Title

Lipid-based nutrient supplements for pregnant women reduce newborn stunting in a cluster-randomized controlled effectiveness trial in Bangladesh 1 , 2

Journal

American Journal of Clinical Nutrition, 103(1)

ISSN

0002-9165

Authors

Mridha, Malay K

Matias, Susana L

Chaparro, Camila M

et al.

Publication Date

2016

DOI

10.3945/ajcn.115.111336

Peer reviewed

Lipid-based nutrient supplements for pregnant women reduce newborn stunting in a cluster-randomized controlled effectiveness trial in Bangladesh[1,2]

*Malay K Mridha,[3,6] Susana L Matias,[3] Camila M Chaparro,[7] Rina R Paul,[6,9] Sohrab Hussain,[6,10] Stephen A Vosti,[4] Kassandra L Harding,[3] Joseph R Cummins,[5] Louise T Day,[8] Stacy L Saha,[8] Janet M Peerson,[3] and Kathryn G Dewey[3]**

Departments of [3]Nutrition and [4]Agricultural and Resource Economics, University of California, Davis, Davis, CA; [5]Department of Economics, University of California, Riverside, Riverside, CA; [6]International Center for Diarrheal Disease Research, Dhaka, Bangladesh; [7]Consultant, Milton, MA; and [8]LAMB, Dinajpur, Bangladesh

ABSTRACT

Background: Maternal undernutrition and newborn stunting [birth length-for-age *z* score (LAZ) <−2] are common in Bangladesh.

Objective: The objective was to evaluate the effect of lipid-based nutrient supplements for pregnant and lactating women (LNS-PLs) on birth outcomes.

Design: We conducted a cluster-randomized effectiveness trial (the Rang-Din Nutrition Study) within a community health program in rural Bangladesh. We enrolled 4011 pregnant women at ≤20 gestational weeks; 48 clusters received iron and folic acid (IFA; 60 mg Fe + 400 μg folic acid) and 16 clusters received LNS-PLs (20 g/d, 118 kcal) containing essential fatty acids and 22 vitamins and minerals. Both of the supplements were intended for daily consumption until delivery. Primary outcomes were birth weight and length.

Results: Infants in the LNS-PL group had higher birth weights (2629 ± 408 compared with 2588 ± 413 g; $P = 0.007$), weight-for-age *z* scores (−1.48 ± 1.01 compared with −1.59 ± 1.02; $P = 0.006$), head-circumference-for-age *z* scores (HCZs; −1.26 ± 1.08 compared with −1.34 ± 1.12; $P = 0.028$), and body mass index *z* scores (−1.57 ± 1.05 compared with −1.66 ± 1.03; $P = 0.005$) than those in the IFA group; in adjusted models, the differences in length (47.6 ± 0.07 compared with 47.4 ± 0.04 cm; $P = 0.043$) and LAZ (−1.15 ± 0.04 compared with −1.24 ± 0.02; $P = 0.035$) were also significant. LNS-PLs reduced the risk of newborn stunting (18.7% compared with 22.6%; RR: 0.83; 95% CI: 0.71, 0.97) and small head size (HCZ <−2) (20.7% compared with 24.9%; RR: 0.85; 95% CI: 0.73, 0.98). The effects of LNS-PL on newborn stunting were greatest in infants born before a 10-wk interruption in LNS-PL distribution ($n = 1301$; 15.7% compared with 23.6%; adjusted RR: 0.69; 95% CI: 0.53, 0.89) and in infants born to women ≤24 y of age or with household food insecurity.

Conclusion: Prenatal lipid-based nutrient supplements can improve birth outcomes in Bangladeshi women, especially those at higher risk of fetal growth restriction. This trial was registered at clinicaltrials.gov as NCT01715038. *Am J Clin Nutr* 2016;103:236–49.

Keywords: lipid-based nutrient supplements, head circumference, iron and folic acid, low birth weight, newborn stunting

INTRODUCTION

The prevalence of low birth weight (LBW)[11] in South Asia is estimated to be ∼30%, accounting for half of all LBW infants in the world (1). In Bangladesh, the prevalence of LBW is 37% (2); in addition, >20% of infants are born stunted [length-for-age *z* score (LAZ) <−2] and >30% are wasted [weight-for-length *z* score (WLZ) <−2] at birth (3). Fetal growth restriction is associated with poor subsequent growth and development and also greater vulnerability to certain chronic diseases in adulthood (1, 4). The economic consequences of fetal growth restriction may also be substantial (5). Although Bangladesh has made progress in reducing child mortality (3), there has been less improvement in anthropometric indicators. For example,

[1] Supported by the US Agency for International Development's Food and Nutrition Technical Assistance III Project (FANTA), managed by Family Health International 360.

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

[9] Present address: CARE (Cooperative for Assistance and Relief Everywhere) Bangladesh, Dhaka, Bangladesh.

[10] Present address: Save the Children International, Dhaka, Bangladesh.

*To whom correspondence should be addressed. E-mail: kgdewey@ucdavis.edu.

[11] Abbreviations used: BMIZ, BMI-for-age *z* score; CHDP, Community Health and Development Program; CHW, community health worker; HCZ, head-circumference-for-age *z* score; ICDDR,B, International Center for Diarrheal Disease Research, Bangladesh; IFA, iron and folic acid; LAZ, length-for-age *z* score; LBW, low birth weight; LMP, last menstrual period; LNS, lipid-based nutrient supplement; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women; MMN, multiple micronutrient; MNP, micronutrient powder; MUAC, midupper arm circumference; RDNS, Rang-Din Nutrition Study; SGA, small for gestational age; SDU, safe delivery unit; UC Davis, University of California, Davis; UNIMMAP, UNICEF/WHO/United Nations University international multiple micronutrient preparation; VHV, village health volunteer; WAZ, weight-for-age *z* score.

Received March 14, 2015. Accepted for publication October 9, 2015.

First published online November 25, 2015; doi: 10.3945/ajcn.115.111336.

Supplemental Material can be found at:
http://ajcn.nutrition.org/content/suppl/2015/11/25/ajcn.115.111336.DCSupplemental.html

between 2007 and 2014, the prevalence of childhood stunting decreased from 43% to 36% (3).

Numerous factors, including maternal malnutrition, contribute to poor birth outcomes (6). Moreover, the degree of micronutrient inadequacy among women in rural Bangladesh is alarming (7). The most common approaches for addressing maternal malnutrition include iron and folic acid supplementation, balanced energy protein supplementation, and multiple micronutrient (MMN) supplementation. Daily or intermittent iron supplementation is effective for reducing maternal anemia and iron deficiency and the incidence of LBW (8). Balanced energy-protein supplementation has been shown to reduce the incidence of small-for-gestational-age (SGA) births by 34% and to increase birth weight by 73 g (9). MMN supplementation is as effective as iron and folic acid in reducing anemia and LBW (10) but may provide additional benefits, including a reduction in SGA and preterm birth (11). A new approach to provide both micronutrients and some key macronutrients, including essential fatty acids, is the use of small-quantity (20 g/d) lipid-based nutrient supplements (LNSs) for enriching home-based foods for pregnant and lactating women (12). Such supplements, herein referred to as LNSs for pregnant and lactating women (LNS-PLs), are similar in ingredients to LNSs used for enriching complementary foods for infants (13, 14) but are fortified with the amounts of micronutrients needed during pregnancy and lactation.

We previously reported that LNS-PLs were well accepted in Bangladesh (15). We subsequently implemented the Rang-Din Nutrition Study (RDNS) in rural Bangladesh to evaluate the effectiveness, within a community-based program, of a 2-pronged approach aimed at preventing maternal and child undernutrition during the first "1000 days": provision of LNS-PLs to women during pregnancy and the first 6 mo postpartum and another formulation of LNSs to their offspring from 6 to 24 mo of age. Our hypothesis was that this approach would result in larger positive changes in maternal and child health and nutrition indicators of the study participants than the current standard of care in Bangladesh, which is the provision of iron and folic acid during pregnancy and the postpartum period. This article reports the effects of LNS-PL supplementation on birth outcomes. To our knowledge, it is the first evaluation of LNS-PLs in the context of an effectiveness trial.

METHODS

Study setting, population, and role of study partners

The study was conducted in 11 rural unions of the Badarganj and Chirirbandar subdistricts of the northwest region of Bangladesh, ~340 km northwest of Dhaka. A union is the lowest administrative unit of the local government of Bangladesh; in 2011, the total population in the study unions was 279,614 (16). The study subdistricts were located in one of the poorest areas of Bangladesh, with ≥48% of people living below the poverty line; in 2011, the average household size was 4, 52% of the population aged >7 y of age were illiterate, 31% of households had electricity, 98% had access to safe drinking water, and 75% had access to toilets or latrines (16). The major economic activities in the area included farming, transportation, construction, and petty trading.

Health services in the area were provided by both the public and private sectors. In each union, there were 3–4 public health facilities that provided primarily maternal and child health services. A number of nongovernment organizations, including LAMB (previously known as Lutheran Aid to Medicine in Bangladesh) and BRAC (previously known as Bangladesh Rural Advancement Committee), also provided community-based health services for women and children. The health services from LAMB, one of the partners for this study, were provided through its Community Health and Development Program (CHDP). For pregnant women, these health services included maternity services at a safe delivery unit (SDU) in each union and regular home visits.

The study was carried out by 3 partners: LAMB; the International Center for Diarrheal Disease Research, Bangladesh (ICDDR,B); and the University of California, Davis (UC Davis). LAMB was responsible for providing the study interventions to the study population, including delivery of nutrient supplements (described below). ICDDR,B and UC Davis jointly evaluated the interventions.

Study design, sample size, and randomization

The overall aim of the RDNS was to evaluate the impact of nutrient supplementation during the first 1000 d on nutritional status of pregnant and lactating women and on growth, nutritional status, and development of their children. The trial was designed as a researcher-blind, longitudinal, cluster-randomized effectiveness trial with 4 arms in a ratio of 1:1:1:1. The study arms were as follows: *1*) comprehensive LNS group, in which women received LNS-PLs (**Table 1**) during pregnancy and the first 6 mo postpartum and their children received LNSs for children from 6 to 24 mo of age; *2*) child-only LNS group, in which women received 1 tablet of 60 mg iron and 400 μg folic acid (IFA) daily during pregnancy (the standard of care) and every alternate day during the first 3 mo postpartum and their children received LNSs for children from 6 to 24 mo of age; *3*) child-only micronutrient powder (MNP) group, in which women received IFA daily during pregnancy and every alternate day during the first 3 mo postpartum and their children received MNP containing 15 micronutrients from 6 to 24 mo of age; and *4*) control group, in which the women received IFA daily during pregnancy and every alternate day during the first 3 mo postpartum and their children received no supplements. We calculated a minimum required sample size of 788 per arm (total of 3152 in 4 arms) on the basis of detecting an effect size of ≥0.2 (difference between groups, divided by pooled SD) for each continuous outcome with power = 80% and α = 0.05, assuming an intracluster correlation = 0.01, and allowing for up to 20% attrition by the end of the study (i.e., when the children reached 24 mo). Because seasonality was reported to be associated with some of the key outcomes of the study (e.g., birth weight) (17), we planned to recruit the women over a 1-y period so that all seasons would be represented.

We defined a cluster as the supervision area of a community health worker (CHW) of LAMB. Each cluster covered a population of ~2500–6000 people and had 3–6 village health volunteers (VHVs) to assist the CHW. The study was implemented in all 64 clusters within the 11 study unions. Each study arm included 16 clusters. We chose a cluster-randomized

TABLE 1
Composition of supplements used in the study[1]

Nutrient	LNS-PL[2]	IFA tablet[3]
Ration, g/d	20	—
Total energy, kcal	118	—
Protein, g	2.6	—
Fat, g	10	—
Linoleic acid, g	4.59	—
α-Linolenic acid, g	0.59	—
Vitamin A, μg RE	800	—
Vitamin C, mg	100	—
Thiamin, mg	2.8	—
Riboflavin, mg	2.8	—
Niacin, mg	36	—
Folic acid, μg	400	400
Pantothenic acid, mg	7	—
Vitamin B-6, mg	3.8	—
Vitamin B-12, μg	5.2	—
Vitamin D, IU	400	—
Vitamin E, mg	20	—
Vitamin K, μg	45	—
Iron, mg	20	60
Zinc, mg	30	—
Copper, mg	4	—
Calcium, mg	280	—
Phosphorus, mg	190	—
Potassium, mg	200	—
Magnesium, mg	65	—
Selenium, μg	130	—
Iodine, μg	250	—
Manganese, mg	2.6	—

[1]IFA, iron and folic acid; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women; RE, retinol equivalents.

[2]Rationale for the content of specific micronutrients is provided in reference 12.

[3]Dosages are based on standard practice and current WHO and the Government of Bangladesh recommendation.

design because it would have been difficult for a CHW to manage distribution of more than one type of supplement to the households in her or his cluster.

For the randomization, the study statistician at UC Davis first stratified the 64 clusters by subdistrict and union, and then assigned each cluster to 1 of 4 sets containing 16 clusters each. This procedure was then replicated several thousand times, and each randomization was tested for balance across groups with respect to mean cluster population, number of clinics and health workers per 1000 people, number of health-/nutrition-related nongovernmental organizations in the cluster, and the source of funding for the CHDP, as well as the SD of the cluster population size. The final randomization to the 4 arms was then 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 (with the use of SAS for Windows, release 9.2; SAS Institute) and assigning them respectively to control, child-only MNP, child-only LNS, and comprehensive LNS treatments.

The study protocol was approved by the institutional review boards of UC Davis, ICDDR,B, and LAMB. The study was registered at clinicaltrials.gov (NCT01715038). Before initiating the study, 11 community-sensitization meetings (one per study union) were arranged and verbal consent from each union was obtained. Consent was not sought at the cluster level, but individual consent was sought after screening for eligibility. Randomization of clusters was completed before seeking individual consent.

Supplements and delivery

The LNS-PL (20 g/d, 118 kcal/d) was modeled on the UNICEF/WHO/United Nations University international MMN preparation (UNIMMAP) for pregnant and lactating women and similar products used in Ghana and Malawi (12). Ingredients included soybean oil, powdered milk, peanut paste, sugar, and MMNs. For certain nutrients (thiamin, riboflavin, niacin, vitamin B-6, vitamin B-12, vitamin D, vitamin E, zinc, copper, and selenium), the level of fortification was twice the amount of each nutrient in the UNIMMAP formulation because this resulted in improved pregnancy outcomes in Guinea-Bissau (18). In addition, the iron content of the LNS-PLs was set at 20 mg, lower than the 30 mg included in the UNIMMAP formulation, for reasons described elsewhere (12). Because production of LNSs in Bangladesh has not yet been established, the LNS-PLs were produced by Nutriset SA in Malaunay, France, in individual 20-g sachets. The dose of IFA was based on WHO recommendations (19). IFA tablets were produced by Hudson Pharmaceuticals Ltd. in Bangladesh. Because this article reports the effect of maternal supplementation on birth outcomes, we will not describe in detail the supplements for children nor the research design pertinent to child outcomes other than newborn outcomes.

Delivery of the supplements was carried out by LAMB CHDP staff in accordance with the randomization plan developed by the statistician at UC Davis, which was shared with CHDP staff members. The study evaluation staff received the randomization plan coded only as "A," "B," "C," and "D." None of the evaluation staff members was involved in supplement delivery.

The intervention activities, including training of the CHWs and VHVs, storage and distribution of supplements, nutrition education and counseling, and record keeping and reporting, were incorporated into the existing CHDP activities of LAMB. The following supplement distribution scheme was identical for all of the study participants, regardless of the study arm into which they were enrolled. The first 1-mo supply of supplements for each woman enrolled was delivered by the CHW at the SDU right after the baseline data were collected by the evaluation staff (SDU visit team). Subsequent monthly supplies were usually delivered by the CHW or VHV to the woman's home, but occasionally delivery occurred during educational sessions given by the CHW or VHV near the woman's home. Each month, all of the CHWs conducted educational sessions on various maternal and child health topics at different places within the cluster allocated to her or him, as part of the regular CHDP program. When the supplements were delivered for the first time (at the SDUs), the CHW gave each woman a registration card to record receipt of future supplies of supplement and on which 9 health education messages in the local language, Bengali, were printed, which were also explained verbally. Depending on the cluster, the CHW also counseled the pregnant woman to consume either 1 IFA tablet with water each day after eating a large meal or 1 sachet of LNS-PL mixed with any food of her choice as part of a large meal each day. Women were told not to

consume more than 1 tablet or sachet per day, even if they did not take the supplement the previous day. In addition, the CHW delivered the following standard nutrition message to all women (which was also printed on the registration card and on the supplement container labels): "Do not forget to eat meat, fish, eggs, fruits and vegetables whenever you can. You still need these foods even as you take the supplement we have given you." All of these messages were repeated by the CHW at the monthly follow-up visits to the woman's home. Women were told to continue taking the study supplement even if they were receiving some other treatment. However, the women in all arms of the study were advised not to take any iron and folic acid supplements (other than the IFA tablets provided to women in those arms). They were also told to contact the CHW immediately if they experienced any side effects during the treatment. A protocol was developed to address each type of side effect reported.

LNS-PL distribution was interrupted from 8 August to 20 October 2012 to comply with a new quality-control criterion for ready-to-use supplementary foods implemented by the World Food Program, which required the absence of *Cronobacter sakazakii* (i.e., no samples testing positive at any amount). *C. sakazakii* is present in many foods and considered an opportunistic pathogen. *C. sakazakii* can cause sepsis and meningitis in young (<2 mo) infants, but potential risks to older infants, children, and adults are considered to be much lower (20). During the interruption, women in all of the arms received IFA.

Enrollment procedures and data collection

The CHWs and VHVs identified pregnant women as part of LAMB's pregnancy surveillance system, which included monthly household visits by VHVs and identification of women who had stopped menstruating. The CHWs visited these women and conducted pregnancy tests with urine strips (Quick Check; Nanjing Hoshin Medical Instrument Co. Ltd.). After confirmation of pregnancy, the CHW recorded basic information [e.g., name, age, address, and date of the first day of the last menstrual period (LMP)] in a register of pregnant women routinely maintained by LAMB. No other data were collected by LAMB CHDP staff for the purposes of this analysis; all baseline and follow-up data described below were collected by evaluation staff from the ICDDR,B.

Data collection was performed by 2 separate teams: the "SDU visit team," which collected clinical and anthropometric data at the SDU, and the "home visit team," which enrolled mothers and collected baseline and follow-up data at participants' homes. The register of pregnant women compiled by LAMB was reviewed each morning to arrange for the assessment of the eligibility of each newly pregnant woman for the study evaluation (on the basis of gestational age calculated from LMP elicited by the CHW). Potentially eligible women were contacted in their homes by evaluation staff members of the home visit team to obtain consent for screening for the evaluation study. The eligibility criteria included gestational age ≤20 wk and no plans to move out of the study area during pregnancy or the following 3 y (i.e., a permanent resident of the study area). Gestational age was calculated on the basis of the first day of the LMP, elicited through maternal recall. The interviewers used Gregorian, Bengali, and Arabic calendars; antenatal cards; and ultrasonogram reports (n = 23) as additional aids to elicit the date of LMP. At the same home visit, details of the study were provided to the eligible women, and they were invited to participate in the study along with their unborn children. The women who consented to take part in the study were interviewed to collect baseline data on socioeconomic status, diet, food security, and knowledge, attitudes, and practices relevant to nutrition. Data collection forms were submitted each evening, and selected information from the forms was entered in a database early the next morning. The database was used to generate weekly schedules for data collection at the SDUs, where baseline assessments for anthropometric measurements were conducted and biological specimens (urine and blood) were collected from an individually randomized subsample. If a woman failed to come to the SDU during the week after her enrollment, she or her family members or neighbors were contacted by phone by an evaluation staff member and the woman was usually scheduled for the next weekly SDU data collection session. Supplement delivery for each woman began after the baseline SDU visit. If a woman missed the SDU visit date for 2 consecutive study appointments, she was considered missing for that visit and supplements were delivered to her by the CHW.

Follow-up during pregnancy included a home visit by the home visit team to collect data on diet and birth preparedness at the 35th wk of gestation and a subsequent SDU visit (at 36 wk) for anthropometric measurements, assessment of depressive symptoms, and collection of biological specimens by the SDU team. After delivery, the study protocol required that each woman be visited within 72 h after birth. To coordinate birth visits, a call center was established to communicate with each study participant and her family. Each woman was called at 28 wk of gestation and every week from 36 wk of gestation until the delivery occurred. The family was given the telephone numbers of the call center and requested to call immediately after the birth of the child.

Data on adherence to LNS-PLs and IFA during pregnancy were collected at another home visit at 6 wk postpartum. The women were asked how often they consumed the nutrient supplements during pregnancy. There were 5 possible responses: "did not take at all," "used to take sometimes (1–3 d/wk)," "used to take almost every day (4–6 d/wk)," "used to take regularly every day," and "other."

Masking and standardization of evaluation staff

To the extent possible, both study evaluation teams were kept blind to group assignment, although this was difficult for home visit team members because they might have seen supplements in the home. The distribution of the supplements was coordinated and implemented by LAMB staff, and study evaluation staff only knew group assignment by the prescribed letter (A–D) as described previously.

All anthropometrists were trained and methods were standardized at the beginning of data collection and thereafter periodically by using methods described by WHO (21). At each of the SDU visits, trained anthropometrists measured maternal weight to the nearest 0.1 kg (Seca 874 Digital Floor Scale; Seca North America), height to the nearest 0.1 cm (ShorrBoards; Weigh and Measure LLC), and midupper arm circumference (MUAC) to the nearest 0.1 cm (ShorrTape; Weigh and Measure

LLC). After delivery (at home or hospital), anthropometrists specially trained for newborn anthropometry measured birth weight to the nearest 0.005 kg (DS 4100 Infant Scale; Doran Scales Inc.), length to the nearest 0.1 cm (ShorrBoards), and head circumference and MUAC to the nearest 0.1 cm (ShorrTape) generally within 72 h of birth. For the 11% of newborns for whom this was not possible, most (367 of 513 or 72%) were measured within 14 d after birth. Infants who were stillborn or those infants who had died before the assessment were not measured. Predefined criteria were used to refer women and children with certain conditions (e.g., severe anemia or depression) to specific hospitals or physicians for treatment as per LAMB's usual integrated rural health approach.

Quality control

Data collectors manually checked all forms for completeness before leaving the participating woman's home or SDU. The data collection supervisors manually checked all of the forms for both completeness and consistency before submitting the forms to the data management center for data entry. A reviewer at the data management center reviewed each form again for completeness and consistency before the entry began. All of the reviewers recorded findings in a data query log, and mistakes in the forms were corrected by the team leaders or supervisors after contacting the data collectors and participating women.

Quality-control procedures included re-interviewing 10% of randomly selected participating women by the data collection supervisors. During the re-visit, selected questions were asked again and the responses were compared with the original data collected. If there was <75% agreement, the data collector repeated the interview in the presence of the supervisor. The home visit and SDU team leaders and the study investigators made scheduled and unscheduled visits at homes and SDUs to ensure quality of the work and to respond to problems and issues.

Data from all data collection forms were double-entered in a database created by using an Oracle platform. Discrepancies between the first and second entry for data from all visits were corrected by checking the original data collection forms. Logic checks for different data domains were performed by using STATA (version 12; StataCorp) to clean the data further. Afterward, the data were further subjected to case-by-case consistency and accuracy examination by using STATA (version 12). Generated queries were either resolved by consulting the original forms or with the help of the data collector, data collection supervisor, or by a repeat home or SDU visit, whenever possible or appropriate.

Statistical analysis

A detailed data analysis plan was developed before starting the analysis and revealing group assignment. For this article, the 3 groups of women who received IFA during pregnancy were combined and compared with the "comprehensive LNS" arm for the analysis of birth outcomes. With the available number of women in these 2 groups, it was possible to detect an effect size of 0.16 with 90% power or an effect size of 0.20 with 98% power. Our primary birth outcomes were birth weight and length, as defined by *1*) crude weight (in g) and length (in cm) and *2*) weight-for-age and length-for-age *z* scores (WAZs and LAZs, respectively). Secondary outcomes included the following: *1*) gestational age (in wk) at the time of delivery; *2*) birth head circumference, defined by crude head circumference (in cm) and birth head-circumference-for-age *z* score (HCZ); *3*) BMI-for-age *z* score (BMIZ); *4*) MUAC; *5*) LBW; *6*) newborn stunting; *7*) preterm delivery; and *8*) SGA. All outcomes were measured at the individual participant level. We used WHO 2006 Child Growth Standards to determine *z* scores for birth weight, length, head circumference, and BMI (22). We used BMIZ as a proxy for weight-for-length *z* score because the latter is not calculated for children with lengths <45 cm (n = 378 in this cohort) (23) and exclusion of those infants would create bias. We defined preterm delivery as delivery at <37 wk of gestation, LBW as a birth weight <2500 g, newborn stunting as LAZ <−2 SDs, small head size as HCZ <−2, and SGA as birth weight below the 10th percentile for infants of the same gestational age from a US population (24).

Imputed values were used for gestational age when the values based on LMP were not credible. Specifically, gestational ages at delivery outside of 28–44 wk or associated with birth weights that were >3.5 SD units outside of reference data generated by LAMB from 16,738 singleton infants born at LAMB Hospital and recorded in the LAMB Hospital database (LT Day, unpublished data, 2010; A Francis, J Gardosi, personal communication, 2010), were recoded as missing and imputed from newborn anthropometric data as well as maternal age, parity, height, and BMI (SAS MI procedure). The outcomes "gestational age at delivery" and "gestational age <37 wk" were analyzed by using the imputed values.

We excluded anthropometric data for infants measured >14 d after delivery. For infants measured between 3 and 14 d after delivery, we back-calculated the weight, length, and head circumference at birth on the basis of their *z* scores at the time of measurement using LMS (L for lambda, M for mu, and S for SD) values and formulas described by WHO (23), assuming that the *z* scores were the same at those time points as they were at birth. Extreme observations for *z* scores were truncated at 4 units from the sample median. A total of 83 infants died within the first 7 d, and anthropometric data were available for 22 of them.

From a number of socioeconomic status variables, we used principal components analysis to calculate the household assets index, in which higher values represented higher socioeconomic status. The Household Food Insecurity Access Scale (25) was used to categorize participants into 4 levels of household food insecurity: severe food insecurity, moderate food insecurity, mild food insecurity, and food security.

To examine temporal trends in the primary and secondary outcomes, eight 2-mo time intervals were defined as the period from the 15th of each even-numbered month to the 14th of the subsequent even-numbered month, which corresponded to the months in the Bangladeshi calendar. One of these intervals corresponded to the period of LNS-PL delivery disruption. Because of small sample sizes, the first and last time intervals were combined with the adjacent time intervals when examining interactions between intervention group and time interval.

Primary analysis was performed by using SAS version 9.3 (SAS Institute) based on intention-to-treat (i.e., no women were excluded from the analysis on the basis of adherence to the supplements). Effects of the intervention were analyzed by using mixed-model ANCOVA for continuous outcomes and mixed-model

logistic regression for dichotomous outcomes. All models, unadjusted and adjusted, accounted for the cluster-randomized design through a random effect of cluster nested within treatment group and fixed effect of union nested within subdistrict. Adjusted models additionally included maternal age, height, BMI, education and parity, household food insecurity and assets index, gestational age at enrollment, time interval of birth, and child sex as covariates, along with a random effect of cluster nested within treatment group and fixed effects of union nested within subdistrict. We included these covariates in the models to reduce the mean square error within groups and thereby increase the precision of the estimated treatment effect (26). In the analysis of continuous outcomes, we first calculated unadjusted group means ± SDs and unadjusted group percentages and 95% CIs for binary outcomes. We then repeated those analyses with adjustments for covariates previously specified in our statistical plan. In the analysis of binary outcomes, statistical comparisons were based on covariate-adjusted log odds of the outcome occurring. We also conducted a sensitivity analysis in which infants measured ≥3 d after birth were excluded.

In predefined subgroup analysis (clinicaltrials.gov NCT01715038), we tested for interactions between intervention group and each of the covariates listed above. For significant effect modifiers ($P < 0.10$), we assessed the group effect at different levels of the effect modifier (SAS LSMEANS option).

We conducted per protocol analyses by confining the analysis to those who reported consuming their assigned supplement at least 4 times/wk, on average, during the pregnancy. A separate exploratory analysis was conducted to examine the effect of the intervention on children who were born before the interruption of LNS-PLs. To account for the interruption in LNS-PLs, we tested models that included the number of days the woman was participating in the study during the interruption period. However, we found that this did not improve the model fit compared with including the time interval variable and its interaction with intervention group in the model, and therefore we did not continue with this approach.

Finally, we used chi-square tests and mixed-model logistic regression to evaluate the occurrence of serious adverse events, including miscarriages/induced abortions, stillbirths (delivery of an infant who showed no sign of life after 28 wk of gestation), deaths of newborns within the first 7 d of life, and maternal deaths.

RESULTS

Between 15 October 2011 and 31 August 2012, we screened 4410 pregnant women for eligibility and enrolled 4011 (1047 in the LNS-PL group and 2964 in the 3 IFA groups). Although we had anticipated enrolling over a period of 1 y, after 8 mo we had already recruited our target of 3152 women, so to conserve resources we stopped enrollment after 10.5 mo. Compared with women who were enrolled, those who were not enrolled because of ineligibility or refusal to consent ($n = 399$) were, on average, slightly older (23.2 ± 5.4 compared with 21.9 ± 5.0 y; $P < 0.001$) and less educated (5.8 ± 3.5 compared with 6.2 ± 3.2 y; $P = 0.03$). Loss of pregnancy or stillbirth occurred in 8.5% of women: 89 (8.5%) in the LNS-PL group and 249 (8.4%) in the IFA group. There was one maternal death during pregnancy (in the IFA group), and 93 mothers were otherwise lost to follow-up (22 in the LNS-PL group and 71 in the IFA group). A total of 3585 live births took place between 15 January 2012 and 5 May 2013, and 1.7% of newborns died before birth anthropometric measurements were completed. We had birth anthropometric data for 3517 infants, but 68 of them were excluded from the analysis due to late measurement (after 14 d of birth) or unknown measurement date. Therefore, anthropometric data for 3449 infants were analyzed (898 in the LNS-PL group and 2551 in the IFA group) (**Figure 1**). There was no significant difference between groups in the percentage of participants with usable birth anthropometric data of those enrolled (85.8% in the LNS-PL group compared with 86.1% in the IFA group; $P = 0.80$). Mean ages of the newborns on the day of anthropometric measurement were 2.11 ± 2.86 d in the LNS-PL group and 2.01 ± 2.70 d in the IFA group. Compared with mothers of infants with birth anthropometric data, the mothers of the infants with no anthropometric data were less educated, less wealthy, more likely to be nulliparous, and were enrolled earlier in gestation (data not shown).

At baseline, sociodemographic, anthropometric, and obstetric characteristics of pregnant women were similar between LNS-PL ($n = 1047$) and IFA ($n = 2964$) groups (**Table 2**), with the exception of "years of formal education" (6.4 ± 3.2 compared with 6.1 ± 3.3 y; $P = 0.023$). On average, the women were ∼22 y of age. Mean maternal height was 151 cm, mean BMI (in kg/m^2) was ∼20, approximately one-third of the women were thin (BMI <18.5), and ∼39–42% were nulliparous. The mean gestational age at enrollment was 13 wk in both groups. The intervention groups were also balanced when we considered only those women whose infants were included in the birth outcomes analyses for this study.

On the basis of maternal retrospective recall (at 6 wk postpartum) of overall adherence throughout pregnancy, the percentages of mothers who reported regular consumption (every day or almost every day) were 64% in the LNS-PL group and 92% in the IFA group ($P < 0.001$). This difference in adherence is consistent with additional adherence data collected during pregnancy from a subgroup of participants (27). Compared with regular adherers, women with lower adherence were taller, younger, more educated, wealthier, and more food secure (data not shown).

Table 3 shows that infants in the LNS-PL and IFA groups differed significantly with respect to birth weight (2629 compared with 2588 g), WAZ (−1.48 compared with −1.59), head circumference (32.75 compared with 32.65 cm), HCZ (−1.26 compared with −1.34), and BMIZ (−1.57 compared with −1.66). Adjustment for predetermined covariates did not change these results. However, after adjustment for covariates, the differences in birth length (47.6 compared with 47.4 cm) and LAZ (−1.15 compared with −1.25) became significant. There was a trend toward a significant difference ($P < 0.10$) with respect to MUAC. There was no significant effect of LNS provision on duration of gestation.

Table 4 shows that infants in the LNS-PL and IFA groups differed significantly with respect to the prevalence of stunting (LAZ <−2; 18.7% compared with 22.6%), small head size (HCZ <−2; 20.7% compared with 24.9%), low BMI (BMIZ <−2; 30.2% compared with 34.7%), and SGA (63.3% compared with 67.3%). There was a trend toward a significant difference in LBW (36.0% compared with 39.5%). There was no significant effect on preterm delivery.

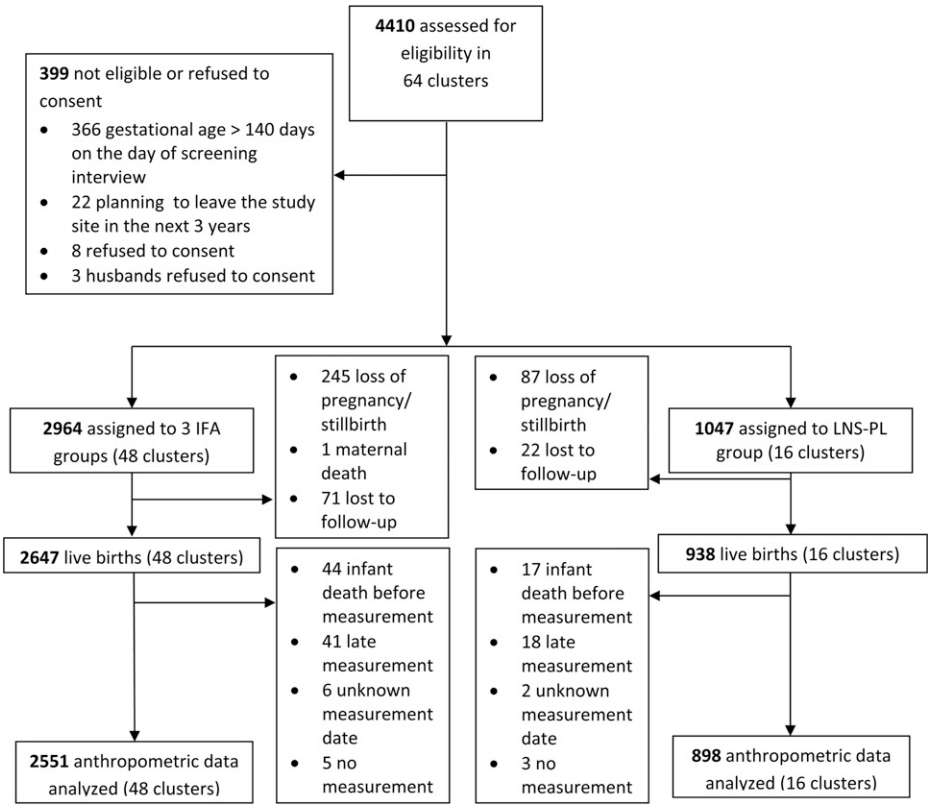

FIGURE 1 Trial profile. IFA, iron and folic acid; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women.

In a sensitivity analysis that excluded infants who were measured ≥3 d after birth (n = 311), the differences between intervention groups reported above for birth weight, WAZ, BMIZ, length, LAZ, stunting, small head size, low BMI, and SGA remained significant in unadjusted and/or adjusted analyses, with the P values for head circumference and HCZ shifting slightly to 0.05–0.06 (compared with <0.05 for the full sample). For all outcomes, the magnitude of the difference between intervention groups in the sensitivity analysis was similar to that for the full-sample analysis. For example, the prevalence of stunting in the cohort measured within the first 2 d was 18.4% and 22.1% in the LNS-PL and IFA groups, respectively (unadjusted P = 0.034).

Tests for interactions with potential effect modifiers were not significant ($P > 0.10$) for maternal education, primiparity, or BMI, but were significant for one or more birth outcomes for household food insecurity, maternal age, height, household assets, child sex, and time of year at birth. Household food insecurity modified the effect of LNS-PLs on gestational age at delivery, birth length, head circumference, WAZ, LAZ, HCZ, preterm birth, underweight, and stunting. The results for stunting are shown in **Figure 2**. The risk of stunting at birth was reduced by LNS-PLs (compared with IFA) in those living in households categorized with severe, moderate, or mild food insecurity, whereas the difference was not significant among those living in households categorized as food secure. LNS-PLs increased the duration of gestation among women in households categorized with severe or moderate food insecurity (but the treatment group differences were not significant within the other 2 categories of food security) (**Figure 3**). The same trends were observed for mean birth length and head circumference (i.e., there was a greater effect of LNS-PLs in households with higher food insecurity) (as shown in **Supplemental Figure 1** for birth length). The distribution of LAZs of the newborns in the LNS-PL and IFA groups, within each of the 4 food-insecurity subgroups (**Figure 4**), suggested that LNS-PLs reduced the proportion of infants with low LAZs at birth, with little effect on the mean or upper end of the distribution.

TABLE 2
Baseline characteristics of women enrolled[1]

Characteristics	LNS-PL (n = 1047)	IFA (n = 2964)
Age, y	21.8 ± 4.9[2]	22.0 ± 5.0
Years of formal education	6.4 ± 3.2	6.1 ± 3.3
Household assets index	0.04 ± 2.24	−0.01 ± 2.26
HFIA score	2.78 ± 3.92	3.15 ± 4.06
Height, cm	151.0 ± 5.4	151.0 ± 5.4
BMI (adjusted to 96 d of gestation), kg/m^2	19.9 ± 2.7	20.0 ± 2.7
BMI <18.5 kg/m^2	32.9 (28.6, 37.5)[3]	30.7 (28.2, 33.3)
MUAC, cm	24.8 ± 2.6	24.9 ± 2.6
Nulliparous	41.7 (38.8, 44.7)	39.1 (37.1, 41.0)
Gestational age at enrollment, wk	13.1 ± 3.8	13.1 ± 3.8

[1]HFIA, Household Food Insecurity Access Scale; IFA, iron and folic acid; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women; MUAC, midupper arm circumference.
[2]Mean ± SD (all such values).
[3]Percentage; 95% CI in parentheses (all such values).

TABLE 3
Continuous birth outcomes, by intervention group[1]

Outcome variable	LNS-PL (n = 898)	IFA (n = 2551)	P^2
Gestational age of women, wk			
Unadjusted	39.5 ± 2.23	39.3 ± 2.31	0.158
Adjusted[3]	39.5 ± 0.08	39.3 ± 0.05	0.153
Birth weight, g			
Unadjusted	2629 ± 408	2588 ± 413	0.007
Adjusted[3]	2632 ± 13.0	2586 ± 7.64	0.004
WAZ			
Unadjusted	−1.48 ± 1.01	−1.59 ± 1.02	0.006
Adjusted[3]	−1.48 ± 0.03	−1.59 ± 0.02	0.004
Length, cm			
Unadjusted	47.6 ± 2.07	47.4 ± 2.17	0.067
Adjusted[3]	47.6 ± 0.07	47.4 ± 0.04	0.042
LAZ			
Unadjusted	−1.15 ± 1.10	−1.25 ± 1.14	0.056
Adjusted[3]	−1.15 ± 0.04	−1.24 ± 0.02	0.035
Head circumference, cm			
Unadjusted	32.7 ± 1.35	32.7 ± 1.40	0.039
Adjusted[3]	32.8 ± 0.04	32.6 ± 0.03	0.033
Head-circumference-for-age z score			
Unadjusted	−1.26 ± 1.08	−1.34 ± 1.12	0.027
Adjusted[3]	−1.25 ± 0.04	−1.35 ± 0.02	0.026
MUAC, cm			
Unadjusted	9.79 ± 0.82	9.73 ± 0.83	0.080
Adjusted[3]	9.78 ± 0.03	9.73 ± 0.02	0.092
BMIZ			
Unadjusted	−1.57 ± 1.05	−1.66 ± 1.03	0.005
Adjusted[3]	−1.56 ± 0.03	−1.67 ± 0.02	0.005

[1]Unadjusted values are means ± SDs; adjusted values are means ± SEs. BMIZ, BMI-for-age z score; IFA, iron and folic acid; LAZ, length-for-age z score; LNS, lipid-based nutrient supplement for pregnant and lactating women; MUAC, midupper arm circumference; WAZ, weight-for-age z score.

[2]P values are based on ANCOVA (PROC MIXED; SAS Institute) accounting for union and the random effect of cluster and controlling for selected covariates in adjusted models. Intracluster correlation was zero for the primary outcomes.

[3]Adjusted for maternal education, assets quintile, time interval (season) at birth, maternal height, maternal BMI, child sex, food-security category, parity, gestational age at enrollment (imputed), and accounting for union and the random effect of cluster.

As shown in **Figure 5**, maternal age modified the effect of LNS-PLs (compared with IFA) on newborn stunting, with larger effects seen among women 14–24 y of age and no significant effect among women ≥25 y of age. There was no between-group difference in the percentage of women aged 14–24 y (72.6% in the LNS-PL group and 72.3% in the IFA group). Maternal age was not a significant effect modifier for any of the other birth outcomes. Maternal height modified the effect of LNS-PLs on the prevalence of LBW (P-interaction = 0.065): among women whose height was above the median (>150.5 cm), there was a significant difference between intervention groups (26.6% in the LNS-PL group and 31.9% in the IFA group; P = 0.027), but there was no difference in shorter women (45.9% and 47.2%, respectively).

Household assets modified the effect of LNS-PLs on birth length, LAZ, MUAC, and SGA, with group differences (greater birth size in the LNS-PL group) seen consistently in the lowest wealth quintile and for some outcomes also in the third wealth quintile (data not shown). The effect of LNS-PLs (compared with IFA) on the duration of gestation (P-interaction = 0.054) was significant for female infants (39.6 ± 0.11 compared with 39.3 ± 0.06 wk; P = 0.020) but not male infants (39.3 ± 0.11 compared with 39.3 ± 0.06 wk; P = 0.775). Time of year at birth (in 2-mo intervals) was a significant effect modifier for birth weight, length, head circumference, MUAC, WAZ, LAZ, HCZ, LBW, stunting, and low HCZ, but the results did not exhibit a consistent seasonal pattern and are confounded by the fact that the disruption in LNS-PL supply occurred during one of those intervals (data not shown).

Exploratory analyses were conducted to examine the influence of the 10-wk disruption in the supply of LNS-PLs by comparing the LNS-PL and IFA groups within the following 3 subgroups of women: *1*) those who delivered before the LNS-PL supply disruption (n = 370 in the LNS-PL group, 0 d of interruption; n = 931 in the IFA group); *2*) those who delivered during the suspension of LNS-PL distribution who were in the last 1–10 wk of pregnancy at that time (n = 212 in the LNS-PL group, 34.9 ± 21.4 d of interruption; n = 656 in the IFA group); and *3*) those who delivered after the disruption but who experienced a 10-wk gap in LNS-PL distribution during pregnancy (at 7–33 wk of gestation) if they had been assigned to the LNS-PL group (n = 401 in the LNS-PL group, 70.3 ± 6.1 d of interruption; n = 1177 in the IFA group). **Figure 6** shows that the prevalence of newborn stunting was significantly lower in the LNS-PL group among infants born before the disruption but not in those born later; the same trend was observed for head circumference (data not shown). In those who were born before the disruption, LNS-PLs reduced the risk of newborn stunting by 31% and the risk of small head size by 21%.

Per protocol analyses (**Supplemental Tables 1** and **2**) were consistent with a stronger apparent impact of the intervention on birth outcomes when women with low reported adherence were excluded. For example, among women reporting "regular" supplement consumption during pregnancy (but not excluding those affected by the disruption in LNS-PL supply), LNS-PLs reduced newborn stunting by 25% and small head size by 19%. There were no significant differences between groups in the incidence of any of the serious adverse events assessed (**Table 5**).

DISCUSSION

In this study, the provision of LNS-PLs during pregnancy (compared with IFA) significantly increased mean birth weight, WAZ, birth length, LAZ, head circumference, HCZ, and BMIZ. Although the differences in mean birth length and LAZ were small, there was a greater shift at the lower end of the distribution of LAZs, resulting in a significant 17% reduction in the prevalence of newborn stunting. We also found significant reductions in the prevalence of small head size and low BMI at birth. The per protocol analyses (excluding women with low reported adherence but not excluding those affected by the disruption in LNS-PL supply) were consistent with the shift being attributable to LNS-PLs, with a 25% reduction in newborn stunting among women who reported regularly consuming LNS-PLs compared with those who reported regularly consuming IFA. Among infants born before the 10-wk disruption in supply of LNS-PLs, the

TABLE 4
Binary birth outcomes, by intervention group[1]

Outcome variable	LNS-PL (n = 898)	IFA (n = 2551)	Unadjusted RR (95% CI)	Unadjusted P[2]	Adjusted RR[3] (95% CI)	Adjusted P[3]
Preterm delivery	13.1 (11.0, 15.5)	13.7 (12.4, 15.1)	0.95 (0.78, 1.16)	0.654	0.94 (0.77, 1.14)	0.693
Low birth weight	36.0 (32.9, 39.3)	39.5 (37.6, 41.4)	0.93 (0.84, 1.03)	0.080	0.93 (0.84, 1.02)	0.062
WAZ <-2	27.5 (24.7, 30.6)	30.0 (28.3, 31.9)	0.94 (0.83, 1.07)	0.174	0.93 (0.83, 1.05)	0.126
LAZ <-2	18.7 (16.2, 21.5)	22.6 (21.0, 24.3)	0.83 (0.71, 0.97)	0.023	0.82 (0.71, 0.95)	0.015
HCZ <-2	20.7 (18.1, 23.6)	24.9 (23.2, 26.6)	0.85 (0.73, 0.98)	0.017	0.84 (0.73, 0.97)	0.015
BMIZ <-2	30.2 (27.2, 33.4)	34.7 (32.9, 36.6)	0.91 (0.81, 1.02)	0.020	0.90 (0.80, 1.00)	0.016
SGA	63.3 (59.8, 66.6)	67.3 (65.3, 69.2)	0.95 (0.89, 1.01)	0.047	0.95 (0.90, 1.01)	0.052

[1]Values are percentages (95% CIs) unless otherwise indicated. BMIZ, BMI-for-age z score; HCZ, head-circumference-for-age z score; IFA, iron and folic acid; LAZ, length-for-age z score; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women; SGA, small for gestational age; WAZ, weight-for-age z score.

[2]P values for analyses are based on logistic regression (PROC GLIMMIX; SAS Institute) accounting for union and the random effect of cluster and controlling for selected covariates in adjusted models. Intracluster correlation was zero for the primary outcomes.

[3]Adjusted for maternal education, assets quintile, time interval (season) at birth, maternal height, maternal BMI, child sex, food-security category, parity, gestational age at enrollment (imputed), and accounting for union and the random effect of cluster.

reduction in newborn stunting was 31%. To our knowledge, this is the first study to report an effect of a prenatal nutrient or food supplement containing MMNs on the prevalence of stunting at birth.

Although the proportion of stunting that occurs before rather than after birth is not well understood and likely varies across populations, there is agreement that stunting often begins in utero (28) and some of the stunting that occurs after birth may be programmed in utero (29). However, meta-analyses have not shown any significant impact on birth length of prenatal MMN (30) or balanced protein-energy supplementation (31) despite significant effects on birth weight, although a recent large prenatal MMN trial in Bangladesh reported a small (0.2 cm) but significant effect on birth length (11). By contrast, in Burkina Faso, there was a 0.5-cm increase in birth length (but no difference in birth weight) in the group who received prenatal LNSs (373 kcal/d) compared with those who received MMNs (32).

In our cohort, the effect of LNS-PLs on mean birth weight (+47 g in the unadjusted and 46 g in the adjusted model) was similar to the pooled effect of MMNs in the most recent meta-analysis (+53 g) (10) but smaller than the estimated pooled effect of balanced protein-energy supplementation (+73 g) (9), which is not surprising given that LNS-PL contributed only 118 kcal/d (compared with ~400–800 kcal/d in most prenatal food supplementation studies) and the RDNS was an effectiveness study, not an efficacy trial. There was a trend toward a reduction in LBW

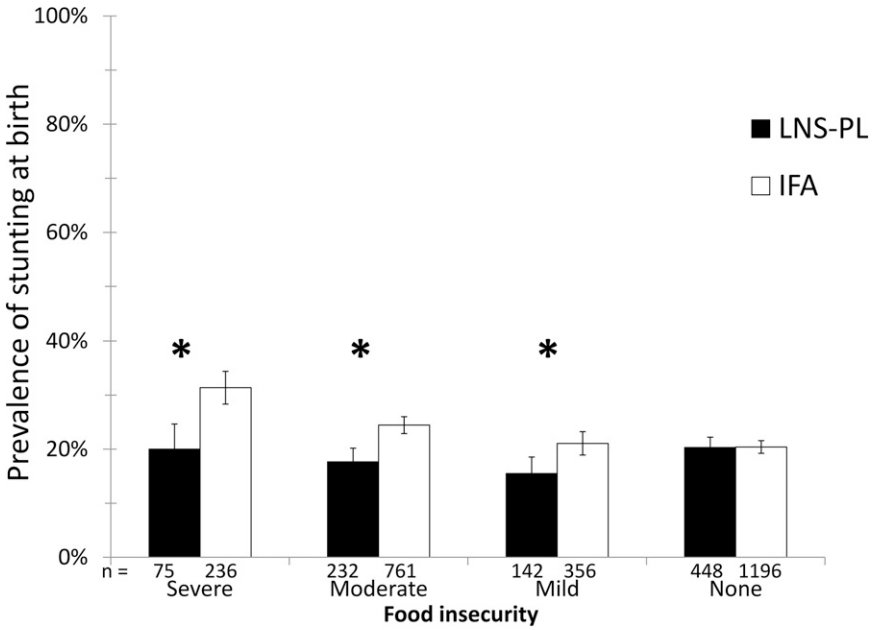

FIGURE 2 Prevalence (±1 SE) of stunting at birth by intervention group and food-security category. Groups were compared by using mixed-model logistic regression. P = 0.043 for group by food-security interaction. *Difference between LNS-PL and IFA groups, P <0.05. IFA, iron and folic acid; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women.

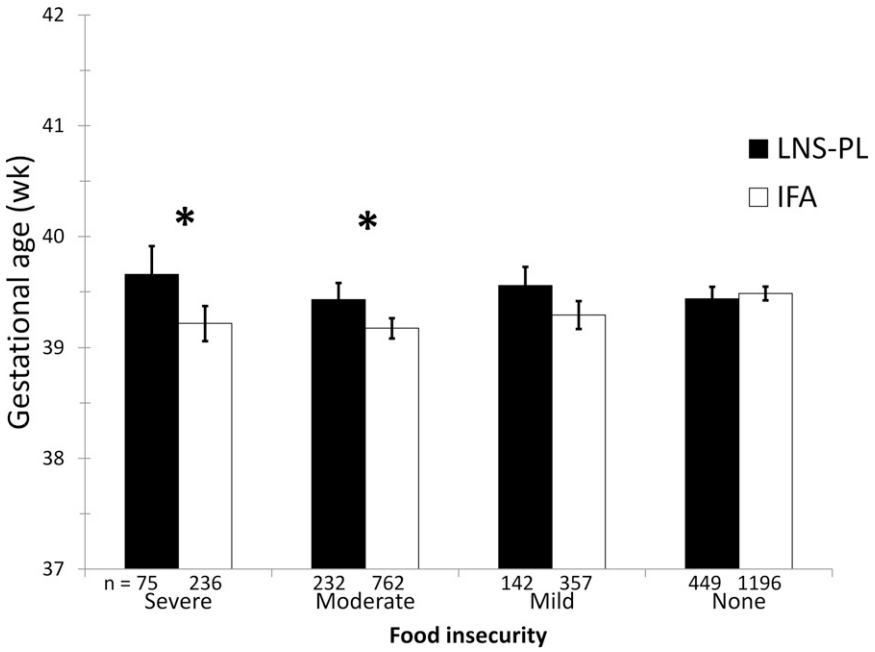

FIGURE 3 Mean (±1 SE) duration of gestation by intervention group and food-security category. Groups were compared by using mixed-model ANCOVA. $P = 0.085$ for group by food-security interaction. *Difference between LNS-PL and IFA groups, $P < 0.05$. IFA, iron and folic acid; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women.

(~7%), whereas the above-mentioned meta-analyses reported reductions in LBW of 14% for MMNs and 32% for balanced protein-energy supplementation. However, in our per protocol analyses, the prevalence of LBW was reduced by 11% ($P = 0.03$), which is similar to what has been observed for efficacy trials with MMNs. We also found a 13% reduction in the prevalence of wasting (low BMI) at birth (a 14% reduction in per protocol analyses).

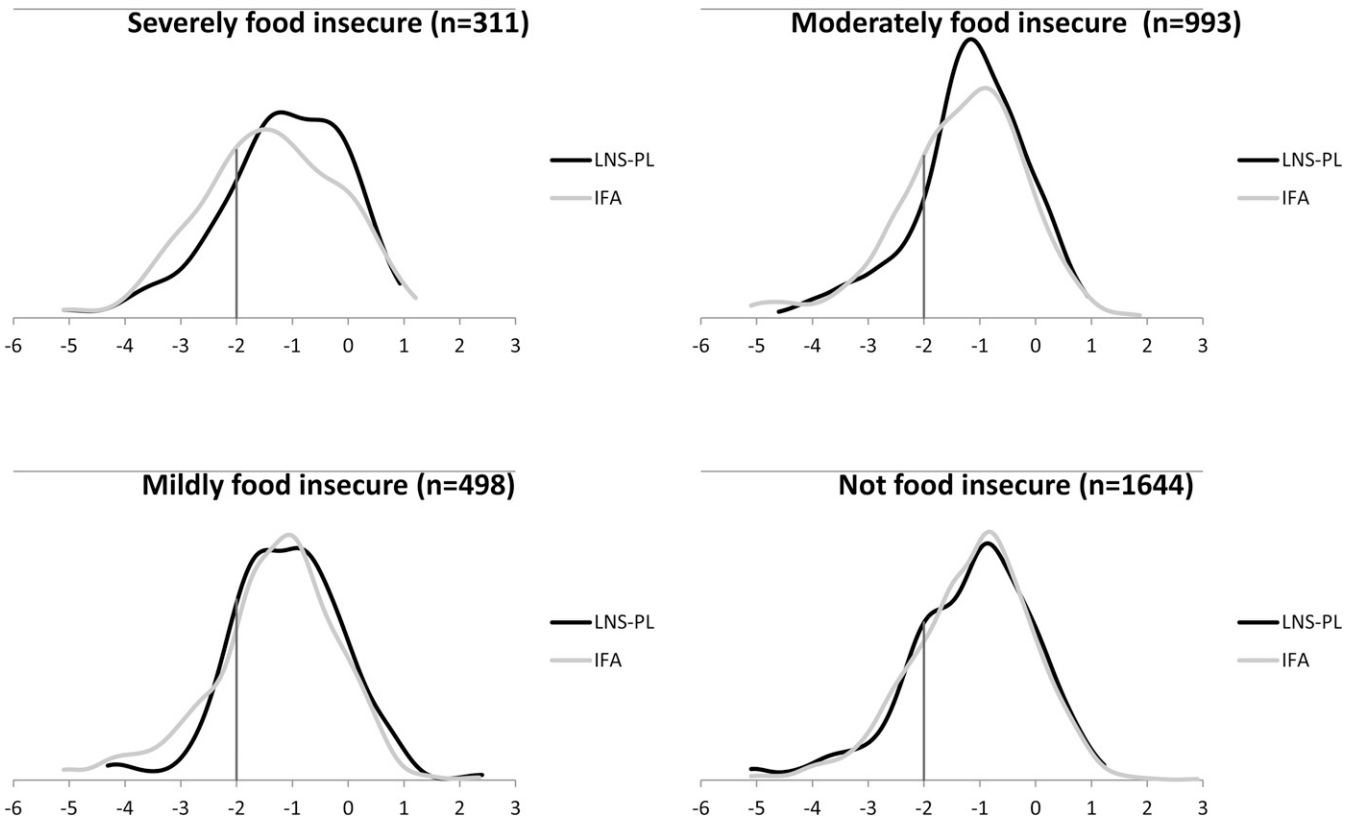

FIGURE 4 Distribution of length-for-age z scores by group and food security. IFA, iron and folic acid; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women.

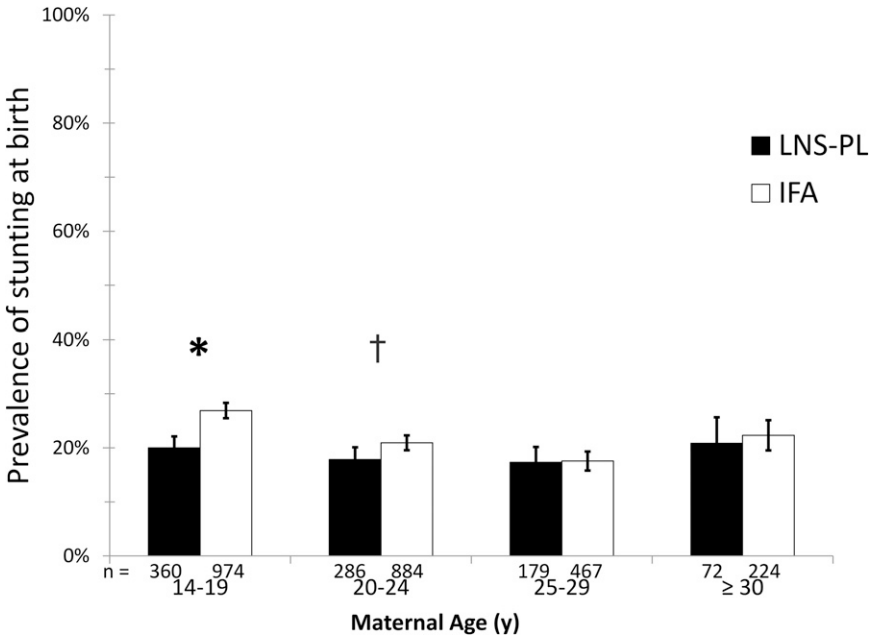

FIGURE 5 Prevalence (±1 SE) of stunting at birth by intervention group and age category. Groups were compared by using mixed-model logistic regression. $P = 0.068$ for group by age interaction. *†Difference between LNS-PL and IFA groups: *$P < 0.05$, †$P < 0.10$. IFA, iron and folic acid; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women.

The significant effects of LNS-PLs on head circumference and percentage with small head size at birth are noteworthy given the association between head circumference and brain size during infancy (33). The percentage of newborns with a small head size was reduced by 17% in the sample as a whole, by 19% in per protocol analyses, and by 22% when limited to infants born before the 10-wk disruption in the supply of LNS-PLs. The MMN supplement meta-analyses mentioned earlier (10, 30) did not report data on head circumference, and some other published MMN (34, 35) and LNS (32) studies did not show any significant differences. However, a recent meta-analysis showed that prenatal MMN supplementation increased child head circumference

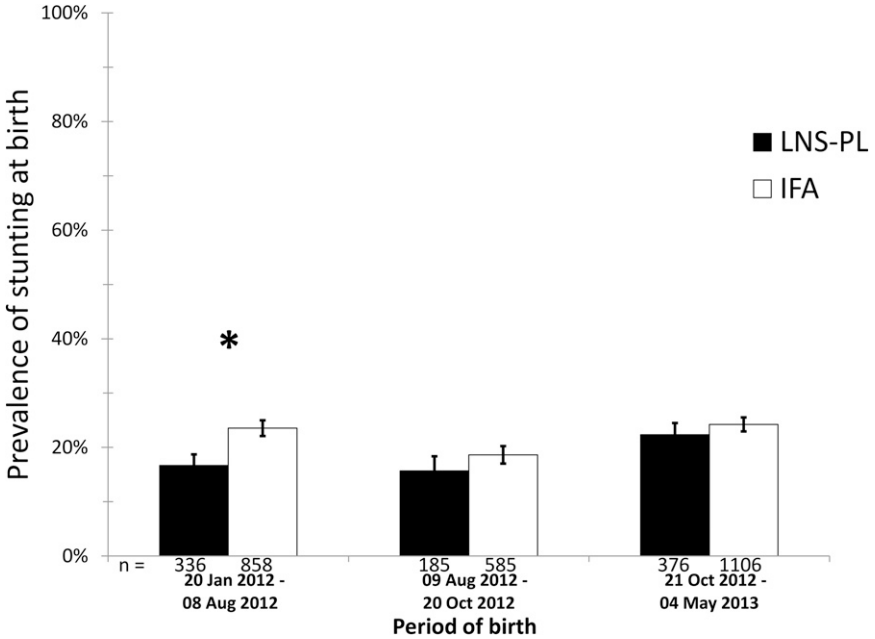

FIGURE 6 Prevalence (±1 SE) of stunting at birth by intervention group and period of birth: 20 January 2012 to 8 August 2012, infants born before the LNS-PL supply disruption; 9 August 2012 to 20 October 2012, infants born during the suspension of LNS-PL distribution whose mothers were in the last 1–10 wk of pregnancy at that time; 21 October 2012 to 4 May 2013, infants born after the disruption but whose mothers experienced a 10-wk gap in LNS-PL distribution during pregnancy (at 7–33 wk of gestation) if they had been assigned to the LNS-PL group. Groups were compared by using mixed-model logistic regression. Difference between LNS-PL and IFA groups, *$P < 0.05$. IFA, iron and folic acid; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women.

TABLE 5
Serious adverse events by intervention group[1]

Variable	LNS-PL (n = 1047)	IFA (n = 2964)	P	RR (95% CI)
Total dyads with serious adverse events	107[2] (10.2)	316 (10.7)	0.62	0.96 (0.78, 1.19)
Miscarriage/induced abortion	56 (5.3)	178 (6.0)	0.84	0.89 (0.66, 1.20)
Stillbirths	34 (3.2)	71 (2.4)	0.25	1.36 (0.90, 2.05)
Maternal death	0 (0)	2[3] (0.07)	0.97	—
Death of newborn within 7 d	18 (1.7)	65 (2.2)	0.09	0.78 (0.46, 1.33)

[1]Values are n (%). Among multiple-fetus pregnancies, some women experienced a miscarriage or stillbirth that involved only one of the fetuses, but these cases are included in this table; for this reason, the number of women who experienced loss of pregnancy in this table is larger than the numbers reported in Figure 1 (which includes all dyads who remained in the study). IFA, iron and folic acid; LNS-PL, lipid-based nutrient supplement for pregnant and lactating women.

[2]One woman in the LNS-PL group suffered a miscarriage of one twin and stillbirth of the other.

[3]One maternal death occurred during the prenatal period, and the other occurred after childbirth before the infant was measured.

later in infancy or childhood, compared with the provision of ≥2 micronutrients (36). In the recent large prenatal MMN intervention in Bangladesh, there was also a significant effect on head circumference (11).

Although the most recent meta-analysis of prenatal MMN supplementation (10) and the latter study in Bangladesh (11) reported a small but significant increase in the duration of gestation, we did not find significant main effects of LNS-PLs on duration of gestation or preterm delivery. However, in subgroup analyses, LNS-PLs increased the duration of gestation by 0.5 wk among women in very-food-insecure households and by 0.3 wk among women carrying female infants. There are at least 2 possible explanations for the lack of a main effect on duration of gestation. First, in contrast to the other study in Bangladesh, ours was an effectiveness trial and adherence to LNS-PLs was significantly lower than adherence to IFA. Second, the average duration of gestation at enrollment was 13 wk (range: 4.6–20.0 wk), whereas all of the women in the other Bangladesh study were recruited in the first trimester.

We explored whether the magnitude of the effect of LNS-PLs on birth size differed depending on several predefined, biologically plausible, potential effect modifiers. There were no significant interactions with maternal education, primiparity, or BMI. However, household food insecurity, household assets, maternal age and height, sex of the child, and time of year at birth modified the effect of LNS-PLs on at least one birth outcome. Women in food-insecure households are more likely to suffer from both macro- and micronutrient deficiencies during pregnancy; therefore, it is not surprising that we found a greater effect of LNS-PLs among such women, not only on newborn stunting but also on mean birth length and head circumference (as well as duration of gestation, as mentioned above). What is surprising is that the differences in the prevalence of newborn stunting across subgroups with higher levels of household food insecurity (as seen in the IFA group) were eliminated in the LNS-PL group (Figure 2), although the supplement provided only 118 kcal/d. As a result, newborn stunting was reduced by 36% among women who were very food insecure. Similarly, the effect of LNS-PLs on birth length, MUAC, and SGA was more evident in the lower household wealth quintiles.

Maternal age was also an effect modifier: LNS-PLs reduced newborn stunting by 21% among infants born to mothers who were 14–24 y of age, with no significant effect observed in older women. Pregnancy during adolescence increases the risk of adverse birth outcomes, poor fetal growth, and infant and maternal morbidity (37), probably at least partly because of competition for nutrients between the young mother and the growing fetus (38). LNS-PLs may reduce this competition by providing extra amounts of both micro- and macronutrients. The meta-analysis of MMN supplementation during pregnancy did not report any interaction between supplement type and maternal age (30).

As the first effectiveness study to examine how small-quantity LNS-PLs affect birth outcomes, this study has several strengths and limitations. Strengths include the following: *1*) the use of 2 independent teams, one to conduct the intervention (led by LAMB) and another to evaluate impact (led by ICDDR,B and UC Davis); *2*) enrollment of ∼4000 women who were representative of the target population; *3*) a low rate of attrition (mostly due to travel out of the study area rather than refusal to participate); *4*) use of well-trained anthropometrists who performed measurements according to WHO standards and were standardized; and *5*) completion of 86% of the newborn anthropometric measurements within 72 h of delivery. Among the limitations, the disruption of the LNS-PL supply for a period of 10 wk, which was beyond our control, compromised our ability to investigate the full potential of LNS-PLs as an intervention. For several key outcomes, we found a larger effect of LNS-PLs among infants born to women who gave birth before the disruption of LNS-PL distribution. We believe that this is consistent with a causal effect of LNS-PLs on birth size, and thus actually strengthens our conclusions. Second, it was not possible to blind the women to the type of supplement provided, because the supplements were very different in appearance and taste. Nonetheless, researchers responsible for the collection of outcome data were kept blind to study assignment. Third, we used LMP to estimate the duration of gestation, because it was not feasible to use ultrasonography for all participants. Fourth, we relied on the women's reported consumption of the supplements to assess adherence, instead of direct observation, so the adherence data could be inaccurate. Finally, we examined effects within several different targeted subgroups, and these exploratory effect modification results need to be interpreted with caution because we examined multiple hypotheses and the study was not powered to test each potential interaction.

We conclude that LNS-PL supplementation during pregnancy reduced newborn stunting, wasting, and small head size in the study population. These effects occurred without a significant impact on duration of gestation, which suggests that LNS-PLs reduce fetal growth restriction but not preterm delivery. As a whole, the study women were at high risk of fetal growth restriction, given that approximately one-third of them had a low BMI and 39% were <20 y of age. A reduction in newborn stunting by LNS-PLs was most evident among younger women and those residing in households that experienced high levels of food insecurity. Because this was an effectiveness study conducted in the context of an operating community

health program, the findings should be relevant to other programs that serve similar populations.

We thank Zeina Maalouf-Manasseh and Megan Deitchler from FANTA (Food and Nutrition Technical Assistance III Project); Tahmeed Ahmed, Laura Reichenbach, Sushil Kanta Dasgupta, Mokbul Hossain, AFM Mostofa Sarker, Barkat Ullah, Showkat Ali Khan, Dhiman Dutt, Atikul Islam Shah, Jyotish Chadra Mallik, Md. Moniruzzaman, and Swapan Kumar Chanda from the ICDDR,B; Swapan Pahan, Altaf Hossain, Shafiul Alam, Peter May, Pronoy Ganguly, Mahtab Liton, and Steve Withington from LAMB; and Andre Francis and Jason Gardosi from the Perinatal Institute, Birmingham, United Kingdom, for their technical input and support during the implementation of the study; and Charles D Arnold from UC Davis for assistance with data management and statistical analysis. Our research intervention was incorporated into the community heath and development program of LAMB, which was supported by Plan-Bangladesh in 6 of the 11 study unions. We also thank Nutriset S.A.S. for the preparation of the LNS supplements for this trial.

The authors' responsibilities were as follows—MKM: was the local principal investigator at ICDDR,B, supervised all study activities in Bangladesh, contributed to data analysis, and wrote the first draft of the manuscript; SLM, CMC, SAV, KLH, and JRC: were involved in many aspects of the study design and implementation and development of the statistical analysis plan; RRP and SH: contributed to study protocols and supervised data collection at the study site; LTD and SLS: were the collaborators from LAMB and were involved in assessing feasibility of implementation and the design of routine pregnancy surveillance data collection; JMP: was responsible for sample size calculations, the cluster-randomization scheme, determination of appropriate statistical procedures, and data analysis; KGD: was the principal investigator for the overall project, was involved in all aspects of the study including writing of the manuscript, had full access to all of the data, and had final responsibility to submit the manuscript for publication; and all authors: contributed to the design or implementation of the study and writing of the manuscript. The authors declared that they had no conflicts of interest.

REFERENCES

1. Christian P, Lee SE, Donahue Angel M, Adair LS, Arifeen SE, Ashorn P, Barros FC, Fall CH, Fawzi WW, Hao W, et al. Risk of childhood undernutrition related to small-for-gestational age and preterm birth in low- and middle-income countries. Int J Epidemiol 2013;42:1340–55.
2. National Low Birth Weight Survey of Bangladesh, 2003-2004. Dhaka (Bangladesh): Bangladesh Bureau of Statistics and United Nations Children's Fund; 2005.
3. Bangladesh Demographic and Health Survey 2014: key indicators. Dhaka (Bangladesh) and Rockville (MD): National Institute of Population Research and Training, Mitra and Associates, and ICF International; 2015.
4. Alam DS. Prevention of low birthweight. Nestle Nutr Workshop Ser Pediatr Program 2009;63:209–21; discussion: 21–5, 59–68.
5. Alderman H, Behrman JR. Estimated economic benefits of reducing low birth weight in low-income countries. Washington (DC): The World Bank; 2004. Contract No.: 35548.
6. Abu-Saad K, Fraser D. Maternal nutrition and birth outcomes. Epidemiol Rev 2010;32:5–25.
7. Arsenault JE, Yakes EA, Islam MM, Hossain MB, Ahmed T, Hotz C, Lewis B, Rahman AS, Jamil KM, Brown KH. Very low adequacy of micronutrient intakes by young children and women in rural Bangladesh is primarily explained by low food intake and limited diversity. J Nutr 2013;143:197–203.
8. Peña-Rosas JP, De-Regil LM, Dowswell T, Viteri FE. Intermittent oral iron supplementation during pregnancy. Cochrane Database Syst Rev 2012;7:CD009997.
9. Imdad A, Bhutta ZA. Maternal nutrition and birth outcomes: effect of balanced protein-energy supplementation. Paediatr Perinat Epidemiol 2012;26(Suppl 1):178–90.
10. Ramakrishnan U, Grant FK, Goldenberg T, Bui V, Imdad A, Bhutta ZA. Effect of multiple micronutrient supplementation on pregnancy and infant outcomes: a systematic review. Paediatr Perinat Epidemiol 2012;26 (Suppl 1):153–67.
11. West KP Jr., Shamim AA, Mehra S, Labrique AB, Ali H, Shaikh S, Klemm RDW, Wu LSF, Mitra M, Haque R, et al. Effect of maternal multiple micronutrient vs iron-folic acid supplementation on infant mortality and adverse birth outcomes in rural Bangladesh: the JiVitA-3 randomized trial. JAMA 2014;312:2649–58.
12. Arimond M, Zeilani M, Jungjohann S, Brown KH, Ashorn P, Allen LH, Dewey KG. Considerations in developing lipid-based nutrient supplements for prevention of undernutrition: experience from the International Lipid-Based Nutrient Supplements (iLiNS) Project. Matern Child Nutr 2013 May 6 (Epub ahead of print; DOI: 10.1111/mcn.12049).
13. Adu-Afarwuah S, Lartey A, Brown KH, Zlotkin S, Briend A, Dewey KG. Randomized comparison of 3 types of micronutrient supplements for home fortification of complementary foods in Ghana: effects on growth and motor development. Am J Clin Nutr 2007;86:412–20.
14. Adu-Afarwuah S, Lartey A, Brown KH, Zlotkin S, Briend A, Dewey KG. 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;87:929–38.
15. Mridha MK, Chaparro CM, Matias SL, Hussain S, Munira S, Saha S, Day LT, Dewey KG. Acceptability of lipid-based nutrient supplements and micronutrient powders among pregnant and lactating women and infants and young children in Bangladesh and their perceptions about malnutrition and nutrient supplements. Washington (DC): University of California, Davis; FANTA-2 Bridge; ICDDR,B; World Mission Prayer League (LAMB Hospital); 2012.
16. Bangladesh Population and Housing Census [Internet]. [cited 2014 Jun 6]. Bangladesh Bureau of Statistics; 2011. Available from: http://203.112.218.66/PageWebMenuContent.aspx?MenuKey=480 and http://203.112.218.66/PageWebMenuContent.aspx?MenuKey=474.
17. Sebayang SK, Dibley MJ, Kelly PJ, Shankar AV, Shankar AH. Determinants of low birthweight, small-for-gestational-age and preterm birth in Lombok, Indonesia: analyses of the birthweight cohort of the SUMMIT trial. Trop Med Int Health 2012;17:938–50.
18. Kaestel P, Michaelsen KF, Aaby P, Friis H. Effects of prenatal multimicronutrient supplements on birth weight and perinatal mortality: a randomised, controlled trial in Guinea-Bissau. Eur J Clin Nutr 2005;59:1081–9.
19. World Health Organization. WHO guidelines: daily iron and folic acid supplementation in pregnant women. Geneva (Switzerland): World Health Organization; 2012.
20. Centers for Disease Control and Prevention. Cronobacter [updated 2014 Feb 12; cited 2014 Jun 6]. Available from: http://www.cdc.gov/cronobacter/technical.html.
21. de Onis M, Onyango AW, Van den Broeck J, Chumlea WC, Martorell R. Measurement and standardization protocols for anthropometry used in the construction of a new international growth reference. Food Nutr Bull 2004;25(1 Suppl):S27–36.
22. World Health Organization. WHO Child Growth Standards. WHO Anthro (version 3.2.2, January 2011) and macros [cited 2014 Jun 6]. Available from: http://www.who.int/childgrowth/software/en/.
23. World Health Organization. WHO Child Growth Standards. Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva (Switzerland): World Health Organization; 2006.
24. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstet Gynecol 1996;87:163–8.
25. Coates J, Swindale A, Bilinsky P. Household Food Insecurity Access Scale (HFIAS) for Measurement of Household Food Access: Indicator Guide. Version 3. Washington (DC): Food and Nutrition Technical Assistance Project, Academy for Educational Development; 2007.
26. Streiner DL. Best (but oft-forgotten) practices: the multiple problems of multiplicity—whether and how to correct for many statistical tests. Am J Clin Nutr 2015;102:721–8.
27. Harding KL, Matias SL, Moniruzzaman M, Stewart CP, Mridha MK, Vosti SA, Dewey KG. Rang-Din Nutrition Study: assessment of participant adherence to lipid-based nutrient and iron-folic acid supplements among pregnant and lactating women in the context of a study on the effectiveness of supplements in Bangladesh. Washington (DC): Family Health International 360/Food and Nutrition Technical Assistance; 2014.

28. de Onis M, Dewey KG, Borghi E, Onyango AW, Blossner M, Daelmans B, Piwoz E, Branca F. The World Health Organization's global target for reducing childhood stunting by 2025: rationale and proposed actions. Matern Child Nutr 2013;9(Suppl 2):6–26.
29. Martorell R, Zongrone A. Intergenerational influences on child growth and undernutrition. Paediatr Perinat Epidemiol 2012;26(Suppl 1):302–14.
30. Fall CH, Fisher DJ, Osmond C, Margetts BM. Multiple micronutrient supplementation during pregnancy in low-income countries: a meta-analysis of effects on birth size and length of gestation. Food Nutr Bull 2009;30(4 Suppl):S533–46.
31. Kramer MS, Kakuma R. Energy and protein intake in pregnancy. Cochrane Database Syst Rev 2003;4:CD000032.
32. Huybregts L, Roberfroid D, Lanou H, Menten J, Meda N, Van Camp J, Kolsteren P. Prenatal food supplementation fortified with multiple micronutrients increases birth length: a randomized controlled trial in rural Burkina Faso. Am J Clin Nutr 2009;90:1593–600.
33. Lorenz JM, Whitaker AH, Feldman JF, Yudkin PL, Shen S, Blond A, Pinto-Martin JA, Paneth N. Indices of body and brain size at birth and at the age of 2 years: relations to cognitive outcome at the age of 16 years in low birth weight infants. J Dev Behav Pediatr 2009;30:535–43.
34. Bhutta ZA, Rizvi A, Raza F, Hotwani S, Zaidi S, Moazzam Hossain S, Soofi S, Bhutta S. A comparative evaluation of multiple micronutrient and iron-folic acid supplementation during pregnancy in Pakistan: impact on pregnancy outcomes. Food Nutr Bull 2009;30(4 Suppl): S496–505.
35. Sunawang, Utomo B, Hidayat A, Kusharisupeni, Subarkah. Preventing low birthweight through maternal multiple micronutrient supplementation: a cluster-randomized, controlled trial in Indramayu, West Java. Food Nutr Bull 2009;30(4 Suppl): S488–95.
36. Lu WP, Lu MS, Li ZH, Zhang CX. Effects of multimicronutrient supplementation during pregnancy on postnatal growth of children under 5 years of age: a meta-analysis of randomized controlled trials. PLoS One 2014;9:e88496.
37. Rah JH, Christian P, Shamim AA, Arju UT, Labrique AB, Rashid M. Pregnancy and lactation hinder growth and nutritional status of adolescent girls in rural Bangladesh. J Nutr 2008;138:1505–11.
38. King JC. The risk of maternal nutritional depletion and poor outcomes increases in early or closely spaced pregnancies. J Nutr 2003; 133(5 Suppl 2):1732S–6S.