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Effectiveness of a Lipid-Based Nutrient Supplement (LNS) Intervention on Pregnancy and Birth Outcomes in Bangladesh

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Abbreviations and Acronyms

AGP	alpha-1 acid glycoprotein
ANC	antenatal care
ANCOVA	analysis of covariance
AOR	adjusted odds ratio
ARR	adjusted relative risk
BMI	body mass index
BMIZ	body mass index z-score
cfu	colony forming units
CHDP	Community Health and Development Program
CHW	community health worker
CI	confidence interval
cm	centimeter(s)
CRP	C-reactive protein
ELISA	enzyme-linked immunosorbent assay
g	gram(s)
Hb	hemoglobin
HCZ	head circumference-for-age z-score
ICC	intracluster correlation
IFA	iron and folic acid
FANTA	Food and Nutrition Technical Assistance III Project
IOM	Institute of Medicine
kcal	kilocalorie(s)
kg	kilogram(s)
LAZ	length-for-age z-score
LBW	low birth weight
L	liter(s)
LMP	last menstrual period
LNS	lipid-based nutrient supplement(s)
LNS-C	lipid-based nutrient supplement(s) for children

LNS-PL	lipid-based nutrient supplement(s) for pregnant and lactating women
m^2	square meter(s)
mg	milligram(s)
MMN	multiple micronutrient(s)
MNP	micronutrient powder(s)
MUAC	mid-upper arm circumference
OLS	ordinary least squares
OR	odds ratio
PNC	postnatal care
RDNS	Rang-Din Nutrition Study
RBP	retinol-binding protein
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SDU	safe delivery unit
SE	standard error
SGA	small for gestational age
sTfR	soluble transferrin receptor
Tk	Bangladeshi taka
UCD	University of California, Davis
UNIMMAP	UNICEF/World Health Organization (WHO)/United Nations University international multiple micronutrient preparation
UIC	urinary iodine concentration
US$	United States dollar(s)
USAID	United States Agency for International Development
VHV	village health volunteer
WAZ	weight-for-age z-score
WHO	World Health Organization

Executive Summary

Research on improving maternal nutrition via provision of nutrient or food supplements during pregnancy has focused mainly on iron and folic acid (IFA), multiple micronutrients, or balanced energy protein supplementation. A new approach—to provide both micronutrients and some key macronutrients including essential fatty acids—is the use of small-quantity (20 g/day) lipid-based nutrient supplements (LNS) for enriching home-based foods for pregnant and lactating women. The Rang-Din Nutrition Study (RDNS) in rural Bangladesh was designed to evaluate the effectiveness (including cost-effectiveness), within a community-based program, of a two-pronged approach aimed at preventing maternal and child undernutrition during the first "1,000 days": provision of LNS for pregnant and lactating women (LNS-PL) to women during pregnancy and the first 6 months postpartum, and provision of another formulation of LNS to their offspring from 6 to 24 months of age. Our hypothesis was that this approach would result in improvements in indicators of maternal and child health and nutrition among the study participants, compared to the provision of IFA during pregnancy and the first 3 months postpartum.[1] This report describes the effects of LNS-PL supplementation on pregnancy and birth outcomes, including infant birth size and gestational age; maternal weight gain during pregnancy; complications of pregnancy and childbirth; maternal hemoglobin, iron status, inflammatory markers, vitamin A status, and iodine status; and health care expenditures during pregnancy and childbirth.

The RDNS was conducted in 11 rural unions of the Badarganj and Chirirbandar subdistricts of the northwest region of Bangladesh and was carried out by three partners: LAMB (previously known as Lutheran Aid to Medicine in Bangladesh); icddr,b; and the University of California, Davis (UCD). LAMB was responsible for providing the study interventions to the study population via their Community Health and Development Program (CHDP), including the delivery of nutrient supplements. UCD and icddr,b jointly evaluated the interventions.

The study was designed as a researcher-blind, longitudinal, cluster-randomized effectiveness trial with four arms:

- Comprehensive LNS group, in which women received LNS-PL during pregnancy and the first 6 months postpartum, and their children received LNS for children (LNS-C) from 6 to 24 months of age
- Child-only LNS group, in which women received IFA (one tablet of 60 mg of iron and 400 µg of folic acid) daily during pregnancy and every alternate day during the first 3 months postpartum, and their children received LNS-C from 6 to 24 months of age
- Child-only micronutrient powder (MNP) group, in which women received IFA daily during pregnancy and every alternate day during the first 3 months postpartum, and their children received MNP containing 15 micronutrients from 6 to 24 months of age
- Control group, in which the women received IFA daily during pregnancy and every alternate day during the first 3 months postpartum, and their children received no supplements

In this report, the results for women in the comprehensive LNS group are compared with results for women in the other three groups combined, all of whom received IFA during pregnancy.

[1] The World Health Organization and the Government of Bangladesh recommend providing IFA daily for at least 3 months postpartum, but we provided IFA (60 mg) every alternate day to the control group because the recommended daily allowance for iron during lactation is only 9 mg and the tolerable upper-intake level is 45 mg (Arimond et al. 2013).

In the RDNS, we defined a cluster as the supervision area of a community health worker of LAMB. The study was implemented in all 64 clusters within the 11 study unions. Each of the four study arms included 16 clusters. The intervention activities of the study were incorporated into the existing CHDP activities of LAMB. The community health workers of the CHDP identified pregnant women as part of LAMB's pregnancy surveillance system, and RDNS staff subsequently screened and enrolled eligible women into the evaluation component of the study. Baseline data at enrollment were collected during a home visit, which was followed by a visit at the local safe delivery unit (SDU) for anthropometry (all women) and collection of bio-specimens from a randomly selected subsample. Follow-up data collection during pregnancy occurred at 35 to 36 weeks of gestation, at the home, and at the SDU. After delivery, the study protocol required that each woman and the newborn child be visited within 72 hours after birth. Data on adherence to LNS-PL and IFA during pregnancy were collected retrospectively at another home visit at 6 weeks postpartum. Health care expenditure data were collected at baseline, 36 weeks of gestation, and 6 weeks postpartum.

Between October 15, 2011, and August 31, 2012, we screened 4,410 pregnant women for eligibility and enrolled 4,011 (1,047 in the LNS group and 2,964 in the three IFA groups). The women received the first supply of LNS-PL or IFA during the first SDU visit. LNS-PL distribution was interrupted from August 8 to October 20, 2012, in order to comply with a new quality-control criterion for ready-to-use supplementary foods, implemented by the World Food Programme, which required the absence of *Cronobacter sakazakii* (i.e., no samples testing positive at any level). During the interruption, women in all arms received IFA. New quality control specifications for this type of bacteria in LNS were issued in January 2014; none of the batches used in the RDNS exceeded the level in the new specifications.

Primary data analysis was performed based on intention-to-treat (i.e., no women were excluded from the analysis based on adherence to the supplements). We also conducted per-protocol analyses by confining the analysis to those who reported consuming their assigned supplement at least four times per week, on average, during the pregnancy. A separate exploratory analysis was done to examine the effects of the intervention on children who were born before the 10-week disruption in the supply of LNS-PL.

At baseline, sociodemographic, anthropometric, and obstetric characteristics of pregnant women were similar between intervention groups. On average, the women were ~22 years of age and had ~6 years of education. Mean height was 151 cm, mean BMI was ~20 kg/m^2, about a third of the women were thin (BMI < 18.5 kg/m^2), and ~39 percent to 42 percent were nulliparous. The mean gestational age at enrollment was 13 weeks in both groups. Based on maternal recall of overall adherence throughout pregnancy, the percentage of mothers reporting regular consumption (at least four times per week) was 64 percent in the LNS group and 92 percent in the IFA group ($p < 0.001$).

With regard to birth size, the intention-to-treat results indicated that provision of LNS-PL during pregnancy (compared with IFA) significantly increased mean birth weight, weight-for-age z-score, length, length-for-age z-score (LAZ), head circumference, head circumference-for-age z-score (HCZ), and body mass index (BMI) z-score (BMIZ) and reduced the prevalence of newborn stunting, small head size, and low BMI at birth. Newborn stunting (LAZ < -2) was reduced by 17 percent in the sample as a whole, by 25 percent in per-protocol analyses, and by 31 percent among infants born before the disruption in supply of LNS-PL. The effect on the prevalence of stunting was greater than would be expected based on the relatively small difference in mean LAZ. This can be explained by the shift in the distribution of LAZ at birth: LNS-PL reduced the proportion of newborns with low LAZ but had much less effect on the mean or upper end of the LAZ distribution. The percentage of newborns with a small head size (HCZ < -2) was reduced by 17 percent in the sample as a whole, by 19 percent in per-protocol analyses, and by 22 percent among infants born before the disruption in supply of LNS-PL. The prevalence of wasting (BMIZ < -2) at

birth was reduced by 9 percent in the sample as a whole and by 11 percent in per-protocol analyses (the difference was not significant among infants born before the disruption in supply of LNS-PL).

We did not find significant main effects of LNS-PL on duration of gestation or preterm delivery. However, subgroup analyses revealed that LNS-PL increased the duration of gestation by 0.5 weeks among women in very food-insecure households, and by 0.3 weeks among women carrying female infants.

We explored whether the magnitude of the effect of LNS-PL on birth size differed depending on several pre-defined, biologically plausible potential effect modifiers. We found a greater effect of LNS-PL among women in food-insecure households, with respect to newborn stunting, birth weight, and head circumference (as well as duration of gestation, as mentioned above). There was also a greater effect of LNS-PL on newborn stunting among mothers who were 14–24 years of age than in older women.

In the study group as a whole, there was no significant effect of LNS-PL on maternal weight gain during pregnancy. This is not surprising given that LNS-PL contains only 118 kcal of energy. However, we found that LNS-PL increased maternal weight gain during pregnancy (+34 g/week) among multiparous women > 25 years of age. In addition, per-protocol analyses indicated a significant group difference of 12 g/week, which points to the potential for broader benefits of LNS-PL if it were consumed regularly.

There were no differences in average blood pressure at 36 weeks of gestation or proportions of women with pregnancy or childbirth complications between the LNS and IFA groups. LNS-PL did not reduce the prevalence of high blood pressure at 36 weeks (a proxy indicator for pre-eclampsia) but < 2 percent of study women had high blood pressure at that time point. It is reassuring that there were no significant differences between intervention groups in the percentage of women with prolonged labor, obstructed labor, or cesarean section, given that infants in the LNS group were larger at birth (including increased head circumference and birth weight).

In this sample of women, there were no differences in hemoglobin levels or risk of low or high hemoglobin at 36 weeks of gestation between those who received LNS-PL and those who received IFA. However, women in the LNS group had lower iron status and higher risk of iron deficiency and iron deficiency anemia at 36 weeks, compared to women in the IFA group. Nevertheless, iron deficiency anemia was relatively uncommon in both groups (14.6 percent for LNS and 8.7 percent for IFA). The difference in iron status between groups was not surprising, given the much larger dose of iron in the IFA group (60 mg/day versus 20 mg/day). It is possible that the amount of iron in LNS-PL was too low. However, it is not clear whether the difference in maternal iron deficiency anemia at 36 weeks observed in the LNS group would have negative functional consequences, given that there is debate about the most appropriate cutoffs to use for both hemoglobin and markers of iron status during pregnancy, and given that birth outcomes were better in the LNS group despite lower maternal iron status at 36 weeks of gestation.

With regard to vitamin A status, average retinol-binding protein (RBP) concentration and prevalence of low RBP (< 1.17 µmol/L) at 36 weeks of gestation did not differ significantly between women who received LNS-PL and those who received IFA. The prevalence of low RBP (23.4 percent in the LNS group and 27.5 percent in the IFA group) was relatively low compared to previous studies. Our dietary recall data revealed that a large proportion of women in this study population had consumed fish, meat, dairy products, and green leafy vegetables during the week prior to data collection. These foods are good sources of vitamin A and β-carotene, so the lack of significant differences in vitamin A status between the LNS and IFA groups may be explained by the relatively high consumption of vitamin A-containing foods, and low prevalence of vitamin A deficiency at baseline.

Surprisingly, there were no significant differences in average urinary iodine concentration (UIC) at 36 weeks of gestation between those who received LNS-PL and those who received IFA, although the women in the LNS group tended to have a lower prevalence of low UIC when the lowest cutoff of < 50 µg/L was used. The prevalence of iodine deficiency (UIC <150 µg/L) was very high at 36 weeks of gestation. We are not sure why daily supplementation of 250 µg of iodine via LNS-PL did not appear to adequately protect pregnant women in the study area from iodine deficiency. One possibility is that the iodine in LNS was indeed taken up, but was stored in the thyroid gland (due to the high prevalence of iodine deficiency) instead of being excreted in urine, which would imply that UIC is not an adequate marker of iodine status in this situation.

Provision of LNS-PL did not change pregnancy-related health care expenditures during late pregnancy or childbirth or during the 42-day postpartum period when compared with the provision of IFA, nor did it affect antenatal and postnatal care-seeking decisions during pregnancy or in the first 6 weeks postpartum. Provision of LNS-PL was associated with a greater likelihood of seeking hospital care, but this effect was based on very few women who sought hospital care during the study period, some several times.

We conclude that LNS-PL supplementation during pregnancy reduced prevalence of newborn stunting, low BMI, and small head size in the study population. These effects occurred without a significant impact on duration of gestation, suggesting that LNS-PL reduces fetal growth restriction but not preterm delivery. To our knowledge, this is the first study to report an effect of a prenatal nutrient or food supplement containing multiple micronutrients on the prevalence of newborn stunting. As a whole, the study women were at high risk for fetal growth restriction, given that about a third of them had low BMI and 39 percent were under 20 years of age. Reduction of newborn stunting by LNS-PL was most evident among younger women and those residing in households experiencing 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 serving similar populations. There was little effect on the other outcomes included in this report, with the exception of the following differences in the LNS group when compared with the IFA group: 1) greater maternal weight gain during pregnancy among multiparous women > 25 years of age; 2) lower iron status and higher risk of iron deficiency and iron deficiency anemia at 36 weeks of gestation; and 3) a trend toward a lower prevalence of low UIC at 36 weeks of gestation, when the lowest cutoff of UIC (< 50 µg/L) was used. Additional research on the optimal composition of LNS-PL for reducing maternal micronutrient deficiencies, while still promoting fetal growth, is needed.

1 Introduction

The most common approaches for improving maternal nutrition and birth outcomes include iron and folic acid (IFA) supplementation, balanced energy protein supplementation, and multiple micronutrient (MMN) supplementation. Daily or intermittent iron supplementation is effective for reducing maternal anemia, maternal iron deficiency, and the incidence of low birth weight (LBW) (Pena-Rosas et al. 2012). Balanced energy protein supplementation has been shown to reduce the incidence of small for gestational age (SGA) by 34 percent and increase birth weight by an average of 73 g (Imdad et al. 2012). MMN supplementation is as effective as IFA in reducing anemia and LBW (Ramakrishnan et al. 2012) but may provide additional benefits including the reduction of SGA and preterm birth (West et al. 2013). 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 (LNS) for enriching home-based foods for pregnant and lactating women (Arimond et al. 2013). Such supplements, herein referred to as LNS for pregnant and lactating women (LNS-PL), are similar in ingredients to LNS used for enriching complementary foods for infants (Adu-Afarwuah et al. 2007; Adu-Afarwuah et al. 2008) but are fortified with the amounts of micronutrients needed during pregnancy and lactation.

The Rang-Din Nutrition Study (RDNS) in rural Bangladesh was designed to evaluate the effectiveness (including cost-effectiveness), within a community-based program, of a two-pronged approach aimed at preventing maternal and child undernutrition during the first "1,000 days": provision of LNS-PL to women during pregnancy and the first 6 months postpartum, and provision of another formulation of LNS to their offspring from 6 to 24 months of age. Our hypothesis was that this approach would result in larger positive changes in indicators of maternal and child health and nutrition among the study participants than the provision of IFA during pregnancy and the postpartum period.[2]

Bangladesh is an appropriate setting in which to evaluate the effectiveness of this approach. The prevalence of LBW is 37 percent (National Low Birth Weight Survey of Bangladesh 2005), more than 20 percent of infants are born stunted [length-for-age z-score (LAZ) < -2], and more than 30 percent are wasted (weight-for-length z-score < -2) at birth (NIPORT et al. 2013). Although Bangladesh has made some progress in reducing child mortality (NIPORT et al. 2013), there has been little improvement in anthropometric indicators. For example, between 2007 and 2011, the prevalence of childhood stunting decreased only slightly, from 43 percent to 41 percent (NIPORT et al. 2013).

Maternal undernutrition is prevalent, with about one in four women of reproductive age being underweight [body mass index (BMI) < 18.5 kg/m^2] (NIPORT et al. 2013). The degree of micronutrient inadequacy among women in rural Bangladesh is also alarming (Arsenault et al. 2013). For example, in 2011-12, 40 percent of non-pregnant and non-lactating women had low vitamin A status (serum retinol < 1.05 µmol/L) (icddr,b et al. 2013), and in 2008, 51 percent of pregnant women were classified with low serum retinol, with 19 percent having vitamin A deficiency (serum retinol < 0.7 µmol/L) (Lee et al. 2008).

Iodine deficiency [urinary iodine concentration (UIC) < 100 µg/L] affected 42 percent of non-pregnant and non-lactating women in 2011-12 (icddr,b et al. 2013). However, the prevalence of iodine deficiency among pregnant women varies widely, from 6 percent in a recently published study in Matlab in central Bangladesh (Rydbeck et al. 2014) to 80 percent in a study in northern Bangladesh (Shamin et al. 2012).

[2] The World Health Organization and the Government of Bangladesh recommend providing IFA daily for at least 3 months postpartum, but we provided IFA (60 mg) every alternate day to the control group because the recommended daily allowance for iron during lactation is only 9 mg and the tolerable upper-intake level is 45 mg (Arimond et al. 2013).

Though Bangladesh is implementing a universal salt iodization program, only 58 percent of salt samples in a nationally representative sample contained adequate iodine (≥ 15ppm) (icddr,b et al. 2013).

The prevalences of anemia and iron deficiency also vary by location within Bangladesh. In Matlab, the prevalence of anemia during pregnancy (~21 weeks of gestation) was 50 percent and the prevalence of iron deficiency was 54 percent (Hyder et al. 2004). By contrast, recent data from a rural area in northwest Bangladesh where iron content of domestic groundwater sources is high indicated much lower rates among pregnant women (19 percent for anemia and < 1 percent for iron deficiency) (Shamim et al. 2013).

There are many adverse consequences of maternal undernutrition during pregnancy. Low maternal weight is linked to poor fetal growth and other suboptimal pregnancy outcomes (Siega-Riz et al. 2009; Abu-Saad and Fraser 2010). Vitamin A deficiency during pregnancy increases the risk of maternal night blindness, anemia, morbidity, and mortality (Lee et al. 2008), as well as fetal growth restriction and preterm birth (Christian et al. 2013). Iodine deficiency during pregnancy is associated with increased risk of spontaneous abortion, stillbirth, perinatal mortality, and impaired neurodevelopment in the offspring (Rydbeck et al. 2014). Anemia during pregnancy has been associated with preterm delivery (Scholl and Riley 2000; Haider et al. 2013), SGA (Kozuki et al. 2012), and perinatal and maternal mortality (Stoltzfus et al. 2004). Complications during pregnancy and childbirth are very common in Bangladesh. In a study of 42,214 pregnant women in northwest Bangladesh, 25 percent suffered from at least one obstetric complication and 2 percent suffered from life threatening conditions; regarding more serious complications, 12 percent of women had hemorrhage, 11 percent had obstructed labor, 8 percent had sepsis, and 1 percent had eclampsia (Sikder and Labrique 2014).

These adverse consequences not only affect maternal and infant health but also may increase both private and public expenditures for health care. Little is known about the determinants of household health care-seeking behavior (Kea et al. 2011), but for households existing near subsistence-level incomes, even small expenditures on health care can be financially difficult (Xu et al. 2003; Su et al. 2006). Households choose their optimal health investments in pregnant women and children based on the prevalence of illness, expected costs of care, and expected benefits of care. The effects of nutrient supplementation on health care-seeking behavior are not well documented.

In the context of the RDNS, households may view LNS as a substitute for seeking antenatal care (ANC) or postnatal care (PNC), or may believe that improved maternal nutrition lessens the need for seeking care for acute illnesses (or may actually reduce the incidence or severity of illnesses), thus leading to a decrease in health expenditures in response to supplementation with LNS. Alternatively, households could view other forms of health care as complements to improved nutrition, increasing the perceived benefits of receiving health care, and thus LNS supplementation could lead to an increase in health care seeking. We seek to better understand the determinants of health care choices in the context of the RDNS, with particular attention to LNS provision and the health care decisions taken during roughly the first third of the critical 1,000-day period, when most of the benefits of LNS are unobserved.

This report describes the effects of LNS-PL supplementation on pregnancy and birth outcomes in the RDNS, including infant birth size and gestational age; maternal weight gain during pregnancy; complications of pregnancy and childbirth; maternal hemoglobin (Hb), iron status, inflammatory markers, vitamin A status, and iodine status; and health care expenditures during pregnancy and childbirth.

2 Methods

2.1 Study Site, Design, and Ethics Statement

2.1.1 Study Setting and Population

The study was conducted in 11 rural unions of the Badarganj and Chirirbandar subdistricts of the northwest region of Bangladesh, approximately 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 (Bangladesh Bureau of Statistics 2011). The study subdistricts are located in one of the poorest areas of Bangladesh, with ≥ 48 percent of people living below the poverty line; in 2011, average household size was four, 52 percent of the population > 7 years of age was illiterate, 31 percent of households had electricity, 98 percent had access to safe drinking water, and 75 percent had access to toilets or latrines (Bangladesh Bureau of Statistics 2011). The major economic activities in the area include farming, transportation, construction, and petty trading.

Health services in the area are provided by both public and private sectors. In each union, three to four public health facilities provide primarily maternal and child health services. Several private-sector nongovernment organizations including LAMB (previously known as Lutheran Aid to Medicine in Bangladesh) and BRAC (previously known as Bangladesh Rural Advancement Committee) also provide community-based health services for women and children. The health services from LAMB, one of the partners for this study, are provided through its Community Health and Development Program (CHDP). For pregnant women, these health services include maternity services at a safe delivery unit (SDU) in each union and regular home visits for antenatal, postnatal, and child care by village health volunteers (VHV) and community health workers (CHW).

The study was carried out by three partners: LAMB; icddr,b; and the University of California, Davis (UCD). LAMB was responsible for providing the study interventions to the study population, including delivery of nutrient supplements (described below). UCD and icddr,b jointly evaluated the interventions.

2.1.2 Study Design and Randomization

The overall aim of the RDNS was to evaluate the impact of nutrient supplementation during the first 1,000 days on the nutritional status of pregnant and lactating women and on the growth, nutritional status, and development of their children. The trial was designed as a researcher-blind, longitudinal, cluster-randomized effectiveness trial with four arms in the ratio of 1:1:1:1 (Table 1). The study arms were:

- Comprehensive LNS group, in which women received LNS-PL (Table 2) during pregnancy and the first 6 months postpartum, and their children received LNS for children (LNS-C) from 6 to 24 months of age
- Child-only LNS group, in which women received IFA (one tablet of 60 mg of iron and 400 µg of folic acid) daily during pregnancy (the standard of care) and every alternate day during the first 3 months postpartum, and their children received LNS-C from 6 to 24 months of age
- Child-only micronutrient powder (MNP) group, in which women received IFA daily during pregnancy and every alternate day during the first 3 months postpartum, and their children received MNP containing 15 micronutrients from 6 to 24 months of age
- Control group, in which the women received IFA daily during pregnancy and every alternate day during the first 3 months postpartum, and their children received no supplements

Table 1. RDNS Interventions for Pregnant and Lactating Women and Their Children by Study Arm

Arm	Interventions for Pregnant and Lactating Women	Interventions for Children
1 Comprehensive LNS	LNS-PL during pregnancy and 6 months postpartum	LNS-C from 6 to 24 months
2 Child-only LNS	IFA during pregnancy and every other day during the first 3 months postpartum	LNS-C from 6 to 24 months
3 Child-only MNP	IFA during pregnancy and every other day during the first 3 months postpartum	MNP from 6 to 24 months
4 Control	IFA during pregnancy and every other day during the first 3 months postpartum	None

As seasonality (time interval) was reported to be associated with some of the key outcomes of the study (e.g., birth weight) (Sebayang et al. 2012), we planned to recruit the women over a 1-year period so that all seasons would be represented.

We defined a cluster as the supervision area of a CHW of LAMB. Each cluster covered a population of approximately 2,500 to 6,000 people and had three to six 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 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 UCD first stratified the 64 clusters by subdistrict and union, and then assigned each cluster to one of four 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 health facilities and health workers per 1,000 people, number of health- or nutrition-related nongovernmental organizations in the cluster, and the source of funding for the CHDP, as well as the standard deviation (SD) of the cluster population size. The final randomization to the four arms was then chosen at random from the acceptable potential randomizations; the letters A, B, C, and D were assigned to the four sets, randomly permuting them by sorting on a randomly generated uniformly distributed number (using SAS for Windows release 9.2) and assigning them to control, child-only MNP, child-only LNS, and comprehensive LNS treatments.

2.1.3 Ethical Review

The study protocol was approved by the institutional review boards of UCD, 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 community representatives 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.

2.2 Study Interventions

LNS-PL (20 g/d, 118 kcal/d) was modeled on the UNICEF/World Health Organization (WHO)/United Nations University international multiple micronutrient preparation (UNIMMAP) for pregnant and lactating women and similar products used in Ghana and Malawi (Arimond 2013). Ingredients included soybean oil, powdered milk, peanut paste, sugar, and MMN. Because production of LNS in Bangladesh has not yet been established, LNS-PL was produced by Nutriset SA in Malaunay, France, in individual 20-g sachets. The dose of IFA was based on WHO recommendations (WHO 2012). IFA tablets were produced by Hudson Pharmaceuticals Ltd. in Bangladesh. As this report only covers pregnancy and childbirth, we will not describe the supplements for children and the research design pertinent to child outcomes (other than newborn outcomes) in detail.

Delivery of the supplements was carried out by LAMB CHDP staff in accordance with the randomization plan developed by the statistician at UCD, 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 were 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 study participants, regardless of the study arm into which they were enrolled. The first 1-month supply of supplements for each woman enrolled was delivered by the CHW at the SDU right after the first SDU visit for anthropometry and bio-specimen collection by the 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 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; nine health education messages were printed on the cards in the local language, Bengali, and were also explained verbally. Depending on the cluster, the CHWs also counseled the pregnant woman to consume either one IFA tablet with water each day after eating a large meal, or one 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 one 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 (which was also printed on the registration card and on the supplement container labels) to all women: "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. These messages were additional to the standard messages given to all pregnant women in the regular CHDP program, which included "eat more during each meal," "avoid heavy work," and "rest two hours during the daytime." Women receiving RDNS supplements 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 IFA 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 August 8 to October 20, 2012, in order to comply with a new quality-control criterion for ready-to-use supplementary foods implemented by the World Food Program that required the absence of *Cronobacter sakazakii* (i.e., no samples testing positive at any level). *C.*

Sakazakii is present in many foods and considered an opportunistic pathogen. *C. sakazakii* can cause sepsis and meningitis in young infants (< 2 months of age), but potential risk to older infants, children, and adults are considered to be much lower (CDC 2014). During the interruption, women in all arms received IFA. Subsequently, new specifications for LNS were issued in January 2014 (http://foodqualityandsafety.wfp.org/specifications) indicating that products must have less than 10 cfu/g (for all Enterobacteriaceae). None of the batches used in the RDNS exceeded that level.

Table 2. Composition of Supplements Used for Women in the Study

Nutrient	LNS-PL	IFA Tablet
Ration (g/day)	20	1 tablet
Total energy (kcal)	118	0
Protein (g)	2.6	0
Fat (g)	10	0
Linoleic acid (g)	4.59	0
α-Linolenic acid (g)	0.59	0
Vitamin A (µg Retinol Equivalents- RE)	800	0
Vitamin C (mg)	100	0
Vitamin B1(mg)	2.8	0
Vitamin B2 (mg)	2.8	0
Niacin (mg)	36	0
Folic acid (µg)	400	400
Pantothenic acid (mg)	7	0
Vitamin B6 (mg)	3.8	0
Vitamin B12 (µg)	5.2	0
Vitamin D (IU)	400	0
Vitamin E (mg)	20	0
Vitamin K (µg)	45	0
Iron (mg)	20	60
Zinc (mg)	30	0
Cu (mg)	4	0
Calcium (mg)	280	0
Phosphorus (mg)	190	0
Potassium (mg)	200	0
Magnesium (mg)	65	0
Selenium (µg)	130	0
Iodine (µg)	250	0
Manganese (mg)	2.6	0
Ration (g/day)	20	1 tablet

2.3 Enrollment 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; such women were subsequently visited by CHWs who conducted pregnancy tests with urine strips (Quick Check®). After confirmation of pregnancy, the CHW recorded basic information (e.g., name, age, address, 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 collection described below were collected by evaluation staff from icddr,b.

Data collection was performed by two separate teams: the "SDU team," who collected clinical and anthropometric data at the SDU and the "home visit team," who 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 assessment of the eligibility of each newly pregnant woman for the study evaluation (based on 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 to screen them for the evaluation study. The eligibility criteria included gestational age ≤ 20 weeks and no plans to move out of the study area during pregnancy or the following 3 years (i.e., a permanent resident of the study area). 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 anthropometry were done and bio-specimens (urine and blood) were collected from an individually randomized subsample. If a woman failed to come to the SDU during the week following 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 two consecutive study appointments, she was considered missing for that visit and her 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 week of gestation and a subsequent SDU visit (at 36 weeks) for anthropometry, assessment of depressive symptoms, collection of health expenditure data, and collection of bio-specimens by the SDU team. The study protocol also required that each woman be visited within 72 hours of giving birth to collect data on care seeking during pregnancy, congenital anomalies, newborn feeding practices, maternal and newborn morbidity, and health expenditures, and to measure the newborn. To coordinate birth visits, a call center was established to communicate with each study participant and her family. Each woman was called at 28 weeks of gestation and every week from 36 weeks gestation until the delivery occurred. The family was given the telephone numbers of the call center and requested to call immediately after the childbirth.

At each SDU assessment, pre-defined criteria were used to refer women and children with certain conditions (e.g., severe anemia, depression) to specific hospitals or physicians for treatment as per LAMB's usual integrated rural health approach.

Data on adherence to LNS-PL and IFA during pregnancy, and on health expenditures since 36 weeks of gestation, were collected at a home visit at 6 weeks postpartum. The women were asked how often they consumed the nutrient supplements during pregnancy. There were five possible responses: "Did not take at all," "Used to take sometimes (1–3 days/week)," "Used to take almost every day (4–6 days/week)," "Used to take regularly every day," and "other."

2.4 Collection of Biological Samples

Blood and urine samples were collected from a randomly selected subsample of women during the SDU visits (Table A-1). Sealed envelopes with information on assignment to subsamples (including those for other assessments) were prepared for each participant (1,200 per arm) before enrollment. Our original target sample size for the biological sample subsample was n=914 (Table A-1).

Capillary puncture using a system specifically designed to collect capillary blood was done. Finger pricks were performed preferably on the middle or ring finger of a woman's left hand while she was sitting. The first drop of blood was wiped with dry cotton, and light pressure was applied to the end of the finger if needed to re-stimulate blood flow. A cuvette and a Microvette CB 300 Z were used for sample collection. The cuvette was used for Hb measurement approximately 45 seconds after collection. The microvette was kept in a rack for at least 15 to 20 minutes and then put in a cool bag. Thereafter, serum and red blood cells were separated at the RDNS field lab using a microcentrifuge and micropipettes to transfer serum to the PCR tubes, and a 0.2 ml PCR tube was used to store serum, which was kept at -20˚C until shipment to the laboratory for analysis.

Urine samples were collected for analysis of proteinuria and urinary iodine. Women were given a urine collection cup with two pieces of tissue paper along with urine collection instructions. Upon return of the cup, we collected 2 ml of urine in a cryo-vial that was kept in a cool box. Afterwards, the samples were stored in a -20^{o}C freezer.

2.5 Quality Assurance

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. Distribution of the supplements was coordinated and implemented by LAMB staff, and study evaluation staff only knew group assignment by the prescribed letter (A to D) as described previously.

Quality-control procedures included having the data collection supervisors re-interview 10 percent of randomly selected participating women. During the re-visit, selected questions were asked again and the responses were compared to the original data collected. If there was less than 75 percent 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 the quality of the work and to respond to problems and issues.

2.6 Measurement of Outcome Variables

2.6.1 Duration of Pregnancy

Gestational age at enrollment was calculated based on the first day of the LMP, elicited through maternal recall. The interviewers used Gregorian, Bengali, and Arabic calendars; antenatal cards; and ultrasonogram reports (if any) as additional aids to elicit the date of LMP. Duration of pregnancy was calculated based on gestational age at enrollment and date of birth or termination of pregnancy.

2.6.2 Maternal and Child Anthropometrics

All anthropometrists were trained and methods were standardized at the beginning of data collection and thereafter periodically using methods described by WHO (WHO 2006). At each of the SDU visits, trained anthropometrists measured maternal weight to the nearest 0.1 kg (adult scale, Seca 874), height to the nearest 0.1 cm (ShorrBoard®, Weigh and Measure LLC), and mid upper-arm circumference (MUAC) to the nearest 0.1 cm (Shorrtape, Shorr Productions, USA). Following delivery (at home or hospital), anthropometrists specially trained for newborn anthropometry measured birth weight to the nearest 0.005 kg (infant scale, Doran DS4100), length to the nearest 0.1 cm (ShorrBoard®, Weigh and Measure LLC), and head circumference and MUAC to the nearest 0.1 cm (Shorrtape®, Shorr Productions, USA) generally within 72 hours of birth. For the 11 percent of newborns for whom this was not possible, most (367/513 or 72 percent) were measured within 14 days after birth. The stillborn infants or those infants who had died before the assessment were not measured.

2.6.3 Complications of Pregnancy or Childbirth

Clinical data on pre-eclampsia were collected at the 36-week SDU visit, and data on complications of childbirth were collected within 72 hours of childbirth. Pre-eclampsia was defined as systolic blood pressure ≥ 140 mm of Hg and/or diastolic blood pressure ≥ 90 mm of Hg with proteinuria detected by a dipstick test. Complications of childbirth included prolonged labor (labor pain ≥ 12 hours), early rupture of membrane (rupture of the membrane of the amniotic sac and chorion ≥ 1 hour before the onset of labor), unconsciousness, convulsions, severe headache, high blood pressure, high fever, blurring of vision, obstructed labor, hand/foot/cord prolapse, retained placenta, antepartum hemorrhage, postpartum hemorrhage, and perineal tear.

2.6.4 Maternal Hemoglobin, Iron Status, Inflammatory Markers, and Vitamin A Status

The concentration of Hb was assessed using a portable photoreflectrometer (HemoCue America, Brea, CA, USA) approximately 45 seconds after blood sample collection.

Five serum proteins [ferritin, soluble transferrin receptor (sTfR), retinol-binding protein (RBP), C-reactive protein (CRP), and alpha-1 acid glycoprotein (AGP) were analyzed by a combined sandwich enzyme-linked immunosorbent assay (ELISA) method (Erhardt et al. 2004) at the VitA-Iron Lab (Willstaett, Germany). Briefly, 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 inter-assay coefficients of variation were 3.0 percent for ferritin, 4.6 percent for sTfR, 4.2 percent for RBP, 6.6 percent for CRP and 6.0 percent for AGP, and.

Ferritin (µg/L) and sTfR (mg/L) were measured as indicators of iron status. CRP (mg/L) and AGP (g/L) were measured as indicators of inflammatory response and to assist in the interpretation of the other biomarkers of nutrient status (e.g. ferritin). RBP was measured as an indicator of vitamin A status.

2.6.5 Urinary Iodine

Urine was digested in a microplate (Cat No. 3365, Corning, NY, USA) at 110°C for 60 minutes using a specially designed stainless steel cassette (sealing cassette; Hitachi Chemical Techno-plant, Japan) to prevent loss of vapor and cross-contamination among wells. After the digestion mixture was transferred to a transparent microplate (Cat No. 296787, Nunc, DK-400, Roskilde, Denmark), the Sandell–Kolthoff reaction was performed at 25°C for 30 minutes and then urinary iodine was measured by a microplate reader at 405 nm.

2.6.6 Health Care Expenditures during Pregnancy and Childbirth

Health care expenditure data were collected at baseline, 36 weeks of gestation, and 42 days postpartum. Expenditure information from the two follow-up visits was used in the calculation of the effect of the intervention on health care expenditures. At the 36-week SDU visit, retrospective expenditure information was solicited for all expenditures incurred within the past month. At the 42-day postpartum follow-up, information was solicited for all expenditures that occurred since the 36-week visit. If the 36-week visit was missed (due to birth or other reasons), information was solicited for expenditures occurring since one month prior to the scheduled date of the 36-week visit.

Expenditure data were collected at the aggregate/total level and for specific expenditure categories. The categories included doctor fees, tests, medicines, travel costs, surgery (for birth visit only), and other. Data on time spent dealing with health-related issues were also collected, soliciting the number of days the woman herself was unable to perform her regular daily functions due to illness, birth, or seeking medical care, as well as the number of days any other household members were unable to perform their regular duties in order to take care of the participant while she was sick or seeking medical care.

2.7 Data Review, Entry, and Management

Data collectors manually checked all forms for completeness before leaving the participating woman's home or SDU. The data collection supervisors manually checked all 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 reviewers recorded findings in a data query log, and the team leaders or supervisors corrected mistakes in the forms after contacting the data collectors and participating women.

Data from all data collection forms were double entered in a database created 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 using STATA (version 12.0) to clean the data further. Afterward, the data were further subjected to case-by-case consistency and accuracy examination using STATA (version 12.0). Generated queries were resolved by consulting the original forms; with the help of the data collector or data collection supervisor; or by a repeat home or SDU visit, whenever possible or appropriate.

2.8 Statistical Analyses

2.8.1 Sample Size and Power

We calculated a minimum required sample size of 788 per arm (total of 3,152 in four arms), based on detecting an effect size of > 0.2 (difference between groups, divided by pooled SD) for each continuous outcome with power=80 percent and α=0.05, assuming an intra-cluster correlation=0.01, and allowing for up to 20 percent attrition by the end of the study (i.e., when the children reached 24 months).

2.8.2 Variable Definitions

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 z-score (WAZ) and length-for-age z-score (LAZ). Secondary outcomes were 1) proportion with LBW; 2) proportion with stunting at birth; 3) gestational age (in weeks) at the time of delivery; 4) birth head circumference, defined by crude head circumference (in cm) and birth HCZ; 3) BMI z-score (BMIZ); 4) MUAC; 5) preterm delivery; 6) SGA; and 7) proportion with low BMI.

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 (WHO Child Growth Standards 2011). We used BMIZ as a proxy for weight-for-length z-score because the latter is not calculated for children with length < 45 cm (WHO Child Growth Standards 2006) and exclusion of those infants would create bias. We defined preterm delivery as delivery at < 37 weeks of gestation, LBW as birth weight < 2,500 g, newborn stunting as LAZ < -2 SD, small head size as HCZ < -2, low BMI as BMIZ < -2, and SGA as birth weight below the 10th percentile for infants of the same gestational age from a U.S. population (Alexander et al. 1996).

Imputed values were used for gestational age when the values based on LMP were not credible. Specifically, gestational ages at delivery outside of 28 to 44 weeks, or gestational ages associated with birth weights that were more than 3.5 SD units outside of reference data generated by LAMB from 16,738 singleton babies born at LAMB Hospital and recorded in the LAMB Hospital database (Day et al. 2010), were re-coded as missing and imputed from newborn anthropometric data as well as data on maternal age, parity, height, and BMI (SAS MI procedure). The outcomes "gestational age at delivery" and "gestational age < 37 weeks" were analyzed using the imputed values.

For infants measured between 3 and 14 days after delivery, we back-calculated the weight, length, and head circumference at birth based on their z-scores at the time of measurement, using LMS (L for lambda, M for mu, and S for SD) values and formulae described by WHO (WHO Child Growth Standards 2006), 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. Eighty-three infants died within the first 7 days, and anthropometric data were available for 22 of them.

Maternal weight gain per week (in g) during pregnancy was calculated as the difference between maternal weight measured at the 36-week visit minus maternal weight measured at baseline, divided by the number of weeks between these two measurements. Low weight gain was defined as weekly weight gain less than 80 percent of the lower end of the Institute of Medicine (IOM) weekly weight gain recommendations (IOM and NRC 2009) according to the mother's BMI category (i.e. cutoffs were < 0.8 lb/week for underweight, < 0.64 lb/week for normal weight, < 0.4 lb/week for overweight, and < 0.32 lb/week for obese women). We based this lower cutoff on the average weekly weight gain of women in the normal weight category in our sample, which was 80 percent of the lower end of the IOM recommended weekly weight gain range for women in the same weight category.

Hb was dichotomized using several different cutoffs. Low Hb was defined as Hb < 100 g/L and high Hb was defined as Hb >130 g/L. We also used other Hb cutoffs for exploratory analyses: Hb < 90 g/L (Kozuki et al 2012), Hb < 110 g/L (WHO 2011), and Hb > 145 g/L (Gonzales et al 2011). These lower and higher cutoffs were selected due to their association with suboptimal birth outcomes (Yip 2000).

For ferritin, we used an adaptation of the approach suggested by Thurnham et al (2010) to mathematically adjust individual values for the presence of inflammation or infection, as measured by acute-phase proteins (i.e., CRP and AGP). Thus, we adjusted ferritin values based on the presence of inflammation or infection according to the following 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). Thurnham et al. proposed mathematical adjustment based on a four-category variable but because there were few women in one of these categories, we combined early and late convalescence into one category (i.e. convalescence). Since ferritin levels differed among these three categories, we followed the Thurnham et al. approach and computed sample-specific adjustment factors from the RDNS data, using the ratio of the geometric mean ferritin in the reference category to the geometric mean ferritin in each of the other two categories. We applied the resulting sample-specific correction factors (i.e. 0.95 for

the incubation and 0.79 for the convalescence category) to create adjusted ferritin values for each individual.

Ferritin and sTfR were dichotomized as follows: low ferritin was defined as ferritin < 12 µg/L (IOM 1990), and high sTfR was defined as sTfR > 8.3 mg/L (Erhardt et al. 2004). Iron deficiency was defined as ferritin < 12 µg/L or sTfR > 8.3 mg/L. Iron deficiency anemia was defined as Hb < 110 g/L and either ferritin < 12 µg/L or sTfR > 8.3 mg/L.

CRP and AGP concentrations were dichotomized to create the following variables: high CRP (CRP > 5.0 mg/L), high AGP (AGP > 1.0 g/L), and inflammation (CRP > 5.0 mg/L or AGP > 1.0 g/L) (Thurnham et al. 2010).

Vitamin A status was based on RBP concentration, with low RBP defined as < 1.17 µmol/L and vitamin A deficiency defined as RBP < 0.83 µmol/L (Engle-Stone et al. 2011).

Iodine status was based on UIC. Three cutoffs were used to examine low UIC: < 150 (WHO), < 100, and < 50 µg/L (Shamim et al. 2012).

From several socioeconomic status variables, we used principal components analysis to calculate a household assets index, in which higher values represented higher socioeconomic status. The index was constructed from a set of 19 yes/no questions about whether or not a household owned a particular item, of which we used the 14 items owned by at least 5 percent of households. These items included televisions, irrigation pumps, tables, bicycles, sewing machines, and other goods. The Household Food Insecurity Access Scale (Coates and Swindale 2007) was used to categorize participants into four 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-month 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 closely to the period of LNS 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.

For health care expenditures, we considered four types of care seeking: ANC/PNC, hospital care, giving birth (including births in the hospital), and acute care, defined as any visits that were not included in the other categories (e.g., regular doctor visits for illness or injury). We examined whether any visits occurred, the number of visits, the total expenditure for the visits, and how many days a woman or another member of her household were unable to perform their regular duties while ill or seeking medical attention. Several women reported “unknown” for total expenditures on a particular medical care-seeking visit. Expenditures and time values for these visits were imputed using mean expenditure (for those with expenditure greater than 0) by expenditure type, survey round, and intervention group. Alternative specifications that considered these visits to have 0 expenditure did not qualitatively change the results, nor did exclusion of all 0 values (a test of the “intensive margin” of treatment, or how much was spent by those who sought care in the first place). Imputation that assigned expenditure a value based only on survey round and expenditure type (pooling the experimental groups without differentiation) also did not qualitatively affect the results.

2.8.3 Hypothesis Testing

A detailed data analysis plan was developed before starting each analysis and revealing group assignment. For this report, the three groups of women who received IFA during pregnancy were combined and compared with the "comprehensive LNS" arm for the analysis of pregnancy and birth outcomes. Primary analysis was performed based on intention-to-treat (i.e., no women were excluded from the analysis based on adherence to the supplements). We also conducted per-protocol analyses by confining analyses to those who reported consuming their assigned supplement at least four times per week, on average, during the pregnancy. A separate exploratory analysis was done to examine the effect of the intervention on children who were born before the interruption of LNS-PL. To account for the interruption in LNS-PL, we tested models that included the number of days a woman participated in the study during the interruption period. However, we found that this did not improve the model fit, when compared with including the time interval variable and its interaction with intervention group in the model; therefore, we did not continue with this approach. All analyses adjusted for the randomization by accounting for union (nested within subdistrict) and the random effect of cluster (except for the health expenditures analyses, in which there was no adjustment for union).

For pregnancy, maternal and birth outcomes, maternal blood pressure, and complications of pregnancy and childbirth, effects of the intervention were analyzed using mixed model analysis of covariance (ANCOVA) for continuous outcomes, and mixed model logistic regression for dichotomous outcomes. Adjusted models 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. Additionally, models for blood pressure outcomes included baseline blood pressure and excluded child sex as covariates. In the analysis of continuous outcomes, we first calculated unadjusted group means, before repeating those analyses with adjustments for covariates previously specified in our statistical plan. In the analysis of dichotomous outcomes, we calculated unadjusted group percentages and 95 percent confidence intervals (CIs); statistical comparisons were based on covariate-adjusted log odds of the outcome occurring. Multivariate-adjusted risk ratios for dichotomous outcomes were calculated using an adaptation of Spiegelman and Hertzmark's (2005) approach.

In pre-defined subgroup analysis (ClinicalTrials.gov [NCT01715038]), we tested for interactions between intervention group and each of the covariates listed above by including each interaction term in the adjusted models. For significant effect modifiers ($p < 0.10$), we assessed the adjusted group effect at different levels of the effect modifier (SAS LSMEANS option). When assessing the group effect at different levels of any significant effect modifier, we adjusted for multiple comparisons using the Tukey-Kramer approach. Adjusted relative risks (ARRs), along with their 95 percent CIs were estimated with the method recommended by Spiegelman and Hertzmark (2005), modified to account for the additional random factors. We used chi-square tests and mixed-model logistic regression to evaluate the occurrence of serious adverse events (SAEs), including miscarriages and early fetal loss (before 28 weeks of gestation), stillbirths (delivery of an infant showing no sign of life after 28 week of gestation), neonatal deaths (death within the first 28 days of life), and maternal deaths.

For maternal weight gain during pregnancy, anemia, iron status, inflammatory markers, vitamin A status, and iodine status, the same general procedures were followed. However, pre-specified covariates were tested for association with the outcome ($p < 0.10$) in a bivariate analysis and only the covariates that met that criterion were included in adjusted models (listed in relevant footnotes). In addition, for maternal weight gain, anemia, iron status, and inflammation markers, we used a $p < 0.05$ for the significance level when testing effect modifiers.

For health care expenditures, adjusted differences between groups were estimated by an ordinary least squares (OLS) regression of the outcome on an indicator for intervention group (LNS group) and a pre-specified set of covariates: number of children under 5 in the household, household asset index, food-insecurity score, maternal age and education, paternal age and education, 11 union dummies, and dummies for missing maternal education and family type (whether the family was a joint or nuclear household). All estimates were made using least-squares estimators that allow for within-cluster correlation in error terms, chosen for ease of interpretability (as a difference in proportions between groups). Several covariates were pre-specified as potential effect modifiers: household asset score, household food-insecurity score, maternal age, and maternal education. These were tested by interacting the covariate with an indicator variable for being in the LNS group and evaluating the statistical significance ($p < 0.05$) of the interaction test.

3 Results

3.1 General Context

3.1.1 Number of Women Enrolled

Between October 15, 2011, and August 31, 2012, we screened 4,410 pregnant women for eligibility and enrolled 4,011 (1,047 in the LNS group and 2,964 in the three IFA groups). Although we had anticipated enrolling over a period of 1 year, after eight months we had already recruited our target of 3,152 women, so we stopped enrollment after 10.5 months to conserve resources. Compared with women enrolled, those who were not enrolled due to ineligibility or refusal to consent (n=399) were, on average, slightly older (23.2 ± 5.4 years versus 21.9 ± 5·0 years; $p < 0.001$) and less educated (5.8 ± 3.5 years of formal education versus 6.2 ± 3.2 years; p=0.03).

3.1.2 Characteristics of the Study Sample and Adherence to Study Supplements

At baseline, sociodemographic, anthropometric, and obstetric characteristics of pregnant women were similar between LNS (n=1047) and IFA (n=2964) groups (Table 3) except for "years of formal education" (6.4 ± 3.2 years versus 6.1 ± 3.3 years; p=0.022). On average, the women were ~22 years of age. Mean maternal height was 151 cm, mean BMI was ~20 kg/m^2, about a third of the women were thin (BMI < 18.5 kg/m^2), and ~39 percent to 42 percent were nulliparous. The mean gestational age at enrollment was 13 weeks in both groups.

Table 3. Baseline Characteristics of Women Enrolled

Characteristic	LNS (n=1,047)	IFA (n=2,964)
Age (y)[a]	21.8 ± 4.9	22.0 ± 5.0
Years of formal education (y)[a]	6.4 ± 3.2	6.1 ± 3.3
Household assets index[a]	0.04 ± 2.24	-0.01 ± 2.26
Household food insecurity access score[a]	2.78 ± 3.92	3.15 ± 4.06
Height (cm)[a]	151.0 ± 5.4	151.0 ± 5.4
BMI (kg/m^2)[a,c]	19.9 ± 2.7	20.0 ± 2.7
BMI < 18.5 kg/m^2 (%)[b]	32.9 (28.6, 37.5)	30.7 (28.2, 33.3)
MUAC (cm)[a]	24.8 ± 2.6	24.9 ± 2.6
Nulliparous (%)[b]	41.7 (38.8, 44.7)	39.1 (37.1, 41.0)
Gestational age at enrollment (weeks)[a]	13.1 ± 3.8	13.1 ± 3.8

y, year(s).

[a] Values are means ± SD (continuous variables).

[b] Values are percentages with 95% CI (categorical variables), accounting for union nested within subdistrict and the random effect of cluster.

[c] Adjusted for 96th day of gestation via polynomial regression with the gestational age at measurement.

Based on maternal retrospective recall (at 6 weeks postpartum) of overall adherence throughout pregnancy, the percentage of mothers reporting regular consumption every day (7 days/week) or almost every day (4–6 days/week) was 64 percent in the LNS group and 92 percent in the IFA group ($p < 0.001$). This difference in adherence was consistent with additional adherence data collected during pregnancy from a subgroup of participants (Harding et al. 2014). Compared with regular adherers, women with lower adherence were taller, younger, more educated, wealthier, and more food secure (data not shown).

3.2 The Impact of Prenatal LNS Supplementation on Pregnancy and Birth Outcomes

3.2.1 Infant Birth Size and Gestational Age

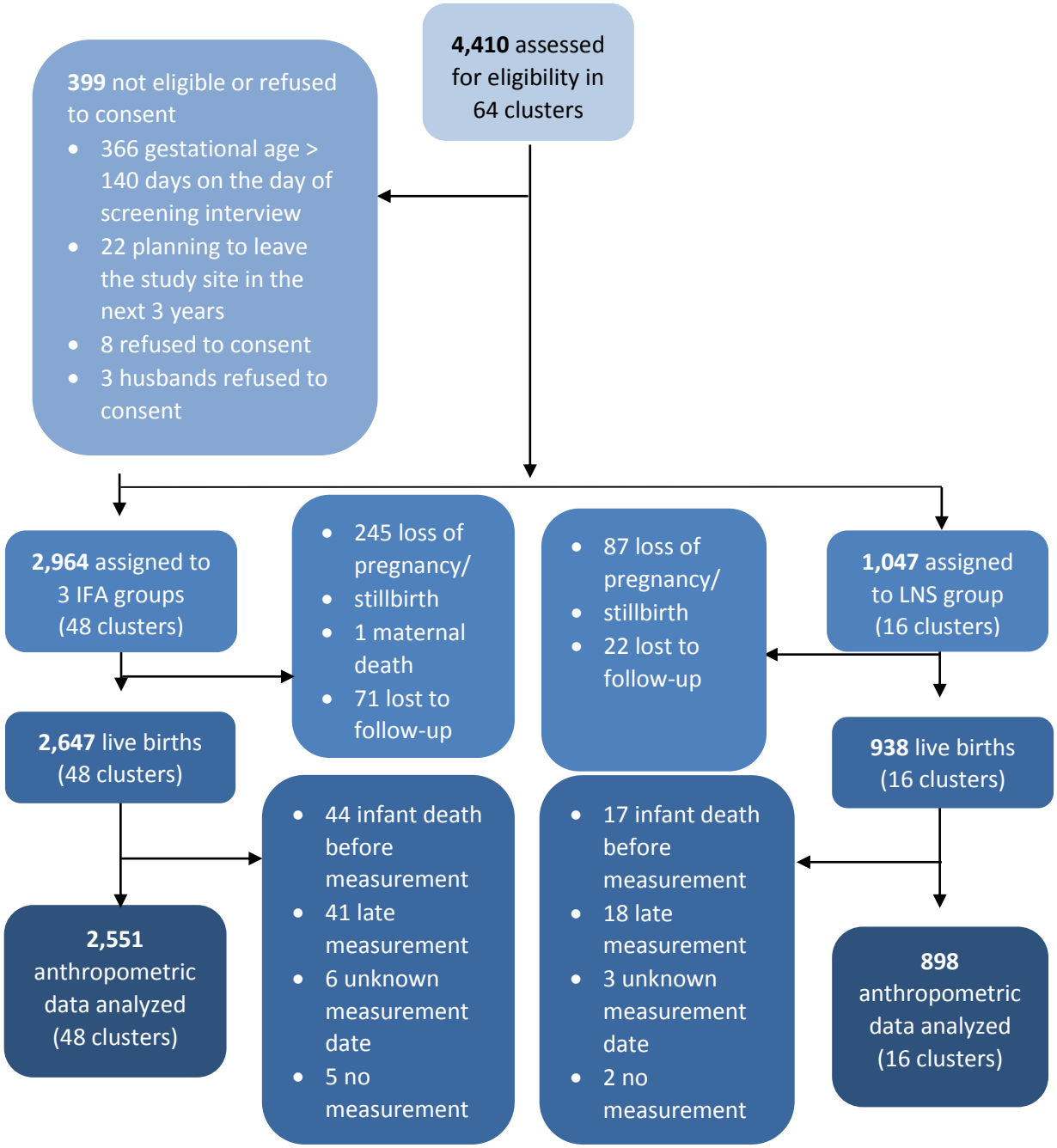
Among the women enrolled, loss of pregnancy or stillbirth occurred in 8.5 percent (89 in the LNS group and 249 in the IFA group).[3] There was one maternal death during pregnancy (in the IFA group) and 93 mothers were otherwise lost to follow-up (22 in the LNS group and 71 in the IFA group). Thirty sets of twins were born and one twin from each pair was randomly selected for analyses. A total of 3,585 live births took place between January 15, 2012, and May 5, 2013, and 1.7 percent of newborns died before birth anthropometry was completed. We had birth anthropometry data for 3,517 infants, but 68 of them were excluded from the analysis due to late measurement (after 14 days of birth) or unknown measurement date. Therefore, anthropometric data for 3,449 infants were analyzed (898 in the LNS group and 2,551 in the IFA group) (Figure 1). There was no significant difference between groups in the percentage of participants with usable birth anthropometry data, out of those enrolled (85.8 percent in the LNS group versus 86.1 percent in the IFA group, $p=0.80$). The mean (± SD) age of the newborns on the day of anthropometry was 2.11 ± 2.86 days in the LNS group and 2.01 ± 2.70 days in the IFA group. Compared with mothers of the infants with birth anthropometry data, the mothers of the infants with no anthropometry data were less educated, less wealthy, more likely to be nulliparous, and enrolled later in gestation (data not shown).

Table 4 shows that infants in the LNS and IFA groups, respectively, differed significantly with respect to birth weight (2,629 g versus 2,588 g), WAZ (-1.48 versus -1.59), head circumference (32.75 cm versus 32.65 cm), HCZ (-1.26 versus -1.34), and BMIZ (-1.57 versus -1.66). Adjustment for pre-determined covariates did not change these results. However, after adjustment for covariates, the differences in birth length (47.6 cm versus 47.4 cm) and LAZ (-1.15 versus -1.24) 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 5 shows that infants in the LNS and IFA groups, respectively, differed significantly with respect to the prevalence of stunting (LAZ < -2: 18.7 percent versus 22.6 percent), small head size (HCZ < -2: 20.7 percent versus 24.9 percent), low BMI (BMIZ < -2: 30.2 percent versus 34.7 percent), and SGA (63.3 percent versus 67.3 percent). There was a trend toward a significant difference in LBW (36.0 percent versus 39.5 percent). There was no significant effect on preterm delivery or low WAZ.

[3] Among women with multiple-fetus pregnancies, some women experienced a miscarriage or stillbirth that involved only one of the fetuses; for this reason, the number of women who experienced loss of pregnancy is larger than the numbers reported in Figure 1 (which includes all dyads who remained in the study). Also, one woman in the LNS group suffered a miscarriage of one twin and stillbirth of the other.

Figure 1. Trial Profile



Results of tests for interactions with potential effect modifiers were not significant ($p > 0.10$) for maternal education, primiparity, or BMI, but they 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-PL on gestational age at delivery, birth length, head circumference, WAZ, LAZ, HCZ, preterm birth, being underweight, and stunting. The results for stunting are shown in Figure 2. The risk of stunting at birth was reduced by LNS-PL (versus 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-PL increased the duration of gestation among women in households categorized with severe food insecurity (but the treatment group differences were not significant within the other three 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-PL in households with higher levels of food insecurity) (Figures 4 and 5). The distribution of LAZ for the newborns in the LNS and IFA groups, within each of the four food-insecurity subgroups (Figure 6), suggested that LNS-PL reduced the proportion of infants with low LAZ at birth, with little effect on the mean or upper end of the distribution.

Figure 2. Prevalence of Stunting at Birth by Intervention Group and Food Security Category

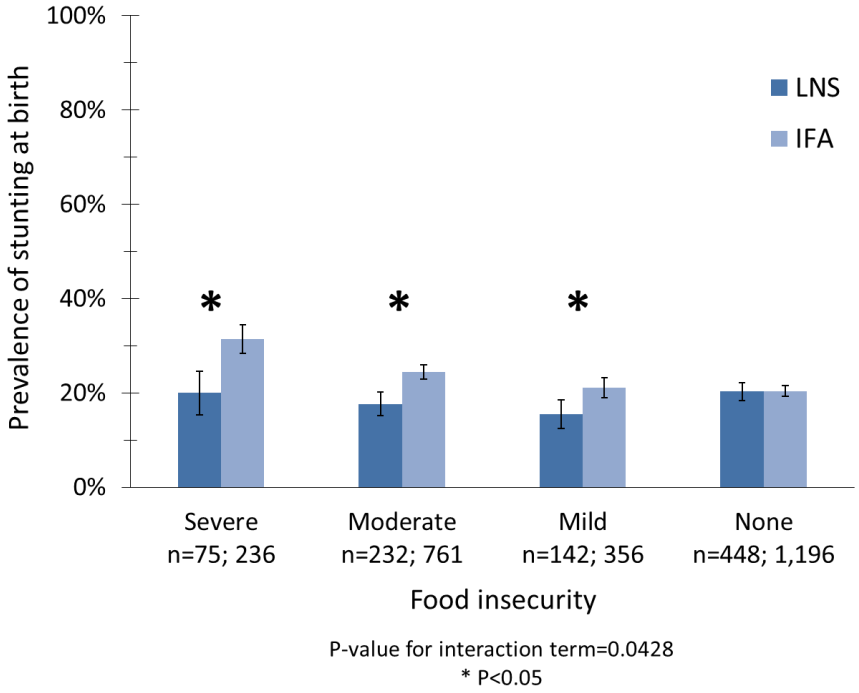
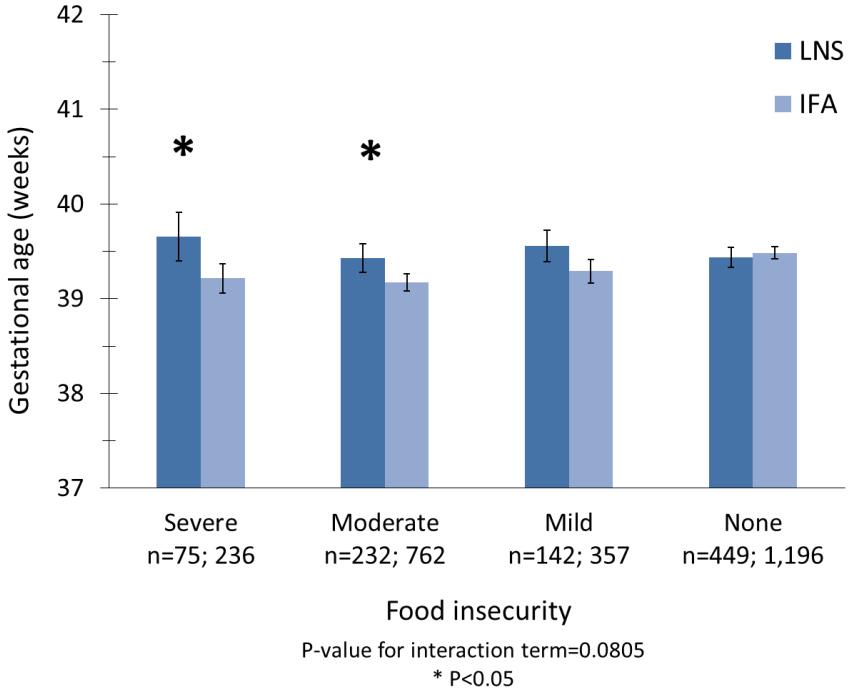
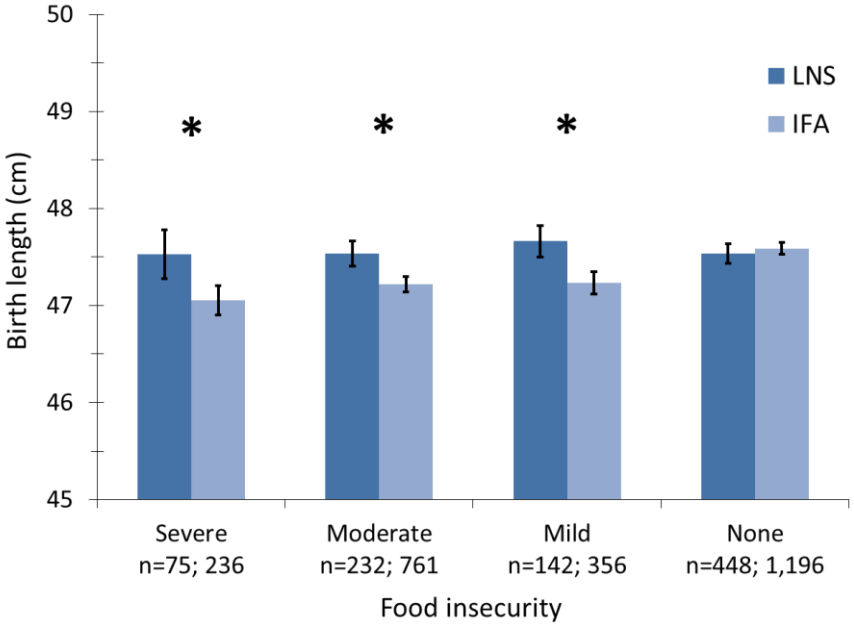


Figure 3. Duration of Gestation by Intervention Group and Food Security Category



P-value for interaction term=0.0805
* P<0.05

Figure 4. Birth Length by Intervention Group and Food Security Category



P-value for interaction term=0.0402
* P<0.05

Figure 5. Birth Head Circumference by Intervention Group and Food Security Category

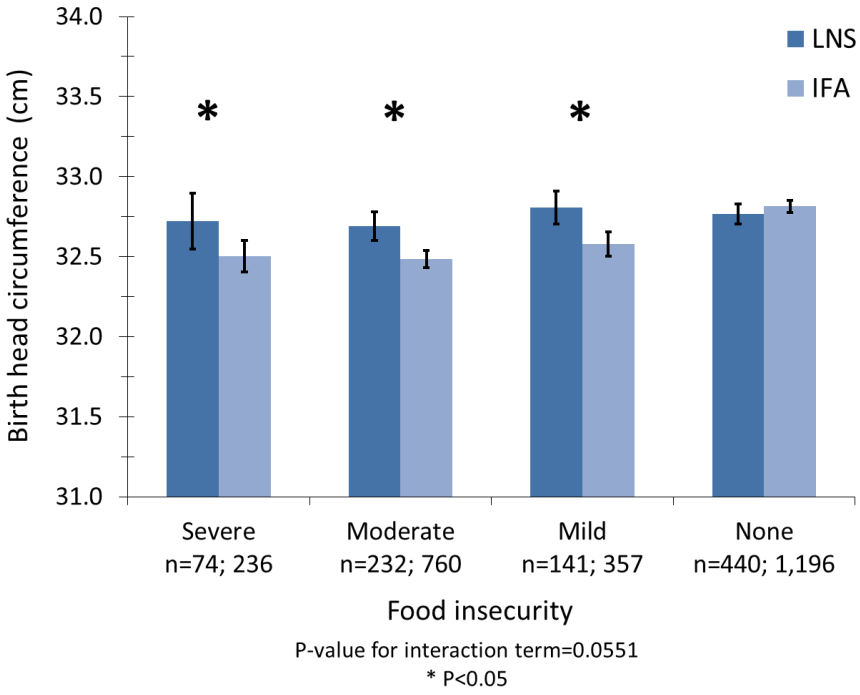
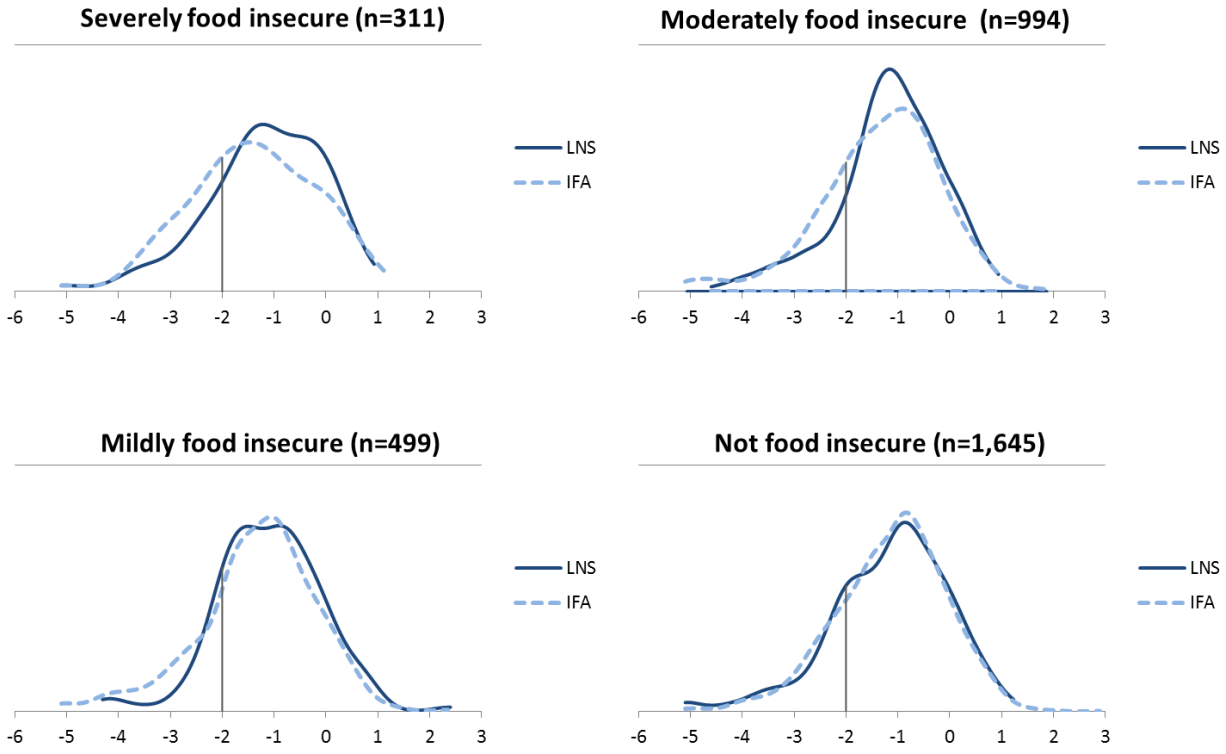
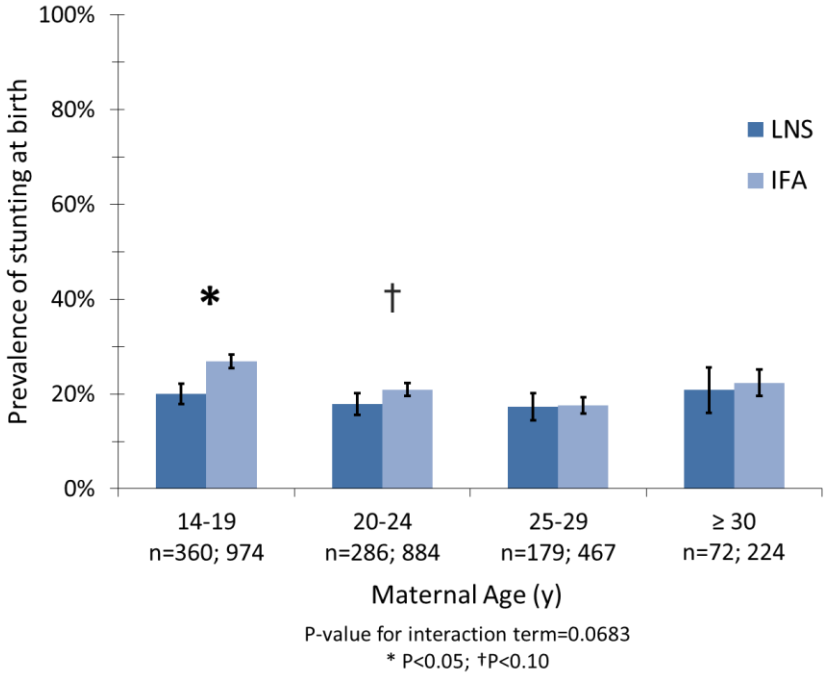


Figure 6. Distribution of Length-for-Age Z-Score by Group and Food Security



As shown in Figure 7, maternal age modified the effect of LNS-PL (versus IFA) on newborn stunting, with larger effects seen among women 14–24 years of age and no significant effect among women ≥ 25 years of age. There was no between-group difference in the percentage of women 14–24 years of age (72.6 percent in the LNS group and 72.3 percent 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-PL on prevalence of low birth weight (p for interaction=0.065): among women whose height was above the median (> 150.5 cm), there was a significant difference between intervention groups (26.6 percent in the LNS group versus 31.9 percent in the IFA group, p=0.027), but there was no difference in shorter women (45.9 percent versus 47.2 percent, respectively). Household assets modified the effect of LNS-PL on birth length, LAZ, MUAC, and SGA, with group differences (greater birth size in the LNS 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-PL (versus IFA) on duration of gestation was significant for female infants (39.6 ± 0.11 weeks versus 39.3 ± 0.06 weeks, p=0.020) but not male infants (39.3 ± 0.11 weeks versus 39.3 ± 0.06 weeks, p=0.775). Time of year at birth (in 2-month 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 were confounded by the fact that the disruption in LNS-PL supply occurred during one of those intervals (data not shown).

Figure 7. Stunting at Birth by Intervention Group and Age Category



Exploratory analyses were conducted to examine the influence of the 10-week disruption in the supply of LNS-PL by comparing the LNS and IFA groups within three subgroups of participants: 1) infants born before the LNS-PL supply disruption (n=370 in LNS group, 0 days of interruption; n=656 in the IFA group); 2) infants born during the suspension of LNS-PL distribution, whose mothers were in the last 1–10 weeks of pregnancy at that time (n=212 in the LNS group, 34.9 ± 21.4 days of interruption; n=656 in the IFA group); and 3) infants born after the disruption, but whose mothers experienced a 10-week gap in LNS-PL distribution during pregnancy (at 7–33 weeks of gestation) if they had been assigned to the LNS group (n=401 in LNS group, 70.3 ± 6.1 days of interruption; n=1177 in the IFA group). Figure 8

illustrates that the prevalence of newborn stunting was significantly lower in the LNS group among infants born before the disruption, but not among those born later; the same trend was observed for head circumference (data not shown). Among infants born before the disruption, LNS-PL reduced the risk of newborn stunting by 31 percent and the risk of small head size by 21 percent.

Per-protocol analyses (Tables 6 and 7) 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-PL reduced newborn stunting by 25 percent and small head size by 19 percent.

Figure 8. Prevalence of Stunting at Birth by Intervention Group and Period of Birth

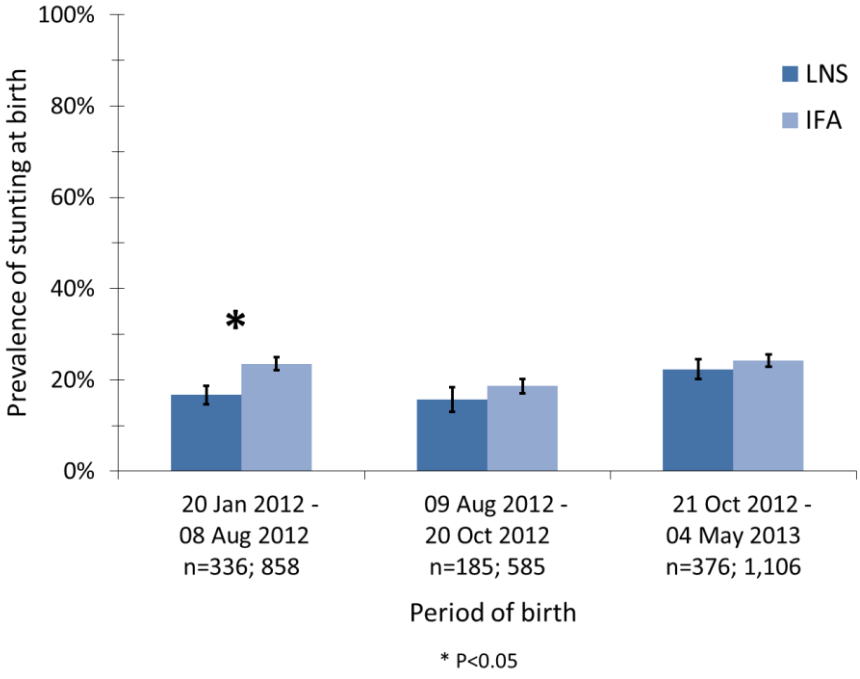


Table 4. Continuous Birth Outcomes, by Intervention Group[a]

Outcome Variable	LNS (n=898)	IFA (n=2,551)	*p*-value[b]
Gestational age of women (weeks)			
Unadjusted	39.5 ± 2.23	39.3 ± 2.31	0.158
Adjusted	39.5 ± 0.08	39.3 ± 0.05	0.153
Birth weight (g)			
Unadjusted	2,629 ± 408	2,588 ± 413	0.007
Adjusted	2,632 ± 13.0	2,586 ± 7.64	0.004
WAZ			
Unadjusted	-1.48 ± 1.01	-1.59 ± 1.02	0.006
Adjusted	-1.48 ± 0.03	-1.59 ± 0.02	0.004
Length (cm)			
Unadjusted	47.6 ± 2.07	47.4 ± 2.17	0.067
Adjusted	47.6 ± 0.07	47.4 ± 0.04	0.042
LAZ			
Unadjusted	-1.15 ± 1.10	-1.25 ± 1.14	0.056
Adjusted	-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	32.8 ± 0.04	32.6 ± 0.03	0.033
HCZ			
Unadjusted	-1.26 ± 1.08	-1.34 ± 1.12	0.027
Adjusted	-1.25 ± 0.04	-1.35 ± 0.02	0.026
MUAC (cm)			
Unadjusted	9.79 ± 0.82	9.73 ± 0.83	0.080
Adjusted	9.78 ± 0.03	9.73 ± 0.02	0.092
BMIZ			
Unadjusted	-1.57 ± 1.05	-1.66 ± 1.03	0.005
Adjusted	-1.56 ± 0.03	-1.67 ± 0.02	0.005

[a] Unadjusted values are mean ± SD; adjusted values are mean ± standard error (SE), adjusted for maternal age, maternal education, assets quintile, time interval (season) at birth, maternal height, maternal BMI, child sex, food security category, parity, and gestational age at enrollment (imputed), and accounting for union (nested within subdistrict) and the random effect of cluster.

[b] p-values are based on ANCOVA (SAS, PROC MIXED), accounting for union (nested within subdistrict) and the random effect of cluster and controlling for selected covariates in adjusted models; intracluster correlation (ICC) was zero for the primary outcomes.

Table 5. Dichotomous Birth Outcomes, by Intervention Group[a]

Outcome Variable	LNS (n=898)	IFA (n=2,551)	Unadjusted RR (95% CI)	p-value	ARR[b,c] (95% CI)	p-value
Preterm delivery, percent (95% CI)	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
LBW, percent (95% CI)	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, percent (95% CI)	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, percent (95% CI)	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, percent (95% CI)	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, percent (95% CI)	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, percent (95% CI)	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

[a] p-values for analyses are based on logistic regression (SAS, PROC GLIMMIX), accounting for union (nested within subdistrict) and the random effect of cluster; ICC was zero for the primary outcomes.

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

[c] Adjusted risk ratios calculated using an adaptation of Spiegelman and Hertzmark's (2005) approach.

Table 6. Per-Protocol Analysis of Continuous Birth Outcomes, by Intervention Group, Excluding Women Who Reported Consuming the Supplement ≥ 4 Days/Week during Pregnancy[a]

Outcome Variable	LNS (n=577)	IFA (n=2,330)	*p*-value[b]
Gestational age (weeks)			
Unadjusted	39.4 ± 2.26	39.3 ± 2.31	0.446
Adjusted	39.4 ± 0.10	39.3 ± 0.05	0.454
Birth weight (g)			
Unadjusted	2,648 ± 405	2,587 ± 412	0.002
Adjusted	2,650 ± 16.2	2,586 ± 7.92	< .001
WAZ			
Unadjusted	-1.43 ± 1.00	-1.59 ± 1.01	0.001
Adjusted	-1.43 ± 0.04	-1.59 ± 0.02	< .001
Length (cm)			
Unadjusted	47.6 ± 2.01	47.4 ± 2.16	0.016
Adjusted	47.7 ± 0.08	47.4 ± 0.04	0.004
LAZ			
Unadjusted	-1.10 ± 1.08	-1.25 ± 1.13	0.009
Adjusted	-1.09 ± 0.04	-1.25 ± 0.02	0.003
Head circumference (cm)			
Unadjusted	32.8 ± 1.31	32.7 ± 1.41	0.021
Adjusted	32.8 ± 0.06	32.7 ± 0.03	0.010
HCZ			
Unadjusted	-1.19 ± 1.06	-1.33 ± 1.12	0.009
Adjusted	-1.20 ± 0.05	-1.34 ± 0.02	0.008
MUAC (cm)			
Unadjusted	9.81 ± 0.84	9.73 ± 0.83	0.042
Adjusted	9.81 ± 0.03	9.73 ± 0.02	0.061

Outcome Variable	LNS (n=577)	IFA (n=2,330)	*p*-value[b]
BMIZ			
Unadjusted	-1.53 ± 1.05	-1.66 ± 1.03	0.004
Adjusted	-1.53 ± 0.04	-1.67 ± 0.02	0.005

[a] Unadjusted values are mean ± SD; adjusted values are mean ± SE, adjusted for maternal age, maternal education, assets quintile, time interval at birth, maternal height, maternal BMI, child sex, food security category, parity, and gestational age at enrollment (imputed), and accounting for union (nested within subdistrict) and the random effect of cluster.
[b] p-values are based on ANCOVA (SAS, PROC MIXED), accounting for union (nested within subdistrict) and the random effect of cluster and controlling for selected covariates in adjusted models; ICC was zero for the primary outcomes.

Table 7. Per-Protocol Analysis of Dichotomous Birth Outcomes, by Intervention Group, Excluding Women Who Reported Consuming the Supplement ≥ 4 Days/Week during Pregnancy[a]

Outcome Variable	LNS (n=576)	IFA (n=2,316)	Unadjusted RR (95% CI)	p-value	ARR[b,c] (95% CI)	p-value
Preterm delivery, percent (95% CI)	13.9 (11.2–17.0)	13.7 (12.4–15.2)	1.01 (0.80, 1.28)	0.933	1.00 (0.80, 1.26)	0.954
LBW, percent (95% CI)	34.3 (30.5–38.4)	39.2 (37.2–41.2)	0.89 (0.79, 1.01)	0.040	0.89 (0.79, 1.00)	0.025
WAZ < -2, percent (95% CI)	26.1 (22.6–29.9)	29.9 (28.0–31.8)	0.89 (0.76, 1.04)	0.086	0.89 (0.77, 1.03)	0.059
LAZ < -2, percent (95% CI)	17.1 (14.2–20.5)	22.5 (20.9–24.3)	0.75 (0.62, 0.92)	0.008	0.75 (0.62, 0.91)	0.004
HCZ < -2, percent (95% CI)	19.8 (16.6–23.3)	24.7 (23.0–26.5)	0.81 (0.67, 0.97)	0.018	0.81 (0.68, 0.97)	0.013
BMIZ < -2, percent (95% CI)	28.5 (24.9–32.4)	34.4 (32.4–36.3)	0.86 (0.74, 0.99)	0.012	0.86 (0.75, 0.99)	0.011
SGA, percent (95% CI)	62.6 (58.3–66.7)	67.8 (65.7–69.8)	0.92 (0.86, 0.99)	0.033	0.93 (0.87, 1.00)	0.047

[a] p-values for analyses are based on logistic regression (SAS, PROC GLIMMIX), accounting for union (nested within subdistrict) and the random effect of cluster; ICC was zero for the primary outcomes.
[b] Adjusted for maternal age, maternal education, assets quintile, time interval at birth, maternal height, maternal BMI, child sex, food security category, parity, and gestational age at enrollment (imputed); and accounting for union (nested within subdistrict) and the random effect of cluster.
[c] Adjusted risk ratios calculated using an adaptation of Spiegelman and Hertzmark's (2005) approach.

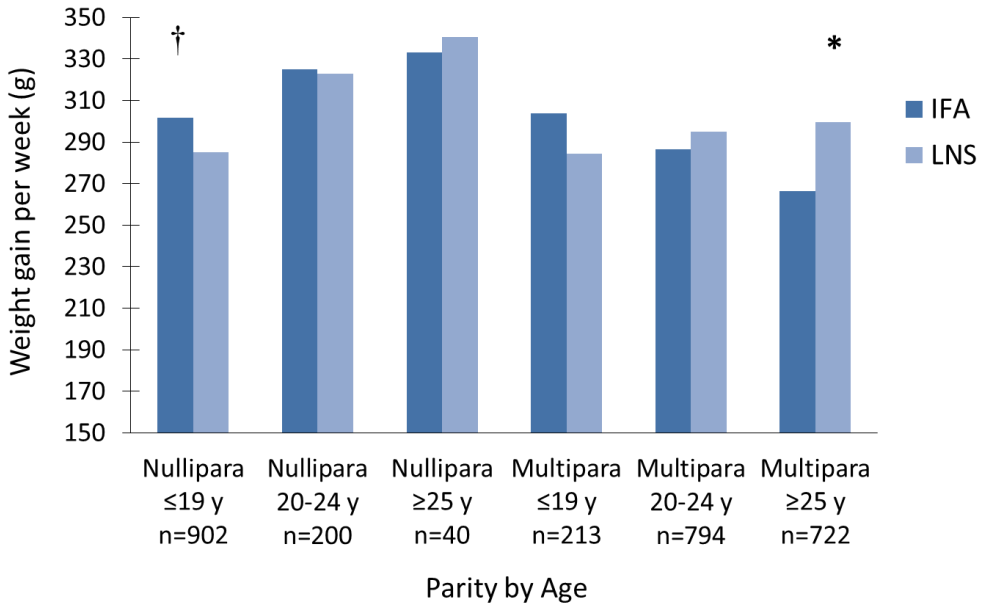
3.2.2 Maternal Weight Gain during Pregnancy

A total of 2,877 participants were included in this analysis on maternal weight gain during pregnancy: 2,128 in the IFA group and 749 in the LNS group. This analytic sample represented 72 percent of the RDNS sample; women included in this analysis were enrolled at lower gestational age ($p < 0.0001$) and had higher assets score ($p=0.0295$) at baseline than those not included; however, these differences were small. Table A-2 in the appendices shows the sample characteristics at baseline, by intervention group.

Mean (± SD) maternal weight at 36 weeks was 52.0 ± 7.3 kg (or 114.7 ± 16.1 lb). Mean (± SD) weight gain per week was 290 ± 130 g (or 0.64 ± 0.29 lb). Low weekly weight gain during pregnancy was observed in 57 percent of women (defined as less than 80 percent of the lower end of the IOM recommended weekly weight gain range per BMI category). By 36 weeks of gestation, no significant differences in maternal weight gain per week ($p=0.296$) or low weight gain per week ($p=0.228$) were observed by treatment group (Tables 8 and 9).

However, maternal characteristics, such as age and parity, modified the effect of the intervention on maternal weight gain per week when tested in separate models. Because of the strong association between these two baseline characteristics, we created a variable that combined both characteristics and tested the interaction between that variable and intervention group. Figure 9 shows results for weight gain per week (in g) among parity-by-age groups. Thus, among multiparous women > 25 years, those in the LNS group gained more weight per week than their counterparts in the IFA group [mean of 300 g (CI: 283–317) versus mean of 266 g (CI: 256–277), respectively; Tukey-Kramer-adjusted $p=0.001$]. No significant effect modifiers were detected for the effect of the intervention on the risk of low weight gain during pregnancy.

Figure 9. Maternal Weight Gain per Week (kg) by Intervention Group and Parity-by-Age[a,b]



[a] Adjusted model plus interaction term: Group X Parity-by-Age (P=0.0068)
[b] P-values adjusted for multiple comparisons (Tukey-Kramer); * P<0.05; †P<0.10

Per-protocol analysis including only women who adhered to the supplementation regimen (i.e., consumed the supplement at least 4 days per week, n=2447) showed that LNS was marginally associated with greater weight gain per week (p=0.066) in this subset of the analytic sample (Tables 10 and 11). We conducted further analysis including only women who were not affected by the LNS disruption (n=1256). Results in this subsample indicated no effect of LNS on maternal weight gain per week (p=0.843) or on the risk of low weight gain per week (p=0.585) (data not shown).

Table 8. Average Maternal Weight Gain per Week (g) from Enrollment through 36 Gestational Weeks, by Intervention Group[a]

Maternal Outcome	LNS (n=749)	IFA (n=2,128)	*p*-value[b]
Weight gain per week (g)			
Unadjusted[c]	297 ± 5	291 ± 3	0.296
Adjusted[d]	294 ± 5	291 ± 3	0.560

[a] Values are mean ± SE.
[b] p-values of treatment effect are based on ANCOVA (SAS PROC MIXED), accounting for union (nested within subdistrict) and the random effect of cluster and controlling for selected covariates in adjusted models.
[c] Accounting for union (nested within subdistrict) and the random effect of cluster.
[d] Adjusted for BMI at baseline, height, age, education, food insecurity, assets index, gestational age at enrollment, parity, age at menarche, season at follow-up, and time between baseline and follow-up, and accounting for union (nested within subdistrict) and the random effect of cluster.

Table 9. Prevalence and Relative Risk for Low Weight Gain per Week from Enrollment through 36 Weeks in the LNS versus IFA Group[a,b,c]

Maternal Outcome	LNS (n=749) % (95% CI)	IFA (n=2,128) % (95% CI)	RR (95% CI)	p-value	ARR (95% CI)[d]	p-value
Low weight gain per week	55.8 (51.7–59.8)	57.2 (54.7–59.7)	0.95 (0.88–1.03)	0.228	0.97 (0.90–1.05)	0.310

[a] RR is for LNS versus IFA group, the reference category; n calculated using an adaptation of Spiegelman and Hertzmark's (2005) approach.
[b] Low weight gain defined as weekly weight gain less than 80% of the lower end of the IOM weekly weight gain recommendation, per BMI category.
[c] p-values of treatment effect are based on logistic regression analysis (SAS, PROC GLIMMIX), accounting for union (nested within subdistrict) and the random effect of cluster.
[d] Adjusted for BMI, height, education, food insecurity, assets index, age at menarche, parity, gestational age at enrollment, season at follow-up, and time between baseline and follow-up, and accounting for union (nested within subdistrict) and the random effect of cluster.

Table 10. Per-Protocol Analysis of Continuous Maternal Anthropometric Outcomes, by Intervention Group, Excluding Women Who Reported Consuming the Supplement < 4 Days/Week during Pregnancy (n=2,447)[a,b]

Maternal Outcome	LNS (n=491)	IFA (n=1,956)	*p*-value
Weight gain per week (g)			
Unadjusted[c]	303 ± 6	291 ± 3	0.066
Adjusted[d]	301 ± 6	291 ± 3	0.137

[a] Values are mean ± SE.
[b] p-values of treatment effect are based on ANCOVA (SAS, PROC MIXED), accounting for union (nested within subdistrict) and the random effect of cluster.
[c] Accounting for union (nested within subdistrict) and the random effect of cluster.
[d] Adjusted for the same covariates as for intention-to-treat analysis (Table 8) and accounting for union (nested within subdistrict) and the random effect of cluster.

Table 11. Per-Protocol Analysis of Low Weight Gain per Week, by Intervention Group, Excluding Women Who Reported Consuming the Supplement < 4 Days/Week during Pregnancy[a,b]

Maternal Outcome	LNS (n=491) % (95% CI)	IFA (n=1,956) % (95% CI)	RR (95% CI)	p-value	ARR (95% CI)[c,d]	p-value
Low weight gain per week (g)	54.8 (51.3–58.3)	57.7 (55.4–60.0)	0.93 (0.85–1.02)	0.109	0.94 (0.86–1.03)	0.123

[a] Low weight gain defined as weekly weight gain less than 80% of the IOM (lower end) recommendation, per BMI.
[b] p-values of treatment effect are based on logistic regression analysis (SAS PROC GLIMMIX), accounting for union (nested within subdistrict) and the random effect of cluster with IFA group as the reference category; RRs calculated using an adaptation of Spiegelman and Hertzmark's (2005) approach.
[c] Adjusted for the same covariates as for intention-to-treat analysis (Table 9) and accounting for union (nested within subdistrict) and the random effect of cluster.
[d] Adjusted risk ratio calculated using an adaptation of Spiegelman and Hertzmark's (2005) approach.

3.2.3 Maternal Blood Pressure, C-Section, Pregnancy and Childbirth Complications, and Severe Adverse Events

A total of 2,931 participants having clinical data from the 36-week visit and 3,747 participants having childbirth-complication data from the birth visit were included in the analysis on maternal blood pressure, C-section, pregnancy and childbirth complications, and SAEs. Table A-3 in the appendices shows baseline characteristics of the women included at 36 weeks, by intervention group. (Table A-4 in the appendices shows this comparison for the birth visit.) Women in the LNS group participating in the 36-week analysis of pregnancy complications had 0.3 more years of education than those in the IFA group (p=0.043).

Mean unadjusted and adjusted systolic and diastolic blood pressure at 36 weeks, as well as average number of pregnancy and childbirth complications, were not significantly different between the LNS and IFA groups (Table 12). In both adjusted (not shown) and unadjusted models, there were no significant differences between the LNS and IFA groups, respectively, in the proportions of women with high blood pressure at 36 weeks (1.7 percent versus 2.0 percent), C-section (15.6 percent versus 14.2 percent), episiotomy (6.3 percent versus 6.4 percent), prolonged labor (8.3 percent versus 8.8 percent), early rupture of membranes (9.3 percent versus 8.5 percent), convulsions (1.6 percent versus 1.1 percent), high blood pressure in labor (1.5 percent versus 1.2 percent), obstructed labor (2.8 percent versus 2.9 percent), antepartum hemorrhage (0.8 percent versus 1.4 percent), or any complication of pregnancy or childbirth (36.0 percent versus 37.1 percent) (Table 13).

Interactions of certain effect modifiers with intervention group were observed for C-section, prolonged labor, and episiotomy (Table 14). Infant sex modified the effect of LNS on C-section in the unadjusted model. For female infants, LNS increased the relative risk (RR) of C-section (RR 1.42 95% CI[1.13, 1.79]). For male infants, there was a non-significant trend in the opposite direction (RR 0.82 95% CI[0.64, 1.05]). Among female infants, the difference between groups became marginally significant (p=0.052) in the adjusted model. Infant sex also modified the effect of LNS on prolonged labor (p for interaction=0.026), but stratified analyses indicated no significant difference between LNS and IFA groups within female or male infants. Gestational age modified the effect of LNS on episiotomy (p for interaction=0.074), but no between-group differences were seen in stratified analyses. Per-protocol analysis including only women who adhered to the supplementation regimen (i.e., consumed the supplement at least 4 days per week; n=2,511 at 36-week visit, and n=3,130 at birth visit) confirmed the results of the intention-to-treat analysis using the full subsample (data not shown). We conducted further analysis including only women who were not affected by the LNS disruption (n=1,391 at 36-week visit, and n=1,201 at birth visit). Results in this subsample were similar to those found in the complete analytic sample (data not shown).

There were no significant differences between groups in the incidence of any of the SAEs assessed (Table 15).

Table 12. Blood Pressure and Number of Childbirth Complications, by Intervention Group (n=2,931 at 36 Weeks of Gestation and n=3,746 at Birth Visit)[a,b]

Variable	LNS	IFA	p-value
Number of participants	766 (36-week visit) 983 (birth visit)	2,165 (36-week visit) 2,763 (birth visit)	
Systolic blood pressure at 36 weeks (mm of Hg)			
Unadjusted	113 ± 10.3	112 ± 10.3	0.169
Adjusted[c]	113 ± 0.31 [742]	112 ± 0.18 [2111]	0.083
Change in systolic blood pressure from baseline to 36 weeks			
Unadjusted	-0.14 ± 10.3 [743]	-0.85 ± 10.0 [2111]	0.184
Adjusted[c]	-0.17 ± 0.31 [742]	-0.82 ± 0.18 [2111]	0.083
Diastolic blood pressure at 36 weeks (mm of Hg)			
Unadjusted	68.9 ± 8.82	68.7 ± 9.34	0.876
Adjusted[c]	68.5 ± 0.28 [742]	68.8 ± 0.16 [2111]	0.466
Change in diastolic blood pressure from baseline to 36 weeks			
Unadjusted	0.12 ± 8.86 [743]	0.10 ± 8.93 [2111]	0.434
Adjusted[c]	-0.03 ± 0.28 [742]	0.21 ± 0.16 [2111]	0.466
Number of pregnancy/childbirth complications			
Unadjusted	0.32 ± 0.60	0.31 ± 0.57	0.861
Adjusted[d]	0.31 ± 0.02 [974]	0.31 ± 0.01 [2742]	0.725

[a] p-values of treatment effect are based on ANCOVA (SAS, PROC MIXED), accounting for union (nested within subdistrict) and the random effect of cluster.

[b] Unadjusted values are mean ± SD [n]; adjusted values are mean ± SE [n].

[c] Adjusted for food security at baseline, age at baseline, education at baseline, height at baseline, BMI at baseline, MUAC at baseline, gestational age at baseline, systolic blood pressure at baseline, diastolic blood pressure at baseline, nulliparity, time interval (season) at 36 weeks of gestation, and asset quintile at baseline, and accounting for union (nested within subdistrict) and the random effect of cluster.

[d] Adjusted for food security at baseline, age at baseline, education at baseline, height at baseline, BMI at baseline, MUAC at baseline, gestational age at baseline, child sex, nulliparity, time interval (season) at 36 weeks of gestation, and asset quintile at baseline, and accounting for union (nested within subdistrict) and the random effect of cluster.

Table 13. Prevalence and Relative Risks of High Blood Pressure at 36 Weeks of Gestation and Complications during Antepartum Period or Childbirth (n=2,931 at 36 Weeks of Gestation and n=3,746 at Birth Visit)[a,b]

Maternal Outcome	LNS % (95% CI) [n]	IFA % (95% CI) [n]	RR (95% CI)[c]	p-value
High blood pressure at 36 weeks	1.74 (1.01–2.98) [766]	2.03 (1.51–2.74) [2165]	0.88 (0.48, 1.62)	0.6237
C-section	15.6 (12.6–19.2) [983]	14.2 (12.5–16.2) [2763]	1.08 (0.91, 1.28)	0.4843
Episiotomy	6.31 (4.74–8.34) [818]	6.44 (5.45–7.59) [2334]	0.99 (0.73, 1.35)	0.9030
Prolonged labor	8.34 (6.70–10.35) [983]	8.79 (7.71–10.00) [2763]	1.04 (0.83, 1.31)	0.6832
Early rupture of membrane	9.30 (7.61–11.34) [983]	8.45 (7.45–9.58) [2763]	1.10 (0.87, 1.38)	0.4297
Convulsions	1.57 (0.94–2.62) [983]	1.08 (0.74–1.57) [2763]	1.45 (0.80, 2.62)	0.2397
High blood pressure in labor	1.54 (0.86–2.73) [983]	1.19 (0.81–1.74) [2763]	1.25 (0.69, 2.27)	0.4627
Obstructed labor	2.83 (1.93–4.15) [983]	2.91 (2.32–3.66) [2763]	1.06 (0.70, 1.61)	0.9003
Antepartum hemorrhage	0.83 (0.41–1.70) [983]	1.39 (0.98–1.98) [2763]	0.60 (0.29, 1.25)	0.2067
Any complications	35.9 (31.6 –40.4) [761]	37.1 (34.6–39.8) [2159]	0.98 (0.88, 1.10)	0.6389

[a] RR is for LNS versus IFA group, the reference category; calculated using an adaptation of Spiegelman and Hertzmark's (2005) approach.
[b] p-values of treatment effect are based on logistic regression analysis (SAS, PROC GLIMMIX), accounting for union (nested within subdistrict) and the random effect of cluster.
[c] RRs account for union (nested within subdistrict) and the random effect of cluster.

Table 14. Effect Modification for Selected Outcome Variables, by Intervention Group[a,b]

Outcome	Explanatory Variable		LNS[c] (%)	IFA[c] (%)	RR (95% CI)[d]	p-value	Interaction test p-value	ARR[e]	p-value
C-section	Infant sex	Female	18.0	12.4	1.42 (1.13, 1.79)	0.017	0.001	1.31 (1.05, 1.63)	0.052
		Male	13.2	16.1	0.82 (0.64, 1.05)	0.210		0.82 (0.65, 1.05)	0.172
Prolonged labor	Infant sex	Female	6.8	9.4	0.81 (0.57, 1.14)	0.081	0.026	0.83 (0.59, 1.17)	0.121
		Male	9.9	8.1	1.31 (0.96, 1.78)	0.233		1.26 (0.93, 1.70)	0.313
Episiotomy	Gestational age at enrollment	Gestational age < 90 days	5.3	7.5	0.75 (0.48, 1.18)	0.160	0.074	0.71 (0.46, 1.09)	0.108
		Gestational age 91–120 days	7.9	5.1	1.53 (0.92, 2.54)	0.100		1.37 (0.82, 2.28)	0.147
		Gestational age 121–140 days	6.2	5.9	1.02 (0.48, 2.19)	0.891		1.08 (0.52, 2.23)	0.880

[a] RR of LNS versus IFA group, the reference category; calculated using an adaptation of Spiegelman and Hertzmark's (2005) approach.
[b] p-values of treatment effect are based on logistic regression analysis (SAS, PROC GLIMMIX), accounting for union (nested within subdistrict) and the random effect of cluster.
[c] Proportion (%) accounting for union (nested within subdistrict) and the random effect of cluster.
[d] RRs accounting for union (nested within subdistrict) and the random effect of cluster.
[e] Adjusted RRs are adjusted for food security at baseline, age at baseline, education at baseline, height at baseline, BMI at baseline, MUAC at baseline, gestational age at baseline, child sex, nulliparity, time interval (season) at 36 weeks of gestation, and asset quintile at baseline, and account for union (nested within subdistrict) and the random effect of cluster.

Table 15. Serious Adverse Events, by Intervention Group[a]

Variable	LNS (n=1,047)	IFA (n=2,964)	p-value[d]	RR (95% CI)
All SAEs (%)	107[2] (10.2)	316 (10.7)	0.62	0.96 (0.78, 1.19)
Miscarriage/induced abortion[b]	56 (5.3)	178 (6.0)	0.84	0.89 (0.66, 1.20)
Stillbirth	34 (3.2)	71 (2.4)	0.25	1.36 (0.90, 2.05)
Maternal death[c]	0 (0)	2 (0.07)	0.97	--
Neonatal death within 7 days	18 (1.7)	65 (2.2)	0.09	0.78 (0.46, 1.33)

[a] Among women with multiple-fetus pregnancies, some women experienced a miscarriage or stillbirth that involved only one of the fetuses, and 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 number reported in Figure 1 (which includes all dyads who remained in the study).
[b] One woman in the LNS group suffered a miscarriage of one twin and stillbirth of the other.
[c] One maternal death occurred during the prenatal period and the other occurred after childbirth, before the infant was measured.
[d] p-values of treatment effect account for union (nested within subdistrict) and the random effect of cluster.

3.2.4 Maternal Blood Hemoglobin, Iron Status, and Inflammatory Markers

A total of 843 participants with biochemical data at baseline and at 36 weeks of gestation were included in this analysis on maternal blood Hb, iron status, and inflammatory markers; of those participants, 383 were in the IFA group and 460 were in the LNS group. This analytic sample represented 21 percent of the RDNS sample; women included in this analysis were enrolled at lower gestational age (p=0.0001) and tended to have higher education (p=0.0695) at baseline than those not included. Table A-5 in the appendices shows the sample characteristics at baseline, by intervention group.

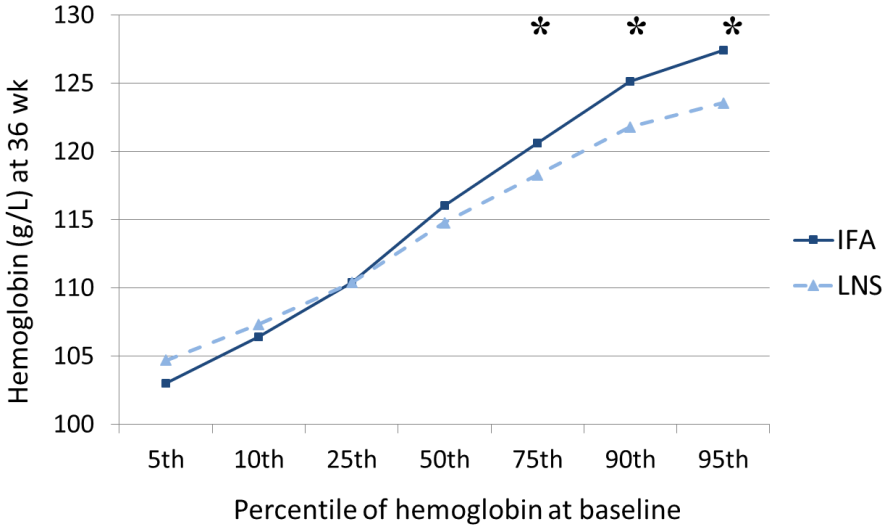
Mean (± SD) maternal Hb concentration at 36 weeks was 114.8 ± 12.7 g/L. Several Hb concentration cutoffs were explored in this analysis: 2.6 percent of women had Hb < 90 g/L, 12.3 percent had Hb < 100 g/L, 33.7 percent had Hb < 110 g/L (the standard definition of anemia during pregnancy), 10.4 percent had Hb > 130 g/L, and 0.6 percent had Hb > 145 g/L. Due to the few cases with Hb < 90 g/L or > 145 g/L, these dichotomous variables were not analyzed further.

Mean (± SD) unadjusted ferritin concentration was 37.3 ± 28.7 µg/L, and 14.5 percent of women had ferritin < 12 µg/L (a cutoff used to identify iron deficiency) at 36 weeks. Mean (± SD) corrected ferritin concentration (corrected for presence of systemic inflammation) was 35.2 ± 26.3 µg/L, and 15.8 percent of women had corrected ferritin < 12 µg/L at 36 weeks. Mean (± SD) sTfR concentration was 6.6 ± 3.5 mg/L, and 16.3 percent of women had sTfR > 8.3 mg/L (also a cutoff used to identify iron deficiency) at 36 weeks. Iron deficiency (defined as ferritin < 12 µg/L or sTfR > 8.3 mg/L) at 36 weeks was present in 23.8 percent of women, and when using ferritin values corrected for inflammation or infection, this prevalence was 24.9 percent. Iron deficiency anemia (defined as ferritin < 12 µg/L or sTfR > 8.3 mg/L and Hb < 110 g/L) at 36 weeks was present in 12.5 percent of women, and the prevalence remained the same when using corrected ferritin instead.

Mean (± SD) maternal CRP concentration at 36 weeks was 3.48 ± 8.51 mg/L, and the prevalence of high CRP (defined as CRP > 5.0 mg/L) was 13.5 percent. Mean (± SD) maternal AGP concentration at 36 weeks was 0.44 ± 0.28 g/L, and the prevalence of high AGP (defined as AGP > 1.0 g/L) was 2.9 percent. At 36 weeks of gestation, the prevalence of systemic inflammation (defined as CRP > 5.0 mg/L or AGP > 1.0 g/L) was 14.5 percent.

No significant differences in mean maternal Hb concentrations were observed by intervention group at 36 weeks (Table 16). Similarly, no significant differences between groups were observed in the proportion of women with Hb < 100 g/L, < 110 g/L, or > 130 g/L (Table 17). However, maternal Hb concentration at baseline modified the effect of the intervention on maternal Hb at 36 weeks of gestation (p=0.025). Figure 10 shows results for Hb at 36 weeks at different percentiles of baseline Hb, by intervention group. Among women with baseline Hb concentrations above the 25th percentile, those in the IFA group had higher Hb concentrations than those in the LNS group at 36 week of gestation. Maternal Hb at baseline also modified the effect of the intervention on the proportion of women with Hb < 110 g/L (p=0.040). The proportion of women with Hb < 110 g/L at 36 weeks was higher in the LNS group than the IFA group among those whose baseline Hb was above the median (Hb > 117 g/L), although there were no significant differences by treatment group among those with baseline Hb ≤ 117 g/L (Figure 11).

Figure 10. Maternal Hemoglobin (g/L) at 36 Weeks of Pregnancy by Intervention Group and Percentile of Hemoglobin at Baseline[a,b]

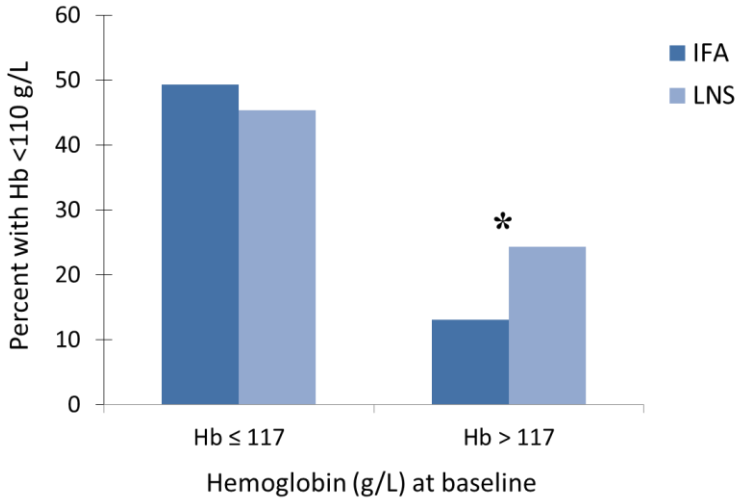


[a] Adjusted model plus interaction term: Group X log of hemoglobin at baseline (P=0.025)
[b] P-values adjusted for multiple comparisons (Tukey-Kramer); * P<0.05

Serum ferritin concentration was significantly higher in the IFA group than in the LNS group at 36 weeks (Table 16). In addition, sTfR concentration was lower in the IFA group than in the LNS group when adjusting for covariates (Table 16). Maternal AGP concentration at baseline modified the effect of the intervention on maternal sTfR at 36 weeks of gestation (p=0.020) (data not shown). The differences in sTfR concentration at 36 weeks between groups were larger among those with less inflammation at baseline.

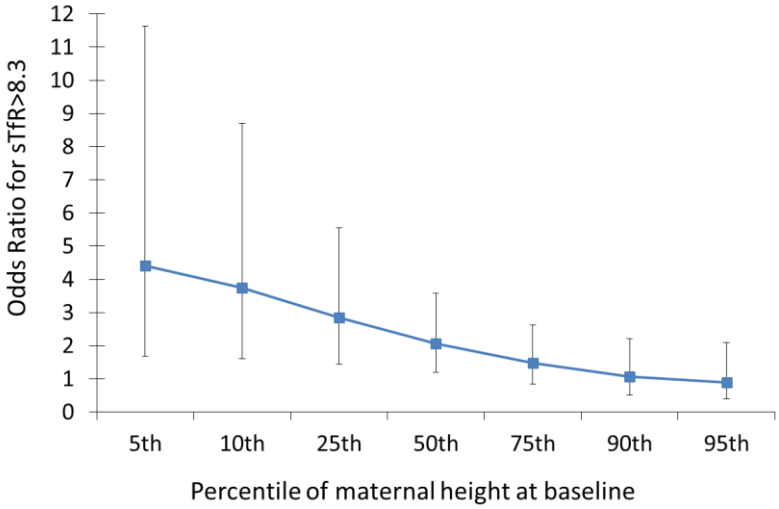
Women in the LNS group were more likely to have low ferritin and high sTfR than those in the IFA group (Table 17). Maternal height modified the effect of the intervention on the risk of high sTfR (p=0.029). Increased odds of high sTfR were only observed among women whose maternal height was in lowest half of the distribution (Figure 12). There was a significant difference between LNS and IFA groups in the prevalence of iron deficiency (29.4 percent versus 19.4 percent, respectively, using corrected ferritin values) and a marginally significant difference in iron deficiency anemia (15.0 percent versus 9.6 percent, respectively).

Figure 11. Percent of Women with Hemoglobin Less Than 110 g/L at 36 Weeks of Pregnancy by Intervention Group and Hemoglobin at Baseline[a,b]



[a] Adjusted model plus interaction term: Group X Hemoglobin ≤117 g/L at baseline (P=0.040)
[b] P-values adjusted for multiple comparisons (Tukey-Kramer); * P<0.05

Figure 12. Odds Ratio for sTfR >8.3 mg/L at 36 Weeks of Pregnancy, by Maternal Height at Baseline[a,b]



[a] Odds ratios are for LNS vs IFA group, the reference category. Bars represent 95% confidence intervals.
[b] Adjusted model plus interaction term: Group X Height at baseline (P=0.029)

No significant differences between groups were observed in mean maternal CRP or AGP concentrations (Table 16) or the proportion of women with high CRP, high AGP, or inflammation (either CRP or AGP elevated) (Table 17). In general, per-protocol analysis including only women who adhered to the supplementation regimen (i.e., consumed the supplement at least 4 days per week; n=675) confirmed the results obtained in the whole analytic sample (Tables 18 and 19). However, differences between intervention groups in the proportions with low ferritin and iron deficiency were not statistically significant, probably due to the reduced sample size. We conducted further analysis including only women who were not affected by the LNS disruption (n=402). Results in this subsample were similar to

those found in the complete analytic sample (Tables 20 and 21), with the exception of a lower Hb concentration and a higher risk of Hb < 110 g/L in the LNS group when compared with the IFA group in adjusted models (p=0.026 and p=0.036, respectively).

Table 16. Hemoglobin, Iron, and Inflammation Indicators at 36 Gestational Weeks, by Intervention Group[a,b]

Maternal Outcome	LNS Mean ± SE	IFA Mean ± SE	p-value
Hemoglobin (g/L)			
Unadjusted	114.3 ± 0.7	115.3 ± 0.7	0.336
Adjusted[e]	114.5 ± 0.5	115.6 ± 0.7	0.138
Ferritin (µg/L)[d]			
Unadjusted	25.53 ± 1.02	32.14± 1.26	< 0.001
Adjusted[e]	25.27 ± 1.01	31.50 ± 1.28	< 0.001
Corrected ferritin (µg/L)[d,f]			
Unadjusted	24.53 ± 0.98	30.27 ± 1.18	0.001
Adjusted[g]	24.53 ± 0.98	29.67 ± 1.21	0.001
sTfR (mg/L)[d]			
Unadjusted	6.11 ± 0.18	5.75 ± 0.12	0.113
Adjusted[h]	6.17 ± 0.12	5.70 ± 0.11	0.005
CRP (mg/L)[d]			
Unadjusted	1.39 ± 0.08	1.36 ± 0.08	0.778
Adjusted[i]	1.36 ± 0.08	1.38 ± 0.08	0.989
AGP (g/L)[d]			
Unadjusted	0.39 ± 0.01	0.41 ± 0.01	0.175
Adjusted[j]	0.39 ± 0.01	0.41 ± 0.01	0.219

[a] p-values of treatment effect are based on ANCOVA (SAS, PROC MIXED), accounting for union (nested within subdistrict) and the random effect of cluster.
[b] Values are mean ± SE, or geometric mean ± SE for log transformed variables. (In the text, log transformed variables are summarized with arithmetic means).
[c] Adjusted for Hb, education, food insecurity and assets index at baseline, tube well iron content, season at follow-up, and time between baseline and follow-up, and accounting for union (nested within subdistrict) and the random effect of cluster; n=798.
[d] Statistical testing conducted using log transformed variable.
[e] Adjusted for ferritin, height, tube well iron content, and season at follow-up, and accounting for union (nested within subdistrict) and the random effect of cluster; n=796.
[f] Corrected for presence of systemic inflammation following the approach of Thurnham et al. (2010).
[g] Adjusted for ferritin, height, tube well iron content, and season at follow-up, and accounting for union (nested within subdistrict) and the random effect of cluster; n=796.
[h] Adjusted for sTfR, CRP, primiparity at baseline, tube well iron content and season at follow-up and accounting for union (nested within subdistrict) and the random effect of cluster; n=796.
[i] Adjusted for CRP, height, and BMI at baseline, and accounting for union (nested within subdistrict) and the random effect of cluster; n=840.
[j] Adjusted for AGP, BMI, maternal age, maternal education, time between baseline and follow-up and primiparity, and accounting for union (nested within subdistrict) and the random effect of cluster; n=840.

Table 17. Prevalence and Odds Ratios of Low or High Hb, Low Ferritin, Elevated sTfR, Iron Deficiency, Iron Deficiency Anemia, Elevated CRP, Elevated AGP, and Inflammation at 36 Weeks[a,b]

Maternal Outcome	LNS % (95% CI)	IFA % (95% CI)	OR (95% CI)	p-value	AOR (95% CI)	p-value
Low Hb (Hb < 100 g/L)[c]	12.7 (10.2–15.3)	12.4 (9.1–15.7)	1.03 (0.70–1.50)	0.886	1.18 (0.72–1.92)	0.507
Hb < 110 g/L[d]	36.1 (32.1–40.1)	32.3 (27.7–37.0)	1.11 (0.91–1.36)	0.273	1.24 (0.87–1.78)	0.226
High Hb (Hb > 130 g/L)[e]	9.2 (6.0–12.4)	11.9 (8.3–15.4)	0.94 (0.58–1.52)	0.776	0.92 (0.60–1.44)	0.732
Ferritin < 12 µg/L[f]	18.4 (15.1–21.6)	9.8 (6.8–12.9)	1.68 (1.16–2.45)	0.007	1.67 (1.14–2.45)	0.010
Corrected ferritin < 12 µg/L[g]	19.8 (16.6–23.1)	10.9 (7.7–14.0)	1.63 (1.15–2.32)	0.006	1.82 (1.15–2.89)	0.011
sTfR > 8.3 mg/L[h]	19.0 (14.8–23.2)	13.1 (8.8–17.4)	1.31 (0.83–2.07)	0.231	1.07 (1.02–1.12)	0.016
Iron deficiency[i]	29.4 (24.7–34.2)	19.4 (14.3–24.6)	1.41 (1.00–1.98)	0.048	1.45 (1.09–1.93)	0.011
Iron deficiency anemia[j]	15.0 (12.6–17.4)	9.6 (6.0–13.2)	1.52 (0.95–2.42)	0.063	1.56 (1.04–2.34)	0.018
CRP > 5 mg/L[k]	12.5 (10.0–15.0)	15.2 (11.8–18.5)	0.95 (0.67–1.36)	0.780	0.96 (0.62–1.49)	0.863
AGP > 1 g/L[l]	2.1 (1.1–3.0)	3.8 (2.1–5.5)	----	---	---	---
Inflammation[m]	12.9 (10.5–15.4)	16.9 (13.4–20.4)	0.86 (0.61–1.21)	0.358	0.81 (0.53–1.24)	0.331

OR, odds ratio; AOR, adjusted odds ratio.

[a] ORs are for LNS versus IFA group, the reference category.

[b] p-values of treatment effect are based on logistic regression analysis (SAS, PROC GLIMMIX), accounting for union (nested within subdistrict) and the random effect of cluster.

[c] Adjusted model included Hb, CRP, food insecurity and assets index at baseline and season at follow-up, and accounted for union (nested within subdistrict) and the random effect of cluster; n=840.

[d] Adjusted model included Hb, tube well iron content and season at follow-up and accounted for union (nested within sub-district) and the random effect of cluster; n=798.

[e] Adjusted model included Hb and food insecurity at baseline, and accounted for union (nested within subdistrict) and the random effect of cluster; n=843.

[f] Adjusted model included ferritin < 12 µg/L, maternal age, height, food insecurity at baseline, tube well iron content, and season at follow-up, and accounted for union (nested within subdistrict) and the random effect of cluster; n=796.

[g] Ferritin was corrected based on presence of inflammation; adjusted for ferritin < 12 µg/L, maternal age, height, food insecurity at baseline, tube well iron content and season at follow-up and accounting for union (nested within subdistrict) and the random effect of cluster; n=796.

[h] Adjusted model included sTfR > 8.3 mg/L, CRP, tube well iron content, season at follow-up, primiparity, and time between baseline and follow-up; cluster effects removed to attain convergence; accounts for union (nested within subdistrict); n=796.

[i] Defined as corrected ferritin < 12 µg/L or sTfR > 8.3 mg/L. Adjusted model included iron deficiency at baseline, maternal age, tube well iron content, and season at follow-up, and accounted for union (nested within subdistrict) and the random effect of cluster; n=796.

[j] Defined as corrected ferritin < 12 µg/L or sTfR > 8.3 mg/L and Hb < 110 g/L. Adjusted model included iron deficiency anemia, CRP, maternal age and low BMI at baseline, and tube well iron content, and accounted for union (nested within subdistrict) and the random effect of cluster; n=796.

[k] Adjusted model included CRP > 5 mg/L, height and BMI and accounted for union (nested within subdistrict) and the random effect of cluster; n=840.

[l] Due to few cases with AGP > 1 g/L (n=24), SAS PROC GLIMMIX did not converge; n=840.

[m] Defined as CRP > 5 mg/L or AGP > 1 g/L. Adjusted model included inflammation, BMI and education at baseline and accounted for union (nested within subdistrict) and the random effect of cluster; n=840.

Table 18. Per-Protocol Analysis of Continuous Outcomes at 36 Gestational Weeks, by Intervention Group, Excluding Women Who Reported Consuming the Supplement < 4 Days/Week during Pregnancy[a,b]

Maternal Outcome	LNS (n=312) Mean ± SE	IFA (n=363) Mean ± SE	p-value
Hg (g/L)			
Unadjusted	114.8 ± 1.0	115.6 ± 0.8	0.546
Adjusted[d]	115.0 ± 0.7	115.8 ± 0.6	0.410
Ferritin (µg/L)[c]			
Unadjusted	26.05 ± 1.56	32.79 ± 1.64	0.004
Adjusted[e]	26.05 ± 1.56	31.82 ± 1.27	0.006
Corrected ferritin (µg/L)[c,f]			
Unadjusted	25.03 ± 1.50	30.88 ± 1.54	0.008
Adjusted[g]	25.28 ± 1.52	30.27 ± 1.21	0.013
sTfR (mg/L)[c]			
Unadjusted	6.05 ± 0.18	5.64 ± 0.11	0.054
Adjusted[h]	6.11 ± 0.12	5.58 ± 0.11	0.010
CRP (mg/L)[c]			
Unadjusted	1.48 ± 0.07	1.36 ± 0.07	0.383
Adjusted[i]	1.43 ± 0.07	1.38 ± 0.06	0.697
AGP (g/L)[c]			
Unadjusted	0.39 ± 0.01	0.401± 0.01	0.222
Adjusted[j]	0.39 ± 0.01	0.40 ± 0.01	0.320

[a] p-values of treatment effect are based on ANCOVA (SAS, PROC MIXED), accounting for union (nested within subdistrict) and the random effect of cluster.
[b] Values are mean ± SE, or geometric mean ± estimated geometric SE for log transformed variables. (In the text, log transformed variables are summarized with arithmetic means.)
[c] Statistical testing conducted using log transformed variable.
[d] Adjusted for Hb, tube well iron content, season at follow-up, and time between baseline and follow-up; and accounting for union (nested within subdistrict) and the random effect of cluster; unadjusted n=675; adjusted n=617.
[e] Adjusted for ferritin, height, tube well iron content, and season at follow-up, and accounting for union (nested within subdistrict) and the random effect of cluster; unadjusted n=675; adjusted n=616.
[f] Corrected for presence of systemic inflammation following the approach of Thurnham et al. (2010).
[g] Adjusted for ferritin, height, tube well iron content, and season at follow-up, and accounting for union (nested within subdistrict) and the random effect of cluster; unadjusted n=675; adjusted n=616.
[h] Adjusted for sTfR, CRP, tube well iron content and season at follow-up and accounting for union (nested within subdistrict) and the random effect of cluster; unadjusted n=675; adjusted n=616.
[i] Adjusted for CRP, height and BMI at baseline and accounting for union (nested within subdistrict) and the random effect of cluster; unadjusted n=675; adjusted n=650.
[j] Adjusted for AGP, BMI, maternal age, maternal education, primiparity, and time between baseline and follow-up and accounting for union (nested within subdistrict) and the random effect of cluster; unadjusted n=675; adjusted n=650.

Table 19. Per-Protocol Analysis of Dichotomous Variables at 36 Weeks, by Intervention Group, Excluding Women Who Reported Consuming the Supplement < 4 Days/Week during Pregnancy[a,b,c,d]

Maternal Outcome	LNS % (95% CI)	IFA % (95% CI)	OR (95% CI)	p-value	AOR (95% CI)	p-value
Low Hb (Hb < 100 g/L)[e]	11.9 (7.9–15.8)	11.8 (8.6–15.1)	0.99 (0.58–1.69)	0.966	1.09 (0.62–1.94)	0.756
Hb <110 g/L[f]	33.3 (26.9–39.8)	31.7 (26.6–36.8)	1.08 (0.72–1.63)	0.706	1.08 (0.69–1.68)	0.736
High Hb (Hb > 130 g/L)[g]	9.3 (6.1–12.5)	12.4 (8.5–16.3)	0.84 (0.47–1.48)	0.534	0.82 (0.45–1.50)	0.514
Ferritin < 12 µg/L[h]	17.3 (12.3–22.3)	9.9 (6.5–13.3)	1.69 (0.93–3.06)	0.083	1.65 (0.85–3.23)	0.137
Corrected ferritin < 12 µg/L[i]	18.3 (13.2–23.4)	11.0 (7.5–14.5)	1.58 (0.91–2.76)	0.102	1.53 (0.83–2.82)	0.168
sTfR > 8.3 mg/L[j]	19.2 (14.2–24.2)	11.3 (7.0–15.6)	1.77 (0.91–3.44)	0.090	2.05 (1.03–4.07)	0.042
Iron deficiency[k]	27.9 (21.5–34.2)	17.9 (12.6–23.2)	1.59 (0.91–2.80)	0.101	1.72 (0.98–3.01)	0.060
Iron deficiency anemia[l]	13.8 (10.2–17.4)	8.5 (5.0–12.1)	1.76 (0.87–3.56)	0.113	2.18 (1.12–4.27)	0.023
CRP > 5 mg/L[m]	12.8 (9.3–16.3)	15.4 (11.9–19.0)	0.98 (0.61–1.58)	0.944	0.97 (0.58–1.62)	0.916
Inflammation[n]	13.5 (10.1–16.8)	17.1 (13.4–20.8)	0.88 (0.56–1.40)	0.594	0.86 (0.53–1.41)	0.546
Low Hb (Hb < 100 g/L)[e]	11.9 (7.9–15.8)	11.8 (8.6–15.1)	0.99 (0.58–1.69)	0.966	1.09 (0.62–1.94)	0.756

[a] ORs are for LNS versus IFA group, the reference category.
[b] p-values of treatment effect are based on logistic regression analysis (SAS, PROC GLIMMIX), accounting for union (nested within subdistrict) and the random effect of cluster.
[c] AGP was excluded from this subsample analysis due to low variation in this outcome.
[d] Unadjusted model sample sizes same as in Table 18 and accounting for union (nested within subdistrict) and the random effect of cluster.
[e] Adjusted model included Hb, CRP, food insecurity and season at follow-up, and accounted for union (nested within subdistrict) and the random effect of cluster; n=650.
[f] Adjusted model included Hb, tube well iron content, season at follow-up, and time between baseline and follow-up, and accounted for union (nested within subdistrict) and the random effect of cluster; n=652.
[g] Adjusted model included Hb, food insecurity at baseline, and time between baseline and follow-up and accounted for union (nested within subdistrict) and the random effect of cluster; n=617.
[h] Adjusted model included ferritin < 12 µg/L, maternal age, height, food insecurity at baseline, tube well iron content and season at follow-up and accounted for union (nested within subdistrict) and the random effect of cluster; n=616.
[i] Ferritin was corrected based on presence of inflammation. Adjusted model included ferritin < 12 µg/L, height, food insecurity at baseline, tube well iron content and season at follow-up and accounted for union (nested within subdistrict) and the random effect of cluster; n=616.
[j] Adjusted model included sTfR > 8.3 mg/L, CRP, tube well iron content, season at follow-up and primiparity and accounted for union (nested within subdistrict) and the random effect of cluster; n=650.
[k] Defined as corrected ferritin < 12 µg/L or sTfR > 8.3 mg/L. Adjusted model included iron deficiency at baseline, maternal age, tube well iron content, and season at follow-up, and accounted for union (nested within subdistrict) and the random effect of cluster; n=616.
[l] Defined as corrected ferritin < 12 µg/L or sTfR > 8.3 mg/L and Hb <110 g/L. Adjusted model included iron deficiency anemia, CRP, maternal age, BMI at baseline, and tube well iron content, and accounted for union (nested within subdistrict) and the random effect of cluster; n=617.
[m] Adjusted model included CRP > 5 mg/L, height, BMI and season at follow-up and accounted for union (nested within subdistrict) and the random effect of cluster; n=650.
[n] Defined as CRP > 5 mg/L or AGP > 1 g/L. Adjusted model included inflammation, primiparity, maternal height and BMI and accounted for union (nested within subdistrict) and the random effect of cluster; n=650.

Table 20. Sensitivity Analysis of Continuous Outcomes at 36 Gestational Weeks, by Intervention Group, Excluding Women Affected by LNS Disruption during Follow-Up[a,b]

Maternal Outcome	LNS (n=224) Mean ± SE	IFA (n=178) Mean ± SE	p-value
Hg (g/L)			
Unadjusted	112.1 ± 0.9	114.7 ± 1.0	0.069
Adjusted[e]	112.2 ± 0.8	114.9 ± 0.9	0.026
Ferritin (µg/L)[c]			
Unadjusted	24.78 ± 1.49	34.12 ± 2.05	0.001
Adjusted[e]	24.53 ± 01.23	33.78 ± 1.61	< 0.001
Corrected ferritin (µg/L)[c,f]			
Unadjusted	24.05 ± 1.44	32.46 ± 1.95	0.001
Adjusted[g]	24.05 ± 1.20	32.14 ± 1.62	< 0.001
sTfR (mg/L)[c]			
Unadjusted	6.49 ± 0.19	5.93 ± 0.18	0.057
Adjusted[h]	6.55 ± 0.13	5.87 ± 0.18	0.007
CRP (mg/L)[c]			
Unadjusted	1.36 ± 0.11	1.30 ± 0.11	0.696
Adjusted[i]	1.34 ± 0.08	1.28 ± 0.12	0.761
AGP (g/L)[c]			
Unadjusted	0.39 ± 0.01	0.40 ± 0.01	0.492
Adjusted[j]	0.39 ± 0.01	0.40 ± 0.01	0.383

[a] p-values for treatment effect are based on ANCOVA (SAS, PROC MIXED), accounting for union (nested within subdistrict) and the random effect of cluster.
[b] Values are mean ± SE, or geometric mean ± estimated geometric SE for log transformed variables. (In the text, log transformed variables are summarized with arithmetic means.)
[c] Statistical testing conducted using log transformed variable.
[d] Adjusted for Hb, asset index, season at follow-up, BMI at baseline, height, and food security, and accounting for union (nested within subdistrict) and the random effect of cluster; unadjusted n=402; adjusted n=390.
[e] Adjusted for ferritin and tube well iron content and accounting for union (nested within subdistrict) and the random effect of cluster; unadjusted n=402; adjusted n=364.
[f] Corrected for presence of systemic inflammation following the approach of Thurnham et al (2010).
[g] Adjusted for ferritin and tube well iron content and accounting for union (nested within subdistrict) and the random effect of cluster; unadjusted n=402; adjusted n=364.
[h] Adjusted for sTfR and tube well iron content and accounting for union (nested within subdistrict) and the random effect of cluster; unadjusted n=402; adjusted n=364.
[i] Adjusted for CRP and BMI at baseline, and accounting for union (nested within subdistrict) and the random effect of cluster; unadjusted n=402; adjusted n=387.
[j] Adjusted for AGP, BMI, maternal age, asset index, food security, and primiparity, and accounting for union (nested within subdistrict) and the random effect of cluster; unadjusted n=402; adjusted n=387.

Table 21. Sensitivity Analysis of Dichotomous Variables at 36 Weeks, by Intervention Group, Excluding Women Affected by LNS Disruption during Follow-Up[a,b,c,d]

Maternal Outcome	LNS % (95% CI)	IFA % (95% CI)	OR (95% CI)	p-value	AOR (95% CI)	p-value
Low Hb (Hb < 100 g/L)[e]	15.6 (11.0–20.2)	15.2 (9.8–20.5)	1.02 (0.56–1.86)	0.950	0.99 (0.48–2.03)	0.974
Hb < 110 g/L[f]	43.3 (37.3–49.3)	33.1 (26.8–39.4)	1.47 (0.94–2.29)	0.088	1.75 (1.04–2.96)	0.036
Ferritin < 12 µg/L[g]	15.6 (11.1–20.1)	7.9 (3.6–12.1)	1.83 (0.91–3.70)	0.091	2.33 (1.07–5.09)	0.034
Corrected ferritin < 12 µg/L[h]	17.4 (12.2–22.7)	7.9 (3.6–12.1)	2.07 (0.99–4.32)	0.053	2.64 (1.15–6.08)	0.023
sTfR > 8.3 mg/L[i]	22.8 (17.5–28.0)	15.2 (10.0–20.3)	1.57 (0.90–2.74)	0.113	2.44 (1.22–4.90)	0.013
Iron deficiency[j]	29.0 (23.2–34.8)	18.5 (12.6–24.5)	1.60 (0.95–2.69)	0.074	1.95 (1.06–3.56)	0.031
Iron deficiency anemia[k]	16.5 (12.5–20.5)	10.1 (5.3–14.9)	1.73 (0.90–3.33)	0.096	3.25 (1.10–9.62)	0.034
CRP > 5 mg/L[l]	11.2 (7.7–14.7)	10.1 (5.6–14.6)	1.25 (0.62–2.51)	0.532	1.21 (0.59–2.50)	0.590
Inflammation[m]	11.6 (7.9–15.3)	12.4 (7.3–17.4)	0.98 (0.50–1.91)	0.956	0.96 (0.48–1.91)	0.901
Low Hb (Hb < 100 g/L)[e]	15.6 (11.0–20.2)	15.2 (9.8–20.5)	1.02 (0.56–1.86)	0.950	0.99 (0.48–2.03)	0.974
Hb < 110 g/L[f]	43.3 (37.3–49.3)	33.1 (26.8–39.4)	1.47 (0.94–2.29)	0.088	1.75 (1.04–2.96)	0.036

[a] ORs are for LNS versus IFA group, the reference category.
[b] p-values of treatment effect are based on logistic regression analysis (SAS, PROC GLIMMIX), accounting for union (nested within subdistrict) and the random effect of cluster.
[c] AGP and high Hb were excluded from this subsample analysis due to low variation in these outcomes.
[d] Unadjusted model sample sizes same as in Table 20 and accounting for union nested within subdistrict and the random effect of cluster.
[e] Adjusted model included Hb, food insecurity, season at follow-up, asset index, and height at baseline, and accounted for union nested within subdistrict and the random effect of cluster; n=390.
[f] Adjusted model included Hb, season at follow-up, asset index, and height at baseline, and accounted for union nested within subdistrict and the random effect of cluster; n=390.
[g] Adjusted model included ferritin < 12 µg/L and maternal age, and accounted for union nested within subdistrict and the random effect of cluster; n=387. Analysis was performed on log transformed values.
[h] Ferritin was corrected based on presence of inflammation. Adjusted model included ferritin < 12 µg/L, height, and tube well iron content, and accounted for union nested within subdistrict and the random effect of cluster; n=364. Analysis was performed on log transformed values.
[i] Adjusted model included sTfR > 8.3 mg/L and season at follow-up, and accounted for union nested within subdistrict and the random effect of cluster; n=364. Analysis was performed on log transformed values.
[j] Defined as corrected ferritin < 12 µg/L or sTfR > 8.3 mg/L. Adjusted model included iron deficiency at baseline and tube well iron content, and accounted for union nested within subdistrict and the random effect of cluster; n=364.
[k] Defined as corrected ferritin < 12 µg/L or sTfR > 8.3 mg/L and Hb < 110 g/L. Adjusted model included iron deficiency anemia, tube well iron content, season at follow-up, and food insecurity, and accounted for union nested within subdistrict and the random effect of cluster; n=366.
[l] Adjusted model included MUAC at baseline and accounted for union nested within subdistrict and the random effect of cluster; n=402.
[m] Defined as CRP > 5 mg/L or AGP > 1 g/L. Adjusted model included MUAC at baseline and accounted for union nested within subdistrict and the random effect of cluster; n=402.

3.2.5 Maternal Vitamin A Status

A total of 1,160 participants were randomly selected for the analysis of maternal vitamin A status. Of those, 1,125 had RBP data (504 in the IFA group and 621 in the LNS group). This subsample represented 28 percent of the RDNS sample. Women included in the analysis did not differ from those not included with respect to any of the baseline characteristics, except for weekly meat, egg, and fish consumption (p=0.039) (data not shown). Table A-6 in the appendices shows baseline characteristics of the women, by intervention group. The women in the LNS group had higher levels of education (p=0.006) and a higher prevalence of CRP > 5 mg/L than those in the IFA group.

At 36 weeks, the mean unadjusted log of RBP concentration was significantly higher (p=0.041) in the LNS group than in the IFA group, but the adjusted log of RBP concentration was not significantly different between groups (Table 22). Mean unadjusted and adjusted changes in the log of RBP concentration in the LNS group were not significantly different from those in the IFA group (Table 22). The prevalence of low RBP was also not significantly different between groups (Table 23).

Per-protocol analysis including only women who adhered to the supplementation regimen (i.e., consumed the supplement at least 4 days per week; n=675) confirmed the results of the intention-to-treat analysis using the full subsample (Tables 24 and 25). We conducted further analysis including only women who were not affected by the LNS disruption (n=402). Results in this subsample were similar to those found in the complete analytic sample (data not shown).

Table 22. Vitamin A Status at 36 Weeks of Gestation, by Intervention Group (n=875)[a,b]

Maternal Outcome	LNS (n=479) Mean ± SE	IFA (n=396) Mean ± SE	p-value
RBP (µmol/L)[c]			
Unadjusted[d]	1.49 ± 0.04	1.40 ± 0.04	0.041
Adjusted[e]	1.48 ± 0.01 [460]	1.42 ± 0.04 [380]	0.106
Change in log of RBP between baseline and 36 weeks (µmol/L)			
Unadjusted[d]	0.07 ± 0.01 [460]	0.04 ± 0.02 [380]	0.283
Adjusted[f]	0.07 ± 0.02 [460]	0.04 ± 0.02 [380]	0.128

[a] p-values for treatment effect are based on ANCOVA (SAS, PROC MIXED), accounting for union (nested within subdistrict) and the random effect of cluster.
[b] Values are mean ± SE, or geometric mean ± estimated geometric SE for log transformed variables.
[c] Analysis performed on the log transformed value.
[d] Adjusted for union (nested within subdistrict) and the random effect of cluster.
[e] Adjusted for age, education, asset quintile, season at baseline, green leafy vegetable consumption, maternal MUAC, maternal BMI, log of RBP at baseline, ownership of a fishpond, and consumption of vitamin A capsule, and accounting for union nested within subdistrict and the random effect of cluster; n=840.
[f] Adjusted for asset quintile, season at baseline, log of RBP at baseline, ownership of a fishpond, gestational age at enrollment, and food security, and accounting for union nested within subdistrict and the random effect of cluster; n=840.

Table 23. Prevalence and Odds Ratios[1] of Low RBP at 36 Weeks of Gestation (n=875)[a,b]

Maternal Outcome	LNS (n=479) % (95% CI)	IFA (n=396) % (95% CI)	OR (95% CI)	p-value	AOR (95% CI)[c,d]	p-value
RBP < 1.17 µmol/L	23.4 (18.96–27.8)	27.5 (23.1–31.9)	0.77 (0.55, 1.08)	0.121	0.84 (0.57, 1.24)	0.374

[a] ORs are for LNS versus IFA group, the reference category.
[b] p-values of treatment effect are based on logistic regression analysis (SAS, PROC GLIMMIX), accounting for union (nested within subdistrict) and the random effect of cluster.
[c] Adjusted model included age, education, asset quintile, season at baseline, log of RBP at baseline, gestational age at enrollment, and maternal height, and accounted for union nested within subdistrict and the random effect of cluster; n=840.

Table 24. Per-Protocol Analysis of Continuous Outcomes at 36 Weeks of Gestation, by Intervention Group, Excluding Women Who Reported Consuming the Supplement < 4 Days/Week during Pregnancy (n=675)[a,b]

Maternal Outcome	LNS (n=312) Mean ± SE	IFA (n=363) Mean ± SE	p-value
RBP (µmol/L)			
Unadjusted[c,d]	1.46 ± 0.03	1.42 ± 0.03	0.093
Adjusted[d,e]	1.46 ± 0.03 [300]	1.42 ± 0.03 [350]	0.314
Change in log of RBP between baseline and 36 weeks (µmol/L)			
Unadjusted[c]	0.07 ± 0.02 [300]	0.05 ± 0.02 [350]	0.555
Adjusted[f]	0.08 ± 0.018 [300]	0.05 ± 0.02 [350]	0.258

[a] p-values for treatment effect are based on ANCOVA (SAS, PROC MIXED), accounting for union (nested within subdistrict) and the random effect of cluster.
[b] Values are geometric mean ± estimated geometric SE for log transformed variables.
[c] Accounts for union nested within subdistrict and the random effect of cluster.
[d] Analysis performed on the log transformed values.
[e] Adjusted for age, education, asset quintile, season at baseline, maternal MUAC, maternal BMI, log of RBP at baseline, and ownership of a fishpond, and accounting for union (nested within subdistrict) and the random effect of cluster; n=650.
[f] Adjusted for education, asset quintile, season at baseline, log of RBP at baseline, ownership of a fishpond, gestational age at enrollment, and food security, and accounting for union (nested within subdistrict) and the random effect of cluster; n=650.

Table 25. Per-Protocol Analysis of Dichotomous Variable at 36 Weeks of Gestation, by Intervention Group, Excluding Women Who Reported Consuming the Supplement < 4 Days/Week during Pregnancy (n=675)[a,b]

Maternal Outcome	LNS % (95% CI)	IFA % (95% CI)	OR (95% CI)	p-value	AOR (95% CI)[c]	p-value
RBP < 1.17 µmol/L	23.7 (17.4–30.1)	27.0 (22.6–31.4)	0.80 (0.54, 1.19)	0.260	0.98 (0.62, 1.56)	0.947

[a] OR is for LNS versus IFA group, the reference category.
[b] p-values of treatment effect are based on logistic regression analysis (SAS, PROC GLIMMIX), accounting for union (nested within subdistrict) and the random effect of cluster.
[c] OR adjusted for gestational age at enrollment, education, asset quintile, season at baseline, maternal MUAC, maternal BMI, log of RBP at baseline, consumption of meat/eggs/fresh fish, and union (nested within subdistrict), and accounting for union (nested within subdistrict) and the random effect of cluster; n=650.

3.2.6 Maternal Iodine Status

At baseline, 1,159 participants were randomly selected for the analysis on maternal iodine status. Of those, 1,128 had UIC data (507 in the IFA group and 621 in the LNS group). This subsample represented 28 percent of the RDNS sample. Women included in the analysis were not significantly different in any of the baseline characteristics from women not included in this analysis. Table A-7 in the appendices shows baseline characteristics of the women, by intervention group. In this subsample, the women in the LNS group had higher levels of education (p=0.012) than those in the IFA group.

Mean unadjusted and adjusted UIC at 36 weeks of gestation were not significantly different between the IFA and LNS groups, nor were the changes in log UIC between baseline and 36 weeks (Table 26). Three cutoffs of iodine deficiency were used for the analysis (UIC < 150 µg/L, < 100 µg/L, and < 50 µg/L). Almost all the women (93.7 percent in the IFA group versus 93.5 percent in the LNS group) were categorized with iodine deficiency when the WHO cutoff (UIC < 150 µg/L) was used. There were no significant differences between the IFA and LNS groups in the prevalence of iodine deficiency using any of the cutoffs. However, the women in the LNS group tended to have a lower prevalence of iodine deficiency (p=0.077) when using the cutoff of < 50 µg/L (Table 27).

Per-protocol analysis including only women who adhered to the supplementation regimen (i.e., consumed the supplement at least 4 days per week; n=671) showed that women in the LNS group tended to have higher adjusted mean urinary iodine (p=0.064) and adjusted change in log urinary iodine between baseline and 36 weeks of gestation (p=0.083) (Table 28). The odds of iodine deficiency when estimated using the cutoff of < 50 µg/L were lower in the LNS group (p=0.019) (Table 29). We conducted further analysis including only women who were not affected by the LNS disruption (n=401). Results in this subsample were similar to those found in the complete analytic sample (data not shown).

Table 26. Urinary Iodine and Change in Log Urinary Iodine at 36 Weeks of Gestation (n=872), by Intervention Group[a,b]

Maternal Outcome	LNS (n=478) Mean ± SE	IFA (n=394) Mean ± SE	p-value
Urinary iodine (µg/L)[d]			
Unadjusted[c]	34.1 ± 1.71	31.8 ± 1.58	0.290
Adjusted[e]	34.1± 1.37 [459]	31.8 ± 1.27 [382]	0.253
Changes in log urinary iodine (µg/L)			
Unadjusted[c]	-0.38 ± 0.06 [459]	-0.49 ± 0.07 [382]	0.160
Adjusted[f]	-0.39 ± 0.04 [459]	-0.47 ± 0.05 [382]	0.210

[a] p-values for treatment effect are based on ANCOVA (SAS, PROC MIXED), accounting for union (nested within subdistrict) and the random effect of cluster.
[b] Values are mean ± SE, or geometric mean ± estimated geometric SE for log transformed variables.
[c] Accounts for union (nested within subdistrict) and the random effect of cluster.
[d] Statistical testing conducted using log transformed variable.
[e] Adjusted for age, education, BMI at baseline, height at baseline, MUAC at baseline, nulliparity, log of baseline urinary iodine, baseline consumption of iodized salt, season at baseline, and household members under 5, and accounting for union (nested within subdistrict) and the random effect of cluster; n=841.
[f] Adjusted for age, gestational age at baseline, BMI at baseline, height at baseline, MUAC at baseline, log of baseline urinary iodine, season at baseline, household members under 5, and food security, and accounting for union (nested within subdistrict) and the random effect of cluster; n=841.

Table 27. Prevalence and Relative Risks of Low Urinary Iodine at 36 Weeks of Gestation[a,b]

Maternal Outcome	LNS (n=478) % (95% CI)	IFA (n=394) % (95% CI)	OR (95% CI)	p-value	AOR (95% CI)	p-value
Urinary iodine < 150 µg/L[c]	93.5 (91.5–95.5)	93.7 (91.3–956.0)	1.00 (0.96, 1.04)	0.969	1.00 (0.97, 1.04)	0.927
Urinary iodine < 100 µg/L[d]	86.8 (84.2–89.4)	88.3 (85.4–91.2)	0.98 (0.93, 1.04)	0.537	0.99 (0.93, 1.04)	0.396
Urinary iodine < 50 µg/L[e]	69.5 (65.1–73.8)	73.4 (69.0–77.7)	0.93 (0.85, 1.02)	0.123	0.94 (0.85, 1.03)	0.077

[a] ORs are for LNS versus IFA group, the reference category.
[b] p-values of treatment effect are based on logistic regression analysis (SAS, PROC GLIMMIX), accounting for union (nested within subdistrict) and the random effect of cluster.
[c] Adjusted model included age, height at baseline, asset quintile, education, nulliparity, baseline consumption of iodine salt, and season at baseline, and accounted for union nested within subdistrict and the random effect of cluster; n=872.
[d] Adjusted model included age, education, MUAC at baseline, log of baseline urinary iodine, nulliparity, baseline consumption of iodine salt, and season at baseline, and accounted for union (nested within subdistrict) and the random effect of cluster; n=872.
[e] Adjusted model included age, education, BMI at baseline, MUAC at baseline, nulliparity, log of baseline urinary iodine, baseline consumption of iodine salt, season at baseline, and household members under 5, and accounted for union (nested within subdistrict) and the random effect of cluster; n=872.

Table 28. Per-Protocol Analysis of Continuous Outcomes at 36 Weeks of Gestation, by Intervention Group, Excluding Women Who Reported Consuming the Supplement < 4 Days/Week during Pregnancy (n=671)[a,b]

Maternal Outcome	LNS (n=310) Mean ± SE	IFA (n=361) Mean ± SE	p-value
Urinary iodine (µg/L)[c]			
Unadjusted	33.8 ± 2.10	30.3 ± 1.48	0.064
Adjusted[d]	34.5 ± 1.72 [298]	30.3 ± 1.51 [351]	0.078
Changes in log urinary iodine (µg/L)			
Unadjusted	-0.43 ± 0.06 [298]	-0.55 ± 0.05[351]	0.113
Adjusted[e]	-0.42 ± 0.05 [298]	-0.55 ± 0.05 [351]	0.083

[a] p-values for treatment effect are based on ANCOVA (SAS, PROC MIXED), accounting for union (nested within subdistrict) and the random effect of cluster.
[b] Values are mean ± SE, or geometric mean ± estimated geometric SE for log transformed variables.
[c] Statistical testing conducted using log transformed variable.
[d] Adjusted for age, education, BMI at baseline, MUAC at baseline, nulliparity, log of baseline urinary iodine, baseline consumption of iodized salt, and season at baseline, and accounting for union (nested within subdistrict) and the random effect of cluster; n=649.
[e] Adjusted for age, education, gestational age at baseline, log of baseline urinary iodine, season at baseline, food security, and season at baseline, and accounting for union (nested within subdistrict) and the random effect of cluster; n=649.

Table 29. Per-Protocol Analysis of Dichotomous Variables at 36 Weeks of Gestation, by Intervention Group, Excluding Women Who Reported Consuming the Supplement < 4 Days/Week during Pregnancy (n=671)[a,b]

Maternal Outcome	LNS % (95% CI)	IFA % (95% CI)	OR (95% CI)	p-value	AOR (95% CI)	p-value
Urinary iodine < 100 µg/L	87.4 (84.4–90.4)	89.5 (86.4–92.6)	0.72 (0.41, 1.27)	0.267	0.75 (0.45, 1.25)[c]	0.246
Urinary iodine < 50 µg/L	69.4 (63.9–74.8)	75.1 (70.4–79.7)	0.65 (0.45, 0.96)	0.031	0.61 (0.41, 0.92)[d]	0.019

[a] ORs are for LNS versus IFA group, the reference category.
[b] p-values of treatment effect are based on logistic regression analysis (SAS, PROC GLIMMIX), accounting for union (nested within subdistrict) and the random effect of cluster.
[c] ORs adjusted for age, education, MUAC at baseline, log of baseline urinary iodine, nulliparity, baseline consumption of iodine salt, and season at baseline, and accounting for union (nested within subdistrict) and the random effect of cluster.; n=649.
[d] ORs adjusted for age, education, BMI at baseline, MUAC at baseline, log of baseline urinary iodine, baseline consumption of iodine salt, season at baseline, and household members under 5, and accounting for union (nested within subdistrict) and the random effect of cluster; n=649.

3.3 Health Care Expenditures during Pregnancy, Childbirth, and Early Postpartum Period

A total of 3,704 participants were included in the analysis of health care expenditures during pregnancy, childbirth, and the early postpartum period: 2,730 in the IFA group and 974 in the LNS group. Women reporting no expenditures were included in the sample and given values of 0 for expenditure, time lost to illness, and number of visits to treatment centers. The results excluding women reporting no expenditures or visits were similar to those for the entire sample, and there were no statistically significant differences between the subgroups regarding health care-seeking behavior or expenditure patterns that were not seen in the full sample. Furthermore, women who reported not knowing their expenditures or the amount of time lost to illnesses were given imputed values for those outcomes, but their exclusion (with the expenditure/days set to 0 for that visit or set to missing) also did not change the patterns of results.

Table A-8 in the appendices reports the sample participant and household characteristics at baseline, by intervention group, for all of the covariates used in the regressions estimated in this section. At baseline, there were no statistically significant differences between intervention groups in the variables used in the adjusted regressions estimates reported below.

Health care expenditures are reported in different ways; total expenditures capture all out-of-pocket expenditures associated with all health care treatment sought, for any reason, from one month prior to the 36-week visit to 42 days postpartum. Birth expenditures represent cash outlays associated with birth and the immediate postpartum period, regardless of where the birth took place or where immediate postpartum services were delivered. ANC/PNC case outlays cover only pre/post birth services that were directly related to pregnancy. Expenditures for acute care are those related to health care visits or services that were unrelated to pregnancy (e.g., injuries), but which were sought or paid for during pregnancy, childbirth, or up to 42 days postpartum. Hospital care expenses are outlays related to hospital visits, for any reason.

Mean total expenditure (Table 30) in the IFA group was 3,083 Tk (~US$40)[4] and 3,211 Tk in the LNS group — a statistically insignificant difference between groups of 128 Tk, or a little more than US$2. Nearly all respondents (96 percent) in both groups reported incurring some expenditure during the birth process (Table 31). Mean birth expenditure was 2,444 Tk (~ US$31) in the IFA group and 2,457 Tk in the LNS group. There was no statistically significant difference in amount of time lost due to childbirth between the IFA group (12.4 days) and the LNS group (12.8 days) (difference = 0.4 days; p=0.72).

Nearly all respondents (97 percent) in each group reported at least some expenditure on ANC or PNC (Table 32). Average expenditure on all ANC/PNC visits was 505 Tk (~US$6.40) in the IFA group and 513 Tk in the LNS group, and the difference between the groups was statistically insignificant. Households in the IFA group reported spending an average of 2.5 days on ANC/PNC care, compared with 2.0 days for those in the LNS group, and there was no statistically significant difference between the LNS and IFA groups (-0.4 days).

In the IFA group, 31 percent of respondents reported seeking medical care for one or more acute conditions during the recall period (Table 33), compared with 32 percent in the LNS group. There were no statistically significant differences in proportion of care seekers, amount of money spent, or days lost due to acute medical care between the groups.

[4] 1 US$ = 78 Tk.

There was a statistically significant difference between groups regarding whether an individual visited a hospital for care (Table 34). Women in the LNS group were more likely than women in the IFA group to have visited a hospital or emergency room for care (6 percent versus 4 percent, respectively). The most common causes of seeking hospital care were lower abdominal pain and bleeding from the vagina. The mean expenditure on hospital visits was significantly higher in the LNS group than in the IFA group (difference of around 100 Tk, or US$1.30), and the LNS group reported spending (per capita) 0.1 extra days on hospital care. The effects of LNS on hospital visits were small because hospital visits were rare, and the result was not statistically significant when analyzing only the small number of women with hospital expenditures greater than 0 (i.e., choosing to seek hospital care in the first place was the key predictor of hospital expenditures).

There was no evidence of effect modification by household asset index, household food insecurity score, or maternal age or education on any of the expenditure categories (data not shown).

Table 30. Total Health Expenditure from 32 Weeks of Gestation through 42 Days Postpartum[a,b]

Outcome	LNS (n=974)	IFA (n=2,730)	Difference (95% CI)[c]	p-value
Expenditure (Tk)				
Unadjusted	3,211 Tk (± 288)	3,083 Tk (± 130)	128 (-502–759	0.69
Adjusted	3,176 Tk (± 185)	3,092 Tk (± 93)	83 (-340–505)	0.70
Days Lost				
Unadjusted	15.8 (± 0.7)	15.8 (± 0.9)	0 (-2.2–2.3)	0.98
Adjusted	15.4 (± 0.3)	15.9 (± 0.4)	-0.1 (-1.5–0.5)	0.28

[a] All adjusted outcomes included adjustments for asset index, food insecurity score, number of children under-5 in the household and age and years of education for both parents (continuous), dummy variables for whether the family is joint (or nuclear), and for missing parental education variables, and accounted for union nested within subdistrict and the random effect of cluster.

[b] Means and (standard errors) come from an OLS regression on dummy variables for LNS vs. IFA groups (no constant).

[c] Difference is the coefficient from an OLS regression on a dummy for LNS group. 95% CIs and p-values are both calculated using SEs clustered at the level of random assignment.

Table 31. Birth Expenditures and Time Spent in Delivery and Recovery[a,b]

Outcome	LNS (n=974)	IFA (n=2,730)	Difference (95% CI)[c]	p-value
% with Expenditure				
Unadjusted	96 (94–98)	96 (95–98)	0 (-.03– .02)	0.65
Adjusted	96 (94–97)	96 (96–97)	0 (-.02– .01)	0.31
Birth Expenditures (Tk)				
Unadjusted	2,457 (± 248)	2,444 (± 119)	13 (-536–563)	0.96
Adjusted	2,425 (±141)	2,454 (±85)	-29 (-361–304)	0.87
Days Lost				
Unadjusted	12.8 (± 0.9)	12.4 (± 0.7)	0.41 (-1.9–2.7)	0.72
Adjusted	12.3 (±0.3)	12.6 (±0.3)	-0.25 (-1.0–0.55)	0.53

[a] All adjusted outcomes included adjustments for asset index, food insecurity score, number of children under-5 in the household and age and years of education for both parents (continuous), dummy variables for whether the family is joint (or nuclear), and for missing parental education variables, and accounted for union nested within subdistrict and the random effect of cluster.
[b] Means and (standard errors) come from an OLS regression on dummy variables for LNS vs. IFA groups (no constant).
[c] Difference is the coefficient from an OLS regression on a dummy for LNS group. 95% CIs and p-values are both calculated using SEs clustered at the level of random assignment.

Table 32. Antenatal and Postnatal Care from 32 Weeks of Gestation through 42 Days Postpartum[a,b]

Outcome	LNS (n=974)	IFA (n=2,730)	Difference (95% CI)[c]	p-value
% with Expenditure				
Unadjusted	97 (96–99)	97 (96–99)	0 (-2–2)	0.98
Adjusted	97 (96– 98)	97 (96– 98)	0 (-1–1)	0.65
ANC/PNC Expenditures (Tk)				
Unadjusted	513 (± 40)	505 (± 21)	7 (-84–98)	0.87
Adjusted	523 (±29)	502 (±15)	21 (-45–88)	0.52
Days Lost				
Unadjusted	2.0 (± 0.26)	2.5 (± 0.18)	-0.4 (-1.0–0.2)	0.18
Adjusted	2.1 (±0.20)	2.4 (±0.16)	-0.4 (-0.9–0.2)	0.18

[a] All adjusted outcomes included adjustments for asset index, food insecurity score, number of children under-5 in the household and age and years of education for both parents (continuous), dummy variables for whether the family is joint (or nuclear), and for missing parental education variables, and accounted for union nested within subdistrict and the random effect of cluster.
[b] Means and (standard errors) come from an OLS regression on dummy variables for LNS vs. IFA groups (no constant).
[c] Difference is the coefficient from an OLS regression on a dummy for LNS group. 95% CIs and p-values are both calculated using SEs clustered at the level of random assignment.

Table 33. Acute Care Seeking and Expenditure from 32 Weeks of Gestation through 42 Days Postpartum[a,b]

Outcome	LNS (n=974)	IFA (n=2,730)	Difference (95% CI)[c]	p-value
% with Expenditure				
Unadjusted	32 (26–37)	31 (28–34)	1 (-5–07)	0.80
Adjusted	30 (26– 32)	32 (30– 33)	-3 (-6–1)	0.12
Acute Care Expenditure				
Unadjusted	68 (± 12)	64 (± 7)	5 (-24–33)	0.32
Adjusted	65 (±10)	65 (±7)	-1 (-24–23)	0.96
Days Lost				
Unadjusted	0.5 (± 0.08)	0.6 (± 0.06)	-0.1 (-0.3–0.1)	0.40
Adjusted	0.5 (±0.08)	0.6 (±0.06)	-0.1 (-0.3–0.1)	0.38

[a] All adjusted outcomes included adjustments for asset index, food insecurity score, number of children under-5 in the household and age and years of education for both parents (continuous), dummy variables for whether the family is joint (or nuclear), and for missing parental education variables, and accounted for union nested within subdistrict and the random effect of cluster.
[b] Means and (standard errors) come from an OLS regression on dummy variables for LNS vs. IFA groups (no constant).
[c] Difference is the coefficient from an OLS regression on a dummy for LNS group. 95% CIs and p-values are both calculated using SEs clustered at the level of random assignment.

Table 34. Hospital Care Seeking and Expenditure from 32 Weeks of Gestation through 42 Days Postpartum[a,b]

Outcome	LNS (n=974)	IFA (n=2,730)	Difference (95% CI)[c]	p-value
% with Expenditure				
Unadjusted	6 (4–7)	4 (3–5)	2 (0–3)	0.04
Adjusted	6 (5–7)	4 (3–4)	2 (0–3)	< 0.01
Hospital Expenditure				
Unadjusted	168 (± 40)	70 (± 16)	99 (13–184)	0.02
Adjusted	161 (± 38)	72 (± 17)	90 (3– 176)	0.04
Days Lost				
Unadjusted	0.4 (± 0.1)	0.3 (± 0.05)	0.13 (-0.1– 0.4)	0.24
Adjusted	0.4 (± 0.1)	0.3 (± 0.0)	0.15 (0–0.3)	0.08

[a] All adjusted outcomes included adjustments for asset index, food insecurity score, number of children under-5 in the household and age and years of education for both parents (continuous), dummy variables for whether the family is joint (or nuclear), and for missing parental education variables, and accounted for union nested within subdistrict and the random effect of cluster.
[b] Means and (standard errors) come from an OLS regression on dummy variables for LNS vs. IFA groups (no constant).
[c] Difference is the coefficient from an OLS regression on a dummy for LNS group. 95% CIs and p-values are both calculated using SEs clustered at the level of random assignment.

4 Discussion

4.1 Birth Outcomes

In this study, provision of LNS-PL 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 LAZ, resulting in a significant 17-percent 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-PL, with a 25-percent reduction in newborn stunting among women who reported regularly consuming LNS-PL compared with those who reported regularly consuming IFA. Among infants born before the 10-week disruption in supply of LNS-PL, the reduction in newborn stunting was 31 percent. To our knowledge, this is the first study to report an effect of a prenatal nutrient or food supplement containing MMN on the prevalence of stunting at birth.

Although the proportion of stunting occurring prior to versus after birth is not well understood and likely varies across populations, there is agreement that stunting often begins *in utero* (de Onis et al. 2013) and that some of the stunting that occurs after birth may be programmed *in utero* (Martorell and Zongrone 2012). However, meta-analyses have not shown any significant impact on birth length of prenatal MMN (Fall et al. 2009) or balanced protein-energy supplementation (Kramer et al. 2003), despite significant effects on birth weight. An effect on birth length was observed in a study in Burkina Faso in which the effects of prenatal LNS (373 kcal/d) were compared with those of MMN alone; there was a 0.5-cm increase in birth length in the former group compared with the latter, yet no significant difference in birth weight (Huybregts et al. 2009).

In the total sample, the effect of LNS-PL on mean birth weight (+47 g in the unadjusted model; +46 g in the adjusted model) was similar to the pooled effect of MMN in the most recent meta-analysis (+53 g) (Ramakrishnan et al. 2012), but smaller than the estimated pooled effect of balanced protein-energy supplementation (+73g) (Imdad et al. 2012), which is not surprising given that the LNS-PL used in our study contributed only 118 kcal/d (versus ~400-800 kcal/d in most prenatal food supplementation studies) and the RDNS was an effectiveness study, not an efficacy trial. The ~9-percent reduction in LBW was only marginally significant, whereas the above-mentioned meta-analyses reported reductions of 14 percent for MMN and 32 percent for balanced protein-energy supplementation. However, in per-protocol analyses, the prevalence of LBW in our study was reduced by 11 percent ($p=0.03$), similar to what has been observed for efficacy trials with MMN. We also found a significant effect of LNS-PL on mean BMIZ and a 13-percent reduction in the prevalence of wasting (low BMIZ) at birth; in per-protocol analyses, the prevalence of wasting was reduced by 14 percent.

The significant effects of LNS-PL on head circumference and percentage with small head size at birth are noteworthy given the association between head circumference and brain size during infancy (Lorenz et al. 2009). The percentage of newborns with small head size was reduced by 17 percent in the sample as a whole, by 19 percent in per-protocol analyses, and by 22 percent when limited to infants born before the 10-week disruption in supply of LNS-PL. The MMN supplement meta-analyses mentioned earlier (Ramakrishnan et al. 2012; Fall et al. 2009) did not report data on head circumference, and other published MMN (Bhutta et al. 2009; Sunawang et al. 2009) and LNS (Huybregts et al. 2009) studies did not show any significant differences. However, a recent meta-analysis showed that prenatal MMN

supplementation increased child head circumference later in infancy or childhood, compared with provision of two micronutrients or less (Lu et al. 2014). (The authors of that meta-analysis did not report the proportion with small head size.) In a recent, large prenatal MMN intervention in Bangladesh, there was also a significant effect on head circumference (West et al. 2014).

Although the most recent meta-analysis of prenatal MMN supplementation (Ramakrishnan et al. 2012) and the latter study in Bangladesh (West et al. 2014) have reported a small but significant increase in the duration of gestation, we did not find significant main effects of LNS-PL on duration of gestation or preterm delivery. However, subgroup analyses revealed that LNS-PL increased the duration of gestation by 0.5 weeks among women in very food-insecure households, and by 0.3 weeks among women carrying female infants. There are at least two possible explanations for the lack of a main effect on duration of gestation. First, in contrast to the other study in Bangladesh (West et al. 2014), ours was an effectiveness trial and adherence to LNS-PL was significantly lower than adherence to IFA. Second, the average duration of gestation at enrollment was 13 weeks (range of 4.6–20.0 weeks), whereas the other Bangladesh study recruited all women in the first trimester.

We explored whether the magnitude of the effect of LNS-PL on birth size differed depending on several pre-defined, biologically plausible, potential effect modifiers. There were no significant interactions with maternal education, BMI, or parity. However, household food insecurity, assets, maternal age and height, sex of the child, and time of year at birth modified the effect of LNS-PL 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-PL among such women, not only on newborn stunting but also on birth weight and head circumference (as well as duration of gestation, as mentioned above). What is surprising is that the differences in prevalence of newborn stunting across subgroups with higher levels of household food insecurity (as seen in the IFA group) were eliminated in the LNS group (Figure 2), even though the supplement provided only 118 kcal/d. As a result, newborn stunting was reduced by 36 percent among women who were very food insecure. Similarly, the effect of LNS-PL on birth length, MUAC, and SGA was more evident in the households in the lower wealth quintiles.

Maternal age was also an important effect modifier in our study: LNS-PL reduced newborn stunting by 21 percent among infants born to mothers who were 14 to 24 years 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 (Rah et al. 2008), which is thought to be attributable at least in part to competition for nutrients between the young mother and the growing fetus (King 2003). LNS-PL 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 (Fall et al. 2009).

Although time of year at birth was a significant effect modifier for nearly all birth outcomes, a consistent seasonal pattern was not apparent, and the LNS delivery disruption complicates the interpretation of these results. The association between season and birth size is widely documented (Pomeroy et al. 2014). An earlier study in Bangladesh showed that the strongest effect of prenatal food supplementation on birth weight occurred among infants born during January and February (Shaheen et al. 2006). However, in our study, the largest difference between the LNS and IFA groups occurred among infants born from mid-June to mid-August, just before the LNS disruption.

4.2 Maternal Weight Gain

In the study group as a whole, there was no significant effect of the intervention on maternal weight gain during pregnancy. Although we observed a difference of 6 g/week in weight gain favoring the LNS group, this difference was not significant. This is not surprising given that LNS-PL only contains 118 kcal. A review of results from balanced protein-energy supplementation trials indicated a significant pooled effect on weight gain of 21 g/week when compared with the non-supplemented group (Kramer and Kakuma 2010). However, in most of those trials the amount of energy provided by supplementation was much higher ($\geq$ 400 kcal) than the amount provided by LNS-PL. We did find, however, that LNS-PL increased maternal weight gain during pregnancy (+34 g/week) among multiparous women > 25 years of age. In addition, the per-protocol analysis (all women who reported consuming the supplement < 4 days/week during pregnancy) indicated a marginally significant group difference of 12 g/week, which points to the potential for broader benefits of LNS, if adherence to the supplementation regime were optimal. LNS-PL was a novel product to the women in the RDNS; thus, it is possible that greater familiarity with it would increase adherence and thereby increase its potential to have positive effects on maternal nutritional status.

4.3 Pregnancy Complications

There were no differences in average blood pressure at 36 weeks or proportions of women with pregnancy or childbirth complications between the LNS and IFA groups. LNS supplementation did not reduce the prevalence of high blood pressure at 36 weeks (a proxy indicator for pre-eclampsia), but < 2 percent of study women had high blood pressure at that time point. It is reassuring that there were no significant differences between intervention groups in the percentage of women with prolonged labor, obstructed labor, or C-section, given that infants in the LNS group were larger at birth (including head circumference). Previous studies in Nepal indicated that prenatal MMN supplements increased the risk of obstructed labor and birth asphyxia, which the researchers attributed to a shift to the right in the entire birth weight distribution in a population in which maternal stunting was very common and access to emergency obstetrical services was minimal (Christian et al. 2003; Christian et al. 2008; Lee et al. 2009). A similar shift to the right in the birth weight distribution in the group receiving MMN (compared to IFA) was observed in the recent JiVita-3 study in Bangladesh; although there was no significant effect on all-cause infant mortality, the RR of death due to birth asphyxia in the MMN group was 1.29 (95 percent CI: 1.05–1.60) (West et al. 2014). Our results indicate that most of the impact of LNS-PL on birth size was in the lower end (left side) of the distribution, with little to no effect on the proportion of larger infants. Our study was not powered to detect differences in birth asphyxia, but the lack of effect on C-section suggests that maternal-fetal disproportion (a major cause of birth asphyxia) was not increased in the LNS group.

4.4 Maternal Anemia, Micronutrient Status, and Inflammation

In this sample of women, there were no differences in Hb levels or risk of low or high Hb in late pregnancy between those who received LNS versus those who received IFA, even though LNS had only one-third the amount of iron as IFA. However, LNS was associated with lower iron status and with higher risk of iron deficiency and iron deficiency anemia in late pregnancy, when compared with IFA supplementation. Nevertheless, iron deficiency anemia was relatively uncommon in both groups (14.6 percent in the LNS group and 8.7 percent in the IFA group). The difference in iron status between groups was not surprising, given the much larger dose of iron in the IFA group (60 mg/day versus 20 mg/day). It is possible that the amount of iron in LNS-PL is too low. The formulation used in the RDNS was developed to meet the nutrient needs of both pregnant and lactating women, given that the recommended intakes for most nutrients are similar for both groups (Arimond et al. 2013). For iron, we chose the target

dose of 20 mg/day because we estimated that this amount, together with iron coming from the diet, would meet the recommended daily allowance of 27 mg during pregnancy while not greatly exceeding the recommended daily allowance of 9 mg/day during lactation. Also, there was evidence that 20 mg/day is adequate to prevent iron deficiency anemia during pregnancy and causes fewer gastrointestinal side effects than higher doses of iron (Zhou et al. 2009). The latter study was conducted in Australia, and it is possible that dietary iron needs during pregnancy are higher among women in Bangladesh because they consume a largely plant-based diet from which iron absorption would be relatively low. However, it is not clear whether the difference in maternal iron deficiency anemia in late pregnancy observed in the LNS group in the RDNS has negative functional consequences, given that there is debate about the most appropriate cutoffs to use for both Hb and markers of iron status during pregnancy. With regard to Hb, the lowest risk of adverse birth outcomes has been seen in women with Hb ~95–105 g/L (Steer et al. 1995), with a higher risk of adverse outcomes observed when Hb is above that range. As discussed above, we observed less fetal growth restriction in the LNS group than in the IFA group despite a higher risk of maternal iron deficiency anemia in the former. We therefore suggest that the iron content of LNS-PL should be re-evaluated to identify the amount most effective for improving both maternal iron status and birth outcomes.

We did not observe any differences in inflammatory response in late pregnancy, based on CRP and AGP concentrations, between those who received LNS and those who received IFA. Higher intake of linoleic acid and alpha-linoleic acid has been associated with lower serum CRP concentration in Japanese (Yoneyama et al. 2007) and U.S. women (Lopez-Garcia et al. 2004; Zhao et al. 2004). Fatty acid intake among Bangladeshi women has been found to be very low (Yakes et al. 2011); thus, it is possible that in this population, longer exposure is needed for inflammatory indicators to be affected.

With regard to vitamin A status, the average RBP concentration and prevalence of low RBP in late pregnancy did not differ significantly between women who received LNS and those who received IFA, after adjusting for baseline values and other covariates. The prevalence of low vitamin A (23.4 percent in the LNS group and 27.5 percent in the IFA group; RBP < 1.17 µmol/L) was lower than the prevalence reported in the earlier studies carried out among pregnant women in Bangladesh (Lee et al. 2008). Our results are consistent with a study that provided 600 µg of vitamin A (retinol activity equivalents) per day to women in Bangladesh and failed to improve vitamin A status (Jamil et al. 2012). Another study in Bangladesh that provided MMN supplements containing 800 µg of vitamin A (retinyl acetate) per day to pregnant women did not reduce the risk of vitamin A deficiency in their children (Eneroth et al. 2010). Our dietary recall data revealed that a large proportion of women in this study population had consumed fish, meat, dairy products, and green leafy vegetables during the previous week. These foods are good sources of vitamin A and β-carotene, so the lack of significant differences in vitamin A status between the LNS and IFA groups may be explained by the relatively low prevalence of vitamin A deficiency at baseline (4.0 percent in the LNS group and 3.8 percent in the IFA group; RBP < 0.83 µmol/L). One study implemented in an area close to our study area in Bangladesh reported that only 8 percent and 14 percent of Bangladeshi pregnant women were vitamin A deficient (serum retinol < 0.7 µmol/L) in the first and third trimester, respectively (Christian et al. 2013). These results suggest that daily vitamin A supplementation of pregnant women does not have a large impact when baseline prevalence of deficiency is low, and alternative strategies, such as large-scale food fortification, might be a better choice in such situations. One recently published study has recommended vegetable oil as an ideal fortification vehicle for vitamin A in Bangladesh (Fiedler et al. 2015). Accordingly, the government of Bangladesh recently took on an initiative to fortify vegetable oils to improve vitamin A status.

Surprisingly, there were no significant differences in average UIC in late pregnancy between those who received LNS-PL and those who received IFA, although the women in the LNS group tended to have a

lower prevalence of low UIC when the lowest cutoff of < 50 µg/L was used. The prevalence of iodine deficiency (UIC < 150 µg/L) was very high at 36 weeks of gestation, as was the case in a previous study in the same region (Shamim et al. 2012). We are not sure why daily supplementation of 250 µg of iodine via LNS did not appear to adequately protect pregnant women in the study area from iodine deficiency. One possibility is that the iodine in LNS-PL was indeed taken up, but was stored in the thyroid gland (due to the high prevalence of iodine deficiency) instead of being excreted in urine, which would imply that UIC is not an adequate marker of iodine status in this situation. Although Bangladesh has a universal salt iodization program in place, it is evident that the program is not sufficient to prevent iodine deficiency during pregnancy. The median iodine content of available salt is~6 ppm in Bangladesh, which is considerably below the level of 15 ppm recommended by WHO (Shamim et al. 2012). Our results suggest that there is a need for further research on meeting iodine requirements of pregnant women.

4.5 Health Care Expenditures

Provision of LNS-PL did not change pregnancy-related health care expenditures during late pregnancy, childbirth, or the 42-day postpartum period, compared with the provision of IFA. It also did not affect ANC/PNC-seeking decisions during pregnancy or in the first 6 weeks postpartum. Provision of LNS-PL was associated with a greater likelihood of seeking hospital care, but this effect was based on very few women who sought hospital care during the study period (some several times).

The lack of a response in health care expenditure to LNS-PL treatment can be interpreted in several ways. First, it could be that households did not perceive any health changes (positive or negative) from LNS-PL during pregnancy, birth or the 42-day postpartum period for either the mother or the child. If the biological improvements measured at birth were unknown to participating women prior to the birth outcome, they would not be expected to respond until after the outcome was realized (i.e., when they gained new information about the health of their child). Second, it could be that households see no link between preventative health care decisions and the future health of their children. Third, it could be that households believe pregnant women and their fetuses are at optimal health at any time when the mother is not obviously sick, and so without an effect of LNS-PL on maternal morbidity, households will not respond to LNS-PL provision by changing their health care expenditures.

All of these explanations rely on assumptions about how households form expectations about the current health status of pregnant women and their fetuses, how investment via LNS-PL affects that health status, and whether the households view LNS-PL as complementary to, or as a substitute for, alternative health expenditures and inputs. By tracing the household decisions regarding health care expenditure after birth (and thus after the effects of LNS-PL supplementation have been seen by the household), we hope to begin to disentangle how households determine economically optimal health investments in their children.

4.6 Strengths and Limitations

As the first effectiveness study to examine how small-quantity LNS-PL affects birth outcomes, this study has several strengths and limitations. Strengths include: 1) the use of two independent teams—one to conduct the intervention (led by LAMB) and another to evaluate impact (led by icddr,b and UCD), 2) enrollment of ~4,000 women who are 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 more than 90 percent of the newborn anthropometric measurements within 72 hours of delivery. Among the limitations, the disruption of LNS-PL supply for a period of 10 weeks, which was

beyond our control, compromised our ability to investigate the full potential of LNS-PL as an intervention. For several key outcomes, we found a larger effect of LNS-PL 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-PL on birth size, and thus actually strengthens our conclusions. Second, it was not possible to blind the women to the type of supplement provided, as the supplements were very different in appearance and taste. Nonetheless, researchers responsible for collecting outcome data were kept blind to study assignment. Third, we used LMP to estimate duration of gestation, as 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 relying on direct observation), so the adherence data could be inaccurate. The same may be true for health care expenditures and for time lost due to illnesses. Finally, we examined effects within several targeted subgroups, and these effect modification results need to be interpreted with caution due to the number of hypotheses being tested.

4.7 Conclusions

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, suggesting that LNS-PL reduces fetal growth restriction but not preterm delivery. As a whole, the study women were at high risk for fetal growth restriction, given that about a third of them had low BMI and 39 percent were under 20 years of age. Reduction of newborn stunting by LNS-PL was most evident among younger women and those residing in households experiencing 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 serving similar populations.

There was little effect on the other outcomes included in this report, with the exception of the following differences in the LNS group when compared with the IFA group: 1) greater maternal weight gain during pregnancy, among multiparous women > 25 years of age, 2) lower iron status with higher risk of iron deficiency and iron deficiency anemia in late pregnancy, and 3) a trend toward a lower prevalence of low UIC in late pregnancy, when the lowest cutoff of < 50 µg/L was used. Additional research on the optimal composition of LNS-PL for reducing maternal micronutrient deficiencies, while still promoting fetal growth, is needed.

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6 Appendices

Table A-1. Number of Women Randomized for and Who Completed Biospecimen Collection by Visit and by Type of Biospecimen

Visit	Biospecimen	Randomized	Completed	Refused	Missed
Baseline	Maternal urine	1,189	1,128	5	61
	Maternal blood	1,189	1,128	5	61
36-week	Maternal urine	1,189	876	0	313
	Maternal blood	1,189	875	0	314

Table A-2. Baseline Characteristics of Women with Maternal Anthropometric Data at Baseline and at the 36-Week Clinic Visit (n=2,877), by Intervention Group[a]

Variable	LNS (n=749)	IFA (n=2,128)
Gestational age at enrollment (weeks)	12.8 ± 3.5	12.8 ± 3.4
Age (y)	21 (18–25)	21 (18–25)
Years of schooling	7 (5–9)	7 (4–9)
Asset index	-0.1 (-1.2–1.4)	0.0 (-1.3–1.3)
Food insecurity		
Food secure	48.1 [360]	47.1 [1,003]
Mildly food insecure	16.7 [125]	14.1 [300]
Moderately food insecure	27.1 [203]	29.5 [628]
Severely food insecure	8.1 [61]	9.3 [197]
Nulliparous	41.1 [308]	39.2 [835]
Weight (kg)	44.8 (40.2–49.5)	44.9 (40.8–49.7)
Height (cm)	150.6 ± 5.4	150.6 ± 5.4
BMI (kg/m^2) (Adjusted for 96th day of gestation)	19.9 ± 2.7	20.0 ± 2.7
Low BMI (< 18.5 kg/m^2)	31.2 [234]	31.3 [666]
MUAC (cm)	24.8 ± 2.6	24.9 ± 2.6
Hb (g/L)[b]	116 ± 13	116 ± 13
Anemia (Hb < 110 g/L)[b]	27.3 [126]	31.8 [122]

[a] Mean ± SD, median (inter-quartile range), or % [n].
[b] Measured in a randomly selected subsample, n=845.

Table A-3. Baseline Characteristics of Women at 36 Weeks of Gestation (n=2,931), by Intervention Group

Variable	LNS (Mean ± SD)	IFA (Mean ± SD)
Number of participants	766	2,165
Age (y)	21.8 ± 5.0	21.9 ± 4.8
Years of education[a]	6.5 ± 3.1	6.2 ± 3.2
Asset index	0.02 ± 2.18	0.03 ± 2.21
Food insecurity (% [n])		
Food secure	48.2 [369]	47.3 [1,024]
Mildly food insecure	17.1 [131]	13.9 [302]
Moderately food insecure	26.8 [205]	29.5 [639]
Severely food insecure	8.0 [61]	9.2 [200]
Nulliparous women (% [n])	41.1 [307]	39.3 [835]
Gestational age at enrollment (weeks)	12.9 ± 3.5	12.8 ± 3.4
Weight (kg)	45.5 ± 7.1 [746]	45.6 ± 7.0 [2,125]
Height (cm)	150.5 ± 5.4 [746]	150.5 ± 5.4 [2,125]
BMI (kg/m^2) (Adjusted for 96th day of gestation)	19.9 ± 2.7 [746]	20.0 ± 2.7 [2,125]
Low BMI (< 18.5 kg/m^2) (% [n])	31.3 [746]	31.4 [2,125]
MUAC (cm)	24.8 ± 2.6 [746]	24.9 ± 2.6 [2,125]

[a] Significantly different by group (p=0.043)

Table A-4. Baseline Characteristics of Women Interviewed Immediately After Childbirth (n=3,747), by Intervention Group

Variable	LNS (Mean ± SD)	IFA (Mean ± SD)
Number of participants	983	2,764
Age (y)	21.8 ± 4.9	22.0 ± 5.0
Years of education[a]	6.5 ± 3.2	6.1 ± 3.3
Asset index	0.04 ± 2.18 [983]	-0.01 ± 2.18 [2,762]
Food insecurity (% [n])		
Food secure	50.1 [492]	46.8 [1,293]
Mildly food insecure	15.5 [152]	14.0 [387]
Moderately food insecure	26.6 [261]	30.0 [830]
Severely food insecure	7.9 [78]	9.2 [254]
Nulliparous women (% [n])	41.8 [948]	39.5 [2,683]
Gestational age at enrollment (weeks)	13.1 ± 3.4	13.1 ± 3.8
Height (cm)	151.0 ± 5.4	151.0 ± 5.4
BMI (kg/m^2) (Adjusted for 96th day of gestation)	19.9 ± 2.7 [948]	20.0 ± 2.7 [2,682]
Low BMI (< 18.5 kg/m^2) (% [n])	32.7 [946]	31.7 [2,678]
MUAC (cm)	24.8 ± 2.6	24.9 ± 2.6

[a] Significantly different by group (p=0.020).

Table A-5. Baseline Characteristics of Women with Biochemical Data (Hb and Iron Status) at Baseline and 36 Weeks of Gestation (n=843), by Intervention Group

Variable	LNS (Mean ± SD)	IFA (Mean ± SD)
Number of participants	460	383
Gestational age at enrollment (weeks)	12.9 ± 3.6	12.5 ± 3.4
Age (y)	21.9 ± 5.2	22.0 ± 5.0
Years of education[a]	6.7 ± 3.0	6.0 ± 3.3
Asset index	0.1 ± 1.8	-0.0 ± 1.7
Food insecurity (% [n])		
Food secure	47.2 [217]	45.4 [174]
Mildly food insecure	15.9 [73]	14.9 [57]
Moderately food insecure	27.8 [128]	29.8 [114]
Severely food insecure	9.1 [42]	9.9 [38]
Nulliparous women (% [n])	40.6 [194]	39.2 [155]
Weight (kg)	45.7 ± 7.1	45.4 ± 6.7
Height (cm)	150.7 ± 5.1	150.6 ± 5.3
BMI (kg/m^2) (Adjusted for 96th day of gestation)	20.0 ± 2.6	19.9 ± 2.7
Low BMI (< 18.5 kg/m^2) (% [n])	29.3 [135]	32.9 [126]
MUAC (cm)	24.9 ± 2.6	24.8 ± 2.5
Hb (g/L)	116 ± 13	116 ± 13
Anemia (Hb < 110 g/L) (% [n])	27.4 [126]	31.6 [121]
Tube well iron content (mg/L)	1.6 ± 3.9 [438]	1.4 ± 2.8 [360]
Inflammation at baseline (% [n])[a,b]	18.7 [86]	13.2 [50]

[a] Significantly different by group.
[b] Defined as CRP > 5 mg/L or AGP > 1 g/L.

Table A-6. Baseline Characteristics of Women with Biochemical Data (Vitamin A) at Baseline (n=1,160) and 36 Weeks of Gestation (n=875), by Intervention Group

Variable	LNS (Mean ± SD)	IFA (Mean ± SD)
Number of participants	640	520
Gestational age at enrollment (weeks)	13.1 ± 3.8	12.9 ± 3.7
Age (y)	21.8 ± 5.0	22.2 ± 5.2
Years of education[a]	6.5 ± 3.2	6.0 ± 3.3
Asset index	-0.01 ± 2.2	-0.11 ± 2.20
Food insecurity (% [n])		
Food secure	48.1 [308]	46.9 [244]
Mildly food insecure	15.5 [99]	13.8 [72]
Moderately food insecure	27.0 [173]	29.2 [152]
Severely food insecure	9.4 [60]	10.0 [52]
Nulliparous women (% [n])	42.3 [639]	38.9 [519]
Weight (kg)	45.5 ± 7.0	45.2 ± 6.5
Height (cm)	150.7 ± 5.3	150.7 ± 5.4
BMI (kg/m^2) (Adjusted for 96th day of gestation)	20.0 ± 2.7	19.9 ± 2.7
Low BMI (< 18.5 kg/m^2) (% [n])	32.3 [640]	32.7 [520]
MUAC (cm)	24.8 ± 2.6	24.8 ± 2.5
RBP at baseline (µmol/L) [n]	1.44 ± 0.43 [621]	1.41 ± 0.43 [504]
Own a fishpond (% [n])	23.0 [640]	24.4 [520]
CRP > 5 mg/L at baseline [a] (% [n])	14.2 [621]	8.9 [504]
AGP > 1 g/L at baseline (% [n])	7.7 [621]	6.0 [504]

[a] Significantly different by group (p=0.006).

Table A-7. Baseline Characteristics of Women with Biochemical Data (Iodine) at Baseline and 36 Weeks of Gestation (n=1,159), by Intervention Group

Variable	LNS (Mean ± SD)	IFA (Mean ± SD)
Number of participants	640	519
Gestational age at enrollment (weeks)	13.1 ± 3.8	12.9 ± 3.7
Age (y)	21.9 ± 5.2	22.2 ± 5.2
Years of education[a]	6.7 ± 3.0	6.0 ± 3.3
Asset index	-0.01 ± 2.2	-0.1 ± 2.1
Food insecurity (% [n])		
Food secure	48.1 [308]	47.0 [244]
Mildly food insecure	15.5 [99]	13.9 [72]
Moderately food insecure	27.0 [173]	29.1 [151]
Severely food insecure	9.4 [60]	10.0 [52]
Nulliparous women (% [n])	42.3 [639]	38.9 [519]
Weight (kg)	45.5 ± 7.0 [626]	45.2 ± 6.4 [510]
Height (cm)	150.7 ± 5.3 [626]	150.7 ± 5.4 [510]
BMI (kg/m^2) (Adjusted for 96th day of gestation)	20.0 ± 2.7 [626]	19.9 ± 2.7 [510]
Low BMI (< 18.5 kg/m^2) (% [n])	32.3 [640]	32.7 [520]
MUAC (cm)	24.8 ± 2.6 [626]	24.8 ± 2.5 [510]
Urinary iodine < 50, baseline (% [n])	49.9 [621]	51.9 [507]
Urinary iodine < 100, baseline (% [n])	77.1 [621]	75.9 [507]
Urinary iodine < 150, baseline (% [n])	87.4 [621]	84.6 [507]

[a] Significantly different by group.

Table A-8. Baseline Characteristics of Sample of Women Included for Medical Care Seeking and Expenditure through 42 Days Postpartum, by Intervention Group

Covariate	LNS (Mean± SD) N=974	IFA (Mean± SD) N=2,730	Difference
Maternal age	22 ± 5	21.8 ± 4,9	-0.2
Maternal education	6.7 ± 2.7	6.9 ±2.7	0.2
Paternal education	5.1 ± 4	5.3 ± 4	0.1
Food insecurity	3.1 ± 4	2.75 ± 3.9	-0.4
Asset score	-0.02 ±1.8	0.05 ± 1.8	0.07
Joint household	0.26 ± .04	0.26 ± 0.44	0.01
Children under 5	0.43 ± 0.6	0.41 ± 0.6	-0.02

Figure A-1. Map of Dinajpur District (Source: Banglapedia)

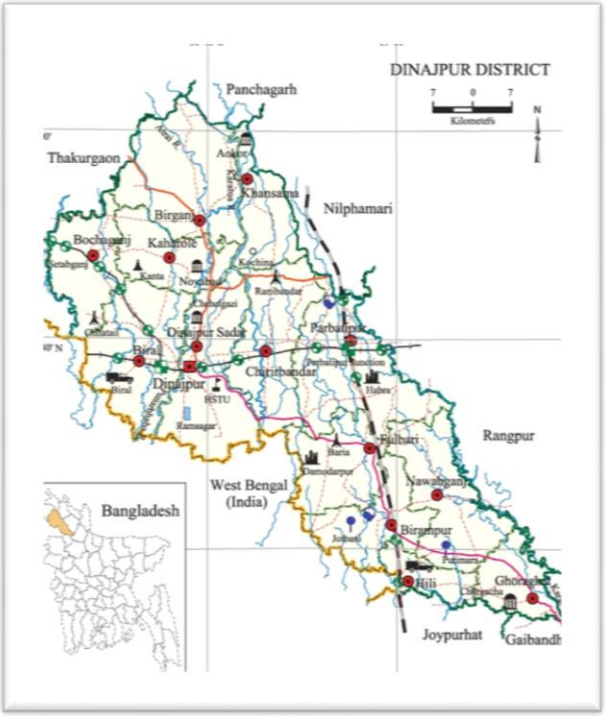

Figure A-2. Map of Rangpur District (Source: Banglapedia)