TECHNICAL REPORT

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FOOD AND NUTRITION TECHNICAL ASSISTANCE

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A Single-Centre, Randomized, Single-Blind, Parallel Group Clinical Trial in Rural Malawi, Testing the Growth Promoting Effect of Long-Term Complementary Feeding of Infants with a High-Energy, Micronutrient Fortified Spread

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March 2012

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Contents

Abbreviations and Acronyms

CDC	U.S. Centers for Disease Control and Prevention
CI	confidence interval
CSB	corn-soy-flour blend
dl	deciliter(s)
g	gram(s)
L	liter(s)
LAZ	length-for-age z-score
LNS	lipid-based nutrient supplement(s)
µ	microgram(s)
ml	milliliter(s)
mm	millimeter(s)
MUAC	mid-upper arm circumference
NGO	nongovernmental organization
RDA	recommended daily allowance
RR	relative risk
SD	standard deviation
WAZ	weight-for-age z-score
WFL	weight-for-length
WLZ	weight-for-length z-score
WHO	World Health Organization

Abstract

Background. The low nutrient and energy content of complementary foods in low-income countries has been associated with growth faltering, increased morbidity, and delayed motor milestone acquisition. Complementation of diet in infancy and early childhood with lipid-based nutrient supplements (LNS) that have high nutrient and energy density has been suggested to improve growth and might also reduce morbidity.

Objective. To compare the incidence and prevalence of very severe linear growth failure and symptoms of common childhood illnesses among infants receiving dietary supplementation with milk-LNS, soy-LNS, a corn-soy-flour blend (CSB), or nothing.

Design. Randomized, controlled, single-blind trial.

Setting. Rural Malawi.

Participants. A total of 840 6-month-old healthy infants.

Intervention. Participants were randomized into one of four intervention schemes for 12 months from the age of 6 to 18 months: control with no supplementation, daily supplementation with 54 g/day of milk-LNS (containing milk protein and 1–2 recommended daily allowances (RDAs) of several important micronutrients), 54 g/day of soy-LNS (containing soy flour but not milk protein and the same number and amounts of micronutrients as in milk-LNS), or 71 g/day of micronutrient fortified CSB. All supplements provided approximately 280 kcal energy/daily dose.

Outcome measures. Mean length, weight, mid-upper arm circumference (MUAC), head circumference, and hemoglobin gain; incidence and prevalence of very severe (length-for-age z-score [LAZ] < −3.50 World Health Organization [WHO] reference) and severe to very severe stunting (LAZ < −3.00 WHO reference) during the intervention; longitudinal prevalence of days with symptoms of common childhood illness; and mortality.

Results. The mean length and weight gains over the 12-month intervention period were 13.0 cm, 13.2 cm, 13.0 cm, and 12.9 cm, and 2.42 kg, 2.53 kg, 2.46 kg, and 2.33 kg in the control, milk-LNS, soy-LNS, and CSB groups, respectively (p=0.43 for length change and p=0.12 for weight change, ANOVA). During the intervention, a total of 50 children developed very severe and 88 severe to very severe stunting. Compared to the control group, the relative risk (RR) of developing very severe stunting was 0.39 (0.16–0.99) in the milk-LNS group, 1.08 (0.55–2.12) in the soy-LNS group, and 0.86 (0.42–1.77) in the CSB group. At the end of the intervention, the prevalence of very severe stunting was 6.4%. Compared to control group, the RR of being very severely stunted at the age of 18 months was 0.65 (0.27–1.54) in the milk-LNS group, 1.39 (0.68–2.84) in the soy-LNS group, and 0.93 (0.42–2.05) in the CSB group. The longitudinal prevalence of days with symptoms of common childhood illnesses was 14.7% in the control group and 13.6%, 13.4%, and 13.5% in the milk-LNS group, soy-LNS group, and CSB group, respectively. During the 1-year follow-up period, a total of 25 children died (8 in the control group, 4 in the milk-LNS group, 5 in the soy-LNS group, and 8 in the CSB group, p=0.54, chi-square test).

Conclusion. The results provide support to a hypothesis that in rural Malawi, 12 months of complementary feeding of infants with milk-LNS, but not soy-LNS or CSB, reduces the incidence of very severe stunting between 6 and 18 months of age. The effect size may, however, be smaller than suggested earlier. The trial did not, however, provide support to a hypothesis that any of the tested supplements would reduce the longitudinal prevalence of common illness symptoms among 6–18-month-old infants.

Trial registration. United States National Institutes of Health (www.clinicaltrials.gov), trial number: NCT00524446.

Funding. Academy of Finland, Finnish Foundation for Pediatric Research (Lastentautien Tutkimussäätiö), Tampere University Hospital, FHI 360/FANTA.

Study Background

Poor growth and severe childhood stunting is very common in rural Malawi. Few interventions have proven successful in promoting linear growth in early childhood. Previous results have suggested that a long-term complementary feeding of infants with high-energy, micronutrient-fortified milk containing lipid-based nutrient supplements (LNS) may promote linear growth and markedly reduce the incidence of severe stunting (Adu-Afarwuah et al., 2007; Phuka et al., 2008). A larger trial with a control arm not receiving any complementary feeding intervention was, however, considered important, to confirm the finding. The trial was also designed to analyze if a modified, soy-protein containing LNS (which is 10%–20% cheaper to produce) would be equally or less effective than the standard version of milk-containing LNS.

The objective of the study was to compare the prevalence and incidence of very severe stunting at age 18 months of infants receiving fortnightly complementary feeding with LNS (with either milk or soy protein) or fortified corn-soy-flour blend (CSB) between 6 and 18 months of age to infants receiving no extra supplements for complementary feeding during the same period. In the previous study by Phuka et al. (2008), the anthropometric indices of weight-for-age z-score (WAZ), length-for-age z-score (LAZ), and weight-for-length z-score (WLZ) were calculated based on the U.S. Centers for Disease Control and Prevention (CDC) 2000 growth reference with severe stunting classified as LAZ < −3.0 (Kuczmarski et al., 2002). In this study, anthropometric indices were calculated using 2006 World Health Organization (WHO) Child Growth Standards (WHO, 2006). Since the LAZ 2006 WHO criteria cutoff of −3.5 (very severe stunting) corresponds to CDC 2000 reference −3.0 (severe stunting), the current study focused on very severe stunting in the primary analysis.

The trial has two points of analysis: main analysis at the end of the 12-month intervention and a further analysis to be done 18 months later. The current report focuses on the growth- and morbidity-related findings of the main analysis.

Methods

Study Area

The study was conducted in Lungwena and Malindi, a rural Malawian community with a total population of approximately 40,000 people. Infant undernutrition in the area was common, with a high prevalence of early childhood stunting and underweight. The main staple, maize, was normally grown and harvested between December and March. The principal complementary food in most households was a thin maize-based porridge, introduced in the diet in early infancy from 2 to 6 months of age.

Eligibility Criteria, Enrollment, and Randomization

Trial participants were recruited from January 28, 2008 to May 25, 2009. The initial inclusion criteria included age 5.5–6.5 months, residence in the study area, and informed consent from at least one authorized guardian. The exclusion criteria were weight-for-length (WFL) < 80% of the reference median (WHO, 2006) or presence of edema, severe illness warranting hospitalization on the enrollment day, a history of peanut allergy, concurrent participation in another clinical trial, or any symptoms of food intolerance within 30 minutes of ingesting a 6 g test dose of LNS (either milk- or soy-based) used in the trial. Initially, the exclusion criteria also included severe stunting (LAZ < −3.0), but this criterion was dropped at 6 weeks into the trial (March 17, 2008, when 97 of the 840 participants had been enrolled) and no subsequent exclusion criteria for stunting was reinstated (i.e., infants could be enrolled regardless of their LAZ). This change in eligibility criteria was prompted by our observation that approximately 23% of the children that underwent the eligibility assessment were excluded based on the stunting criterion. The proportion was much higher than we had anticipated, mostly due to the fact that in this study we were using the 2006 WHO Child Growth Standards, whereas our earlier studies had used the CDC 2000 references. Our earlier results suggested that those initially more severely stunted would be the most likely ones to benefit from the LNS interventions and hence we did not want to exclude such a big proportion of children in this category (Phuka et al., 2008).

Eligible participants were identified through a community census conducted in the study area, with a preliminary screening done to assess for eligibility. During recruitment, trained data collectors contacted all the families of children of eligible age whose parents showed a preliminary interest in the trial. Infants were invited to an enrollment session where they were screened for eligibility and guardians were given detailed information on the trial contents. Before enrollment, a guardian signed a written consent form for trial participation.

Sample size was based on the assumption that the prevalence of severe stunting at the end of the 12-month intervention period would be 15% in the control group and 5% in the intervention groups. With a type I error of 5% and power of 85% and allowing for an attrition of 10%, the sample size required per group was calculated as 210. The sample size also takes into account the multiple comparisons between the different groups by a gatekeeping procedure of first testing the global null hypothesis of all four proportions being equal, and then proceeding to the testing of the individual null hypotheses only if the global null hypothesis is rejected.

Blocked randomization, with each block containing 16 allocations, was used to assign participants to intervention groups. For group allocation, a set of identical-appearing opaque envelopes from one randomization block were shuffled and a guardian was requested to choose one envelope. The envelope contained a piece of paper indicating an identification number and randomly assigned allocation to one of the four interventions. The randomization list and envelopes were made by an individual not involved in trial implementation, and the code was not disclosed to the researchers or to those assessing the outcomes until all data had been entered and verified in a database.

Interventions and Follow-Up

The study compared the efficacy of four intervention schemes. Infants in the control group were not provided with any supplemental complementary food during the primary follow-up, but received a delayed supplementation with 71 g/day fortified CSB between 18 and 30 months of age. Participants in the other three groups received 71 g/day of micronutrient-fortified CSB, 54 g/day of micronutrient- fortified LNS with

milk protein base (milk-LNS), or 54 g/day of micronutrient-fortified LNS with soy protein base (soy-LNS) between 6 and 18 months of age. The daily CSB and LNS dose provided approximately 285 kcal of energy.

The supplements were home delivered at 2-week intervals (at each supplement delivery, either two 500 g bags of CSB or five 150 g jars of LNS were given). The CSB was purchased from a local producer (Rab Processors, Blantyre, Malawi). LNS was produced at a Malawian nongovernmental organization (NGO), Project Peanut Butter (Blantyre), from peanut paste, milk powder or soy flour, vegetable oil, sugar, and premade micronutrient mixture (Nutriset, Inc., Malaunay, France).

Table 1 shows the micronutrients' content and their quantities in the three supplements. Milk-LNS and soy-LNS contained an identical range and quantities of micronutrients. CSB contained fewer micronutrients and for most of them the daily supplement ration contained a lower micronutrient content than that for LNS. Phytate content of the supplements was not assessed.

Guardians for infants in the intervention groups were provided with spoons and advised to feed their babies normal healthy diets and additionally offer them daily either 10 spoonfuls of CSB, cooked into a complementary porridge, or 8 spoonfuls of milk-LNS or soy-LNS, divided into 2–4 daily doses. All mothers were encouraged to continue breastfeeding on demand and to feed their infants only as much of the food supplement as the infants wanted to consume at a time.

Participants were visited every 2 weeks at their homes to collect information on supplement use, possible adverse events, morbidity (history of symptoms for common illnesses and physical examination), and development. Empty food containers were collected at these visits. At 12-week intervals after enrollment, up to week 52, participants had a visit at the trial office, where they underwent an anthropometric assessment, morbidity assessment, and laboratory tests. The illness history checked for symptoms of malaria, diarrhea, cough, and other illnesses, and the physical examination checked for signs of fever, respiratory infection, dehydration, and skin infections. The laboratory tests checked for hemoglobin, malaria parasiteamia, and stool parasites.

Measurement of outcome variables

The primary outcomes were the incidence of very severe stunting (LAZ < −3.5) during the 12-month follow-up and prevalence of the condition at the end of that period. Secondary outcomes included the prevalence of severe or moderate-to-severe stunting (LAZ < −3 or < −2), wasting (WLZ < −3 or < −2), or underweight (WAZ < −3 or < −2) at 12 or 18 months of age; incidence of severe or moderate-to-severe stunting (LAZ < −3 or < −2), wasting (WLZ < −3 or < −2), or underweight (WAZ < −3 or < −2) by 18 months of age; length and weight gain; change in the anthropometric indices of WAZ, LAZ, and WLZ; change in head or mid-upper arm circumference; change in blood hemoglobin concentrations; longitudinal prevalence of symptoms for common childhood illnesses; and mortality. For the calculation of incidence, participants with the particular form of malnutrition (e.g., very severe stunting, severe wasting) at enrollment were excluded. Incidence was calculated as the first time a participant developed a given form of malnutrition (e.g., very severe stunting). Relapses after recovery from the malnutrition were not counted as "new" cases of malnutrition.

Unclothed infants were weighed using an electronic infant weighing scale (SECA 735, Chasmors Ltd., London, England), and weights were recorded to the nearest 10 g. Length was measured to the nearest 1 mm using a high-quality length board (Kiddimetre, Raven Equipment Ltd., Essex, England). MUAC and head circumference were measured using non-stretchable plastic tape measures (Lasso-o Tape, Harlow Printing Ltd., South Shields, Tyne & Wear, England).

Anthropometric indices (WAZ, LAZ, and WLZ) were calculated using WHO Child Growth Standards (2010 Stata igrowup package) (WHO, 2006). In addition, we calculated anthropometric indices using the CDC 2000 growth reference(Kuczmarski et al., 2002) (EPI Info 3.3.2), to allow comparison to the results with previous studies that used this reference (Lin et al., 2008; Phuka et al., 2008)

Disease surveillance was conducted daily by the guardian. With the aid of a pictorial morbidity calendar, guardians recorded daily whether a child had diarrhea, cough, fever, or any other symptom of common childhood illnesses. Information on the calendar was verified by fieldworkers through a recall interview done every 2 weeks. Diarrhea was defined as three or more loose, liquid stools in a single day. Fever was defined as unusually high body temperature observed by the mother.

Further morbidity data were collected through a non-scheduled clinic visit to the health facilities within the study area. Whenever such a visit was made, a local health professional attended the child and filled in a structured form, including questions on the medical history and clinical condition of the participant. The health professional made a clinical diagnosis, placed it one of seven predefined, mutually exclusive diagnostic categories, and recorded it in the form. The diagnostic categories consisted of the following: malaria, pneumonia, other respiratory infections, gastroenteritis, trauma, skin infection, other illnesses.

A 3 ml venous blood sample was collected at enrollment (along with a 5 ml blood sample at 18 months of age) to study blood hemoglobin concentration and malaria parasiteamia. The same analyses were preformed from a finger-prick blood sample at 9, 12, and 15 months of age. Hemoglobin concentration was measured using cuvettes and a reader (HemoCue AB, Angelholm, Sweden). Thick and thin blood smears were stained with Giemsa and screened microscopically for malaria parasites. Besides the scheduled visits, peripheral blood malaria parasiteamia was assessed at non-scheduled outpatient visits to a local health center.

Malaria treatment was provided according to the national guidelines to all participants with clinical malaria. All participants found to have a blood hemoglobin concentration below 80 g/L were treated with iron supplementation in accordance with the national treatment guidelines (100 mg iron sulphate per 5 ml per day according to age and body weight). Participants developing moderate or severe wasting (WFL < 80% of reference median) during the intervention were withdrawn from the study and referred for appropriate management, but continued follow-up and resumed trial supplementation after nutrition treatment.

Data management and analysis

Collected data were recorded on paper forms, transcribed to paper case report forms, and double entered into a tailor-made database (Microsoft Access 2003, Microsoft Corp, Redmond, Washington). The two entries were electronically compared, and extreme or otherwise suspicious values were confirmed or corrected. Statistical analysis was performed using Stata 11.0 (Stata Corp, College Station, Texas) on an intention-to-treat basis. For continuous and categorical outcomes, the four intervention groups were compared using analysis of variance and the Fisher exact test, respectively. Survival function was calculated for each form of malnutrition, and mortality with plots of Kaplan-Meir estimates for survival function and cumulative incidence functions of the various forms of malnutrition were made. The survival distributions between the groups were assessed using a log-rank test.

For morbidity analysis, morbidity indices were calculated for each child that indicated either the proportion of days with a specific symptom or the number of health professional-diagnosed illness episodes over the total number of days at risk for that individual. Group means were calculated from and group comparisons were based on these individual indices, i.e., the unit of analysis was a child, not a day or an illness episode. This approach was chosen to account for the possible cluster effect for morbidity.

Results

Enrollment and baseline characteristics

Of the 1,385 participants that were identified through community census, 73 were too old (age > 6.5 months) at the time of the screening. The remaining 1,312 participants were invited over the course of the recruitment period; 405 did not turn up at the enrollment session. Of the remaining 907 participants that came to the enrollment session, 67 were ineligible (23 severely stunted, 16 aged > 6.5 months, 15 aged < 5.5 months, 1 severely wasted, and 12 whose parents declined participation after receiving full information about the trial). The remaining 840 infants were randomized into four intervention groups (**Figure 1**). None of the eligible participants that received the 6 g test dose were allergic to either milk-LNS or soy-LNS.

Table 2 shows the baseline characteristics of the participants by intervention group. The mean anthropometric measurements and indices were comparable between the intervention groups. At enrollment, the prevalence of very severe stunting (WHO LAZ < −3.50) in the control, milk-LNS, soy-LNS, and CSB groups was 3.4%, 2.8%, 4.8%, and 2.9%, respectively; that of severe stunting 6.7%, 8.0%, 11.4%, and 7.7%, respectively; and that of severe underweight 1.9%, 1.9%, 1.9%, and 4.3%, respectively. None of these differences was statistically significant. No participant had severe wasting at the beginning of the intervention period. Maternal and household characteristics were also comparable between the intervention groups (**Table 3**).

Growth and undernutrition

The primary outcome was the prevalence of very severe stunting at 18 months of age, and 747 participants had anthropometric data at the end of follow-up. Compared to the control, those in the milk-LNS group had a relative risk (RR) (95% CI) of 0.65 (0.27–1.55) of being very severely stunted at the end of the intervention period. Comparable figures were 1.39 (0.68–2.84) and 0.94 (0.42–2.07) for soy-LNS and CSB, respectively (**Table 4a**). Corresponding RRs of prevalence of very severe stunting and other forms of malnutrition were also calculated at the mid-point of intervention and showed a similar pattern to the RRs at the end of the 12-month intervention period (**Table 4b**).

The overall cumulative incidences of very severe stunting, severe underweight, and severe wasting during the intervention were 6.2%, 4.4% and 1.3%, respectively. Compared to the controls, participants in the milk-LNS group had a RR (95% CI) of 0.39 (0.16–0.99) for the incidence of very severe stunting, 0.27 (0.08–0.95) for severe underweight, and 0.99 (0.14–6.93) for severe wasting. Comparable figures were 1.08 (0.55–2.12), 0.91 (0.39–2.08), and 1.99 (0.37–10.80) for those in the soy-LNS group, and 0.86 (0.42–1.77), 1.12 (0.51–2.48), and 1.50 (0.25–8.88) for those in the CSB group, respectively. There were no significant differences between the treatment arms in the proportion of those developing moderate to severe stunting, underweight, or wasting (**Table 5**).

The cumulative incidence of very severe and severe stunting during the 12-month period was also calculated using survival analysis methods. Very severe stunting developed less often and later in the milk-LNS group compared to the soy-LNS, CSB and control groups (**Figure 2**). Similar results were also found with severe stunting (**Figure 2**). The findings were not statistically significant, using the traditional cutoff points for significance of 0.05.

The mean gains in weight and length over the 12-month intervention period were 110 g (−45.9–266.0) and 0.2 cm (−0.2–0.6) higher in the milk-LNS group than in the control group. Comparable figures were 40 g (−127.0–207.0) and −90 g (−258.0–77.8) and 0.0 cm (−0.4–0.4) and −0.1 cm (−0.6–0.4) for soy-LNS and CSB, respectively, compared to the control group. Mean gain in MUAC in the milk-LNS group was 0.11 cm (−0.08–0.30) higher compared to controls, with no difference in head circumference gain relative to controls (0 cm, CI 0.15–0.15). Corresponding values for the soy-LNS group were 0.00 cm (CI −0.21–0.21) for MUAC and 0 cm (CI −0.17–0.17) for head circumference; for the CSB group, these were 0.02 cm (−0.18–0.22) for MUAC and 0 cm (CI −0.19–0.19) for head circumference, relative to controls. None of these differences were statistically significant (**Table 6**).

The mean length-for-age remained constant between 6 and 12 months of age among participants that received milk-LNS, but decreased by approximately 0.2 z-score units among other infants; after 12 months of age, the mean length-for-age fell at approximately equal rates in all intervention groups (**Figure 3**).

Morbidity symptoms and non-scheduled outpatient visits

The overall longitudinal prevalence of any symptom for common childhood illnesses (i.e., cough, fever, diarrhea, other symptoms) was 14.7% in the control group. The comparative figures were 13.6%, 13.4%, and 13.5% in the milk-LNS, soy-LNS, and CSB groups, respectively. The groups were also quite similar when the longitudinal prevalence was calculated for each individual symptom separately (**Table 7**).

Over the 12-month intervention period, the participants made a total of 3,392 non-scheduled visits to the nearby health facilities. The incidence of such illness episodes leading to a health facility visit and a clinical diagnosis ranged from 4.28 to 5.02/child/year at risk, with no statistically significant differences between the groups. Again, the groups were quite similar when the incidence of non-scheduled visits was calculated for each individual diagnosis separately (**Table 8**).

Mortality

Twenty-five children (3.0% of the enrolled participants) were registered to have died during the follow-up. Four of these children were in the milk-LNS group, 5 in soy-LNS, 8 in CSB group and 8 in control group. Nine of the children were judged to have died from lower respiratory tract infections, five from severe anemia, four from severe malaria, and seven from other causes. There were no statistically significant intergroup differences in the characteristics for the participants that died during the follow-up (**Table 9**).

The cumulative survival curves for the participants are illustrated in **Figure 4**, for all groups separately and for LNS groups together compared to control and CSB groups. As indicated, there were more deaths among the control infants or those receiving CSB than among those supplemented with either version of the LNS. However, the differences were not statistically significant (**Figure 4**).

Discussion

This trial was carried out to study the impact of a 12-month-long dietary supplementation with LNS on linear growth, development of severe growth faltering, and morbidity among rural Malawian infants and young children. Among study participants, those receiving dietary complementation with milk-containing LNS gained on average approximately 0.2 cm more in length and 100 g more in weight than control children or those receiving milk-free LNS or CSB supplementation did. The mean length-for-age remained constant between 6 and 12 months of age among participants who received milk-LNS, but decreased by approximately 0.2 z-score units among other infants; after 12 months of age, the mean length-for-age fell at approximately equal rates in all intervention groups. The incidence of very severe and severe stunting during the 12-month intervention and the prevalence of the condition at the end of the intervention was also lower among children that received milk-containing LNS than among other participants. There were no major intergroup differences in terms of morbidity symptoms. Nine infants died in the control group and another nine in the CSB group, compared to four in the milk-containing LNS group and four in the milk-free LNS group.

The probability of bias was low because of broad inclusion criteria, random group allocation, similarity of the intervention groups at enrollment, comprehensive follow-up, and blinding of the outcome assessors. Although CI calculations and hypothesis testing in several analyses indicated a slightly larger probability of type I error than the traditional cutoff for statistical significance (5%), the inherent consistency of the findings, their biological plausibility and coherence with earlier studies, and their logical chronology lead us to believe that the sample findings were reliable and representative of the target population from which the sample was drawn. We therefore conclude that in rural Malawi, 12 months of complementary feeding of infants with milk-LNS, but not soy-LNS or CSB, promotes linear growth and reduces the incidence of very severe stunting between 6 and 18 months of age. In contrast, the study did not support a hypothesis that any of the supplementation schemes would have a marked impact on incidence of symptoms for common childhood infections.

Results from the current study are consistent with those of three earlier trials, where LNS have been used as low-dose supplements, aimed at promoting growth, rather than treating malnutrition. In Ghana, infants receiving 20 g milk-LNS/day had no decline in their mean length-for-age between 6 and 12 months of age, whereas control infants receiving either no supplements or only micronutrients lost approximately 0.1 z-score units during the same age interval (Adu-Afarwuah at al., 2007). In Malawi, at the same site where the current study was carried out, infants that received 50 g/day milk-LNS from 6 to 18 months of age did show some reduction in their length-for-age, but the reduction was smaller than among control infants receiving CSB and there was a marked difference in the incidence of severe stunting between the intervention and control infants (Phuka et al., 2008). In another Malawian trial, infants provided with 40 g/day LNS lost approx. 0.3 z-score units in their mean LAZ between 6 and 12 months of age (Lin et al., 2008). Both of the earlier Malawian trials used an older CDC growth reference (Kuczmarski et al., 2002), the use of which typically yields higher values for LAZ at the age of 6 months and a larger drop between 6 and 12 months than if the new WHO growth reference were used (WHO, 2006).

Put together, the results from the current trial and those of the three earlier ones suggest that in the sub-Saharan African context LNS provision can slow down the process of growth faltering between 6 and 12 months of age, but it is not likely to reverse it. This is not surprising, since linear growth failure in such conditions typically has multiple etiologies (Waterlow, 1994) and very few single-pronged interventions have ever achieved a catch-up growth, either in a trial or programmatic setting (Dewey and Adu-Afarwuah, 2008). Prevention appears more feasible, but even then, the typical effect sizes have been rather modest (0.2–0.3 z-score units), i.e., comparable to the current trial (Dewey and Adu-Afarwuah, 2008). As indicated in the current trial and the earlier one by Phuka et al. (2008), this may result in a significant reduction in the incidence of the severest forms of stunting, but this is not likely to alleviate most of the negative consequences associated with growth failure (Grantham-McGregor et al., 2007). Earlier interventions would therefore be needed, supporting normal growth right from the fetal period, before any growth faltering could have happened. Based on the current study, it also appears that supplementation of the diet with milk-LNS will support normal linear growth only between 6 and 12 months of age, but not thereafter in the rural Malawian context.

Like two earlier trials (Adu-Afarwuah et al., 2007; Lin et al., 2008), our study provided no support to a hypothesis that dietary supplementation of 6–18-month-old infants with milk-LNS or soy-LNS would have any impact on the incidence of fever, diarrhea, or cough, i.e., the symptoms of common childhood infections. While the failure to see a reduction in morbidity may be disappointing, it is reassuring to notice no increase in fever/malaria incidence, despite the fact that both the LNS and the CSB supplements provided approximately 6 mg of iron per daily ration. Thus, while long-term supplementation with iron may increase morbidity for malaria and other infectious disease among iron-replete individuals in malaria-endemic areas (Sazawal et al., 2007), similar supplementation may be safe when iron is given as part of LNS that is usually mixed with normal baby food when given to the infants. The lower number of deaths among children that received LNS than those that received either nothing or CSB in our trial is an interesting but quite possibly spurious finding. An ongoing trial (iLiNS-DOSE, http://www.ilins.org) has a larger sample size and will be better powered to study the impact of LNS on infant mortality.

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Figures

Figure 1. Flow of participants in the study

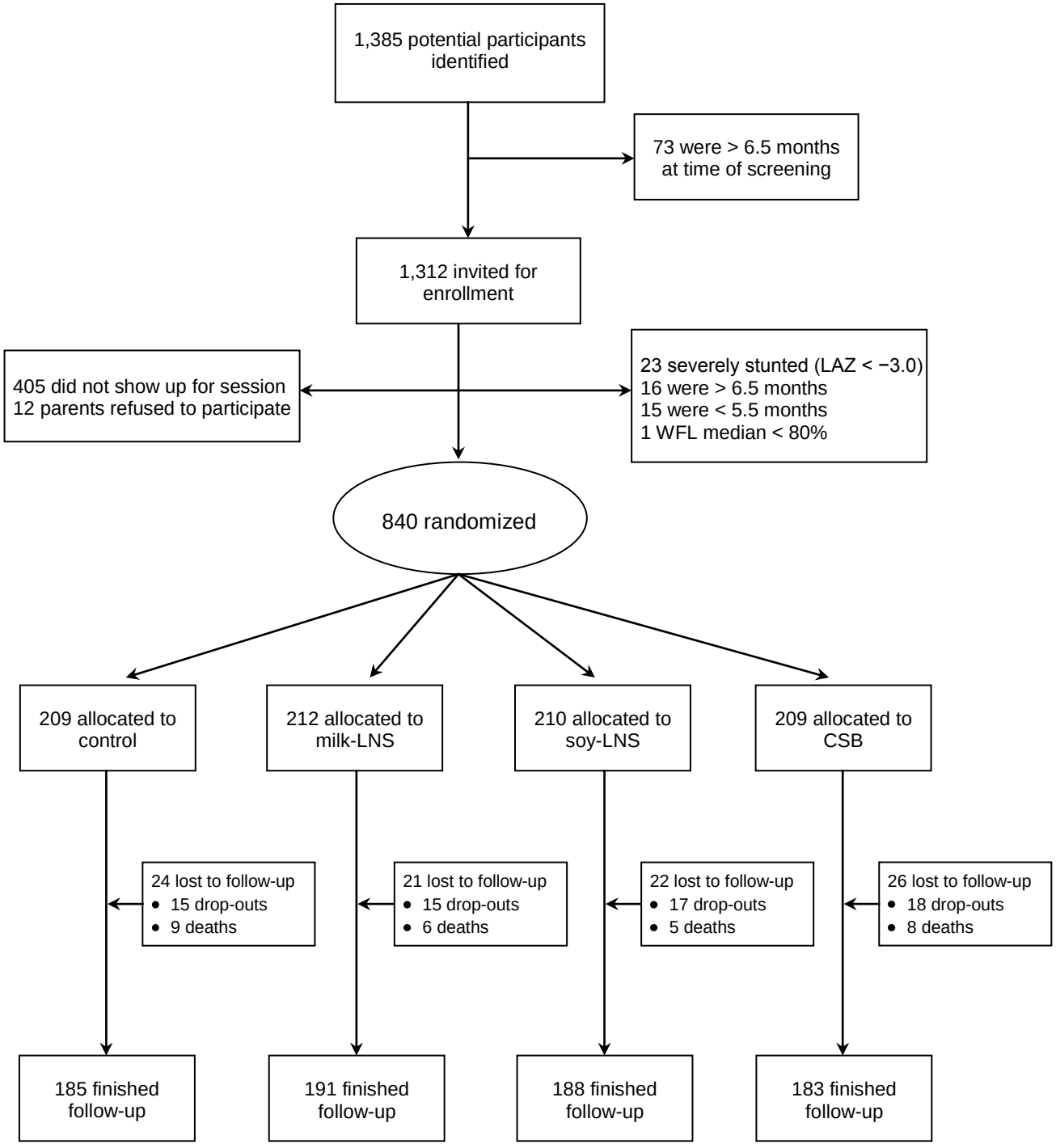
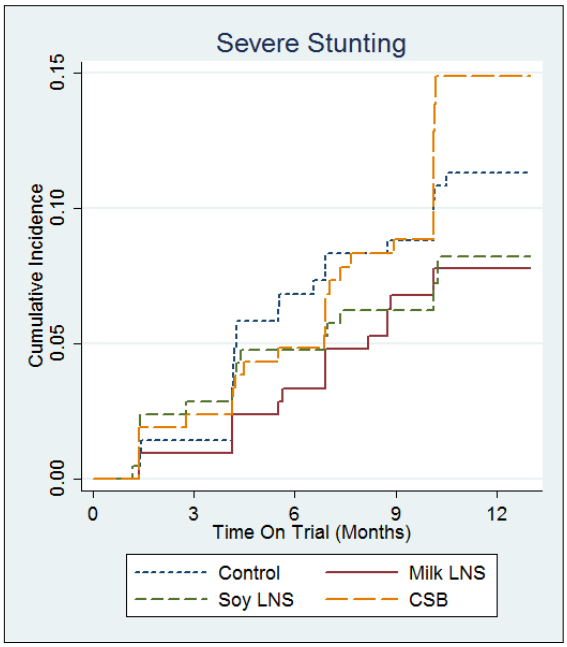
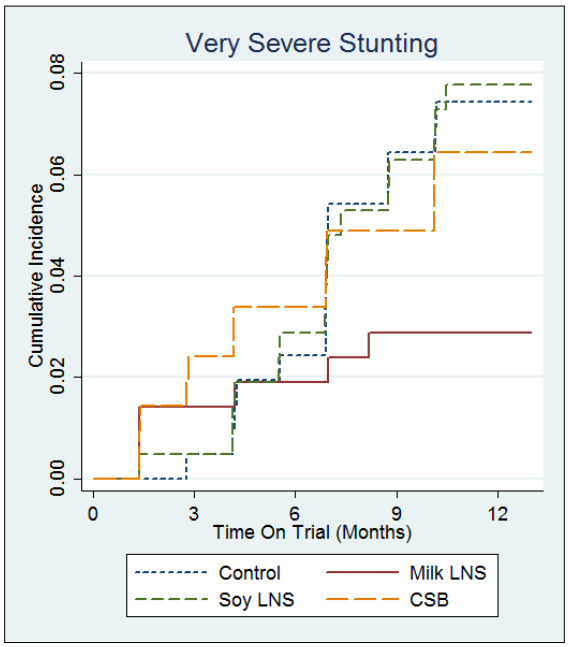


Figure 2. Cumulative incidence of severe (LAZ < −3.0) or very severe (LAZ < −3.5) stunting

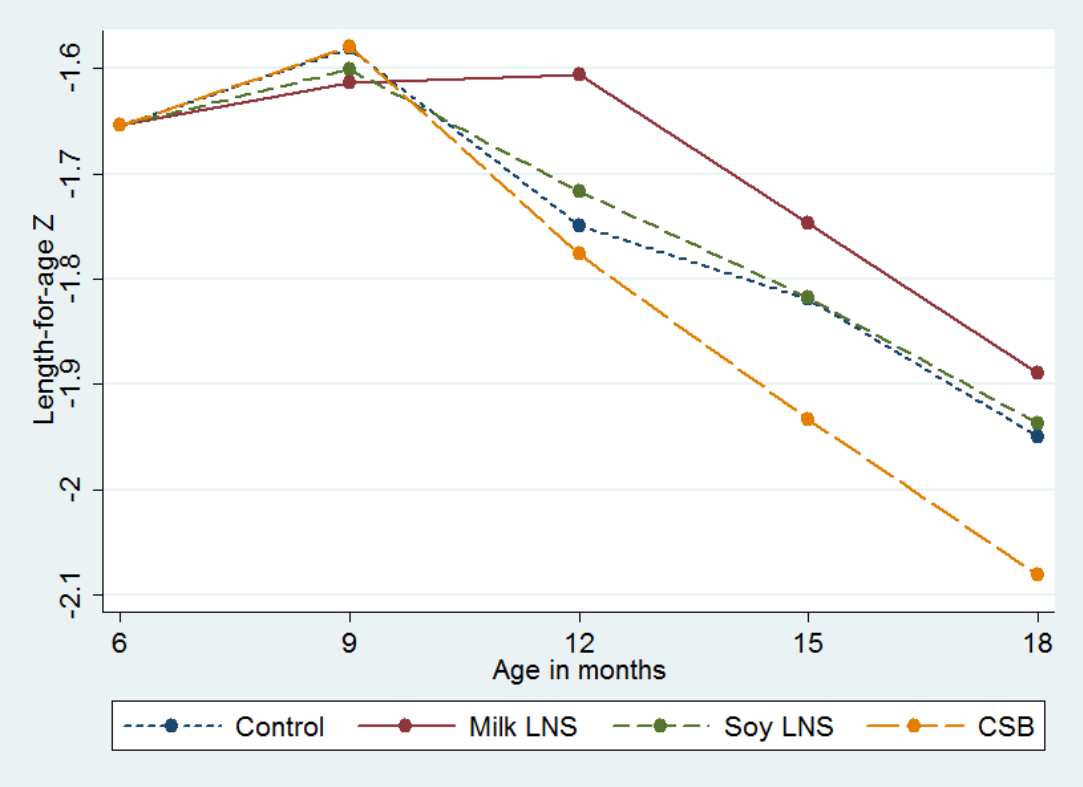


p=0.08, log rank test



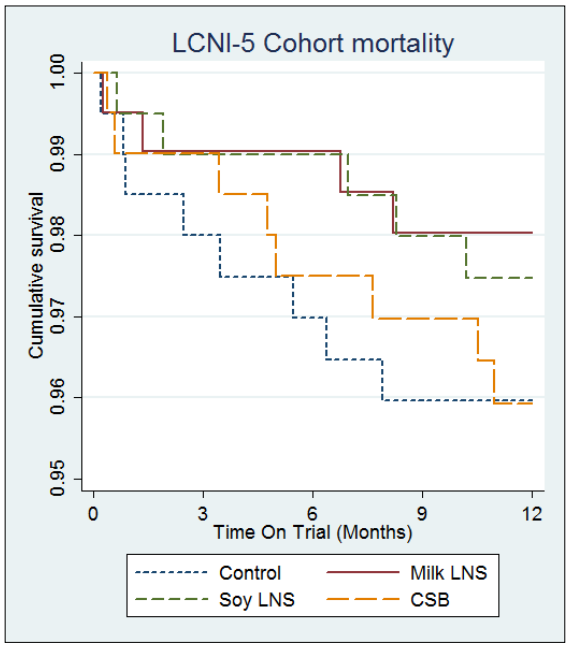
p=0. 17, log rank test

Figure 3. Mean length-for-age as a function of age, by study group

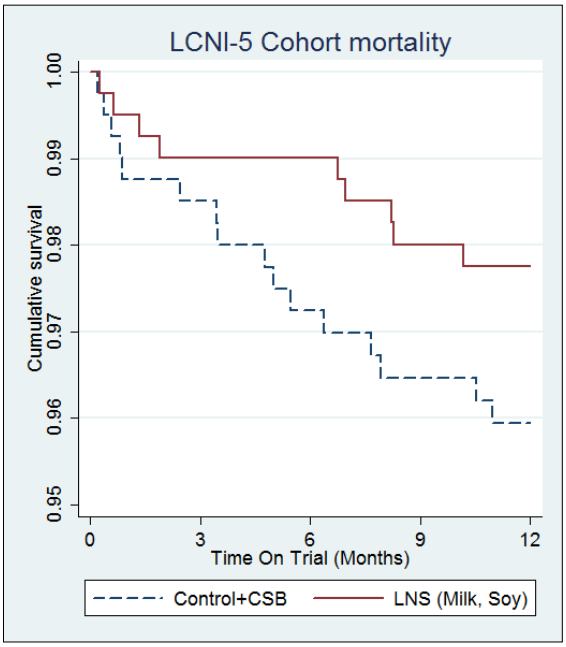


Adjusted for baseline LAZ and WLZ, gender, maternal height, and age at measurement (p=0.002, ANOVA)

Figure 4. Survival of study participants, by intervention group



p=0.5221, log rank test



p=0.1422, log rank test

Tables

Table 1. Energy and nutrient contents of the daily ration of the various supplements

	CSB	Milk-LNS	Soy-LNS
Nutrient amount	72 g	54 g	54 g
Energy (kcal)	284.4	284.8	276.1
Protein (g)	10.44	8.2	7.5
Fat (g)	3.08	17.9	18.5
Retinol (µg RE)	139	400	400
Folate (µg)	43.2	160	160
Niacin (mg)	3.456	6	6
Panthothenic ac.(mg)		2	2
Riboflavin (mg)	0.322	0.5	0.5
Thiamin (mg)	0.128	0.5	0.5
Vit. B6 (mg)	0.336	0.5	0.5
Vit. B12 (µg)	0.86	0.9	0.9
Vit. C (mg)	48	30	30
Vit. D (µg)		5	5
Ca (mg)	72	366	366
Cu (mg)		0.4	0.4
I (µg)		90	90
Fe (mg)	5.46	6	6
Mg (mg)		78.5	78.5
Se (µg)		20	20
Zn (mg)	3.6	6.0	6.0
Phosphorus (mg)		185.6	185.6
K (mg)		318.6	307.3
Manganese (mg)		0.6	0.6

Table 2. Background characteristics of participants at enrollment

Variable	Control	Milk-LNS	Soy-LNS	CSB
Male sex, No./total No. (%)	111/209 (53.1)	107/212 (50.5)	103/210 (49.1)	98/209 (46.9)
Mean age (SD), months	6.02 (0.23)	6.02 (0.25)	6.04 (0.25)	6.03 (0.24)
Mean weight (SD), kg	7.02 (0.89)	7.09 (0.97)	7.00 (0.88)	6.95 (1.01)
Mean length (SD), cm	63.2 (2.2)	63.2 (2.4)	63.0 (2.4)	62.9 (2.3)
Mean MUAC (SD), cm	13.3 (1.1)	13.4 (1.2)	13.3 (1.0)	13.3 (1.3)
Mean head circumference (SD), cm	42.6 (1.3)	42.8 (1.4)	42.7 (1.2)	42.6 (1.4)
Mean WAZ (SD); WHO 2006	−0.80 (1.06)	−0.70 (1.10)	−0.80 (1.12)	−0.85 (1.21)
Mean WAZ (SD); CDC 2000	−0.71 (1.03)	−0.61 (1.10)	−0.71 (1.11)	−0.76 (1.20)
Mean LAZ (SD); WHO 2006	−1.64 (0.97)	−1.59 (1.05)	−1.68 (1.11)	−1.72 (0.97)
Mean LAZ (SD); CDC 2000	−1.23 (0.88)	−1.19 (0.94)	−1.28 (1.02)	−1.31 (0.89)
Mean WLZ (SD); WHO 2006	0.41 (1.05)	0.50 (1.05)	0.46 (1.00)	0.42 (1.11)
Mean WLZ (SD); CDC 2000	0.46 (1.00)	0.55 (0.99)	0.51 (0.97)	0.47 (1.05)
Very severely stunted, No./total No. (%)	7/209 (3.4)	6/212 (2.8)	10/210 (4.8)	6/209 (2.9)
Mean blood hemoglobin concentration (SD), g/dl	9.4 (1.7)	9.6 (1.7)	9.3 (1.7)	9.5 (1.6)

Table 3. Maternal and household baseline characteristics

Variable	Control	Milk-LNS	Soy-LNS	CSB
Mean maternal height (SD), cm	157.0 (5.9)	156.8 (5.4)	156.2 (5.4)	156.5 (5.6)
Mean maternal weight (SD), kg	50.9 (6.8)	50.8 (6.6)	51.1 (6.7)	50.7 (6.3)
Mean maternal BMI (SD), kg/m^2	20.6 (2.4)	20.7 (2.2)	21.0 (2.4)	20.7 (2.4)
Mean maternal MUAC (SD), cm	25.1 (2.4)	25.2 (2.3)	25.3 (2.4)	25.2 (2.1)
Mean maternal education (SD), years	3.6 (3.4)	4.0 (3.7)	3.0 (3.1)	3.7 (3.1)
Mean paternal education (SD), years	3.7 (3.6)	4.3 (4.1)	3.7 (3.9)	4.7 (4.6)
Mean main guardian age (SD), years	27.4 (7.6)	28.7 (10.6)	29.1 (10.1)	26.7 (8.0)
Mean total number of persons in the household (SD)	4.8 (1.9)	5.0(2.0)	4.9 (1.7)	4.6 (1.5)
Mean total number of children below 5 years of age in the household (SD)	1.6 (0.7)	1.6 (0.8)	1.6 (0.7)	1.7 (0.9)
Mean number of bednets in the household (SD)	1.2 (0.9)	1.2 (0.9)	1.1 (0.8)	1.1 (0.9)

Table 4a. Point prevalence of malnutrition at 18 months of age (12 months of intervention)

Variable	Control	Milk-LNS	Soy-LNS	CSB	p value
Number of participants	185	190	188	181	
Percentage with very severe stunting (LAZ < −3.5) Relative risk (95% CI)	6.5 1.00 (ref.)	4.2 0.65 (0.27-1.55)	9.0 1.39 (0.68-2.84)	6.1 0.94 (0.42-2.07)	0.29
Percentage with severe stunting (LAZ < −3) Relative risk (95% CI)	14.1 1.00 (ref.)	11.1 0.79 (0.46-1.35)	16.0 1.14 (0.70-1.84)	16.0 1.14 (0.70-1.86)	0.47
Percentage with moderate to severe stunting (LAZ < −2) Relative risk (95% CI)	43.8 1.00 (ref.)	41.6 0.95 (0.75-1.20)	47.3 1.08 (0.87-1.35)	54.1 1.24 (1.00-1.53)	0.08
Percentage with severe underweight (WAZ < −3) Relative risk (95% CI)	3.2 1.00 (ref.)	2.1 0.65 (0.19-2.26)	4.8 1.48 (0.54-4.06)	5.0 1.53 (0.56-4.22)	0.42
Percentage with moderate to severe underweight (WAZ < −2) Relative risk (95% CI)	18.4 1.00 (ref.)	13.7 0.74 (0.47-1.19)	16.5 0.90 (0.58-1.40)	18.8 1.02 (0.67-1.57)	0.54
Percentage with severe wasting (WHZ < −3), No./total No. Relative risk (95% CI)	1.1 1.00 (ref.)	0 -	1.6 1.48 (0.25-8.73)	1.1 1.02 (0.15-7.18)	0.43
Percentage with moderate to severe wasting (WHZ < −2) Relative risk (95% CI)	3.8 1.00 (ref.)	5.3 1.39 (0.54-3.58)	4.3 1.13 (0.42-3.04)	4.4 1.17 (0.43-3.15)	0.92

Table 4b. Point prevalence of malnutrition at 12 months of age (6 months of intervention)

Variable	Control	Milk-LNS	Soy-LNS	CSB	p value
Number of participants	162	161	157	152	
Percentage with very severe stunting (LAZ < −3.5) Relative risk (95% CI)	3.7 1	1.9 0.50 (0.13-1.98)	5.7 1.55 (0.56-4.25)	5.9 1.60 (0.58-4.38)	0.24
Percentage with severe stunting (LAZ < −3) Relative risk (95% CI)	11.7 1	7.5 0.64 (0.32-1.27)	13.4 1.14 (0.64-2.04)	11.2 0.95 (0.52-1.77)	0.38
Percentage with moderate to severe stunting (LAZ < −2) Relative risk (95% CI)	39.5 1	34.2 0.86 (0.65-1.15)	42.0 1.06 (0.82-1.39)	44.1 1.12 (0.86-1.45)	0.30
Percentage with severe underweight (WAZ < −3) Relative risk (95% CI)	1.9 1	1.2 0.67 (0.11-3.96)	3.2 1.72 (0.42-7.08)	5.9 3.20 (0.88-11.6)	0.08
Percentage with moderate to severe underweight (WAZ < −2) Relative risk (95% CI)	18.5 1	9.9 0.54 (0.30-0.95)	14.0 0.76 (0.46-1.25)	16.5 0.89 (0.55-1.44)	0.16
Percentage with severe wasting (WHZ < −3) Relative risk (95% CI)	0 -	0 -	0.6 -	0.7 -	0.55
Percentage with moderate to severe wasting (WHZ < −2) Relative risk (95% CI)	2.5 1	0 0	1.9 0.77 (0.18-3.40)	5.3 2.13 (0.66-6.93)	0.02

Table 5. Incidence of various forms of undernutrition by intervention group

Variable	Control	Milk-LNS	Soy-LNS	CSB	p value
Ever developed very severe stunting (LAZ < −3.50), No./total No. (%) Relative risk (95% CI)	15/202 (7.4) 1.00 (ref)	6/206 (2.9) 0.39 (0.16-0.99)	16/200 (8.0) 1.08 (0.55-2.12)	13/203 (6.4) 0.86 (0.42-1.77)	0.14
Ever developed severe stunting (LAZ < −3), No./total No. (%) Relative risk (95% CI)	23/195 (11.8) 1.00 (ref)	17/195 (8.7) 0.70 (0.38-1.28)	17/186 (9.1) 0.77 (0.43-1.40)	30/193 (15.5) 1.32 (0.79-2.18)	0.10
Ever developed moderate to severe stunting (LAZ < −2), No./total No. (%) Relative risk (95% CI)	41/138 (29.7) 1.00 (ref)	40/140 (28.6) 0.96 (0.67-1.39)	46/128 (35.9) 1.21 (0.86-1.71)	50/126 (39.7) 1.34 (0.96-1.87)	0.18
Ever developed severe underweight (WAZ < −3), No./total No. (%) Relative risk (95% CI)	11/205 (5.4) 1.00 (ref)	3/208 (1.4) 0.27 (0.08-0.95)	10/206 (4.9) 0.91 (0.39-2.08)	12/200 (6.0) 1.12 (0.51-2.48)	0.11
Ever developed moderate to severe underweight (WAZ < −2), No./total No. (%) Relative risk (95% CI)	26/181(14.4) 1.00 (ref)	22/190 (11.6) 0.81 (0.47-1.37)	24/180 (13.3) 0.93 (0.55-1.55)	25/171 (14.6) 1.02 (0.61-1.69)	0.82
Ever developed severe wasting (WHZ < −3), No./total No. (%) Relative risk (95% CI)	2/209 (1.0) 1.00 (ref)	2/212 (0.9) 0.99 (0.14-6.93)	4/210 (1.9) 1.99 (0.37-10.80)	3/209 (1.4) 1.50 (0.25-8.88)	0.80
Ever developed moderate to severe wasting (WHZ < −2), No./total No. (%) Relative risk (95% CI)	11/205 (5.4) 1.00 (ref)	13/210 (6.2) 1.15(0.53-2.52)	11/205 (5.4) 1.00(0.44-2.25)	18/206 (8.7) 1.63(0.79-3.36)	0.45

Table 6. Mean change in various anthropometric outcomes, by intervention group

Variable	Control	Milk-LNS	Soy-LNS	CSB	p value
Mean change in weight (SD), kg	2.42 (0.77)	2.53 (0.79)	2.46 (0.89)	2.33 (0.88)	0.12
Difference in mean compared to controls (95% CI), g		110 (−45.9–266.0)	40 (−127.0–207.0)	−90 (−258.0–77.8)	
Mean change in length (SD), cm	13.0 (2.0)	13.2 (1.7)	13.0 (2.0)	12.9 (2.6)	0.43
Difference in mean compared to controls (95% CI), cm		0.2 (−0.2–0.6)	0.0 (−0.4–0.4)	−0.1 (−0.6–0.4)	
Mean change in MUAC (SD), cm	0.51 (0.96)	0.62 (0.95)	0.51 (1.09)	0.53 (0.98)	0.62
Difference in mean compared to controls (95% CI), cm		0.11 (−0.08–0.30)	0.00 (−0.21–0.21)	0.02 (−0.18–0.22)	
Mean change in head circumference (SD), cm	3.9 (0.8)	3.9 (0.7)	3.9 (0.9)	3.9 (1.0)	0.90
Difference in mean compared to controls (95% CI), cm		0 (−0.15–0.15)	0 (−0.17–0.17)	0 (−0.19–0.19)	
Mean change in WAZ (SD)	−0.31 (0.72)	−0.21 (0.77)	−0.24 (0.92)	−0.35 (1.00)	0.37
Difference in mean compared to controls (95% CI)		0.10 (−0.50–0.25)	0.07 (−0.10–0.24)	−0.04 (−0.22–0.14)	
Mean change in LAZ (SD)	−0.31 (0.71)	−0.23 (0.68)	−0.28 (0.76)	−0.31 (1.00)	0.70
Difference in mean compared to controls (95% CI)		0.08 (−0.06–0.22)	0.03 (−0.12–0.18)	0.00 (−0.18–0.18)	
Mean change in WLZ (SD)	−0.65 (0.93)	−0.57 (1.02)	−0.61 (1.05)	−0.73 (1.15)	0.48
Difference in mean compared to controls (95% CI)		0.08 (−0.12–0.28)	0.04 (−0.16–0.24)	−0.08 (−0.30–0.13)	
Mean change in blood hemoglobin concentration (SD), g/L	7.7 (23.6)	5.9 (22.2)	7.6 (22.4)	7.0 (20.8)	0.88
Difference in mean compared to controls (95% CI), g/L		−1.8 (−6.7–3.1)	−0.1 (−5.1–4.9)	−0.7 (−5.6–4.1)	

Table 7. Longitudinal prevalence of common childhood illness symptoms recorded by guardians

Illness symptom	Control (n=62,278 days)	Milk-LNS (n=65,557 days)	Soy-LNS (n=64,165 days)	CSB (n=62,433 days)	p value[c]
Cough	3,778[a] (6.4%[b])	3,684 (5.6%)	3,406 (5.5%)	3,265 (5.2%)	0.23
Fever	3,316 (5.5%)	3,190 (4.8%)	3,010 (4.7%)	3,029 (4.8%)	0.33
Diarrhea	2,809 (4.6%)	3,109 (4.8%)	2,897 (4.8%)	2,780 (4.5%)	0.89
Other symptom	1,101 (1.7%)	812 (1.3%)	781 (1.2%)	879 (1.4%)	0.33
Any symptom	8,982 (14.7%)	8,998 (13.6%)	8,392 (13.4%)	8,488 (13.5%)	0.57

[a] Mean days with the defined illness symptom (from all days at risk). The analysis was done by first calculating the proportion of days for each child and then by calculating a group mean for the values for individual children.
[b] Percentage of days with the defined symptom in group.
[c] ANOVA (mean percentage of days with symptom per child).

Table 8. Yearly incidence of common childhood illnesses leading to a non-scheduled visit to a local health centre

Clinical diagnosis	Control (69,928 days)	Milk-LNS (72,699 days)	Soy-LNS (71,133 days)	CSB (70,264 days)	p value[c]
Malaria	2.26[a] (434[b])	2.08 (427)	2.03 (385)	2.15 (413)	0.68
Pneumonia	1.33 (218)	1.13 (214)	1.16 (232)	1.07 (200)	0.65
Other respiratory infections	0.66 (72)	0.48 (92)	0.39 (78)	0.39 (75)	0.59
Gastroenteritis	0.13 (27)	0.24 (45)	0.19 (38)	0.27 (24)	0.67
Trauma	0.01 (1)	0.00 (1)	0.00 (0)	0.00 (1)	0.69
Skin infection	0.11 (23)	0.14 (27)	0.17 (29)	0.15 (30)	0.63
Other Illnesses	0.51 (96)	0.39 (78)	0.33 (66)	0.36 (66)	0.14
Total	**5.02 (871)**	**4.46 (884)**	**4.28 (828)**	**4.40 (809)**	**0.33**

[a] Mean number of episodes/year at risk/child. The analysis was done by first calculating the number of episodes/year for each child and then by calculating a group mean for the values for individual children.
[b] Total number of episodes in the defined intervention group.
[c] ANOVA (mean number of episodes/year at risk per child).

Table 9. Mortality and characteristics of participants that died

Variable	Control	Milk-LNS	Soy-LNS	CSB	p value
Number of deaths	8	4	5	8	0.54
Number (%) of males	7 (88%)	2 (50%)	4 (80%)	5 (63%)	0.49
Mean age at death (SD), months	9.5 (2.8)	10.4 (4.0)	11.6 (4.1)	13.0 (6.0)	0.47
Mean duration of illness before death (SD), days	10.7 (7.8)	9.0 (3.9)	7.0 (5.0)	7.4 (5.8)	0.70