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Effects of maternal and child lipid-based nutrient supplements on infant development: a randomized trial in Malawi[1,2]

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ABSTRACT

Background: Maternal and infant undernutrition is associated with poor infant development; however, few studies have examined the impact of combined pre- and postnatal dietary supplementation on infant development.

Objective: Our objective was to determine whether provision of small-quantity lipid-based nutrient supplements (SQ-LNSs) to mothers during pregnancy and the first 6 mo postpartum, and to children aged 6–18 mo, improves infant development in Malawi.

Design: We randomly assigned 869 pregnant women to receive one of the following daily: an iron and folic acid (IFA) capsule, a multiple micronutrient (MMN) capsule containing 18 micronutrients, or a 20-g sachet of SQ-LNSs containing 22 vitamins and minerals, protein, carbohydrates, essential fatty acids, and 118 kcal. Children in the lipid-based nutrient supplement (LNS) group only received SQ-LNSs from 6 to 18 mo of age. We monitored the acquisition of 11 developmental milestones monthly by maternal report; observed the attainment of 7 motor milestones at 6, 12, and 18 mo of age; and conducted a comprehensive assessment of motor, language, and socioemotional development and executive function at 18 mo of age. The primary analysis was by intention-to-treat.

Results: By maternal report, children in the LNS group achieved walking alone (B = 0.53; 95% CI: 0.11, 0.94; P = 0.034) and waving goodbye (B = 0.60; 95% CI: 0.12, 1.08; P = 0.040) earlier than the IFA group and standing with assistance earlier than the MMN group (B = 0.51; 95% CI: 0.12, 0.89; P = 0.029). By researcher observation, there was a trend (P = 0.052) for a greater percentage of children in the LNS group (58%) to walk alone at age 12 mo than in the IFA (49%) and MMN (49%) groups. At age 18 mo, there were no significant differences between groups in any scores.

Conclusion: Although provision of SQ-LNSs to pregnant women and infants in Malawi may affect the age of acquisition of certain developmental milestones, it did not affect our assessments of motor, language, socioemotional, or executive function skills at 18 mo of age. This trial was registered at clinicaltrials.gov as NCT01239693. *Am J Clin Nutr* doi: 10.3945/ajcn.115.114579.

Keywords: cognitive development, iLiNS project, infant development, lipid-based nutrient supplements, maternal micronutrient supplements

INTRODUCTION

Brain development occurs rapidly during the first 1000 d after conception, laying the foundation for motor, cognitive, and socioemotional function throughout the rest of life. More than 200 million children in low- and middle-income countries fail to reach their developmental potential in these areas, partly because of undernutrition (1). Nutritional conditions that are associated with poor child development are severe acute malnutrition (very low weight for height), chronic undernutrition as evidenced by intrauterine or postnatal growth retardation, iron-deficiency anemia, and iodine deficiency (2). Various strategies have been found to be effective in preventing or improving these conditions; however, with the exception of a few studies on food supplementation (3–8) and micronutrient powders (9, 10), direct evidence of the impact of these strategies on child development is scarce. To our knowledge, no study since the 1970s (3, 4) has examined the impact of supplementation with a full suite of micronutrients and fatty acids during most of the 1000-d window after conception on motor, cognitive, and socioemotional development.

Small-quantity lipid-based nutrient supplements (SQ-LNSs)[8] were originally designed to be used for home fortification of complementary foods, and subsequent formulations were developed to provide key nutrients for pregnant and lactating women (11). SQ-LNSs are 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 (11). Although

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[2] Supplemental Material and Supplemental Tables 1–4 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[8] Abbreviations used: FCI, family care indicators; IFA, iron and folic acid; iLiNS, International Lipid-Based Nutrient Supplements; KDI, Kilifi Developmental Inventory; LNS, lipid-based nutrient supplement; MMN, multiple micronutrient; PSED, Profile of Social and Emotional Development; SQ-LNS, small-quantity lipid-based nutrient supplement.

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several studies have reported the developmental effects of provision of small- or medium-quantity lipid-based nutrient supplements (LNSs) (20–54 g/d) during infancy (12–15), to our knowledge, no studies have yet examined the effects of SQ-LNSs beginning during pregnancy on child development.

The objective of the current study was to determine whether the provision of SQ-LNSs to mothers in Malawi during pregnancy and the first 6 mo postpartum, and to their children aged 6–18 mo, improves child development compared with the provision of iron and folic acid (IFA) during pregnancy only or a multiple micronutrient (MMN) tablet during pregnancy and the first 6 mo postpartum. We also examined the effect of the provision of SQ-LNSs on caregiver–child interactions as a potential mechanism through which improved maternal and child nutrition may affect child development. Well-nourished mothers may be more active in providing stimulating experiences, such as talking to their children, singing to them, and playing with them. Well-nourished children may also elicit more stimulating experiences from their caregivers.

METHODS

Study participants and design

This study was conducted in a partly semiurban and partly rural area of Mangochi district, Malawi, as a part of the International Lipid-Based Nutrient Supplements (iLiNS) project. Here, we report a set of secondary outcomes of a trial described in more detail by Ashorn et al. (16). Pregnant women who attended antenatal care at 2 hospitals and 1 health center during the enrollment period and met the inclusion criteria were enrolled from February 2011 to March 2012. Details of randomization and inclusion criteria have been published previously (16).

At enrollment, women were randomly assigned to 1 of 3 groups. The IFA group received standard antenatal care according to Malawian health policy, including supplementation from enrollment to delivery with 1 capsule/d containing 60 mg Fe and 400 μg folic acid. The IFA group received a placebo tablet containing 200 mg Ca from delivery to 6 mo postpartum. The MMN group received 1 capsule/d from enrollment to 6 mo postpartum that contained IFA and 16 additional micronutrients, as shown in **Table 1**. The LNS group received daily 20-g sachets of SQ-LNSs produced by Nutriset SAS from enrollment to 6 mo postpartum that contained the same micronutrients as the MMN capsules, 4 additional minerals, protein, and fat (Table 1). From 6 to 18 mo of age, children in the LNS group also received 20 g SQ-LNSs/d designed for children (Table 1) (11). All groups also received 2 doses of intermittent preventive malaria treatment during pregnancy. The sample size of 290 per group, allowing for 20% attrition, provided 83% power to detect a difference of 0.3 SD in developmental scores between groups, with α at 0.05 (17).

At the time of enrollment, data collectors recorded maternal anthropometric data and information concerning parental education and family socioeconomic characteristics. Research nurses assessed the duration of pregnancy and measured the women's peripheral blood malaria parasitemia and HIV infection with rapid tests. Research staff delivered supplements to participants' homes every 2 wk and collected remaining supplements. Adherence was calculated as the percentage of delivered supplements that were not returned to research staff. For a detailed description of these variables, see Ashorn et al. (16).

TABLE 1
Nutrient and energy contents of the dietary supplements[1]

	IFA,[2] 1 tablet	MMN, 1 tablet	Maternal LNS, 20-g sachet	Child LNS, 20-g sachet
Total energy, kcal	0	0	118	118
Protein, g	0	0	2.6	2.6
Fat, g	0	0	10	9.6
Linoleic acid, g	0	0	4.59	4.46
α-Linolenic acid, g	0	0	0.59	0.58
Vitamin A, mg RE	0	800	800	400
Vitamin C, mg	0	100	100	30
Vitamin B-1, mg	0	2.8	2.8	0.3
Vitamin B-2, mg	0	2.8	2.8	0.4
Niacin, mg	0	36	36	4
Folic acid, mg	400	400	400	80
Pantothenic acid, mg	0	7	7	1.8
Vitamin B-6, mg	0	3.8	3.8	0.3
Vitamin B-12, mg	0	5.2	5.2	0.5
Vitamin D, mg	0	10	10	5
Vitamin E, mg	0	20	20	6
Vitamin K, mg	0	45	45	30
Iron, mg	60	20	20	6
Zinc, mg	0	30	30	8
Copper, mg	0	4	4	0.34
Calcium, mg	0	0	280	280
Phosphorus, mg	0	0	190	190
Potassium, mg	0	0	200	200
Magnesium, mg	0	0	65	40
Selenium, mg	0	130	130	20
Iodine, mg	0	250	250	90
Manganese, mg	0	2.6	2.6	1.2

[1]IFA, iron and folic acid; LNS, lipid-based nutrient supplement; MMN, multiple micronutrient; RE, retinol equivalent.

[2]The group that received IFA from enrollment to delivery received 200 mg Ca/d from delivery to 6 mo postpartum.

Ethical approval for the study procedures was obtained from the ethics committees at the University of Malawi College of Medicine and Tampere University Hospital District, Finland. All participants provided informed consent. The study was registered with the NIH as a clinical trial (NCT01239693).

Developmental assessment measures

From birth through 18 mo of age, data collectors visited participants monthly and asked whether the study child had acquired 7 motor, 2 language, and 2 personal-social milestones. Six of the motor milestones were based on the WHO Multicentre Growth Reference Study (18). The 5 additional milestones were selected from the Malawi Developmental Assessment Tool, comprising milestones that were valid in the local context and generally achieved between the ages of 6 and 18 mo (19). When the child was 6, 12, and 18 mo of age, participants visited their local hospital or clinic, where project staff observed whether the child had acquired the same 7 motor milestones. One week after the 18-mo clinic visit, a separate team of project staff conducted comprehensive developmental assessments.

In the comprehensive assessment, we assessed motor development by the Kilifi Developmental Inventory (KDI), which is a tool developed in Kenya based on several standard tests,

including the Griffiths Mental Development Scales and the Merrill-Palmer Scales (20). Assessors scored children on their ability to perform 34 fine motor skills, such as putting coins in a box and threading beads on a string, and 35 gross motor skills, such as walking backward and climbing onto a platform. The child's score was the total number of skills he or she was able to perform. The child's mood during the KDI assessment was rated as positive (smiling/laughing or occasional smiles) or not positive (crying/inconsolable, occasional crying, changeable/mood swings, or no visible emotions). The child's interaction with the assessor during the KDI was rated as positive (friendly) or not positive (avoidant and withdrawn, clings to family member, hesitant/when approached will accept reluctantly, difficult to engage in tasks, or inappropriate approaches to assessor). The child's activity level during the KDI was rated as positive (active and maintains interest) or not positive (unarousable, sleepy, can hardly be awakened, sleepy but easily awakened, does not spontaneously engage in activity, and awake but loses interest).

We assessed language development with the use of a 100-word vocabulary checklist based on the MacArthur-Bates Communicative Development Inventory (21), developed in part by following previous adaptations of this tool in Bangladesh (22) and Kenya (23). First, project staff conducted interviews with 41 mothers of children aged 14–33 mo (mean ± SD: 21.0 ± 5.2 mo), asking mothers what words their children said, and probing specific categories from the MacArthur-Bates Communicative Development Inventory, such as animals, food and drink, and clothing. We used the results of these interviews to develop a list of 352 words. We then asked 41 additional mothers of children aged 13–23 mo (mean ± SD: 17.9 ± 2.2 mo) whether their children said each of these 352 words. Finally, 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.

We assessed socioemotional 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 to assess social cognition, independence, emotional lability, maladaptive behavior, and social competence (A Abubakar, P Holding, M Mwangome, B Kabunda, R Kalu, K Maitland, C Newton, F Van de Vijver, unpublished results, 2015). The PSED was designed as a structured interview to elicit from a caregiver descriptions of the child's behavior, which are then used to code 19 items on a scale from 0 to 2. The items were summed for a total score, then reversed, so that a higher score indicated fewer socioemotional problems.

We assessed executive function with the use of a version of the A-not-B task, which is a widely used test of working memory and executive function in very young children that previously has been used successfully in Kenya and Uganda (24–26). In each of 10 trials, a small piece of a cracker was hidden under one of 2 identical cups on a wooden board. The board was removed from sight for 5 seconds, during which the child was distracted with a song. The board was then returned and the child was invited to find the cracker. Every time the child achieved 2 correct consecutive trials, the cracker was then hidden at the alternate location. The scores included *1*) total correct trials (the sum of all trials in which the child selected the correct location); *2*) perseverative errors (the total number of errors committed after the first set of 2 correctly solved trials); and *3*) whether the child was able to complete all 10 trials.

Caregiver–child interactions

We assessed the child's interaction with caregivers with the family care indicators (FCI) interview (27, 28), which was developed by UNICEF and validated in Bangladesh (29). For each of 6 activities (read books or looked at picture books; told stories; sang songs; took the child outside the home; played with the child; and spent time naming, counting, or drawing things), we asked the caregiver (98% mothers) whether the child's mother, father, and any other adult had engaged in that activity with the child in the past 3 d. Before using this tool, we confirmed that these activities were appropriate for the study context by conducting 4 focus group discussions 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 3 categories of potential caregivers).

FCI score

We also evaluated overall household stimulation with the use of the FCI items, including the items indicating whether any caregiver had engaged the child in the 6 activities described above, and 12 additional items regarding toys and books in the home. Through the same focus group discussions with community mothers, described above, we specified locally appropriate examples of toys for each category, such as toys for pretending. We calculated the total score because 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 $\alpha = 0.66$), indicating that all items measured the same construct.

Developmental assessment training and quality control

We trained 10 data collectors to administer the developmental tests and interviews. All data collectors were required to pass knowledge- and practice-based evaluations before administering the tests and interviews. Interscorer agreement, which is the percentage of items coded identically when 2 data collectors independently score the same test session or interview, was high (KDI and A-not-B task: 92%; PSED: 80%; vocabulary checklist: 98%; and FCI interview: 95%). Intertester reliability, or the Pearson's correlation coefficient between scores when different testers administer the test to the same group of children on 2 different occasions, was also reasonable (KDI: 0.65; A-not-B task: 0.75; PSED: 0.65; vocabulary checklist: 0.82; and FCI score: 0.47). We conducted additional training for items that showed low agreement or reliability.

Statistical analyses

A statistical analysis plan was posted to the project website (www.ilins.org) before the intervention group code was broken. This plan included prespecified outcomes, covariates, and effect

modifiers, as described below. All analyses were conducted with the use of SAS version 9.4 (SAS Institute). The primary analysis was by intention to treat. We also conducted per protocol analyses in 2 ways: *1*) only including mothers with ≥80% adherence to supplement consumption during pregnancy; and *2*) only including mothers with ≥70% adherence during pregnancy and postpartum and, for the LNS group, children with ≥70% adherence.

Calculation of age of acquisition of developmental milestones

For the age of acquisition of developmental milestones, we considered a milestone to be achieved when the mother reported that the child had achieved the skill on 2 consecutive visits. The age of acquisition was calculated as the mean age between the first of these visits and the previous visit in which the child had not yet achieved the skill. For further details, see **Supplemental Material**.

Calculation of developmental scores and categorical outcomes

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

Effect of intervention

We estimated the difference between the intervention groups in the age to achieve each milestone with the use of survival analysis (SAS PROC LIFEREG), with right censoring if the child was not recorded to have achieved the milestone. We used the normal distribution option if skewness was <1 and the log-logistic distribution if skewness was ≥1. We estimated the difference between groups for continuous outcomes with the use of ANCOVA, and for categorical outcomes with the use of logistic regression. If the F value was significant at $P < 0.05$, we used the Tukey-Kramer test for pairwise comparisons between groups. We first estimated the unadjusted model, and then adjusted for child age and any of 23 prespecified covariates that independently predicted each outcome score at $P < 0.1$. All potential covariates are listed in the supplemental material, and the covariates included in each model are listed in the footnotes of each table.

Effect modifiers

We examined the following 13 potential effect modifiers defined a priori: baseline maternal malaria, height, BMI, education, age, anemia, and gestational age; primiparity; child sex; season at enrollment; study site; household food insecurity access score; and household asset index. We examined these effect modifiers for 12 outcomes: 7 observed milestones for which 5–95% of children had achieved the skill (see below) and the five 18-mo comprehensive developmental assessment scores. In addition, for these 5 comprehensive scores, we examined FCI score as a potential effect modifier. If any interaction between the potential effect modifier and intervention group was significant at $P < 0.1$, we further explored the pattern of the effect at various levels of the effect modifier (Supplemental Material).

RESULTS

The trial profile is shown in **Figure 1**. Of 869 children enrolled, 755 participated in developmental assessment: 746 in milestone monitoring; 720 in milestone observation at 6, 12, and/or 18 mo; and 675 in comprehensive developmental assessment. The proportion of children who were not assessed because of death or dropout was not significantly different between the 3 intervention groups (milestone monitoring: chi-square = 0.45, $P = 0.799$; milestone observation: chi-square = 0.03, $P = 0.987$; comprehensive assessment: chi-square = 0.07, $P = 0.967$).

Group characteristic comparisons

The characteristics of the developmental sample in each intervention group, as well as the characteristics of the children who were enrolled but did not participate in developmental assessment, are presented in **Table 2**. Children in the 3 intervention groups did not differ significantly in any of the 16 characteristics presented in Table 2, with the exception of the household food insecurity access score. Participants in the MMN group had significantly higher food insecurity than those in the LNS group ($P = 0.03$).

A large proportion of the mothers of children who did not participate in developmental assessment (70%) had enrolled at the public hospital in Mangochi, which was a more transient area than the other 2 sites at Malindi and Lungwena. Compared with those who did participate in developmental assessment, enrolled mothers whose children did not participate were significantly younger and had a higher BMI. A greater proportion were primiparous, and a smaller proportion had a household asset index below the median (Table 2).

Timing of milestone acquisition

The age of acquisition of each motor milestone was significantly negatively associated with the 18-mo motor z score, indicating that the later the child acquired the milestone, the lower the 18-mo motor z score. We found the same pattern for the association between the age of acquisition of each language milestone and the 18-mo language z score (**Supplemental Table 1**).

The mean age of acquisition of each developmental milestone in each intervention group is shown in **Table 3**. The first column shows the mean age of acquisition of the 6 motor milestones monitored in the WHO Multicentre Growth Reference Study (18). Children in the study sample achieved the milestones at an age similar to that of the WHO sample.

The intervention groups differed in the age at which they waved goodbye (unadjusted $P = 0.058$; adjusted $P = 0.041$), stood with assistance (unadjusted $P = 0.028$; adjusted $P = 0.029$), and walked alone (unadjusted $P = 0.056$; adjusted $P = 0.032$), and there was a trend for a difference in the age at which they stood alone (unadjusted $P = 0.084$; adjusted $P = 0.073$). For waving goodbye and walking alone, the LNS group achieved these milestones about one-half of a month earlier than did the IFA group (waving goodbye—unadjusted: B = 0.57; 95% CI: 0.08, 1.06, $P = 0.058$; adjusted: B = 0.60; 95% CI: 0.12, 1.08; $P = 0.040$; walking alone—unadjusted: B = 0.49; 95% CI: 0.08, 0.91; $P = 0.054$; adjusted: B = 0.53; 95% CI: 0.11, 0.94; $P = 0.034$)

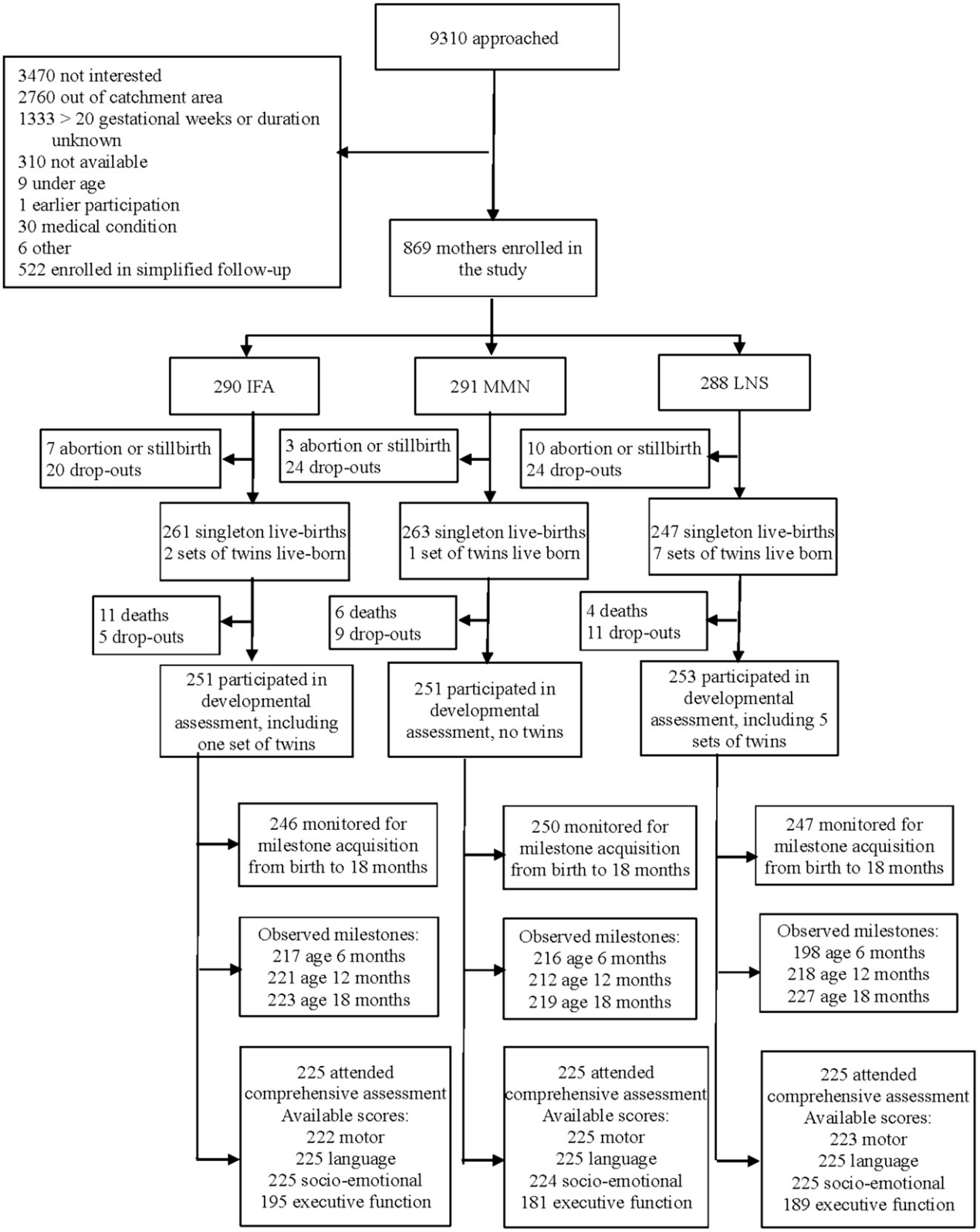

FIGURE 1 Trial profile. IFA, iron and folic acid; LNS, lipid-based nutrient supplement; MMN, multiple micronutrient.

whereas the MMN group did not differ significantly from either group ($P > 0.1$). For standing with assistance, the LNS group achieved this milestones about one-half of a month earlier than did the MMN group (unadjusted: B = 0.51; 95% CI: 0.12, 0.90; $P = 0.028$; adjusted: B = 0.51; 95% CI: 0.12, 0.89; $P = 0.029$), whereas the IFA group did not differ significantly from either group ($P > 0.1$). There were no significant differences between groups in the age of acquisition of any other milestones ($P > 0.2$).

TABLE 2
Group characteristics of each intervention group, the sample that participated in developmental assessment, and those lost to follow-up[1]

	IFA (n = 251)	MMN (n = 251)	LNS (n = 253)	P^2	DS (n = 755)	Non-DS (n = 124)	P^2 (DS vs. non-DS)
Baseline characteristics							
Maternal age, y	25 ± 6	25 ± 6	25 ± 6	0.84	25 ± 6	24 ± 6	0.02
Maternal education, y	3.8 ± 3.6	3.9 ± 3.4	3.9 ± 3.6	0.99	3.9 ± 3.5	4.7 ± 3.9	0.05
Maternal BMI, kg/m^2	21.9 ± 2.4	22.0 ± 2.7	22.0 ± 3.0	0.88	22.0 ± 2.7	22.8 ± 3.0	<0.001
Maternal hemoglobin, g/L	110 ± 17	111 ± 15	111 ± 17	0.69	111 ± 16	108 ± 17	0.09
Mother HIV positive	34 (14)	26 (10)	29 (12)	0.57	89 (12)	13/91 (14)	0.53
Maternal malaria (positive RDT)	57 (23)	57 (23)	56 (22)	0.99	170 (23)	30/124 (24)	0.70
Gestational age at enrollment, wk	16.9 ± 2.0	16.9 ± 2.1	16.9 ± 2.1	0.91	16.9 ± 2.1	17.1 ± 2.1	0.34
Primiparous	51 (20)	53 (21)	54 (21)	0.96	158 (21)	48/123 (39)	<0.001
Household Food Insecurity Access score	5.0 ± 4.3[a,b]	5.5 ± 4.4[a]	4.5 ± 4.1[b]	0.04	5.0 ± 4.3	4.0 ± 3.7	0.05
Household Asset Index below median	123 (50)	116 (48)	115 (46)	0.65	354 (48)	29/85 (34)	0.02
Site				0.98			<0.001
Lungwena	123 (55)	125 (56)	129 (57)		377 (50)	28/124 (23)	
Malindi	46 (20)	48 (21)	44 (20)		138 (18)	9/124 (7)	
Mangochi	82 (36)	78 (35)	80 (36)		240 (32)	87/124 (70)	
Other group characteristics							
Male child	116 (47)	117 (47)	123 (49)	0.87			
Child age at comprehensive assessment, y	18.4 ± 0.4	18.4 ± 0.4	18.4 ± 0.3	0.98			
FCI z score	0.04 ± 1.02	0.01 ± 0.98	−0.05 ± 1.00	0.60			
Child's primary language Chiyao (vs. Chichewa)	168 (75)	166 (74)	165 (73)	0.95			
Child exposed to >1 language	55 (24)	46 (20)	57 (25)	0.41			

[1]Values are means ± SDs, n (%), or n/total n (%). Values in a row without a common superscript letter are significantly different, $P < 0.05$. DS, developmental sample; FCI, family care indicators; IFA, iron and folic acid; LNS, lipid-based nutrient supplement; MMN, multiple micronutrient; RDT, rapid diagnostic test.
[2]P values were determined with the use of ANOVA for the continuous variables and Wald chi-square for the categorical variables.

The per protocol analysis revealed a similar pattern of results. The LNS group achieved the same 4 milestones at an earlier age; however, there were fewer significant differences between groups. For details, see **Supplemental Tables 2** and **3**.

Milestone attainment at ages 6, 12, and 18 mo

The percentage of children in each group who were observed to have attained each motor milestone at ages 6, 12, and 18 mo for the 7 observed milestones for which 5–95% of children had achieved the skill is shown in **Table 4**. There were no significant differences between groups; however, there was a trend for a greater percentage of children in the LNS group to have achieved walking alone at age 12 mo (unadjusted P = 0.083; adjusted P = 0.052). In the LNS group, 58% of children were able to walk alone at age 12 mo compared with 49% in the IFA group (unadjusted RR = 1.19; 95% CI: 0.97, 1.47; P = 0.121; adjusted RR = 1.20, 95% CI: 0.98, 1.47; P = 0.094) and 49% in the MMN group (unadjusted RR = 1.19; 95% CI: 0.96, 1.47; P = 0.137; adjusted RR = 1.20; 95% CI: 0.98, 1.48; P = 0.083).

The per protocol analyses showed the same pattern of results for the percentage of children walking alone at age 12 mo. When only including mothers with ≥80% adherence to supplement consumption during pregnancy (n = 455), 61% of children in the LNS group were able to walk alone compared with 51% in the IFA group (unadjusted RR = 1.19; 95% CI: 0.94, 1.51; P = 0.193; adjusted RR = 1.22; 95% CI: 0.97, 1.53; P = 0.108) and 50% in the MMN group (unadjusted RR = 1.24; 95% CI: 0.97, 1.59; P = 0.099; adjusted RR = 1.29; 95% CI: 1.02, 1.64; P = 0.043). The only other significant difference between groups was in the percentage of children able to run at age 12 mo when only including mothers with ≥ 80% adherence during pregnancy. In the LNS group, 26% of children were able to run, compared with 18% in the IFA group (unadjusted RR = 1.47; 95% CI: 0.88, 2.44; P = 0.181; adjusted RR = 1.51; 95% CI: 0.93, 2.45; P = 0.105) and 17% in the MMN group (unadjusted RR = 1.53; 95% CI: 0.90, 2.60; P = 0.143; adjusted RR = 1.58; 95% CI: 0.95, 2.63; P = 0.084).

Comprehensive assessment at age 18 mo

The mean motor, language, socioemotional, and executive function z scores in the 3 intervention groups are shown in **Table 5**. Scores were not significantly different between groups for any outcome. Adjusting for covariates that independently predicted each score at $P < 0.1$ (Table 5, footnote) resulted in similar findings. The caregiver–child interaction z score also did not differ significantly between the 3 intervention groups in unadjusted or adjusted analyses (Table 5). No significant differences between groups were found in the proportion of children in the lowest decile or quartile of each score, or in the other binary outcomes. For details, see **Supplemental Table 4**. The per protocol analyses likewise showed no significant differences between groups.

Modifiers of the effect of intervention

Of the 13 effect modifiers examined for the 12 outcomes, 14 of 156 (10%) interactions between the effect modifier and group were found to be significant at $P < 0.1$. The maximum number of interactions found to be significant for any effect modifier was 2 of 12 outcomes. Thus, no variable emerged as a consistent effect modifier across developmental outcomes.

Of these interactions, we further explored the only one that was found for an outcome that showed marginally significant group

TABLE 3
Age of acquisition of developmental milestones by intervention group[1]

	WHO[2]	IFA	MMN	LNS	Unadjusted *P*	adjusted *P*
Sitting without support[3]	6.0	5.01 ± 0.11	4.88 ± 0.10	4.81 ± 0.10	0.47	0.47
Hands and knees crawling[4]	8.5	7.84 ± 0.13	7.79 ± 0.13	7.58 ± 0.14	0.29	0.29
Standing with assistance[5]	7.6	8.58 ± 0.14	8.71 ± 0.14	8.20 ± 0.14	0.03	0.03
Walking with assistance[6]	9.2	10.14 ± 0.15	10.10 ± 0.15	9.83 ± 0.15	0.27	0.27
Standing alone[7]	11.0	10.69 ± 0.15	10.81 ± 0.15	10.35 ± 0.15	0.08	0.07
Walking alone[8]	12.1	13.04 ± 0.15	12.93 ± 0.15	12.52 ± 0.15	0.06	0.03
Running[9]	—	14.71 ± 0.17	14.91 ± 0.17	14.49 ± 0.17	0.30	0.20
Pronouncing single words[10]	—	10.03 ± 0.28	10.46 ± 0.28	10.15 ± 0.29	0.38	0.48
Waving goodbye[11]	—	10.94 ± 0.17	10.80 ± 0.18	10.35 ± 0.18	0.06	0.04
Eating by self[12]	—	10.50 ± 0.17	10.54 ± 0.17	10.49 ± 0.18	0.99	0.98
Drinking from a cup[8]	—	11.04 ± 0.16	11.05 ± 0.17	11.03 ± 0.17	0.98	0.99

[1]Values are means ± SEs. Means are adjusted for covariates and right-censoring with the use of survival analysis with SAS PROC LIFEREG. Geometric means are unadjusted. The mean is shown for variables for which skewness is <1 and the geometric mean is shown for variables for which skewness is ≥1. IFA, iron and folic acid; LNS, lipid-based nutrient supplement; MMN, multiple micronutrient.

[2]WHO Multicentre Growth Reference Study Group (18).

[3] Values are geometric means ± SEs. Adjusted for baseline maternal height, BMI, and education; asset index; child sex; season at enrollment; and site.

[4]Adjusted for baseline maternal height, asset index, season at enrollment, and site.

[5]Adjusted for baseline maternal age.

[6]Adjusted for baseline maternal height and education, gestational age at enrollment, and site.

[7]Adjusted for baseline maternal height, child sex, and site.

[8]Adjusted for baseline maternal height and site.

[9]Adjusted for baseline maternal height and midupper arm circumference and site.

[10]Adjusted for baseline maternal age and hemoglobin, household food insecurity access, asset index, number of persons in the household, child sex, season at enrollment, and site.

[11]Adjusted for baseline maternal height, BMI, midupper arm circumference, education, and age; household food insecurity access; asset index; season at enrollment; and child sex.

[12]Adjusted for baseline maternal age, education, and height; child sex; primiparity; and site.

differences in the full set of children, which was for the percentage of children walking alone at age 12 mo. For this outcome, the interaction between child sex and intervention group was significant ($P < 0.01$). Although a marginally significant effect of LNSs was found in the full group of children, subgroup analysis revealed that this effect was only evident for boys. In boys, 63% in the LNS group were walking alone at age 12 mo compared with 45% in the MMN group (unadjusted RR = 1.41; 95% CI: 1.03, 1.93; $P = 0.025$; adjusted RR = 1.40; 95% CI: 1.04, 1.90; $P = 0.024$) and 41% in the IFA group (unadjusted RR = 1.55; 95% CI: 1.12, 2.15; $P = 0.003$; adjusted RR = 1.50; 95% CI: 1.10, 2.05; $P = 0.006$). The percentage of girls able to walk alone at age 12 mo was similar in the 3 groups (LNSs: 53%; MMNs: 53%; IFA: 57%; $P > 0.8$).

DISCUSSION

In this randomized trial, provision of SQ-LNSs to mothers during pregnancy and until 6 mo postpartum and to their infants aged 6–18 mo did not affect 18-mo motor, language, socioemotional, executive function, or caregiver–child interaction scores. Mothers in the LNS group reported that their children achieved several developmental milestones about one-half of a month earlier than did children of mothers who received IFA (walking alone and waving goodbye) or MMNs (standing with assistance). By researcher observation, a greater proportion of children in the LNS group was able to walk alone at age 12 mo compared with the other 2 groups. Although this difference was marginally significant in the full group of children, subgroup analysis revealed that it was significant in boys but not in girls. However, by age 18 mo, no group differences were evident in the full sample or in any subgroups.

This study had a number of strengths. Participants were allocated randomly to intervention groups, data collectors who conducted observational developmental assessments were blind to intervention groups, 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 and intertester reliability. A weakness of the study was that the participants were not blind to intervention group and a number of the developmental outcomes relied on parent report, thus introducing potential bias. However, the age of milestone acquisition by parent report was associated with the observed motor and language scores at age 18 mo, showing the validity of these measures. In addition, the positive effect on walking alone at age 12 mo by researcher observation suggests that such bias cannot completely account for the results. Another weakness was that the group that participated in the developmental assessment differed significantly from the group that dropped out of the study on a number of characteristics. Thus, the developmental sample may not have been representative of the full sample.

The significant results reported here should be interpreted with caution because we examined multiple outcomes. We did not correct for multiplicity because all outcomes were specified a priori in the analysis plan. Whereas an advantage of correcting for multiplicity is that it decreases the chance of a type I error, a disadvantage is that it increases the chance of a type II error (30). Although the significant effects might be due to chance, our study helps to identify outcomes for which significant effects are

TABLE 4
Percentage of children able to perform each motor skill at ages 6, 12, and 18 mo by intervention group[1]

	IFA	MMN	LNS	Unadjusted *P*	Covariate-adjusted *P*
Hands and knees crawling at 6 mo	59/217 (27)	66/215 (31)	66/198 (33)	0.39	0.47[2]
Standing with assistance at 6 mo	31/217 (14)	39/214 (18)	38/196 (19)	0.35	0.37[3]
Walking with assistance at 12 mo	204/220 (93)	188/212 (89)	199/217 (92)	0.32	0.36[4]
Standing alone at 12 mo	180/219 (82)	176/212 (83)	189/218 (87)	0.40	0.28[5]
Walking alone at 12 mo	108/221 (49)	104/212 (49)	127/218 (58)	0.08	0.05[6]
Running at 12 mo	40/220 (18)	35/210 (17)	52/218 (24)	0.14	0.12[7]
Running at 18 mo	203/223 (91)	195/218 (89)	212/226 (94)	0.26	0.18[8]

[1]Values are *n*/total *n* (%). *P* values are estimated with the use of logistic regression. IFA, iron and folic acid; LNS, lipid-based nutrient supplement; MMN, multiple micronutrient.
[2]Adjusted for child age; baseline maternal education, height, midupper arm circumference, and malaria; number of persons in the household; and site.
[3]Adjusted for child age and gestational age at enrollment.
[4]Adjusted for child age; baseline maternal age, hemoglobin, midupper arm circumference, and malaria; primiparity; and site.
[5]Adjusted for child age, baseline maternal height, and site.
[6]Adjusted for child age, baseline maternal hemoglobin, and site.
[7]Adjusted for child age, baseline maternal BMI, primiparity, and site.
[8]Adjusted for child age and baseline maternal education and height.

likely to be found in other studies of LNSs that are currently underway. Findings that are not replicated in other studies likely are due to chance. The finding that a greater proportion of children in the LNS group was able to walk alone at age 12 mo is consistent with a previous trial in Ghana, which showed that a higher percentage of children who received 20 g LNSs/d from age 6 to 12 mo walked independently at age 12 mo compared with a nonsupplemented group (12). The finding is also consistent with another trial conducted as a part of the iLiNS project in Ghana, with the same intervention groups as the trial reported here (E Prado, S Adu-Afarwuah, A Lartey, M Ocansey, P Ashorn, S Vosti, K Dewey, unpublished data, 2015). However, 3 other studies did not find any effect of infant LNSs in doses ranging from 20 g to 54 g (~108–280 kcal/d) on the age of attainment of developmental milestones (14, 15), or on Griffiths's Mental Development Scale (31) scores (13). These 3 studies provided LNSs during infancy only, but not during pregnancy. The only 2 studies that provided nutritional supplementation during both pregnancy and childhood found positive effects on child cognition at preschool age (4) and from school-age to adulthood (3, 32). These trials provided supplements for a longer duration, from pregnancy through age 3 y (4) or age 7 y (3).

The finding in our study that the provision of LNSs to boys but not girls had an effect on walking at age 12 mo has not yet been replicated and may be due to chance. One potential reason that boys but not girls exhibited this difference in our study in Malawi

TABLE 5
Mean motor, language, socioemotional, executive function, and caregiver–child interaction *z* scores at the end of the intervention period[1]

	IFA	MMN	LNS	Unadjusted *P*	Covariate-adjusted *P*
Motor *z* score	0.03 ± 0.99	−0.04 ± 1.03	0.01 ± 0.99	0.76	0.87[2]
Language *z* score	−0.01 ± 1.00	0.01 ± 1.01	0.00 ± 0.99	0.99	0.69[3]
Socioemotional *z* score	0.00 ± 1.04	−0.01 ± 0.93	0.01 ± 1.03	0.98	0.59[4]
A-not-B correct *z* score	0.03 ± 1.00	0.02 ± 1.00	−0.05 ± 1.00	0.67	0.89[5]
A-not-B perseverative errors *z* score	−0.06 ± 0.99	0.01 ± 1.00	0.05 ± 1.01	0.57	0.59[6]
Caregiver–child interaction *z* score	0.04 ± 1.03	−0.02 ± 0.96	−0.02 ± 1.01	0.80	0.76[7]

[1]Values are unadjusted means ± SDs. *P* values are estimated with the use of ANOVA/ANCOVA. FCI, family care indicators; IFA, iron and folic acid; LNS, lipid-based nutrient supplement; MMN, multiple micronutrient.
[2]Adjusted for child age; FCI score; asset index; whether the child was exposed to multiple languages; season at enrollment; site; the child's mood, activity, and interaction with the tester during assessment; and data collector.
[3]Adjusted for child age, baseline maternal height and education, FCI score, asset index, primiparity, child's primary language, whether the child was exposed to multiple languages, season at enrollment, and data collector.
[4]Adjusted for child age, baseline maternal hemoglobin, FCI score, number of persons in the household, child's primary language, whether the child was exposed to multiple languages, season at enrollment, site, and data collector.
[5]Adjusted for child age, sex, and primary language; baseline maternal education, hemoglobin, and HIV; household food insecurity access; season at enrollment; site; the child's mood, activity, and interaction with the tester during assessment; and data collector.
[6]Adjusted for child age, sex, and primary language; baseline maternal midupper arm circumference; FCI score; whether the child was exposed to multiple languages; and data collector.
[7]Adjusted for child age, baseline maternal midupper arm circumference and HIV, household food insecurity access, primiparity, whether the child was exposed to multiple languages, site, and data collector.

may be that boys are more prone to iron-deficiency anemia in infancy (33). In our study sample, hemoglobin concentration at age 18 mo was significantly lower in boys than in girls (data not shown). Thus, boys may have been more likely to benefit from the postnatal supplementation with LNSs.

We did not find differences between intervention groups in 18-mo development scores, despite sufficient power to detect a difference of 0.3 SD in the full group of children. We also did not find such effects despite the provision of 2 times the amount of micronutrients used in most previous prenatal MMN trials for thiamin, riboflavin, niacin, vitamin B-6, vitamin B-12, vitamin D, vitamin E, zinc, copper, and selenium (11). Thus, it is possible that insufficient dietary quality did not constrain infant development in this population. It is not likely that provision of LNSs changed infant feeding patterns in this sample, because previous studies in Malawi have shown that LNS provision does not decrease breast milk or complementary food intake (34, 35).

The pattern of positive effects of SQ-LNSs on infant development earlier in infancy, which were not evident later at 18 mo of age, is consistent with the pattern that we observed for children's growth in this trial (36). Soon after birth, infants in the LNS and MMN groups had a nonsignificantly higher mean length than the IFA group. After birth, length gain was faster in the IFA than the LNS group, and at 18 mo of age the mean lengths were similar in all groups. This suggests that any positive effects of maternal supplementation were not sustained, even with SQ-LNS supplementation in infancy. However, infant development assessments before age 2 y may not be sensitive enough to detect effects. In particular, the executive function and socioemotional scores were not associated with measures of infant growth in this sample, such as length-for-age and weight-for-length z scores, suggesting that these measures at this age may not be sensitive to nutritional factors. Previous studies have found effects of early nutritional deficiency when the children reached school age, despite lack of effects at earlier ages. For example, a group of children who experienced thiamin deficiency in infancy did not show neurological symptoms at the time of deficiency, but showed language impairment at age 5–7 y (37). Similarly, in a randomized, controlled trial, infants who received formula containing DHA (22:6n–3) and arachidonic acid (20:4n–6) showed higher vocabulary and IQ scores at age 5–6 y than did infants who received formula without these fatty acids, even though they did not differ in vocabulary or Bayley Scales of Infant Development scores at age 18 mo (38). These examples show that long-term effects may be found even when early effects are not detected.

Although we found some evidence of a positive effect of supplementation with SQ-LNSs during pregnancy and infancy on developmental milestone attainment, we found no evidence of any effects on 18-mo motor, language, socioemotional, or executive function scores. Further research is needed to understand the nutritional and contextual factors that influence brain development and to develop interventions to protect children from those negative influences.

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REFERENCES

1. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B, The International Child Development Steering Group. Developmental potential in the first 5 years for children in developing countries. Lancet 2007;369:60–70.
2. Prado EL, Dewey KG. Nutrition and brain development in early life. Nutr Rev 2014;72:267–84.
3. Pollitt E. Early supplementary feeding and cognition: effects over two decades. Monogr Soc Res Child Dev 1993;58:1–99.
4. Waber DP, Vuori-Christiansen L, Ortiz N, Clement JR, Christiansen NE, Mora JO, Reed RB, Herrera MG. Nutritional supplementation, maternal education, and cognitive development of infants at risk of malnutrition. Am J Clin Nutr 1981;34(Suppl 4):807–13.
5. Joos SK, Pollitt E, Mueller WH, Albright DL. The Bacon Chow study: maternal nutritional supplementation and infant behavioral development. Child Dev 1983;54:669–76.
6. Husaini MA, Karyadi L, Husaini YK, Sandjaja, Karyadi D, Pollitt E. Developmental effects of short-term supplementary feeding in nutritionally at-risk Indonesian infants. Am J Clin Nutr 1991;54:799–804.
7. Pollitt E, Saco-Pollitt C, Jahari A, Husaini MA, Huang J. Effects of an energy and micronutrient supplement on mental development and behavior under natural conditions in undernourished children in Indonesia. Eur J Clin Nutr 2000;54:S80–90.
8. Grantham-McGregor SM, Powell CA, Walker SP, Himes JH. Nutritional supplementation, psychosocial stimulation, and mental development of stunted children: the Jamaican Study. Lancet 1991;338:1–5.
9. Aboud FE, Akhter S. A cluster-randomized evaluation of a responsive stimulation and feeding intervention in Bangladesh. Pediatrics 2011;127:e1191–7.
10. Singla DR, Shafique S, Zlotkin SH, Aboud FE. A 22-element micronutrient powder benefits language but not cognition in Bangladeshi full-term low-birth-weight children. J Nutr 2014;144:1803–10.
11. Arimond M, Zeilani M, Jungjohann S, Brown KH, Ashorn P, Allen LH, Dewey KG. Considerations in developing lipid-based nutrient supplements for prevention of undernutrition: experience from the International Lipid-Based Nutrient Supplements (iLiNS) Project. Matern Child Nutr 2015;11:31–61.
12. Adu-Afarwuah S, Lartey A, Brown KH, Zlotkin S, Briend A, Dewey KG. Randomized comparison of 3 types of micronutrient supplements for home fortification of complementary foods in Ghana: effects on growth and motor development. Am J Clin Nutr 2007;86:412–20.
13. Phuka JC, Gladstone M, Maleta K, Thakwalakwa C, Cheung YB, Briend A, Manary MJ, Ashorn P. Developmental outcomes among 18-month-old Malawians after a year of complementary feeding with lipid-based nutrient supplements or corn-soy flour. Matern Child Nutr 2012;8:239–48.
14. Iannotti LL, Dulience SJ, Green J, Joseph S, Francois J, Antenor ML, Lesorogol C, Mounce J, Nickerson NM. Linear growth increased in young children in an urban slum of Haiti: a randomized controlled trial of a lipid-based nutrient supplement. Am J Clin Nutr 2014;99:198–208.
15. Mangani C, Cheung YB, Maleta K, Phuka J, Thakwalakwa C, Dewey K, Manary M, Puumalainen T, Ashorn P. Providing lipid-based nutrient supplements does not affect developmental milestones among Malawian children. Acta Paediatr 2014;103:e17–26.
16. Ashorn P, Alho L, Ashorn U, Cheung YB, Dewey KG, Harjunmaa U, Lartey A, Nkhoma M, Phiri N, Phuka J, et al. The impact of lipid-based nutrient supplement provision to pregnant women on newborn size in rural Malawi: a randomized controlled trial. Am J Clin Nutr 2015;101:387–97.
17. Zhao W, Li AX. A generalized approach to estimating sample sizes Los Angeles, CA: SAS Institute Inc; 2012.

18. WHO Multicentre Growth Reference Study Group. WHO Motor Development Study: windows of achievement for six gross motor development milestones. Acta Paediatr Suppl 2006;450:86–95.
19. Gladstone M, Lancaster GA, Umar E, Nyirenda M, Kayira E, van den Broek NR, Smyth RL. The Malawi Developmental Assessment Tool (MDAT): the creation, validation, and reliability of a tool to assess child development in rural African settings. PLoS Med 2010;7: e1000273.
20. Abubakar A, Holding PA, Van Baar A, Newton CRJC, Van de Vijver FJR. Monitoring psychomotor development in a resource-limited setting: an evaluation of the Kilifi Developmental Inventory. Ann Trop Paediatr 2008;28:217–26.
21. Fenson L, Marchman VA, Thal D, Dale PS, Reznick JS, Bates E. The MacArthur-Bates communicative development inventories, second edition: user's guide and technical manual. Baltimore: Brookes Publishing, 2007.
22. Hamadani JD, Baker-Henningham H, Tofail F, Mehrin F, Huda SN, Grantham-McGregor SM. The validity and reliability of mothers' report of language development in 1-year-old children in a large scale survey in Bangladesh. Food Nutr Bull 2010;31(2 Suppl):S198–206.
23. Alcock KJ, Prado EL, Rimba K, Kalu R, Newton CRJC, Holding P. Parent report of language development in illiterate families—the CDI in two developing country settings. 21st Congress of the International Society for the Study of Behavioral Development. Lusaka, Zambia, 2010.
24. Espy KA, Kaufmann PM, McDiarmid MD, Glisky ML. Executive functioning in preschool children: performance on A-Not-B and other delayed response format tasks. Brain Cogn 1999;41:178–99.
25. Abubakar A, Holding P, Van Baar A, Newton C, Van de Vijver F, Espy K. The performance of children prenatally exposed to HIV on the A-Not-B task in Kilifi, Kenya: a preliminary study. Int J Environ Res Public Health 2013;10:4132–42.
26. Nampijja M, Apule B, Lule S, Akurut H, Muhangi L, Webb EL, Lewis C, Elliott AM, Alcock KJ. Effects of maternal worm infections and anthelminthic treatment during pregnancy on infant motor and neurocognitive functioning. J Int Neuropsychol Soc 2012;18:1019–30.
27. Kariger P, Frongillo EA, Engle P, Britto PM, Sywulka SM, Menon P. Indicators of family care for development for use in multicountry surveys. J Health Popul Nutr 2012;30:472–86.
28. Fernald LC, Kariger P, Hidrobo M, Gertler PJ. Socioeconomic gradients in child development in very young children: evidence from India, Indonesia, Peru, and Senegal. Proc Natl Acad Sci 2012;109(Suppl 2): 17273–80.
29. Hamadani JD, Tofail F, Hilaly A, Huda SN, Engle P, Grantham-McGregor SM. Use of family care indicators and their relationship with child development in Bangladesh. J Health Popul Nutr 2010;28:23–33.
30. Streiner DL. Best (but oft-forgotten) practices: the multiple problems of multiplicity-whether and how to correct for many statistical tests. Am J Clin Nutr 2015;102:721–8.
31. Griffiths R. The abilities of young children. High Wycombe (United Kingdom): The Test Agency; 1976.
32. Li H, Barnhart HX, Stein AD, Martorell R. Effects of early childhood supplementation on the educational achievement of women. Pediatrics 2003;112:1156–62.
33. Domellöf M, Lonnerdal B, Dewey KG, Cohen RJ, Rivera LL, Hernell O. Sex differences in iron status during infancy. Pediatrics 2002;110: 545–52.
34. Kumwenda C, Dewey KG, Hemsworth J, Ashorn P, Maleta K, Haskell MJ. Lipid-based nutrient supplements do not decrease breast milk intake of Malawian infants. Am J Clin Nutr 2014;99:617–23.
35. Thakwalakwa CM, Ashorn P, Phuka JC, Cheung YB, Briend A, Maleta KM. Impact of lipid-based nutrient supplements and corn-soy blend on energy and nutrient intake among moderately underweight 8-18-month-old children participating in a clinical trial. Matern Child Nutr 2014;Feb 27 (Epub ahead of print).
36. Ashorn P, Alho L, Ashorn U, Cheung YB, Dewey KG, Gondwe A, Harjunmaa U, Lartey A, Phiri N, Phiri TE, et al. Supplementation of maternal diets during pregnancy and for 6 months postpartum and infant diets thereafter with small-quantity lipid-based nutrient supplements does not promote child growth by 18 months of age in rural Malawi: a randomized controlled trial. J Nutr 2015;145:1345–53.
37. Fattal I, Friedmann N, Fattal-Valevski A. The crucial role of thiamine in the development of syntax and lexical retrieval: a study of infantile thiamine deficiency. Brain: a journal of neurology 2011;134(Pt 6):1720–39.
38. Colombo J, Carlson SE, Cheatham CL, Shaddy DJ, Kerling EH, Thodosoff JM, Gustafson KM, Brez C. Long-term effects of LCPUFA supplementation on childhood cognitive outcomes. Am J Clin Nutr 2013;98:403–12.