Impact of food supplements on hemoglobin, iron status and inflammation in children with moderate acute malnutrition: a 2x2x3 factorial randomized trial in Burkina Faso

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Short running head: Impact of supplementary foods on hemoglobin, iron status and inflammation.

List of abbreviations: corn-soy blend (CSB); dehulled soy (DS); dry-skimmed milk (DSM); hemoglobin (Hb); iron-deficiency anemia (IDA); intention-to-treat (ITT); per protocol (PP); lipid-based nutrient supplements (LNS); moderate acute malnutrition (MAM); mid-upper-arm circumference (MUAC); ready-to-use therapeutic foods (RUTF); serum α_1-acid glycoprotein (AGP); serum c-reactive protein (CRP); serum ferritin (SF); serum ferritin adjusted for inflammation (SFAI); serum soluble transferrin receptor (sTfR); severe acute malnutrition (SAM); soy isolate (SI); weight-for-height z-score (WHZ).

Trial registration: The trial is registered at www.controlled-trials.com (ISRCTN42569496).

Abstract

Background: Children with moderate acute malnutrition (MAM) are treated with lipid-based nutrient supplements (LNS) or corn-soy-blends (CSB) but little is known about their impact on hemoglobin (Hb), iron status and inflammation.

Objective: The objective was to investigate the impact of supplementary foods for treatment of MAM on Hb, iron status, inflammation and malaria.

Design: A randomized 2x2x3 factorial trial was conducted in Burkina Faso. Children aged 6-23 months with MAM received 500 kcal/day as LNS or CSB, containing either dehulled soy (DS) or soy isolate (SI) and different quantities of dry skimmed milk (0, 20 or 50% of total protein) for 12 weeks. The trial was double-blind with regard to quality of soy and quantity of milk, but not matrix (CSB vs LNS). Hb, serum ferritin (SF), serum soluble transferrin receptor (sTfR), serum C-reactive protein (CRP), serum α_1-acid glycoprotein (AGP) and malaria antigens were measured at inclusion and after supplementation (ISRCTN42569496).

Results: Between September 2013 and August 2014, 1609 children were enrolled. Among these, 61 (3.8%) were lost to follow-up. During the 12-week supplementation period, prevalence of anemia, low SF adjusted for inflammation (SFAI), elevated sTfR and iron deficiency anemia decreased by 16.9, 8.7, 12.6 and 10.5 percentage points. Children who received LNS compared to CSB had higher Hb (2 g/L, 95% CI: 1, 4), SFAI (4.2 µg/L, 95% CI: 2.9, 5.5), and CRP (0.8 mg/L, 95% CI: 0.4, 1.2) and lower sTfR (-0.9 mg/L, 95% CI: -1.3, -0.6) after the intervention. Replacing dehulled soy with soy isolate or increasing milk content, did not affect Hb, SFAI, sTfR or CRP.

Conclusion: Supplementation with LNS compared to CSB led to better Hb and iron status, but overall prevalence of anemia remained high. The higher concentrations of acute phase proteins in children who received LNS requires further investigation.

Key words: Acute phase proteins, Africa, anemia, corn-soy blends, young children, iron status, inflammation, lipid-based nutrient supplements, malaria, moderate acute malnutrition.

Introduction

Moderate acute malnutrition (MAM) is defined by a weight-for-height z-score (WHZ) <-2 and ≥-3 (moderate wasting) and/or a mid-upper arm circumference <125 mm and ≥115mm (1). While the number of children with MAM based on the above definition is unknown, it has been estimated that 33 million children suffer from moderate wasting alone (2). MAM occurs in both non-emergency and emergency settings. In non-emergency settings it may be possible to improve nutritional status through nutrition counselling and optimizing intake of family foods. In emergency settings however, where energy and nutrient needs cannot be met using local foods, MAM is treated with supplementary foods either in the form of fortified blended foods, such as corn-soy blends, or lipid-based nutrient supplements (LNS) (3). To date there are still questions regarding the effectiveness of MAM programs in emergencies (3). In 2012, WHO published a proposed nutrient composition for supplementary foods for children with MAM but called for more research (4).

Studies investigating different food supplements for MAM treatment have mainly assessed anthropometric outcomes (5–11). However, anthropometric deficits are likely to be accompanied by micronutrient deficiencies and the return to anthropometric measurements in the normal range does not necessarily mean that children are well-nourished in terms of micronutrient status. Anemia affects an estimated 71% of under 5 year old children in west and central Africa (12). Anemia leads to shortness of breath, fatigue and has been associated with poor cognitive development, impaired work capacity and increased susceptibility to infections (13). Two of its predominant causes, namely iron deficiency and infection, especially malaria, are common in children with MAM in Burkina Faso (14,15).

We have previously described the impact of food supplements either in the form of LNS or corn-soy blends (CSB), with either soy isolate (SI) or dehulled soy (DS) and with different quantities of dry skimmed milk (DSM) on anthropometric outcomes and accretion of fat-free tissue in children with MAM (16). The objective of this paper was to investigate the impact of these supplements on hemoglobin, iron status, inflammation and malaria.

Subjects and methods

Study area and participants

This study was part of the Treatfood trial, a randomized trial with a 2x2x3 factorial design, investigating the effectiveness of food supplements for the treatment of MAM. As previously described (16), research sites were constructed at 5 governmental health centers (Gomponsom, Latoden, Bagaré, Bokin and Samba) in the Province du Passoré, Northern Region, Burkina Faso and staffed by the Alliance for International Medical Action. The catchment area covered 143 villages with a total population of ~258,000.

Screening for participants took place in villages either by community health workers using mid-upper arm circumference (MUAC) tapes or by designated screening teams using both MUAC and WHZ. Children could also present at the site based on the caregiver's initiative or be referred from a health center. A final assessment for eligibility was carried out by study staff at the sites. Children with MAM were enrolled in the trial if they were aged 6-23 months, resident in the catchment area and their parents/caregivers had given informed consent for the children to participate. Children who were enrolled in another nutritional program, had been treated for severe acute malnutrition (SAM) or been hospitalized in the last two months, had an illness requiring hospitalization, a hemoglobin <50 g/L, a suspected

allergy to milk, peanuts, CSB or LNS, or a severe disability were not eligible. Recruitment took place from September 2013 until August 2014.

Randomization and supplementary foods

Stratified, block randomization was used to allocate participants to one out of 12 supplements, where stratification was done by site and block sizes were either 12 or 24. Blocked randomization was used to ensure that children were allocated evenly to the trial arms and different block sizes were used to make the allocation process less predictable. Random sequences were created by a person otherwise not involved in the trial using www.randomization.com.

Supplements were either a LNS or a CSB (referred to as the matrix) with either DS or SI and either 0%, 20% or 50% of protein from DSM (M0, M20 or M50) (**Table 1**). The trial was double-blind with respect to soy quality and milk content, but not matrix. Supplements were designated by a 1-letter code by the manufacturer, and a code-key was kept in a sealed envelope in a safe. The supplements were packed in individual boxes containing a full 12-week treatment for 1 participant (either 6 bags of CSB or 84 sachets of LNS). During production, each box, bag and sachet was labelled with a 12-letter sequence containing the relevant 1-letter code in a fixed position and the 11 remaining letters in random order. Only one individual in Burkina Faso, otherwise not involved in recruitment and data collection was aware of the position of the 1-letter code. This individual relabelled boxes and supplements with individual study identification numbers (IDs). At enrolment, children were given a study ID by staff without access to the random sequences or supplements.

Each participant received the allocated supplement for a 12-week period, even if they recovered from MAM before. LNS products were provided in individual sachets of 92 g per daily ration and CSB products were provided in 1.7 kg bags per 14-day ration. All supplements consisted of 500 kcal per daily serving (120 g of CSB or 92 g of LNS). LNS products were ready-to-use and CSB products needed to be cooked using water and consumed as a porridge. Supplements were manufactured by GC Rieber Compact A/S (Bergen, Norway), who were otherwise not involved in the trial design or interpretation of data. Nutrient composition of products complied with WHO's technical note for the management of MAM (4). The recipes (16) and micronutrient composition (17) of these products have previously been published. Briefly, the supplements contained approximately 12 mg of elemental iron added in the form of ferrous gluconate, 14 mg of zinc (as zinc gluconate) and 1.15 mg of copper in the form of copper gluconate. Content of water soluble vitamins was higher in CSBs to account for degradation during cooking. Vitamin C content for example was doubled in CSB compared to LNS (188 mg vs 94 mg) and vitamin B_{12} was 4.1 µg in CSB products and 3.2 µg in LNS.

Data collection

During the intervention period children visited the health center every 2 weeks. Children who missed scheduled visits were visited by community health workers and encouraged to return for follow-up. At baseline, study nurses collected information about sociodemographic characteristics, 2-week retrospective morbidity as well as vaccination status and carried out a clinical examination. Children who were not up-to-date with vaccinations were referred to a health center. Children received albendazole (200 mg if < 8 kg; 400 mg > 8 kg) and vitamin A (100,000 IU if 4-8 kg; 200,000 IU if >8 kg) if they had not received a supplement in the previous 6 months. Weight was measured to the nearest 100 g using an electronic scale with

125 double weighing function (Seca model 881 1021659). Length was measured to the nearest 1
126 mm with a wooden height board once a month. WHZ was determined at sites using WHO
127 field tables and later recalculated using the package "zscore06" in STATA 12 (College
128 Station, Texas, USA). MUAC was measured on the left arm to the nearest 1 mm using a
129 standard measuring tape. Anthropometric measurements were taken in duplicate by trained
130 staff. A qualitative 24-hour recall was used to collect dietary data. Venous blood was
131 collected from the arm at baseline and after the supplementation period. One drop was used
132 for diagnosis of malaria (*Plasmodium falciparum)* using a rapid diagnostic test (SD Bioline
133 Malaria Ag Pf) and one drop was used to measure hemoglobin (Hb) on site using a HemoCue
134 device (Hb 301, Ängelholm, Sweden). The HemoCue was calibrated at the end of every
135 month with a control solution. The remaining blood was put into a sample tube with clot
136 activator (BD reference #368492) and transported to the trial laboratory in a cold box at 2-
137 8°C. Serum was isolated following centrifugation (EBA 20 S Hettich) and stored at -20°C
138 until shipment to VitMin Lab in Willstaedt, Germany for analysis. Serum C-reactive protein
139 (CRP), α1-acid glycoprotein (AGP), serum soluble transferrin receptor (sTfR) and serum
140 ferritin (SF) were determined using a combined sandwich enzyme-linked immunosorbent
141 assay (18). All samples were measured in duplicate and the intra- and interassay coefficients
142 of variation were <10%. Samples were frozen and thawed only once prior to analysis.
143 The thresholds used for defining abnormal values were as follows: Hb <110 g/L (19), SF <12
144 µg/L (19), sTfR >8.3 mg/L (18), CRP >10mg/l (20), AGP >1 g/L (21). Since SF is affected
145 by inflammation and therefore does not reliably reflect iron status in populations where
146 inflammation is common, SF was adjusted for inflammation prior to analysis using regression
147 models as previously described (15) and is referred to as SF adjusted for inflammation
148 (SFAI). Iron deficiency anemia (IDA) was defined as Hb < 110g/L and SFAI < 12 µg/L.
149

150 ***Statistical analyses***

151 To be able to detect a 0.6 SD difference between any 2 combinations of the 3 factors with
152 80% power and a 5% significance level, while allowing for 20% loss to follow-up the
153 required sample size was 134 children per arm or 1608 in total (16). A 0.6 SD difference
154 approximately translates to a 10g/L difference for Hb, a 1.6µg/L difference for SFAI, a
155 0.9mg/L difference for sTfR, a 3.4 mg/L difference for CRP and a 0.95 g/L difference for
156 AGP. The outcomes reported here, namely Hb, sTfR, SF, CRP and AGP were secondary
157 outcomes of the trial. The primary outcome which was an increment in fat-free tissue has
158 been reported elsewhere (16).

159

160 Data were double entered into Epidata 3.1. software (Epidata Association, Odense, Denmark)
161 and double entry checks were carried out on a daily basis. All statistical analyses were carried
162 out using STATA 12. Characteristics of the study population were summarized as percentage,
163 mean ± SD or, if not normally distributed, as median (interquartile range). Chi^2 tests were
164 used to test for differences in proportions. T-tests and one-way ANOVAs were used to test
165 for differences in means for 2 or more groups, respectively. Changes in concentrations of Hb,
166 and of biomarkers of iron status and inflammation before and after the intervention were
167 assessed using t-tests. McNemar's Chi^2 was used to test for differences in proportions over
168 time.

169

170 The main analysis was based on the intention-to-treat (ITT) principle using available-case
171 data. A per protocol (PP) analysis was also carried out. Linear mixed models were used to
172 evaluate the effect of matrix, soy quality and amount of DSM on Hb, SF, SFAI, sTfR, CRP
173 and AGP and logistic mixed models for the effect on malaria. Site was included in the model
174 as a random effect. As a first step, all 3-way interactions between the 3 factors (matrix,

quality of soy and quantity of milk) were tested for using likelihood ratio tests and, where possible, reduced to 2-way interactions or main effects. Pairwise comparisons of means were then performed using model-based post-hoc tests in the reduced models. Where it was not possible to reduce models, multiplicity was taken into account by adjusting all pairwise comparisons using the Bonferroni method. Results were presented in terms of estimated means with 95% confidence intervals. Analyses were done based on two models: model 1 was adjusted only for baseline measure of the outcome and site, and model 2 included adjustment for baseline measure of the outcome, age, sex, MUAC, WHZ and month of admission. Log transformations were applied to achieve normally distributed variables if needed and estimates were subsequently back-transformed (22). Effect modification was assessed for the factors and if present, investigated through sub-group analysis. Effect modification was assessed for the following variables: admission criteria (MUAC only, WHZ and MUAC, WHZ only), season, elevated CRP, elevated AGP, anemia, malaria and stunting at baseline. Model checking was based on residual and normal probability plots.

Ethical considerations

All children in need received treatment free of charge according to an adapted version of the Integrated Management of Childhood Illnesses guidelines (23,24) and the national protocol. Children who developed SAM during the intervention period were treated with ready-to-use therapeutic food (RUTF; Plumpy'Nut®, Nutriset, Malaunay, France). Children who did not recover from MAM during the trial subsequently received treatment with RUTF. If they did still not recover at the end of 4 weeks of supplementation with RUTF, they were referred to the hospital for medical investigation. Children who had an Hb <110 g/L at the end of the intervention period received iron and folic acid supplements; children who at any point had an Hb <50 g/L were referred to the hospital. The study was carried out in accordance with the

declaration of Helsinki. Consent was obtained from caregivers, prior to inclusion, verbally and in writing (signature or fingerprints). Data were kept confidential and in a locked facility. The study was approved by the Ethics Committee for Health Research of the government of Burkina Faso (2012-8-059) and consultative approval was obtained from the Danish National Committee on Biomedical Research Ethics (1208204). The trial was registered in the International Standard Randomized Controlled Trial Number registry under the number ISRCTN42569496.

Results

As previously described (16), of the 3398 children assessed, 1613 were randomized according to the 2x2x3 factorial design and four were later excluded as ineligible. A total of 1609 children were enrolled in the study (**Figure 1**). Baseline equivalence was achieved with regard to key potential confounders (**Table 2**). Furthermore, there were no differences between treatment groups in proportion of children who consumed foods from any of 7 food groups, i.e. grains, legumes and nuts, dairy foods, eggs, flesh foods, vitamin A rich foods and other fruit and vegetables.

Among the 1609 children who were randomized, 61 (3.8%) were lost to follow-up. Among the 1548 children who completed the intervention, 1546 (96.1%) children had baseline and end-line data for hemoglobin, 1523 (94.7%) for malaria and 1480 (92%) for iron status and inflammation biomarkers and were included in the ITT analysis. Children who developed SAM and were switched to RUTF (n=102), children who received ready-to-use supplementary foods (Plumpy'Sup®, Nutriset, Malaunay, France) because of an unconfirmed suspicion of *Salmonella* in one of the CSB products (n=17), and children who received iron

and folic acid supplements by error (n=69) or a combination were excluded from per protocol analysis (**Figure 1**).

As previously described, mean baseline Hb was 100 ±16 g/L, median SFAI was 16 (8,30) µg/L and median sTFR was 12.6 (9.1,17.3) mg/L (15). Baseline Hb differed by admission criteria after adjusting for age and sex (p=0.001): it was 4 g/L (95% CI: 2, 7) higher in children admitted based on only low WHZ compared to those admitted based on low MUAC only and 3 g/L (95% CI: 1, 4) higher in children admitted based on low MUAC and WHZ compared to MUAC only. There were no differences in baseline SFAI and sTfR according to admission criteria. Hb increased by 7 g/L (95% CI: 6, 7) during the intervention (p<0.001), which corresponded to 16.9 percentage points drop in prevalence of anemia (**Table 3**). SFAI increased and sTfR, CRP and AGP decreased during the intervention period (p<0.001). Prevalence of low SFAI, elevated sTfR and IDA decreased 8.7, 12.6 and 10.5 percentage points, respectively. Prevalence of elevated CRP, elevated AGP and malaria decreased by 5.9, 19.9 and 9.2 percentage points, respectively (**Table 3**).

Impact of supplements on Hb and biomarkers of iron status

Compared to CSB, LNS resulted in higher Hb (2 g/L, 1, 4), higher SFAI (4.2 µg/L, 2.9, 5.5) and lower sTfR (-0.9 mg/L, -1.3, -0.6) after adjustment for baseline measure, MUAC, WHZ, age, sex, month of admission and site (**Table 4**). Results were similar if adjusted only for baseline measure and site (**Table 4**) and in PP analysis (**Supplemental Table 1**). After the intervention, the prevalence of anemia was 8 percentage points lower (p=0.001), of low SFAI 10 percentage points lower (P<0.001), and of elevated sTfR 5 percentage points lower (p=0.004) in children who had received LNS compared to children who received CSB supplements (**Table 4**). Similarly, the prevalence of IDA was 24.2% (n=183) in the CSB

group and 14.3% (n=110) in the LNS group after the intervention (p<0.001). There was no effect of soy quality and milk protein content in ITT (**Supplemental Table 2 and 3**) and PP analysis (**Supplemental Table 1**).

Season modified the effect of LNS vs CSB on SFAI (interaction, p=0.02) and sTfR (interaction, p=0.007): SFAI was 5.3 µg/L (95% CI: 3.7, 6.9) higher and sTfR 1.3 mg/L (95% CI: -1.7, -0.9) lower in children who had received LNS compared to CSB during the dry season but there was no difference during the rainy season. The effect of LNS vs CSB on Hb was modified by baseline AGP (interaction, p=0.03), whereby the effect of LNS was greater in children with elevated AGP at baseline (0.36 g/L, 95% CI: 0.2, 0.53) and was not significant if AGP was <1 g/L (0.04 g/L, 95% CI: -0.18, 0.27). The effect of LNS vs CSB on SFAI was modified by CRP (interaction, p=0.045) and malaria (interaction, p=0.02) at baseline, i.e. it was greater in children who had elevated CRP at baseline (6 µg/L, 95% CI: 3.8, 8.2) than those who did not (3.2 µg/L, 95% CI: 1.5, 4.8) and in children with malaria (6.1, 95% CI: 4.1, 8.2) than those without (2.9 µg/L, 95%CI: 1.2, 4.6). We did not find any effect modification of admission criteria (MUAC only, WHZ and MUAC, WHZ only), anemia, low SFAI or elevated sTfR or stunting at baseline on Hb or biomarkers of iron status.

Impact of supplements on acute phase proteins

After the intervention, children who received LNS supplements had a 0.8 mg/L (95% CI: 0.4, 1.2) higher mean CRP than those who received CSB (**Table 4**) after adjustment for baseline measure, MUAC, WHZ, age, sex, month of admission and site (**Table 4**). Results were similar if adjusted only for baseline measure and site (**Table 4**) and in PP analysis (**Supplemental Table 1**). The prevalence of elevated CRP was 4.5 percentage points higher among children who had received LNS compared to those who received CSB supplements

(**Table 4**). There was no effect of soy quality and milk protein content in ITT (**Supplemental Table 2 and 3**) and PP analysis (**Supplemental table 1**). We found an interaction between stunting and matrix, whereby the effect of LNS compared to CSB on CRP was greater in children who were stunted (1.2 mg/L, 95% CI: 0.7, 1.8 mg/L) than in those who were not (0.4 mg/L, 95% CI: -0.12, 0.86). We did not find any effect modification between admission criteria, elevated acute phase proteins, anemia, low SFAI or elevated sTfR and malaria at baseline with any of the factors (interaction, p >0.05).

Similarly to CRP, AGP was also higher in children who received LNS compared to those who received CSB. However, there was a significant 3-way interaction between the factors (p=0.03 in model 1, p=0.045 in model 2) whereby LNS-DS-50M led to higher AGP than LNS-SI-50M (0.2 g/L, 95% CI: 0.1, 0.4). Results were similar in PP analysis (**Supplemental Table 1**) but in the latter the interaction was not significant. There were no effects of soy quality or milk protein content in ITT analysis (**Supplemental Table 2 and 3**) or PP analysis (**Supplemental Table 1**). The effect of LNS vs CSB was modified by season (interaction, p=0.01), whereby AGP was higher in children who received LNS vs CSB if they were admitted during the rainy season (0.17g/L, 95% CI: 0.08, 0.26) compared to the dry season (0.03 g/L, 95%CI: -0.04, 0.09).

Impact on malaria prevalence

There was no effect of matrix **(Table 4)**, quality of soy **(Supplemental Table 2)** and quantity of milk **(Supplemental Table 3)** on prevalence of malaria. Results were similar in the PP analysis. There were no interactions between any of the factors and season, admission criteria, anemia, low SFAI or elevated sTfR, CRP or AGP at baseline.

Discussion

In this randomized trial we have shown that LNS was more effective in improving Hb and iron status than CSB but that concentrations of inflammatory markers were higher in children who received LNS. There was no impact of quality of soy and quantity of milk.

Studies in children with MAM have previously reported better outcomes from LNS compared to CSB or CSB++ (also known as supercereal+) in terms of weight gain (6,9,25), MUAC gain and time to recovery (6). Better recovery rates have been found if LNS were compared to standard CSB (5,9,25) but not if compared to CSB++ (6,26). Furthermore, based on data from the same trial, we have recently shown that gain of fat-free tissue and rates of anthropometric recovery were higher in children who received LNS compared to those who received CSBs (16). Data on the impact of supplements for treatment with MAM on Hb and iron status is, however, limited. One study carried out in Mali by Ackatia-Armah et al found lower concentrations of sTfR in children who received LNS compared to CSB++ or locally blended flours (26). In the same study, Ackatia-Armah et al also found higher Hb and SFAI in children who received LNS compared to a locally produced blended flour, but there was no difference between those who received LNS and CSB++ (26).

Several possible mechanisms could explain the greater impact of LNS: better absorption of iron, better acceptability, or less sharing of the products. Absorption of iron from food depends on the type of iron, content of iron enhancers (e.g. vitamin C) or iron inhibitors (e.g. phytate), as well as iron stores of the individual and presence of infection (27). While products contained the same type of iron the amount of vitamin C or phytate may play a role. It has been estimated that 50% of vitamin C in CSB is lost during cooking (28). Double the amount of vitamin C was therefore added to CSB compared to LNS; while this should be sufficient, it is unclear how much vitamin C was present at the time of consumption since

losses depend on cooking time and temperature. Furthermore, the amount of soy products per daily serving of CSB, and thus phytate from soy, was on average double than that of the LNS. However, the total amount of phytate in the products is unknown since other ingredients, i.e. corn and peanuts, are also sources of phytate and no analysis of phytate content was carried out after production. We have previously shown that in this population, children and caregivers preferred LNS and that more leftovers were reported in CSB groups (17). The preference for LNS as well as the finding that appreciation of foods was greater and leftovers less during the rainy season when food availability is reduced (17) may also explain why the impact of LNS vs CSB on iron status was more pronounced during the dry season when a better availability of family foods may have led to more leftovers of the less preferred product. Furthermore, the effect of LNS vs CSB on Hb was greater in children who had elevated AGP. In line with this, the effect of LNS vs CSB on SFAI was greater in children with malaria or elevated CRP. While the latter could be an artefact since SFAI was adjusted for inflammation, the general trend of LNS having greater effect in children with infection or inflammation suggests that this may also have other reasons, such as the impact of infection on appetite. Lastly, while previous studies have shown that CSBs are more likely to be shared than LNS (29,30), this did not seem to be a problem in our study population (17).

We did not find an effect of soy quality. However, while SI contains less phytate than DS, soy isolates do contain phytate, even small amounts of phytate have been shown to affect absorption, (31,32) and soy is not the only phytate-containing ingredient in the products. We did not find an effect of DSM quantity or an interaction between milk and soy. This means that reducing milk and replacing it with soy did not negatively impact iron status and this was not different if SI or DS was used. The lack of impact of milk may also be linked to the high breastfeeding rate, which was 95% at baseline.

While the prevalence of inflammation reduced throughout the intervention period, at the end of the intervention 20% of children had elevated CRP and 45% elevated AGP. This is not surprising considering the high burden of diseases in the study location (14). Higher concentrations of acute phase proteins in children who received LNS may be related to the higher linoleic acid content in LNS which can be converted to inflammatory metabolites via arachidonic acid (33) or the amount of absorbed iron. Iron status was better in children who received LNS at the end of the intervention indicating that more iron was absorbed. While iron is an essential nutrient, the safety of iron supplementation particularly in malaria-endemic areas has been questioned (34,35). Even though a recent systematic review on this issue concluded that iron supplements can be given to children if services to treat and prevent malaria are provided (36), it is not clear whether iron supplementation would also be safe in malnourished children, where iron withholding mechanisms may be impaired. In addition to iron supplementation, studies have also found higher morbidity among children who received micronutrient fortified complementary foods (37–39). We did not find an impact on malaria, which is not unexpected since participants received regular treatment for malaria and we only had data from rapid tests and not parasitemia. Nevertheless, the impact on inflammation reported here, which occurred despite regular medical follow-up and treatment for all identified infections, deserves further attention as both causes and implications are unclear.

In this population of children with MAM, anemia was very common. The lower Hb in children admitted based on low MUAC only compared to those with low WHZ only at baseline may be linked to a higher prevalence of malaria in this group as previously reported (14). While the prevalence of anemia decreased during the intervention period, by 13% points in the CSB and 21% points in LNS group, the prevalence in both groups remained high after supplementation. Similar results have previously been reported (26). It is important to note

462 that, the iron content of the supplements was lower than therapeutic doses (40) and may have
463 been insufficient particularly for children with a Hb <110 g/L. However, considering the
464 large burden of infection and inflammation in this setting (14) it is unclear whether further
465 supplementation would have been beneficial. It is also worth mentioning that doubts about
466 the validity of current cut-offs for definition of anemia have been raised (41–44) and the
467 110g/L cut-off may be too high in young children living in Burkina Faso.
468
469 This study had a number of strengths and limitations. First it is one of few studies
470 investigating the effects of supplements on hemoglobin, iron status and inflammation in
471 children with MAM. The use of a factorial design enabled us to assess the effect of three key
472 factors in foods supplements and testing for interactions between the factors enabled us to
473 investigate the potential impact of different combinations of these factors, e.g. whether
474 removing DSM and adding more soy of different qualities and thus different amounts of anti-
475 nutrients affect iron status. However, a limitation of this design is that the ingredients differed
476 somewhat between products, e.g. since SI contains more protein than DS, content of other
477 ingredients had to be adapted to keep the overall energy and protein content constant. Other
478 limitations include the lack of an unsupplemented control group, the lack of data on malaria
479 parasitaemia and that we did not carry out a nutrient composition analysis to determine the
480 total phytate content in the products and vitamin C content in CSB after cooking.
481
482 In conclusion, we have shown that children supplemented with LNS had significantly better
483 Hb and iron status at the end of the supplementation period than those who received CSB
484 products but overall prevalence of anemia remained high. The higher concentrations of
485 inflammation biomarkers reported in children who received LNS requires further
486 investigation.

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Matrix	Soy quality	Milk protein %		
		0	20	50
Corn-soy blend	Dehulled	a	b	c
	Isolate	d	e	f
Lipid-based nutrient supplement	Dehulled	g	h	i
	Isolate	j	k	l

Table 1. The experimental food supplements based on corn-soy blend or lipid-based nutrient supplement, with either dehulled soy or soy isolate, and with 0, 20 or 50% of total protein from milk. Product "a" is similar to CSB+ (also known as Supercereal) and product "b" to CSB++ (also known as Supercereal+). Product “i” is similar to Plumpy´Sup®, (Nutriset, Malaunay, France), but Plumpy´Sup® contains whey instead of dry skimmed milk.

Table 2. Baseline characteristics of 1609 6-23 months old children enrolled in the study by factorial design[1,2,3]

	Matrix		Soy quality		Milk protein %		
	CSB (n=800)	LNS (n=809)	Dehulled (n=800)	Isolate (n=809)	0% (n=541)	20% (n=528)	50% (n=540)
Sociodemographic data							
Sex, male	356 (45)	374 (46)	373 (47)	357 (44)	246 (46)	241 (46)	243 (45)
Age, months, median (IQR)	11 (8-16)	12 (8-16)	11 (8-16)	11 (8-16)	11 (8-16)	11 (8-16)	11 (8-16)
Anthropometry							
MUAC, mm, mean (SD)	123 (4.0)	123 (4)	123 (4)	123 (4)	122 (4)	123 (4)	123 (4)
WHZ, mean (SD)	-2.2 (0.5)	-2.2 (0.5)	-2.2 (0.5)	-2.2 (0.5)	-2.2 (0.5)	-2.2 (0.5)	-2.2 (0.5)
Admission by:							
Low MUAC only	225 (28)	243 (30)	226 (28)	242 (29)	154 (29)	143 (27)	171 (32)
Low WHZ and low MUAC	404 (50)	400 (50)	406 (51)	398 (49)	276 (51)	275 (52)	253 (47)
Low WHZ only	171 (21)	166 (21)	168 (21)	169 (20)	111 (21)	110 (21)	116 (22)
Morbidity							
Ill in the previous two weeks	303 (38)	305 (38)	318 (40)	290 (36)	207 (39)	206 (39)	195 (36)
Positive malaria rapid test	324 (41)	320 (40)	322 (41)	322 (40)	216 (40)	207 (39)	221 (41)
Breastfed	755 (95)	766 (95)	755 (95)	766 (95)	515 (95)	93 (93)	513 (95)

[1]Data are n (% of non-missing data) unless otherwise stated; [2] Data missing: ill in the previous two weeks (n=9), malaria rapid test (n=8), breastfeeding (n=2).
[3] Abbreviations: CSB= corn-soy blend, IQR=interquartile range; LNS=lipid nutrient supplements; MUAC=mid upper arm circumference; SD= standard deviation

Table 3. Changes in hemoglobin, biomarkers of iron status, inflammation and malaria prevalence in the full cohort during the 12-week supplementation period[1,2]

	Baseline		After supplementation		Difference[4]		
	n		n		n		p
Hemoglobin, g/L	1608	100 ± 16	1546	107 ± 14	1546	+7 (+6, +7)	<0.001
% (n) < 110 g/L	1608	70.2 (1129)	1546	53.2 (821)	1546	-16.9 (-56.5, -12.6)	<0.001
SFAI, µg/L	1564	16 (8-30)	1511	18.1 (11.0-28.8)	1462	+2 (+1.2, +2.6)	<0.001
% (n) < 12 µg/L	1564	38.3 (595)	1511	29.3 (443)	1462	-8.7 (-14.5, -3.0)	0.004
sTfR, mg/L	1564	12.6 (9.1-17.3)	1520	10.2 (8-13.5)	1480	-2.2 (-2.5, -2.0)	<0.001
% (n) > 8.3 mg/L	1564	82.9 (1296)	1520	70.1 (1065)	1480	-12.6 (-16.0, -9.1)	<0.001
Iron deficiency anemia[3], % (n)	1555	30.0 (469)	1511	19.4 (293)	1462	-10.5 (-16.8, -4.2)	0.001
C-reactive protein, mg/L	1564	2.3 (0.8-9.3)	1520	1.7 (0.6-6.2)	1480	-0.6 (-0.8, -0.4)	<0.001
% (n) >10 mg/L	1564	25.4 (398)	1520	19.9 (302)	1480	-5.9 (-12.2, 0.2)	0.06
α1-acid glycoprotein, g/L	1564	1.2 (0.9-1.6)	1520	1 (0.7-1.4)	1480	-0.21 (-0.24, -0.17)	<0.001
% (n) >1 g/L	1564	66.4 (1039)	1520	45.7 (695)	1480	-19.9 (-24.6, -15.4)	<0.001
Rapid malaria test, % positive	1601	40.2 (644)	1531	31.3 (479)	1523	-9.2 (-14.8, -3.5)	0.002

[1] Data are mean ± SD for hemoglobin, median (IQR) SFAI, sTfR, C-reactive protein, α1-acid glycoprotein or mean (95%CI) for the differences unless otherwise stated; [2] Abbreviations: SFAI, serum ferritin adjusted for inflammation; sTfR, serum soluble transferrin receptor; IQR, interquartile range; Iron deficiency anemia (IDA) was defined as hemoglobin < 110g/L and SFAI < 12 µg/L; [4]Changes in concentrations before and after the intervention were assessed using t-tests. McNemar's Chi[2] was used to test for differences in proportions over time.

Table 4. Hemoglobin, markers of iron status and inflammation and malaria prevalence after 12 weeks of supplementation with CSB compared to LNS in the intention-to-treat population[1,2]

			Model 1[3]		Model 2[4]	
	CSB	LNS	Mean difference	p	Mean difference	p
Hemoglobin, g/L	105 ±14	108 ± 13	3 (1, 4)	<0.001	2 (1, 4)	<0.001
% (n) < 110 g/L	57.4 (445)	49 (382)				
Serum ferritin, µg/L	23 [13-48.4]	30.6 [18-58.7]	9.5 (6.6, 12.3)	<0.001	9.8 (7.02, 12.6)	<0.001
% (n) < 12µg/L	22.1 (168)	11.3 (87)				
SFAI, µg/L	16.3 [9.5-25.5]	19.6 [12.2-30.9]	4.3 (2.9, 5.6)	<0.001	4.2 (2.9, 5.5)	<0.001
% (n) < 12µg/L	34.3 (257)	24.4 (186)				
sTfR, mg/L	10.6 [8.2-14.2]	9.8 [7.8-12.8]	-1 (-1.4, -0.6)	<0.001	-0.9 (-1.3, -0.6)	<0.001
% (n) > 8.3mg/L	72.8 (549)	67.4 (516)				
C-reactive protein, mg/L	1.4 (0.5-5.1)	2.2 [0.7-8.1]	0.7 (0.3, 1.1)	<0.001	0.8 (0.4, 1.2)	<0.001
% (n)>10 mg/L	17.6 (133)	22.1 (169)				
α1-acid glycoprotein, g/L	0.9 [0.7-1.4]	1 [0.7-1.5]	0.07 (0.02, 0.12)[5]	0.02	0.08 (0.02, 0.13)[6]	0.004
% (n)>1g/L	44.8 (344)	49.9 (389)				
Rapid malaria test, % (n) positive	29.7 (225)	32.9 (254)	3.1 (-1.6, 7.7)	0.19	2.7 (-1.0, 10.7)	0.16

[1] Data are mean ± SD for hemoglobin, median (IQR) for serum ferritin, SFAI, sTfR, C-reactive protein, α1-acid glycoprotein or mean difference (95% CI) unless otherwise stated.
[2] Abbreviations: CSB, Corn-soy blend; DS, dehulled soy; IQR, interquartile range; LNS, lipid nutrient supplement; SFAI, serum ferritin adjusted for inflammation; SI, soy isolate; sTfR, serum soluble transferrin receptor.
[3] Results are based on linear mixed models for continuous outcomes and logistic mixed models for malaria adjusted only for baseline measure and site.
[4] Results are based on linear mixed models for continuous outcomes and logistic mixed models for malaria adjusted for baseline measure, mid-upper arm circumference, weight-for-height z-score, age, sex, month of admission and site.
[5] Interaction between matrix, soy quality and milk (p=0.03): LNS-DS-50% milk vs LNS-SI-50% milk= 0.22 (0.1; 0.44)
[6] Interaction between matrix, soy quality and milk (p=0.045): LNS-DS-50% milk vs LNS-SI-50% milk= 0.21(0.06; 0.42)

Figure 1. Trial Profile