The Journal of Nutrition
Community and International Nutrition

Prenatal and Postnatal Supplementation with Lipid-Based Nutrient Supplements Reduces Anemia and Iron Deficiency in 18-Month-Old Bangladeshi Children: A Cluster-Randomized Effectiveness Trial

Susana L Matias,[1] Malay K Mridha,[1,3] Rebecca T Young,[1] Md Showkat A Khan,[3] Zakia Siddiqui,[4] Md Barkat Ullah,[1] Stephen A Vosti,[2] and Kathryn G Dewey[1]

Department of [1]Nutrition and [2]Agricultural and Resource Economics, University of California, Davis, Davis, CA; [3]James P Grant School of Public Health, BRAC University, Dhaka, Bangladesh; and [4]Initiative for Climate Change and Health, Health System and Population Studies Division, International Center for Diarrheal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh

Abstract

Background: Anemia, iron deficiency (ID), and iron deficiency anemia (IDA) among young children are public health concerns in developing countries.

Objective: We evaluated the effects of small-quantity lipid-based nutrient supplements (LNSs) and micronutrient powder (MNP) on anemia, ID, and IDA in 18-mo-old Bangladeshi children.

Methods: We enrolled 4011 pregnant women in a cluster-randomized effectiveness trial with 4 arms—*1*) LNS-LNS: LNSs (including 20 mg Fe) for women daily during pregnancy and 6 mo postpartum and LNSs (including 9 mg Fe) for children daily from 6 to 24 mo of age (LNS-C); *2*) IFA-LNS: iron (60 mg) and folic acid (IFA) for women daily during pregnancy and every other day for 3 mo postpartum and LNS-C for children; *3*) IFA-MNP: IFA for women, and MNP (including 10 mg Fe) for children daily from 6 to 24 mo; and *4*) IFA-Control: IFA for women and no child supplement. Hemoglobin, serum ferritin, and soluble transferrin receptor (sTfR) were assessed in a subsample of children ($n = 1121$) at 18 mo to identify anemia (hemoglobin <110g/L), ID (ferritin <12 μg/L or sTfR >8.3 mg/L), and IDA. Data were analyzed with the use of mixed-effects modeling.

Results: Compared with the IFA-Control arm, hemoglobin was higher in the LNS-LNS and IFA-LNS arms and ferritin was higher and sTfR was lower in the LNS-LNS, IFA-LNS, and IFA-MNP arms; LNS-LNS children had reduced odds of anemia (OR: 0.46; 95% CI: 0.25, 0.84), high sTfR (OR: 0.47; 95% CI: 0.29, 0.73), and ID (OR: 0.45; 95% CI: 0.28, 0.71); and all 3 groups had lower odds of low ferritin [corrected for inflammation; OR (95% CI)—LNS-LNS: 0.29 (0.13, 0.63); IFA-LNS: 0.25 (0.11, 0.59); and IFA-MNP: 0.37 (0.18, 0.76)] and IDA [LNS-LNS: 0.35 (0.18, 0.67); IFA-LNS: 0.45 (0.24,0.85); and IFA-MNP: 0.47 (0.26, 0.87)].

Conclusions: Home fortification using LNSs or MNP reduced IDA in 18-mo-old Bangladeshi children. The provision of LNSs in both pregnancy and childhood also reduced child anemia and ID. These findings are relevant to programs targeting similar populations. This trial was registered at www.clinicaltrials.gov as NCT01715038. *J Nutr* 2018;148:1167–1176.

Keywords: anemia, iron deficiency, lipid-based nutrient supplements, micronutrient powders, children, effectiveness trial, Bangladesh

Introduction

Anemia in children is a severe global health problem, with the highest prevalence in South Asia and Central and West Africa (1). Iron deficiency (ID) is considered the most common cause of anemia, although other nutritional causes, such as vitamin B-12 or folate deficiency (2, 3), and nonnutritional factors (4) also play a role. In Bangladesh, ∼52% of children aged 6–59 mo were anemic (hemoglobin <110 g/L) in 2011, with those <2 y or whose mothers were also anemic being at higher risk (5). Among rural Bangladeshi infants (6–11 mo), 68% were anemic (hemoglobin <105 g/L) (6). ID in early childhood, with or without anemia, is associated with delayed motor, cognitive, and socioemotional development (7–10).

Manuscript received November 21, 2017. Initial review completed January 5, 2018. Revision accepted March 26, 2018.
First published online June 13, 2018; doi: https://doi.org/10.1093/jn/nxy078.

Home fortification has been used in situations in which diets do not provide sufficient amounts of essential nutrients, such as vitamins, minerals, and essential FAs (11). Micronutrient powders (MNPs) are the most commonly used home-fortification products for infants and young children, and they are effective for reducing anemia and ID in this age group (12). Small-quantity (SQ) lipid-based nutrient supplements (LNSs; 20 g/d) are a relatively novel home-fortification approach. SQ-LNS products contain energy, protein, and essential FAs along with a mix of vitamins and minerals (including iron) and are designed to be mixed with home-prepared foods. A few studies have reported positive effects of child supplementation with SQ-LNSs on anemia, ID, and iron deficiency anemia (IDA) (13, 14), but to our knowledge the effects on these outcomes of providing SQ-LNSs to both the mother during pregnancy and to the child in early life have not been reported.

We implemented a cluster-randomized trial, the Rang-Din Nutrition Study (RDNS), to evaluate the effectiveness of home fortification with SQ-LNSs provided to women during pregnancy and lactation (LNS-PL) and to their children (LNS-C) from 6 to 24 mo of age for the prevention of maternal and child undernutrition during the first 1000 d in rural Bangladesh. In the RDNS, supplements were distributed by community health workers (CHWs) and clusters were defined as their area of work; thus, a CHW was responsible for delivering only 1 type of supplement to the households in her area (cluster). Our previously published findings from the RDNS indicated that the provision of LNS-PL reduced stunting and small head size at birth (15) and that the provision of LNS-PL plus LNS-C improved child linear growth and head size (16) and children's motor and language development at 24 mo of age (17), whereas the provision of MNPs resulted in similar benefits for child development but not growth. This article describes the effects of the RDNS interventions on several secondary outcomes, hemoglobin, anemia, ID, and IDA, of the children at 18 mo. We chose 18 mo as the endline for these outcomes for the following reasons: *1*) the risk of ID begins to decline by 24 mo because iron requirements are lower in the second year of life than during the first year (18), whereas iron intake increases due to greater consumption of complementary foods; *2*) we sought to reduce participant burden at the 24-mo follow-up visit, which included a comprehensive child development assessment; and *3*) by 18 mo, children would have received their supplements (LNS-C or MNPs) for a full year, long enough for an effect to be apparent.

Methods

Study setting and design

The RDNS was an effectiveness trial conducted in 2 subdistricts of the Northwest region of Bangladesh, Badarganj and Chirirbandar. Further details of the study setting have been previously described (15, 19). The RDNS was conducted in partnership with a local nongovernment organization (formerly known as Lutheran Aid to Medicine in Bangladesh [LAMB]) that was implementing a Community Health and Development Program (CHDP). The CHDP offered a programmatic platform for supplement distribution, with its field staff (CHWs, with support from village health volunteers) assuming responsibility for delivering the study supplements.

The RDNS was a cluster-randomized effectiveness trial with 4 equally sized arms: *1*) an LNS-LNS arm, 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; *2*) an IFA-LNS arm, in which women received iron plus folic acid (IFA; 1 tablet containing 60 mg Fe and 400 μg folic acid) daily during pregnancy and every other day during the first 3 mo postpartum and their children received LNS-C from 6 to 24 mo of age; *3*) an IFA-MNP arm, in which women received IFA daily during pregnancy and every other day during the first 3 mo postpartum, and their children received MNPs from 6 to 24 mo of age; and *4*) a control arm (IFA-Control), in which the women received IFA daily during pregnancy and every other day during the first 3 mo postpartum and their children received no supplements. Procedures for conducting the randomization included multiple replications and testing for balance across groups. The final randomization to the 4 arms was chosen at random from the acceptable potential randomizations, and the letters A, B, C, and D were assigned to the 4 sets, randomly permuting them by sorting on a randomly generated uniformly distributed number, and assigning them respectively to the IFA-Control, IFA-MNP, IFA-LNS, and LNS-LNS arms. The trial was implemented in a total of 64 clusters (i.e., work area of a CHW), with 16 clusters randomized to each of the 4 arms by the study statistician, after stratification by subdistrict and union. The mean cluster size was 63 ± 16 (mean ± SD) women (enrolled in the RDNS). Further aspects of the study design and randomization procedures are described elsewhere (15).

All clusters, or CHWs, that were participating in the CHDP in the 2 subdistricts of the study were included in the RDNS. Similarly, all pregnant women residing in the area of work of any of the 64 CHWs were eligible if they met the following eligibility criteria at enrollment: *1*) their gestational age was ≤20 wk and *2*) they had no plans to move out of study area for 3 y after enrollment. A total of 4011 pregnant women were enrolled in the RDNS. The study protocol was approved by the institutional review boards of the University of California, Davis; the International Center for Diarrheal Disease Research, Bangladesh (icddr,b; the local research partner); and LAMB. The study was registered at clinicaltrials.gov (NCT01715038). Participants provided individual written consent before implementation of data collection procedures.

Nutritional composition and distribution of study supplements

The nutritional composition of the study supplements is shown in **Table 1**. All LNS products were produced by Nutriset SA in France. 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. Iron content was 20 mg/sachet. Further details on the rationale for its formulation are described elsewhere (19). IFA was produced by Hudson Pharmaceuticals Ltd. in Bangladesh, with each tablet containing 60 mg Fe and 400 μg folic acid; women were advised to consume

Some of the results of this study were included in a report to the sponsor that was published online (http://www.fantaproject.org/sites/default/files/resources/RDNS-Child-Outcomes-Report-Dec2017.pdf) before the date of acceptance.

Supported by funding from the Office of Health, Infectious Diseases, and Nutrition, Bureau for Global Health, US States Agency for International Development (USAID), under 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 Health and Development Program of Lutheran Aid to Medicine in Bangladesh (LAMB), which was supported by Plan-Bangladesh in 6 of the 11 study unions.

Author disclosures: SLM, MKM, RRY, MSAK, ZS, MBU, SAV, and KGD, no conflicts of interest.

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

SLM and MKM are joint first authors.

Supplemental Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.

Address correspondence to SLM (e-mail: slmatias@ucdavis.edu).

Abbreviations used: AGP, α1-glycoprotein; CHDP, Community Health and Development Program; CHW, community health worker; CRP, C-reactive protein; ICC, intracluster correlation; ID, iron deficiency; IDA, iron deficiency anemia; IFA, iron and folic acid; 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; RDNS, Rang-Din Nutrition Study; SDU, safe delivery unit; SQ, small-quantity; sTfR, soluble transferrin receptor.

TABLE 1 Nutrient content of study supplements[1]

Nutrient	Amount per daily dose			
	IFA[2] (1 tablet)	LNS-PL[3] (20 g/d)	LNS-C[4] (20 g/d)	MNP[5] (1 sachet/d)
Energy, kcal	0	118	118	0
Protein, g	0	2.6	2.6	0
Fat, g	0	10	9.6	0
Linoleic acid, g	0	4.59	4.46	0
α-Linolenic acid, g	0	0.59	0.58	0
Vitamin A, μg RE	0	800	400	400
Thiamin, mg	0	2.8	0.5	0.5
Riboflavin, mg	0	2.8	0.5	0.5
Niacin, mg	0	36	6	6
Folic acid, μg	400	400	150	150
Pantothenic acid, mg	0	7	2.0	0
Vitamin B-6, mg	0	3.8	0.5	0.5
Vitamin B-12, μg	0	5.2	0.9	0.9
Vitamin C, mg	0	100	30	30
Vitamin D (cholecalciferol), μg	0	10	5	5
Vitamin E (d,l-α-tocopherol acetate), mg	0	20	6	5
Vitamin K (phylloquinone 5%), μg	0	45	30	0
Calcium, mg	0	280	280	0
Copper, mg	0	4	0.34	0.56
Iodine, μg	0	250	90	90
Iron, mg	60	20	9	10
Magnesium, mg	0	65	40	0
Manganese, mg	0	2.6	1.2	0
Phosphorus, mg	0	190	190	0
Potassium, mg	0	200	200	0
Selenium, μg	0	130	20	17
Zinc, mg	0	30	8	4.1

[1] IFA, iron and folic acid; 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 based on standard recommendations for pregnant women (20). Daily dose: 1 tablet/d during pregnancy; 1 tablet every other day during lactation.
[3] Nutrient content the same as LNS-PL used in other trials (21, 22).
[4] Nutrient content similar to LNS-C used in other trials (21, 22), 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.
[5] Nutrient content the same as MNP being distributed by Bangladesh Rural Advancement Committee (BRAC) and Renata Ltd. in Bangladesh.

1 tablet/d during pregnancy and 1 tablet every other day during the first 3 mo postpartum (20). LNS-C was similar to the LNS-C used in Ghana (21) and Malawi (22), except for a slightly higher content of iron (9 compared with 6 mg/d) and some of the B vitamins; the daily dose was two 10-g sachets. The MNP was produced by Renata Ltd. in Bangladesh and contained 15 micronutrients, including 10 mg Fe.

On the basis of cluster (i.e., CHW) allocation to study arm, supplements were delivered by CHDP staff monthly, at the local health center (first month's supply) or during monthly home visits. The distribution format and messages on how to use LNS-PL (15) and LNS-C or MNPs (17) have been previously described. Briefly, participants (or caregivers) were instructed to mix the entire sachet of the LNS with a small portion of their homemade food. While we were implementing the RDNS, the government of Bangladesh started distributing MNPs (containing vitamin A, vitamin C, folic acid, iron, and zinc) for children aged 6–24 mo in the Badarganj subdistrict. Caregivers of the children assigned to receive LNS-C or MNPs (but not those in the control group) were instructed not to feed any other vitamin and mineral tablets, capsules, or MNP sachets to the study children.

Data collection

Data collection was performed by 2 separate teams: the "home visit team," which enrolled mothers and collected baseline and follow-up data at participants' homes, and the "SDU visit team," which collected anthropometric data and biospecimen samples at a health center known as a safe delivery unit (SDU). Team members were blinded to group assignment to the extent feasible, although those conducting home visits may have been exposed to the study supplements at the participants' homes. Data collected at home included socioeconomic status, maternal diet, infant and young child feeding practices, food security, and other maternal and household-level information (15). A subsample of women was randomly selected at enrollment for collection of blood at enrollment, 36 wk of gestation, and 6-mo postpartum (maternal biochemical subsample). Another subsample was randomly selected (also at enrollment) for collection of blood from children at 6 and 18 mo (child biochemical subsample). At each SDU assessment time point, predefined criteria were used to refer participants with certain conditions (e.g., hemoglobin <80 g/L) for treatment.

Outcome variables. All of the outcomes were measured at the individual participant level. Capillary blood was collected in the randomly selected subsample of children by heel prick. After the prick, the first drop of blood was discarded. Hemoglobin (grams per liter) was then measured by using the HemoCue Hb 301 System (HemoCue America), ~45 s after collection. A microvette was used for sample collection, which was kept in a rack for ~15–20 min after the collection and then put in a cold box. Thereafter, serum and RBCs were separated by using a centrifuge, and a 0.2-mL PCR tube was used for serum storage and kept at –20°C until shipment to an external laboratory for analysis of biomarkers of iron status and inflammation.

Serum ferritin (micrograms per liter) and soluble transferrin receptor (sTfR; milligrams per liter) were analyzed by a combined sandwich ELISA method (23). This technique uses a small amount of serum (~30 μL) and an ELISA with different capture and detection antibodies and different solutions of the sample. The interassay CVs for these indicators were 3.0% (ferritin) and 4.6% (sTfR).

Child anemia was defined as hemoglobin <110 g/L (24). As indicators of iron status, low ferritin was defined as a ferritin concentration <12 μg/L (25) and high sTfR was defined as an sTfR concentration >8.3 mg/L (23). ID was defined as ferritin <12 μg/L or sTfR >8.3 mg/L. IDA was defined as hemoglobin <110 g/L and either ferritin <12 μg/L or sTfR >8.3 mg/L.

Other variables. Serum C-reactive protein (CRP; milligrams per liter) and α1-glycoprotein (AGP; grams per liter) were analyzed with the use of the same ELISA method described above (23). These biomarkers were measured to detect the presence of inflammation and correct ferritin values if needed, as described below.

To measure the iron content of tube-well water, samples were collected from the tube-wells that were used as sources of drinking water in the households of a subsample of the women randomly selected for the biochemical assessment. Iron in tube-well water was measured immediately after collection of the water sample in milligrams per liter, to the nearest 0.2 mg/L, by using the Hach color disc test kit (model IR-18C).

Caregiver-reported data on adherence to LNS-PL, IFA, LNS-C, and MNPs at different points in time (e.g., pregnancy, 6–24 mo postpartum) were also collected by asking caregivers how often she or her child had consumed the nutrient supplements using 2 recall periods: the previous 6 mo and the previous week. Possible answers for the previous-6-mo recall period included the following: *1*) not at all, *2*) sometimes (1–3 d/wk), *3*) almost every day (4–6 d/wk), or *4*) regularly (every day); we defined high adherence as consuming the supplement "almost every day" or "regularly (every day)." For the previous-week recall period, we asked how many sachets the child consumed during that week and defined high adherence as consuming ≥8 sachets of LNSs (10 g each) or ≥4 sachets of MNPs.

Statistical analysis

Sample size calculations for child hemoglobin and micronutrient status were based on detecting an effect size (difference between the means of 2 groups, divided by the average SD) of ≥0.35 for each continuous outcome on the basis of previous evidence (26, 27). Assuming 80% power, a 95% level of significance, 2-sided hypothesis testing, a 0.01 intracluster correlation (ICC), and allowing for 25% attrition, 263 children per arm ($n = 1052$ total) were needed for the child biochemical subsample to detect such differences in continuous outcome variables.

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 (using a complete-case approach), and outcomes were measured at the individual participant level. To evaluate potential bias due to losses to follow-up, we compared baseline characteristics of the mothers whose children were selected for the biochemical subsample and included in this analysis with those who were selected but not included in this analysis with the use of a cluster-adjusted *t* test for continuous variables and Wald chi-square test for categorical variables.

For ferritin concentration, analyses were performed both with and without correction for the presence of inflammation. Correction for inflammation was done by using an adaptation of the approach proposed by Thurnham et al. (28), by mathematically adjusting individual values for the presence of inflammation using the following inflammation categories: reference (if CRP ≤5.0 mg/L and AGP ≤1.0 g/L), incubation (if CRP >5.0 mg/L and AGP ≤1.0 g/L), and convalescence (if AGP >1.0 g/L, regardless of CRP values). We combined the 2 convalescence categories proposed by Thurnham et al. (i.e., early and late convalescence) into 1 category (i.e., convalescence) because there were few cases in these categories. We computed adjustment factors with the use of the ratio of the geometric mean log of the ferritin variable in the reference category to the geometric mean log of the ferritin variable in each of the other 2 categories and applied the resulting correction factors to create corrected individual values for this variable.

Effects of the intervention were analyzed by using linear mixed-effects model ANCOVA for continuous outcomes, and mixed-effects logistic regression for dichotomous outcomes. All models included cluster ($n = 64$) nested within treatment group and union ($n = 11$) nested within subdistrict as random effects and treatment group as fixed effect. Corresponding ICCs were calculated for both cluster and union random effects. For continuous outcomes, we calculated group means and 95% CIs and tested for significant differences ($P < 0.05$). For binary outcomes, we calculated cluster-adjusted group proportions and based our statistical testing on the log odds of the outcomes. We also estimated RRs using an adaptation of the log-binomial model estimation methods proposed by McNutt et al. (29) to account for the random factors related to our design. For all of the analyses, when the global null hypothesis was rejected at $P < 0.05$, we performed post hoc Tukey-Kramer–adjusted pairwise comparisons. For models with continuous outcomes, residuals were assessed for conformance to the normal distribution; natural log transformations of the continuous variables ferritin, inflammation-corrected ferritin, and sTfR were used.

The following baseline variables were tested as potential covariates: maternal age, education, BMI, height, parity, gestational age at enrollment, and household socioeconomic status index and food security. In addition, child's sex, time of year at birth, and tube-well iron content were included as potential covariates. Covariates associated with an outcome ($P < 0.10$) were included in the adjusted analysis for that outcome.

One of the covariates, iron content in tube-well water, was collected in the maternal biochemical subsample only; thus, we imputed values for missing data with the use of tube-well iron content in the same village. For cases with no such information, we created a category for unknown value, and used the tube-well iron content variable as a categorical one (in quintiles).

Because of the Bangladesh government program distributing MNPs for children, we conducted a sensitivity analysis excluding children from the Badarganj subdistrict (who were more likely to have received MNPs from the government).

Analyses were conducted with the use of SAS software (version 9.4; SAS Institute, Inc.).

Results

We screened 4410 pregnant women for eligibility and enrolled 4011 (**Figure 1**) between 15 October 2011 and 31 August 2012. During enrollment, a total of 1346 (unborn) children were randomly assigned to the child biochemical subsample (353 in the LNS-LNS group, 311 in the IFA-LNS group, 353 in the IFA-MNP group, and 329 in the IFA-Control group). Maternal baseline characteristics among those randomly assigned compared with those not randomly assigned to the subsample were similar. Of these, 1226 live births occurred between 15 January 2012 and 5 May 2013 to women who remained in the study. Data from 7 sets of twins (out of 30 in the RDNS cohort) were available for biochemical outcomes, and 1 twin from each pair was randomly selected for analyses. Child biochemical data were available for 1121 children aged 18 mo (293 in the LNS-LNS group, 257 in the IFA-LNS group, 299 in the IFA-MNP group, and 272 in the IFA-Control group), corresponding to 33% of the total number of children in the study at 18 mo of age. Nine children in the biochemical subsample (evenly distributed across the 4 intervention groups) were referred for low hemoglobin (<80 g/L) during the follow-up period. Rates of losses to follow-up did not differ by intervention group ($P = 0.51$). Children included in this analysis did not differ from those not included with respect to the baseline characteristics of their mothers and households (data not shown), except for gestational age at enrollment

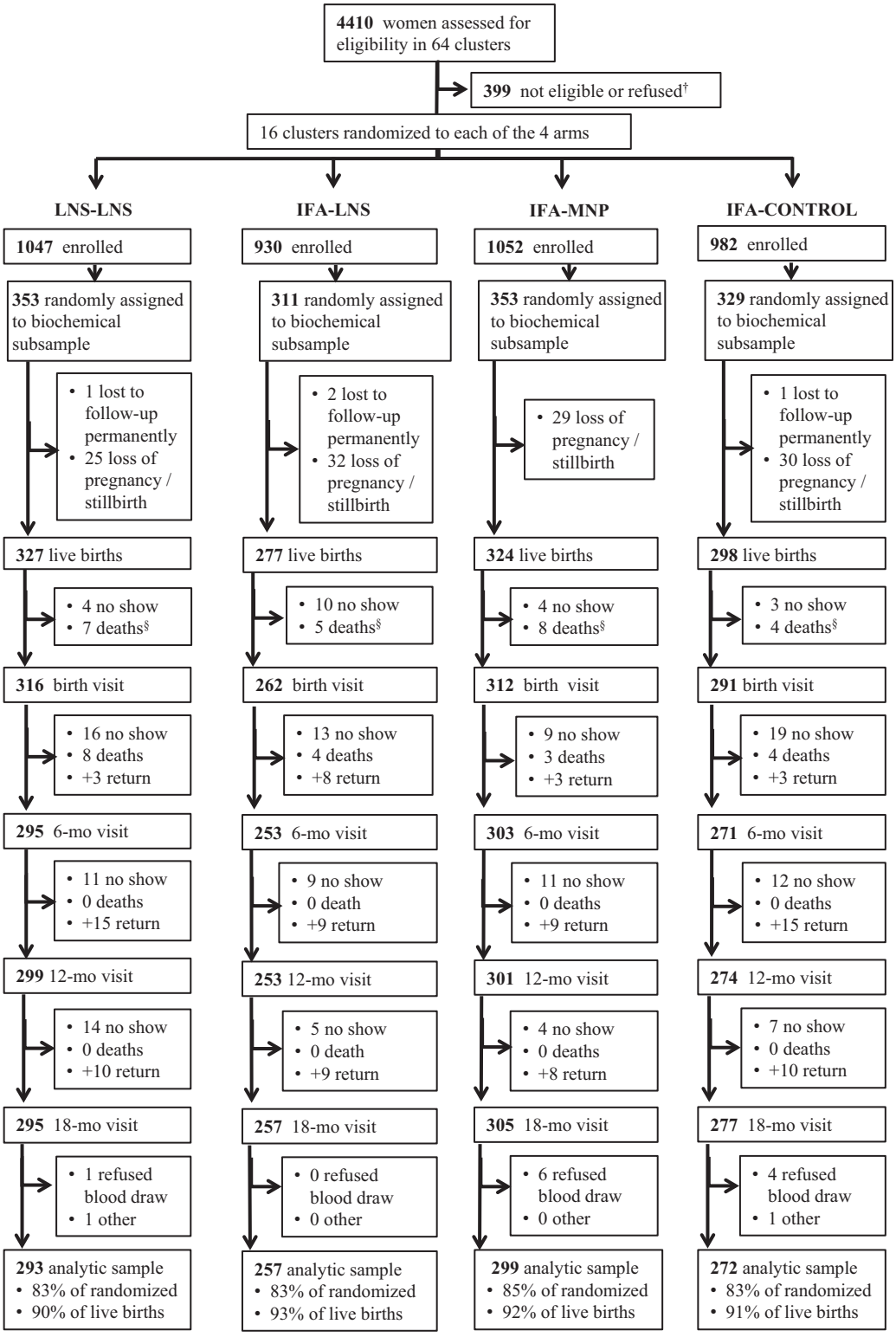

FIGURE 1 Study participation flow diagram. For twin births, numbers include 1 randomly selected twin from each twin pair. †Three hundred sixty-six with a gestational age >140 d; 22 planned to leave the study site; 8 refused; 3 husbands refused. §Most of these deaths occurred <14 d postpartum: 17 LNS-LNS, 15 IFA-LNS, 15 IFA-MNP, and 14 IFA-Control. IFA, iron and folic acid; IFA-Control, women who received IFA daily during pregnancy and every other day during the first 3 mo postpartum and their children received no supplements; IFA-LNS, women received IFA daily during pregnancy and every other day during the first 3 mo postpartum and their children received LNS-C from 6 to 24 mo of age; IFA-MNP, women received IFA daily during pregnancy and every other day during the first 3 mo postpartum and their children received micronutrient powder from 6 to 24 mo of age; LNS, lipid-based nutrient supplement; LNS-C, lipid-based nutrient supplement for children; LNS-LNS, women received LNS during pregnancy and the first 6 mo postpartum and their children received LNS-C from 6 to 24 mo of age; MNP, micronutrient powder.

TABLE 2 Baseline characteristics of women whose children were included in the biochemical analytic subsample at 18 mo of age[1]

Characteristic	LNS-LNS ($n = 293$)	IFA-LNS ($n = 257$)	IFA-MNP ($n = 299$)	IFA-Control ($n = 272$)
Age, y	22.0 ± 4.8	22.1 ± 4.9	22.3 ± 5.0	22.3 ± 5.4
Years of formal education	6.5 ± 3.2	6.1 ± 3.4	6.0 ± 3.3	6.1 ± 3.2
Socioeconomic index	0.03 ± 2.3	0.04 ± 2.3	−0.10 ± 2.2	0.03 ± 2.2
Food insecure, *n* (%)	150 (51.0)	141 (54.2)	150 (50.0)	145 (52.9)
Height, cm	151.0 ± 5.2	150.9 ± 5.6	150.7 ± 5.1	150.6 ± 5.6
BMI, kg/m^2	19.9 ± 2.6	20.0 ± 2.6	20.1 ± 2.6	20.0 ± 2.7
Nulliparous, *n* (%)	113 (38.4)	98 (37.7)	114 (38.1)	102 (37.2)
Gestational age, wk	12.8 ± 3.8	13.1 ± 3.7	12.9 ± 3.7	13.0 ± 3.8

[1] Values are means ± SDs unless otherwise specified, $n = 1121$. IFA, iron and folic acid; IFA-Control, women received IFA daily during pregnancy and every other day during the first 3 mo postpartum and their children received no supplements; IFA-LNS, women received IFA daily during pregnancy and every other day during the first 3 mo postpartum and their children received LNS-C from 6 to 24 mo of age; IFA-MNP, women received IFA daily during pregnancy and every other day during the first 3 mo postpartum and their children received MNP from 6 to 24 mo of age; LNS, lipid-based nutrient supplement; LNS-C, lipid-based nutrient supplement for children; LNS-LNS, women received LNS during pregnancy and the first 6 mo postpartum and their children received LNS-C from 6 to 24 mo of age; MNP, micronutrient powder.

(mean ± SD: 12.9 ± 3.7 wk for women whose children were included compared with 13.2 ± 3.8 wk for those not included; $P = 0.033$). The overall mean birth weight of children in the analytic sample was 2615 ± 400 g, 17% of them were born preterm (<37 wk of gestation), and 51% were female. Baseline characteristics of women whose children were included in this analysis were similar across intervention groups (Table 2). In addition, the distribution of children by time of year at birth, sex, and age at assessment did not differ by group ($P = 0.70$, 0.70. and 0.40, respectively). At 18 mo, 15.2% of children had elevated CRP (CRP >5.0 mg/L) and 33.5% had elevated AGP (AGP >1.0 g/L).

With regard to supplement consumption, the proportion of caregivers reporting high adherence to LNS-C or MNP consumption by their children did not differ between groups ($P = 0.816$ for previous-6-mo recall period and $P = 0.654$ for previous-week recall period). On the basis of the previous-6-mo recall, 93–96% (depending on the arm) of caregivers reported high adherence at 12 mo and 95–96% did so at 18 mo. On the basis of the previous-week recall, these reports were 78–80% at 12 mo and 83–85% at 18 mo.

Hemoglobin and anemia

Overall mean hemoglobin concentration at 18 mo was 115.2 g/L (95% CI: 114.4, 115.9 g/L; ICC for cluster: 0.003; ICC for union: 0.0) and 31.9% of children were anemic (ICC for cluster: 0.041; ICC for union: 0.0). The distribution of anemia by severity was as follows: 21.1% had mild anemia (i.e., hemoglobin 100–109 g/L), 10.7% had moderate anemia (hemoglobin 70–99 g/L), and only 1 (out of 1120) had severe anemia (hemoglobin <70 g/L).

Table 3 shows that there were significant differences between intervention groups in children's hemoglobin concentration. Pairwise tests between groups indicated that the LNS-LNS ($P < 0.001$), IFA-LNS ($P = 0.032$), and IFA-MNP ($P = 0.065$) groups all differed (positively) from the IFA-Control group, although the difference between children in the IFA-MNP and IFA-Control groups was only marginally significant. In adjusted analyses, only the difference between the LNS-LNS and IFA-Control group remained significant (Supplemental Table 1). The prevalence of anemia was significantly different between intervention groups (Table 4). Pairwise comparisons indicated that children in the LNS-LNS group had lower odds of anemia than those in the IFA-Control group ($P = 0.007$), whereas differences between the IFA-LNS and IFA-Control groups, and between the IFA-MNP and the IFA-Control groups, tended toward significance ($P = 0.080$ and 0.094, respectively). After adjustment for prespecified covariates, the difference between the IFA-MNP and the IFA-Control groups was attenuated (Supplemental Table 2).

Ferritin

The overall geometric mean for (uncorrected) ferritin at 18 mo was 34.6 μg/L (95% CI: 33.2, 36.0 μg/L; ICC for cluster: 0.0;

TABLE 3 Continuous biochemical outcomes among children at 18 mo of age, by treatment group[1]

Outcome	LNS-LNS ($n = 293$)	IFA-LNS ($n = 257$)	IFA-MNP ($n = 299$)	IFA-Control ($n = 272$)	*P*
Hemoglobin, g/L	117.3 (115.8, 118.7)[a]	115.6 (114.1, 117.2)[a]	115.2 (113.7, 116.6)[a,b]	112.4 (110.8, 114.0)[b]	0.001
Ferritin,[2] μg/L	36.6 [34.0, 39.2][a]	40.2 [37.3, 43.5][a]	38.0 [35.2, 41.2][a]	25.5 [23.4, 27.8][b]	<0.001
Corrected ferritin,[2,3] μg/L	33.5 [31.1, 35.9][a]	35.9 [33.3, 38.7][a]	33.4 [31.1, 36.1][a]	22.8 [21.1, 24.9][b]	<0.001
sTfR,[2] mg/L	7.9 [7.6, 8.1][a]	8.4 [8.1, 8.8][a,b]	8.5 [8.2, 8.8][b]	9.4 [9.0, 9.8][c]	<0.001

[1] Values are arithmetic means (95% CIs) or geometric means [95% CIs]. Means in a row without a common letter differ, $P < 0.05$. *P* values were obtained by using mixed-effects ANCOVA. For global null hypotheses rejected at the 0.05 level, significant post hoc pairwise comparisons between treatment groups were conducted by using Tukey-Kramer correction. IFA, iron and folic acid; IFA-Control, women received IFA daily during pregnancy and every other day during the first 3 mo postpartum and their children received no supplements; IFA-LNS, women received IFA daily during pregnancy and every other day during the first 3 mo postpartum and their children received LNS-C from 6 to 24 mo of age; IFA-MNP, women received IFA daily during pregnancy and every other day during the first 3 mo postpartum and their children received MNP from 6 to 24 mo of age; LNS, lipid-based nutrient supplement; LNS-C, lipid-based nutrient supplement for children; LNS-LNS, women received LNS during pregnancy and the first 6 mo postpartum and their children received LNS-C from 6 to 24 mo of age; MNP, micronutrient powder; sTfR, soluble transferrin receptor.
[2] Hypothesis testing was conducted by using transformed (natural logarithm) values; estimates were calculated by back transformation.
[3] Values were corrected for presence of inflammation (C-reactive protein >5.0 mg/L or α1-glycoprotein >1.0 g/L).

TABLE 4 Dichotomous biochemical outcomes among children at 18 mo of age, by treatment group[1]

Outcome	LNS-LNS ($n = 293$)	IFA-LNS ($n = 257$)	IFA-MNP ($n = 299$)	IFA-Control ($n = 272$)	P
Anemia[2]					
%	25.9[a]	29.3[a,b]	30.8[a,b]	41.9[b]	0.009
OR (95% CI)	0.46 (0.25, 0.84)	0.57 (0.31, 1.05)	0.59 (0.33, 1.06)	—	
RR	0.59	0.69	0.70	—	
Low ferritin[3]					
%	3.8[a]	4.3[a]	7.0[a,b]	13.2[b]	<0.001
OR (95% CI)	0.25 (0.10, 0.66)	0.29 (0.11, 0.76)	0.49 (0.23, 1.06)	—	
RR	0.28	0.32	0.53	—	
Low inflammation-corrected ferritin[3]					
%	5.8[a]	5.1[a]	7.4[a]	17.6[b]	<0.001
OR (95% CI)	0.29 (0.13, 0.63)	0.25 (0.11, 0.59)	0.37 (0.18, 0.76)	—	
RR	0.33	0.29	0.42	—	
High sTfR[4]					
%	33.8[a]	44.7[a,b]	46.5[b]	52.2[b]	<0.001
OR (95% CI)	0.47 (0.29, 0.73)	0.73 (0.46, 1.15)	0.79 (0.51, 1.23)	—	
RR	0.65	0.86	0.90	—	
ID[5]					
%	35.2[a]	45.9[a,b]	48.2[b]	54.8[b]	<0.001
OR (95% CI)	0.45 (0.28, 0.71)	0.70 (0.44, 1.11)	0.77 (0.49, 1.20)	—	
RR	0.64	0.84	0.88	—	
IDA[6]					
%	12.6[a]	15.6[a]	16.4[a]	29.0[b]	<0.001
OR (95% CI)	0.35 (0.18, 0.67)	0.45 (0.24, 0.85)	0.47 (0.26, 0.87)	—	
RR	0.42	0.53	0.55	—	

[1] P values were obtained by using mixed-effects logistic regression. For global null hypotheses rejected at the 0.05 level, significant post hoc pairwise comparisons between treatment groups were conducted by using Tukey-Kramer correction. Percentages in a row without a common letter differ, $P < 0.05$. ID, iron deficiency; IDA, iron deficiency anemia; IFA, iron and folic acid; IFA-Control, women received IFA daily during pregnancy and every other day during the first 3 mo postpartum and their children received no supplements; IFA-LNS, women received IFA daily during pregnancy and every other day during the first 3 mo postpartum and their children received LNS-C from 6 to 24 mo of age; IFA-MNP, women received IFA daily during pregnancy and every other day during the first 3 mo postpartum and their children received MNP from 6 to 24 mo of age; LNS, lipid-based nutrient supplement; LNS-C, lipid-based nutrient supplement for children; LNS-LNS, women received LNS during pregnancy and the first 6 mo postpartum and their children received LNS-C from 6 to 24 mo of age; MNP micronutrient powder; sTfR, soluble transferrin receptor.
[2] Defined as hemoglobin <110 g/L.
[3] Defined as (inflammation-corrected) ferritin <12.0 μg/L.
[4] Defined as sTfR >8.3 mg/L.
[5] Defined as inflammation-corrected ferritin <12.0 μg/L or sTfR >8.3 mg/L.
[6] Defined as ID and hemoglobin <110 g/L.

ICC for union: 0.004), and 7.1% of children had low (uncorrected) ferritin (ICC for cluster: 0.0; ICC for union: 0.01). There were significant differences between intervention groups in children's ferritin concentrations, with or without correction for the presence of inflammation (Table 3). Pairwise tests between groups indicated that children in all 3 intervention groups had higher ferritin concentrations than those in the IFA-Control group ($P < 0.001$ for each group with the use of either uncorrected or inflammation-corrected ferritin values). The proportions of children with low ferritin (Table 4) were significantly different between intervention groups, based on both uncorrected and inflammation-corrected values. Pairwise comparisons indicated lower odds of low ferritin in the LNS-LNS ($P = 0.002$ for uncorrected and $P = 0.001$ for inflammation-corrected values), IFA-LNS ($P = 0.006$ for uncorrected and $P < 0.001$ for inflammation-corrected values), and IFA-MNP ($P = 0.003$ for inflammation-corrected values) groups than in the IFA-Control group, although the difference between the IFA-MNP and IFA-Control groups when ferritin values were uncorrected did not reach significance ($P = 0.079$). Adjustment for predetermined covariates yielded similar results (Supplemental Tables 1 and 2).

sTfR

The overall geometric mean for sTfR at 18 mo was 8.5 mg/L (95% CI: 8.3, 8.7 mg/L; ICC for cluster: 0.0; ICC for union: 0.004), and 44.2% of children had high sTfR (ICC for cluster: 0.0; ICC for union: 0.0). There were significant differences between intervention groups in children's sTfR concentrations (Table 3). Pairwise tests between groups indicated that the LNS-LNS, IFA-LNS, and IFA-MNP groups all had lower concentrations (i.e., higher iron status) than did the IFA-Control group ($P < 0.001$, $P = 0.001$, and $P = 0.001$, respectively). In addition, the LNS-LNS group had lower sTfR than the IFA-MNP group ($P = 0.037$) and tended to have lower values than those in the IFA-LNS group ($P = 0.060$). In adjusted analysis, the difference in sTfR concentration between the LNS-LNS and the IFA-MNP group was attenuated ($P = 0.083$). There were significant differences between groups in the proportions of children with high sTfR (Table 4). Pairwise comparisons indicated that only children in the LNS-LNS group had lower odds of high sTfR, compared with the IFA-Control group ($P < 0.001$). Decreased odds of high sTfR were also observed in the LNS-LNS group when the IFA-MNP group was the reference ($P = 0.014$), whereas a tendency toward decreased odds was seen when IFA-LNS was

the reference group ($P = 0.052$). Adjustment for prespecified covariates yielded similar results (Supplemental Tables 1 and 2).

ID

The overall prevalence of ID at 18 mo was 45.7% (ICC for cluster: 0.0; ICC for union: 0.0). Table 4 shows that there were significant differences between intervention groups in the prevalence of ID. Pairwise tests between groups indicated that the odds of ID were lower in the LNS-LNS group than in the IFA-Control group ($P < 0.001$), and also lower than those in the IFA-MNP group ($P = 0.012$). In addition, children in the LNS-LNS group tended to have decreased odds of ID compared with those in the IFA-LNS group ($P = 0.061$). Similar results were observed after adjustment for covariates (Supplemental Table 2).

IDA

The overall prevalence of IDA at 18 mo was 19.3% (ICC for cluster: 0.025; ICC for union: 0.0). There were significant differences between intervention groups in the prevalence of IDA (Table 4). Pairwise tests between groups indicated that children in all 3 intervention groups had lower odds of IDA than did those in the IFA-Control group ($P < 0.001$ for LNS-LNS, $P = 0.013$ for IFA-LNS, and $P = 0.016$ for IFA-MNP). Adjustment for predetermined covariates did not change these results (Supplemental Table 2).

Sensitivity analyses

Results of the sensitivity analyses ($n = 594$) excluding children from the subdistrict that received the government MNP program were similar to those reported above (data not shown).

Discussion

All 3 RDNS interventions (i.e., provision of LNSs to both mother and child, provision of LNSs to the child only, and provision of MNPs to the child only) resulted in significant improvements in child hemoglobin and iron status at 18 mo, with the LNS-LNS group showing the strongest and most consistent differences relative to the control group. Significant reductions in anemia and ID were seen only in the LNS-LNS group, but all 3 RDNS interventions reduced the prevalence of IDA compared with the control group.

Our results are generally consistent with those of other studies on the effects of both MNPs and LNSs on hemoglobin and iron status of young children. In a meta-analysis of MNP studies (5–15 micronutrients including 12.5 mg Fe), the mean hemoglobin of children receiving MNPs was 5.9 g/L higher compared with that of children receiving no treatment or placebo (12). Similar results have been achieved with LNSs for children in Ghana (13) and Burkina Faso (14), although it should be noted that children in the LNS intervention group in the latter study also received treatment for diarrhea and malaria, which may have contributed to the effect. In our study, the increase in hemoglobin in the LNS-LNS group (+5 g/L) was comparable to the pooled effect in the MNP meta-analysis, but smaller increases were seen in the IFA-LNS and IFA-MNP groups. This may be explained by the fact that our study was an effectiveness trial, not an efficacy trial, although adherence to LNS-C and MNPs was reported to be high. With regard to markers of iron status, we found that ferritin increased and sTfR decreased significantly in all 3 intervention groups compared with the control group, which is consistent with the meta-analysis of MNP interventions (12) and other studies of LNSs for children (13, 14). However, the prevalence of ID at age 18 mo was significantly lower only in the LNS-LNS group (35.2% compared with 54.8% in the control group) and was significantly lower in the LNS-LNS group than in the IFA-MNP group (48.2%). Similarly, only the LNS-LNS group exhibited a significant reduction in anemia prevalence (a decrease of 41% compared with the control group, which compares favorably with the estimated anemia reduction of 31% in the meta-analysis of MNP interventions) (12). This suggests that maternal supplementation with LNSs pre- and postpartum might have played a role. Women in the LNS-LNS group received less iron during pregnancy (20 mg/d) than did those in the other 3 groups (60 mg/d), yet their children at age 18 mo had the highest hemoglobin concentrations and the lowest prevalence of ID and anemia. It is not likely that the iron received postpartum by mothers in the LNS group is responsible for these differences, because the other 3 groups also received iron during the postpartum period (albeit for 3 mo rather than 6 mo), and maternal iron intake during lactation is not related to breast-milk iron concentrations (30). One possibility is that the vitamin A and B vitamins in LNS-PL may have influenced the child's iron status and risk of anemia, through prenatal or postnatal (i.e., via breast-milk composition) mechanisms. Vitamin A is important for iron metabolism (31), and maternal intake of vitamin A during lactation is known to affect milk vitamin A content (32), which could have influenced the infant's vitamin A and iron status. Vitamin B-12 deficiency can result in anemia due to ineffective erythropoiesis (33), and maternal vitamin B-12 status during pregnancy and lactation influences the newborn's vitamin B-12 status (34) and intake of vitamin B-12 from human milk (32, 35). It is also possible that prenatal or postnatal LNSs (or both) may have affected the infants' immune function or gut inflammation, which, in turn, could have improved iron absorption.

Although anemia was significantly reduced only in the LNS-LNS group, all 3 intervention groups experienced large relative reductions in IDA. Compared with the control group, the relative reductions were 45% in the IFA-MNP group, 47% in the IFA-LNS group, and 58% in the LNS-LNS group. These effects are similar to those reported in another meta-analysis of MNP supplementation (RR: 0.43; 95% CI: 0.35, 0.52) (36). Our results confirm that the provision of LNSs or MNPs to children is effective for reducing IDA, but suggest that reduction in all-cause anemia in Bangladeshi children may require a broader approach, including prenatal nutrition as well as attention to non-nutritional causes of anemia, such as infectious diseases and certain parasites.

Strengths of this study include the use of a randomized design with 16 clusters/arm, a large sample representative of the target population, and a low and balanced attrition rate. An important limitation of this study was our inability to blind participants to the intervention because of differences in appearance and taste of the study supplements. Other limitations were that our assessment of adherence was based on caregivers' report and thus may be biased, and we may have lacked sufficient statistical power to detect small but meaningful differences in the dichotomous outcomes because our sample size calculations were based on the continuous outcomes.

We conclude that all 3 RDNS interventions were effective in improving iron status and reducing IDA in Bangladeshi children. However, the effects were strongest and most consistent in the LNS-LNS group, and the reduction in overall anemia was significant only in that group. Because this study was

conducted within a community-based health program, the findings are relevant to programs targeting similar populations. The programmatic implications depend on the goals of decision-makers. We previously reported that all 3 RDNS interventions improved child development outcomes (17), whereas increased child linear growth and head size at age 24 mo were seen only when LNSs were provided to both the mother and child (16). Thus, if the goal of program planners is to reduce IDA or improve child development but not necessarily growth or overall anemia prevalence, all 3 interventions tested in the RDNS appear to be effective. However, if reductions in stunting and overall anemia prevalence are a high priority, LNS provision to both pregnant women and their children appears to be most effective in this setting.

Acknowledgments

We thank Camila Chaparro, Zeina Maalouf-Manasseh, and Megan Deitchler from FANTA; Rina Rani Paul, Sohrab Hussain, Mostofa Sarker, Mokbul Hossain, Md Rabiul Islam, Abu Emran Md Motiur Rahman, Md Nurunnabi Ashakhy, Golam Sarwar, Jyotish Chadra Mallik, Atikul Islam Shah, and other collaborators from icddr,b; Stacy Saha, Louise Tina Day, Swapan Pahan, Altaf Hossain, Pronoy Ganguly, and other collaborators from LAMB; and Steve Vosti, Joseph Cummins, Kassandra Harding, and Charles Arnold from the University of California, Davis, for their technical input and support during the implementation of the study. We also thank Juergen Erhardt from the VitMin Lab, Willstaett, Germany, for the analysis of blood samples. The authors' responsibilities were as follows—SLM, MKM, SAV, and KGD: designed the research; MKM, MSAK, ZS, and MBU: implemented the research; RTY: performed the statistical analysis; SLM: supervised the statistical analysis, wrote the first draft of the manuscript, and had primary responsibility for final content; KGD: was the principal investigator for the overall project; and all authors: read and approved the final manuscript.

References

1. Stevens GA, Finucane MM, De-Regil LM, Paciorek CJ, Flaxman SR, Branca F, Peña-Rosas JP, Bhutta ZA, Ezzati M. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data. Lancet Glob Health 2013;1(1):e16–25.
2. Ahmed F, Khan MR, Banu CP, Qazi MR, Akhtaruzzaman M. The coexistence of other micronutrient deficiencies in anaemic adolescent schoolgirls in rural Bangladesh. Eur J Clin Nutr 2008;62(3):365–72.
3. Gonzales E, Huamán-Espino L, Gutiérrez C, Aparco JP, Pillaca J. Characterization of anemia in children under 5 y in urban areas in Huancavelica and Ucayali in Peru. Rev Peru Med Exp Public Health 2015;32:431–9.
4. Petry N, Olofin I, Hurrell R, Boy E, Wirth J, Moursi M, Donahue Angel M, Rohner F. The proportion of anemia associated with iron deficiency in low, medium, and high human development index countries: a systematic analysis of national surveys. Nutrients 2016;8(11):693.
5. Khan JR, Awan N, Misu F. Determinants of anemia among 6–59 months aged children in Bangladesh: evidence from nationally representative data. BMC Pediatr 2016;16(1):3.
6. Rawat R, Saha KK, Kennedy A, Rohner F, Ruel M, Menon P. Anaemia in infancy in rural Bangladesh: contribution of iron deficiency, infections and poor feeding practices. Br J Nutr 2014;111(1):172–81.
7. Chang S, Wang L, Wang Y, Brouwer ID, Kok FJ, Lozoff B, Chen C. Iron-deficiency anemia in infancy and social emotional development in preschool-aged Chinese children. Pediatrics 2011;127(4):e927–33.
8. Carter RC, Jacobson JL, Burden MJ, Armony-Sivan R, Dodge NC, Angelilli ML, Lozoff B, Jacobson SW. Iron deficiency anemia and cognitive function in infancy. Pediatrics 2010;126(2):e427–34.
9. Shafir T, Angulo-Barroso R, Jing Y, Angelilli ML, Jacobson SW, Lozoff B. Iron deficiency and infant motor development. Early Hum Dev 2008;84(7):479–85.
10. Lozoff B, Beard J, Connor J, Felt B, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev 2006;64(5 Part 2):S34–91.
11. Home Fortification Technical Advisory Group. Home page [Internet]. [cited 2016 Dec 29]. Available from: http://www.hftag.org/page.asp?content_id=33983.
12. De-Regil LM, Suchdev PS, Vist GE, Walleser S, Peña-Rosas JP. Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age [review]. Evid Based Child Health 2013;8(1):112–201.
13. Adu-Afarwuah S, Lartey A, Brown K, Zlotkin S, Briend A, Dewey K. Home fortification of complementary foods with micronutrient supplements is well accepted and has positive effects on infant iron status in Ghana. Am J Clin Nutr 2008;87(4):929–38.
14. Abbeddou S, Yakes Jimenez E, Somé JW, Ouédraogo JB, Brown KH, Hess SY. Small-quantity lipid-based nutrient supplements containing different amounts of zinc along with diarrhea and malaria treatment increase iron and vitamin A status and reduce anemia prevalence, but do not affect zinc status in young Burkinabe children: a cluster-randomized trial. BMC Pediatr 2017;17(1):46.
15. Mridha MK, Matias SL, Chaparro CM, Paul RR, Hussain S, Vosti SA, Harding KL, Cummins JR, Day LT, Saha SL, et al. Lipid-based nutrient supplements for pregnant women reduce newborn stunting in a cluster-randomized controlled effectiveness trial in Bangladesh. Am J Clin Nutr 2016;103(1):236–49.
16. Dewey KG, Mridha MK, Matias SL, Arnold CD, Cummins JR, Khan MSA, Maalouf-Manasseh Z, Siddiqui Z, Ullah MB, Vosti SA. Lipid-based nutrient supplementation in the first 1000 d improves child growth in Bangladesh: a cluster-randomized effectiveness trial. Am J Clin Nutr 2017;105(4):944–57.
17. Matias SL, Mridha MK, Tofail F, Arnold CD, Khan MSA, Siddiqui Z, Ullah MB, Dewey KG. Home fortification during the first 1000 d improves child development in Bangladesh: a cluster-randomized effectiveness trial. Am J Clin Nutr 2017;105(4):958–69.
18. Institute of Medicine. Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington (DC): National Academies Press; 2001.
19. Matias SL, Mridha MK, Paul RR, Hussain S, Vosti SA, Arnold CD, Dewey KG. Prenatal lipid-based nutrient supplements affect maternal anthropometric indicators only in certain subgroups of rural Bangladeshi women. J Nutr 2016;146(9):1775–82.
20. WHO. Guideline: daily iron and folic acid supplementation in pregnant women. Geneva (Switzerland): WHO; 2012.
21. Adu-Afarwuah S, Lartey A, Okronipa H, Ashorn P, Peerson JM, Arimond M, Ashorn U, Zeilani M, Vosti S, Dewey KG. Small-quantity, lipid-based nutrient supplements provided to women during pregnancy and 6 mo postpartum and to their infants from 6 mo of age increase the mean attained length of 18-mo-old children in semi-urban Ghana: a randomized controlled trial. Am J Clin Nutr 2016;104(3):797–808.
22. Ashorn P, Alho L, Ashorn U, Cheung YB, Dewey KG, Gondwe A, Harjunmaa U, Lartey A, Phiri N, Phiri TE, et al. Supplementation of maternal diets during pregnancy and for 6 months postpartum and infant diets thereafter with small-quantity lipid-based nutrient supplements does not promote child growth by 18 months of age in rural Malawi: a randomized controlled trial. J Nutr 2015;145(6):1345–53.
23. Erhardt JG, Estes JE, Pfeiffer CM, Biesalski HK, Craft NE. Combined measurement of ferritin, soluble transferrin receptor, retinol binding protein, and C-reactive protein by an inexpensive, sensitive, and simple sandwich enzyme-linked immunosorbent assay technique. J Nutr 2004;134(11):3127–32.
24. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva (Switzerland): WHO; 2011. (Publication WHO/NMH/NHD/MNM/111.)
25. WHO. Iron deficiency anemia: assessment, prevention, and control. A guide for programme managers. Geneva (Switzerland): WHO; 2001. (Publication WHO/NHD/013.)

26. Allen L, Peerson J. Impact of multiple micronutrient versus iron-folic acid supplements on maternal anemia and micronutrient status in pregnancy. Food Nutr Bull 2009;30(4):S527–32.
27. Dewey K, Yang Z, Boy E. Systematic review and meta-analysis of home fortification of complementary foods. Matern Child Nutr 2009;5:283–321.
28. Thurnham DI, McCabe LD, Haldar S, Wieringa FT, Northrop-Clewes CA, McCabe GP. Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: a meta-analysis. Am J Clin Nutr 2010;92(3):546–55.
29. McNutt L-A, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol 2003;157(10):940–3.
30. Lönnerdal B. Trace element transport in the mammary gland. Annu Rev Nutr 2007;27(1):165–77.
31. Zimmermann MB, Biebinger R, Rohner F, Dib A, Zeder C, Hurrell RF, Chaouki N. Vitamin A supplementation in children with poor vitamin A and iron status increases erythropoietin and hemoglobin concentrations without changing total body iron. Am J Clin Nutr 2006;84(3):580–6.
32. Allen LH. Multiple micronutrients in pregnancy and lactation: an overview. Am J Clin Nutr 2005;81(Suppl):1206S–12S.
33. Koury MJ, Ponka P. New insights into erythropoiesis: the roles of folate, vitamin B12, and iron. Annu Rev Nutr 2004;24(1):105–31.
34. Molloy AM, Kirke PN, Brody LC, Scott JM, Mills JL. Effects of folate and vitamin B12 deficiencies during pregnancy on fetal, infant, and child development. Food Nutr Bull 2008;29(2 Suppl 1):S101–11.
35. Duggan C, Srinivasan K, Thomas T, Samuel T, Rajendran R, Muthayya S, Finkelstein JL, Lukose A, Fawzi W, Allen LH, et al. Vitamin B-12 supplementation during pregnancy and early lactation increases maternal, breast milk, and infant measures of vitamin B-12 status. J Nutr 2014;144(5):758–64.
36. Salam RA, MacPhail C, Das JK, Bhutta ZA. Effectiveness of micronutrient powders (MNP) in women and children. BMC Public Health 2013;13(3):S22.