted children, could offer benefits to less severely affected individuals. We conducted a clinical randomized trial to determine whether LNS or CSB supplementation improves weight gain of moderately underweight children. A total of 182 underweight [weight-for-age Z-score (WAZ) < −2] 6- to 15-mo-old children were randomized to receive for 12 wk a ration of 43 g/d LNS or 71 g/d CSB, providing 1189 and 921 kJ, respectively, or no supplementation (control). The primary outcome was weight change; secondary outcomes included changes in anthropometric indices, hemoglobin levels, and morbidity. The body weight increases (mean ± SD) did not differ and were 620 ± 470, 510 ± 350, and 470 ± 350 g in the LNS, CSB, and control groups, respectively (P = 0.11). Compared with controls, infants and children in the LNS group gained more weight [mean (95% CI) = 150 g (0–300 g); P = 0.05] and had a greater increase in WAZ (0.33 (−0.02–0.65); P = 0.04). Weight and WAZ changes did not differ between the control and CSB groups. In exploratory stratified analysis, the weight increase was higher in the LNS group compared with the control group among those with lower initial WAZ [250 g (60–430 g); P = 0.01]. Supplementation with LNS but not CSB modestly increases weight gain among moderately underweight children and the effect appears most pronounced among those with a lower initial WAZ. J. Nutr. 140: 2008–2013, 2010.

Introduction

Childhood undernutrition is an important public health and development problem in low- and middle-income countries. Children who are mildly underweight with weight-for-age Z-scores (WAZ) between −1.0 and −2.0 have twice the risk of death of children with WAZ > −1.0. The relative risk increases to 5 and 8 times for those moderately underweight (WAZ between −2.0 and −3.0) and severely underweight (WAZ < −3.0), respectively (1). In Malawi, 22–48% of children are undernourished by the age of 18 mo (2) and moderately underweight is the most common presentation (2,3). The epidemiology of undernutrition in Malawi necessitates emphasis on prevention or early home-based management of children who have developed signs of malnutrition but who do not yet require hospitalization. Thus, there is need to develop and test new, inexpensive, and effective food supplements that could easily be used at the community level.

Cereal and legume mixtures that resemble the indigenous diet and are prepared in a manner similar to staple food are recommended for supplementary feeding of moderately undernourished children (4). In Malawi, porridge made of maize and soy flour, corn-soy blend (CSB), is promoted both as a complementary food for primary prevention of undernutrition as well as supplemental feeding for moderately undernourished...
children. However, only a few studies have evaluated the effect of supplemental fortified blended foods such as CSB on growth or other health outcomes (5,6); hence, the efficacy and effectiveness of CSB remain to be conclusively demonstrated.

Recently, therapeutic feeding with lipid-based nutrient supplements (LNS), such as Ready-to-Use Therapeutic Food (7,8), has become the standard of care for severely malnourished infants and young children in low-income countries (9–12). LNS are energy-dense pastes that typically contain protein, carbohydrates, and micronutrients embedded in a lipid base (7). Their manufacture is flexible and the exact recipe and energy contents can be tailored to specific needs, such as those of and nutrient a fast-growing child or those recovering from mild or moderate undernutrition.

In 2 recent trials from Malawi, certain LNS products were suggested to modestly increase weight gain among moderately wasted or underweight individuals (13,14). A 3rd Malawan trial documented no differences in mean weight or length gain among underweight 6- to 15-mo-old children supplemented for 12 wk with either 50 g/d LNS or an isoenergetic supply of CSB (15). The latter trial was conducted immediately after the harvest season when food was plentiful and included no unsupplemented control children. Because of this, it was not possible to determine conclusively the effect of either of the supplements compared with no food supplementation and effect on growth during the lean season of the year before harvest. To address these questions, we conducted a 3-arm clinical trial in which underweight infants and young children received no supplementation, CSB, or LNS during the lean season.

Methods

This was a single-center, randomized, controlled, investigator-blinded clinical trial testing the growth-promoting effect and other health benefits to infants and children of daily provision of LNS or CSB for 12 wk.

The primary outcome measure was weight change during the follow-up period. Secondary outcomes included mean changes in length (mm), hemoglobin (Hb) concentration (g/L), weight-for-length Z-score (WLZ), length-for-age Z-score (LAZ), mid-upper arm circumference (MUAC), head circumference, and incidence of adverse events (AE) or serious AE (SAE). The researcher and data collector responsible for collecting the outcome measures were unaware of participants’ group allocations but the other data collectors were aware of the allocations.

Study area. The study was conducted in Lungwena, Mangochi district of Malawi, southeastern Africa. Exclusive breastfeeding for 6 mo is almost nonexistent in the study area and infant diets are typically complemented with maize porridge (“phala;” 10% dry weight maize flour) already as soon as 2 mo after birth. Underweight (WAZ < −2) and stunting (LAZ < −2) are very common, with a prevalence of 40% and almost 80% by 18 mo of age, respectively (3). The study area has a rainy season between December and March during which the staple food, maize, and other crops are grown. Enrollment in the trial was conducted during this growing season when food levels were at the lowest, i.e. from December to February 2007. The 12-wk follow-up of the last participant ended in May 2007.

Randomization and enrollment. The allocation for each consecutive consented participant was sealed in an individual opaque randomization envelope. The envelopes were marked with the trial code and stored in a locked cabinet until use. A consenting guardian of an eligible individual was asked to choose 1 randomization envelope from the remaining unused envelopes at a time. The identification number found in the envelope was recorded in a logbook and on the participant’s picture identification card. The identification card was given to the guardian and used for participant identification during the trial.

The target population for enrollment included moderately underweight infants and children who met the following inclusion criteria: a signed, informed consent from at least 1 guardian, aged between 6 and 15 mo, WAZ < −2 based on the National Centre for Health Statistics/Centers for Disease Control and Prevention (NCHS/CDC) growth reference (16), availability during the study period, and permanent residence in the study catchment area. Exclusion criteria included WLZ < −3 or presence of edema, history of peanut allergy, history of any serious allergic reaction to any substance requiring emergency medical care, history of anaphylaxis, severe illness warranting hospital referral, and concurrent participation in another clinical trial with nutrition intervention for the child.

Sample size. The target sample size was 63 infants and children per group (189 in total) calculated from the expected difference in the primary outcome, i.e. weight gain, among those provided either LNS or CSB and those provided nothing. The expected difference was based on an assumed weight gain (mean ± SD) of 530 ± 440 g among the control infants and children and 800 ± 440 g among those receiving either LNS or CSB supplementation (14,17). This gave the trial 85% power and a type 1 error of no more than 5% to detect a difference of ≥250 g in the mean weight gain between the control and intervention groups and allowed a 10% loss to follow-up.

Trial interventions. Participants in the control group did not receive any food supplement during the trial period. Those in the first intervention group received 500 g of CSB weekly and those in the second intervention group received 300 g of LNS weekly for 12 wk. Food supplements were delivered to their homes. The guardians were provided with spoons and advised to give their infants twice daily either 3 spoonfuls of LNS or porridge made from 3 spoonfuls of CSB. The mean daily dose was 43 g of LNS (921 kJ) or 71 g of CSB (1189 kJ). The LNS could be eaten alone or mixed with other infant foods, whereas the CSB required processing, typically through cooking into porridge. Mothers were encouraged to give the supplement in addition to breastfeeding.

Information about breastfeeding status was collected monthly during health center visits. Rab Processors produced the CSB locally in Malawi. LNS was produced at a Malawian nongovernmental organization, Project Peanut Butter, from locally purchased peanut paste (26%), dried skimmed milk (25%), vegetable oil (20%), icing sugar (27.5%), and a premade mineral and vitamin mix (1.5%) from Nutriset. Both supplements were fortified with micronutrients, but the level of fortification varied between the products. Table 1 provides the energy and nutrient content of a daily ration of each supplement.

Table 1. Nutritional Composition of CSB and LNS Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Calories (kJ)</th>
<th>Protein (g)</th>
<th>Fat (g)</th>
<th>Carbohydrate (g)</th>
<th>Fiber (g)</th>
<th>Iron (mg)</th>
<th>Calcium (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSB</td>
<td>1189</td>
<td>14</td>
<td>78</td>
<td>168</td>
<td>3</td>
<td>8.5</td>
<td>9.5</td>
</tr>
<tr>
<td>LNS</td>
<td>921</td>
<td>20</td>
<td>70</td>
<td>358</td>
<td>5</td>
<td>7.5</td>
<td>10.5</td>
</tr>
</tbody>
</table>

Measurement of outcome variables. Infant nude weights were measured to the nearest 10 g using an electronic infant weighing scale (SECA 735, Chasmons). Head circumference and MUAC were measured to the nearest 1 mm by a nonstretchable measuring tape (Lasoo-o-tape, Harlow Printing). Length was measured to the nearest 0.1 cm using a high quality length board (infantometer, Child Growth Foundation). All anthropometric measurements were done in triplicate by 1 investigator (C.T.) assisted by 1 trained research assistant, both of whom were unaware of the participants’ group allocations. Anthropometric indices (WAZ, WLZ, LAZ) were calculated using Epi Info 3.3.2 software (CDC) based on the CDC 2000 growth reference (16), because the WHO 2006 growth standards (18) became available only after enrollment. As a sensitivity analysis to assess if the use of the WHO growth standards would give similar results, we conducted exploratory analyses based on the WHO 2006 standards.

During weekly home visits, trained research assistants asked if the participants had experienced any problems eating the food supplements. If the guardians spontaneously reported that the participant had suffered from diarrhea, abdominal discomfort, vomiting, or skin rash, they were advised to bring the trial participant to the local health center. At these and any untimely, nonscheduled visits, a medical assistant assessed and managed the participant and recorded all information on structured forms. A trial physician (J.P.) who was unaware of the participants’ group allocations reviewed the data on suspected AE and determined and classified the severity of AE and the likelihood of their association to the trial interventions. All suspected SAE were reported to the trial’s Data Safety Monitoring Board (DSMB).
Because of the high background infectious morbidity in the study population, only the following medical occurrences were considered as possible AE: abdominal discomfort; vomiting or diarrhea for more than 2 consecutive days; skin rash for 2 or more consecutive days; noisy, wheezy, rapid, or difficult breathing; and any other medical conditions that were judged by the study physician as abnormal or not typical childhood illnesses. SAE included death, life-threatening condition, in-patient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or any other serious medical condition.

**Ethics.** The trial was performed according to International Conference of Harmonization-Good Clinical Practice guidelines and the ethical standards of Declaration of Helsinki. The College of Medicine Research and Ethics Committee and the Ethical Committee of Pirkannaa Hospital District, Finland, reviewed and approved the protocol. A guardian signed or thumbprinted an informed consent form before enrollment of each participant. An independent DSMB monitored the incidence of suspected SAE.

**Statistical analysis.** All statistical analyses were conducted using Stata 9.0 (Stata Corp) based on an intention-to-treat method. For the analysis of gains in anthropometric measurements, 2 values that were missing (not collected within 2 wk of the target date) at the end of follow-up (12 wk) were imputed from those recorded 4 wk earlier. This imputation was done by carrying forward the last observed Z-score and then back-transforming to a metric scale for child’s age at the later point.

We compared group means between control and each of the supplemented groups at a single time point using t test and results expressed as absolute differences and their 95% CI. We estimated risk ratio (RR) and risk difference for comparison of binary end-points between the control and each of the supplemented groups using Fisher’s test. To prevent inflated type I errors due to multiple comparisons, we began hypothesis testing by testing the global null hypothesis of all 3 groups being identical, using Fisher’s test (categorical variables) and ANOVA (quantitative variables). Only if the global null hypothesis was rejected would the pairwise comparisons be interpreted in a confirmatory manner. No post hoc test was used for pairwise comparison after the aforementioned procedures. We tested the effects of adjusting for baseline factors (sex, weight, and age) on the main outcomes using multiple linear regression models. Values in the text are mean ± SD or mean difference (95% CI). All confirmatory analyses were considered significant if P < 0.05. There is prior evidence that the response to LNS may depend on baseline degree of undernutrition (17,19), but the sample size of the trial was not powered to confirm this. We conducted exploratory analysis to assess the interaction between intervention and baseline WAZ (using P < 0.10 as an approximate guide) and stratified analysis based on WAZ below and above the median.

**Results**

Of the 1304 infants and children who were initially screened, 951 (73%) did not meet inclusion criteria for further eligibility assessment (≥15 mo of age, WAZ > –1.7). Of the remaining 353 infants and children, 57 (10%) did not attend the enrollment session or refused participation and 124 (35%) were not eligible for inclusion. The remaining 192 infants and children enrolled and were randomized into 1 of the 3 trial arms (Supplemental Fig. 1). At enrollment, there were slightly more children in the LNS (66) and CSB (67) groups compared with the control group (59), but the groups were comparable for baseline characteristics (Table 2).

A total of 188 participants (98%) completed the intervention, i.e. underwent medical and anthropometric assessment after the 12-wk intervention. The deaths and/or losses to follow-up did not differ among the 3 groups. All mothers reported that their children readily ate the provided supplement and diversion of any portion to anyone other than the intended beneficiary was reported at 2/795 (0.3%) food delivery interviews in CSB and none in LNS delivery interviews. From the weekly home visits during which trial products were checked, the percentage of visits when leftovers were found were 4/795 (0.5%) in the CSB and 4/780 (0.5%) in the LNS group. All infants and children except 1 from the control group were breastfed during the entire study period.

During the 12-wk follow-up, the mean weight increase was 620 g in the LNS group, 510 g in the CSB group, and 470 g in the control group but did not differ among the groups (P = 0.11). The corresponding changes in WAZ were +0.02, –0.31, and –0.32 units, respectively (P = 0.03), and none of the participants had a WLZ > 2.00 at the end of the trial period. Compared with the controls, infants and children in the LNS group gained more weight (150 g; P = 0.05) and had a greater increase in WAZ (0.33; P = 0.04). Changes in weight and WAZ did not differ between the control and CSB groups. Changes in length, head circumference, MUAC, and Hb concentration did not differ between the control and either of the intervention groups (Table 3). In exploratory analyses based on the WHO 2006 growth standard, infants in the LNS group tended to have a greater change in WAZ [mean (95% CI) 0.15 (0.00–0.30); P = 0.08]

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Nutrient composition of the participants’ daily dose of LNS or CSB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSB</td>
</tr>
<tr>
<td>Weight, g</td>
<td>71</td>
</tr>
<tr>
<td>Energy,1 kJ</td>
<td>1189</td>
</tr>
<tr>
<td>Protein, g</td>
<td>10.4</td>
</tr>
<tr>
<td>Carbohydrates, g</td>
<td>NA2</td>
</tr>
<tr>
<td>Fat, g</td>
<td>3.1</td>
</tr>
<tr>
<td>Retinol, µg</td>
<td>139</td>
</tr>
<tr>
<td>Folate, µg</td>
<td>43.2</td>
</tr>
<tr>
<td>Nicacin, mg</td>
<td>3.5</td>
</tr>
<tr>
<td>Pantothenic acid, mg</td>
<td>NA2</td>
</tr>
<tr>
<td>Riboflavin, mg</td>
<td>0.3</td>
</tr>
<tr>
<td>Thiamin, mg</td>
<td>0.13</td>
</tr>
<tr>
<td>Vitamin B-6, mg</td>
<td>0.3</td>
</tr>
<tr>
<td>Vitamin B-12, µg</td>
<td>0.9</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>48</td>
</tr>
<tr>
<td>Cholecalciferol, µg</td>
<td>NA2</td>
</tr>
<tr>
<td>Calcium, mg</td>
<td>72</td>
</tr>
<tr>
<td>Copper, mg</td>
<td>NA2</td>
</tr>
<tr>
<td>Copper, mg</td>
<td>5.46</td>
</tr>
<tr>
<td>Copper, mg</td>
<td>5</td>
</tr>
<tr>
<td>Copper, mg</td>
<td>5.46</td>
</tr>
<tr>
<td>Copper, mg</td>
<td>5</td>
</tr>
<tr>
<td>Copper, mg</td>
<td>5.46</td>
</tr>
<tr>
<td>Copper, mg</td>
<td>5</td>
</tr>
<tr>
<td>Copper, mg</td>
<td>5.46</td>
</tr>
<tr>
<td>Copper, mg</td>
<td>5</td>
</tr>
<tr>
<td>Copper, mg</td>
<td>5.46</td>
</tr>
</tbody>
</table>

1 1 kcal = 4.186 kJ.
2 No information provided by the manufacturer.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Characteristics of participants at enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Control</td>
</tr>
<tr>
<td>Participants, n (% male)</td>
<td>59 (58)</td>
</tr>
<tr>
<td>Age, mo</td>
<td>11.3 ± 2.5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>7.03 ± 0.74</td>
</tr>
<tr>
<td>Length, cm</td>
<td>66.1 ± 3.2</td>
</tr>
<tr>
<td>Mid upper arm circumference, cm</td>
<td>13.5 ± 0.8</td>
</tr>
<tr>
<td>Head circumference</td>
<td>44.5 ± 1.5</td>
</tr>
<tr>
<td>WAZ</td>
<td>2.98 ± 0.86</td>
</tr>
<tr>
<td>WLZ</td>
<td>0.89 ± 0.78</td>
</tr>
<tr>
<td>LAZ</td>
<td>2.80 ± 0.97</td>
</tr>
<tr>
<td>Hb, g/L</td>
<td>97 ± 14</td>
</tr>
</tbody>
</table>

1 Values are mean ± SD or n (%).
compared with the control group. Changes in WAZ did not differ between the control and CSB groups [0.04 (−0.08 to 0.17); $P = 0.65$] (Supplemental Table 1).

When adjusted for baseline weight and age, the LNS group gained more weight [mean (95% CI) 150 g (0–291); $P = 0.04$] and had a greater increase in WAZ [0.33 (0.06–0.60); $P = 0.02$]. Changes in weight and WAZ between the control and CSB groups did not differ (data not shown). The results remained similar whether extrapolated Z-scores for 2 participants in the CSB group did not differ ($P = 0.65$) (Supplemental Table 1).

Changes in weight and WAZ between the control and CSB groups differed from the control group in length gain or change ($P = 0.01$) than the control group. The control and CSB groups did not differ in WAZ change. There were also no differences among those with an initial WAZ below the median ($P = 0.91$) (Table 2). In contrast, supplementation with CSB was not associated with significantly higher stratified, changes in WAZ among those with lower initial WAZ were higher (95% CI = 0.28; $P = 0.02$) in the LNS group compared with the control group. Neither of the supplemented groups differed from the control group in length gain or change in Hb concentration (Supplemental Table 3).

In total, 36 participants experienced any clinician-documented AE and 10 participants an SAE, with no differences among the groups (Table 5). Compared with the controls, infants and children in the LNS group had a higher proportion of documented episodes of vomiting ($P = 0.02$) and skin rash ($P = 0.04$). All SAEs were assessed as unlikely related to the intervention.

### Discussion

We tested and compared the growth-promoting effects of 2 micronutrient-fortified supplementary foods among 6- to 18-mo-old underweight infants and children. Participants receiving LNS for 12 wk gained significantly more weight (150 g) than did the unsupplemented controls. The differences appeared more among the most undernourished participants, i.e. those who had lower initial WAZ before the intervention. In contrast, supplementation with CSB was not associated with significantly higher

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**TABLE 3** Anthropometric outcomes among infants and children that received LNS, CSB, or no supplement (control) for 12 wk

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control</th>
<th>LNS</th>
<th>CSB</th>
<th>$P^2$</th>
<th>LNS vs. control (95% CI)</th>
<th>$P^3$</th>
<th>CSB vs. control (95% CI)</th>
<th>$P^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight increase, kg</td>
<td>0.47 ± 0.35</td>
<td>0.62 ± 0.47</td>
<td>0.51 ± 0.35</td>
<td>0.11</td>
<td>0.15 (0.00 to 0.30)</td>
<td>0.05</td>
<td>0.04 (−0.08 to 0.17)</td>
<td>0.49</td>
</tr>
<tr>
<td>Length increase, cm</td>
<td>3.3 ± 1.2</td>
<td>3.4 ± 1.1</td>
<td>3.5 ± 1.1</td>
<td>0.60</td>
<td>0.1 (−0.3 to 0.5)</td>
<td>0.51</td>
<td>0.2 (−0.2 to 0.6)</td>
<td>0.34</td>
</tr>
<tr>
<td>MUAC increase, cm</td>
<td>0.6 ± 0.6</td>
<td>0.2 ± 0.8</td>
<td>−0.1 ± 0.6</td>
<td>0.06</td>
<td>0.2 (−0.1 to 0.4)</td>
<td>0.23</td>
<td>−0.1 (−0.3 to 0.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>HC increase, cm</td>
<td>0.6 ± 0.4</td>
<td>0.6 ± 0.6</td>
<td>0.7 ± 0.9</td>
<td>0.36</td>
<td>0.0 (−0.2 to 0.2)</td>
<td>0.99</td>
<td>0.1 (−0.1 to 0.4)</td>
<td>0.25</td>
</tr>
<tr>
<td>WAZ change</td>
<td>−0.32 ± 0.54</td>
<td>0.02 ± 1.11</td>
<td>−0.31 ± 0.59</td>
<td>0.03</td>
<td>0.33 (−0.02 to 0.65)</td>
<td>0.04</td>
<td>0.01 (−0.19 to 0.21)</td>
<td>0.91</td>
</tr>
<tr>
<td>WLZ change</td>
<td>−0.55 ± 0.73</td>
<td>−0.34 ± 0.77</td>
<td>−0.58 ± 0.76</td>
<td>0.16</td>
<td>0.21 (−0.06 to 0.48)</td>
<td>0.13</td>
<td>−0.02 (−0.29 to 0.25)</td>
<td>0.87</td>
</tr>
<tr>
<td>LAZ change</td>
<td>0.11 ± 0.42</td>
<td>0.29 ± 1.07</td>
<td>0.14 ± 0.37</td>
<td>0.29</td>
<td>0.19 (−0.11 to 0.48)</td>
<td>0.21</td>
<td>0.04 (−0.10 to 0.18)</td>
<td>0.59</td>
</tr>
<tr>
<td>Hb change, g/L</td>
<td>−5.3 ± 17</td>
<td>−3.5 ± 20</td>
<td>−2.8 ± 13</td>
<td>0.70</td>
<td>1.8 (−4.9 to 8.4)</td>
<td>0.60</td>
<td>2.5 (−2.8 to 7.9)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

1 Values are mean ± SD or Mean difference (95% CI). 2 ANOVA. 3 t test.

**TABLE 4** Anthropometric outcomes among infants and children stratified by WAZ at enrollment that received LNS, CSB, or no supplement (control) for 12 wk

<table>
<thead>
<tr>
<th>Baseline WAZ below median (−2.74)</th>
<th>Control</th>
<th>LNS</th>
<th>CSB</th>
<th>$P^2$</th>
<th>LNS vs. control (95% CI)</th>
<th>$P^3$</th>
<th>CSB vs. control (95% CI)</th>
<th>$P^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>29</td>
<td>34</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight increase, kg</td>
<td>0.45 ± 0.32</td>
<td>0.70 ± 0.41</td>
<td>0.49 ± 0.37</td>
<td>0.02</td>
<td>0.25 (0.06 to 0.43)</td>
<td>0.01</td>
<td>0.04 (−0.13 to 0.22)</td>
<td>0.62</td>
</tr>
<tr>
<td>Length increase, cm</td>
<td>3.1 ± 1.4</td>
<td>3.4 ± 1.0</td>
<td>3.6 ± 1.1</td>
<td>0.25</td>
<td>0.3 (−0.3 to 0.9)</td>
<td>0.31</td>
<td>0.5 (−0.1 to 1.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>WAZ change</td>
<td>−0.27 ± 0.50</td>
<td>0.20 ± 1.21</td>
<td>−0.32 ± 0.72</td>
<td>0.03</td>
<td>0.47 (−0.01 to 0.96)</td>
<td>0.05</td>
<td>−0.05 (−0.37 to 0.29)</td>
<td>0.76</td>
</tr>
<tr>
<td>Hb change, g/L</td>
<td>−7.6 ± 20</td>
<td>−1.6 ± 17</td>
<td>−3.0 ± 15</td>
<td>0.38</td>
<td>0.0 (−0.2 to 0.2)</td>
<td>0.99</td>
<td>0.1 (−0.1 to 0.4)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline WAZ above median (≥−2.74)</th>
<th>Control</th>
<th>LNS</th>
<th>CSB</th>
<th>$P^2$</th>
<th>LNS vs. control (95% CI)</th>
<th>$P^3$</th>
<th>CSB vs. control (95% CI)</th>
<th>$P^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>30</td>
<td>32</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight increase, kg</td>
<td>0.49 ± 0.38</td>
<td>0.53 ± 0.53</td>
<td>0.53 ± 0.34</td>
<td>0.90</td>
<td>0.04 (−0.20 to 0.28)</td>
<td>0.72</td>
<td>0.04 (−0.14 to 0.23)</td>
<td>0.64</td>
</tr>
<tr>
<td>Length increase, cm</td>
<td>3.4 ± 1.0</td>
<td>3.4 ± 1.2</td>
<td>3.4 ± 1.1</td>
<td>0.97</td>
<td>−0.0 (−0.6 to 0.5)</td>
<td>0.91</td>
<td>−0.1 (−0.6 to 0.5)</td>
<td>0.79</td>
</tr>
<tr>
<td>WAZ change</td>
<td>−0.36 ± 0.58</td>
<td>−0.18 ± 0.97</td>
<td>−0.29 ± 0.44</td>
<td>0.57</td>
<td>0.19 (−0.23 to 0.60)</td>
<td>0.37</td>
<td>0.07 (−0.19 to 0.33)</td>
<td>0.58</td>
</tr>
<tr>
<td>Hb change, g/L</td>
<td>−3.1 ± 12</td>
<td>−5.6 ± 23</td>
<td>−2.6 ± 11</td>
<td>0.74</td>
<td>2.5 (−11.9 to 6.9)</td>
<td>0.60</td>
<td>0.5 (−5.5 to 6.4)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

1 Values are mean ± SD or mean difference (95% CI). 2 ANOVA. 3 t test.
weight gain than no supplementation. Using the WHO 2006 growth standard (18), about one-half of the study children would be regarded as moderately underweight and some results lost significance or were of borderline significance. The observation that the WHO standard results in lower rates of undernutrition than the NCHS/CDC reference (16) has been previously documented (20). In the stratified analysis, just like with the NCHS/CDC 2000 growth reference, benefit from LNS supplementation was confined to those with lower initial WAZ, which is consistent with those defined moderately underweight using the WHO standards.

The study design included a nonsupplemented control group and random group allocation, and individuals assessing the outcomes were not aware of the group allocation. The refusal rate for participation was low, trial groups were comparable at enrollment, compliance with the intervention appeared good, loss to follow-up was infrequent and balanced between the groups, and the calculated probability of random error was low. Additionally, because calculation of anthropometric indices (WAZ, LAZ, and WLZ) standardizes for age and sex, small inter-group differences in the sex ratio are unlikely to affect the interpretation of the main results. Hence, the sample findings are likely to be unbiased and representative of the population from which the sample was drawn, lending support to the hypothesis that supplementation of underweight infants and young children with LNS can in some conditions boost their weight gain and thereby promote recovery from undernutrition. At the same time, the findings do not support a hypothesis that CSB has a similar growth-promoting effect in the same target group.

LNS were initially designed for use as a rehabilitation food for severely malnourished children (7). Recently, there has been a major interest to expand the use of LNS for the treatment of less severe conditions. Initial results in this target group have been promising. Two trials enrolling moderately wasted children and 1 trial with underweight participants suggested that fortified spreads could also promote recovery from moderate wasting or underweight more efficiently than no supplementation (13,14,21). Our results are consistent with these earlier findings and suggest that in certain conditions, the achievable mean effect size is −0.3 SD, similar to the effect size typically seen in successful preventive interventions (19). The severity of the recipient’s condition may, however, significantly modify the impact, as in our sample and many earlier complementary feeding trials (17,19). The season of intervention appears to be another important effect modifier; our earlier trial that documented no difference in weight gain between individuals given either LNS or CSB was carried out mainly after the harvest, whereas the current study and that by Kuusipalo et al. (14) were mostly implemented during the rainy season when weight gains were otherwise very low. Unlike the Maradi (22) setting where the population had a high incidence of wasting in a lean season, wasting is very uncommon in Malawi. WAZ is used as a screening tool in under-five clinics to identify children who need an intervention. Based on the current evidence, we would thus not recommend LNS supplementation to all underweight children but would suggest a selective strategy focusing on lean seasons and targeting infants and children with mild or moderate wasting.

There are several alternative explanations why LNS might promote weight gain more efficiently than CSB. Whereas the energy content of the daily dose was not very different in the 2 supplements, the volume of ready-to-use LNS (−50 mL) was only a fraction of that of the porridge made out of CSB (700 mL). This may have led to incomplete consumption and sharing with family members of the supplement more frequently among participants who were given CSB. Whereas the parents in our study typically reported no diversion of the supplement to unintended beneficiaries, earlier studies suggest sharing of both CSB and LNS, but this seems to occur more often with porridges (23). Additionally, due to its volume, CSB may not be a true supplement, because it likely displaces other home foods. LNS also contain cow milk powder and the essential fatty acids linoleic acid and α-linolenic acid, all of which may be critical for infant growth promotion (6,24,25). In contrast, and unlike CSB, LNS contain few phytates that might inhibit the absorption of some nutrients critical for growth such as zinc (26).

The observed lack of differences in length increase between the controls and either of the intervention groups after a 12-wk supplementation with LNS or CSB is not a new finding. It has been previously reported that acceleration in length gain follows weight gain increase with a certain lag period, which is 3 mo in rural Malawi (27). The small improvement in length gains may therefore imply an inadequate duration of supplementation in the present trial.

There was a slightly increased risk for suspected AE, which included vomiting or skin rash among infants and children given LNS. This finding may be partly explained by the study design that included a weekly parental interview on problems with the supplements by assistants who knew the group allocations. These assistants were advised to recommend a clinic visit if vomiting, diarrhea, abdominal complaints, or rash were spontaneously reported, and they may well have put more emphasis on this message if the child was actually receiving a supplement rather than being in the control group. However, true adverse

TABLE 5 Proportion with confirmed AE and SAE among infants and children that received LNS, CSB, or no supplement (control) for 12 wk

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control</th>
<th>LNS</th>
<th>CSB</th>
<th>LNS vs. control</th>
<th>CSB vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, n</td>
<td>59</td>
<td>66</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAE, n (%)</td>
<td>1 (2)</td>
<td>6 (9)</td>
<td>3 (5)</td>
<td>0.20</td>
<td>5.4 (0.7–3.0)</td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>8 (14)</td>
<td>15 (23)</td>
<td>13 (19)</td>
<td>0.25</td>
<td>1.7 (0.8–3.7)</td>
</tr>
<tr>
<td>Vomiting symptoms, n (%)</td>
<td>0 (0)</td>
<td>6 (9)</td>
<td>2 (3)</td>
<td>0.03</td>
<td>NA</td>
</tr>
<tr>
<td>Abdominal discomfort, n (%)</td>
<td>2 (3)</td>
<td>8 (12)</td>
<td>6 (9)</td>
<td>0.21</td>
<td>3.6 (0.8–16.2)</td>
</tr>
<tr>
<td>Diarrhea, n (%)</td>
<td>4 (7)</td>
<td>9 (14)</td>
<td>11(16)</td>
<td>0.25</td>
<td>2.0 (0.6–6.2)</td>
</tr>
<tr>
<td>Skin rash, n (%)</td>
<td>0 (0)</td>
<td>5 (8)</td>
<td>4 (6)</td>
<td>0.09</td>
<td>NA</td>
</tr>
<tr>
<td>Wheeze, difficulty breathing, n (%)</td>
<td>5 (8)</td>
<td>5 (8)</td>
<td>2 (3)</td>
<td>0.40</td>
<td>0.9 (0.3–2.9)</td>
</tr>
</tbody>
</table>

1 Fisher’s test.
2 NA = No values computed.
reactions caused by allergy to the milk or peanut component of LNS cannot be ruled out. Strong allergic reactions seem uncommon altogether among severely undernourished individuals (28) and to our knowledge none have been associated with LNS use in that target group. Less severely affected children might have an intact immune system, rendering them more prone to immunological reactions. In the current sample, all episodes of vomiting or rash were transient, possibly suggesting a mechanism other than allergy to explain the finding.

In conclusion, our results suggest that a 12 wk-long supplemental feeding with LNS can boost weight gain in moderately underweight children and may promote recovery from undernutrition. Further studies should assess if LNS supplementation is associated with an increased risk for allergic reaction or other symptoms in this target group.

Acknowledgments

We thank Daniel Pondani, the medical assistant for Lungwena Health Centre, for his support in all the stages of the study; the DSMB members (Kamija Phiri, Paul Ndebele, Tom Heikens) for monitoring the trial; Laszlo Csonka for designing the data entry program; and Matti Kataja for his excellent technical advice on statistical analyses. All authors designed the trial; P. A. wrote the protocol; C.T. was responsible for data collection; Y.B.C. designed the details of statistical analysis; and C.T. conducted the analysis and wrote the first draft of the manuscript under the supervision of K.M., P.A., and Y.B.C. All authors commented on the analysis and participated in writing of the manuscript. C.T. had full access to all the data in the study and takes responsibility for data integrity and accuracy of the data analysis. All authors read and approved the final manuscript.

Literature Cited


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