Lipid-based nutrient supplementation in the first 1000 d improves child growth in Bangladesh: a cluster-randomized effectiveness trial[1–3]

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ABSTRACT

Background: Stunting in linear growth occurs mainly during the first 1000 d, from conception through 24 mo of age. Despite the recognition of this critical period, there have been few evaluations of the growth impact of interventions that cover most of this window.

Objective: We evaluated home fortification approaches for preventing maternal and child undernutrition within a community-based health program. We hypothesized that small-quantity lipid-based nutrient supplements (LNSs) provided to women during pregnancy and the first 6 mo postpartum, LNSs provided to their offspring from 6 to 24 mo of age, or both would result in greater child length-for-age *z* score (LAZ) at 24 mo than iron and folic acid (IFA) provided to women during pregnancy and postpartum plus micronutrient powder (MNP) or no supplementation for their offspring from 6 to 24 mo.

Design: We conducted a cluster-randomized effectiveness trial with 4 arms: *1*) women and children both received LNSs (LNS-LNS group), *2*) women received IFA and children received LNSs (IFA-LNS group), *3*) women received IFA and children received MNP (IFA-MNP group), and *4*) women received IFA and children received no supplements (IFA-Control group). We enrolled 4011 women at ≤20 wk of gestation within 64 clusters, each comprising the supervision area of a community health worker. Analyses were primarily performed by using ANCOVA *F* tests and Tukey-Kramer–corrected pairwise comparisons.

Results: At 24 mo, the LNS-LNS group had significantly higher LAZ (+0.13 compared with the IFA-MNP group) and head circumference (+0.15 *z* score compared with the IFA-Control group); these outcomes did not differ between the other groups. Stunting prevalence (LAZ <-2) was lower in the LNS-LNS group at 18 mo than in the IFA-MNP group (OR: 0.70; 95% CI: 0.53, 0.92), but the difference diminished by 24 mo (OR: 0.81; 95% CI: 0.63, 1.04).

Conclusion: Home fortification with small-quantity LNSs, but not MNP, during the first 1000 d improved child linear growth and head size in rural Bangladesh. This trial was registered at clinicaltrials.gov as NCT01715038. *Am J Clin Nutr* 2017;105:944–57.

Keywords: growth faltering, lipid-based nutrient supplements, malnutrition, micronutrient powder, stunting

INTRODUCTION

Childhood stunting is highly prevalent and is a key global health concern because of its links with impaired development, increased mortality from infectious diseases, and adverse consequences through adulthood (1). The global target is a 40% reduction in stunting among children <5 y of age by 2025 (1). However, there are no simple solutions for achieving this target given the complex etiology of linear growth faltering (2). The process of stunting often begins in utero and continues to ∼2 y of age; thus, the key "window" for intervention is the first 1000 d (1). Despite the recognition of this critical period, there have been remarkably few attempts to evaluate the impact of interventions that cover the majority of this 1000-d window (3, 4).

This study, the Rang-Din Nutrition Study (RDNS)[10], was designed to evaluate within a community-based program the effectiveness of home fortification approaches for the prevention of maternal and child undernutrition during the first 1000 d. The most common type of home fortification is the use of micronutrient powders (MNPs) to enrich complementary foods for infants and young children (5). A newer approach is to provide both micronutrients and some key macronutrients, including essential fatty acids, in small-quantity (20 g/d) lipid-based nutrient supplements (LNSs), developed to enrich the local diets of

[1] Supported by the Office of Health, Infectious Diseases, and Nutrition, Bureau for Global Health, US Agency for International Development (USAID) under the terms of cooperative agreement AID-OAA-A-12-00005, through the Food and Nutrition Technical Assistance III Project (FANTA), managed by FHI 360. Our research intervention was incorporated into the community heath and development program of LAMB, which was supported by Plan-Bangladesh in 6 of the 11 study unions. Nutriset S.A.S. prepared the lipid-based nutrient supplements for this trial, and Hudson Pharmaceuticals Ltd. prepared the iron and folic acid tablets.

[2] The findings and conclusions contained within the article are those of the authors and do not necessarily reflect positions or policies of the USAID or of the US government. One of the co-authors (ZM-M) is employed by FHI 360, which provided USAID funding for the study to the University of California, Davis, through the FANTA project.

[3] Supplemental Material and Supplemental Figures 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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pregnant and lactating women (LNS-PL) and of infants and young children (LNS-C) (5). Most studies of MNPs have shown little or no effect on growth (6, 7), whereas there is some evidence, although mixed, of a positive growth impact of products that contain both micro- and macronutrients (2, 8). One potential explanation is that MNPs typically do not include many of the nutrients essential for growth, categorized as the "type II" nutrients [protein, sulfur, potassium, magnesium, phosphorus, zinc, and sodium (9)], except for zinc. Dietary fat may also play a key role because PUFAs are essential for brain development, immune function, and growth (10–12). Long-chain PUFAs make up a substantial proportion of brain tissue, much of which is accreted during the first 1000 d (10). In countries such as Bangladesh, the PUFA content of maternal and infant diets may be below recommended levels (13, 14). For this reason, providing essential fatty acids in home fortification products could be beneficial (15).

The overall hypothesis of the RDNS was that the provision of LNS-PL to women during pregnancy and the first 6 mo postpartum and/or provision of LNS-C to their offspring from 6 to 24 mo of age would result in larger positive changes in maternal and child nutrition outcomes than the provision of iron and folic acid (IFA) to women (during pregnancy and for 3 mo postpartum) plus MNP or no supplementation for their offspring from 6 to 24 mo of age. We used a cluster-randomized design to simplify the delivery of supplements by community health workers (CHWs). Bangladesh was chosen for the study because >20% of newborns are stunted [length-for-age z score (LAZ) <-2] and >30% are wasted [weight-for-length z score (WLZ) <-2] (16), the prevalence of stunting of children under 5 is 36% (17), and micronutrient deficiencies in both mothers and children are common (18). We previously reported that LNS-PL reduced newborn stunting and small head size in the RDNS infants (19). This article describes the effects of the RDNS intervention on child growth through 24 mo of age.

METHODS

Study setting and design

The study was conducted in 11 rural unions of the Badarganj and Chirirbandar subdistricts in northwest Bangladesh, as described previously (19). The study was carried out by 3 partners: LAMB, icddr,b, and the University of California, Davis (UCD), with technical support provided by the Food and Nutrition Technical Assistance Project (FANTA). It was implemented within the Community Health and Development Program (CHDP) operated by a local nongovernmental organization (LAMB), which delivered the study interventions. UCD and icddr,b jointly evaluated the interventions. LAMB has been implementing multisectoral development programs for the local population for >40 y. The CHDP is one of those programs and was modeled after the health, nutrition, and population program of BRAC, the largest nongovernmental organization in Bangladesh. Health services normally provided by the CHDP include maternity services at a safe delivery unit (SDU) in each union; regular home visits for antenatal, postnatal, and child care by village health volunteers (VHVs) and CHWs; and monthly educational sessions to promote maternal and child health.

TABLE 1
Nutrient content of LNSs and MNP used in the study[1]

Nutrient (amount per daily dose)	LNS-PL[2] (20 g/d)	LNS-C[3] (20 g/d)	MNP[4] (1 sachet/d)
Energy, kcal	118	118	0
Protein, g	2.6	2.6	0
Fat, g	10	9.6	0
Linoleic acid, g	4.59	4.46	0
α-Linolenic acid, g	0.59	0.58	0
Vitamin A, μg RE	800	400	400
Thiamin, mg	2.8	0.5	0.5
Riboflavin, mg	2.8	0.5	0.5
Niacin, mg	36	6	6
Folic acid, μg	400	150	150
Pantothenic acid, mg	7	2.0	0
Vitamin B-6, mg	3.8	0.5	0.5
Vitamin B-12, μg	5.2	0.9	0.9
Vitamin C, mg	100	30	30
Vitamin D, μg	10	5	5
Vitamin E, mg	20	6	5
Vitamin K, μg	45	30	0
Calcium, mg	280	280	0
Copper, mg	4	0.34	0.56
Iodine, μg	250	90	90
Iron, mg	20	9	10
Magnesium, mg	65	40	0
Manganese, mg	2.6	1.2	0
Phosphorus, mg	190	190	0
Potassium, mg	200	200	0
Selenium, μg	130	20	17
Zinc, mg	30	8	4.1

[1] LNS, lipid-based nutrient supplement; LNS-C, lipid-based nutrient supplement for children; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women; MNP, micronutrient powder; RE, retinol equivalents.

[2] Nutrient content was the same as the LNS-PL used in other trials in Ghana and Malawi (20).

[3] Nutrient content was similar to the LNS-C used in recent trials in Africa (20), except that the iron content was 9 mg (instead of being reduced to 6 mg, as was done in the Africa trials to reduce the potential risk of malaria associated with iron supplementation) and amounts of folic acid, niacin, pantothenic acid, thiamin, riboflavin, vitamin B-6, and vitamin B-12 were slightly higher to cover the wider age range of 6–24 mo.

[4] Nutrient content was the same as the MNP being distributed by BRAC and Renata Ltd. in Bangladesh.

[10] Abbreviations used: CHDP, Community Health and Development Program; CHW, community health worker; HCZ, head circumference-for-age z score; IFA, iron and folic acid supplement; IFA-Control, women received iron and folic acid supplement during pregnancy and the first 3 mo postpartum and no supplement for the children; IFA-LNS, women received iron and folic acid during pregnancy and the first 3 mo postpartum and lipid-based nutrient supplements for the children from 6 to 24 mo of age; IFA-MNP, women received iron and folic acid during pregnancy and the first 3 mo postpartum and micronutrient powder for the offspring from 6 to 24 mo of age; LAZ, length-for-age z score; LNS, lipid-based nutrient supplement; LNS-C, lipid-based nutrient supplement for children; LNS-LNS, women received lipid-based nutrient supplements during pregnancy and the first 6 mo postpartum and offspring received lipid-based nutrient supplements from 6 to 24 mo of age; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women; MNP, micronutrient powder; MUACZ, midupper arm circumference-for-age z score; RDNS, Rang-Din Nutrition Study; SES, socioeconomic status; SDU, safe delivery unit; UCD, University of California, Davis; VHV, village health volunteer; WAZ, weight-for-age z score; WLZ, weight-for-length z score.

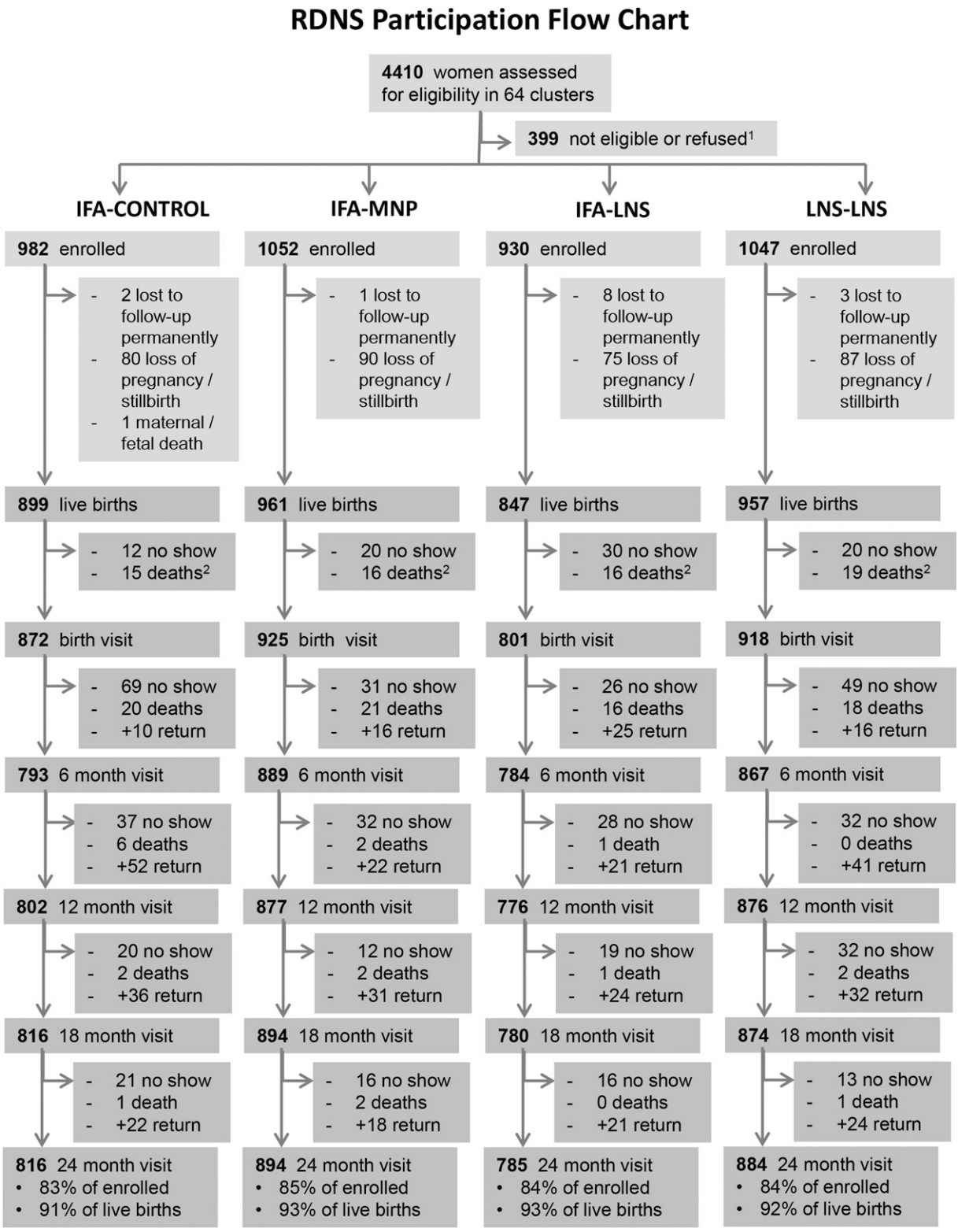

FIGURE 1 Study flowchart. For twin births, numbers include 1 randomly selected twin from each twin pair. [1]366 gestational age >140 d; 22 planned to leave study site, 8 refused, and 3 husbands refused. [2]Most of these deaths occurred at <14 d postpartum: 14 IFA-Control, 15 IFA-MNP, 15 IFA-LNS, and 17 LNS-LNS. IFA-Control, women received iron and folic acid supplement during pregnancy and the first 3 mo postpartum and children did not receive supplements; IFA-LNS, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received lipid-based nutrient supplements from 6 to 24 mo of age; IFA-MNP, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received micronutrient powder from 6 to 24 mo of age; LNS-LNS, women and children received lipid-based nutrient supplements.

TABLE 2
Maternal baseline characteristics[1]

	LNS-LNS	IFA-LNS	IFA-MNP	IFA-Control
Age, y	21.8 ± 4.9[2]	21.9 ± 4.9	22.2 ± 5.0	22.0 ± 5.2
Years of formal education	6.4 ± 3.2	6.3 ± 3.4	6.0 ± 3.2	6.1 ± 3.2
Height, cm	150.7 ± 5.4	150.4 ± 5.3	150.5 ± 5.4	150.7 ± 5.4
BMI (adjusted to 96 d of gestation), kg/m^2	19.9 ± 2.7	20.1 ± 2.6	20.0 ± 2.6	20.0 ± 2.8
Low BMI (<18.5), *n* (%)	331 (31.6)	278 (29.9)	306 (29.1)	298 (30.3)
Nulliparous, *n* (%)	435 (41.7)	386 (41.6)	397 (37.8)	373 (38.0)
Gestational age at enrollment, wk	13.1 ± 3.8	13.2 ± 3.9	13.1 ± 3.8	13.1 ± 3.8
Household socioeconomic status index	0.04 ± 2.24	0.01 ± 2.33	−0.06 ± 2.22	0.02 ± 2.23
Household food insecurity score	2.8 ± 3.9	3.1 ± 4.0	3.1 ± 4.1	3.3 ± 4.1
Sanitation, *n* (%)				
No toilet	266 (25.4)	261 (28.1)	286 (27.2)	265 (27.0)
Latrine	662 (63.2)	547 (58.8)	614 (58.4)	593 (60.4)
Flushing toilet	118 (11.3)	121 (13.0)	151 (14.4)	123 (12.5)
Exposed disposal of garbage	251 (24.0)	267 (28.7)	254 (24.2)	244 (24.9)

[1] IFA-Control, women received iron and folic acid supplement during pregnancy and the first 3 mo postpartum and children did not receive supplements; IFA-LNS, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received lipid-based nutrient supplements from 6 to 24 mo of age; IFA-MNP, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received micronutrient powder from 6 to 24 mo of age; LNS-LNS, women and children received lipid-based nutrient supplements.
[2] Mean ± SD (all such values).

The trial was a researcher-blind, longitudinal, cluster-randomized effectiveness trial with 4 equal-sized arms: *1*) a comprehensive LNS group, in which women received LNS-PL during pregnancy and the first 6 mo postpartum and their children received LNS-C from 6 to 24 mo of age (LNS-LNS group); *2*) a child-only LNS group, in which women received IFA (1 tablet of 60 mg Fe and 400 μg folic acid) daily during pregnancy and every alternate day during the first 3 mo postpartum and their children received LNS-C from 6 to 24 mo of age (IFA-LNS group); *3*) a child-only MNP group, in which women received IFA (as described above) and their children received MNP containing 15 micronutrients from 6 to 24 mo of age (IFA-MNP group); and *4*) a control group, in which women received IFA (as described above) and their children received no supplements (IFA-Control). We defined a cluster as the supervision area of a CHW. For the randomization, the study statistician at UCD first stratified all 64 clusters in the 11 unions by subdistrict and union and then randomly assigned each cluster to 1 of the 4 arms (each containing 16 clusters) (19).

The study protocol was approved by the institutional review boards of UCD, icddr,b, and LAMB. The study was registered at clinicaltrials.gov (NCT01715038). We obtained verbal consent from union representatives before beginning the study and completed randomization of clusters before seeking individual participant consent (19).

Study interventions

Table 1 shows the supplement composition. LNS-PL (one 20-g sachet/d) was modeled on the UNICEF/WHO/United Nations University international multiple micronutrient preparation for pregnant and lactating women and similar products used in Ghana and Malawi (20). LNS-C (two 10-g sachets/d) was similar to the LNS-C used in Ghana and Malawi (4, 21, 22). LNS-PL and LNS-C were produced by Nutriset S.A.S. in Malaunay, France. MNP was produced by Renata Ltd. in Bangladesh and had the same nutrient composition as the MNP being scaled-up in Bangladesh by BRAC. We chose this option so that the results for the MNP group in the RDNS would be programmatically relevant. The dose of IFA was based on WHO recommendations (23). IFA tablets were produced by Hudson Pharmaceuticals Ltd. in Bangladesh.

Supplements were delivered to participants by CHDP staff. The distribution scheme and key educational messages during pregnancy are described elsewhere (19, 24). When child supplementation began at 6 mo of age, the first month's supply of

TABLE 3
Percentage of caregivers who reported high adherence for child supplementation in the study cohort, by intervention group[1]

Period	LNS-LNS	IFA-LNS	IFA-MNP	*P*
Past week[2]				
12 mo of age	694 (76.9)	647 (80.5)	700 (77.5)	0.355
18 mo of age	740 (83.1)	678 (85.8)	753 (84.8)	0.571
24 mo of age	803 (90.3)	733 (92.1)	791 (89.7)	0.450
Past 6 months[3]				
12 mo of age	873 (96.7)	778 (97.0)	850 (94.2)	0.155
18 mo of age	870 (97.4)	771 (97.5)	848 (95.1)	0.052
24 mo of age	884 (99.3)[a]	788 (99.0)[a,b]	862 (97.5)[b]	0.007

[1] Values are *n* (%). *P* values were derived from mixed-model logistic regression. When the global null hypothesis was rejected at the 0.05 level, post hoc pairwise comparisons used Tukey-Kramer adjustment. Groups that do not share a common superscript letter differ, $P < 0.05$. IFA-Control, women received iron and folic acid supplement during pregnancy and the first 3 mo postpartum and children did not receive supplements; IFA-LNS, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received lipid-based nutrient supplements from 6 to 24 mo of age; IFA-MNP, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received micronutrient powder from 6 to 24 mo of age; LNS-LNS, women and children received lipid-based nutrient supplements.
[2] High adherence was defined as consuming ≥8 sachets of LNSs (10 g each) or ≥4 sachets of MNP.
[3] High adherence was defined as "Almost every day" or "Regularly every day."

LNS-C or MNP was provided at the SDU along with a card with messages on supplement use (see **Supplemental Material**), which the CHWs explained verbally. Thereafter, monthly supplies were usually delivered by the CHW or VHV to the child's home and the messages were repeated, in addition to the standard messages given to all CHDP participants (see Supplemental Material). In the Badarganj subdistrict, the government of Bangladesh distributed MNPs (containing vitamin A, vitamin C, folic acid, iron, and zinc) for 6- to 24-mo-old children. For study participants receiving LNS-C or MNPs from the RDNS, the study team told caregivers not to feed any other vitamin and mineral tablets, capsules, or MNP sachets.

As described elsewhere (19), LNS-PL distribution (but not the distribution of LNS-C) was interrupted from 8 August to 20 October 2012 to comply with a new quality-control criterion. During that period, women assigned to receive LNS-PL were provided with IFA instead.

Enrollment and data collection

The CHWs and VHVs identified pregnant women via LAMB's pregnancy surveillance system (19). Women who were potentially eligible for the RDNS evaluation were contacted at home by evaluation staff to obtain consent for screening. Eligibility criteria included gestational age ≤20 wk and no plans to move away during pregnancy or the following 3 y. All eligible women were invited to participate in the study. Women who consented were interviewed to collect baseline data and scheduled for anthropometric and clinical data collection at the SDU. Supplement delivery began after each woman's baseline SDU visit.

Follow-up during pregnancy and just after childbirth is described elsewhere (9). Subsequent follow-up visits occurred at ∼42 d and at ∼6, 12, 18, and 24 mo postpartum. All of the anthropometrists were trained and methods standardized at the beginning of data collection and periodically thereafter with the use of recommended procedures (25). More than 90% of infants were measured within 72 h after birth with the use of methods described elsewhere (19, 24). The 42-d home visits included infant weight; at other time points, the SDU team measured child weight to the nearest 0.05 kg (infant scale; Seca 876), length to the nearest 0.5 cm (ShorrBoard; Weigh and Measure LLC), and head circumference and midupper arm circumference to the nearest 0.5 cm (Shorrtape; Shorr Productions). At each SDU assessment, predefined criteria were used to refer women and children with certain conditions (e.g., moderate or severe wasting) for treatment.

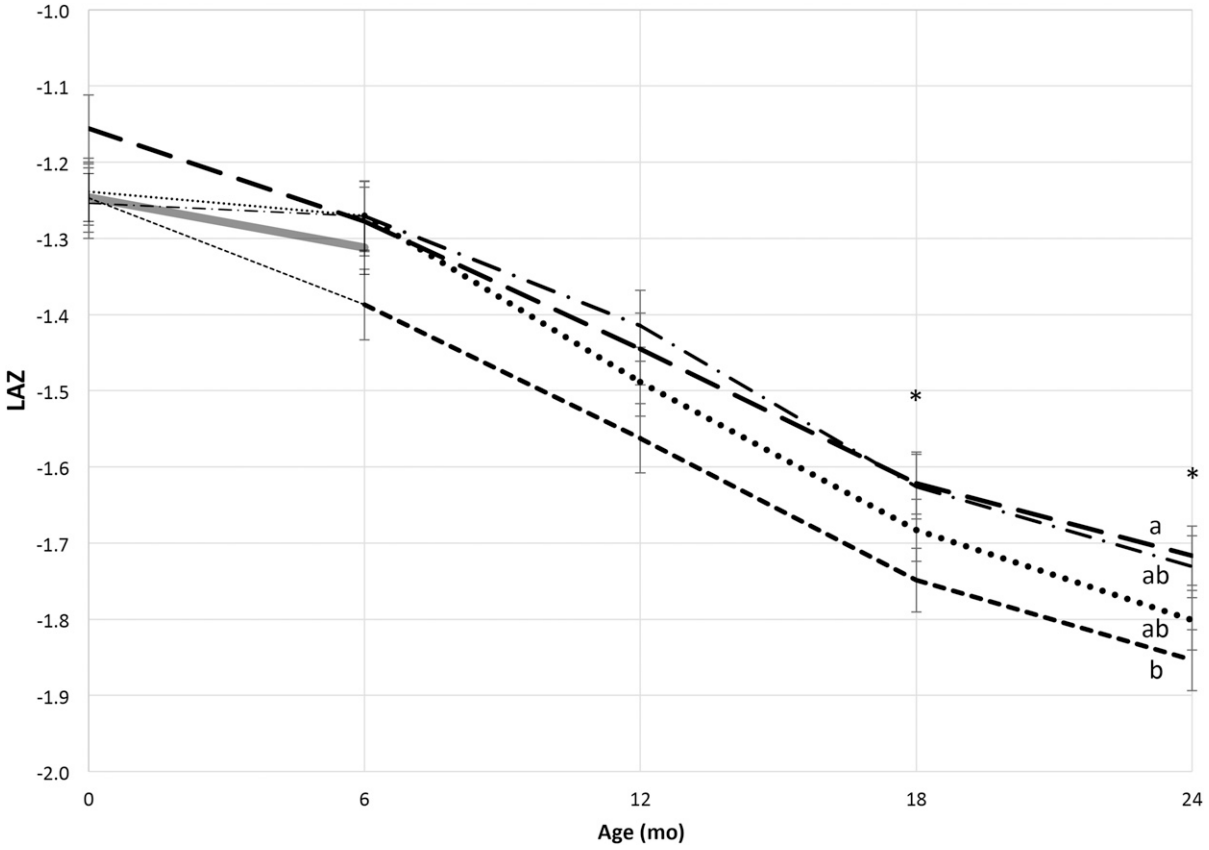

FIGURE 2 LAZ by child age and intervention group. The solid gray line at 0–6 mo represents the combined control group for that interval (IFA-Control + IFA-MNP + IFA-LNS). The dotted line represents the IFA-Control group; the short-dashed line indicates the IFA-MNP group; the dashed and dotted line represents the IFA-LNS group; and the long-dashed line represents the LNS-LNS group. The sample size at each time point ranges from 775 to 925 children in each of the 4 groups. Mean values and significant differences between the 4 groups at 18 and 24 mo are shown in Table 4. *P* values were derived from mixed-model ANCOVA. *Global difference, $P < 0.05$. Groups that do not share a common letter differ, $P < 0.05$ (Tukey-Kramer–corrected pairwise differences). IFA-Control, women received iron and folic acid supplement during pregnancy and the first 3 mo postpartum and children did not receive supplements; IFA-LNS, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received lipid-based nutrient supplements from 6 to 24 mo; IFA-MNP, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received micronutrient powder from 6 to 24 mo; LAZ, length-for-age *z* score; LNS-LNS, women and children received lipid-based nutrient supplements.

We collected data on adherence to LNS-C and MNP at 12, 18, and 24 mo of age by asking caregivers how often the child had consumed the nutrient supplements during the previous 6 mo [not at all, sometimes (1–3 d/wk), almost every day (4–6 d/wk), or regularly (every day)] and how many sachets were consumed during the previous week. To the extent possible, evaluation team members were kept blinded to group assignment, although those conducting home visits might have seen supplements in the home. SDU team members conducting anthropometric measurements were not aware of group assignment. Quality-control procedures (19) included having supervisors re-interview ≥10% of randomly selected participants.

Sample size calculation and statistical analyses

When designing the study, we calculated a minimum required sample size of 788/arm (total of 3152) on the basis of detecting an effect size of ≥0.2 (difference between groups, divided by pooled SD) for each continuous outcome with 1-sided hypotheses, a power of 0.8, and an α of 0.05, assuming an intracluster correlation of 0.01 and allowing for 20% attrition by the time all children reached 24 mo. The primary child outcome was LAZ at 24 mo. The hypotheses were that mean LAZ would be higher *1*) in the LNS-LNS group than in each of the other 3 groups, *2*) in the IFA-LNS group than in the IFA-MNP and IFA-Control groups, and *3*) in the IFA-MNP group than in the IFA-Control group. We chose a minimum effect size of ≥0.2 because a previous efficacy study in Ghana (26) had shown an effect size of 0.26 between the group receiving child LNS compared with the control group, and we expected that the difference between LNS-LNS and IFA-LNS groups would be smaller than that. Because we exceeded the target sample size during enrollment (19), we subsequently decided to conduct our analyses by using a more conservative 2-sided hypothesis approach to be consistent with other recent trials.

All of the outcomes were measured at the individual-participant level. We used WHO 2006 Child Growth Standards to determine *z* scores for weight-for-age (WAZ), LAZ, WLZ, head circumference-for-age (HCZ), and midupper arm circumference-for-age (MUACZ) (27). For infants measured between 3 and 14 d after delivery, we back-calculated the weight, length, and head circumference at birth as described elsewhere (19). Extreme observations for *z* scores were truncated at 4 units from the sample median. We defined stunting as

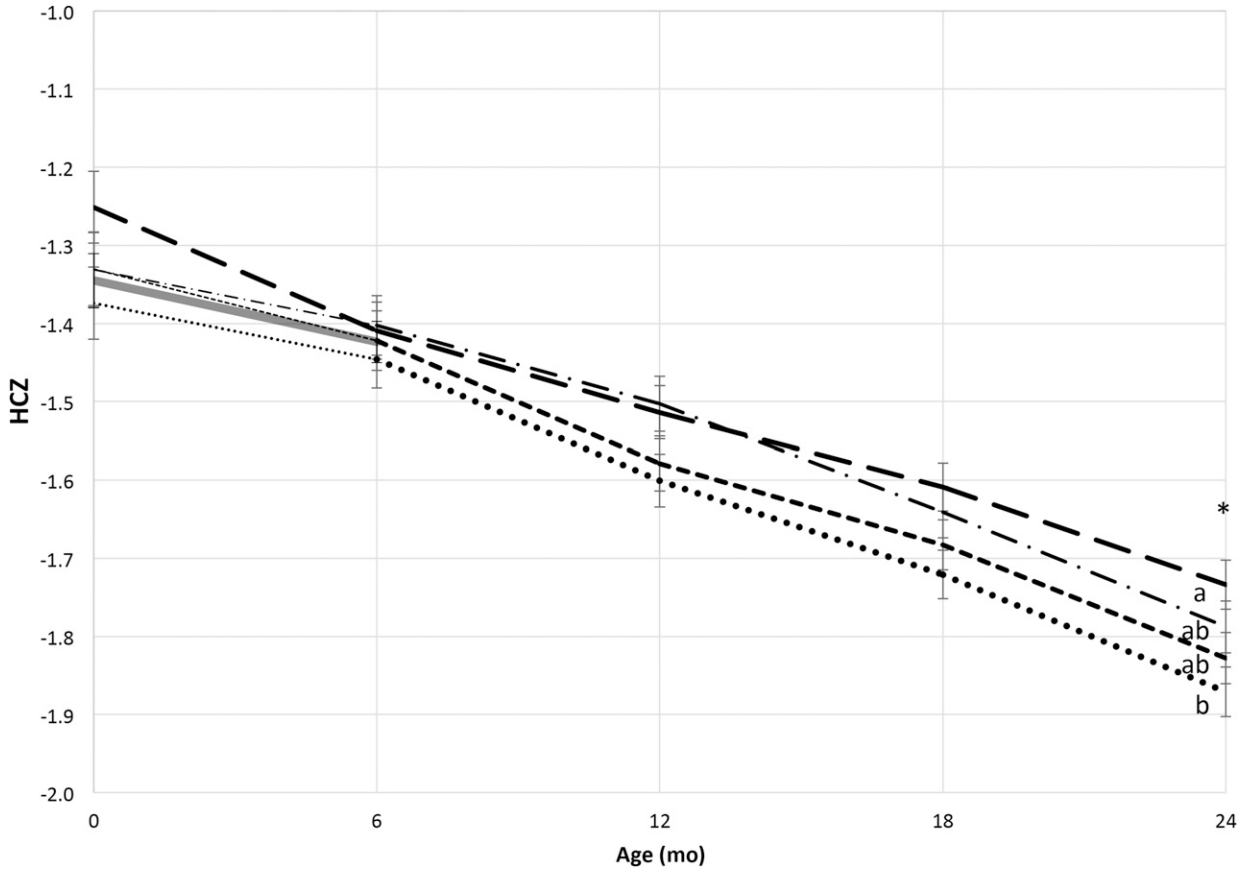

FIGURE 3 HCZ by child age and intervention group. The solid gray line at 0–6 mo represents the combined control group for that interval (IFA-Control + IFA-MNP + IFA-LNS). The dotted line represents the IFA-Control group; the short-dashed line represents the IFA-MNP group; the dashed and dotted line represents the IFA-LNS group; and the long-dashed line represents the LNS-LNS group. The sample size at each time point ranges from 775 to 925 children in each of the 4 groups. Mean values and significant differences between the 4 groups at 18 and 24 mo are shown in Table 4. *P* values were derived from mixed-model ANCOVA. *Global difference, $P < 0.05$. Groups that do not share a common letter differ, $P < 0.05$ (Tukey-Kramer–corrected pairwise differences). HCZ, head circumference-for-age *z* score; IFA-Control, women received iron and folic acid supplement during pregnancy and the first 3 mo postpartum and children did not receive supplements; IFA-LNS, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received lipid-based nutrient supplements from 6 to 24 mo of age; IFA-MNP, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received micronutrient powder from 6 to 24 mo of age; LNS-LNS, women and children received lipid-based nutrient supplements.

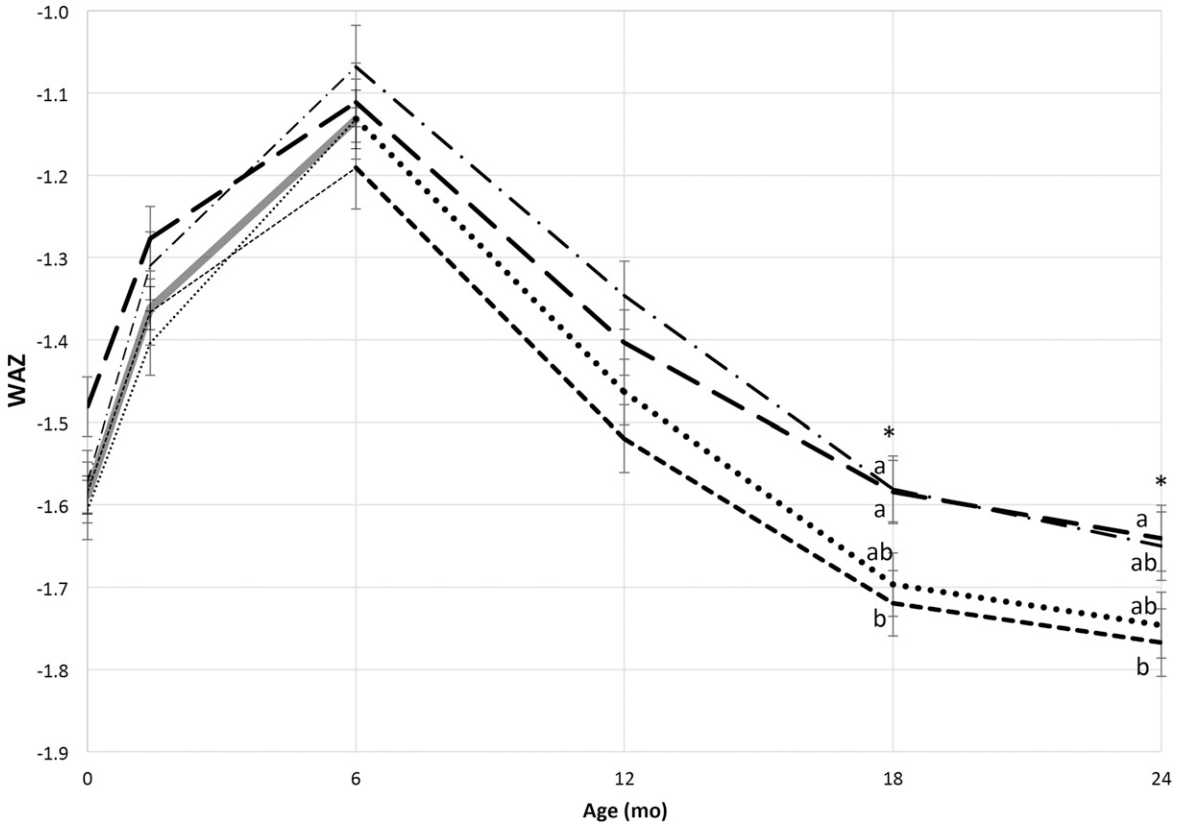

FIGURE 4 WAZ by child age and intervention group. The solid gray line at 0–6 mo represents the combined control group for that interval (IFA-Control + IFA-MNP + IFA-LNS). The dotted line represents the IFA-Control group; the short-dashed line represents the IFA-MNP group; the dashed and dotted line represents the IFA-LNS group; and the long-dashed line represents the LNS-LNS group. The sample size at each time point ranges from 775 to 925 children in each of the 4 groups. Mean values and significant differences between the 4 groups at 18 and 24 mo are shown in Table 4. *P* values were derived from mixed-model ANCOVA. *Global difference, $P < 0.05$. Groups that do not share a common letter differ, $P < 0.05$ (Tukey-Kramer–corrected pairwise differences). IFA-Control, women received iron and folic acid supplement during pregnancy and the first 3 mo postpartum and children did not receive supplements; IFA-LNS, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received lipid-based nutrient supplements from 6 to 24 mo of age; IFA-MNP, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received micronutrient powder from 6 to 24 mo of age; LNS-LNS, women and children received lipid-based nutrient supplements; WAZ, weight-for-age *z* score.

LAZ <-2, small head size as HCZ <-2, underweight at WAZ <-2, and wasting as WLZ <-2.

Prespecified secondary child anthropometric outcomes at 24 mo included stunting, HCZ, and wasting. We also examined all anthropometric outcomes at 18 mo to compare results with those of other trials. In addition, we examined the postnatal rate of growth in length, weight, and head circumference between birth and 6 mo (with maternal IFA groups combined, before the initiation of child supplements) and between 6 and 24 mo of age (all 4 intervention groups). Growth rate was calculated as the difference in measurements divided by the actual time between measurements for each child, then converted to a 6-mo growth rate.

From several socioeconomic status (SES) variables, we used principal components analysis to calculate a household SES index from a set of 19 "yes" or "no" questions about whether or not a household owned a particular item. These items included televisions, irrigation pumps, tables, bicycles, sewing machines, and other goods (19, 24). We used the Household Food Insecurity Access Scale (28) to categorize participants into 4 levels of household food insecurity (severe, moderate, mild, and none). The time period of enrollment was categorized into 7 intervals (19).

We developed a detailed data analysis plan before starting the analysis and revealing group assignment. Analysis was by intention-to-treat. We analyzed effects of the intervention by using mixed-model ANCOVA for continuous outcomes and mixed-model logistic regression for dichotomous outcomes. All of the models included a random effect of cluster nested within treatment group and a random effect of union nested within subdistrict. We first evaluated the unadjusted effect of treatment and then repeated the analysis with adjustments for prespecified covariates (maternal height, BMI, age, education, gestational age at enrollment, and primiparity; household SES and food insecurity; time period in study; and child sex) if they were associated with the outcome ($P < 0.10$) in bivariate analysis (29). For dichotomous outcomes, we calculated cluster-adjusted group percentages and 95% CIs and based statistical comparisons on unadjusted and covariate-adjusted log odds of the outcome occurring. We also estimated multivariate-adjusted RRs by using log-binomial model estimation methods (30) to account for the additional random factors related to our design. For all of the analyses, when the global null hypothesis was rejected at the 0.05 level, we performed post hoc pairwise comparisons with the use of Tukey-Kramer adjustment.

In predefined subgroup analyses, we tested for interactions between intervention group and the covariates listed above by including each interaction term in the adjusted models. Significant

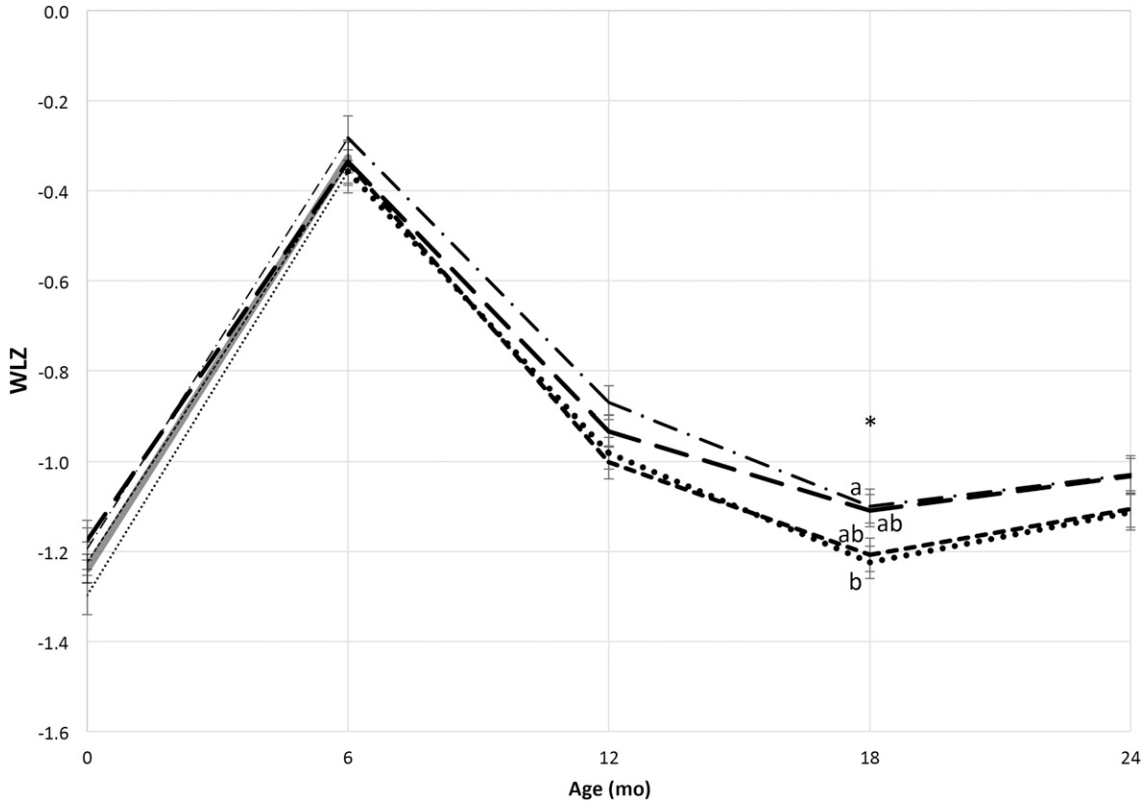

FIGURE 5 WLZ by child age and intervention group. The solid gray line at 0–6 mo represents the combined control group for that interval (IFA-Control + IFA-MNP + IFA-LNS). The dotted line represents the IFA-Control group; the short-dashed line represents the IFA-MNP group; the dashed and dotted line represents the IFA-LNS group; and the long-dashed line represents the LNS-LNS group. The sample size at each time point ranges from 775 to 925 children in each of the 4 groups. Mean values and significant differences between the 4 groups at 18 and 24 mo are shown in Table 4. *P* values were derived from mixed-model ANCOVA. *Global difference, $P < 0.05$. Groups that do not share a common letter differ, $P < 0.05$ (Tukey-Kramer–corrected pairwise differences). IFA-Control, women received iron and folic acid supplement during pregnancy and the first 3 mo postpartum and children did not receive supplements; IFA-LNS, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received lipid-based nutrient supplements from 6 to 24 mo; IFA-MNP, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received micronutrient powder from 6 to 24 mo; LNS-LNS, women and children received lipid-based nutrient supplements; WLZ, weight-for-length *z* score

interactions ($P < 0.10$) were further examined with stratified analyses, with adjustment for multiple comparisons by using the Tukey-Kramer approach.

RESULTS

Trial profile, study participants, and adherence

Between 15 October 2011 and 31 August 2012, we screened 4410 pregnant women for eligibility and enrolled 4011 (**Figure 1**). Of these, 3664 live births occurred between 15 January 2012 and 5 May 2013 to women remaining in the study. Thirty sets of twins were born (including stillbirths) and 1 twin from each pair was randomly selected for analyses. For ∼84% of enrolled women, we had child anthropometric data at 24 mo. Most of the losses were due to pregnancy loss (52.7% of losses) or child deaths (25.5% of losses). Approximately 4.4% of children born alive died before 24 mo and another 3.4% were lost to follow-up postnatally; these rates of loss did not differ by intervention group. We completed anthropometric measurements for 3516 infants at birth and 3379 children at 24 mo (92.2% of live births) by 31 May 2015. The actual intracluster correlation was 0.000314; a post hoc power calculation indicated >93% power to detect an effect size of ≥0.2 in LAZ at 24 mo.

The women whose children were not measured at 24 mo had slightly fewer years of education (5.9 ± 0.2 compared with 6.3 ± 0.2 y) and were slightly shorter (150.1 ± 0.2 compared with 150.6 ± 0.1 cm), but otherwise did not differ from those whose children were measured. At baseline, maternal age, education, and anthropometric and obstetric characteristics and household socioeconomic and sanitation indicators were similar across intervention groups (**Table 2**). Local tube wells were the source of drinking water for 99% of households in all 4 groups.

The percentages of children with high adherence to LNS-C or MNP increased with age in all 3 intervention groups (**Table 3**). On the basis of recall for the previous 6 mo, adherence increased from 94–97% at 6–12 mo to 97–99% at 18–24 mo and was somewhat lower in the IFA-MNP group at 18–24 mo ($P = 0.007$). On the basis of consumption during the previous week, adherence increased from 77–80% at 12 mo to 90–92% at 24 mo and did not differ between intervention groups.

Child growth status

Figures 2–5 show the pattern of growth between birth and 24 mo. The solid gray line between birth and 6 mo in the figures represents the combined groups of infants whose mothers received IFA during pregnancy and postpartum (IFA-Control, IFA-MNP,

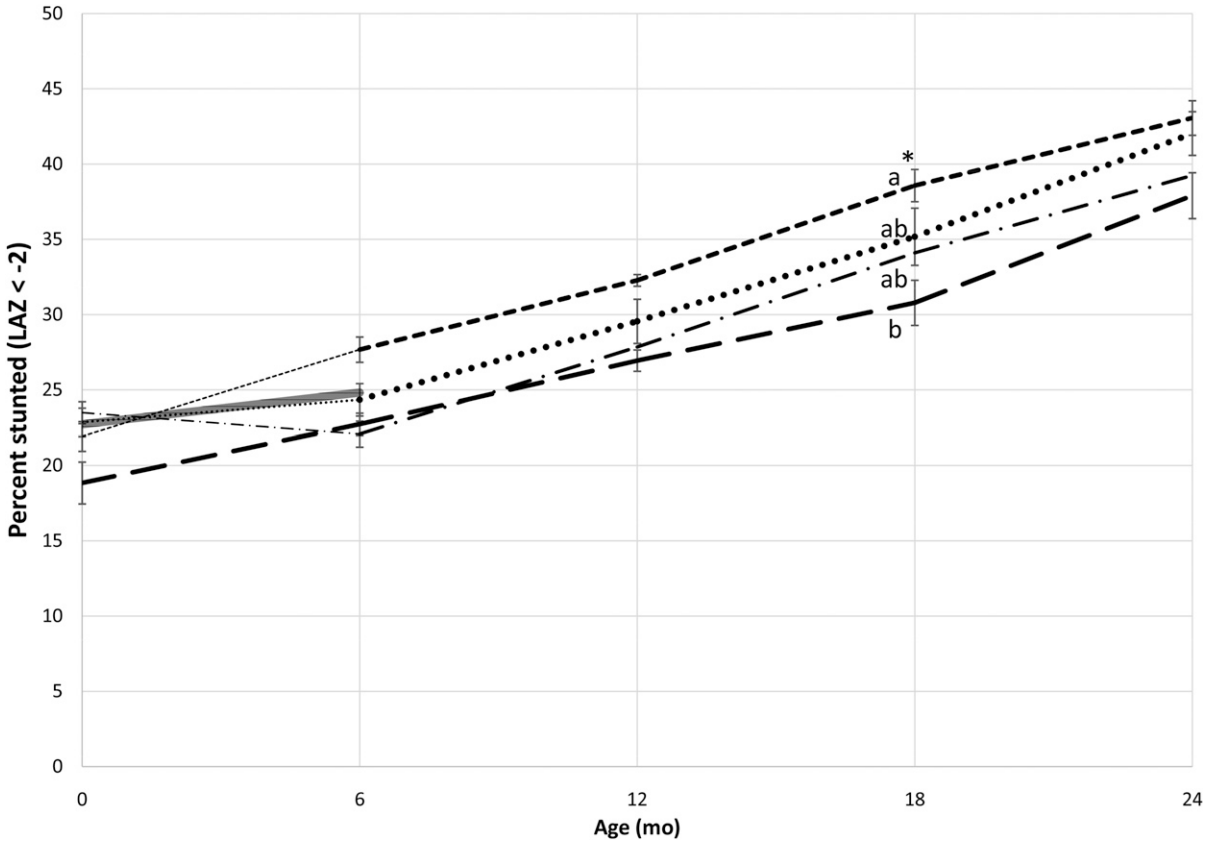

FIGURE 6 Stunting prevalence (LAZ <-2) by child age and intervention group. The solid gray line at 0–6 mo represents the combined control group for that interval (IFA-Control + IFA-MNP + IFA-LNS). The dotted line represents the IFA-Control group; the short-dashed line represents the IFA-MNP group; the dashed and dotted line represents the IFA-LNS group; and the long-dashed line represents the LNS-LNS group. The sample size at each time point ranges from 775 to 925 children in each of the 4 groups. Significant differences between the 4 groups at 18 and 24 mo are shown in Table 5. *P* values were derived from mixed-model logistic regression. *Global difference, $P < 0.05$. Groups that do not share a common letter differ, $P < 0.05$ (Tukey-Kramer–corrected pairwise differences). IFA-Control, women received iron and folic acid supplement during pregnancy and the first 3 mo postpartum and children did not receive supplements; IFA-LNS, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received lipid-based nutrient supplements from 6 to 24 mo of age; IFA-MNP, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received micronutrient powder from 6 to 24 mo of age; LAZ, length-for-age *z* score; LNS-LNS, women and children received lipid-based nutrient supplements.

and IFA-LNS) and shows the difference in birth size between the IFA-combined and LNS-LNS groups reported previously (19). In all 4 groups, LAZ and HCZ declined steadily between birth and 24 mo, whereas WAZ and WLZ rebounded between birth and 6 mo and then declined thereafter. **Figure 6** shows that stunting rates increased from ~20% at birth to 38–43% at 24 mo.

At 24 mo, there were significant differences between intervention groups in LAZ, HCZ, and WAZ but not in WLZ or MUACZ (**Table 4**). Pairwise tests indicated significant differences between the LNS-LNS and the IFA-MNP groups for LAZ (-1.72 compared with -1.85) and WAZ (-1.64 compared with -1.77) and between the LNS-LNS and the IFA-Control groups for HCZ (-1.73 compared with -1.87). There were no significant differences between the IFA-LNS group and either the IFA-Control or IFA-MNP groups nor between the LNS-LNS and the IFA-LNS groups for any of these outcomes. The trends for the dichotomous outcomes (**Table 5**) were in the same direction, but the differences in rates of stunting, underweight, and wasting were not significant; for small head size, there was a marginally significant difference ($P = 0.099$), with the largest difference in prevalence between the LNS-LNS group (37.4%) and the IFA-Control group (43.0%). Adjustment for predetermined covariates did not change these results (data not shown).

In secondary analyses at 18 mo, there were significant differences between intervention groups overall in LAZ, WAZ, and WLZ and a marginally significant difference in HCZ; there were no significant differences in MUACZ (Table 4). Pairwise tests indicated that the LNS-LNS and IFA-LNS groups both differed (positively) from the IFA-MNP group for WAZ (with similar but marginally significant differences for LAZ); for WLZ, the difference was significant for the IFA-LNS group compared with the IFA-Control group. There were no significant differences between the IFA-MNP group and the IFA-Control group or between the LNS-LNS group and the IFA-LNS group for any of these outcomes. The prevalences of stunting, underweight, and wasting (Table 5) were significantly different between intervention groups. For stunting, the LNS-LNS group had a lower rate of stunting (30.8%) than the IFA-MNP group (38.6%). For underweight, the significant difference was between the IFA-LNS group (29.6%) and the IFA-MNP group (38.3%); for wasting, the significant difference was between the IFA-LNS group (14.0%) and the IFA-Control group (19.1%). Adjustment for covariates did not change these results (data not shown).

Results of tests for interactions with potential effect modifiers were generally not significant ($P > 0.10$), except when head circumference was the outcome. For HCZ at 24 mo, there was a

TABLE 4
LAZ, HCZ, WAZ, WLZ, and MUACZ at 18 and 24 mo, by intervention group[1]

	LNS-LNS	IFA-LNS	IFA-MNP	IFA-Control	*P*
LAZ					
18 mo	−1.62 ± 0.99	−1.63 ± 0.96	−1.75 ± 0.97	−1.68 ± 0.95	0.042
24 mo[2]	−1.72 ± 0.96[a]	−1.73 ± 0.95[a,b]	−1.85 ± 0.95[b]	−1.80 ± 0.94[a,b]	0.016
HCZ					
18 mo	−1.61 ± 0.87	−1.64 ± 0.85	−1.68 ± 0.88	−1.72 ± 0.87	0.058
24 mo[3]	−1.73 ± 0.86[a]	−1.79 ± 0.84[a,b]	−1.83 ± 0.88[a,b]	−1.87 ± 0.88[b]	0.015
WAZ					
18 mo[4]	−1.58 ± 0.95[a]	−1.58 ± 0.90[a]	−1.72 ± 0.97[b]	−1.70 ± 0.92[a,b]	0.004
24 mo[5]	−1.64 ± 0.92[a]	−1.65 ± 0.93[a,b]	−1.77 ± 0.94[b]	−1.75 ± 0.93[a,b]	0.011
WLZ					
18 mo[6]	−1.11 ± 0.90[a,b]	−1.10 ± 0.85[a]	−1.21 ± 0.93[a,b]	−1.22 ± 0.91[b]	0.009
24 mo	−1.03 ± 0.88	−1.03 ± 0.87	−1.11 ± 0.89	−1.11 ± 0.89	0.105
MUACZ					
18 mo	−0.59 ± 0.83	−0.57 ± 0.79	−0.66 ± 0.85	−0.62 ± 0.81	0.206
24 mo	−0.66 ± 0.85	−0.66 ± 0.81	−0.75 ± 0.84	−0.70 ± 0.82	0.151

[1] Values are means ± SDs. *P* values were derived from mixed-model ANCOVA. When the global null hypothesis was rejected at the 0.05 level, post hoc pairwise comparisons with the use of Tukey-Kramer adjustment are presented as footnotes. Groups that do not share a common superscript letter differ, $P < 0.05$. HCZ, head circumference-for-age *z* score; IFA-Control, women received iron and folic acid supplement during pregnancy and the first 3 mo postpartum and children did not receive supplements; IFA-LNS, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received lipid-based nutrient supplements from 6 to 24 mo of age; IFA-MNP, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received micronutrient powder from 6 to 24 mo of age; LAZ, length-for-age *z* score; LNS-LNS, women and children received lipid-based nutrient supplements; MUACZ, mid-upper arm circumference-for-age *z* score; WAZ, weight-for-age *z* score; WLZ, weight-for-length *z* score.
[2] LNS-LNS compared with IFA-MNP, $P = 0.022$.
[3] LNS-LNS compared with IFA-Control, $P = 0.011$.
[4] LNS-LNS compared with IFA-MNP, $P = 0.022$; IFA-LNS compared with IFA-MNP, $P = 0.021$.
[5] LNS-LNS compared with IFA-MNP, $P = 0.034$.
[6] IFA-LNS compared with IFA-Control, $P = 0.039$.

significant interaction with maternal BMI. As shown in **Supplemental Figure 1**, there was a significant difference between the LNS-LNS and IFA-MNP groups among children of mothers with a baseline BMI (in kg/m^2) <18.5. For low HCZ at both 18 and 24 mo, there was a significant interaction with child sex, with group differences being significant among girls but not among boys (**Supplemental Figure 2**). For HCZ and low HCZ at 24 mo, group differences were more evident among children born in 1 of the time periods (midstudy) than those born in other periods (data not shown).

Postnatal growth rate

Between birth and 6 mo, there were no significant differences in length gain, head circumference gain, or weight gain between the maternal LNS-PL and IFA-combined groups (**Table 6**). Adjustment for covariates did not change these results (data not shown). From 6 to 24 mo, there were significant differences between the 4 intervention groups in length gain, head circumference gain, and weight gain (**Table 7**). Pairwise tests indicated that the LNS-LNS and IFA-LNS groups had greater length gain than the IFA-Control group but did not differ significantly from the IFA-MNP group. The LNS-LNS group had greater head circumference gain than the IFA-Control group. None of the other pairwise tests was significant. For weight gain, none of the pairwise tests was significant, but the patterns were similar to those for length gain. Adjustment for predetermined covariates did not change these results (data not shown).

There were no significant interaction effects observed for growth rate from birth to 6 mo. For growth rate from 6 to 24 mo, maternal height modified the effect of intervention group on length gain, with group differences evident in children of taller mothers but no significant difference in children of shorter mothers (**Supplemental Figure 3**). For head circumference gain from 6 to 24 mo, differences between intervention groups were more evident in children of mothers aged ≥25 y than in children of younger women (**Supplemental Figure 4**).

DISCUSSION

We observed significant positive effects on several indicators of child growth in response to the provision of small-quantity LNSs during the first 1000 d within a community-based health program, compared with the provision of MNP or no supplement to children. For the primary outcome, mean LAZ at 24 mo, the significant difference (+0.13) was between children exposed to both prenatal and postnatal LNSs (LNS-LNS) and children provided with MNP (IFA-MNP); this difference was already apparent by 6 mo of age and was not due to a reduced growth rate between 6 and 24 mo in children receiving MNP. At 24 mo, the LNS-LNS and IFA-LNS groups were very similar in mean LAZ (−1.72 compared with −1.73). Therefore, although mean birth LAZ was slightly greater in the LNS-LNS group [+0.09 (19)], children exposed only to LNS-C achieved the same mean LAZ by 24 mo. Differences in stunting prevalence were most evident at 18 mo, when there was a 21% reduction in stunting in the LNS-LNS group compared with

TABLE 5
Prevalence of stunting, small head size, underweight, and wasting at 18 and 24 mo, by intervention group[1]

	LNS-LNS	IFA-LNS	IFA-MNP	IFA-Control	*P*
Stunting (LAZ <-2)					
18 mo[2]					
Prevalence, %	30.8[a]	34.1[a,b]	38.6[b]	35.2[a,b]	0.010
OR (95% CI)	0.83 (0.63, 1.09)	0.96 (0.73, 1.28)	1.18 (0.90, 1.55)	—	
RR	0.88	0.98	1.11	—	
24 mo					
Prevalence, %	37.9	39.2	43.1	42.0	0.114
OR (95% CI)	0.84 (0.65, 1.09)	0.89 (0.68, 1.17)	1.04 (0.81, 1.35)	—	
RR	0.90	0.93	1.03	—	
Small head size (HCZ <-2)					
18 mo					
Prevalence, %	31.5	33.3	36.1	35.5	0.166
OR (95% CI)	0.83 (0.63, 1.10)	0.90 (0.68, 1.19)	1.03 (0.79, 1.34)	—	
RR	0.89	0.94	1.02	—	
24 mo					
Prevalence, %	37.4	39.5	41.8	43.0	0.099
OR (95% CI)	0.79 (0.61, 1.03)	0.86 (0.66, 1.13)	0.95 (0.74, 1.23)	—	
RR	0.87	0.92	0.97	—	
Underweight (WAZ <-2)					
18 mo[3]					
Prevalence, %	33.3[a,b]	29.6[a]	38.3[b]	35.3[a,b]	0.005
OR (95% CI)	0.91 (0.69, 1.20)	0.77 (0.58, 1.03)	1.14 (0.87, 1.48)	—	
RR	0.94	0.84	1.09	—	
24 mo					
Prevalence, %	35.4	34.0	38.8	37.9	0.177
OR (95% CI)	0.90 (0.69, 1.18)	0.85 (0.65, 1.13)	1.05 (0.80, 1.37)	—	
RR	0.94	0.90	1.03	—	
Wasting (WLZ <-2)					
18 mo					
Prevalence, %	15.9[a,b]	14.0[a]	17.6[a,b]	19.1[b]	0.040
OR (95% CI)	0.77 (0.54, 1.09)	0.69 (0.47, 0.99)	0.9 (0.64, 1.27)	—	
RR	0.80	0.73	0.92	—	
24 mo					
Prevalence, %	13.0	13.0	13.5	15.2	0.486
OR (95% CI)	0.82 (0.56, 1.19)	0.84 (0.57, 1.23)	0.87 (0.60, 1.26)	—	
RR	0.84	0.86	0.89	—	

[1] *P* values were derived from mixed model logistic regression. When the global null hypothesis was rejected at the 0.05 level, post hoc pairwise comparisons with the use of Tukey-Kramer adjustment are presented as footnotes. RRs were approximated by using multivariate-adjusted log-binomial model estimation methods. Groups that do not share a common superscript letter differ, $P < 0.05$. HCZ, head circumference-for-age *z* score; IFA-Control, women received iron and folic acid supplement during pregnancy and the first 3 mo postpartum and children did not receive supplements; IFA-LNS, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received lipid-based nutrient supplements from 6 to 24 mo of age; IFA-MNP, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received micronutrient powder from 6 to 24 mo of age; LAZ, length-for-age *z* score; LNS-LNS, women and children received lipid-based nutrient supplements; WAZ, weight-for-age *z* score; WLZ, weight-for-length *z* score.

[2] LNS-LNS compared with IFA-MNP—OR: 0.70; 95% CI: 0.53, 0.92; RR = 0.79.

[3] IFA-LNS compared with IFA-MNP—OR: 0.68; 95% CI: 0.52, 0.89; RR = 0.77.

the IFA-MNP group (7.8 percentage points). By 24 mo, the difference in stunting prevalence between those 2 groups was 5.2 percentage points (NS). These results suggest modest improvements in linear growth status among children provided with LNSs but not among those given MNP.

For head circumference, there was a significant difference of 0.14 *z* scores between the LNS-LNS and IFA-Control groups at 24 mo. The difference between these 2 groups in the prevalence of small head size (<-2 *z* scores) at 24 mo was marginally significant overall (11% reduction) but was highly significant among girls (33% reduction). These results indicate that the increase in newborn head size attributable to prenatal LNSs (19) was sustained throughout the first 2 y of life. Children exposed only to LNS-C did not differ in head circumference at 24 mo compared with the IFA-Control group, suggesting that postnatal supplementation alone was insufficient. Given the relation between head circumference and brain growth during infancy (31), these results may

TABLE 6
Growth in length, head circumference, and weight between 0 and 6 mo, by intervention group[1]

	LNS	IFA	*P*
Length gain, cm/6 mo	16.1 ± 1.8	16.1 ± 1.9	0.380
Head circumference gain, cm/6 mo	8.1 ± 1.2	8.1 ± 1.2	0.147
Weight gain, g/6 mo	4055 ± 742	4086 ± 739	0.385

[1] Values are means ± SDs. *P* values were derived from models of growth rate per month and by using mixed-model ANCOVA. IFA, women received iron and folic acid; LNS, women received lipid-based nutrient supplements.

TABLE 7
Growth in length, head circumference, and weight between 6 and 24 mo, by intervention group[1]

	LNS-LNS	IFA-LNS	IFA-MNP	IFA-Control	*P*
Length gain,[2] cm/6 mo	5.9 ± 0.6[a]	5.9 ± 0.6[a]	5.8 ± 0.6[a,b]	5.8 ± 0.6[b]	0.003
Head circumference gain,[3] cm/6 mo	1.41 ± 0.24[a]	1.40 ± 0.23[a,b]	1.38 ± 0.25[a,b]	1.37 ± 0.24[b]	0.011
Weight gain, g/6 mo	1009 ± 225	1005 ± 213	985 ± 219	981 ± 211	0.033

[1] Values are means ± SDs. *P* values were derived from models of growth rate per month and by using mixed-model ANCOVA. When the global null hypothesis was rejected at the 0.05 level, post hoc pairwise comparisons with the use of Tukey-Kramer adjustment are presented as footnotes. Groups that do not share a common superscript letter differ, $P < 0.05$. IFA-Control, women received iron and folic acid supplement during pregnancy and the first 3 mo postpartum and children did not receive supplements; IFA-LNS, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received lipid-based nutrient supplements from 6 to 24 mo of age; IFA-MNP, women received iron and folic acid during pregnancy and the first 3 mo postpartum and children received micronutrient powder from 6 to 24 mo of age; LNS-LNS, women and children received lipid-based nutrient supplements.

[2] LNS-LNS compared with IFA-Control, $P = 0.013$; IFA-LNS compared with IFA-Control, $P = 0.013$.

[3] LNS-LNS compared with IFA-Control, $P = 0.009$.

have important implications with regard to neurobehavioral development. A greater proportion of brain growth occurs in utero for girls than for boys (32), which may explain the sex difference in the impact of pre- and postnatal LNSs on small head size.

There was no effect of the maternal component of the intervention on postnatal growth rate from birth to 6 mo. Thus, if there were any effects of maternal LNSs consumed after delivery on maternal health or breast-milk composition [e.g., iodine, selenium, or vitamin content (33)], they did not affect infant growth between 0 and 6 mo. From 6 to 24 mo, there was a small but significantly greater rate of growth in length and head circumference in children given LNSs compared with IFA-Control children, although most of the difference in attained size at 24 mo was already present at birth among children exposed to both prenatal and postnatal LNSs. We observed that a linear growth response to postnatal LNSs was more likely among children of taller (compared with shorter) mothers, implying that short maternal stature may constrain child growth response to such interventions, a finding also observed in Ghana (4).

There are several potential explanations for the intervention group differences in growth summarized above. First the prenatal provision of LNSs to the mother, compared with IFA, contributed both micro- and macronutrients required for fetal growth, as well as a small amount of energy; and the essential fatty acid content may have been particularly important for brain growth. Although it is not possible to identify which nutrients were most critical to this response, the LNS trial in Ghana (4) showed that among the primiparous mothers (who were the most responsive to the prenatal component of the intervention), there were significant differences in birth length, weight, and head circumference not only between the LNS and IFA groups but also between the LNS group and those who received multiple micronutrient tablets during pregnancy. This suggests that the nutrients included in LNSs but not included in the micronutrient tablets played a role in fetal growth. These included energy, macronutrients, and 4 macrominerals (calcium, potassium, phosphorus, and magnesium); otherwise, the micronutrient content was identical. In the RDNS, postnatal provision of LNSs to the children sustained the supply of energy and macro- and micronutrients in the LNS-LNS group. Again, it is not possible to identify the most critical nutrients, but the difference in attained length at 24 mo between the LNS-LNS and IFA-MNP groups suggests that the differences in nutrient content of LNS-C compared with MNP could have played a role. LNS-C provided energy, macronutrients, and macrominerals (calcium, potassium, phosphorus, and magnesium) not typically included in MNPs, but also included pantothenic acid, vitamin K, and manganese (not included in the MNP); more zinc (8 compared with 4.1 mg), selenium (20 compared with 17 mg), and vitamin E (6 compared with 5 mg); and slightly less copper and iron. The energy, macronutrients, and macrominerals are the most likely candidates contributing to the postnatal linear growth response, because there is little evidence that the other differences would affect growth very much [including the higher zinc content, based on the results of a zinc-dosing LNS trial in Burkina Faso (34)].

In comparable intervention trials that used small-quantity LNSs, supplementation ended at 18 mo or earlier. In Malawi, no impact on linear growth was observed with postnatal supplementation (22) or with combined pre- and postnatal supplementation (21). By contrast, in Ghana, combined pre- and postnatal LNS provision increased linear growth (+0.28 LAZ) and reduced stunting by 41% (6.2 percentage points) (4). In postnatal trials in Ghana (26), Haiti (35), and Burkina Faso (34), LNS provision alone (26, 35) or in combination with other interventions (34) had positive effects on linear growth. In the JiVitA-4 trial conducted in an area of Bangladesh near the area where the RDNS was conducted (36), there was a small but significant effect of child LNS provision (small-quantity LNSs from 6 to 12 mo, then medium-quantity LNSs from 12 to 18 mo) on LAZ at 18 mo (+0.07 to 0.10 Z) and a reduction in stunting of 4–5 percentage points. In the RDNS, effects of combined pre- and postnatal LNSs on linear growth and stunting at 18 mo were similar to the impact of postnatal supplementation seen in the JiVitA-4 trial, but the latter was an efficacy trial, whereas the RDNS was an effectiveness trial. Evidence is now accumulating to show that when stunting is reduced by such interventions, the likely reduction is in the range of 4–10 percentage points, or a relative reduction of ~10–40% depending on the prevalence of stunting in the study population.

Strengths of this study include the following: *1*) randomized design with 16 clusters/arm, yielding balance across intervention groups; *2*) enrollment of >4000 women in early gestation who were representative of the target population; *3*) anthropometric data collection by a well-trained and standardized team that was separate from those delivering the intervention and blinded to group assignment; and *4*) a low rate of attrition in all intervention groups, with 24-mo measurements for >92% of children born alive. The key limitations are the differences in micronutrient

content of the LNSs and MNP and the inability to blind participants to the type of supplement provided because of differences in supplement appearance and taste. In addition, adherence was assessed primarily by retrospective, qualitative caregiver report, which could be biased. Finally, the interaction results should be interpreted with caution because we examined 10 potential effect modifiers and the study was not powered to test each potential interaction.

We conclude that home fortification with small-quantity LNSs during the first 1000 d improved child linear growth and head size in a programmatic setting in rural Bangladesh. By contrast, MNP had no growth-promoting effect in the RDNS, which is consistent with results of systematic reviews (6, 7). This has important policy implications because MNP distribution is being scaled-up nationally in Bangladesh and in other countries (5), mainly to reduce anemia. Although enhanced formulations of MNPs with 22 micronutrients may promote growth in low-birth-weight infants (37), their efficacy and effectiveness for the general population of infants have not been tested. It should be noted that postnatal growth faltering in the RDNS and other studies (34, 36) was still evident (although reduced) despite the provision of fortified supplements, pointing to the need for more comprehensive interventions that target the multiple causes of poor growth, including both prenatal and postnatal infections (2). Thus, although programmatic efforts to scale-up successful nutrition interventions should move forward (38), the impact of fortified supplements such as LNSs should continue to be evaluated in the context of broader strategies to reduce stunting.

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