Serum insulin-like growth factor 1 in young children with moderate acute malnutrition: secondary analysis of a randomized trial in Burkina Faso

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This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI

10.1017/S0007114525000212

The British Journal of Nutrition is published by Cambridge University Press on behalf of The Nutrition Society

ABSTRACT

Insulin-like growth factor 1 (IGF-1) is an important growth factor in childhood. We aimed to investigate the impact of food supplements for treatment of moderate acute malnutrition (MAM) on serum IGF-1 (sIGF-1). Secondary analysis of a randomized 2×2×3 factorial nutrition trial was performed. Children aged 6-23 months with MAM received 2093 kJ/day as lipid-based nutrient supplement (LNS) or corn-soy blend (CSB), containing either dehulled soy or soy isolate and different quantities of dried skimmed milk (0%, 20% or 50% of total protein) for 12 weeks. The trial was double-blind with regard to soy and milk, but not to matrix (LNS vs. CSB). sIGF-1 was measured at inclusion and after 12 weeks supplementation. Of 1609 children enrolled, 1455 (90%) had sIGF-1 measured at both time points. During supplementation sIGF-1 increased 6.7 (95%CI 6.1; 7.3) ng/ml compared with an expected age-dependent decrease of 0.3 (95%CI 0.2; 0.4) ng/ml. Children who received LNS vs. CSB had lower increase in sIGF-1 (-8%, 95%CI -12; -3). The effect of LNS was partly attenuated when sIGF-1 was corrected for inflammation. Children who received soy isolate compared with dehulled soy had higher increase in sIGF-1 (6%, 95%CI 1; 12). Milk content did not affect sIGF-1. Overall, sIGF-1 increased during supplementation. The lower increase with LNS vs. CSB was only partly explained by increased inflammation with LNS, and needs further investigation. Isolate vs. dehulled soy led to a higher increase which may be due to antinutrients in dehulled soy.

Key words: Insulin-like growth factor-1 (IGF-1), moderate acute malnutrition, lipid-based nutrient supplement (LNS), inflammation, low-income country

Abbreviations:

sAGP: Serum α-1-acid glycoprotein; sCRP: Serum C-reactive protein; CSB: Corn-soy blend; LAZ: Length-for-age Z-score; LNS: Lipid-based nutrient supplement; MAM: Moderate acute malnutrition; MUAC: Mid-upper arm circumference; sIGF-1: Serum insulin-like growth factor 1; WHO: World Health Organization; WHZ: Weight-for-height Z-score; WLZ: Weight-for-length Z-score

INTRODUCTION

Moderate acute malnutrition (MAM), defined as moderate wasting or low mid-upper arm circumference (MUAC), is estimated to affect 31 million children below 5 years globally [(1)]. MAM is associated with increased morbidity and mortality, mainly due to infectious diseases [(2)]. A new guideline recommends that children with MAM should be considered for supplementary foods if they fulfill certain individual or social risk criteria or live in a high-risk context. Furthermore, lipid-based nutrient supplement (LNS) is the preferred type of food supplement compared to corn soy blend (CSB) or other fortified blended foods (FBF) [(3)]; however, the certainty of evidence for the recommendation of food supplement type is low. Several studies have evaluated the effects of the supplement matrix or different protein sources on recovery from MAM and growth. Reviews and meta-analyses have often found superior recovery among children treated with LNS vs FBF [(4–7)]. Some reviews found higher gain in weight, weight-for-height z-score (WHZ), or MUAC [(5–8)], but not height [(8)] when children with MAM were treated with LNS compared to CSB. However, when LNS was compared to FBF with milk and/or improved micronutrients, there was no or marginal differences in anthropometric outcomes of children with MAM [(5,8)].

Few studies evaluated the physiological effects of food supplements on growth factors. Insulin-like growth factor 1 (IGF-1) is produced in the liver and is an important endocrine growth factor in young children [(9)]. Both malnutrition [(10,11)] and inflammation [(12,13)] are associated with reduced synthesis of IGF-1, possibly via down-regulation of the growth hormone-IGF-1 axis [(10–13)]. As the reduction in serum IGF-1 (sIGF-1) in response to starvation or illness takes place within days [(13–15)], short-term effects of nutrition on growth may be easier to detect by measuring sIGF-1 than linear growth. Linear growth changes slowly and is difficult to measure accurately in young children as they tend to move during assessments. We have previously shown that both stunting and wasting as well as systemic inflammation were associated with remarkably lower sIGF-1 among 6-23 month-old Burkinabe children [(16)]. In the same children, we aimed to assess the effect of food matrix, soy protein quality, and content of milk protein content on changes in sIGF-1 and we assessed for effect modifiers of these effects.

SUBJECTS AND METHODS

Study design and participants

This study was based on secondary analysis of a randomized 2x2x3 factorial trial assessing the effects of food supplements with two different food matrices (LNS vs CSB), two soy qualities (isolate vs. dehulled) and three levels of milk protein (0%, 20%, 50% of the total protein content) on body composition and linear growth among children with MAM [17]. The study took place at five sites in the Province du Passoré, Northern Region, Burkina Faso. Children were screened for MAM either by community health workers using MUAC tapes or by designated screening teams using both MUAC and weight-for-length z-score (WLZ). Children could also be referred from a health center or be taken to a site based on the caregiver's initiative. The final eligibility assessment was carried out by study staff at the sites. Children aged 6-23 months who lived in the catchment area and were confirmed to have MAM (MUAC ≥ 115 mm and < 125 mm and/or WLZ ≥ -3 and < -2) were enrolled. Children were excluded if they were already in a nutritional programme; were treated for severe acute malnutrition or hospitalized within the past 2 months; had an illness requiring hospitalization; had haemoglobin <50 g/l; suspected allergy to milk, peanuts, CSB or LNS; or had a severe disability. Only one child per household was included. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Ethics Committee for Health Research in Burkina Faso (2012-8-059). In addition, consultative approval was obtained from the Danish National Committee on Biomedical Research Ethics (1208204). Information leaflets and informed consent forms were translated into the local language, Mooré, and caregivers gave verbal and written consent (signature or fingerprint) prior to enrolment. The original trial was registered in the ISRCTN registry (ISRCTN42569496).

Intervention, randomization, and blinding

Children received 2093 kJ/day (500 kcal/day) of one of 12 food supplements for 12 weeks. The food matrix was either CSB (120 g/day) or LNS (92 g/day), soy quality was dehulled or isolate and 0%, 20%, or 50% of the total protein was from dried skimmed milk. The contents of protein and fat were 15.9-16.8 g/day and 11.4-11.7 g/day in CSB and 12.5-13.5 g/day and 31.4-32.1 g/day in LNS [17]. The compositions complied with the WHO technical note on food supplements for management of MAM [18]. LNS was ready to use whereas CSB had to

be cooked into porridge before intake. The supplements were manufactured by GC Rieber Compact A/S (Søfteland, Norway).

Individual, stratified block randomization was used. Block sizes were 12 or 24, and stratification was done by site. Investigators, outcome assessors, and other staff were blinded with respect to matrix, soy quality, and milk content; however, participants were only blinded to soy quality and milk content but not matrix. Further information about randomization, allocation concealment and blinding is described elsewhere [17]

Data collection

At baseline, trained study nurses collected data on sociodemographic information, breastfeeding status, and 2-week medical history, and carried out a physical examination.

Anthropometric assessments were taken by trained staff and measured at baseline and week 12. Weight, length, and MUAC were measured in duplicate to the nearest 100 g, 1 mm, and 1 mm using an electronic scale with a double weighing function (Seca 881 1021659, Hamburg, Germany), a wooden height board, and a standard measuring tape, respectively. Knee-heel length was measured 5 times with a digital caliper (Mitutoyo, Germany) which we mounted with knee and heel caps cast in hard plastic. The mean values were used.

Venous blood samples were collected at baseline and 12 weeks. On-site, a drop of blood was used for diagnosis of malaria (rapid diagnostic test, Bioline Malaria Ag Pf, Abbott, California), and the remaining blood was collected in a serum vacutainer tube (Becton Dickinson #368492) and transported to the trial laboratory in a cooler box at 2-8°C. After centrifugation at 700 g for 5 minutes (EBA 20S Hettich, Tuttlingen, Germany), serum samples were stored at -20°C until shipment on dry ice for further analysis. Serum C-reactive protein (sCRP) and α-1-acid glycoprotein (sAGP) were analysed at VitminLab, Wilstaedt, Germany using sandwich enzyme-linked immune sorbent assay with intra- and interassay coefficients of variation between 5 and 14% [19,20]. IGF-1 was analysed on Immulite 2000 Analyzer (Siemens Healthcare, Erlangen, Germany) at University of Copenhagen (Denmark). Values below 25 ng/ml were not shown automatically but were calculated using algorithms provided by the manufacturer. The intra-assay coefficient of variation was 20% when sIGF-1 was 10 ng/ml and 6% when sIGF-1 was 25 ng/ml. All samples were measured in duplicate and the mean was used.

Statistics

Data were double-entered in EpiData 3.1 (Epidata Association, Odense, Denmark). STATA 12 or 17 was used for all statistical analyses. Baseline characteristics were summarized as mean ± standard deviation (SD) for normally distributed variables, median (interquartile range) for non-normally distributed variables, and frequency % (n) for categorical variables. Distribution was assessed by visual inspection of histograms and normal probability plots. Mean change in sIGF-1 during the intervention was assessed by paired t-test with 95% confidence intervals (CI).

Linear mixed models were used to assess the effects of the interventions on sIGF-1. Data on sIGF-1 were log-transformed. Model reductions were carried out using likelihood ratio tests. A model containing the 3-way interactions, corresponding to the 2×2×3 factorial design, was compared to a model containing only main effects of the factors. If there were no interactions in the factorial layout, the main effects of food matrix (LNS vs CSB), soy quality (soy isolate vs. dehulled soy) and content of milk protein (0% vs 20% or 0% vs 50 %) were extracted from the models. The models included sex, age, season (month of inclusion), baseline MUAC, WLZ, length-for-age z-score (LAZ) and sIGF-1 as fixed effects and site as random effect. Further adjustment for inflammation was done using CRP > 5 or AGP >1 mg/l. Effects were presented as estimated means with 95% CIs. We further assessed if sex, age, breastfeeding, inclusion criteria (MUAC only, WHZ only, or MUAC and WHZ), fever, malaria, and elevated CRP (>2 mg/l) and AGP (>1.2 g/l) modified the effect of the interventions (food matrix, soy quality and milk protein content) on sIGF-1 using the linear mixed model with adjustment for sex, age, season, baseline MUAC, WLZ, LAZ and sIGF-1 as fixed effects and site as random effect. Model assumptions were assessed by visual inspection of residual and normal probability plots.

As we did not have an unsupplemented reference group, baseline values were analyzed in relation to age and sex to estimate the typical changes in sIGF-1 over a period equivalent to the length of the intervention. This “calculated reference” was used for descriptive purposes only and not for the linear mixed models. Specifically, changes in sIGF-1 during 12 weeks were estimated using linear regression of baseline IGF-1 with age as a fractional polynomial. Separate regressions were prepared for boys and girls and selection of the best model was based on the Akaike information criterion. We did not impute missing data in any analyses. P-values below 0.05 were considered significant.

RESULTS

As previously reported [17], we enrolled 1,609 children with MAM from September 2013 to August 2014. The randomisation resulted in baseline equivalence (**Table 1**). Of 1609 enrolled children, 1548 (96.2%) were followed up for 12 weeks (**Figure 1**). During the intervention, 102 (6.9%) children developed SAM, four children died and no child developed an allergic reaction to the supplements. The proportion of these adverse events were similar between treatment groups, and none attributed to the food supplements. Children lost to follow-up had similar baseline characteristics as those followed-up (**Supplementary table 1**). However, children without data on sIGF-1 were generally younger with lower weight and height, but not lower LAZ or WHZ, and were more likely to have fever and inflammation (**Supplementary table 2**).

At baseline, the median (IQR) age was 11.3 (8.2; 16.0) months, 45.4 % (730) were boys and the mean (SD) LAZ was -1.7 (1.1). Median [IQR] levels of the inflammatory markers CRP and AGP were 2.3 [0.8; 9.4] mg/l and 1.22 [0.88; 1.64] g/l and 40% (n=644) had a positive malaria test. sIGF-1 was available on 1549 (96%) of the 1609 children at baseline and 1509 out of 1548 (97%) at week 12 (Figure 1) and 1455 (90%) had sIGF-1 data at both time points.

Median [IQR] sIGF-1 was 12.0 [8.2; 18.2] ng/ml at baseline and 18.4 [12.3; 26.9] ng/ml at endline. The mean (SD) increase in sIGF-1 during the 12-week supplementation was 6.7 ng/ml (95% CI 6.1; 7.3).

There were no three- or two-way interactions between the experimental factors with respect to effects on sIGF-1 (p=0.66), hence the main effects could be assessed (**Table 2**). LNS (vs CSB) resulted in an 8% (95%CI: 3; 12) lower change in sIGF-1, and soy isolate (vs dehulled soy) resulted in a 6% (95%CI: 1; 12) higher change in sIGF-1. There was no effect of either 50% or 20% (vs 0%) milk protein ($p \geq 0.43$) on sIGF-1. After adjustment for inflammation, the effect size of the difference between soy isolate vs dehulled soy was maintained (5%, 95% CI: -0.0008;10), but the effect size of LNS vs CSB was reduced (-4%, 95% CI: -9;4).

We assessed effect modification by sex, age, LAZ, WLZ, inclusion criteria for MAM (MUAC only, WLZ only, or WLZ and MUAC), malaria, fever, and elevated sCRP and sAGP (**Table 3**). For LNS (vs CSB), there were no interactions between matrix and any of the potential effect modifiers. For soy isolate (vs dehulled), there was an interaction by age (age ≥16 months, p=0.026), reflecting that the positive effect of soy isolate on change in IGF-1

was larger in children above (17%, 95%CI 6;30) than below 16 months (2%, 95%CI: -4; 9). As for 20% milk protein content, we found a trend for interaction with wasting (WLZ <-2, p=0.050) and fever (≥37.5^{o}C, p=0.046) with tendencies to larger increases in sIGF-1 for children with WLZ >-2 and fever. There were no interactions between 50% milk protein and any of the potential effect modifiers.

The increase in sIGF-1 by matrix, soy quality, and age was further explored in **Figure 2**. For matrix (panel A), the increase in sIGF-1 was lowest in the youngest children and then plateaued starting around 9 months of age. The same pattern was seen for children given CSB and LNS but was higher for those given CSB across all ages. As there was no un-supplemented control group, a reference curve was calculated based on baseline data. As seen, the change in sIGF-1 in this reference was negative in the youngest children, and then increased and plateaued around 0. For soy quality (panel B), the interaction between age and soy quality is seen as no difference between those given soy isolate and dehulled soy among children below 16 months, whereas among children above 16 months soy isolate was associated with a greater increase in sIGF-1 that seemed to increase with age.

DISCUSSION

Serum IGF-1 increased 6.7 ng/ml among children receiving food supplement for 12 weeks. For ethical reasons, the trial did not have an unsupplemented reference. However, by using baseline data, we estimated that sIGF-1 would have declined in the youngest and barely changed in the remaining children. This pattern among the “calculated reference” is expected [(21)], however, the increase in sIGF-1 in the supplemented children is quite remarkable as the baseline level was only 12.7 ng/ml, around half of better nourished children from the same country [(21)] and much lower than children from a high-income country [(22)]. Both increased energy and protein intake may have contributed to the overall increase in sIGF-1 in the supplemented children [(11)].

We found a greater increase in sIGF-1 in children receiving CSB than LNS. This may be due to a higher protein content of CSB versus LNS supplements: 15.9-16.8 g/day with CSB and 12.5-13.5 g/day with LNS. Protein intake has been associated with an increase in sIGF-1 in both young infants [(23)] and older children [(24)], but the source of protein may have a differential effect on sIGF-1 [(25)]. However, the actual difference in protein intake is difficult to estimate as more children had leftovers and higher amounts of leftovers when given CSB compared to LNS, as measured in a subsample of children from the current trial [(26)]. The difference

between CSB and LNS with regards to change in sIGF-1 was not reflected in more linear or ponderal growth among children receiving CSB [17]. After adjustment for inflammation, the difference between CSB and LNS was attenuated but remained significant. This may be due to an inflammatory effect of LNS. We have previously reported that LNS intake was associated with an increase in inflammation, perhaps due to higher content of linoleic acid or better iron status with LNS [27]. Inflammation is known to decrease the production of IGF-1 [12,13,16].

Soy isolate resulted in a higher increase in sIGF-1 than dehulled soy. This effect was modified by age; only children above 16 months had a higher increase in sIGF-1 when given soy isolate vs dehulled soy. Soybeans contain insoluble fibers and antinutritional factors including trypsin inhibitors and phytate that negatively affect digestibility of protein and bioavailability of amino acids [28]. In dehulled soy, fibers of the hull have been removed. However, in soy isolate, trypsin inhibitors have also been inactivated to a large extent, and thereby protein digestibility has been improved [28]. This may have resulted in higher production of sIGF-1, and maybe more in older children as they consumed a higher proportion of their supplements [26]. In addition, the protein requirements may have been covered better by home diet and food supplement among the older children. Children with wasting all have high requirements for protein quality and quantity [29], but the overall requirements for protein in terms of g/kg/day decreases between 6-23 months [30]. The higher increase in sIGF-1 was not manifested in higher linear or ponderal growth. This may be because linear growth is also determined by other factors than endocrine production of IGF-1 or because there may be a delay in linear growth response after an increase in IGF-1.

There was no effect of the content of milk protein on sIGF-1 in this trial where milk was mainly replaced with soy protein. This is in line with an RCT among 1-5-year-old Ugandan children with stunting [31]. The trial found no difference in the increase in sIGF-1 between children receiving LNS with milk protein isolate vs. LNS with soy protein isolate. The Ugandan trial had an unsupplemented control group and found an increase in sIGF-1 in supplemented vs. unsupplemented children similar to the difference observed between supplemented children and a calculated reference in the current trial. In both trials, there was also no effect of milk protein on anthropometric outcomes. The effect of different protein sources was also analysed among 5-month-old formula-fed infants receiving either dairy or meat-based complementary food until 12 months of age [[32]]. No difference was found between groups regarding sIGF-1. However, infants receiving meat-based complementary

food increased by 0.33 in LAZ whereas infants receiving dairy-based complementary foods decreased by 0.30 in LAZ and increased by 0.76 in WLZ. Some [25,33–35], but not all [36] trials among young school children from high- or low-income settings have found different increases in sIGF-1 depending on the source of protein, typically with a higher increase in sIGF-1 after intake of milk protein. The age of the children, the total amount of milk protein supplied, the comparator and the overall composition of the diet may contribute to these differences.

The main limitation of the study was a high (20%) intra-assay coefficient of variation when sIGF-1 was low (10 ng/mL). The large sample size was considered a strength.

During the supplementation period an increase in sIGF-1 was observed which far exceeds levels in a calculated reference group. While the increase in LNS was lower than in the CSB group, the difference was modest and partly explained by increased inflammation with LNS. This finding needs further investigation. Soy isolate, compared to dehulled soy led to a higher increase in sIGF-1 which may be due to a higher level of antinutrients in dehulled soy. Although sIGF-1 cannot predict growth alone, it may be a more sensitive marker of growth than anthropometric measurements in nutrition trials among young children.

Financial Support: The study was funded by the Danish International Development Agency (KFM, 09-097 LIFE); Médecins Sans Frontières (Denmark, Norway); Arvid Nilsson's Foundation; The World Food Program, which was part of a donation to the World Food Program from the American people through the support of the US Agency for International Development's Office of Food for Peace; the Alliance for International Medical Action; the European Union's humanitarian aid funds, in partnership with Action Contre la Faim and a private donation from Merete and Mogens Brix Christensen. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Declaration of Interests: HF has received research grants from Arla Food for Health Centre, HF and BG have received research grants from the Danish Dairy Research Foundation, KFM received funds from Arla Foods Amba and finally HF, KFM, BG, SF and AB have had research collaboration with Nutriset, a producer of LNS. Other authors declare no financial relationships with any organisations that might have an interest in the submitted work in the previous five years, and declare no other relationships or activities that could appear to have influenced the submitted work.

Authorship: HF, KFM, SF, AB, VBC: designed the Treatfood trial, CWY, CF, BC and AI-B: conducted the research, TWH, CR: analyzed data, BG: wrote the manuscript and had primary responsibility for final content, TWH, HF, KFM, VBC: contributed to data analysis, and all authors: read and approved the final manuscript.

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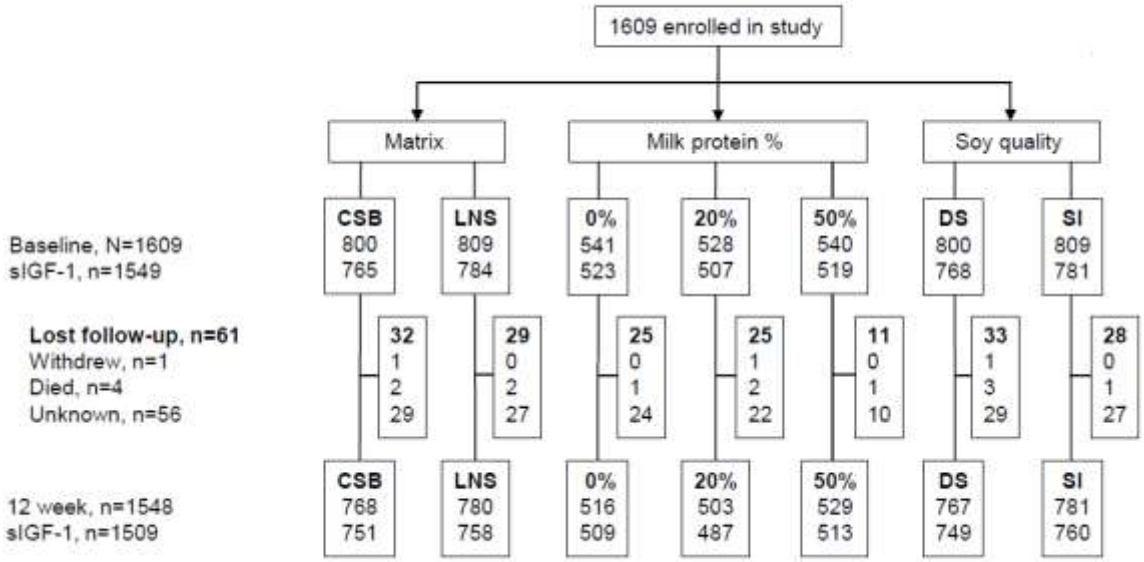
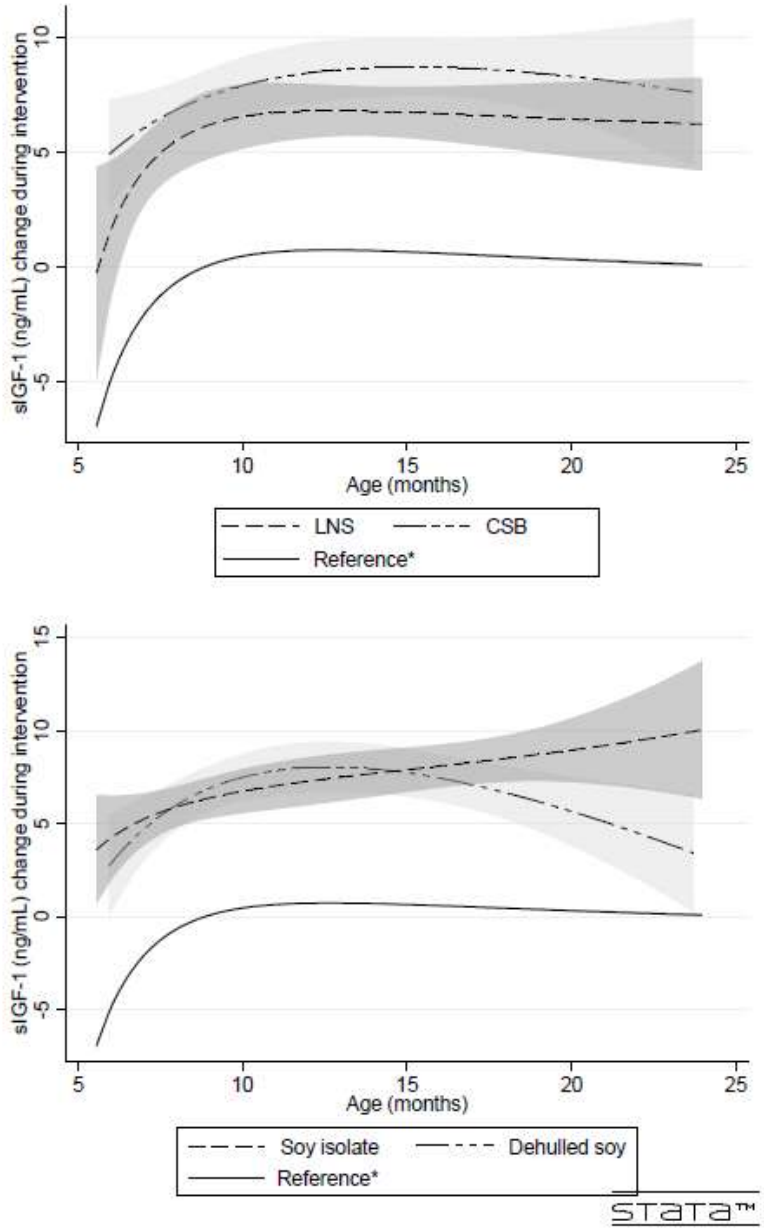


Title figure 1: Flow chart showing the total number of children and the number of children with serum insulin-like growth factor-1 (sIGF-1) data available at baseline and at week 12

Footer figure 1: CSB Corn soy blend, DS dehulled soy, LNS lipid-based nutrient supplement, SI soy isolate



Title figure 2: Change in serum insulin-like growth factor-1 (sIGF-1) by age among 1455 children with moderate acute malnutrition during 12 weeks supplementation. Panel A: Supplementation with lipid-based nutrient supplement (LNS) vs corn soy blend (CSB). Panel B: Supplement containing soy isolate vs dehulled soy.

Footer figure 2: *As we did not have an unsupplemented reference group, we estimated changes in sIGF-1 during 12 weeks using linear regression of baseline IGF-1 with age as a fractional polynomial.

Table 1. Baseline characteristics of 1609 children age 6−23 months with moderate acute malnutrition

	Matrix				Soy quality				Milk protein content					
	CSB, n=800		LNS, n=809		Dehulled, n=800		Isolate, n=809		0%, n=541		20%, n=528		50%, n=540	
Characteristics	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Sociodemographics														
Age (months)														
Median	11.1		11.5		11.2		11.4		11.1		11.4		11.1	
IQR	8.2; 15.5		8.3;16.4		8.4;16.0		8.0;16.0		8.1;16.2		8.4;16.2		7.9;15.6	
Sex, male (%)	45		46		47		44		45		46		45	
Anthropometry														
Weight (kg)	6.9	0.9	6.9	0.9	6.9	0.9	6.9	0.9	6.9	0.9	6.9	0.9	6.9	0.9
Length (cm)	70.3	5.2	70.5	5.4	70.4	5.2	70.4	5.4	70.5	5.6	70.6	5.2	70.2	5.2
Length-for-age (Z-score)	-1.6	1.1	-1.7	1.1	-1.7	1.1	-1.7	1.1	-1.7	1.1	-1.7	1.1	-1.7	1.2
Weight-for-age (Z-score)	-2.5	0.6	-2.6	0.7	-2.5	0.6	-2.5	0.7	-2.5	0.7	-2.5	0.6	-2.5	0.7
Weight-for-length (Z-score)	-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
MUAC (mm)	123	4	123	4	123	4	123	4	122	4	123	4	123	4
Knee heel length, n=1608 (mm)	192	18	192	18	192	18	192	18	192	19	193	18	192	17
Inclusion criteria														
WLZ and MUAC (%)	51		50		51		49		51		52		47	
WLZ only (%)	21		21		21		21		21		21		21	
MUAC only (%)	28		30		28		30		29		27		22	
Morbidity and inflammation														
Ill in the last 2 weeks[a], n=1597 (%)	77		77		78		76		76		80		75	
Diarrhea[a] (%)	19		21		21		18		21		20		19	
Cough[a], n=1606 (%)	29		30		30		29		27		32		30	

Fever, ≥37.5°C[b], n=1607 (%)	19	16	16	19	18	16	19
Malaria rapid test, positive, n=1601 (%)	41	40	41	40	40	40	41
CRP, n=1564 (mg/L)							
Median	2.2	2.6	2.6	2.2	2.2	3.0	2.1
IQR	0.7;9.4	0.8;9.3	0.8;10.3	0.7;8.9	0.7; 10.0	0.9;11.1	0.7;7.7
AGP, n=1564 (g/L)							
Median	1.23	1.21	1.23	1.21	1.19	1.27	1.21
IQR	0.87;1.66	0.89;1.63	0.88;1.69	0.87;1.62	0.84;1.62	0.95;1.68	0.86;1.64
Breastfeeding, n=1607 (%)	94	95	95	95	95	93	95
IGF-1, n=1549 (ng/mL)							
Median	12.1	12.0	12.4	11.9	12.1	11.6	12.7
IQR	8.4;18.5	8.0;18.1	8.2;17.4	8.2;18.9	8.0;18.1	8.2;17.2	8.5;19.1

Values are presented as median (IQR), mean (SD) or %

Abbreviations: MUAC = Mid-upper arm circumference, CRP = C-reactive protein, AGP = α_1-acid glycoprotein, IGF-1 = Insulin-like growth factor 1

[a]Based on maternal recall and physical examination, [b]Based on physical examination

Table 2. The effect of matrix, soy quality and milk content of food supplements on serum insulin-like growth factor-1 (sIGF-1) among children with moderate acute malnutrition

Type of supplement		Baseline Median [IQR] ng/ml n=1549		12 weeks Median [IQR] ng/ml n=1509		Change (95% CI) ng/ml n=1455		Difference in change[a] (95% CI) n=1455		p
		Median	IQR	Median	IQR	Mean	95% CI	Ratio	95% CI	
Food matrix	CSB	12.1	8.3;18.5	19.1	12.4;29.9	7.3	6.7; 8.5			
	LNS	12.0	8.0;18.1	17.5	12.1;25.1	5.8	4.9; 6.8	-8%	-12, -3	0.003
Soy quality	Dehulled	12.4	8.2;17.4	17.1	12.0;26.4	6.5	5.5; 7.4			
	Isolate	11.9	8.2;18.9	19.3	12.7;27.6	7.0	6.1; 7.9	+6%	(1, 12)	0.026
Milk protein content	0%	12.1	8.0;18.1	18.2	12.6;26.7	6.3	5.3; 7.3			
	20%	11.6	8.2;17.2	18.5	11.6;26.5	7.2	6.2; 8.3	-0.003%	-7, 6	0.93
	50%	12.7	8.5;19.1	18.8	12.7;27.4	6.6	5.4;7.9	+3%	-4, 9	0.43

Abbreviations: CSB, Corn-soy blend; CI, Confidence interval; LNS, lipid-based nutrient supplement; SD, Standard deviation. [a]sIGF-1 data were log-transformed. Results are therefore presented as the ratio of change based on linear mixed models adjusted for sex, age, season, baseline MUAC, WLZ, LAZ and sIGF-1 as fixed effects and site as random effect.

Table 3. Effect modifiers of change in sIGF-1 during intervention (12 weeks) in children age 6-23 months with moderate acute malnutrition

	N	Matrix LNS vs CSB		Soy quality Isolate vs dehulled			Milk protein 20% vs 0%			50% vs 0%		
		P^{int}	% 95% C	P^{int}	%	95% CI	P^{int}	%	95% CI	P^{int}	%	95% CI
Sex		0.54		0.51			0.22			0.84		
Boys	659		-6 -13; 2		4	-4; 13		4	-5: 15		2	-7; 12
Girls	787		-9 -15; 2		8	0.01; 16		-4	-12; 5		3	-5; 13
Age (months)		0.83		0.026			0.16			0.32		
6-15	1075		-7 -13; -1		2	-4; 9		3	-5; 11		1	-6; 9
16-24	371		-8 -18; 2		17	6; 30		-8	-19; 5		9	-4; 23
Breastfeeding		0.83		0.058			0.69			0.74		
Not	76		-1(-28; 14		32	5; 66		-6	- 29;25		-2	-27; 31
Breastfeeding	1368		-7 -12; -2		5	-1; 11		0.00	-6;-7		3	-4; 10
Breastfeeding												
Length-for-age Z		0.70		0.26			0.28			0.97		
≥*-3*	1300		-7 -12; -2		5	-1; 11		- 0.00	-7; 7		1	-5; 9
<*-3*	146		-1 -24; 6		16	-2; 37					14	-7; 40

Weight-for-length Z		0.096		0.67		0.050		0.38		
≥-2	424	-14	-22; -5	8	-2; 19	-10	-21; 2	-2	-13; 10	
<-2	1022	-5	-11; -1	5	-1; 12	4	-4; 12	4	-3; 13	
Inclusion criteria		0.13		0.87		0.37[a]		0.37[a]		
WLZ and MUAC	722	-8	-14; 0.00	5	-3; 13	2	-6; 12	5	-4; 15	
WLZ only	302	1	-10; 13	6	-5, 13	7	-7; 24	5	-9; 20	
MUAC only	422	-14	-22; -5	8	-2; 20	-10	-21; 1	-3	-13; 10	
Fever (≥37.5˚C)		0.36		0.66		0.046		0.53		
No	1197	-8	-13; -3	5	-1; 11	-3	-9; 4	2	-5; 9	
Yes	248	-2	-14; 11	9	-4; 23	16	-1; 36	7	-8; 25	
Malaria (Rapid test)		0.73		0.39		0.74		0.41		
Negative	856	-8	-14; -2	8	1; 16	1	-7; 10	1	-8; 9	
Positive	584	-6	-14; -2	3	-5; 12	-1	-11; 9	6	-4; 17	
CRP (mg/l)		0.20		0.89		0.89[a]		0.89[a]		
≤2	672	-8	-15; -1	5	-3; 13	-3	-11; 7	2	-7; 11	

>2 and ≤5	255	2	-10; 16	10	-3; 24	4	-11; 21	4	-11; 21	
>5 and ≤10	169	-5	-19; 11	9	-6; 27	-8	-24; 12	6	-13; 28	
>10	348	-1	-23; -5	4	-7; 16	4	-8; 18	4	-9; 19	
AGP g/l		0.073		0.49		0.94		0.47		
≤1.2	696	-1	-18; -5	4	-3; 13	-0.01	-9; 9	-0.00	-9; 9	
>1.2	748	-3	-10; 4	8	1; 16	-1	-9; 8	5	-4; 15	

Abbreviations: CRP = C-reactive protein, AGP = α_1-acid glycoprotein, IGF-1= Insulin-like growth factor 1, P^{int}, P-value of interaction

[a]P-value of interaction for 0% vs 20% vs 50% is combined due to more than two subgroups sIGF-1 data were log transformed. Results were back transformed and presented as the relative change based on linear mixed models adjusted for sex, age, season, baseline MUAC, WLZ, LAZ and sIGF-1 as fixed effects and site as random effect