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Provision of Lipid-Based Nutrient Supplements from Age 6 to 18 Months Does Not Affect Infant Development Scores in a Randomized Trial in Malawi

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Abstract *Objectives* Undernutrition during early life contributes to more than 200 million children globally not fulfilling their developmental potential. Our objective was to determine whether dietary supplementation with several formulations of lipid-based nutrient supplements (LNS), which differed in dose per day and milk content, positively affect infant development in Malawi. *Methods* We randomly assigned 1932 infants age 6 months to receive one of the following for 12 months: 10, 20 g, or 40 g/day milk-containing LNS, 20 g or 40 g/day milk-free LNS, or no supplement until 18 months of age (control group). We assessed motor, language, socio-emotional, and executive function at age 18 months. Primary analysis was by intention-to-treat and we also examined 13 potential effect modifiers, including the child's initial nutritional status and level of developmental stimulation. The study is registered as clinical trial NCT00945698. *Results* We found no significant differences between intervention groups in any scores. The difference in mean *z*-scores between children in the control group and children in the intervention groups ranged from −0.08 to 0.04 for motor development ($p = 0.76$), −0.05 to 0.01 for language development ($p = 0.97$), −0.15 to 0.11 for socio-emotional development ($p = 0.22$), and −0.02 to 0.20 for executive function ($p = 0.24$). We did not find that initial nutritional status, developmental stimulation, or other factors modified the effect LNS versus control group. *Conclusions for Practice* Our results suggest that in a population such as this one, provision of LNS from age 6 to 18 months would not affect motor, language, socio-emotional, or executive function skills at age 18 months.

Keywords Lipid-based nutrient supplements · Infant development · Motor development · Language development · Socio-emotional development · Executive function · iLiNS project

Significance

What is already known on this subject? Infant undernutrition contributes to millions of children not fulfilling their developmental potential. Provision of small-quantity lipid-based nutrient supplements (LNS) to infants is a new strategy to reduce infant undernutrition.

What this study adds? We did not find any differences in 18-month motor language socio-emotional or executive function scores between children who received 10 g, 20 g or 40 g LNS/day from age 6 to 18 months compared to children who received no supplements suggesting that in a

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population such as the one we studied in Malawi provision of LNS might not affect development of these skills.

Introduction

Many nutrients, including fatty acids, B-vitamins, iron, iodine, and zinc, are necessary for the rapid brain development that occurs during early life and underlies the development of motor, cognitive, and socio-emotional skills [13, 28]. Over 200 million children in low- and middle-income countries fail to reach their developmental potential in these domains, partly due to undernutrition [15]. From age 6 to 23 months, as children transition from exclusive breastfeeding to sharing the meals of the household, they require foods that contain these nutrients to complement breast milk. In resource-poor areas, many caregivers are not able to provide sufficient nutrient-dense foods, especially when animal-source or fortified foods are not available or affordable [8].

Addition of small-quantity lipid-based nutrient supplements (SQ-LNS, at less than 20 g or ~110 to 120 kcal per day) to infant diets may help to provide the nutrients needed for growth and development during these crucial months. SQ-LNS is typically made from vegetable oil, peanut paste, milk powder, and sugar, with added vitamins and minerals, thus providing many of the fatty acids and micronutrients that are necessary for brain development [6].

The objective of the current study was to determine whether several formulations of LNS, which differed in dose per day and milk content and therefore varied in cost, positively affect motor, language, socio-emotional, and executive function scores, when provided from age 6 to 18 months. We also examined the effect of LNS on caregiver–child interactions as a potential mechanism through which improved child nutrition may affect child development. For example, caregivers may treat children who are small for their age as younger than they actually are, and thus may not provide age-appropriate stimulation to an undernourished child. Finally, we examined the extent to which pre-specified individual and household characteristics, such as the child's initial nutritional status and developmental support and stimulation from the environment, modified the effects of these various doses and formulations of LNS on developmental scores. Motor and language development are supported and stimulated by aspects of the environment such as opportunities to explore, play, interact with objects and people, and hear a rich variety of language, including songs and stories. We hypothesized that children with lower levels of developmental stimulation or lower initial nutritional status may have greater potential to benefit from supplementation with LNS.

Methods

Study Participants and Design

This study was conducted in a partly semi-urban and partly rural area of Mangochi district, Malawi. Here, we report a set of secondary outcomes of a trial described in more detail by Maleta and others [22]. Six-month old healthy infants were identified through community surveys in the study area. Eligibility criteria are listed in the supplementary material.

From November, 2009 to May, 2011, 1932 eligible infants were randomly assigned to receive one of the following interventions between 6 and 18 months of age: (1) standard health care from 6 to 18 months (ST-DI), i.e. no supplements, with delayed intervention between 18 and 30 months of age (2) 10 g/day milk-containing LNS (LNS-10 gM), (3) 20 g/day milk-containing LNS (LNS-20 gM), (4) 20 g/day milk-free LNS (LNS-20 gNoM), (5) 40 g/day milk-containing LNS, (LNS-40 gM), or (6) 40 g/day milk-free LNS (LNS-40 gNoM). The daily LNS doses provided ~55 to 241 kcal and generally met the RDA for 22 micronutrients, including B-vitamins, iron, iodine, and zinc. For details, see supplementary material.

The sample size of 320 per group was determined to detect a clinically significant difference between groups in change in length-for-age z-score (LAZ), which was the main outcome of the trial [22]. Allowing for 15 % attrition, a sample size of 320 per group provided the trial with 72 % power to detect a difference of 0.3 *SD* in developmental scores between the six groups at $p < 0.05$.

At the time of enrollment, project staff collected maternal and child anthropometric data, information concerning parental education and family socio-economic characteristics, and a finger-prick blood sample to measure hemoglobin (Hb) concentration (HemoCue AB, Angelholm, Sweden), and peripheral blood malaria parasitemia using a rapid diagnostic test (RDT; Clear view Malaria Combo, British Biocell International Ltd., Dundee, UK). Project staff delivered supplements to participants' homes every 2 weeks, collected remaining supplements, and gathered information regarding supplement consumption. Adherence was calculated as the percent of days in study that the supplement was both delivered to the household and reported by the mother to be consumed by the enrolled child. For further details, see Maleta et al. [22]. Once a month, the home visitor also asked the mother whether the child had acquired six motor milestones, based on the World Health Organization Multi-Centre Growth Reference Study [31]. Baseline developmental status was quantified as whether the child had acquired more than one of these milestones at the first home visit.

All six groups of study participants received all normal under-five clinic services provided by the Malawian health care system. For further details, see supplementary material. At 18 months of age, project staff conducted developmental assessments at a clinic visit, as secondary outcomes of the trial. Ethical approval for the study procedures was obtained from the University of Malawi, College of Medicine Research and Ethics Committee and the Ethics Committee at Tampere University Hospital District, Finland. All participants provided written informed consent, by signature or thumb-print. The study was registered with the U.S. National Institutes of Health as a clinical trial (www.ClinicalTrials.gov; NCT00945698).

Developmental Assessment Measures

We assessed motor development by the Kilifi Developmental Inventory (KDI), which is a tool developed in Kenya based on several standard tests [3]. The child's score was the total number of skills he or she was able to perform, out of 34 fine motor skills and 35 gross motor skills, as observed by a data collector. All testing materials were purchased or made locally, according to the specifications in the KDI manual. Prior to using the tool, we confirmed that the materials and items were appropriate for the local context through pilot testing. The child's mood, interaction with the assessor, and activity level during the KDI assessment were rated by the data collector. For further details, see supplementary material.

We assessed language development using a 100-word vocabulary checklist based on the MacArthur-Bates Communicative Development Inventory (CDI) [11]. Through pilot testing in the local languages (Chichewa and Chiyao), we selected 100 words with a positive correlation with total vocabulary score and a positive correlation with child age, comprising 18 easy words (words said by >50 % of children), 60 moderate words (words said by 30–50 % of children) and 22 advanced words (words said by 10–30 % of children). The child's score was the total number of words the child said, out of the 100 word list, as reported by the caregiver, which was the mother for 98 % of children. For further details, see supplementary material.

We assessed socio-emotional development by the Profile of Social and Emotional Development (PSED), a test developed in Kenya based in part on the Brief Infant/Toddler Social Emotional Assessment [2]. Nineteen items, rated on a scale from 0 to 2, were summed for a total score, then reversed, so that a higher score indicated fewer socio-emotional problems.

We assessed executive function using a version of the A not B task, which is a widely used test of working memory and executive function in young children that has been previously used successfully in Kenya and Uganda [4, 9, 24]. In each of ten trials, a small biscuit was placed under one of two identical opaque cups on a wooden board in front of the child. The board was removed from sight for 5 s, during which the child was distracted with a song. The board was then returned and the child was invited to find the biscuit. Every time the child achieved two correct consecutive trials, the biscuit was then hidden at the alternate location. The scores were total correct trials; perseverative errors (the total number of errors committed after the first switch to the alternate location); and whether the child was able to complete all ten trials.

Caregiver–Child Interaction

We assessed caregiver–child interaction using the family care indicators (FCI) interview [12, 20], which was developed by the United Nations Children's Fund and validated against the Home Observation for the Measurement of the Environment (HOME) Inventory in Bangladesh [16]. For each of six activities (e.g., told stories, sang songs), the mother reported whether the child's mother, father, and any other adult had engaged in that activity with the child in the past 3 days. Prior to using this tool, we confirmed that these activities were appropriate for the study context by conducting four focus group discussions (FGDs) with mothers of young children in the study areas regarding the activities they did with their children. We calculated the caregiver–child interaction score as the sum of these 18 item scores (6 activities for each of the three categories of potential caregivers).

Family Care Indicators Score

We also evaluated overall household stimulation by an interview with the mother, using the FCI items, including the 6 items concerning activities with caregivers (described above) and 12 additional items regarding toys and books in the home. The total of all 18 FCI items was more strongly correlated with the developmental scores than any individual item or subscale score, and the internal consistency of the 18 items was high (Cronbach's Alpha = 0.71), indicating that all items measured the same construct. For further details, see supplementary material. While the caregiver–child interaction score was examined as a trial outcome, the overall FCI score was used as a covariate and effect modifier in analyses on developmental scores.

Translation, Training, and Quality Control

Test instructions and interview questions were translated into Chichewa and Chiyao then independently back-translated to English. A third person checked the translations and back-translations and corrected the translations where

necessary. Seven data collectors were trained to administer the developmental tests and interviews. All data collectors were unaware of intervention group and were required to pass knowledge and practice-based evaluations before administering the tests and interviews. Inter-scorer agreement was high (KDI and A not B task: 95 %, PSED: 89 %, vocabulary checklist: 96 %, FCI interview: 97 %). Every 6 months, we evaluated inter-tester reliability and test–retest reliability. We then conducted re-training on items that showed inconsistency between testers or between test sessions. Reliability improved over time, across the three rounds of reliability testing. For the KDI, reliability (Pearson's correlation) ranged from 0.57 to 0.87, for the A not B task, from −0.53 to 0.32, for the PSED from 0.29 to 0.86, for the vocabulary checklist from 0.81 to 0.97, and for the FCI score from 0.56 to 0.70. Internal reliability of all tests was also high (*Cronbach's Alpha* = 0.79 for the KDI, 0.71 for the PSED, 0.98 for the vocabulary checklist, and 0.71 for the FCI).

Statistical Analyses

A statistical analysis plan for the analyses presented here was posted to the project website (www.ilins.org) before the group codes were revealed to the investigators. This plan included pre-specified covariates and effect modifiers. Analyses were conducted using SAS version 9.3 or 9.4 (SAS Institute, Cary, NC). The primary analysis was by intention to treat. We also conducted a per protocol analysis only including children with at least 70 % adherence to supplement consumption.

We computed *z*-scores based on the distribution of our sample, by standardizing each score to a mean of zero and standard deviation of one. We examined the lowest decile (10 %) and the lowest quartile (25 %) of the total sample for each score, as a proxy for children likely to be experiencing a severe (lowest 10 %) and moderate-to severe (lowest 25 %) developmental delay.

We estimated the difference between the six trial groups using ANCOVA for continuous outcomes, and logistic regression for categorical outcomes. We estimated each model first adjusting only for the child's age at developmental assessment, and second, adjusting for child age and any potential covariates that independently predicted each outcome score at $p < 0.1$. All potential covariates are listed in the supplementary material and the covariates included in each model are listed in the footnote of Table 2.

If the dose by milk interaction was not significant at $p < 0.1$, we examined potential effect modifiers of the effect of the four doses of LNS (0, 10, 20, and 40 g), combining the groups who received LNS with and without milk (within the 20 and 40 g groups). We examined the following 13 effect modifiers, defined a priori: child sex; baseline child LAZ, WLZ, Hb concentration, and capillary ZPP; baseline maternal height, BMI, education, and age; household food insecurity access (HFIA) index, number of children under age 5 years in the household, cohabitation of the child's father with the family, and FCI score. For further details, see supplementary material. If a significant effect was found on any developmental outcome and on caregiver–child interaction, we would examine the hypothesis that the effect on the developmental outcome was mediated by the effect on caregiver–child interaction; in the absence of such effects, there is no potential for mediation.

Results

Figure 1 shows the trial profile. Out of 1932 children enrolled, 1385 attended the clinic for developmental assessment at age 18 months. The proportion of children who were not assessed, due to death or drop-out, was not significantly different between the six trial groups (*Chi Square* = 6.67, $p = 0.248$).

Group characteristics are presented in Table 1. At age 6 months, children in the study sample already showed substantial linear growth faltering. The mean LAZ was more than one standard deviation below the mean of WHO norms and 29 % of the sample was stunted (LAZ < −2). However, weight-for-length was on average slightly higher than WHO norms. Mothers had completed, on average, less than 5 years of formal education. The percentage of children who had acquired more than one of the six WHO motor milestones [31] at baseline ranged from 29 to 39 % and was not significantly different between groups.

Children in the six trial groups did not differ significantly in any of the characteristics examined. The 547 children who were enrolled but did not participate in developmental assessment did not significantly differ from the developmental sample in any of the baseline characteristics presented in Table 1, except maternal education. Mothers of children in the developmental sample had slightly lower mean years of education (*mean* = 4.56, *SD* = 3.53) compared to those lost to follow-up (*mean* = 4.97, *SD* = 3.65; $p = 0.03$).

Table 2 shows the mean motor, language, socio-emotional, executive function, and caregiver–child interaction *z*-scores in the six intervention groups at age 18 months. Scores in the six groups were not significantly different from each other in any outcome. Adjusting for covariates that independently predicted each score at $p < 0.1$ (see footnote to Table 2) resulted in similar findings. Likewise, in the per protocol analysis, including 978 children with greater than 70 % reported adherence, no significant differences were found between groups.

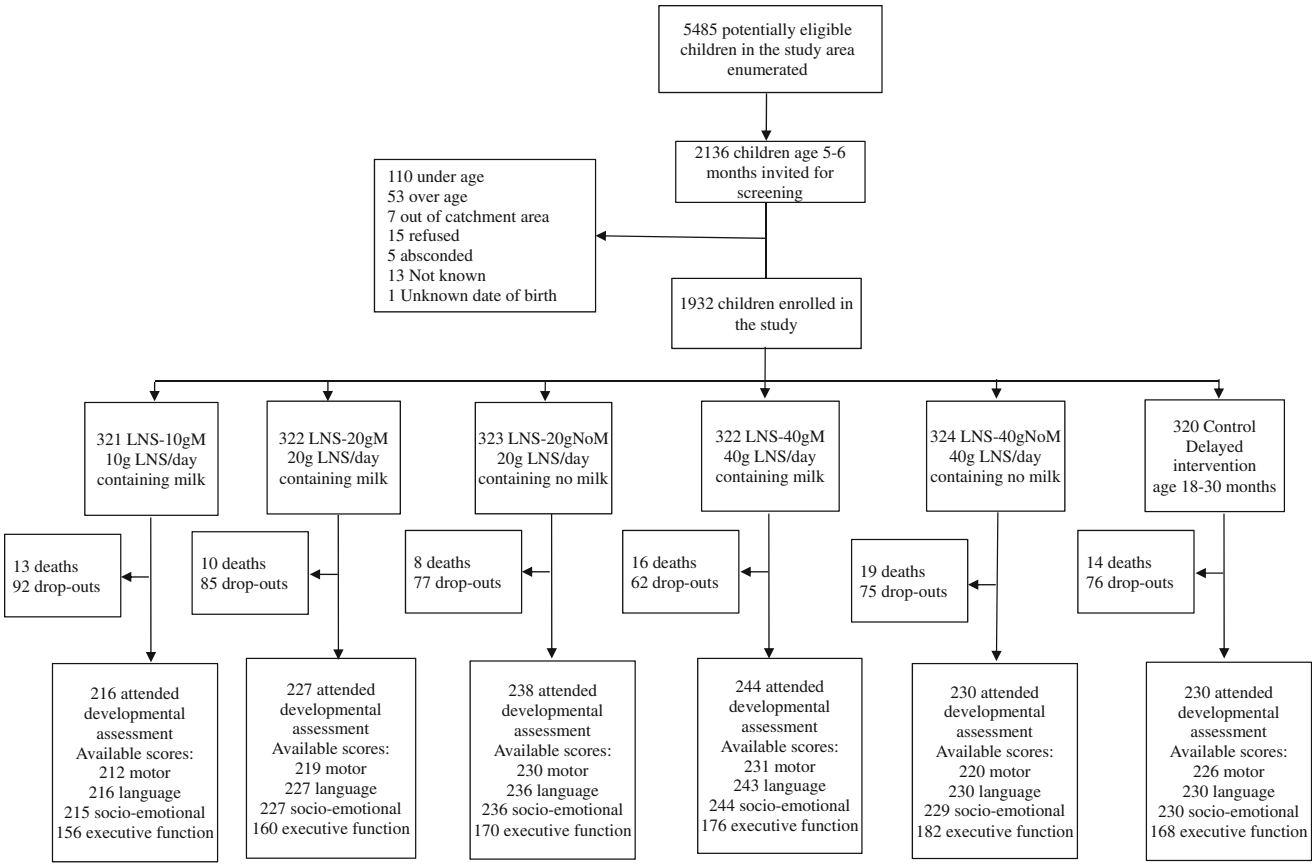

Fig. 1 Trial profile

Table 3 presents the effect of the intervention on categorical outcomes. Similar to the findings for the continuous scores, no significant differences were found between the six groups. The pattern for children in the lowest quartile of each score was also similar, with no significant differences between groups (data not shown). These results were consistent when controlling for covariates that independently predicted each score and in the per protocol analysis.

Of the five continuous developmental outcomes, the dose by milk interaction was significant only for the socio-emotional *z*-score ($p = 0.05$; all other $ps > 0.3$). Thus, we examined potential effect modifiers for the combined data from the 20 and 40 g/day groups for all outcomes except the socio-emotional *z*-score.

Out of the 13 effect modifiers examined for the 5 continuous developmental outcome scores, only three significant interactions were found at $p < 0.1$: for motor *z*-scores, the interaction between dose (0, 10, 20, and 40 g) and maternal BMI ($p = 0.060$), for language z-scores, the interaction between dose and children under age 5 in the household ($p = 0.052$), and for socio-emotional z-scores, the interaction between group (6 groups) and FCI score ($p = 0.048$).

When we explored the interaction between dose and maternal BMI for motor z-scores, no significant differences were found between doses at the 10th, 50th or 90th percentile of maternal BMI. Likewise, no significant differences in language z-scores were found between doses in households with or without children under age 5 years. For socio-emotional z-scores, two significant differences were found: in households in the 10th percentile of FCI score, children who received 20 gNoM scored significantly higher than those who received 40 gM; in households in the 50th percentile of FCI score, children who received 40 gNoM scored significantly higher than those who received 40 gM.

Discussion

In this randomized trial in Malawi, there were no differences in 18-month motor, language, socio-emotional, executive function, or caregiver–child interaction scores between children who received various doses and formulation of LNS from age 6 to 18 months, compared to children who received no supplements. Out of 13 potential effect modifiers examined, no consistent pattern was found.

Table 1 Group characteristics

	ST-DI $n = 230$ Mean (SD) or n (%)	LNS-10gM $n = 216$ Mean (SD) or n (%)	LNS-20gM $n = 227$ Mean (SD) or n (%)	LNS-20gNoM $n = 238$ Mean (SD) or n (%)	LNS-40gM $n = 244$ Mean (SD) or n (%)	LNS-40gNoM $n = 230$ Mean (SD) or n (%)	p value for the difference between 6 trial groups
Baseline characteristics							
Child sex (number of boys)	123 (53 %)	106 (49 %)	116 (51 %)	119 (50 %)	114 (47 %)	117 (51 %)	0.79
Baseline child length-for-age z (LAZ) score	−1.46 (1.07)	−1.35 (1.05)	−1.35 (0.99)	−1.49 (0.97)	−1.37 (1.04)	−1.41 (1.09)	0.66
Baseline child weight-for-length z (WLZ) score	0.36 (1.22)	0.24 (1.01)	0.35 (1.17)	0.19 (1.09)	0.18 (1.05)	0.29 (1.08)	0.36
Baseline child haemoglobin (Hb) concentration (g/L)	104 (16)	103 (15)	105 (17)	103 (17)	103 (16)	103 (16)	0.64
Baseline child malaria (positive RDT)	43 (20 %)	31 (16 %)	31 (15 %)	38 (17 %)	34 (15 %)	42 (20 %)	0.51
Baseline maternal age (years)	27 (7)	26 (6)	26 (7)	26 (7)	27 (6)	26 (6)	0.50
Baseline maternal education (years of formal education)	4.6 (3.7)	4.6 (3.7)	4.5 (3.6)	4.8 (3.2)	4.2 (3.5)	4.7 (3.6)	0.50
Baseline maternal body mass index (BMI)	21.9 (2.7)	21.7 (3.2)	21.9 (2.9)	22.0 (2.6)	21.7 (2.7)	22.1 (3.1)	0.69
Child had acquired more than 1 of the 6 WHO motor milestones[a] at baseline	81 (39 %)	76 (38 %)	61 (29 %)	67 (31 %)	85 (37 %)	73 (33 %)	0.18
Data collected at 18-month developmental assessment							
Child age at developmental assessment (months)	18.3 (0.6)	18.4 (0.7)	18.3 (0.7)	18.3 (0.8)	18.3 (0.9)	18.3 (0.6)	0.84
Family care indicators (FCI) z-score	0.10 (0.99)	0.03 (1)	−0.05 (1.01)	−0.04 (1.01)	−0.04 (0.98)	0.00 (1.01)	0.54
Child's primary language Chiyao (vs. Chichewa)	156 (68 %)	144 (67 %)	146 (64 %)	157 (67 %)	164 (67 %)	153 (67 %)	0.98
Child exposed to more than one language	50 (22 %)	52 (24 %)	57 (25 %)	66 (28 %)	55 (23 %)	66 (29 %)	0.44

[a] WHO Multicentre Growth Reference Study Group [31]

Given that a total of 65 interactions were examined, one would expect about six significant effects by chance. Thus, the two significant differences between groups in socio-emotional development at the low and middle levels of FCI score were probably due to chance.

Strengths of the study were that children were allocated randomly to intervention groups, data collectors who conducted developmental assessments were blind to intervention group, the developmental assessment tools had been developed in Africa and were suitable for the local context, and data collectors were rigorously trained and demonstrated high inter-rater agreement. Inter-tester reliability was also high in the later rounds of reliability testing, though this was lower at the beginning of the data collection period. Another strength of the study was the examination of a number of potential effect modifiers. Several previous studies have found effects of nutrition interventions on developmental scores only in sub-groups of children [21, 27, 30]. However, in our study, we did not find that contextual factors such as socio-economic status, maternal education, initial nutritional status, or household stimulation modified the effects of the intervention on 18-month development scores.

A weakness of the study was a relatively high rate of attrition (28 %). However, the proportion lost to follow-up did not differ between groups, and those lost to follow-up differed significantly from children who participated in developmental assessment in only one out of eight baseline characteristics examined, suggesting that the developmental sample was likely representative of the full sample. Another weakness was that the language and socio-emotional assessments relied on maternal report, and mothers were aware whether or not they were receiving LNS.

In addition, we did not directly verify that the supplement was consumed by the enrolled child. As reported previously by Maleta et al. [22], average self-reported

Table 2 Mean motor, language, socio-emotional, executive function, and caregiver–child interaction z-scores at the end of the intervention period (age 18 months)

	ST-DI Mean (SD)	LNS-10 gM Mean (SD)	LNS-20 gM Mean (SD)	LNS-20 gNoM Mean (SD)	LNS-40 gM Mean (SD)	LNS-40 gNoM Mean (SD)	*p* value for the difference between the 6 trial groups	Covariate-adjusted *p* value for the difference between the 6 trial groups
Motor z-score	−0.02 (0.99)	0.06 (0.90)	0.05 (1.05)	−0.06 (0.98)	−0.02 (0.93)	0.01 (1.14)	0.82[a]	0.76[b]
Language z-score	−0.02 (1.01)	−0.01 (1.03)	0.01 (0.96)	0.00 (0.98)	−0.01 (1.01)	0.03 (1.02)	0.99[a]	0.97[c]
Socio-emotional z-score	−0.03 (0.99)	0.00 (1.01)	0.03 (1.01)	0.03 (1.04)	−0.14 (0.92)	0.12 (1.02)	0.11[a]	0.22[d]
A not B correct z-score	0.05 (0.97)	−0.15 (0.99)	−0.02 (1.08)	0.07 (1.00)	0.01 (1.02)	0.02 (0.94)	0.37[a]	0.24[e]
A not B perseverative errors z-score	0.02 (1.01)	0.05 (0.98)	−0.04 (1.04)	−0.04 (0.99)	0.02 (1.00)	−0.01 (0.99)	0.96[a]	0.95[f]
Caregiver–child interaction z-score	0.12 (1.06)	0.10 (1.04)	0.00 (1.04)	−0.10 (0.92)	−0.06 (0.97)	−0.05 (0.97)	0.11[a]	0.06[g]

Means and SDs are unadjusted

[a] Adjusted for child age at developmental assessment

[b] Adjusted for child age and sex; baseline child developmental status, LAZ, WLZ, MUACZ, HCZ, Hb concentration, ZPP, and malaria; baseline maternal height, BMI, and education; baseline paternal education; data collector, child's mood, activity level, and interaction with the assessor during the KDI assessment, and FCI score

[c] Adjusted for child age and sex; baseline child developmental status, LAZ, MUACZ, and ZPP; baseline maternal education; baseline paternal age and education; data collector, whether the child was exposed to multiple languages, and FCI score

[d] Adjusted for child age and sex; baseline maternal BMI, height, and education; number of persons in the household, data collector, and FCI score

[e] Adjusted for child age, baseline child ZPP, baseline maternal MUAC, baseline paternal education, data collector, number of children under age 5 in the household, and child's mood, activity level, and interaction with the assessor during the KDI assessment

[f] Adjusted for child age, baseline child HCZ and Hb concentration, baseline maternal age, baseline paternal education, and data collector

[g] Adjusted for child age; baseline child HCZ, Hb concentration, and malaria; baseline maternal height, age, and education; baseline paternal age and education, data collector, and number of children under age five in the household

adherence to the recommended daily LNS dose was high (93 % for successfully delivered supplements). Considering also the missed supplement delivery visits, due to reasons such as temporary migration out of the study area and inability of the study team to locate the participant during periods of active farm work, the average reported consumption was still relatively high (72 %) [22]. However, in a subset of study children ($n = 568$) whose intake of LNS was assessed using two non-consecutive 24-h dietary recalls at age 9 months, the mean percentage consumed of the intended LNS dose was considerably lower [17]. Thus, the lack of observed effects on development could be due to lower than intended intakes of LNS by the enrolled child. However, it is unlikely that low adherence fully accounts for the lack of observed effects for two reasons. First, no effects were found in the per protocol analysis only including children with >70 % reported adherence. Second, another trial in Burkina Faso found a positive effect of infant LNS plus malaria and diarrhea surveillance and treatment on 18-month development despite the same finding that reported adherence was higher than observed intakes in 12-h home observations in a subset of children in the study sample [1]. This shows that effects of LNS, at least when provided with illness surveillance and treatment, could be found even when true adherence may be lower than intended or reported.

The finding that provision of LNS from age 6 to 18 months did not positively affect developmental scores is consistent with three out of five previous trials. Five randomized controlled trials have investigated the

Table 3 Categorical outcomes in the six trial groups

	ST-DI $n = 230$ n/total (%)	LNS-10gM $n = 216$ n/total (%) Odds ratio (95 % CI)	LNS-20gM $n = 227$ n/total (%) Odds ratio (95 % CI)	LNS-20gNoM $n = 238$ n/total (%) Odds ratio (95 % CI)	LNS-40gM $n = 244$ n/total (%) Odds ratio (95 % CI)	LNS-40gNoM $n = 230$ n/total (%) Odds ratio (95 % CI)	p value for the difference between the 6 trial groups
Children in the lowest decile of language scores	22/230 (10 %)	21/216 (10 %) 1.02 (0.54–1.91)	15/227 (7 %) 0.67 (0.34–1.33)	22/236 (9 %) 0.97 (0.52–1.81)	25/243 (10 %) 1.08 (0.59–1.98)	20/230 (9 %) 0.90 (0.48–1.70)	0.80
Children in the lowest decile of motor scores	19/226 (8 %)	17/212 (8 %) 0.95 (0.48–1.88)	16/219 (7 %) 0.86 (0.43–1.72)	29/230 (13 %) 1.57 (0.85–2.89)	19/231 (8 %) 0.98 (0.50–1.90)	19/220 (9 %) 1.03 (0.53–2.00)	0.57
Children in the lowest decile of socio-emotional scores	15/230 (7 %)	18/215 (8 %) 1.31 (0.64–2.67)	20/227 (9 %) 1.38 (0.69–2.78)	23/236 (10 %) 1.55 (0.79–3.05)	25/244 (10 %) 1.64 (0.84–3.19)	19/229 (8 %) 1.30 (0.64–2.62)	0.78
Children in the lowest decile of A not B correct scores	19/168 (11 %)	24/156 (15 %) 1.43 (0.75–2.72)	25/160 (16 %) 1.45 (0.77–2.76)	19/170 (11 %) 0.99 (0.50–1.94)	23/176 (13 %) 1.18 (0.62–2.25)	24/182 (13 %) 1.19 (0.63–2.26)	0.76
Children who completed all 10 trials of the A not B task	146/168 (87 %)	131/156 (84 %) 0.79 (0.42–1.47)	135/160 (84 %) 0.81 (0.44–1.51)	149/170 (88 %) 1.07 (0.56–2.03)	154/176 (88 %) 1.05 (0.56–1.99)	160/182 (88 %) 1.10 (0.58–2.06)	0.83

developmental effects of provision of small- or medium-quantity LNS during infancy, starting at age 6–11 months and ending at age 12–18 months. One trial in Haiti and two in Malawi did not find any effect of doses ranging from 20 to 54 g (~108 to 280 kcal) per day on the age of attainment of developmental milestones [18, 23], or on Griffith's Mental Development Scale scores [26]. However, two other trials have shown positive effects of LNS. One trial in Ghana showed that a higher percentage of children who received 20 g LNS/day from age 6 to 12 months walked independently at age 12 months, compared to a non-supplemented group [5]. In Burkina Faso, provision of 20 g LNS/day and malaria and diarrhea treatment from age nine to 18 months increased motor, language, and personal-social scores and reduced the prevalence of developmental delay at age 18 months [29].

The lack of effects among children in Malawi, despite some evidence of positive effects in other contexts, such as Burkina Faso, suggests that development may be constrained by factors other than child dietary intake in Malawi. Based on Demographic Health Surveys, there was lower dietary diversity in infant diets after age 6 months in Burkina Faso than in Malawi, suggesting a greater need for adding nutrient-rich foods to infant diets in Burkina Faso. From birth to 6 months, the typical pattern in Burkina Faso was for some fluids but little food to be given in addition to breast milk, whereas early introduction of maize porridge was common in Malawi [19, 25]. This early introduction of complementary food could lead to a high burden of infection and environmental enteropathy, which may constrain growth and development regardless of subsequent dietary intake [14]. Another difference between the trials was that in Burkina Faso, the intervention package included both LNS and malaria and diarrhea treatment. Therefore, it seems that LNS may promote development only in some settings or in combination with other interventions.

It is also possible that the developmental assessments we used were not sensitive enough to detect effects at age 18 months. Of the developmental scores, only motor scores differed significantly between children who were wasted (WLZ <-2) and non-wasted, while motor and language scores differed between children who were stunted (LAZ <-2) and non-stunted, when adjusting for other factors, suggesting that these measures were sensitive to these indicators of nutritional status. However, they may not have been sensitive enough to detect effects of the intervention. At least two previous studies of nutritional deficiency in infants have found no effects on developmental measures before age 2 years, while follow-up studies detected impairments in measures of language and IQ at

age 5–7 years [7, 10]. Further research is needed to clarify the contextual factors or intervention combinations that result in a positive effect on infant development in Malawi and across contexts.

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