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Original Research Article

Effect of lipid-based nutrient supplements on micronutrient status and hemoglobin among children with stunting: secondary analysis of a randomized controlled trial in Uganda

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A B S T R A C T

Background: Micronutrient deficiencies and anemia are widespread among children with stunting.

Objectives: We assessed the effects of lipid-based nutrient supplements (LNS) containing milk protein (MP) and/or whey permeate (WP) on micronutrient status and hemoglobin (Hb) among children with stunting.

Methods: This was a secondary analysis of a randomized controlled trial. Children aged 12–59 mo with stunting were randomly assigned to LNS (100 g/d) with milk or soy protein and WP or maltodextrin for 12 wk, or no supplement. Hb, serum ferritin (S-FE), serum soluble transferrin receptor (S-TfR), plasma cobalamin (P-Cob), plasma methylmalonic acid (P-MMA), plasma folate (P-Fol), and serum retinol-binding protein (S-RBP) were measured at inclusion and at 12 wk. Data were analyzed using linear and logistic mixed-effects models.

Results: Among 750 children, with mean age ± SD of 32 ± 11.7 mo, 45% (n = 338) were female and 98% (n = 736) completed follow-up. LNS, compared with no supplementation, resulted in 43% [95% confidence interval (CI): 28, 60] greater increase in S-FE corrected for inflammation (S-FEci), 2.4 (95% CI: 1.2, 3.5) mg/L greater decline in S-TfR, 138 (95% CI: 111, 164) pmol/L greater increase in P-Cob, 33% (95% CI: 27, 39) reduction in P-MMA, and 8.5 (95% CI: 6.6, 10.3) nmol/L greater increase in P-Fol. There was no effect of LNS on S-RBP. Lactation modified the effect of LNS on markers of cobalamin status, reflecting improved status among nonbreastfed and no effects among breastfed children. LNS increased Hb by 3.8 (95% CI: 1.7, 6.0) g/L and reduced the odds of anemia by 55% (odds ratio: 0.45, 95% CI: 0.29, 0.70). MP compared with soy protein increased S-FEci by 14% (95% CI: 3, 26).

Conclusions: : LNS supplementation increases Hb and improves iron, cobalamin, and folate status, but not vitamin A status among children with stunting. LNS should be considered for children with stunting.

This trial was registered at ISRCTN as 13093195.

Keywords: lipid-based nutrient supplement, micronutrient status, hemoglobin, stunting, anemia

Abbreviations: AGP, α_1-acid glycoprotein; CI, confidence interval; CRP, C-reactive protein; CSB, corn–soy blend; HAZ, length/height-for-age z-score; Hb, hemoglobin; LNS, lipid-based nutrient supplements; MAGNUS, Milk Affecting Growth, Cognition, and the Gut in Child Stunting; MP, milk protein; OR, odds ratio; P-Cob, plasma cobalamin; P-Fol, plasma folate; P-MMA, plasma methylmalonic acid; S-FE, serum ferritin; S-FEci, S-FE corrected for inflammation; SP, soy protein; S-RBP, serum retinol-binding protein; S-RBPci, S-RBP corrected for inflammation; S-TfR, serum soluble transferrin receptor; WP, whey permeate; WHZ, weight-for-length/height z-score.

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Introduction

Stunting, anemia, and micronutrient deficiencies contribute to mortality, morbidity, and poor cognitive development [1–4]. Globally, 2 of 5 children under 5 y who are stunted live in Africa [5]. We have previously shown that children with stunting often have micronutrient deficiencies and anemia [6,7].

Insufficient food access [8] and poor dietary diversity characterized by cereal-based diets that are low in animal-source foods [9], fruits, and vegetables contribute to micronutrient deficiencies and anemia in low-income settings. In addition, the consumption of foods that contain phytic acid affects micronutrient absorption [10]. Furthermore, exposure to pathogens or mycotoxins may impair nutrient absorption and utilization [11]. In this context, supplementation of a child's home diet, in addition to other interventions, may play a role in the prevention and correction of micronutrient deficiencies and anemia. Lipid-based nutrient supplements (LNS) contain both macro- and micronutrients and hence have the potential to improve multiple nutritional deficits [12]. A recent meta-analysis of randomized controlled trials showed that small-quantity LNS provided to children aged 6–24 mo resulted in improvements in hemoglobin (Hb) and iron status, and reduced the prevalence of anemia [13]. That analysis found an inconclusive effect on vitamin A status with no effect on plasma retinol but a small increase in plasma retinol-binding protein. There are insufficient data on the effect of LNS on cobalamin and folate status. A trial among 6- to 23-mo-old Burkinabe children with moderate acute malnutrition reported a modest increase in serum cobalamin after 3-mo supplementation with large-quantity LNS compared with corn–soy blend (CSB) [14]. However, the trial lacked a control group, was missing cobalamin results in a quarter of children, and used only 1 marker (serum cobalamin) to assess cobalamin status.

We aimed to assess the effect of LNS with different milk ingredients on markers of iron, cobalamin, folate, vitamin A status, and Hb among Ugandan children with stunting aged 12–59 mo.

Methods

Trial design, setting, and ethics

This interventional study was based on the secondary analysis of data from the Milk Affecting Growth, Cognition, and the Gut in Child Stunting (MAGNUS) trial (ISRCTN13093195), a randomized controlled, 2 × 2 factorial community trial with an additional non-supplemented control group [12,15]. The primary objective of the MAGNUS trial was to assess the effect of milk protein (MP) and whey permeate (WP) in LNS on growth among children with stunting [12, 15]. The MAGNUS trial was conducted in Jinja District, eastern Uganda. Two community health centers in Walukuba Division and Buwenge Town council were used as study sites. Ethical approval was obtained from the School of Medicine Research Ethics Committee at Makerere University (#REC REF 2019–013), the Ugandan National Council of Science and Technology (SS 49270), and the Danish National Committee on Biomedical Research Ethics gave consultative approval (1906848). Caregivers gave written informed consent before inclusion of their children in the trial.

Study participants

Village Health Teams mobilized their communities to bring 12- to 59-mo-old children for the initial screening. Children with stunting were identified on the basis of length/height-for-age *z*-score (HAZ) < −2 and referred to study sites for final eligibility screening. Length and height were measured in triplicate, using a wooden length/height measuring board-stadiometer (Weigh and Measure), to the nearest 0.1 cm in <24- and ≥24-mo-old children, respectively, and the median values were used in analyses. At the study sites, children were enrolled into the study if they were stunted (HAZ < −2), aged 12–59 mo, and resident in the catchment area and their caregivers agreed to home visits as well as gave written informed consent. Children with severe acute malnutrition [weight-for-length/height *z*-score (WHZ) < −3, mid-upper arm circumference < 115 mm, or bilateral pedal edema], a medical condition requiring hospitalization, a disability that impeded measurement of length/height, a disability that impeded eating capacity, or a known allergy to milk or peanuts were not eligible. These children were referred to health services as needed. In addition, children were excluded if the family planned to move away from the catchment area within 6 mo, the child participated in another study, or another child from the same household had already been included in the study.

Randomization and blinding

Site-stratified, block randomization, with variable block sizes of 10 and 20 were used to allocate the sequential list of identification numbers to 10 unique codes (2 codes per study arm). Children were individually randomly assigned to 1 of the 4 formulations (1:1:1:1) or the control group (4:1). The sequences were computer generated using R (R Core Team, 2021. R: A language and environment for statistical computing) by a person otherwise not involved in the study. At enrolment, children received a sequential identification number from an administrative staff member. At the end of the baseline visit, after all procedures and assessments had been done, the site pharmacist allocated the intervention to each child according to the allocation sequence list. Only the site pharmacist had access to the allocation sequence list at each site. Participants were blinded to the type of LNS they received but could not be blinded with respect to receiving LNS or no supplement. Investigators and outcome assessors were blinded with respect to receiving LNS or not.

Intervention

Children in the intervention group received 1 of 4 formulations of LNS in addition to the family diet, whereas those in the control group continued with the family diet alone. The nutritional composition of the different LNS formulations is shown in Supplemental Table 1. All 4 LNS formulations had the same packaging with a corresponding unique 3-letter code and were fortified with vitamin and mineral premix but differed in the incorporation of MP and WP. All children randomly assigned to LNS got 1 ready-to-eat 100-g sachet (~530–535 kcal) per day for a period of 12 wk. At each scheduled study visit, LNS was supplied to cover a period of 14 d. To assess compliance, caregivers were requested to return all empty or unused sachets at each study visit. More than 80% returned empty sachets were considered as good compliance. Supplements were manufactured by Nutriset, who were not involved in the trial design, data collection, or analysis. Children randomly assigned to continue with the family diet alone received a bar of laundry soap at each scheduled visit. All study participant caregivers received nutritional counseling at enrolment and transport reimbursement at each study visit.

Data collection

Baseline data were collected using interviewer-administered questionnaires. Trained study staff collected information on

sociodemography, lactation status, food intake based on 24-h recall, and high-dose vitamin A supplementation (200,000 IU) in the past 6 mo.

Outcomes

The outcomes were serum ferritin (S-FE), serum soluble transferrin receptor (S-TfR), serum retinol-binding protein (S-RBP), plasma cobalamin (P-Cob), plasma methylmalonic acid (P-MMA), plasma folate (P-Fol), and Hb. Blood samples were collected by venipuncture from the forearm in vacuum tubes at baseline and week 12. A maximum of 6.0 mL in total was collected in serum, lithium-heparin, and ethylene-diamine-tetra-acetic acid vacutainers. Hb was estimated from whole blood using HemoCue (Hb201+). The HemoCue device was calibrated with a control solution on a weekly basis. The rest of the blood was processed on the same day into either serum or plasma by centrifugation at 2300 $\times g$ for 10 min, and then transfered to cryovials and frozen at −20°C. On a weekly basis, the processed samples were transferred in a cold box to the IBRH3AU biorepository at Makerere University in Kampala for temporary storage at −80°C and thereafter transferred to Denmark and Germany for the analysis of the micronutrient markers and acute phase proteins. S-FE and S-TfR as markers of iron status, S-RBP as a marker of vitamin A, and C-reactive protein (CRP) and α_1-acid glycoprotein (AGP) as markers of inflammation were analyzed at the VitMin Lab using a combined sandwich ELISA, and inter- and intra-assay coefficients of variation were 5%–14% [16]. P-Cob and P-MMA as markers of cobalamin status and P-Fol as a marker of folate status were measured at the Department of Clinical Biochemistry, Aarhus University Hospital, Denmark, employing the Advia Centaur CP Immunoassay System (Siemens) (P-Cob and P-Fol) and liquid chromatography–tandem mass spectrometry on the AB SCIEX Triple Quad 5500 System (AB SCIEX) (P-MMA). The total imprecisions were 7.5% and 11.8%. The thresholds for low status were defined as follows: Hb < 110 g/L (anemia), S-FE < 12 μg/L, S-TFR > 8.3 mg/L, S-RBP < 0.7 μmol/L, P-Cob < 222 pmol/L, and P-Fol < 14 nmol/L [17]. There are no agreed cutoffs for P-MMA. S-FE and S-RBP were corrected for inflammation using regression correction described by Cichon et al. [18], and reported as S-FE corrected for inflammation (S-FEci) and S-RBP corrected for inflammation (S-RBPci). The cutoffs used were 10 mg/L for serum CRP and 1.2 g/L for AGP. Iron-deficiency anemia was defined as Hb < 110 g/L and S-FE (or S-FEci) < 12 μg/L.

Sample size and statistical analyses

In this study, the main analysis was considered as the effect of LNS irrespective of milk ingredients. We therefore compared 600 children supplemented with LNS to 150 unsupplemented control group. We had 80% power to detect a difference of 0.27 SD at 5% significance and 80% power. Data were double entered into EpiData 3.1 software (Epidata Association), and double entry checks were done regularly. All analyses were carried out using STATA v15.1 (StataCorp). Anthropometric indices—HAZ, weight-for-age, and WHZ—were calculated using the STATA module zscore06 [19].

Baseline characteristics were summarized as mean ± SD or median [IQR] for continuous variables, and percentage (%) for categorical variables. Skewed data were logarithm transformed and effects were reported as percentages. For longitudinal data analysis, we followed a modified intension-to-treat analysis using available outcome laboratory results. Changes in the mean concentrations of micronutrient markers and Hb before and after the intervention were assessed using paired *t*-tests. Main effects of LNS intervention were considered as mean differences or percentages of changes in the outcomes from baseline to week 12 between the intervention and control groups. The effects of LNS were analyzed using linear mixed regression models for continuous variables and logistic regression models for categorical variables. Effect estimates were adjusted for the baseline value of the outcome alone and reported as unadjusted. In addition, we adjusted for age and sex as fixed effects, and month of inclusion and site as random-effects and reported this as adjusted analyses. Using linear mixed models adjusting for baseline value, age, sex, month of inclusion, and site, we further assessed whether sex, lactation, severe stunting, or inflammation modified the effect of LNS on micronutrient status and Hb. Severe stunting was defined as HAZ < −3 and moderate stunting as HAZ < −2 to −3, and inflammation as AGP > 1.2 g/L. In addition to prespecified subgroup analyses, we also assessed for subgroup effects by baseline anemia and positive malaria test, and combinations thereof. Chi-squared test was used to compare the proportions of children with good compliance. Missing data were not imputed, and we did not adjust for multiplicity. Statistical significance was set at P value < 0.05.

Results

From 7 February to 17 September, 2020, 7611 children were screened and 1112 were stunted thus referred to the study sites for eligibility assessment (Figure 1). Of these, 750 were eligible and randomly assigned to 1 of the 4 formulations of LNS ($n = 600$) or no supplement ($n = 150$). Of the 750 enrolled, 98% ($n = 736$) completed the 12-wk follow-up. Eleven serious adverse events were reported among 1.3% ($n = 10$) of children during the trial. All were because of hospitalization with life-threatening conditions, mostly malaria and anemia; and were considered unrelated to the trial intervention.

The randomization resulted in baseline equivalence (Table 1). The mean ± SD age was 32.0 ± 11.7 mo, 45.1% ($n = 338$) were female, and 42% ($n = 314$) were severely stunted. Ninety-five (13%) were currently breastfed, and 30% ($n = 227$), 30% ($n = 227$), 9% ($n = 71$), and 8% ($n = 59$) had consumed dairy, fish, meat, and eggs in the past 24 h, respectively.

Over the duration of the trial, children in the control group had a 51% [95% confidence interval (CI): 32, 73] relative increase in S-FEci along with a 2.7 (95% CI: 1.4, 4.1) mg/L decline in S-TfR (Table 2). In contrast, there were no changes over time among children in the control group with respect to P-Cob, P-MMA, P-Fol, and S-RBPci. There was a 4.4 (95% CI: 2.2, 6.7) g/L increase in Hb in the control group.

The LNS intervention resulted in improvements in markers of iron, cobalamin, and folate status, but not vitamin A status (Table 2). The effect of LNS on iron status was seen as a 43% (95% CI: 28, 60) greater increase in S-FEci, and a 2.4 (95% CI: 1.2, 3.5) mg/L greater decline in S-TfR. LNS increased P-Cob by 138 (95% CI: 111, 164) pmol/L and correspondingly reduced P-MMA by 33% (95% CI: 27, 39). LNS increased P-Fol by 8.5 (95% CI: 6.6, 10.3) nmol/L and resulted in an additional 3.8 (95% CI: 1.7, 6.0) g/L increase in Hb.

We assessed if the effects of LNS were modified by sex, lactation, severe stunting, or inflammation (Table 3). Lactation modified the effect of LNS on cobalamin (P-interaction < 0.001) and folate (P-interaction = 0.016) status. As such, LNS increased P-Cob by 155 (95% CI: 127, 183) pmol/L accompanied by a reduction in P-MMA by 37% (95% CI: 31, 43) among nonlactating but had no effect on P-Cob (−4 pmol/L, 95% CI: −87, 80) or P-MMA (−5%, 95% CI: −28, 26) among breastfed children. LNS increased P-Fol by 9.3 (95% CI: 7.4, 11.3) nmol/L among the nonbreastfed and had no effect among the breastfed (1.6 nmol/L, 95% CI: −4.4, 7.6). Notably, there was no

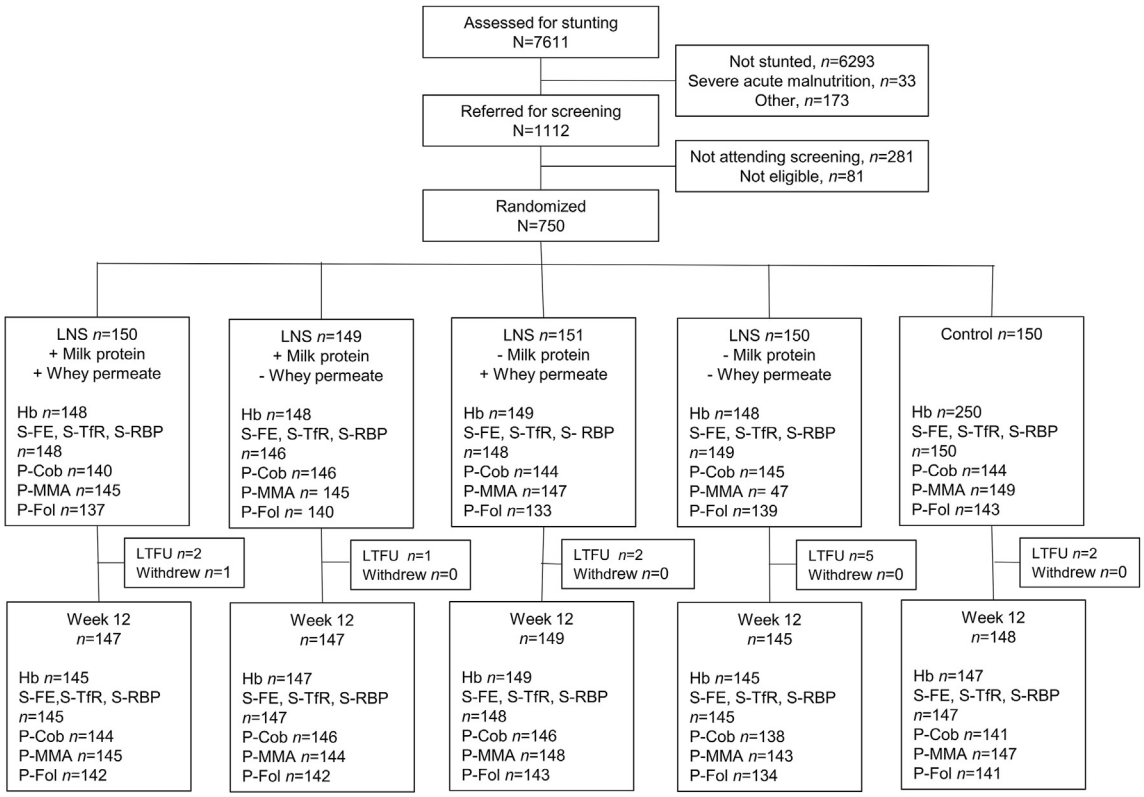

FIGURE 1. Trial flow diagram, 2 × 2 factorial design plus unsupplemented control group. Hb, hemoglobin; LNS, lipid-based nutrient supplement; LTFU, lost to follow-up; P-Cob, plasma cobalamin; P-Fol, plasma folate; P-MMA, plasma methylmalonic acid; S-FE, serum ferritin; S-RBP, serum retinol-binding protein; S-TfR, serum transferrin receptors.

difference in baseline P-Cob (304 pmol/L compared with 319 pmol/L, $P = 0.16$) or P-Fol (36 nmol/L compared with 34 nmol/L, $P = 0.16$) between the breastfed and nonbreastfed children. However, there was a difference in baseline P-MMA seen as a 31% (95% CI: 18, 41) higher P-MMA among the breastfed. We performed a sensitivity analysis to assess if the interaction with lactation was because of age and found no interaction by age above or below 2 y, irrespective of lactation.

The effect of LNS on Hb was 1.2 (95% CI: −0.3, 7.8) g/L and 4.8 (95% CI: 1.5, 8.1) g/L in those with and without malaria (*P*-interaction = 0.159), and 3.5 (95% CI: 0.4, 6.5) g/L and 3.7 (95% CI: −0.4, 7.8) g/L in those with and without anemia (*P*-interaction = 0.921). Among those with neither anemia nor malaria, anemia only, malaria only, and both, the effect of LNS was 2.9 (95% CI: −1.8, 7.5) g/L, 6.5 (95% CI: 2.4, 10.7) g/L, 4.4 (95% CI: −2.7, 11.4) g/L, and 0.4 (95% CI: −3.7, 4.6) g/L (*P*-interaction = 0.148). The changes in Hb in both the control and LNS group, and the difference in change, are shown for each combination of baseline anemia and positive malaria test (Supplemental Table 2 and Supplemental Figure 1). The estimates did not change with adjustments for baseline Hb, and age, sex, month of inclusion, and site.

LNS supplementation reduced the odds of having low S-FEci by 81% [adjusted odds ratio (OR): 0.19, 95% CI: 0.10, 0.35], and high S-TfR by 53% (adjusted OR: 0.49, 95% CI: 0.32, 0.75) (Table 4). LNS supplementation reduced the odds of low or marginal P-Cob by 89% (adjusted OR: 0.11, 95% CI: 0.06, 0.22). No child had low P-Fol < 14 nmol/L in either the intervention or the control group at the end of the trial. There was no difference in risk of low S-RBPci (adjusted OR: 1.06, 95% CI: 0.70, 1.61). At the end of the trial, the prevalence of anemia was still high with 39% and 52% being anemic in the supplemented and control groups, respectively. After adjustment for baseline Hb, age, sex, month of inclusion, and site, LNS reduced the odds of anemia by 55% (adjusted OR: 0.45, 95% CI: 0.29, 0.70) and odds of having iron deficiency anemia by 83% (adjusted OR: 0.17, 95% CI: 0.09, 0.35).

Among the 600 children randomly assigned to LNS supplementation, we analyzed the effect of the milk ingredients (MP and WP) on Hb and micronutrient markers. There were no interactions between MP and WP (Supplemental Table 3). MP was associated with a 14% (95% CI: 3, 26) increase in S-FEci compared with soy protein (SP). However, there were no other effects of either MP or WP.

Of the children supplemented with LNS, 86% of caregivers returned >80% of empty sachets. Compliance was lower among children below compared with above 2 y (80% compared with 88%, $P = 0.013$), but there was no difference between breastfed and nonbreastfed children below 2 y (both 80%, $P = 1.00$). There were also no differences in compliance by LNS formulation (87%, 86%, 84% and 87%, $P = 0.87$).

Discussion

LNS supplementation for 12 wk improved biomarkers of iron, cobalamin, and folate status, whereas no effect was seen on the marker of vitamin A status. In addition, LNS intervention compared with the control group increased Hb and reduced the odds of anemia by half.

The positive effect on both markers of iron status is similar to findings from a meta-analysis of randomized controlled trials done in Africa and Asia, providing small-quantity LNS containing 6–9 mg/d of iron [13]. Whereas the LNS in our trial provided a higher amount of iron (~12 mg/d), there was a lower relative increase in iron stores (S-FEci) of 43% compared with 56% in the above meta-analysis. This

TABLE 1
Baseline characteristics of 750 children with stunting randomly assigned to supplementation with LNS with/without MP and with/without WP ($n = 4 \times 150 = 600$) or no supplementation ($n = 150$)[1]

	LNS ($n = 600$)					
	Milk vs. soy protein		Whey permeate vs. maltodextrin		LNS vs. control	
	+MP ($n = 299$)	−MP ($n = 301$)	+WP ($n = 301$)	−WP ($n = 299$)	LNS ($n = 600$)	Control ($n = 150$)
Sociodemographic characteristics						
Age (mo)	32.4 ± 11.5	31.5 ± 12.0	32.6 ± 12.1	31.2 ± 11.4	31.9 ± 11.8	32.3 ±11.7
Sex, male	52% (156)	57% (172)	53% (159)	57% (169)	55% (328)	56% (84)
Residence, rural	44% (133)	44% (131)	43% (129)	45% (135)	44% (264)	47% (71)
Anthropometry						
Height (cm)	81.9 ± 7.1	81.3 ± 7.5	81.9 ± 7.6	81.4 ± 7.1	81.6 ± 7.3	81.9 ± 7.5
Weight (kg)	10.7 ± 1.9	10.5 ± 2.0	10.6 ± 2.0	10.5 ± 1.9	10.6 ± 2.0	10.6 ± 2.1
Mid-upper arm circumference (cm)	14.5 ± 1.1	14.4 ± 1.2	14.5 ± 1.1	14.4 ± 1.2	14.4 ± 1.1	14.4 ± 1.3
Weight-for-height (*z*-score)	−0.27 ± 1.03	−0.42 ± 0.93	−0.34 ± 0.95	−0.35 ± 1.01	−0.35 ± 0.98	−0.43 ± 1.03
Height-for-age (*z*-score)	−3.02 ± 0.74	−3.04 ± 0.73	−3.06 ± 0.75	−2.99 ± 0.72	−3.03 ± 0.73	−2.99 ± 0.75
Clinical						
Received high-dose vitamin A in past 6 mo	46% (138)	47% (140)	45% (134)	48% (144)	46% (278)	49% (73)
Positive rapid malaria test	40% (117)	37% (108)	40% (119)	36% (106)	38% (225)	45% (67)
Serum C-reactive protein (mg/L)	1.45 [0.33; 7.96]	1.74 [0.33; 9.45]	1.51 [0.33; 7.99]	1.51 [0.31; 9.44]	1.52 [0.33; 8.58]	1.64 [0.37; 5.94]
Serum α_1-acid glycoprotein (g/L)	1.31 ± 0.51	1.26 ± 0.51	1.27 ± 0.51	1.30 ± 0.52	1.28 ± 0.51	1.30 ± 0.56
Breastfed, currently	14% (42)	13% (38)	11% (32)	16% (48)	13% (80)	10% (15)
24-h recall food intake						
Dairy	28% (83)	31% (93)	27% (80)	32% (96)	29% (176)	34% (51)
Fish	30% (91)	31% (93)	29% (86)	33% (98)	31% (184)	29% (43)
Meat	12% (36)	8% (24)	8% (23)	12% (37)	10% (60)	7% (11)
Eggs	7% (22)	8% (25)	6% (19)	9% (28)	8% (47)	8% (12)
Pulses, legumes, and nuts	69% (207)	65% (195)	68% (206)	66% (196)	67% (402)	69% (104)
Grains, roots, or tubers	97% (301)	97% (290)	97% (291)	97% (292)	97% (583)	96% (144)
Vitamin A-rich fruits and vegetables	44% (113)	43% (130)	44% (133)	43% (130)	44% (263)	43% (64)
Other fruits and vegetables	89% (265)	90% (270)	89% (299)	89% (268)	89% (535)	88% (132)
Fats and oil	79% (236)	83% (250)	82% (246)	80% (299)	81% (486)	75% (112)

Abbreviations: LNS, lipid-based nutrient supplement; MP, milk protein; WP, whey permeate.
[1] Data are mean ± SD, median [IQR], or % (*n*).

may be because of the difference in duration of supplementation, because the randomized controlled trials included in the meta-analysis provided LNS for 6–18 mo compared with our 3-mo supplementation. Of relevance, the prevalence of iron deficiency (S-FEci < 12 μg/L) at the end of the LNS intervention reduced to 11.5% compared with 27.2% in the control group. Iron deficiency is common among children in low-income setting and is associated with anemia as well as poor cognitive development [20,21]. Compared with SP, LNS containing MP resulted in higher iron stores. Many dietary factors can affect iron absorption (mostly nonheme iron), including phytate and protein [22, 23]. Both SP [24] and casein [25] have been shown to reduce iron absorption. In a complex food matrix, absorption of iron depends on the amount and affinity of inhibitors or enhancers that compete to bind iron [22]. Because SP may contain iron absorption inhibitors [24,26, 27], we suggest that phytate and other inhibitors in SP resulted in a lower absorption of iron from LNS containing SP compared with MP.

There was a large positive effect of LNS intervention on P-Cob (138 pmol/L) and P-Fol (8.5 nmol/L). The effect on P-Cob was correspondingly accompanied by a relative 33% reduction in P-MMA. Compared with our study, a trial in Burkina Faso found a smaller increase in cobalamin (72 pmol/L) after 3-mo supplementation with LNS or CSB in moderately malnutrition children [14]. In the same trial, there was a slightly greater effect of LNS (16 pmol/L) compared with CSB on P-Cob. Notably, the above trial recruited from a much younger age group, 6–23 mo, compared with 12–59 mo in this study and 94% (compared with 13%) of children were breastfed. On the basis of our findings, lactation modified the effect of LNS on cobalamin status. Although only 13% of the children were still breastfed, we found strong interactions by lactation with respect to the effect of LNS on cobalamin status, based on both markers. The interaction reflected that there was no effect of LNS among breastfed children, but a considerable effect among nonbreastfed children. Cobalamin in breastmilk is dependent on the mother's cobalamin status and often inadequate in low-resource settings [28,29]. Because there was no difference in compliance between the breastfed and nonbreastfed, we would expect breastfed children to gain cobalamin in addition to that received from breastmilk. Furthermore, breastfed children, being younger, should have received more cobalamin per kg body weight from the 1 sachet per day received. However, children not breastfed may get relatively more from the family diet, which could also contain cobalamin. We found that LNS supplementation improved folate status. A few related studies of supplementation with LNS or micronutrient powders in young children have reported a similar positive effect on folate status [30–32]. Unlike folate, which is easily available in most diets, animal-source or fortified foods are the sole source of cobalamin [29]. Consequently, LNS can be beneficial in settings where diets are inadequate in animal-source foods by preventing anemia [33] and neurocognitive deficits [34] arising from cobalamin deficiency.

All LNS contained ≥619 μg of vitamin A, which is within the recommended dietary allowance for age; however, we found no overall effect of LNS on S-RBP and almost one-third of children had vitamin A deficiency (S-RBP < 0.7 μmol/L) at the end of the trial in both study groups. In contrast, pooled data from 9 trials showed a small (7%) increase in S-RBPci and 56% reduction in the prevalence of vitamin A deficiency among children receiving SQ-LNS for 6–18 mo compared with the control group [13]. However, the same authors found no effect of LNS

TABLE 2
Changes in markers of iron, cobalamin, folate, vitamin A status, and hemoglobin among 750 children with stunting over the duration of the trial, and the effect of LNS[1]

	LNS (n = 600)		Control (n = 150)		Difference in change (n = 600 vs. n = 150)	
	n		n		Unadjusted[5]	Adjusted[6]
Serum ferritin[2] (μg/L)						
Baseline	591	38.8 [79.6; 16.7]	150	34.8 [76.5; 17.2]	—	—
Endline	585	47.3 [85.0; 28.9]	147	38.4 [72.9; 18.9]	—	—
Change[4] (%)	576	33 (25, 42)	147	1 (−13, 16)	33 (18, 50)	34 (20, 50)
Serum ferritin (corrected)[2,3] (μg/L)						
Baseline	591	13.6 [7.93; 22.5]	150	13.6 [6.73; 26.2]	—	—
Endline	585	30.0 [18.1; 46.2]	147	22.3 [10.7; 35.6]	—	—
Change[4] (%)	576	116 (103, 131)	147	51 (32, 73)	42 (26, 60)	43 (28, 60)
Serum soluble transferrin receptor (mg/L)						
Baseline	591	14.2 ± 10.1	150	16.2 ± 11.5	—	—
Endline	585	10.0 ± 7.5	147	13.4 ± 9.7	—	—
Change[4]	576	−4.1 (−4.8, −3.4)	147	−2.7 (−4.1, −1.4)	−2.4 (−3.6, −1.3)	−2.4 (−3.5, −1.2)
Plasma cobalamin (pmol/L)						
Baseline	575	314 ± 136	144	327 ± 121	—	—
Endline	574	442 ± 190	141	312 ± 126	—	—
Change[4]	554	128 (115, 141)	136	−10 (−26, 7)	136 (109, 163)	138 (111, 164)
Plasma methylmalonic acid[2] (μmol/L)						
Baseline	584	0.32 [0.54; 0.2]	149	0.33 [0.57; 0.2]	—	—
Endline	580	0.23 [0.35; 0.15]	147	0.34 [0.55; 0.21]	—	—
Change[4] (%)	572	−31 (−35, −28)	146	4 (−5, 14)	−33 (−39, −27)	−33 (−39, −27)
Plasma folate (nmol/L)						
Baseline	549	34.3 ± 10.9	143	36.2 ± 12.2	—	—
Endline	561	43.0 ± 10.5	141	35.5 ± 11.6	—	—
Change[4]	518	8.6 (7.4, 9.7)	135	−1.2 (−3.4, 1.0)	8.4 (6.4, 10.3)	8.5 (6.6, 10.3)
Serum retinol-binding protein (μmol/L)						
Baseline	591	0.76 ± 0.30	150	0.74 ± 0.23	—	—
Endline	585	0.78 ± 0.26	147	0.81 ± 0.31	—	—
Change[4]	576	0.01 (−0.01, 0.04)	147	0.07 (0.02, 0.13)	−0.04 (−0.09, 0.00)	−0.04 (−0.09, 0.00)
Serum retinol-binding protein (corrected)[3] (μmol/L)						
Baseline	591	0.90 ± 0.28	150	0.87 ± 0.20	—	—
Endline	585	0.84 ± 0.24	147	0.87 ± 0.30	—	—
Change[4]	576	−0.06 (−0.08, −0.03)	147	0.00 (−0.05, 0.05)	−0.04 (−0.08, 0.00)	−0.04 (−0.08, 0.01)
Hemoglobin (g/L)						
Baseline	593	104 ± 14.5	150	105 ± 15.4	—	—
Endline	586	112 ± 14.6	147	109 ± 14.1	—	—
Change[4]	582	8.8 (7.7, 10.0)	147	4.4 (2.2, 6.7)	3.9 (1.7, 6.18)	3.8 (1.7, 6.0)

Abbreviation: LNS, lipid-based nutrient supplement.
[1] Data are number of samples analyzed, means ± SD, median [IQR], mean differences or percentages (95% confidence intervals).
[2] Log-transformed for analysis and differences expressed as a percentage.
[3] Corrected for inflammation on the basis of the regression model using both C-reactive protein > 5 mg/L and α_1-acid glycoprotein > 1 g/L.
[4] A paired t-test was used to determine the change over time.
[5] Mean difference or percentage of changes between LNS and control on the basis of linear mixed-effects models adjusting for the baseline value.
[6] Mean difference or percentage of changes between LNS and control on the basis of linear mixed-effects models adjusting for baseline value, age, sex, month of inclusion, and site.

(compared with the control group) on retinol, a more specific marker of vitamin A status. Approximately half of the children in our trial had received a high dose of vitamin A (200,000 IU) within 6 mo before the trial; hence, a small daily dose supplementation for only 3 mo may not show any effect. It is also possible that vitamin A in the current LNS formulations may not be bioavailable or adequate in children with stunting. Nonetheless, for logistic reasons, our vitamin A deficiency prevalence was based on S-RBP but not the preferred specific marker, serum retinol; hence, results should be interpreted with caution. We considered S-RBP as a proxy retinol marker and used the recommended serum retinol cutoff value < 0.7 μmol/L, and although not the case always [35], we assumed a 1:1 molar equivalence with S-RBP.

In addition to the overall improvements in markers of iron, cobalamin, and folate status, LNS intervention compared with the control group resulted in higher Hb and reduced prevalence of anemia. Similar effects of LNS have previously been reported [13,36,37]. Iron, cobalamin, and folate are the most important micronutrients for Hb synthesis and account for the majority of nutritional anemias [20,33]. Despite the observed effects of micronutrients in LNS on Hb, more than one-third of the children still had anemia at the end of the trial. This highlights the contribution of nonnutritional causes of anemia that include inflammation, infections, especially malaria and intestinal parasites, and hemoglobinopathies [20]. We found no interaction by baseline anemia or malaria test result separately with respect to the effect of LNS on Hb. This was surprising, because it is biologically plausible that LNS with its content micronutrients of importance for hematopoiesis/erythropoiesis would have had a greater effect on Hb among children with anemia without malaria. Indeed, in a 3-way interaction analysis, we

TABLE 3
Subgroup effects of LNS on markers of micronutrient status and hemoglobin among the 750 children with stunting who receive LNS ($n = 600$) or no supplement ($n = 150$)[1]

	Sex		Lactation		Stunting severity[4]		Inflammation[5]	
	Male ($n = 412$)		No ($n = 651$)		Moderate ($n = 436$)		No ($n = 372$)	
	Female ($n = 338$)		Yes ($n = 95$)		Severe ($n = 314$)		Yes ($n = 370$)	
	P	10^B or B (95% CI)	*P*	10^B or B (95% CI)	*P*	10^B or B (95% CI)	*P*	10^B or B (95% CI)
Serum ferritin[2,3] (%)	0.09	56 (34, 82) 28 (8, 52)	0.73	43 (27, 62) 34 (−6, 92)	0.96	44 (24, 66) 43 (20, 71)	0.85	41 (21, 65) 44 (23, 69)
Serum soluble transferrin receptor (mg/L)	0.44	−1.97 (−3.52, −0.41) −2.87 (−4.59, −1.16)	0.025	−1.93 (−3.14, −0.73) −6.34 (−9.98, −2.70)	0.06	−1.58 (−3.03, −0.12) −3.78 (−5.64, −1.92)	0.76	−2.42 (−4.05, −0.81) −2.43 (−4.05, 0.80)
Plasma cobalamin (pmol/L)	0.98	137 (101, 174) 138 (98, 177)	<0.001	155 (127, 183) −4 (−87, 80)	0.05	160 (125, 194) 106 (64, 148)	0.69	137 (100, 173) 136 (98, 173)
Plasma methylmalonic acid[2] (%)	0.41	−31 (−39, −22) −36 (−44, −27)	0.008	−37 (−43, −31) −5 (−28, 26)	0.44	−36 (−42, −27) −30 (−40, −19)	0.98	−33 (−41, −25) −34 (−42, −24)
Plasma folate (nmol/L)	0.45	9.1 (6.6, 11.6) 7.7 (4.9, 10.5)	0.016	9.3 (7.4, 11.3) 1.6 (−4.4, 7.6)	0.71	8.2 (5.9, 10.6) 8.9 (6.0, 11.9)	0.87	8.6 (6.1, 11.2) 8.3 (5.7, 11.0)
Serum retinol-binding protein[3] (μmol/L)	0.80	−0.04 (−0.10, 0.02) −0.03 (−0.10, 0.03)	0.28	−0.03 (−0.08, 0.01) −0.11 (−0.25, 0.03)	0.045	−0.07 (−0.12, −0.02) 0.02 (−0.05, 0.09)	0.22	−0.06 (−0.12, 0.00) −0.01 (−0.07, 0.05)
Hemoglobin (g/L)	0.91	3.7 (1.0, 6.6) 4.0 (0.8, 7.1)	0.87	3.6 (1.3, 5.9) 4.2 (−2.7, 11)	0.32	3.0 (0.3, 5.8) 5.2 (1.8, 8.7)	0.042	6.0 (3.0, 9.0) 1.5 (−1.5, 4.6)

Data are *P*-interaction and stratum-specific effect estimates (95% confidence intervals).
Abbreviation: LNS, lipid-based nutrient supplement.
[1] On the basis of linear mixed effect models adjusted for baseline value, age, sex, month of inclusion, and site.
[2] Log-transformed for analysis and difference expressed as a percentage.
[3] Corrected for inflammation on the basis of the regression model using both C-reactive protein > 5 mg/L and α_1-acid glycoprotein > 1 g/L.
[4] Stunting is defined as height-for-age *z*-score: <−3 for severe stunting and <−2 to −3 for moderate stunting.
[5] Inflammation on the basis of α_1-acid glycoprotein > 1.2 g/L.

TABLE 4
Effect of LNS on the prevalence of anemia, low: iron, cobalamin, and retinol status among 750 children with stunting at the end of the trial

	Baseline				Endline					
	LNS		Control		LNS		Control		Unadjusted OR	Adjusted OR[4]
	n	%	*n*	%	*n*	%	*n*	%		
Serum ferritin < 12 μg/L	591	16.2	150	18.0	585	5.1	147	16.3	0.24 (0.13, 0.44)	0.17 (0.08, 0.34)
Serum ferritin (corrected)[1] < 12 μg/L	591	42.5	150	44.7	585	11.5	147	27.2	0.25 (0.17, 0.50)	0.19 (0.10, 0.35)
Serum soluble transferrin receptor > 8.3 mg/L	591	60.7	150	65.3	585	38.5	147	56.5	0.50 (0.33, 0.75)	0.49 (0.32, 0.75)
Plasma cobalamin < 222 pmol/L	575	25.0	144	17.4	574	7.1	141	24.1	0.12 (0.07, 0.23)	0.11 (0.06, 0.22)
Serum retinol-binding protein < 0.7 μmol/L	591	45.5	150	46.0	585	42.4	147	38.1	1.23 (0.84, 1.80)	1.23 (0.84, 1.80)
Serum retinol-binding protein (corrected)[1] < 0.7 μmol/L	591	22.2	150	18.0	585	30.6	147	29.3	1.06 (0.77, 1.60)	1.06 (0.70, 1.61)
Anemia (hemoglobin < 110 g/L)	593	64.8	150	63.3	586	38.6	147	51.7	0.49 (0.33, 0.74)	0.45 (0.29, 0.70)
Iron deficiency anemia[2]	587	13.1	150	13.3	573	2.8	147	10.2	0.20 (0.09, 0.45)	0.19 (0.08, 0.45)
Iron deficiency anemia (corrected ferritin)[3]	587	30.2	150	31.3	573	5.3	147	18.0	0.19 (0.10, 0.37)	0.17 (0.09, 0.35)

Data are *n* number of samples analyzed, % prevalence, or odds ratio (OR) (95% confidence intervals).
Abbreviation: LNS, lipid-based nutrient supplement.
[1] Corrected for inflammation on the basis of the regression model using both C-reactive protein > 5 mg/L and α_1-acid glycoprotein > 1 g/L.
[2] Iron deficiency anemia is anemia plus iron ferritin < 12 μg/L.
[3] Iron deficiency anemia is anemia plus iron ferritin corrected for inflammation < 12 μg/L.
[4] On the basis of the logistic regression model adjusted for baseline value, age, sex, month of inclusion, and site.

found an effect of LNS on Hb among children with anemia and a negative malaria test, but not among children with other combinations of anemia and malaria.

Strengths of this study include the large sample size with very low loss to follow-up in addition to having a nonsupplemented control group to estimate the effect of LNS intervention. Furthermore, we were able to assess the effects of LNS on multiple micronutrient markers and included markers of cobalamin and folate status, which previously have not been assessed in most of LNS trials. Because of the nature of the intervention, we were unable to blind the study participants; however, efforts were made to ensure that outcome assessors were blinded. Another limitation was the lack of detailed data on home dietary intake over the period of the trial. In addition, most of the data were collected from February to October. It is possible that the micronutrient intake is better or worse in this period, compared with the rest of the year. Lastly, with the large number of significance tests, there is risk of chance findings.

In conclusion, our findings suggest that the provision of LNS in children with stunting offers considerable benefits on iron, cobalamin, and folate status, in addition to reducing anemia. Such benefits should be considered when designing interventions to address the double burden of stunting and micronutrient deficiencies. We believe our findings are generalizable to children under 5 y with stunting in similar resource-poor settings in Africa. However, LNS did not fully replete iron, cobalamin, and vitamin A status in all supplemented children; thus, the current duration of supplementation or micronutrient composition of LNS may need to be revised. Furthermore, the lack of effect of LNS on cobalamin status among the breastfed requires further investigation.

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Author contributions

The authors' responsibilities were as follows – BG, HF, EM: designed the study; RM, HP, JM, EM, BG: conducted the research; RM, HF: analyzed the data, and all coauthors: interpreted the findings; RM: drafted the initial manuscript; all authors: contributed to review and editing of the manuscript; HF, BG: had primary responsibility for final content; and all authors: read and approved the final version of the manuscript.

Conflict of interest

HF and CM have received research grants from Arla Food for Health; HF, BG, and CM have received research grants from the Danish Dairy Research Foundation; CM and KFM also received funds from Arla Foods Amba; and finally, HF, CM, KFM, BG, SF, and AB have had research collaboration with Nutriset, a producer of LNS. Other authors declare no financial relationships with any organizations that might have had an interest in the submitted work in the previous 5 y and declare no other relationships or activities that could appear to have influenced the submitted work.

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Data availability

The Ugandan Act on Data Protection and Privacy and the European Act on General Data Protection Regulation do not allow for personal data to be made available to other researchers without prior written approval from relevant instructions and authorities.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2024.01.018.

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