Home fortification during the first 1000 d improves child development in Bangladesh: a cluster-randomized effectiveness trial[1–3]

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ABSTRACT

Background: Nutrition during the first 1000 d is critical for brain development.

Objective: We evaluated the effects on child development of home fortification with lipid-based nutrient supplements (LNSs) for mothers and/or children or micronutrient powder (MNP) for children.

Design: We conducted a cluster-randomized effectiveness trial with 4 arms: *1*) LNSs during pregnancy and the first 6 mo postpartum and LNSs for the offspring from 6 to 24 mo (LNS-LNS), *2*) iron and folic acid (IFA) during pregnancy and the first 3 mo postpartum and LNSs for the children from 6 to 24 mo (IFA-LNS), *3*) IFA (as above) and MNP for the offspring from 6 to 24 mo (IFA-MNP), and *4*) IFA (as above) and no child supplement (IFA-Control). Women were enrolled at ≤20 wk of gestation; children were assessed at 12 (n = 3331), 18 (n = 3364), and 24 (n = 3379) mo.

Results: Compared with the IFA-Control group, motor development scores were higher in the LNS-LNS (P = 0.016) and IFA-LNS groups (P = 0.006) at 18 mo and in the IFA-MNP group (P = 0.048) at 24 mo. Receptive language scores were higher for the LNS-LNS group (P = 0.028) at 18 mo and for all 3 groups at 24 mo (P = 0.008 for LNS-LNS, P = 0.022 for IFA-LNS, and P = 0.009 for IFA-MNP compared with IFA-Control). Expressive language scores did not differ at 18 mo (P = 0.236) but were higher in the LNS-LNS (P = 0.035) and IFA-MNP (P = 0.002) groups than in the IFA-Control group at 24 mo. Groups did not differ in personal-social scores at 18 (P = 0.233) or 24 (P = 0.146) mo or in executive function score at 24 mo (P = 0.467).

Conclusion: Prenatal LNSs, postnatal LNSs, or both, or postnatal MNP had a positive effect on motor and language development in Bangladeshi children. This trial was registered at clinicaltrials.gov as NCT01715038. *Am J Clin Nutr* 2017;105:958–69.

Keywords: lipid-based nutrient supplements, micronutrient powder, language development, motor development, executive function, young children, Bangladesh

INTRODUCTION

Adequate nutrition is critical for brain growth and development, particularly during the first 1000 d, when a large proportion of nutrient-sensitive brain growth occurs (1). Although all nutrients are important for neuronal cell growth and development, certain nutrients have greater effects on the rapidly developing brain than others, including protein, energy, and long-chain PUFAs and, among the micronutrients, iron, zinc, copper, iodine, selenium, vitamin A, choline, and folate (2). Accordingly, nutritional deficiency or supplementation during this early period could be critical for long-lasting effects on child development.

Home fortification entails adding specialized products [e.g., multiple micronutrient powder (MNP)[8]] or food-based complementary food supplements [e.g., small-quantity lipid-based nutrient supplements (SQ-LNSs) or full-fat soy flour],

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[2] The contents are the responsibility of the authors and do not necessarily reflect the views of USAID or the US government.

[3] Supplemental Figures 1–5 are available from the "Online Supplemental 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: CDI, Communicative Development Inventories; CHDP, Community Health and Development Program; CHW, community health worker; DMC-II, Developmental Milestones Checklist II; FCI, Family Care Indicators; IFA, iron and folic acid supplement; IFA-Control, iron and folic acid supplement during pregnancy and the first 3 mo postpartum and no supplement for the children; IFA-LNS, 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; IFA-MNP, iron and folic acid during pregnancy and the first 3 mo postpartum and micronutrient powder for the offspring from 6 to 24 mo; LAMB, Lutheran Aid to Medicine in Bangladesh; LNS, lipid-based nutrient supplement; LNS-C, lipid-based nutrient supplement for children; LNS-LNS, lipid-based nutrient supplements during pregnancy and the first 6 mo postpartum and lipid-based nutrient supplements for the offspring from 6 to 24 mo; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women; MNP, micronutrient powder; RDNS, Rang-Din Nutrition Study; SES, socioeconomic status; SDU, safe delivery unit; SQ-LNS, small-quantity lipid-based nutrient supplement.

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containing a mix of vitamins and minerals, into home-prepared foods (3). MNPs are the most commonly used home fortification products, whereas SQ-LNSs represent a newer approach to address undernutrition during the first 1000 d, initially developed for young children and now extended to pregnant and lactating women (4). Lipid-based nutrient supplement (LNS) products provide key macronutrients, including essential fatty acids, and several micronutrients in amounts appropriate for the needs of these population groups (4). Postnatal SQ-LNS supplementation from 6 to 12 mo of age showed positive effects on motor development at 12 mo in Ghana (5), but no such effects were observed in Haiti (6). When SQ-LNSs were given along with malaria and diarrhea treatment and for a longer period (i.e., 9 mo) in Burkina Faso, they were associated with positive effects on language, motor, and personal-social development at 18 mo of age (7). SQ-LNSs were provided both pre- and postnatally from 6 to 18 mo of age in 2 efficacy trials, 1 in Ghana (8) and 1 in Malawi (9). Although positive effects on motor development were observed at age 12 mo, there were no significant effects on motor, cognitive, or socio-emotional development at age 18 mo in these trials (10, 11). The lack of sensitivity of development assessments in children younger than 2 y for detecting effects of improved nutrition was suggested as a potential explanation (among others) for these results (11).

We conducted the Rang-Din Nutrition Study (RDNS) to evaluate the effectiveness of home fortification approaches for the prevention of maternal and child undernutrition during the first 1000 d in rural Bangladesh. In the RDNS, we evaluated the effects of SQ-LNSs provided to women during pregnancy and lactation (LNS-PL) and to their children (LNS-C) from 6 to 24 mo of age. The overall hypothesis of the study was that the provision of LNS-PL to women and/or LNS-C to their offspring would result in larger positive changes in maternal and child nutrition outcomes than would the provision of iron and folic acid (IFA) to women and MNP or no supplementation for their children. We previously reported that LNS-PL reduced stunting and small head size at birth in the RDNS sample (12). This report describes the effects of the RDNS intervention on child development (secondary) outcomes during the first 24 mo. Findings on the primary outcome of the RDNS (i.e., growth) are reported separately (13).

METHODS

Study setting and design

The study was conducted in 11 rural unions of the Badarganj and Chirirbandar subdistricts in northwestern Bangladesh. Lutheran Aid to Medicine in Bangladesh (LAMB), a nongovernment organization operating in the study area, offered the programmatic platform for conducting the RDNS through its Community Health and Development Program (CHDP) and was responsible for distributing the study supplements to the study population. Other regular services provided by CHDP included maternity services at a safe delivery unit (SDU) in each union; home visits for antenatal, postnatal, and primary child care by community health workers (CHWs) and village health volunteers; and educational group sessions to promote maternal and child health. A further description of the study setting is reported elsewhere (12).

The RDNS was a community-based, cluster-randomized effectiveness trial with 4 equal-sized arms: *1*) 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*) child-only LNS group, in which women received IFA during pregnancy and the first 3 mo postpartum and their children received LNS-C from 6 to 24 mo of age (IFA-LNS group); *3*) child-only MNP group, in which women received IFA (as described above) and their children received MNP from 6 to 24 mo of age (IFA-MNP group); and *4*) control group, in which women received IFA (as described above) and their children received no supplements (IFA-Control group). The study was implemented in 64 clusters (defined as the supervision area of a CHW), with 16 clusters randomly assigned to each of the 4 arms by the study statistician, after stratification by subdistrict and union, as previously described (12).

The study protocol was approved by the institutional review boards of the University of California, Davis; icddr,b; and LAMB. The trial was registered at clinicaltrials.gov (NCT01715038). All of the participants provided written consent.

Study supplements

Table 1 shows the nutritional composition of the study supplements. LNS-PL (one 20-g sachet/d) was partially modeled on the UNICEF/WHO/United Nations University international multiple micronutrient preparation (UNIMMAP) for pregnant and lactating women. Further details on the rationale for its formulation are described elsewhere (14). IFA was provided as 1 tablet including 60 mg Fe and 400 μg folic acid and was produced by Hudson Pharmaceuticals Ltd. in Bangladesh. Women were instructed to consume 1 IFA tablet/d during pregnancy and 1 IFA tablet every other day during the first 3 mo postpartum (15). LNS-C (two 10-g sachets/d) was similar to the LNS-C used in Ghana (8) and Malawi (9). Both LNS products were produced by Nutriset SA in France. MNPs contained 15 micronutrients in a 1-g/d sachet and was produced by Renata Ltd. in Bangladesh.

Maternal supplements were delivered by CHDP staff during monthly home visits. The distribution format and the use messages for LNS-PL are described elsewhere (12). Child supplementation started at 6 mo of age with a first month's supply of either LNS-C or MNP given at the SDU along with the use messages. Subsequent monthly supplies were usually delivered by the CHW or village health volunteers to the child's home, and use messages were repeated. In the Badarganj subdistrict, the government of Bangladesh started distributing MNP (containing vitamin A, vitamin C, folic acid, iron, and zinc) for children aged 6–24 mo while we were implementing the study. Participants receiving LNS-C or MNP from the RDNS were instructed not to feed any other vitamin and mineral tablets, capsules, or MNP sachets to the study children. Participants in the IFA-Control group (children not receiving any supplement from the RDNS) were not given such instructions.

Enrollment and data collection

Eligibility criteria included gestational age of $\leq$20 wk and no plans to move out of the study area during pregnancy or the following 3 y. Further details on participant enrollment are reported elsewhere (12). Data collection was conducted in 2

TABLE 1
Nutrient content of study supplements[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-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 LNS-PL used in other trials (8).
[3] Nutrient content was similar to LNS-C used in other trials (4), except that iron content was 9 mg instead of 6 mg 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 MNP being distributed by BRAC and Renata Ltd. in Bangladesh.

settings, by 2 different teams, as follows: at the participant's home (e.g., sociodemographic characteristics; nutrition-related knowledge, attitudes, and practices; food security; infant and young feeding practices; medical expenditures) and at the SDU [e.g., anthropometric measurements (except for measurements at birth and at 42 d), bio-specimens, clinical data, and developmental assessments]. Information on data collected and follow-up procedures during pregnancy and around childbirth are published elsewhere (12, 14). Subsequent follow-up visits occurred at 42 d and at 6, 12, 18, and 24 mo postpartum. Predefined criteria were used to refer women and children with certain conditions (e.g., severe anemia) for treatment.

Because child development is affected by stimulation in the home (16, 17), we assessed home stimulation at 12, 18, and 24 mo of age by using the Family Care Indicators (FCI) scale, developed by UNICEF (18) and validated in Bangladesh (19). We used the most parsimonious FCI scale, which consisted of 9 items (scored as yes = 1 and no = 0) about play materials, activities with the child, and availability of reading materials at home. The total score was calculated as the sum of scores of all 9 items.

Data on adherence to the LNS-C and MNP were collected at 12, 18, and 24 mo of age by asking caregivers the following: *1*) how often (from "not at all" to "regularly/every day") the child consumed the supplements during the previous 6 mo and *2*) how many packets were consumed during the previous week. High adherence was defined as *1*) consuming the supplement "almost every day" or "regularly/every day" (based on previous-6-mo recall) and *2*) consuming $\geq$8 sachets of LNSs (10 g each) or $\geq$4 sachets of MNP (based on previous-week recall).

Evaluation team members were blinded to group assignment to the extent feasible, considering that those conducting home visits may have seen the supplements at the participants' homes. Other quality-control procedures have been previously reported (12).

Child development assessments

Motor development at 12 mo of age

We assessed 6 gross motor milestones (sitting without support, crawling, standing with support, standing without support, walking with assistance, walking without assistance) with the use of the WHO Multicentre Growth Reference Study tool (20). "Walking without assistance" (assessed by direct observation) was selected as the outcome to report because it is expected to be achieved by $\sim$50% of children at 12 mo of age (21).

Motor and personal-social development at 18 and 24 mo of age

We used the Developmental Milestones Checklist II (DMC-II) (22), with minor adaptations, to assess motor [including locomotor skills (gross motor) and eye-hand coordination (fine motor); 32 items] and personal-social (28 items) development. We did not use the DMC-II language subscale; instead, we assessed language as described below. The DMC-II is a caregiver report tool. However, when a caregiver reported not knowing whether the child could perform the task, items were directly tested by the evaluator. The raw score for each domain (subscale) was calculated as the sum of the item scores in that domain. The internal, inter-interviewer, and test-retest reliability of the DMC-II scores have been reported to be $>$0.7 (22). We piloted the DMC-II with 32 mother-child dyads (children aged 15–27 mo) and found satisfactory internal consistency indicators (Cronbach's α coefficients were 0.78 for motor and 0.82 for personal-social).

Language development at 12, 18, and 24 mo of age

Language was assessed by using a vocabulary inventory based on the principles of the MacArthur Communicative Development Inventories (CDI) (23) and including words specifically selected for Bangladesh (24). This caregiver-report tool initially had 60 words of various levels of difficulty across 15 categories of words (e.g., animals, toys, food and drink, body parts). For each word in the CDI, the caregiver was asked to indicate whether the child could understand (receptive or comprehensive language) and whether the child could say (expressive language) the word. Pilot data (n = 48; ages 11–23 mo) indicated positive and significant correlations with child's age and maternal education. Short-term test-retest reliability (n = 15; ages 17–18 mo) was r = 0.89 for comprehensive and r = 0.88 for expressive language. We used the 60-word version at 12 and 18 mo. For assessing children at

24 mo of age, we added 40 more words with the use of a list of additional words made available by the same research group that developed the CDI for younger Bangladeshi children. This extended CDI version was piloted before implementation (n = 45; ages 17–34 mo). Two different raw scores were computed: *1*) the total number of words the child understood and *2*) the total number of words the child could say.

Executive function at 24 mo of age

We assessed executive function by direct testing with the use of the A-not-B task (25), which was previously used in 18-mo-old children in Ghana (10) and Malawi (11). At each of the 10 trials of this task, a small candy (or potato chip) was hidden underneath 1 of 2 identical (upside-down) cups positioned on a wooden board. The board was then removed from the child's sight for 5 s, after which the board was returned and the child was asked to find the hidden snack. After 2 correct consecutive trials, the snack was then hidden at the alternate location. We piloted the A-not-B task (n = 45; ages 21–29 mo) and rigorously trained data collectors before implementing this direct test. Field observations by the SDU team leader and RDNS investigators were conducted to monitor standardized administration of this test. Due to constraints on personnel resources, we administered this task to a randomly selected subsample of children (target sample: n = 1346). Two types of raw scores were calculated: *1*) total correct trials (the sum of all trials in which the child selected the correct location) and *2*) perseverative errors (the total number of errors committed after the first set of 2 correctly solved trials).

Developmental assessment training and quality control

Six testers received 5–10 d of hands-on training on all the tests, including practical sessions in which test administration and scoring were monitored thoroughly. For standardization of the CDI, inter-tester reliability (or the correlation coefficient between scores of testers and trainers on the same occasion) was determined as follows: the 6 testers were divided into 2 groups each led by 1 trainer (considered the gold standard) and each of the 6 testers interviewed 8 mothers of 12- to 27-mo-old children and scored responses from 14 to 16 interviews (a total of 24 mothers participated in this training exercise). The resulting inter-tester reliability for the CDI was good ($r > 0.90$). For standardization of the DMC-II, inter-rater reliability between scores of the trainer and the field supervisor was evaluated for 8 mother-child dyads, and the results showed high correlation coefficients for both domains (motor and personal-social; $r > 0.90$). Later, the field supervisor trained 6 testers and ensured their appropriate performance during data collection. For the A-not-B test, the field supervisor received a 3-d hands-on training by a psychologist and conducted pilot testing with 45 children (21–29 mo of age). She subsequently trained and monitored the field staff and used a criterion for trainer-tester agreement of ≥80% before deploying staff for data collection. Standardization of testing procedures also included the use of the same testing materials, administering the tests in the same order and on the same day, and conducting the assessments at local clinics (as opposed to the participant's home) in a separate room (to avoid distractions) with similar furniture (table or desk and 2 chairs). Five percent of all development tests were monitored for quality-control measures by study supervisors throughout the data collection period, during which 3 refresher trainings were also conducted.

Statistical analysis

The target sample size for the RDNS was 788 participants/arm (n = 3152 total) based on detecting an effect size of ≥0.2 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 of age (12). Later, on the basis of evidence linking MNP to diarrhea and possibly other negative morbidity outcomes (26), we decided to use a 2-sided hypothesis approach. A data analysis plan was developed before starting the analysis and revealing group assignment. Analysis was performed on the basis of the intention-to-treat principle; all outcomes were measured at the individual participant level. Because of losses to follow-up, we compared baseline characteristics of the mothers whose children were included with those not included in the analyses of 24-mo outcomes (study endpoint) by using the cluster-adjusted t test for continuous variables and Wald chi-square test for categorical variables.

We imputed missing developmental scores on the basis of the other items in the same subscale with the use of the method described by Raghunathan et al. (27). Raw developmental scores were standardized on the basis of the distribution of the RDNS sample. For each developmental score, we also created a dichotomous variable by using the lowest quartile (25%) of the total sample score distribution as a proxy indicator of potential moderate-to-severe developmental delay.

Effects of the intervention were analyzed by using linear mixed-model ANCOVA for continuous outcomes and mixed-effects logistic regression for dichotomous outcomes. All of the models included cluster nested within treatment group and union nested within subdistrict as random effects and treatment group and child's age as fixed effects. The df for testing the treatment effect in all analyses reflected the number of clusters. In the analysis of continuous outcomes, we first calculated group means ± SDs and tested for significant differences ($P < 0.05$). For the analysis of the binary outcomes, we calculated cluster-adjusted group percentages and based our statistical comparisons on log odds of the outcome occurring. We also estimated multivariate-adjusted RR by using log-binomial model estimation methods (28) 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.

We included an interaction term in the ANCOVA or logistic regression model to test potential effect modifiers for outcomes at 24 mo of age. We tested the following prespecified potential effect modifiers: maternal age and education, socioeconomic status (SES) index, food security, presence of young children in the household, maternal BMI and height, parity, gestational age, child's sex, time of year at birth, and FCI score. Further details on maternal and sociodemographic variables are reported elsewhere (12). All of these variables were assessed at baseline, except for child's sex, time of year at birth, and FCI score. For the FCI variable, we created a composite value combining the standardized FCI total scores available until the time point of the relevant outcome assessment. Significant interactions ($P < 0.05$) were further examined with stratified analyses to understand the nature of the effect modification.

We also conducted a sensitivity analysis for the 24-mo outcomes excluding participants from the Badarganj subdistrict

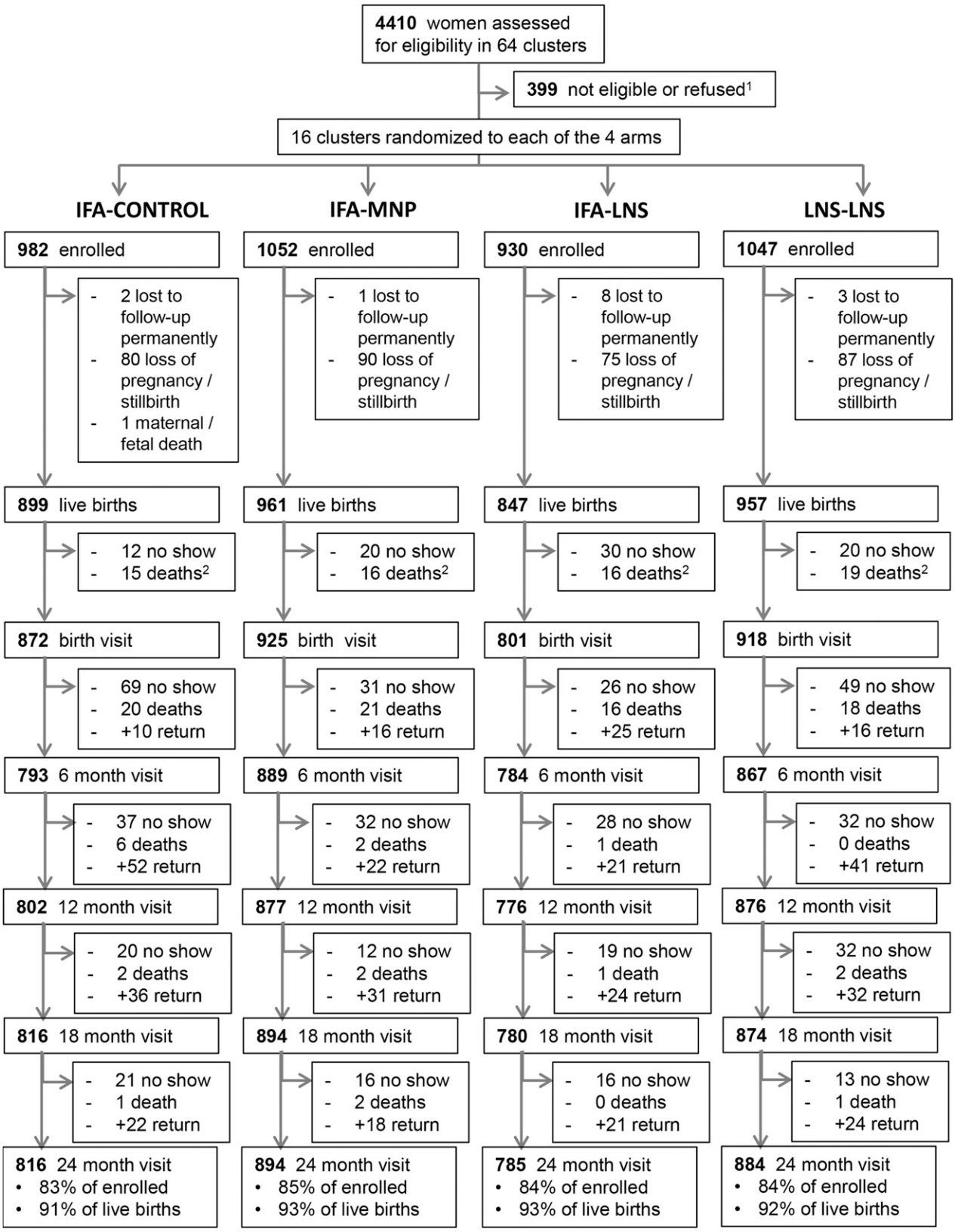

FIGURE 1 Study participation flow diagram. For twin births, numbers include 1 randomly selected twin from each twin pair. [1]n = 366 with a gestational age >140 d, 22 planned to leave study site, 8 refused, and 3 husbands refused. [2]Most of these deaths occurred at <14 d postpartum: n = 14, IFA-Control; n = 15, IFA-MNP; n = 14, IFA-LNS; and n = 17, LNS-LNS. IFA-Control, iron and folic acid supplement during pregnancy and the first 3 mo postpartum and no supplement for the children; IFA-LNS, 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; IFA-MNP, iron and folic acid during pregnancy and the first 3 mo postpartum and micronutrient powder for the offspring from 6 to 24 mo; LNS-LNS, lipid-based nutrient supplements during pregnancy and the first 6 mo postpartum and lipid-based nutrient supplements for the offspring from 6 to 24 mo.

where the Bangladesh government distributed MNP for children. Analyses were conducted using by SAS software (version 9.4; SAS Institute).

RESULTS

We screened 4410 pregnant women for eligibility and enrolled 4011 (**Figure 1**) between 15 October 2011 and 31 August 2012. Of these, 3664 live births occurred between 15 January 2012 and 5 May 2013 to women who remained in the study. Data from 20 sets of twins were available for developmental outcomes, and 1 twin from each pair was randomly selected for analyses. Child development data were available for 3379 children (n = 1096 for executive function) at 24 mo (24.2 ± 0.14 mo), corresponding to 92.2% of live births and 84.2% of enrolled women; for 3364 children at 18 mo (18.1 ± 0.10 mo); and for 3331 children at 12 mo (12.2 ± 0.10 mo). Rates of loss did not differ by intervention group. On the basis of the highest actual intracluster correlation (0.008), α = 0.05, and 2-sided hypothesis testing, we had at least 78% power to detect an effect size of ≥0.2 for 24-mo outcomes (excluding executive function).

The women whose children were not assessed at 24 mo of age had ~0.4 fewer years of education (P = 0.035) and were ~0.5 cm shorter (P = 0.035) but otherwise did not differ from those whose children were assessed (data not shown). Baseline characteristics of women whose children were included in the 24-mo analysis were similar across intervention groups, except for maternal years of education (**Table 2**).

High adherence to the LNS-C or MNP increased with age in all 3 intervention groups. On the basis of the previous-6-mo recall, it increased from 94–97% at 6–12 mo to 97–99% at 18–24 mo (depending on the arm) and was somewhat lower in the IFA-MNP group at 18–24 mo (P = 0.007). On the basis of the previous-week recall, it increased from 77–80% at 12 mo to 90–92% at 24 mo (depending on the arm) and did not differ between groups.

Motor development

At 12 mo of age, 31.7%, 33.9%, 33.7%, and 25.6% of children were walking without assistance in the LNS-LNS, IFA-LNS, IFA-MNP, and IFA-Control groups, respectively (P = 0.012). Pairwise comparisons indicated higher odds of achieving this milestone among children in the IFA-LNS (OR: 1.54; 95% CI: 1.07, 2.20) and the IFA-MNP (OR: 1.47; 95% CI: 1.03, 2.10) groups compared with the IFA-Control group.

There were significant differences between all intervention groups in motor development z scores at ages 18 and 24 mo (**Table 3**). Pairwise tests between groups indicated higher z scores in the LNS-LNS and the IFA-LNS groups than in the IFA-Control group at 18 mo and in the IFA-MNP group than in the IFA-Control group at 24 mo (Table 3).

At 18 mo of age, the proportion of children in the lowest quartile (P = 0.004) differed by group (**Table 4**). Pairwise comparison showed that a lower proportion of children in the LNS-LNS, IFA-LNS, and IFA-MNP groups were in the lowest quartile than those in the IFA-Control group. We did not observe significant differences between all intervention groups in the proportion of children in the lowest quartile at 24 mo of age (Table 4).

Among the potential effect modifiers tested, only FCI modified the association between intervention groups and motor development z scores. Among children from households with lower home stimulation (FCI score below the median), those in the LNS-LNS and IFA-MNP groups had higher z scores than those in the IFA-Control group, whereas no group difference was observed among children from households with greater home stimulation (**Supplemental Figure 1**).

Language development

Comprehensive (receptive) language

A trend toward a difference between all intervention groups in receptive language z scores was observed at 12 mo of age (P = 0.088; **Figure 2**). There were no significant differences in the percentage of children in the lowest quartile (P = 0.235) between intervention groups at this age.

There were significant differences between intervention groups overall in receptive language z scores at 18 and 24 mo of age (Figure 2, Table 3). Pairwise tests between groups indicated that, at 18 mo of age, children in the LNS-LNS group had higher

TABLE 2
Maternal baseline characteristics[1]

	Group			
Characteristic	LNS-LNS (n = 884)	IFA-LNS (n = 785)	IFA-MNP (n = 894)	IFA-Control (n = 816)
Age, y	21.8 ± 4.9	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
Household asset index	0.04 ± 2.24	0.01 ± 2.33	−0.06 ± 2.22	0.02 ± 2.23
Food insecurity score	2.8 ± 3.9	3.1 ± 4.0	3.1 ± 4.1	3.3 ± 4.1
Height, cm	150.7 ± 5.4	150.4 ± 5.3	150.5 ± 5.4	150.7 ± 5.4
BMI, 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, wk	13.1 ± 3.8	13.2 ± 3.9	13.1 ± 3.8	13.1 ± 3.8

[1] Values are means ± SDs unless otherwise indicated. IFA-Control, iron and folic acid supplement during pregnancy and the first 3 mo postpartum and no supplement for the children; IFA-LNS, 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; IFA-MNP, iron and folic acid during pregnancy and the first 3 mo postpartum and micronutrient powder for the offspring from 6 to 24 mo; LNS-LNS, lipid-based nutrient supplements during pregnancy and the first 6 mo postpartum and lipid-based nutrient supplements for the offspring from 6 to 24 mo.

z scores than those in the IFA-Control group, whereas at 24 mo of age those in the LNS-LNS, IFA-LNS, and IFA-MNP groups had higher *z* scores than children in the IFA-Control group.

No significant difference between all intervention groups in the percentage of children in the lowest quartile ($P = 0.415$) was observed at 18 mo of age (Table 4). At 24 mo of age, the percentages of children in the lowest quartile (Table 4) were significantly different between all intervention groups ($P = 0.009$). The LNS-LNS and IFA-LNS groups had lower percentages of children in the lowest quartile than did the IFA-Control group.

Expressive language

At 18 mo of age, no significant differences between all intervention groups in expressive language *z* scores were observed ($P = 0.236$; Table 3, **Figure 3**). Similarly, no significant differences between intervention groups in the percentage of children in the lowest quartile were observed at this age (Table 4).

Overall, there were significant differences between all intervention groups in expressive language development *z* scores at age 24 mo (Table 3, Figure 3). Pairwise tests between groups indicated that the LNS-LNS and IFA-MNP groups both differed (positively) from the IFA-Control group. There were no significant differences between the IFA-LNS group and the IFA-Control group or between the LNS-LNS group and the IFA-LNS group. In addition, a trend toward a difference between all groups ($P = 0.094$) in the percentage of children in the lowest quartile was observed at this age (Table 4).

We identified 2 effect modifiers of the intervention on language outcomes at age 24 mo: gestational age at enrollment and SES score. For receptive language, significant group differences in the proportion of children in the lowest quartile were observed among children whose mothers were enrolled in their first trimester of pregnancy but not in children of those enrolled later in pregnancy (**Supplemental Figure 2**). A similar pattern was observed for receptive language *z* score (*P* value for interaction with gestational age = 0.004; data not shown).

SES score was a consistent effect modifier for language development. For receptive language, the LNS-LNS group had a lower percentage of children in the lowest quartile than the IFA-Control group among those with SES scores below the median, but there were no group differences among those with higher SES scores (**Supplemental Figure 3**). Among children with lower SES scores, children in the LNS-LNS and IFA-MNP groups had higher *z* scores in expressive language than did those in the IFA-Control group, whereas no group differences were observed among those with higher SES scores (**Supplemental Figure 4**).

Personal-social development

No significant differences between all intervention groups in personal-social *z* scores were observed at 18 ($P = 0.233$) or 24 ($P = 0.146$) mo of age (Table 3). Similarly, no significant differences between all intervention groups in the percentage of children in the lowest quartile ($P = 0.662$) were observed at 18 mo of age

TABLE 3
Developmental *z* scores at 18 ($n = 3364$) and 24 ($n = 3379$) mo of age, by intervention group[1]

	Group				
Domain	LNS-LNS	IFA-LNS	IFA-MNP	IFA-Control	*P*
Motor *z* score					
18 mo[2]	0.05 ± 1.13[a]	0.07 ± 0.92[a]	−0.01 ± 1.04[a,b]	−0.11 ± 0.88[b]	0.005
24 mo[3]	0.04 ± 0.74[a,b]	0.03 ± 0.95[a,b]	0.04 ± 0.92[a]	−0.11 ± 1.32[b]	0.028
Receptive language *z* score					
18 mo[4]	0.06 ± 1.03[a]	0.02 ± 1.01[a,b]	0.00 ± 0.99[a,b]	−0.09 ± 0.97[b]	0.043
24 mo[5]	0.05 ± 0.97[a]	0.03 ± 0.99[a]	0.04 ± 0.98[a]	−0.13 ± 1.05[b]	0.003
Expressive language *z* score					
18 mo	0.05 ± 0.97	0.02 ± 1.04	−0.02 ± 0.97	−0.05 ± 1.02	0.236
24 mo[6]	0.08 ± 1.00[a]	0.00 ± 1.02[a,b]	0.02 ± 0.98[a]	−0.11 ± 0.99[b]	0.003
Personal-social *z* score					
18 mo	0.08 ± 1.04	0.04 ± 0.97	−0.01 ± 1.04	−0.06 ± 0.94	0.233
24 mo	0.03 ± 0.89	−0.01 ± 1.00	0.05 ± 0.92	−0.08 ± 1.18	0.146
Executive function[7]					
A-not-B correct *z* score	0.00 ± 1.05	0.07 ± 0.97	0.00 ± 0.95	−0.07 ± 1.02	0.467
A-not-B perseverative errors *z* score	−0.08 ± 0.98	−0.04 ± 0.98	0.04 ± 0.98	0.08 ± 1.06	0.233

[1] Values are means ± SDs. *P* values were obtained by using mixed-model ANCOVA. For global null hypotheses rejected at the 0.05 level, post hoc pairwise comparisons using Tukey-Kramer correction are presented as footnotes. Groups that do not share a common superscript differ, $P < 0.05$. IFA-Control, iron and folic acid supplement during pregnancy and the first 3 mo postpartum and no supplement for the children; IFA-LNS, 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; IFA-MNP, iron and folic acid during pregnancy and the first 3 mo postpartum and micronutrient powder for the offspring from 6 to 24 mo; LNS-LNS, lipid-based nutrient supplements during pregnancy and the first 6 mo postpartum and lipid-based nutrient supplements for the offspring from 6 to 24 mo.

[2] LNS-LNS compared with IFA-Control, $P = 0.016$; IFA-LNS compared with IFA-Control, $P = 0.006$.

[3] IFA-MNP compared with IFA-Control, $P = 0.048$.

[4] LNS-LNS compared with IFA-Control, $P = 0.028$.

[5] LNS-LNS compared with IFA-Control, $P = 0.008$; IFA-LNS compared with IFA-Control, $P = 0.022$; IFA-MNP compared with IFA-Control, $P = 0.009$.

[6] LNS-LNS compared with IFA-Control, $P = 0.035$; IFA-MNP compared with. IFA-Control, $P = 0.002$.

[7] $n = 1096$.

TABLE 4
Dichotomous developmental outcomes (lowest quartile) at 18 (n = 3364) and 24 (n = 3379) mo of age, by intervention group[1]

	Group				
Domain and age	LNS-LNS	IFA-LNS	IFA-MNP	IFA-Control	P
Motor					
18 mo					
Prevalence, %	24.9[a]	23.0[a]	25.0[a]	30.9[b]	0.004
OR (95% CI)	0.74 (0.56, 0.99)	0.66 (0.49, 0.89)	0.75 (0.56, 1.00)	—	
RR	0.81	0.74	0.81	—	
24 mo					
Prevalence, %	28.3	27.8	27.9	32.7	0.141
OR (95% CI)	0.81 (0.59, 1.10)	0.78 (0.57, 1.07)	0.80 (0.59, 1.09)	—	
RR	0.87	0.84	0.86	—	
Receptive language					
18 mo					
Prevalence, %	25.5	27.3	27.2	29.2	0.415
OR (95% CI)	0.82 (0.60, 1.12)	0.91 (0.66, 1.24)	0.90 (0.66, 1.22)	—	
RR	0.86	0.93	0.93	—	
24 mo					
Prevalence, %	24.6[a]	25.5[a]	26.2[a,b]	31.6[b]	0.009
OR (95% CI)	0.70 (0.53, 0.94)	0.74 (0.55, 1.00)	0.77 (0.58, 1.02)	—	
RR	0.78	0.81	0.83	—	
Expressive language					
18 mo					
Prevalence, %	23.3	25.0	24.9	27.0	0.479
OR (95% CI)	0.81 (0.58, 1.15)	0.90 (0.64, 1.28)	0.89 (0.64, 1.25)	—	
RR	0.86	0.93	0.92	—	
24 mo					
Prevalence, %	23.4	27.8	25.5	28.3	0.094
OR (95% CI)	0.77 (0.58, 1.04)	0.98 (0.73, 1.31)	0.87 (0.65, 1.16)	—	
RR	0.83	0.98	0.90	—	
Personal-social					
18 mo					
Prevalence, %	26.7	26.4	27.6	28.9	0.662
OR (95% CI)	0.89 (0.67, 1.19)	0.88 (0.66, 1.19)	0.94 (0.71, 1.25)	—	
RR	0.92	0.91	0.96	—	
24 mo[2]					
Prevalence, %	27.8[a,b]	29.0[a]	23.1[b]	28.6[a,b]	0.040
OR (95% CI)	0.96 (0.71, 1.30)	1.03 (0.75, 1.40)	0.75 (0.55, 1.03)	—	
RR	0.97	1.02	0.81	—	
Executive function[3]					
24 mo					
Prevalence, %	31.9	28.3	30.9	35.3	0.394
OR (95% CI)	0.86 (0.53, 1.38)	0.72 (0.44, 1.20)	0.82 (0.51, 1.31)	—	
RR	0.90	0.80	0.87	—	

[1] IFA-Control was the reference group. P values were obtained by using mixed-model logistic regression. For global null hypotheses rejected at the 0.05 level, post hoc pairwise comparisons using Tukey-Kramer correction are presented as footnotes. Groups that do not share a common superscript differ, $P < 0.05$. RRs were approximated by using multivariate-adjusted log-binomial model estimation methods. IFA-Control, iron and folic acid supplement during pregnancy and the first 3 mo postpartum and no supplement for the children; IFA-LNS, 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; IFA-MNP, iron and folic acid during pregnancy and the first 3 mo postpartum and micronutrient powder for the offspring from 6 to 24 mo; LNS-LNS, lipid-based nutrient supplements during pregnancy and the first 6 mo postpartum and lipid-based nutrient supplements for the offspring from 6 to 24 mo.

[2] IFA-LNS compared with IFA-MNP (OR: 1.37; 95% CI: 1.00, 1.89).

[3] Based on A-not-B correct scores; n = 1096.

(Table 4). Table 4 shows that there were significant differences between all intervention groups in the percentage of children in the lowest quartile at age 24 mo (P = 0.040). Pairwise comparison between groups indicated that the IFA-LNS group had a higher percentage (29.0%) than the IFA-MNP group (23.1%). No effect modifiers were identified for any personal-social development outcome.

Executive function

Executive function data were available for 1096 children. Mothers of children in this subsample were similar to the rest of the RDNS women, except that they were enrolled ~2 d earlier in pregnancy (P = 0.013). We observed no significant differences between all intervention groups in z scores of correct responses (P = 0.467) or perseverative errors (P = 0.233) in the A-not-B

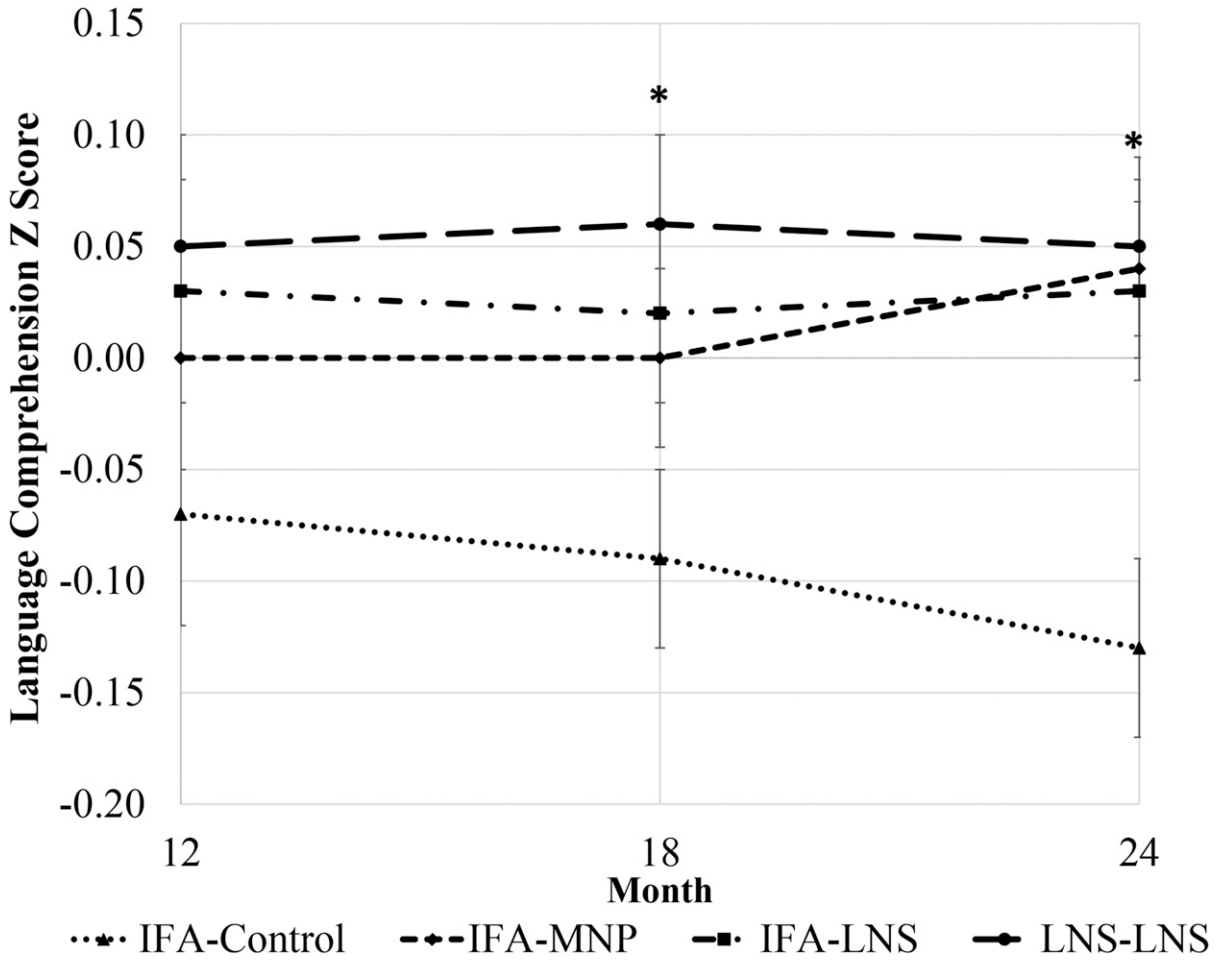

FIGURE 2 Language comprehension *z* scores by child age. Sample sizes: n = 3331 (12 mo), n = 3364 (18 mo), and n = 3379 (24 mo). Vertical lines represent SEs. Mixed-model ANCOVA was used. For global null hypotheses rejected at the 0.05 level (*overall $P < 0.05$), post hoc pairwise comparisons using Tukey-Kramer correction are presented. At 18 mo: difference between LNS-LNS and IFA-Control group, P = 0.028; at 24 mo: difference between LNS-LNS and IFA-Control, P = 0.008; IFA-LNS compared with IFA-Control, P = 0.022; IFA-MNP compared with IFA-Control, P = 0.009. IFA-Control, iron and folic acid supplement during pregnancy and the first 3 mo postpartum and no supplement for the children; IFA-LNS, 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; IFA-MNP, iron and folic acid during pregnancy and the first 3 mo postpartum and micronutrient powder for the offspring from 6 to 24 mo; LNS-LNS, lipid-based nutrient supplements during pregnancy and the first 6 mo postpartum and lipid-based nutrient supplements for the offspring from 6 to 24 mo.

task (Table 3). Similarly, there were no significant differences between all groups in the percentages of children in the lowest quartile (P = 0.394) of the distribution of correct responses (Table 4).

Child's sex was an effect modifier for executive function, with a significant difference between the IFA-LNS and the IFA-Control groups in the percentage of children in the lowest quartile of correct responses among girls but not boys (**Supplemental Figure 5**).

Sensitivity analysis

A total of 1788 children aged 24 mo were included in the sensitivity analysis restricted to participants in the Chirirbandar subdistrict (which did not have a government MNP distribution program). Results were very similar to those in the overall sample (data not shown). The most notable difference with respect to the results presented above was an increase from +0.19 to +0.27 in the *z* score difference between the LNS-LNS and IFA-Control groups in expressive language at 24 mo of age.

DISCUSSION

All 3 RDNS interventions showed significant positive effects on child development during the first 24 mo of life, particularly for motor and language development. However, no consistent effects on personal-social development or executive function were observed.

The positive effect of the interventions on motor development was observed at all 3 time points: 12, 18, and 24 mo of age. In the efficacy trials conducted in Malawi (n = 869) (11) and Ghana (n = 1320) (10) in which both prenatal and postnatal LNSs were provided (the latter given from ages 6 to 18 mo), effects were observed at 12 mo but not at 18 mo of age. It should be noted that a different (direct-testing) assessment method was used at age 18 mo in those 2 trials. However, in a randomized trial carried out in Burkina Faso (n = 1122 in the developmental subsample) in which the DCM-II was also used, LNSs (with various amounts of zinc) given to children from 9 to 18 mo of age resulted in greater positive effects on children's motor *z* scores at 18 mo (+0.34) than those observed in the RDNS

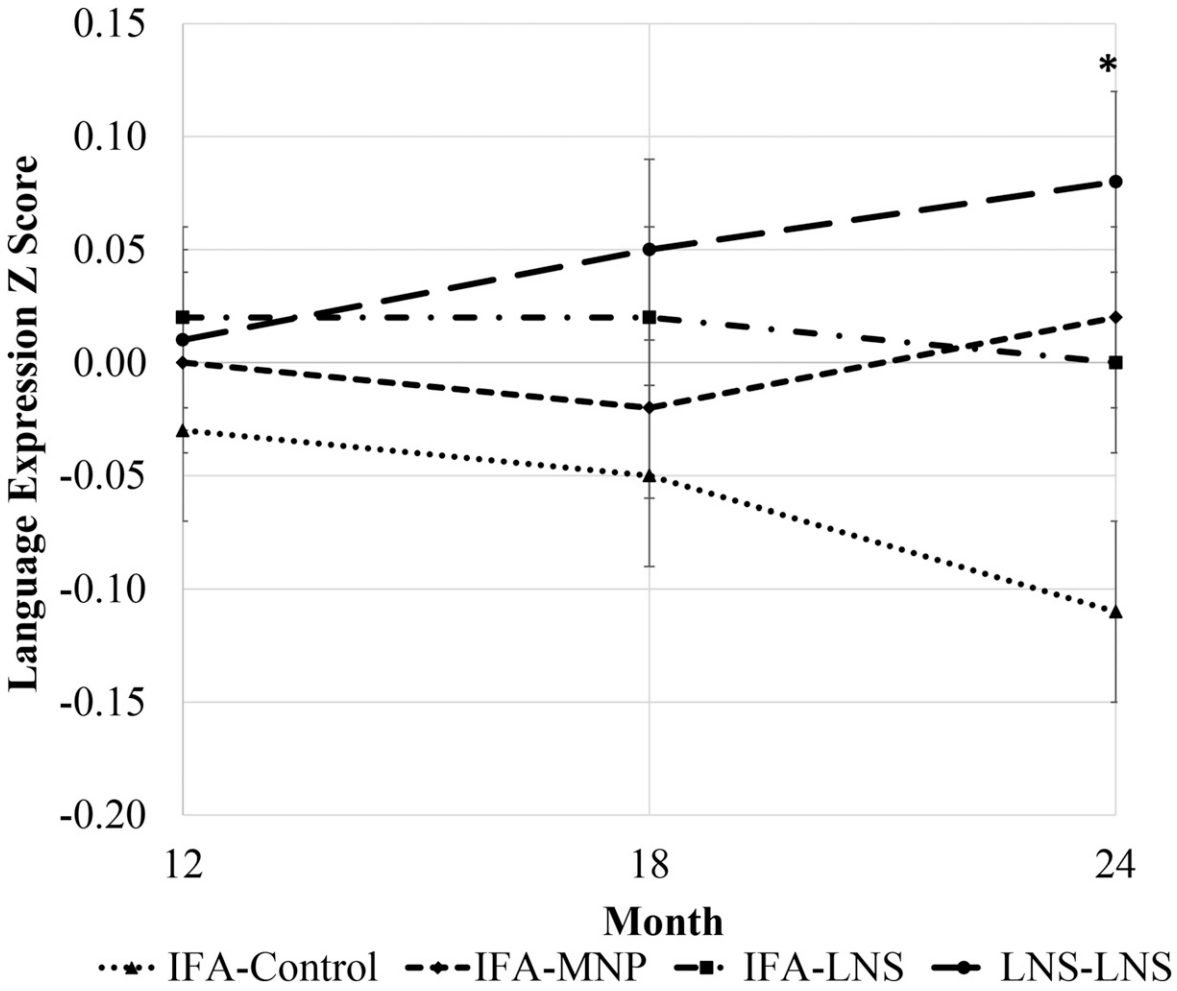

FIGURE 3 Language expression *z* scores by child age. Sample sizes: $n = 3331$ (12 mo), $n = 3364$ (18 mo), and $n = 3379$ (24 mo). Vertical lines represent SEs. Mixed-model ANCOVA was used. For global null hypotheses rejected at the 0.05 level (*overall $P < 0.05$), post hoc pairwise comparisons using Tukey-Kramer correction are presented. At 24 mo: difference between LNS-LNS and IFA-Control, $P = 0.002$; IFA-MNP compared with IFA-Control, $P = 0.035$. IFA-Control, iron and folic acid supplement during pregnancy and the first 3 mo postpartum and no supplement for the children; IFA-LNS, 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; IFA-MNP, iron and folic acid during pregnancy and the first 3 mo postpartum and micronutrient powder for the offspring from 6 to 24 mo; LNS-LNS, lipid-based nutrient supplements during pregnancy and the first 6 mo postpartum and lipid-based nutrient supplements for the offspring from 6 to 24 mo.

(+0.16–0.18) at that age. Children in the Burkina Faso trial also received malaria and diarrhea treatment, which may have contributed to the greater effect size observed in that trial. The larger effect observed in Burkina Faso could also relate to the different study design compared with the RDNS (efficacy compared with effectiveness trial).

At 24 mo of age, mean motor *z* scores were very similar between the 3 intervention groups in the RDNS, which suggests that the micronutrients present in both LNSs and MNP may have played a role. Intervention group differences in motor development at 24 mo of age were most evident among children receiving less stimulation at home, with no significant group differences observed among children from households in which more stimulation was provided. A greater effect of postnatal LNSs on motor development at 18 mo of age in children from low-stimulation households was also observed in Burkina Faso (7). These findings highlight the potential for these interventions to benefit children who may be at higher risk of motor development delays.

No intervention effects on language development were observed at age 12 mo, which is not surprising given that, at this age, vocabulary acquisition is just emerging (29). Positive effects of the RDNS interventions on receptive language were observed starting at age 18 mo. This may relate to the timing of myelination in several language-correlated brain regions, which reaches maturity at ~1.5 y of age (30). Consistent with reports from Malawi (11) and Ghana (10), where a similar language inventory was used, we did not detect effects on expressive language at age 18 mo. However, at age 24 mo, children in all 3 intervention groups had higher *z* scores in receptive and expressive language than did those in the control group, with effects ranging from +0.16 to +0.18 and +0.11 to +0.19, respectively. The manifestation of consistent effects on language at 24 mo but not at younger ages, in accord with the increasing language development that occurs during the first 2–3 y of life, suggests that effects of nutritional supplementation may be more evident at age 2 y and beyond. In addition, differences in receptive language scores between all groups were more marked in children whose mothers were enrolled in the trial earlier in their pregnancy than in those whose mothers enrolled later. It is possible that women who enrolled earlier in their

pregnancy differed in some ways that enhanced the effect of the intervention—for instance, in their level of health awareness. However, given the multiple-hypothesis testing we conducted, chance cannot be ruled out as a potential explanation for this result. With regard to expressive language, differences in scores between all groups were more evident in children from households with SES scores below the median. Low SES is a well-known risk factor for poor developmental outcomes (31) and affects language in particular (32). Thus, this finding could indicate that these interventions may be particularly beneficial for children at higher risk of poor language development.

We did not observe any significant overall group differences in personal-social development scores at 18 or 24 mo of age. The 18-mo results are consistent with those reported in the Malawi (11) and Ghana (10) trials, which used a different socioemotional development assessment tool, but they differed from those reported in Burkina Faso, which used the same tool, in which the postnatal LNS intervention (plus treatment of diarrhea and malaria) resulted in a significant effect on personal-social *z* scores (+0.37) and lower odds of being in the lowest decile (7). Again, illness treatment may have played a role in these conflicting findings.

No significant differences between groups were observed for children's executive function at 24 mo of age. Similar results were reported in the Malawi (11) and Ghana (10) trials, which used the same executive function task (i.e., A-not-B task), although at a younger age (18 mo). The prefrontal cortex, which is responsible for higher cognitive functions such as executive function, is one of the last brain regions to mature, with significant development still occurring throughout childhood and adolescence (33, 34). It is possible that any benefits of nutritional supplementation will manifest at a later age. Furthermore, because this assessment was implemented in a subsample, we may have lacked sufficient statistical power to detect an effect. However, among girls, there was a significantly lower proportion in the lowest quartile for executive function in the group who received LNSs postnatally compared with the control group (no difference was seen among boys). This finding may be linked to the greater impact of the RDNS intervention on head size in girls than in boys observed at 24 mo of age (13).

Taken together, our findings indicate that all 3 interventions are beneficial for improving child development. This suggests that the micronutrients that LNSs and MNPs have in common may be responsible for the observed effects, in particular those known to affect early brain development such as iron, zinc, iodine, and copper (1). For 1 outcome (receptive language at age 18 mo), the LNS-LNS group was the only group that differed significantly from the IFA-Control group, but there were no significant differences between the LNS-LNS group and either of the other 2 intervention groups for any of the outcomes. This suggests that prenatal nutrient supplementation (other than iron and folic acid) was not required to obtain the effects observed when the child received nutrients directly between 6 and 24 mo of age. However, we cannot rule out the possibility that differences between the intervention groups may emerge at a later age, when it is more feasible to assess specific cognitive and behavioral functions. Further research to identify the potential mediating factors linked to the beneficial effects on development in the RDNS, such as improved iron status, is warranted.

This study has several limitations, the most important being our inability to blind participants to the intervention because of differences in the appearance and taste of the supplements. Second, adherence was assessed by caregiver report, which could be biased. However, adherence levels were mostly similar among groups. Third, the study was not powered for testing effect modification; thus, such results should be interpreted with caution. Strengths of this study include the use of a randomized design with 16 clusters/arm, a large sample representative of the target population, a low and balanced attrition rate, and the rigorous implementation of developmental assessments conducted by a separate team who was blinded to group assignment.

In conclusion, the provision of pre- and/or postnatal LNSs or postnatal MNP appears to be beneficial for children's motor and language development in this setting of rural Bangladesh. Our findings also suggest that these effects may be greater among those potentially at higher risk of developmental delays, such as children from households with low SES and those receiving less stimulation at home or, in the context of gender inequality, among girls.

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