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Effectiveness of Home Fortification with Lipid-Based Nutrient Supplements (LNS) or Micronutrient Powder on Child Growth, Development, Micronutrient Status, and Health Expenditures in Bangladesh

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Contents

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
ID	iron deficiency
IDA	iron deficiency anemia
ICC	intracluster correlation
IFA	iron and folic acid
FANTA	Food and Nutrition Technical Assistance III Project
FCI	Family Care Indicators
HFIAS	Household Food Insecurity Access Scale Score
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

The process of stunting in growth and development often begins *in utero* and is most pronounced during the first 1000 days of life. Despite recognition of this critical period, there have been remarkably few attempts to evaluate the impact of interventions that cover the majority of this 1000-day window. The Rang-Din Nutrition Study (RDNS) was designed to evaluate the effectiveness, within a community-based program, of home fortification approaches for prevention of maternal and child undernutrition during the first 1000 days. The most common type of home fortification is the use of micronutrient powders (MNP) to enrich complementary foods for infants and young children. A newer approach is to provide both micronutrients and some key macronutrients, including essential fatty acids, in small-quantity (20 g/d) lipid-based nutrient supplements (LNS), developed to enrich the local diets of pregnant and lactating women (LNS-PL) and of infants and young children (LNS-C). The overall hypothesis of the RDNS was that provision of LNS-PL to women during pregnancy and the first 6 months postpartum, and/or provision of LNS-C to their offspring from 6 to 24 months of age, would result in larger positive changes in maternal and child nutrition outcomes than the provision of iron and folic acid (IFA) to women (during pregnancy and for 3 months postpartum) plus MNP or no supplementation for their offspring from 6 to 24 months of age. We previously reported the effects of LNS-PL on pregnancy outcomes (Dewey et al. 2016). This report describes the effects of the RDNS interventions on child growth, development, micronutrient status, and health care-seeking behavior through 24 months of age.

The RDNS was conducted in 11 rural unions of the Badarganj and Chirirbandar subdistricts in the northwest region of Bangladesh 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 interventions, including the delivery of nutrient supplements, to the study population via the Community Health and Development Program (CHDP). 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-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 women received IFA daily during pregnancy and every alternate day during the first 3 months postpartum, and their children received no supplements

In the RDNS, we defined a cluster as the supervision area of a LAMB community health worker. 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 (CHW) 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 other assessments. Follow-up data collection occurred at 35 to 36 weeks of gestation; within 72 hours after birth; at 42 days

postpartum; and at 6, 12, 18, and 24 months postpartum. Micronutrient status was assessed for a random subsample of 1,128 children at 18 months. Data on adherence to LNS-PL and IFA during pregnancy were collected retrospectively at 42 days postpartum, and adherence to LNS-C and MNP during the previous six months were collected at 12, 18, and 24 months of age. Health care expenditure data for the child were collected retrospectively at 6, 12, 18, and 24 months.

Between October 15, 2011 and August 31, 2012, we screened 4,410 pregnant women for eligibility and enrolled 4,011. Among the women who remained in the study, 3,664 live births took place between January 15, 2012 and May 5, 2013. Anthropometric data were collected for 3,516 infants at birth and for 3,379 children at 24 months (92.2% of live births). Primary data analysis was performed based on intention-to-treat (i.e., no women or children were excluded from the analysis based on adherence to the supplements).

At baseline, the sociodemographic, anthropometric, and obstetric characteristics of the pregnant women were similar among 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 ~39–42% were nulliparous. The mean gestational age at enrollment was 13 weeks in all groups. The percentage of children with high adherence (regular, every day or almost every day), based on caregiver recall for the previous 6 months, increased from 94–97% at 6–12 months to 97–99% at 18–24 months, and was somewhat lower in the IFA-MNP group at 18–24 months ($p = 0.007$). When the caregiver was asked about adherence in the previous week, high adherence (defined as consuming 8+ 10 g sachets of LNS [out of 14 recommended] or 4+ sachets of MNP [out of 7 recommended] in the past week) increased from 77–80% at 12 months to 90–92% at 24 months, and did not differ significantly among the three intervention groups.

There were significant positive effects of small-quantity LNS on the primary outcome, length-for-age z-score (LAZ) at 24 months. The main difference was between the Comprehensive LNS and Child MNP groups (+0.13 Z). This difference was already apparent by 6 months of age and there was no evidence of reduced growth in the MNP group between 6 and 24 months. By 24 months, only the Comprehensive LNS group differed significantly from any of the other groups, but the mean LAZ scores at 24 months for the Comprehensive and Child LNS groups were very similar (-1.72 vs. -1.73). Therefore, even though mean LAZ at birth was slightly greater in the Comprehensive LNS group (+0.09 Z), the Child LNS group achieved the same mean LAZ by 24 months. Significant differences in stunting prevalence were evident at 18 months, when there was a ~20% reduction in stunting in the Comprehensive LNS group compared to the Child MNP group (7.8 percentage points). By 24 months, the difference in stunting prevalence between those two groups was 5.2 percentage points (but not statistically significant). There were also positive effects of LNS on head circumference-for-age z-score, with a significant difference of 0.15 Z between the Comprehensive LNS and Control groups at 24 months. The difference between these two groups in the prevalence of small head size (< -2 Z) at 24 months was marginally significant overall (11% reduction), but highly significant among girls (33% reduction). Although we did not hypothesize differences in wasting (weight-for-length z-score < -2), at 18 months wasting was reduced by 27% in the Child LNS group (and by a non-significant 20% in the Comprehensive LNS group) compared to the Control group.

There were significant positive effects on child development at 24 months in all three intervention groups. For motor development, the Child MNP had significantly higher mean scores than the Control group, though mean scores were very similar among the three intervention groups (Comprehensive LNS, Child LNS and Child MNP). Children in all three intervention groups had higher scores in receptive language, and those in the Comprehensive LNS and Child MNP groups had higher scores in expressive language, when compared to those in the Control group. We did not observe any significant group differences in

personal-social development or executive function. However, among girls, we found a significantly lower proportion in the lowest quartile for executive function in the Child LNS group compared to the Control group.

The RDNS interventions had significant positive effects on child hemoglobin and iron status at 18 months, with the Comprehensive LNS group showing the strongest and most consistent effects compared to the Control group. Anemia was reduced by 29% in the Child MNP and Child LNS groups and by 40% in the Comprehensive LNS group. Iron deficiency was reduced by 20% in the Child MNP and Child LNS groups and by 39% in the Comprehensive LNS group, and iron-deficiency anemia was reduced by 43%, 44%, and 55% in the Child MNP, Child LNS, and Comprehensive LNS groups, respectively.

With regard to vitamin A status, average retinol-binding protein (RBP) concentration and prevalence of vitamin A deficiency did not differ significantly among groups, probably because most children in all groups received high-dose vitamin A supplements on a regular basis. There was also no evidence that the interventions altered behaviors related to seeking health care for the study children, including number of visits, total expenditures, or time lost in tending to sick children.

Because this study was conducted within a community-based health program, the findings should be relevant to programs targeting similar populations. The programmatic implications depend on the goals of decision-makers. If the goal is to improve child growth, provision of both pre- and postnatal LNS appears to be the most effective approach, but also the most costly. By contrast, MNP had no growth-promoting effect in the RDNS, which is consistent with results of systematic reviews (DeRegil et al. 2013; Salam et al. 2013). If the goal of program planners is to reduce iron-deficiency anemia or improve child development but not necessarily growth, all three interventions tested in the RDNS appear to be effective, though anemia reduction was greatest in the Comprehensive LNS group.

1 Introduction

The Rang-Din Nutrition Study (RDNS) in rural Bangladesh was designed to evaluate the effectiveness, within a community-based program, of home fortification approaches for prevention of maternal and child undernutrition during the first 1,000 days of life. The most common type of home fortification is the use of micronutrient powders (MNP) to enrich complementary foods for infants and young children 6 to 24 months of age (http://www.hftag.org/). A newer approach is to provide both micronutrients and some key macronutrients, including essential fatty acids, in small-quantity (20 g/d) lipid-based nutrient supplements (LNS). These have been developed for enriching home-based foods for pregnant and lactating women (LNS-PL) as well as for infants and young children (LNS-C) (Arimond et al. 2013). The main objective of the RDNS was to evaluate whether provision of LNS-PL to women during pregnancy and the first 6 months postpartum, and/or provision of LNS-C to their offspring from 6 to 24 months of age, would result in larger positive changes in indicators of maternal or child health and nutrition among the study participants than provision of IFA during pregnancy and the postpartum period[1] and MNP or no supplementation for their children from 6 to 24 months of age.

Bangladesh is an appropriate setting in which to evaluate the effectiveness of this approach. More than 20% of infants are born stunted [length-for-age z-score (LAZ) < -2], and more than 30% are wasted (weight-for-length z-score < -2) at birth (NIPORT et al. 2013). Although Bangladesh has made some progress in reducing stunting in children under 5 years of age (from 43% to 36% between 2007 and 2014) (NIPORT et al. 2016), the prevalence is still quite high, and micronutrient deficiencies in both mothers and children are common (NMSS 2013).

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

This report describes the effects of the RDNS intervention on child outcomes, including growth through 24 months of age; developmental outcomes at 24 months of age; and micronutrient status at 18 months of age. It also describes the effects of the intervention on health care expenditures during the first two years of life.

[1] The World Health Organization and the Government of Bangladesh recommend providing IFA daily for at least 3 months postpartum, but we provided IFA (containing 60 mg of iron) 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).

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 in one of the poorest areas of Bangladesh, where ≥ 48% of people live below the poverty line. In 2011, the average household size was four; 52% of the population > 7 years of age were illiterate; 31% of households had electricity; 98% had access to safe drinking water; and 75% 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 the 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. Funding for the study was provided by the Office of Health, Infectious Diseases and Nutrition, in the Bureau for Global Health, at the U.S. Agency for International Development through the Food and Nutrition Technical Assistance III Project (FANTA) at FHI 360.

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 of life 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 consisted of:

- A Comprehensive LNS group (also referred to as the “LNS-LNS group”), in which women received LNS-PL during pregnancy and the first 6 months postpartum, and their children received LNS-C from 6 to 24 months of age
- A Child-only LNS group (also referred to as the “IFA-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

- A Child-only micronutrient powder (MNP) group (also referred to as the "IFA-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
- A Control group (also referred to as the "IFA-Control" group), in which 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-LNS)	LNS-PL during pregnancy and 6 months postpartum	LNS-C from 6 to 24 months
2 Child-only LNS (IFA-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-MNP)	IFA during pregnancy and every other day during the first 3 months postpartum	MNP from 6 to 24 months
4 Control (IFA-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 community health worker (CHW) of LAMB. Each cluster covered a population of approximately 2,500 to 6,000 people and had three to six village health volunteers (VHVs) to assist the CHW. The study was implemented in all 64 clusters within the 11 study unions. Each study arm included 16 clusters. We chose a cluster-randomized 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 the 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

Tables 2 and 3 show the composition of the supplements used in the study. The dose of IFA was based on WHO recommendations (WHO 2012), and IFA tablets were produced by Hudson Pharmaceuticals Ltd. in Bangladesh. LNS-PL (20 g/d, 118 kcal/d, one sachet per day) 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 multiple micronutrients (MMN). LNS-C ("Sonamoni", 20 g/d, 118 kcal/d) was very similar to the small-quantity LNS used in the iLiNS Project, except that iron content was 9 mg instead of 6 mg (a lower iron content was used in the iLiNS Project because of concerns that excess iron might increase the risk of malaria), and levels of folate, niacin, pantothenic acid, riboflavin, thiamine, vitamin B_{12} and vitamin B_6 were slightly higher to cover nutrient needs throughout the second year of life (i.e., for the wider age range of 6–24 months in the RDNS, compared to 6–18 months in the iLiNS Project). LNS-C was provided as two 10-g sachets per day. Because production of LNS in Bangladesh has not yet been established, LNS-PL and LNS-C were produced by Nutriset SA in Malaunay, France. MNP ("Pushtikona," containing 15 micronutrients) was produced by Renata Ltd. in Bangladesh. In comparison to the MNP, the micronutrient content of LNS-C included four additional macro-minerals (Ca, K, P, and Mg), pantothenic acid, vitamin K, and Mn; more zinc, selenium, and vitamin E; and slightly less copper and iron.

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 supplement distribution scheme was identical for all study participants, regardless of the study arm into which they were enrolled. The distribution scheme and key messages during pregnancy have been described elsewhere (Dewey et al. 2016). When child supplementation began at 6 months of age, the first month's supply of LNS-C or MNP was provided at the SDU. After that, monthly supplies were usually delivered by the CHW or VHV to the child's home, but occasionally, delivery occurred during educational sessions given by the CHW or VHV near the caregiver's home. Each month, all CHWs conducted educational sessions on various maternal and child health topics at different places within their cluster, as part of the regular CHDP program. When the maternal 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 supplements; nine health education messages for the mother were printed on the cards in the local language, Bengali, and were also explained verbally. A new card with messages on the use of the child supplements (see Appendix 1) was given at 6 months postpartum, and the CHWs also explained the messages verbally. Depending on the cluster, the CHWs counseled the caregiver to feed the child two sachets of LNS-C per day (at different times of the day) and to mix each sachet with 2–3 spoonfuls of already prepared food that is normally fed to the child, or to mix

one sachet of MNP with 2–3 spoonfuls of already prepared food. Caregivers were told not to provide more than two sachets of LNS-C or one sachet of MNP per day, even if the child did not take the supplement the previous day. All of the messages in Appendix 1 were repeated by the CHW at monthly follow-up visits to each child's home. These messages were additional to the standard messages given to participants in the regular CHDP program, which are also shown in Appendix 1. In the Badarganj sub-district, the government of Bangladesh distributed MNP (Sprinkles, a five-micronutrient version containing vitamin A, vitamin C, folic acid, iron, and zinc) to families with children 6–24 months of age. For RDNS participants, the RDNS team told caregivers not to feed their children these or any other vitamin and mineral tablets, capsules, or MNP sachets if they received RDNS supplements (LNS-C or MNP). Caregivers were told to contact the CHW immediately if their child experienced any perceived side effects from the supplements. A protocol was developed to address commonly reported side effects (e.g., vomiting, stomach pain, diarrhea, black stool, perceived allergy, and skin rash).

LNS-PL distribution (but not distribution of LNS-C) was interrupted from August 8 to October 20, 2012, 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 the potential risk to older infants, children, and adults are considered to be much lower (CDC 2014). During the interruption, women in all study 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 Maternal Supplements Used 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

Nutrient	LNS-PL	IFA Tablet
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

Table 3. Composition of Child Supplements Used in the Study

Nutrient	Unit	LNS-C	MNP
Dose	g	20	1
Energy	kcal	118	0
Protein	g	2.6	0
Fat	g	9.6	0
Linoleic acid	g	4.46	0
α-Linolenic acid	g	0.58	0
Calcium	mg	280	0
Copper	mg	0.34	0.56
Folate	µg	150	150
Iodine	µg	90	90
Iron	mg	9	10
Magnesium	mg	40	0
Manganese	mg	1.2	0
Niacin	mg	6	6
Pantothenic acid (B5)	mg	2.0	0
Phosphorous	mg	190	0
Potassium	mg	200	0
Riboflavin (B2)	mg	0.5	0.5
Selenium	µg	20	17
Thiamine (B1)	mg	0.5	0.5
Vitamin A	µg	400	400
Vitamin B12	µg	0.9	0.9
Vitamin B6	mg	0.5	0.5
Vitamin C	mg	30	30
Vitamin D	µg	5	5
Vitamin E	mg	6	5
Vitamin K	µg	30	0
Zinc	mg	8	4.1

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 described below were collected by evaluation staff from icddr,b.

Data were collected 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 (based on gestational age calculated from the LMP). Potentially eligible women were contacted in their homes by evaluation staff members from the home visit team to obtain consent to screen them for the evaluation study. The eligibility criteria included gestational age $\leq$ 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. They were also scheduled for anthropometric and clinical data collection at the SDU. Supplement delivery for each woman began after the baseline SDU visit. If a woman missed her baseline 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, and collection of health expenditure data and 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 of gestation until the delivery occurred. The family was given the telephone numbers of the call center and requested to call immediately after the childbirth.

Follow-up visits of the mother-child dyad were administered at 42 days, 6 months, 12 months, 18 months, and 24 months postpartum. The 42-day postpartum visits comprised only home interviews, whereas the rest of the follow-up visits included both home and SDU visits. During the 42-day postpartum visits, data were collected on maternal weight; child weight/length/MUAC/head circumference; food security; infant feeding practices; maternal nutritional knowledge, attitudes, and practices; maternal and child morbidity; health expenditures; and willingness to pay for maternal supplements. Data on socio-economic status, food security, infant feeding practices, maternal and child morbidity, health expenditures, child anthropometry, and child motor development were collected during the 6, 12, 18, and 24-month interviews. At the 6-month postpartum visits, data were also collected on maternal diet, maternal depression, maternal weight, and willingness to pay for child supplements; and samples of maternal blood and urine and child blood were collected. At the 12-month postpartum visits, data collection on child

language expression started. At the 18-month postpartum visits, child blood samples were also collected. At the 18 and 24-month postpartum visits, additional data collection took place on child language expression and child cognitive development.

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-C and MNP were collected at home visits at 12, 18, and 24 months of age. The caregivers were asked how often the child had consumed the nutrient supplements during the previous six months (not at all, sometimes (1–3 days/week), almost every day (4–6 days/week), or every day) and how many packets were eaten during the previous week.

2.4 Collection of Biological Samples and Tube-Well Water

Blood samples were collected from a randomly selected subsample of children during the SDU visits at 6 and 18 months (Appendix 2). Sealed envelopes with information on assignment to subsamples (including those for other assessments) were prepared for each participant before enrollment.

Capillary puncture (finger or heel pricks) using a system specifically designed to collect capillary blood was done. Finger pricks were performed preferably on the middle or ring finger of the child's left hand. Heel pricks were performed on a suitable part of the left heel excluding the posterior curvature of the heel. The first drop of blood was wiped with dry cotton, and light pressure was applied to the end of the finger or heel 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 the serum to PCR tubes. A 0.2 ml PCR tube was used to store serum, which was kept at -20˚C until shipment to the laboratory for analysis.

Tube-well water was collected from the tube-wells that were used as sources of drinking water by the households of a subsample of women randomized for the assessment of Hb, iron status, and RBP at baseline, 36 weeks gestation and 6 months postpartum.

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% of randomly selected participants. 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% 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 Child Anthropometrics

All anthropometrists were trained and methods were standardized at the beginning of data collection and periodically thereafter, using methods described by WHO (WHO 2006). Most infants (91%) were measured within 72 hours after birth, using methods described elsewhere (Dewey et al. 2016). At each of the SDU visits at 6, 12, 18, and 24 months, trained anthropometrists measured child weight to the nearest 0.1 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).

2.6.2 Child Development

Motor and Personal-Social Development

We used the Developmental Milestones Checklist (DMC) II (Prado et al. 2014) to assess motor and personal-social development. The DMC-II also includes items to assess the language domain, but we did not administer those items in the RDNS, instead we measured language as described below. The DMC-II was administered as a caregiver report tool, although it also includes some items that can be directly tested by the evaluator, if needed (i.e., when a caregiver indicates not knowing whether the child can do the task in question). However, total scores were based on caregiver report and only included scores from observation items if these were administered. The raw score for each DMC-II domain was calculated as the sum of the item scores in that domain. The internal, inter-interviewer and test-retest reliability of the DMC-II scores were reported to be >0.7 in Burkina Faso (Prado et al. 2014). We piloted the DMC-II with 32 non-RDNS mother-child dyads in our study area; the children's ages were between 15 and 27 months. We found that the scale had internal consistency: the Cronbach's Alpha coefficients were 0.78 and 0.82 for the motor and personal-social development domains respectively.

Language Development

In the RDNS, language development was assessed using a caregiver report tool that was based on the principles of the MacArthur Communicative Development Inventories (CDI) (Fenson et al. 2007) but included words that were selected specifically for Bangladesh (Hamadani et al. 2010). This tool initially had 60 words across 15 categories—animals, vehicles, toys, food and drink, clothing, body parts, furniture, small household items, outside things and places to go, people, verbs, sounds (animal noises and others), phrases, games and routines, and descriptive words. It included 40 words of moderate difficulty (known by 40–60% of the children), 10 easy words, and 10 difficult words. For each word in the language inventory, the caregiver was asked to indicate whether the child could 1) understand and 2) say the word. The short-term test–retest reliability for comprehension and expression over 14 days was r=0.84 at 12 months, and r=0.99 at 18 months (Hamadani et al. 2010). During RDNS piloting (n=48) the CDI scores showed positive and significant correlations with the child's age and maternal education. The 60-word version was used to assess RDNS children at 12 and 18 months. For assessing children at 24 months, 40 more words were added; the list of additional words was provided by the same research group that developed the 60-word version for younger Bangladeshi children. To make sure that the extended tool worked well in our sample, we piloted the extra 40 words with caregivers of 45 non-RDNS children (17–34 months of age) from the study area. Caregivers' responses for these extra words in the pilot test ranged from 2–98% for understanding and 7–70% for speech. Two different raw scores were computed: 1) the total number of words the child understood (comprehensive language) and 2) the total number of words the child said (expressive language).

Executive Function

Executive function was assessed by direct testing of the child's performance using the A-not-B task (Espy et al. 1999), a widely-used test of working memory and executive function, previously used in Kenya (Abubakar et al. 2013), Uganda (Nampijja et al. 2012), and more recently, in an LNS efficacy trial with 18-month-old children in Malawi (Prado et al. 2016). The A-not-B task consisted of 10 trials, in which a small piece of a cookie was hidden underneath one of two identical (upside down) cups on a wooden board. The board was removed from the child's sight for 5 seconds, during which the evaluator sang a standardized song. The board was then returned and the child was asked to find the hidden cookie. Every time the child achieved 2 correct consecutive trials, the cookie was then hidden at the alternate location. Two types of raw scores were calculated: 1) total correct trials (the sum of all trials in which the child selected the correct location) and 2) perseverative errors (the total number of errors committed after the first set of 2 correctly solved trials).

Home Stimulation

Stimulation in the home affects child development (Caldwell & Bradley, 2003; Walker et al. 2007). To assess home stimulation, we used the Family Care Indicators (FCI) tool, which has been validated in Bangladesh (Hamadani et al. 2010). Specifically, we used the most parsimonious scale proposed by the scale validators, which included 4 items about play materials, 4 items about activities in which any caregiver may have engaged the child, and 1 item about the availability of reading materials in the home. All these items were scored: yes=1 and no=0 (presence or absence of play/reading material or activity). The total scale score was calculated as the sum of scores of all 9 FCI items.

Standardization of Developmental Scores and Dichotomous Developmental Outcomes

Raw scores of each developmental measurement were standardized by computing z-scores based on the distribution of the RDNS sample, standardizing raw scores to a mean of zero and an SD of one. Also, for each developmental measurement, we created two dichotomous variables using the lowest decile (10%) and the lowest quartile (25%) of the total sample scores; these dichotomous variables were examined as proxy indicators of potentially severe (lowest decile) and moderate-to-severe (lowest quartile) developmental delay.

2.6.3 Child Hemoglobin, Iron Status, Inflammatory Markers, Vitamin A Status, and Iron in Tube-Well Water

The concentration of Hb was assessed using a portable photoreflectometer (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). 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% for ferritin, 4.6% for sTfR, 4.2% for RBP, 6.6% for CRP, and 6.0% for AGP.

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 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.

Iron in tube-well water was measured in mg/L by using the Hach color disc test kit (Model IR-18C). The precision for the test kit was 0.2 mg/L.

2.6.4 Postnatal Health Care Expenditures

Data on health care seeking and expenditures on study children were collected at 6, 12, 18, and 24 months. Retrospective information was solicited for all health care visits and expenditures incurred within the 3 months prior to the visit. For each visit within the 3-month recall window, data were collected on monetary and time costs for medical care and travel to and from the health care facility. Respondents were also asked how much time they or other household members had been unable to spend on their regular work in order to care for a sick child. We used these data to generate aggregate measures for the number of visits to a health care provider, the amount of money spent on health care, and the amount of household time lost to provide sick child care.

2.7 Data Review, Entry, and Management

Data collectors manually checked all forms for completeness before leaving the participant's home or SDU. The data collection supervisors also manually checked the forms for completeness and consistency before submitting them to the data management center for data entry. A reviewer at the data management center reviewed each form again for completeness and consistency before entering the data. 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 participants.

Data from the forms were double entered in an Oracle database. Discrepancies between the first and second entries 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 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 primary continuous outcome with power=80% and α=0.05, assuming an intra-cluster correlation=0.01, and allowing for up to 20% attrition by the end of the study (i.e., when the children reached 24 months).

2.8.2 Outcome and Covariate Variable Definitions

All outcomes were measured at the individual participant level. We used WHO 2006 Child Growth Standards to determine z-scores for weight-for-age (WAZ), length-for-age (LAZ), weight-for-length (WLZ), head circumference-for-age (HCZ), and mid-upper arm circumference-for-age (MUACZ) (WHO Child Growth Standards 2011). We defined stunting as LAZ < -2 SD, small head size as HCZ < -2, underweight at WAZ < -2 and wasting as WLZ < -2. The primary child outcome was LAZ at 24 months. Pre-specified secondary child anthropometric outcomes at 24 months included stunting, HCZ and wasting. In addition, we examined all anthropometric outcomes at 18 months to compare results with those of other trials with endpoints at 18 months of age. We also examined postnatal rate of growth via length, weight, and head circumference between birth and 6 months, and between 6 and 24 months of age. Growth rate was calculated as the difference in measurements divided by the time between measurements in months, multiplied by six for presentation as a six-month growth rate. 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 z-scores were truncated at 4 units from the sample median.

The secondary outcomes for anemia and micronutrient status included hemoglobin, anemia, iron status (ferritin and sTfR), iron deficiency, iron-deficiency anemia, and vitamin A status (RBP) at 18 months. Anemia was defined as Hb < 110 g/L (WHO, 2011). Ferritin and sTfR were dichotomized as follows: low ferritin was defined as ferritin < 12 µg/L (WHO, 2001), 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. Low RBP was defined as < 1.17 µmol/L and vitamin A deficiency was defined as RBP < 0.83 µmol/L (Engle-Stone et al. 2011). For ferritin and RBP, analyses were done both with and without correction for inflammation. For those corrections, 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 and RBP 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), early convalescence (if CRP > 5.0 mg/L and AGP > 1.0 g/L), and late convalescence (if CRP ≤ 5.0 mg/L and AGP > 1.0 g/L). We computed sample-specific adjustment factors from the RDNS data, using the ratio of the geometric mean ferritin or RBP in the reference category to the geometric mean ferritin or RBP in each of the other categories. We applied the resulting sample-specific correction factors to create corrected values for each individual. For iron status and Hb, we included tube-well iron content (as a categorical variable, in quintiles) as a potential covariate, using imputed values based on tube-well iron content in the same village, if that information was available. If the information was not available, there was a category for unknown tube-well iron content.

From several socioeconomic status variables, we used principal components analysis to calculate a household asset index, in which higher values represented higher socioeconomic status. The index was constructed using principal components analysis (PCA) from a set of 19 yes/no questions asking whether a household owned a particular item, of which we used 14 items owned by at least 5% of households. These items included televisions, irrigation pumps, tables, bicycles, sewing machines, and other consumer durable goods. The resulting first principal component was standardized to have a mean of 0. The Household Food Insecurity Access Scale (Coates and Swindale 2007) was used to calculate the HFIAS score and to categorize participants into four levels of household food insecurity: severely food insecure, moderately food insecure, mildly food insecure, and food secure. For the FCI covariate, we combined "standardized" FCI scores at 12, 18, and 24 months to create a composite value for the period from 6 to 24 months of age.

To examine interactions associated with time periods during the trial, nine 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. Nine time periods were required to cover the ~17-month period during which the births occurred (January 2012–May 2013). Because of small sample sizes, the first and last time periods were combined with the adjacent time periods for data analysis.

For health care expenditures, we examined the number of visits, the total expenditure for the visits, and the number of days that caregivers or other household members were unable to perform their regular duties in order to care or seek medical care for the sick child. Several households reported "unknown" total expenditures for medical care-seeking visits; these observations were omitted from the analysis. However, households with more than one visit during a given survey round appeared in the final dataset if

they reported complete information for any one visit, even if expenditures were not available for every visit. Missing observations were not significantly correlated with treatment group status. Final round-level sample sizes are reported in the results section.

2.8.3 Hypothesis Testing

A detailed data analysis plan was developed before starting each analysis and revealing group assignment. Primary analysis was performed based on intention-to-treat (i.e., no children were excluded from the analysis based on adherence to the supplements). All analyses adjusted for the randomization by accounting for the random effect of union (nested within subdistrict) and the random effect of cluster (except for the health expenditures analyses, which employed fixed-effects for union).

For child growth, development, hemoglobin, and micronutrient status, effects of the intervention were analyzed using mixed model analysis of covariance (ANCOVA) for continuous outcomes, and mixed model logistic regression for dichotomous outcomes. For all analyses, if the global null hypothesis was rejected at the 0.05 level, we performed post-hoc pairwise comparisons of groups, correcting for multiple-comparisons using the Tukey-Kramer method. All models first evaluated the unadjusted effect of treatment, then repeated the analyses with adjustments for covariates previously specified in our statistical plan. The 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. In the analyses of continuous outcomes, we first calculated unadjusted group means, before repeating the analyses with adjustments for covariates. In the analysis of dichotomous outcomes, we calculated unadjusted group percentages and 95% confidence intervals (CIs); statistical comparisons in the unadjusted and covariate-adjusted models were based on the log odds of the outcome occurring. Multiple variable-adjusted risk ratios for dichotomous outcomes were calculated using log-binomial model estimations (McNutt et al. 2003).

In pre-defined subgroup analyses, we tested for interactions between intervention group and selected covariates by including each interaction term in the adjusted models and using a continuous variable for the potential effect modifier, whenever possible. For significant effect modifiers ($p < 0.10$), we assessed the adjusted group effect at different levels of the effect modifier (SAS LSMEANS option). Based on this assessment, selected effect modifiers were further examined in analyses stratified by subgroups of participants to illustrate the nature of the interaction. When assessing the group effect at different levels of any significant effect modifier, we adjusted for multiple comparisons using the Tukey-Kramer approach.

For all child outcomes, the following covariates and effect modifiers were examined: baseline maternal age, education, BMI, height, duration of gestation at enrollment, primiparity, SES, and food security score, as well as time interval (season) at birth and child sex. For child development outcomes, the additional covariates and effect modifiers examined were: presence of other children under 5 years in the household at enrollment, child age at assessment, and FCI score. For iron status and hemoglobin analysis, the additional covariates were tube-well iron content quintile and maternal baseline value of the outcome (forced into adjusted models), and additional potential effect modifiers examined were tube-well iron content and maternal AGP and CRP at baseline. For child vitamin A status, the additional covariates were maternal baseline AGP and CRP and maternal baseline value of the outcome (forced into adjusted models), and additional potential effect modifiers were maternal AGP and CRP at baseline.

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 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 dummy variables, and dummy variables 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 included union-level fixed effects and allowed for within-cluster correlation in error terms to account for the randomization procedure, chosen for ease of interpretability (as the 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 evaluated by testing the interaction between the covariate and intervention group, with statistical significance at $p < 0.05$.

3 Results

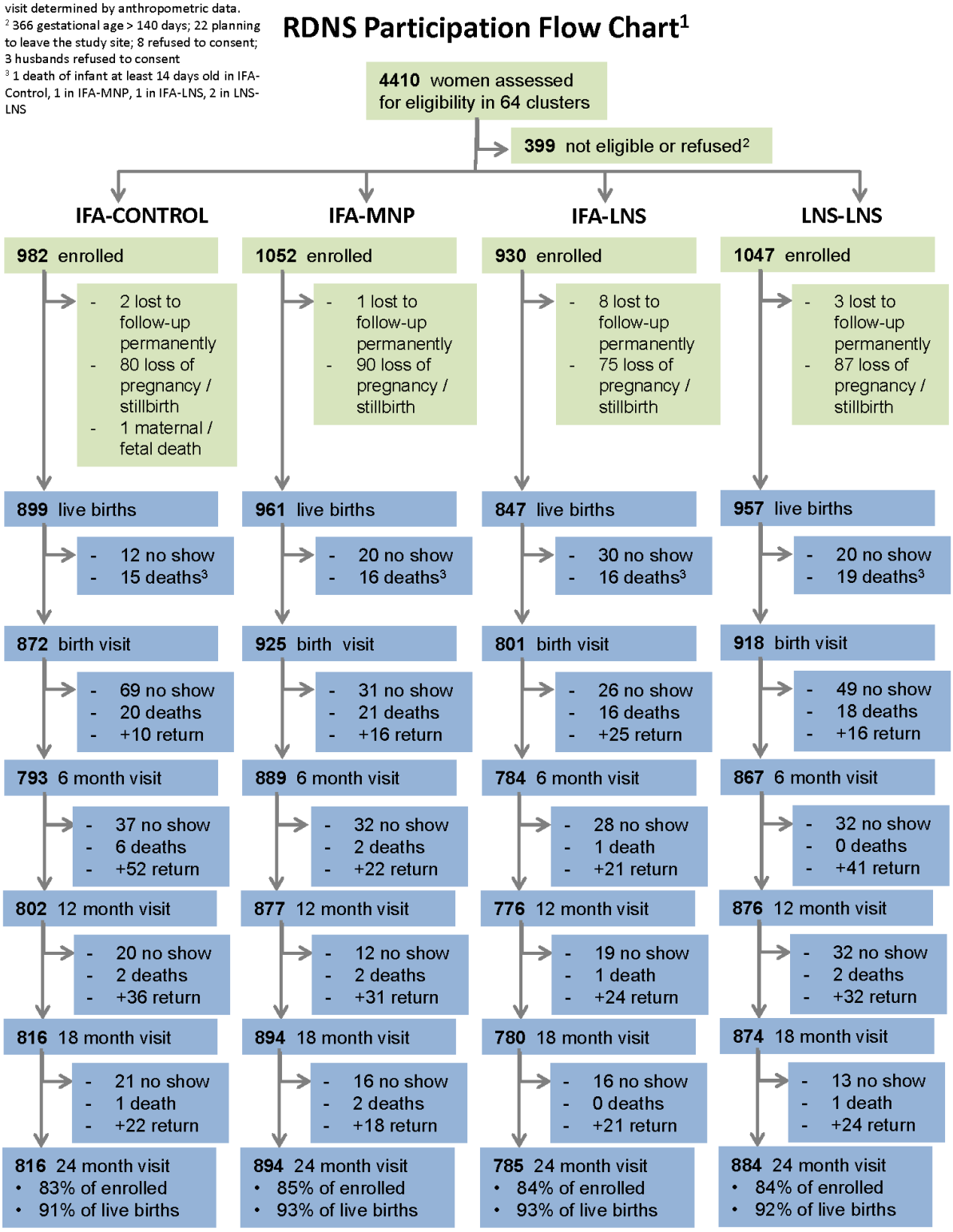
3.1 General Context

3.1.1 Number of Women and Children 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). Of these, 3,664 live births took place between January 15, 2012, and May 5, 2013, to women/children who remained in the study. Thirty sets of twins were born and in general one twin from each pair was randomly selected for analyses. Figure 1 shows the trial profile. For approximately 84% of enrolled women, we had anthropometric data for their children at 24 months of age. Most of the losses were due to pregnancy loss or postnatal deaths. Anthropometric data were collected for 3,516 infants at birth and for 3,379 children at 24 months (92.2% of live births). Approximately 4.4% of children born alive died before the 24-month visit and another 3.4% were lost to follow-up postnatally. The women whose children were not measured at 24 months had slightly fewer years of education (5.9 vs 6.3) and were slightly shorter (150.1 cm vs 150.6 cm) than the women whose children were measured.

Figure 1. Trial Profile

[1] Includes only target children. Attendance to visit determined by anthropometric data.
[2] 366 gestational age > 140 days; 22 planning to leave the study site; 8 refused to consent; 3 husbands refused to consent
[3] 1 death of infant at least 14 days old in IFA-Control, 1 in IFA-MNP, 1 in IFA-LNS, 2 in LNS-LNS



3.1.2 Characteristics of the Study Sample and Adherence to Study Supplements

At baseline, sociodemographic, anthropometric, and obstetric characteristics of participants were similar across intervention groups (Table 4). 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 40 % were nulliparous. The mean gestational age at enrollment was 13 weeks.

Table 4. Maternal Baseline Characteristics[a]

	Comprehensive LNS	Child-only LNS	Child-only MNP	Control
Age, years	21.8 ± 4.9	21.9 ± 4.9	22.2 ± 5.0	22.0 ± 5.2
Years of formal education	6.4 ± 3.2	6.3 ± 3.4	6.0 ± 3.2	6.1 ± 3.2
Household asset index	0.04 ± 2.24	0.01 ± 2.33	-0.06 ± 2.22	0.02 ± 2.23
HFIA severe insecurity	86 (8.2)	78 (8.39)	99 (9.4)	103 (10.5)
HFIA moderate insecurity	279 (26.7)	287 (30.9)	308 (29.3)	289 (29.4)
HFIA mild insecurity	163 (15.6)	120 (12.9)	146 (13.9)	152 (15.5)
HFIA secure	519 (49.6)	445 (47.9)	499 (47.4)	438 (44.6)
Height, cm	150.7 ± 5.4	150.4 ± 5.3	150.5 ± 5.4	150.7 ± 5.4
BMI (adjusted to 96 d of gestation)[b] kg/m^2	19.9 ± 2.7	20.1 ± 2.6	20.0 ± 2.6	20.0 ± 2.8
Low BMI (< 18.5 kg/m^2)	331 (31.6)	278 (29.9)	306 (29.1)	298 (30.3)
Nulliparous	435 (41.7)	386 (41.6)	397 (37.8)	373 (38.0)
Gestational age at enrollment, weeks	13.1 ± 3.8	13.2 ± 3.9	13.1 ± 3.8	13.1 ± 3.8

[a] Mean ± SD or n (%)

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

The percentages of children with high adherence (every day or almost every day), based on caregiver recall for the previous 6 months, or for the week preceding the interviews at 12, 18, and 24 months, are shown in Table 5. Reported high adherence increased with child age in all three intervention groups. When based on the previous 6 months, it increased from 94–97% at 6–12 months to 97–99% at 18–24 months, and was lowest in the IFA-MNP group ($p = 0.007$ at 24 months). When based on the previous week, it increased from 77–80% at 12 months to 90–92% at 24 months, and did not differ significantly among the three intervention groups.

Table 5. Percentage of Caregivers Reporting High Adherence to Child Supplementation in the RDNS Cohort, by Study Arm

Period	Comprehensive LNS	Child-only LNS	Child-only MNP	P-value[a]
Past week:[b]				
12 months of age	76.9	80.5	77.5	0.355
18 months of age	83.1	85.8	84.8	0.571
24 months of age	90.3	92.1	89.7	0.450
Past six months:[c]				
12 months of age	96.7	97.0	94.2	0.155
18 months of age	97.4	97.5	95.1	0.052
24 months of age[d]	99.3[e]	99.0[e,f]	97.5[f]	0.007

[a] Global p-value for three-group comparison

[b] High adherence defined as consuming 8+ 10g sachets of LNS (out of 14 recommended) or 4+ sachets of MNP (out of 7 recommended) in the past week

[c] High adherence defined as "Almost every day" or "Every day" over the past six months

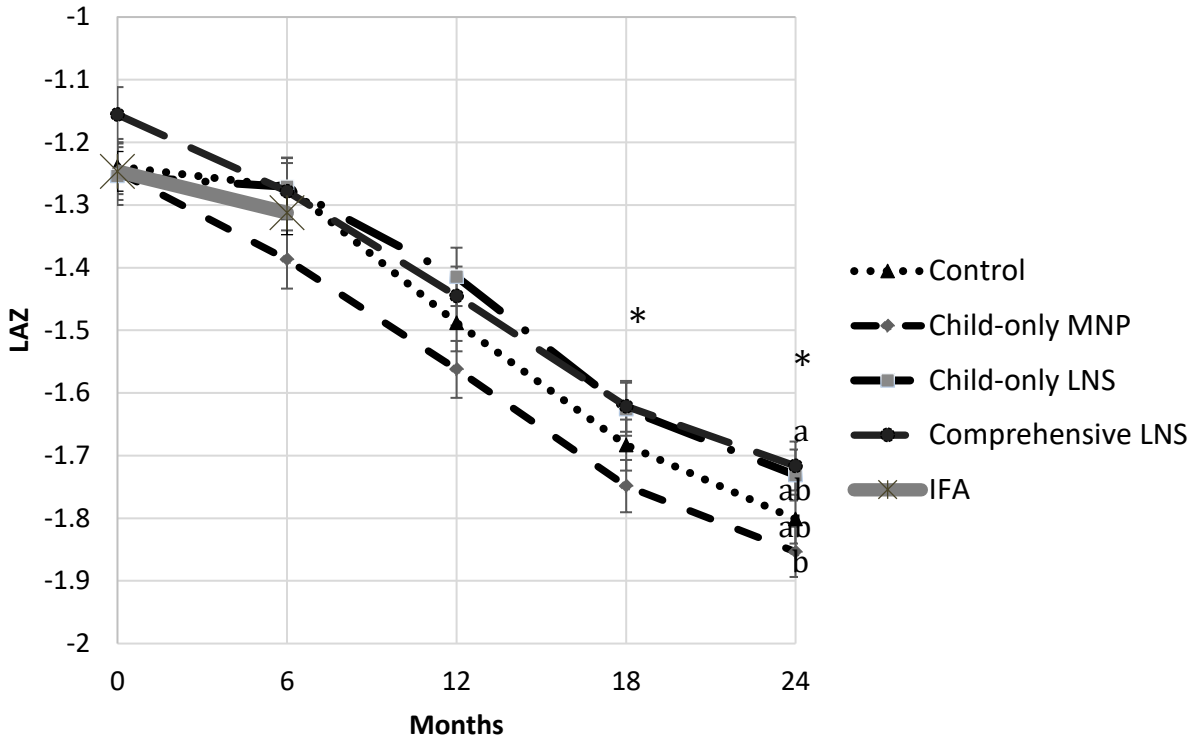
[d] LNS-LNS vs IFA-MNP, $p = 0.013$

[e,f] Groups that do not share a common superscript differ significantly from each other ($p < 0.05$).

3.3 Impact on Child Growth

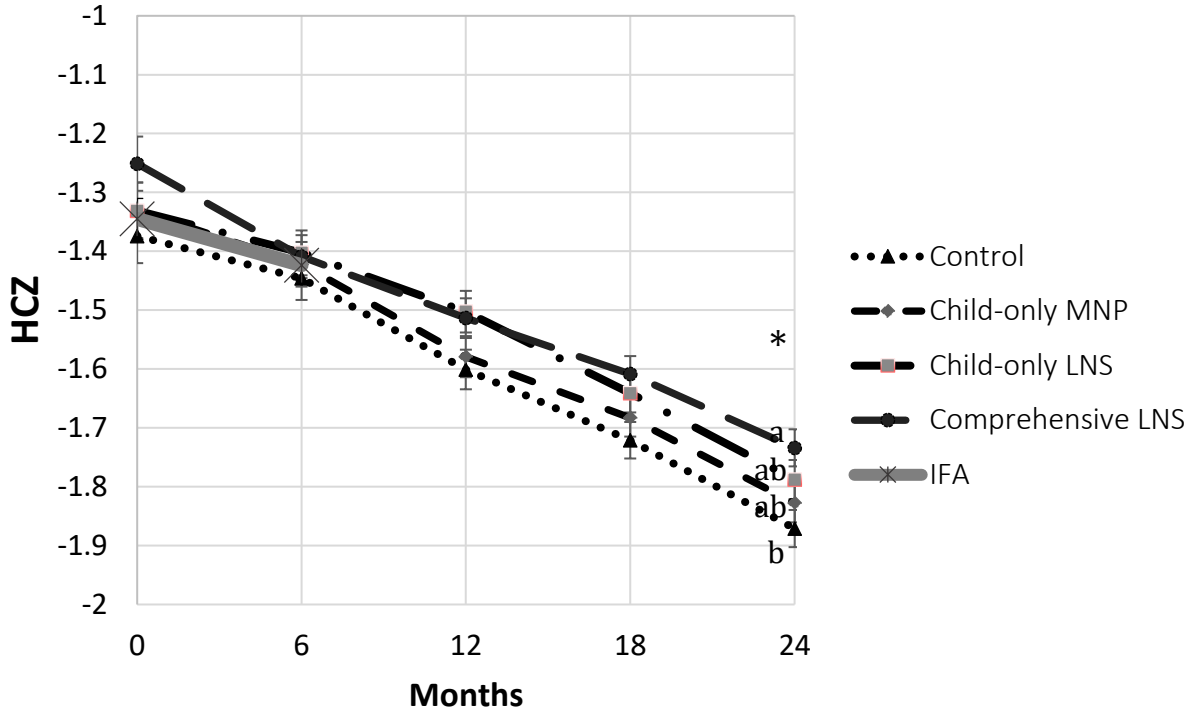
Figures 2–6 show the growth patterns of children between birth and 24 months for LAZ, HCZ, WAZ, WLZ, and MUACZ, respectively, and Figure 7 illustrates the prevalence of stunting at each time point. Statistically significant differences in attained size (growth status) and postnatal growth rate are described below.

Figure 2. Length-for-Age Z-Score (LAZ) by Child Age



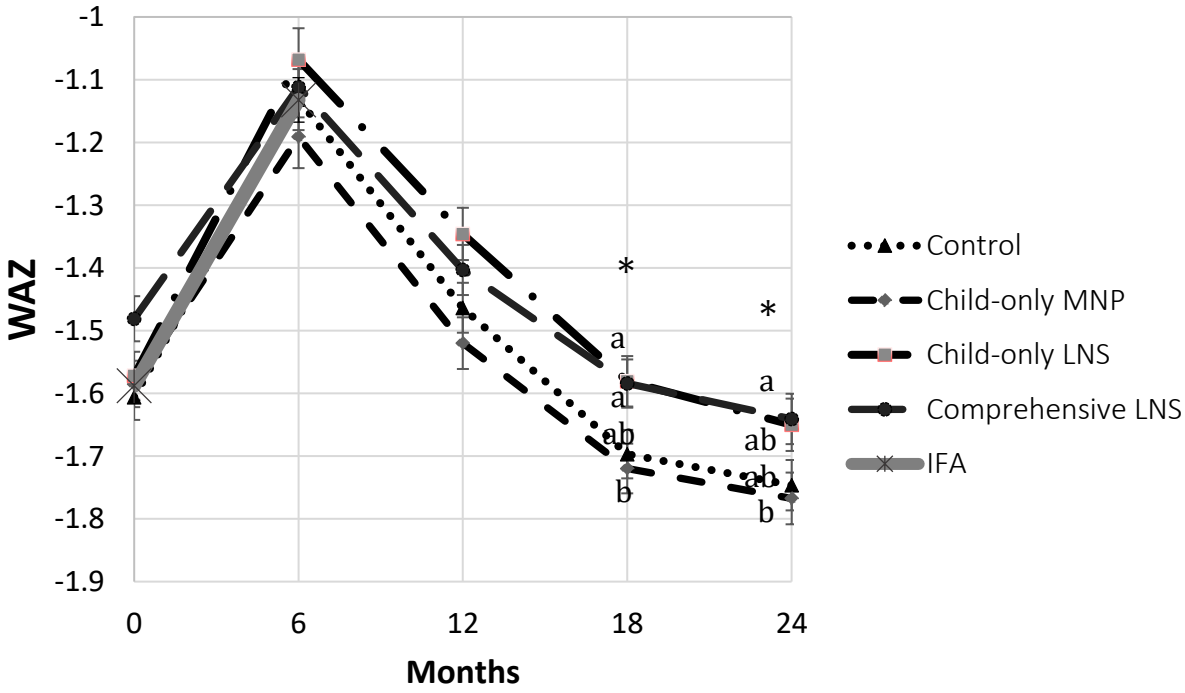
*Global difference, P < 0.05. Groups that do not share a common letter differ, P < 0.05 (Tukey-Kramer–corrected pairwise differences).

Figure 3. Head Circumference-for-Age Z-Score (HCZ) by Child Age



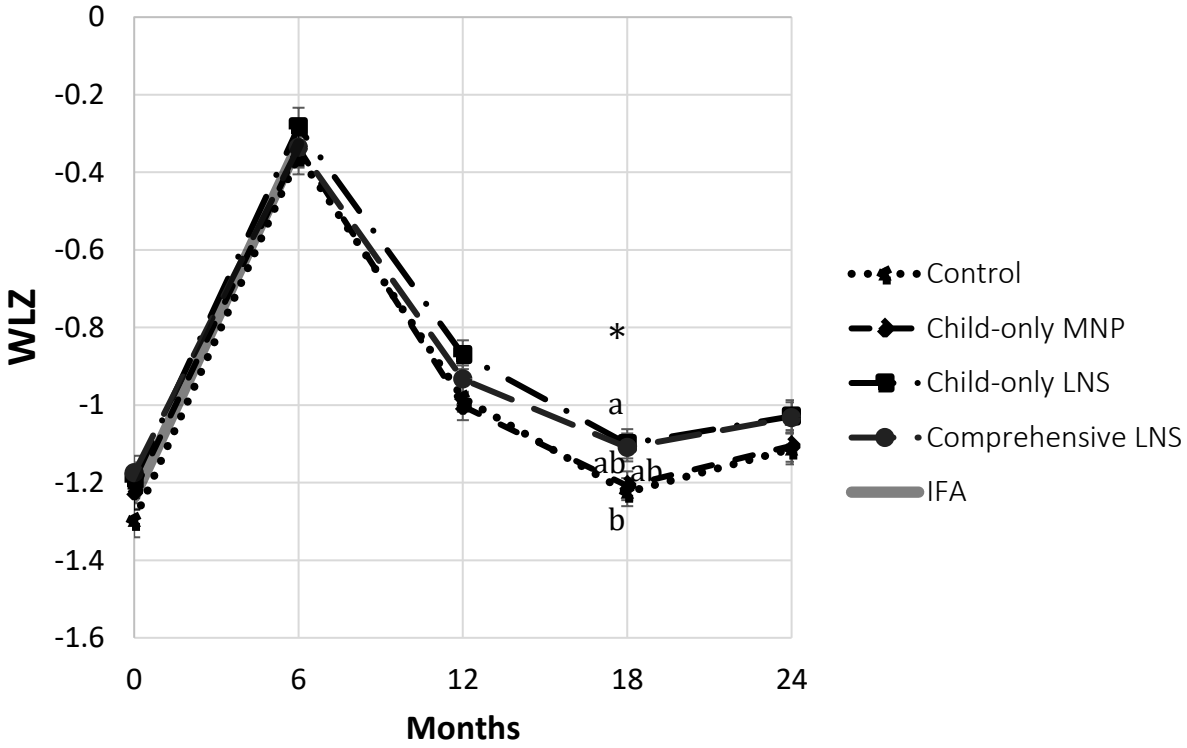
*Global difference, P < 0.05. Groups that do not share a common letter differ, P < 0.05 (Tukey-Kramer–corrected pairwise differences).

Figure 4. Weight-for-Age Z-Score (WAZ) by Child Age



*Global difference, P < 0.05. Groups that do not share a common letter differ, P < 0.05 (Tukey-Kramer–corrected pairwise differences).

Figure 5. Weight-for-Length Z-Score (WLZ) by Child Age



*Global difference, P < 0.05. Groups that do not share a common letter differ, P < 0.05 (Tukey-Kramer–corrected pairwise differences).

Figure 6. MUAC-for-Age Z-Score (MUACZ) by Child Age

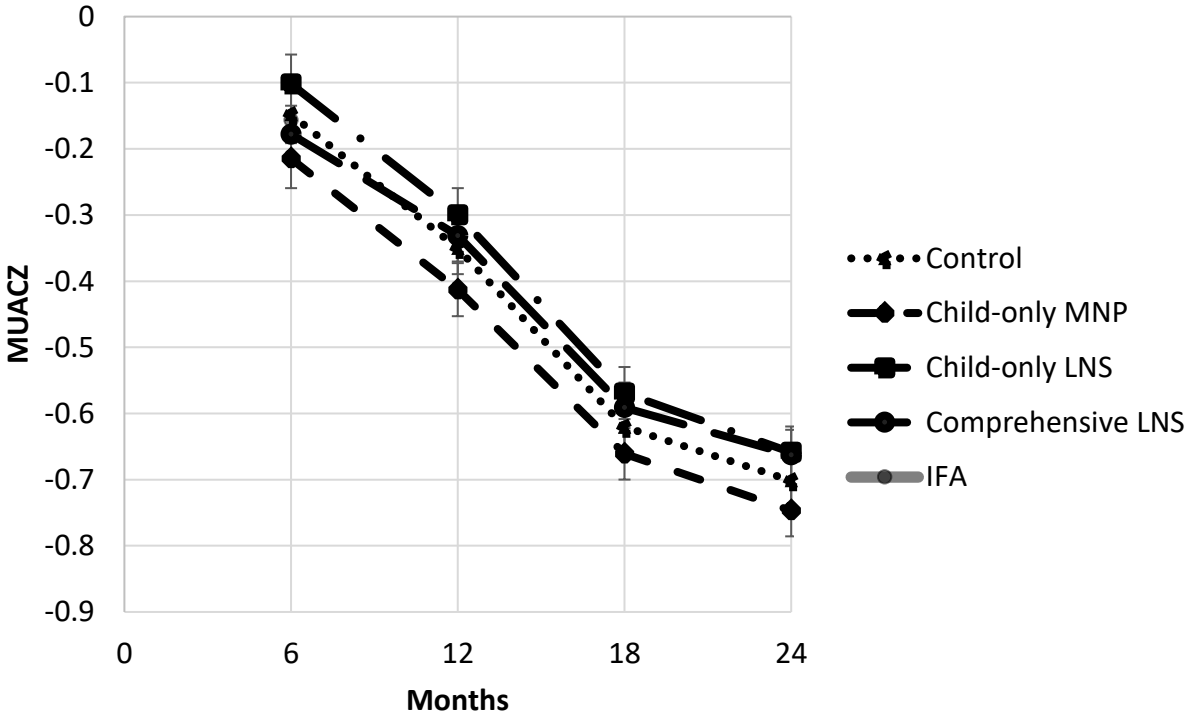
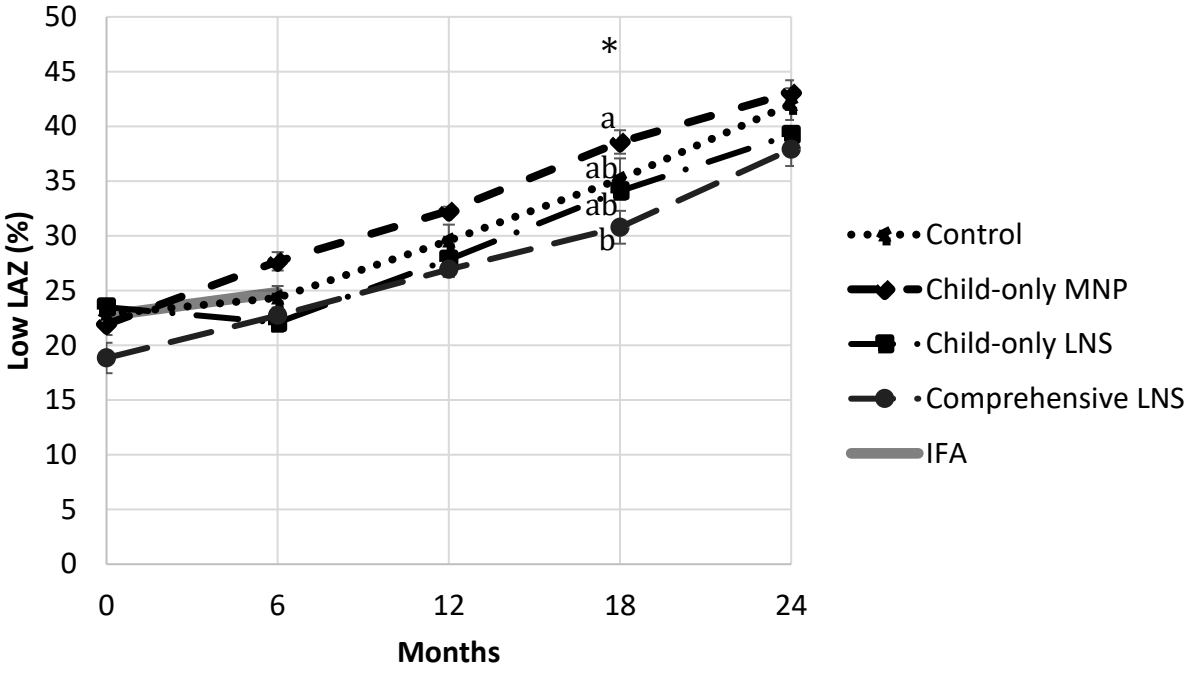


Figure 7. Stunting by Child Age



*Global difference, P < 0.05. Groups that do not share a common letter differ, P < 0.05 (Tukey-Kramer–corrected pairwise differences).

3.3.1 Comparison of Attained Size (Growth Status)

Growth Status at 24 Months (Primary Endpoint)

Table 6 shows that there were significant differences among intervention groups at 24 months in LAZ, HCZ, and WAZ; there were no significant differences in WLZ or MUACZ. Pairwise tests between the groups indicated significant differences between the LNS-LNS and the IFA-MNP groups for LAZ (-1.72 vs. -1.85) and WAZ (-1.64 vs. -1.77) and between the LNS-LNS and the IFA-Control groups for HCZ (-1.73 vs. -1.87). There were no significant differences between the IFA-LNS group and either the IFA-Control or IFA-MNP groups, nor between the LNS-LNS and the IFA-LNS groups in any of these continuous outcomes.

The trends for the dichotomous outcomes (Table 7) were the same as for the continuous outcomes, but the differences in the prevalence of stunting, underweight, and wasting were not significant; for small head size, there was a marginally significant difference (p=0.0993), with the largest difference in prevalence between the LNS-LNS group (37.4%) and the IFA-Control group (43.0%).

Adjustment for pre-determined covariates did not change these results (data not shown).

Growth Status at 18 Months (Secondary Endpoint)

At 18 months, there were significant differences among intervention groups overall in LAZ, WAZ, and WLZ, and a marginally significant difference in HCZ; there were no significant differences in MUACZ (Table 6). Pairwise tests between the groups indicated that the LNS-LNS and IFA-LNS groups both

differed (positively) from the IFA-MNP group for WAZ (with similar but marginally significant differences for LAZ); for WLZ the difference was significant for IFA-LNS vs. IFA-Control. There were no significant differences between the IFA-MNP group and the IFA-Control group, or between the LNS-LNS group and the IFA-LNS group, for any of these outcomes.

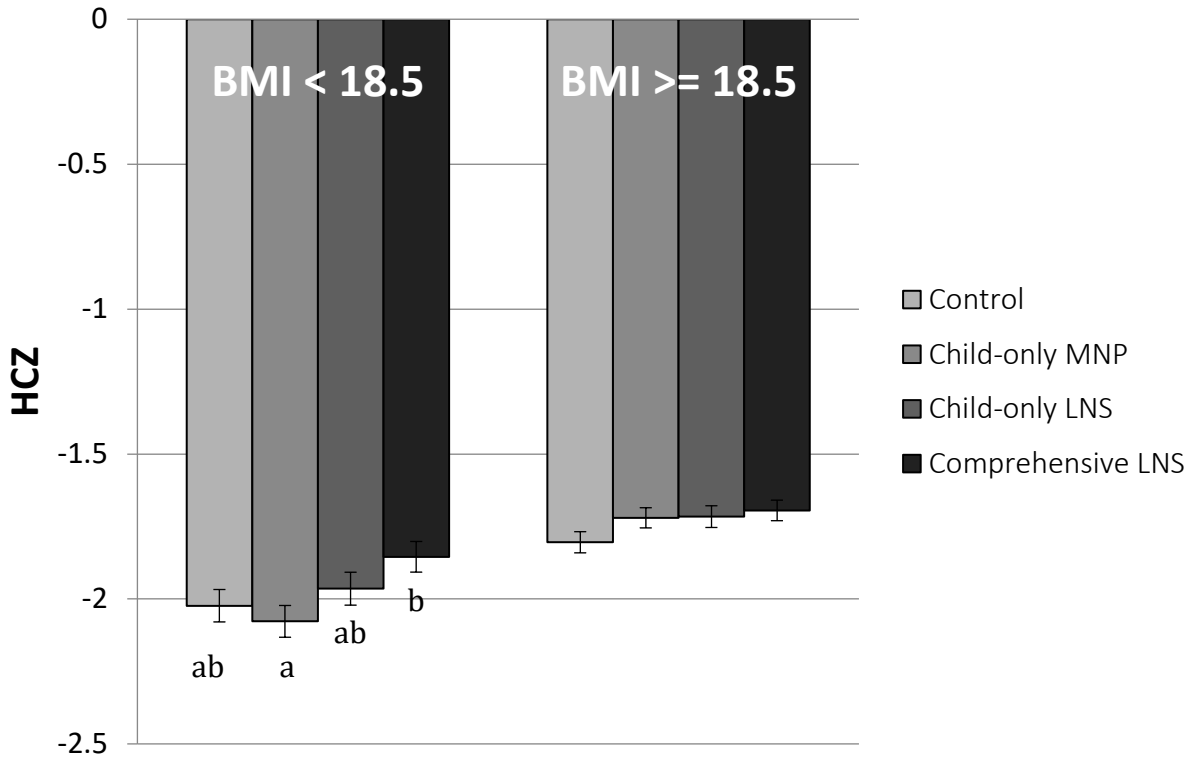
The prevalence of stunting, underweight, and wasting (Table 7) differed by intervention group at 18 months. For stunting, the LNS-LNS group had a lower prevalence (30.8%) compared to the IFA-MNP group (38.6%). For underweight, there was a difference between the IFA-LNS group (29.6%) and the IFA-MNP group (38.3%) and for wasting, there was a difference between the IFA-LNS group (14.0%) and the IFA-Control group (19.1%).

Adjustment for pre-determined covariates did not change these results (data not shown).

Effect Modification for Attained Size

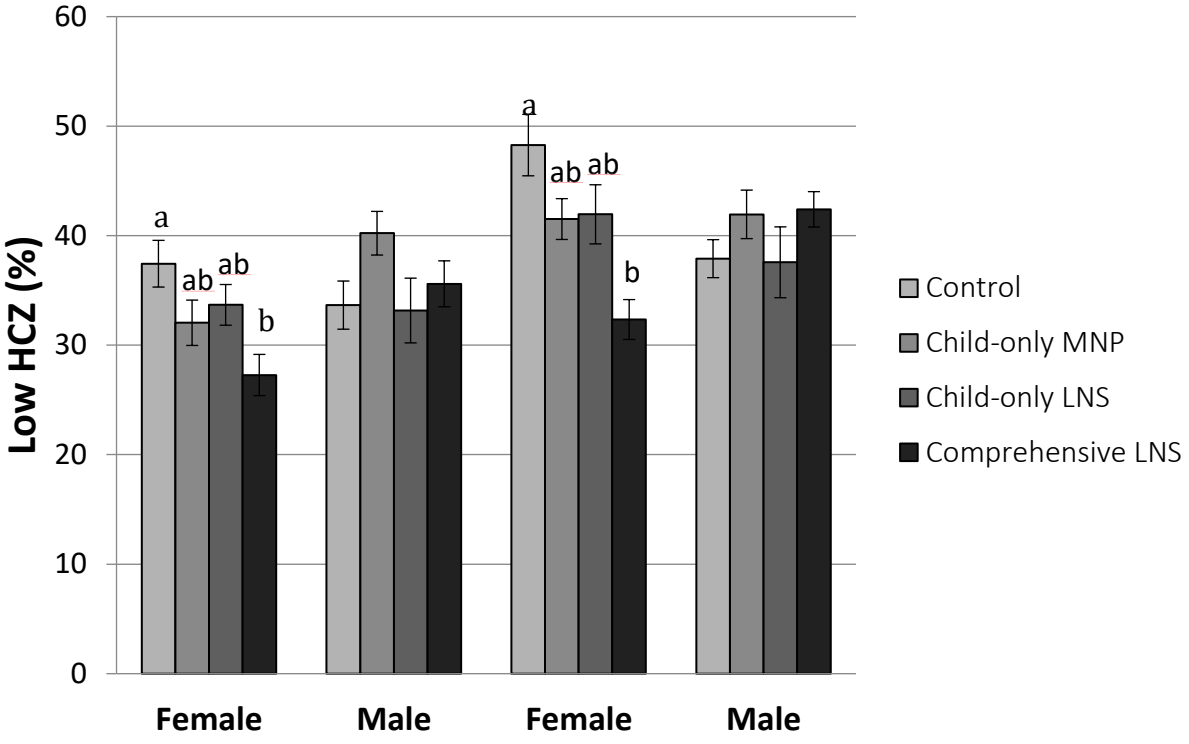
Results of tests for interactions with potential effect modifiers were generally not significant ($p > 0.10$), except when head circumference was the outcome. For HCZ at 24 months, there was a significant interaction with maternal BMI; as shown in Figure 8, among children of mothers with baseline BMI < 18.5 kg/m^2, the HCZ of children in the LNS-LNS group was significantly greater than that of children in the IFA-MNP group. For low HCZ at both 18 and 24 months, there was a significant interaction with child sex, with significant group differences among females but not among males (Figure 9). Girls in the IFA-Control group had a significantly higher prevalence of low HCZ compared to girls in the LNS-LNS group.

Figure 8. HCZ at 24 Months, Stratified by Baseline Maternal BMI



P for interaction with continuous BMI: p=0.025
BMI < 18.5: Child-only MNP vs Comprehensive LNS, p=0.025
Groups that do not share a common letter differ, P < 0.05

Figure 9. Small Head Size at 18 and 24 Months, Stratified by Child Sex



18 Month p for interaction: p=0.043
24 Month p for interaction: p=0.002
18 Months- Among Females: Control vs Comprehensive LNS, p=0.035
24 Months- Among Females: Control vs Comprehensive LNS, p=0.001
Groups that do not share a common letter differ, P < 0.05

3.3.2 Comparison of Postnatal Growth Rate

Growth Rate from Birth to 6 Months

Postnatal growth rates from birth to 6 months are shown in Table 8 for the maternal LNS vs. IFA-combined groups. There were no significant differences between groups in length gain, head circumference gain, or weight gain. Adjustment for pre-determined covariates did not change these results (data not shown).

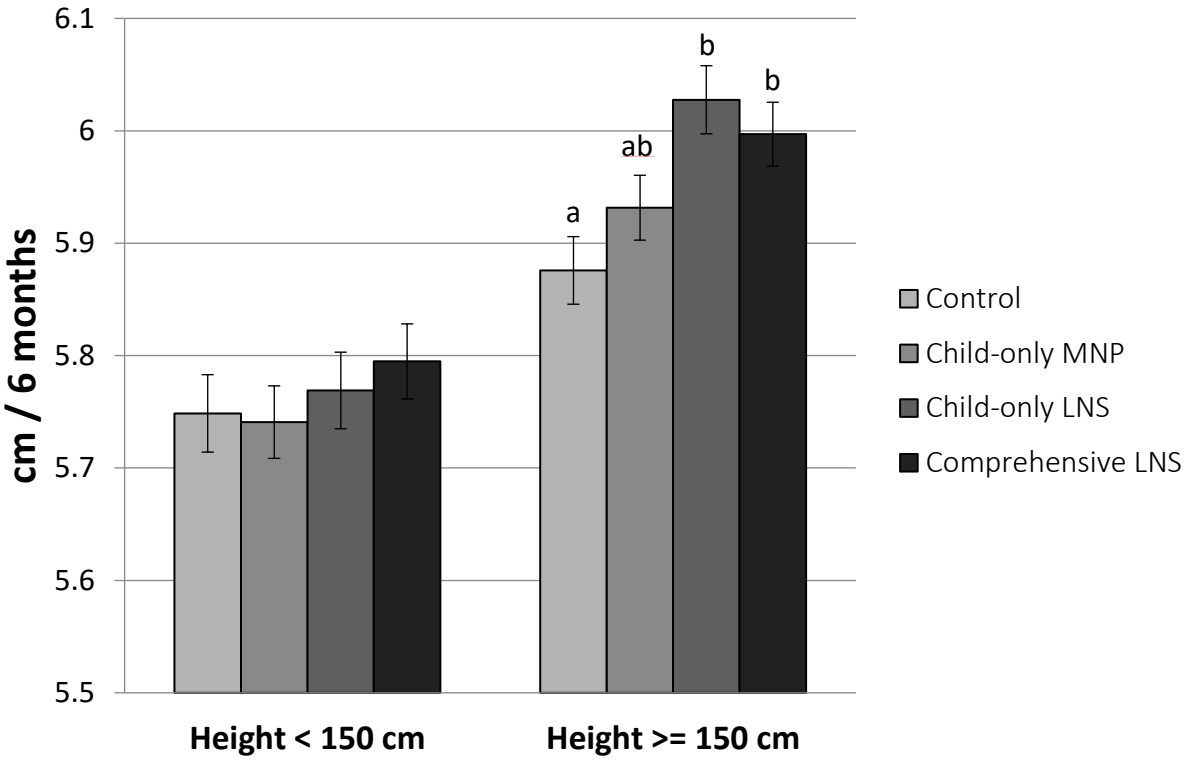
Growth Rate from 6 to 24 Months

Postnatal growth rates from 6 to 24 months are shown in Table 9 for all four intervention groups. There were significant differences between groups in length gain, head circumference gain, and weight gain. Pairwise tests between the groups indicated that the LNS-LNS and IFA-LNS groups had greater length gain than the IFA-Control group, but did not differ significantly from the IFA-MNP group. The LNS-LNS group had greater head circumference gain than the IFA-Control group; none of the other pairwise tests were significant. For weight gain, none of the pairwise tests were significant. Adjustment for pre-determined covariates did not change these results (data not shown).

Effect Modification for Postnatal Growth Rate

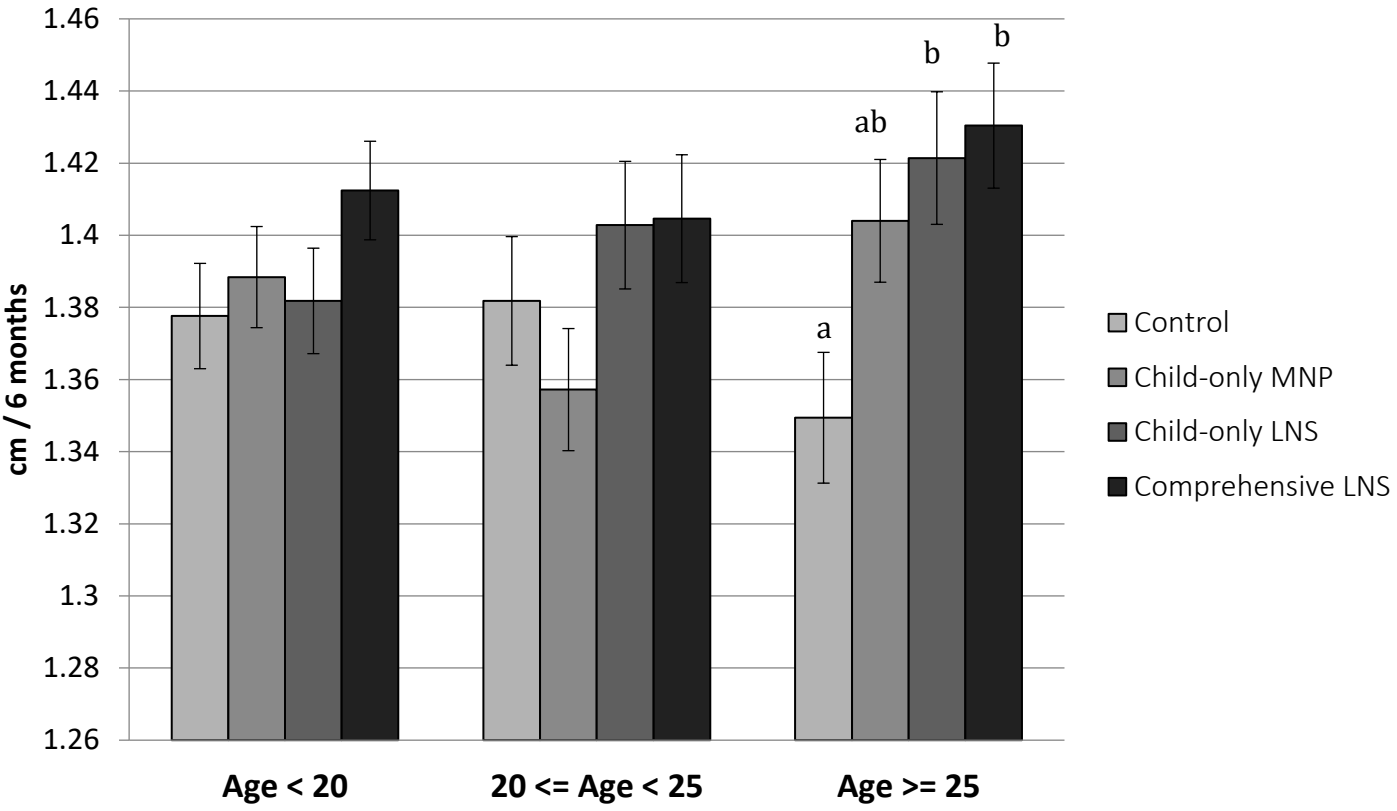
There were no significant interaction effects observed for growth rate from birth to 6 months. For growth rate from 6 to 24 months, maternal height modified the effect of intervention group on length gain, with group differences evident in children of taller mothers, but not in children of shorter mothers (Figure 10). For head circumference gain from 6 to 24 months, differences between intervention groups were more evident in children of mothers ≥ 25 years of age than in children of younger women (Figure 11).

Figure 10. Length Gain from 6 to 24 Months, Stratified by Maternal Height



P for interaction with continuous height: p=0.074
Among taller mothers: Control vs Comprehensive LNS, p=0.015; Control vs Child-only LNS, p=0.002
Groups that do not share a common letter differ, P < 0.05

Figure 11. Head Circumference Gain from 6 to 24 Months, Stratified by Maternal Age



P for interaction with continuous age: p=0.060
Among older mothers: Control vs Child-only LNS, p=0.035; Control vs Comprehensive LNS, p=0.011
Groups that do not share a common letter differ, P < 0.05

Table 6. LAZ, HCZ, WAZ, WLZ, and MUACZ at 18 and 24 Months, by Intervention Group[a]

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

[a] Values are means ± SD
[b] LNS-LNS vs IFA-MNP, p=0.022
[c,d] Groups that do not share a common superscript differ significantly from each other ($p < 0.05$)
[e] LNS-LNS vs IFA-Control, p=0.011
[f] LNS-LNS vs IFA-MNP, p=0.022; IFA-LNS vs IFA-MNP, p=0.021
[g] LNS-LNS vs IFA-MNP, p=0.034
[h] IFA-LNS vs IFA-Control, p=0.039

Table 7. Prevalence of Stunting, Small Head Size, Underweight, and Wasting at 18 and 24 Months, by Intervention Group[a]

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

[a] Results presented as prevalence, OR (95% CI), RR

[b] LNS-LNS vs IFA-MNP, OR=0.70 (0.53,0.92), RR=0.79

[c,d] Groups that do not share a common superscript differ significantly from each other ($p < 0.05$)

[e] IFA-LNS vs IFA-MNP, OR=0.68 (0.52, 0.89), RR=0.77

Table 8. Growth in Length, Head Circumference, and Weight between 0 and 6 Months, by Intervention Group[a]

	Comprehensive LNS (LNS-LNS)	IFA Combined (Child LNS, Child MNP, and Control)	P-value[b]
Length Gain (cm/6 mo)	16.1 ± 1.8	16.1 ± 1.9	0.380
Head Circ Gain (cm/6 mo)	8.1 ± 1.2	8.1 ± 1.2	0.147
Weight Gain (g/6 mo)	4055 ± 742	4086 ± 739	0.385

[a] Values are means ± SD

[b] P-values from models of growth rate per month

Table 9. Growth in Length, Head Circumference, and Weight between 6 and 24 Months, by Intervention Group[a]

	Comprehensive LNS (LNS-LNS)	Child LNS (IFA-LNS)	Child MNP (IFA-MNP)	Control (IFA-Control)	P-value[b]
Growth, 6–24 mo[a]					
Length Gain (cm/6 mo)[c]	5.9 ± 0.6[d]	5.9 ± 0.6[d]	5.8 ± 0.6[d,e]	5.8 ± 0.6[e]	0.003
Head Circ Gain (cm/6 mo)[f]	1.41 ± 0.24[d]	1.40 ± 0.23[d,e]	1.38 ± 0.25[d,e]	1.37 ± 0.24[e]	0.011
Weight Gain (g/6 mo)	1009 ± 225	1005 ± 213	985 ± 219	981 ± 211	0.033

[a] Values are means ± SD
[b] P-values from models of growth rate per month
[c] LNS-LNS vs IFA-Control, p= 0.013; IFA-LNS vs IFA-Control, p= 0.013
[d,e] Groups that do not share a common superscript differ significantly from each other (p < 0.05)
[f] LNS-LNS vs IFA-Control, p= 0.009

3.4 Impact on Child Development

This section presents results on the effect of the interventions on child development outcomes, measured at 24 months of age (primary endpoint) and described in section 2.6.2.

3.4.1 Comparison of Child Development Outcomes at 24 Months

Motor Development

Table 10 shows that there were significant differences among intervention groups overall in motor development z-scores (p=0.028). However, this association was attenuated (p=0.052) after adjustment for pre-determined covariates including FCI score, gestational age at enrollment, child's age and sex, SES index, HFIAS score, and maternal education, BMI, and height (data not shown). Pairwise tests between the groups indicated significant differences between the IFA-MNP and the IFA-Control groups in unadjusted motor development z-scores (0.04 vs. -0.11). There were no significant differences between the IFA-LNS group and the other three groups, nor between the LNS-LNS and the other three groups.

We did not observe significant differences among intervention groups for the motor development dichotomous outcomes (Table 11). Adjustment for pre-determined covariates resulted in similar findings (data not shown).

Language Development

Comprehensive Language

There were significant differences among intervention groups overall in comprehensive language development z-scores (Table 10). Pairwise tests between the groups indicated that children in the LNS-LNS, IFA-LNS, and IFA-MNP groups had higher comprehensive language development z-scores than those in the IFA-Control group (0.05, 0.03, and 0.04 vs. -0.13, respectively). There were no significant differences in pairwise tests between the IFA-LNS, IFA-MNP, or LNS-LNS groups.

The percentages of children in the lowest quartile and lowest decile for comprehensive language (Table 11) were significantly different among intervention groups (p=0.009 and p=0.012, respectively). For the

lowest quartile, the LNS-LNS and IFA-LNS groups (25.5% and 26.2%, respectively) had lower percentages compared to the IFA-Control group (31.6%). For the lowest decile, the IFA-LNS and the IFA-MNP groups (9.2%, both) had lower percentages compared to the IFA-Control group (13.5%).

Adjustment for pre-determined covariates did not change these results (data not shown).

Expressive Language

Overall, there were significant differences among intervention groups in expressive language development z-scores (Table 10). Pairwise tests between the groups indicated that the LNS-LNS and IFA-MNP groups both differed (positively) from the IFA-Control group. There were no significant differences between the IFA-LNS group and the IFA-Control group, or between the IFA-LNS group and either of the other two intervention groups (i.e., LNS-LNS and IFA-MNP groups).

There was a marginally significant difference among groups (p=0.094) in the percentage of children in the lowest quartile, and no significant differences among groups in the percentage in the lowest decile for expressive language (Table 11).

Adjustment for pre-determined covariates did not change these results (data not shown), except for the comparison among groups regarding moderate-to-severe delay (i.e., lowest quartile of the distribution), for which adjustment for covariates (p=0.145) attenuated the marginal association observed in unadjusted analysis.

Personal-Social Development

No significant differences among intervention groups in personal-social development z-scores were observed (p=0.146, Table 10).

The percentage of children in the lowest quartile for personal-social development (Table 11) was significantly different among intervention groups (p=0.0397). Pairwise comparison between groups indicated that the IFA-LNS group had a higher percentage in the lowest quartile (29.0%) compared to the IFA-MNP group (23.1%). There were no significant differences among groups in the percentage in the lowest decile for personal-social development (Table 11) (p=0.305).

Adjustment for pre-determined covariates did not change these results (data not shown).

Executive Function

No significant differences among intervention groups in z-scores of correct responses (p=0.467) or perseverative errors (p=0.233) in the A-not-B task were observed (Table 10).

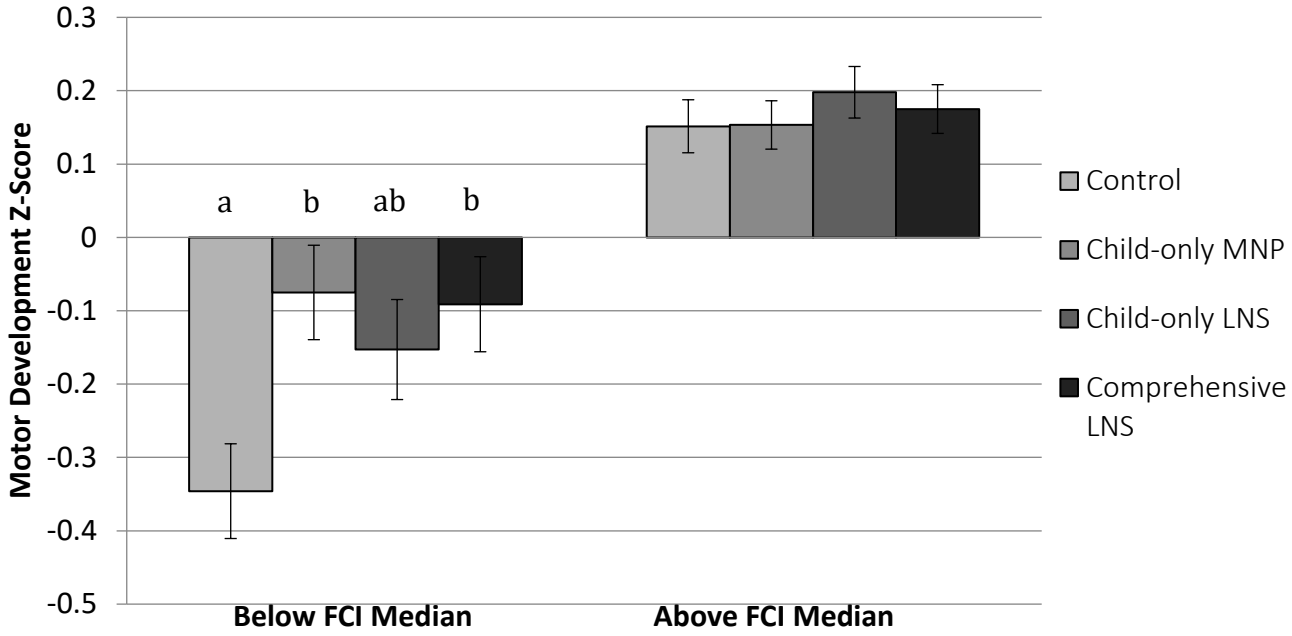
Similarly, there were no significant differences among groups in the percentages of children in the lowest quartile (p=0.394) or the lowest decile (p=0.748) of the distribution of correct responses (Table 11).

Adjustment for pre-determined covariates did not change these results (data not shown).

Effect Modification for Child Development Outcomes

For motor development z-score, FCI score modified the effect of the intervention. Among children from households with lower home stimulation, those in the LNS-LNS and the IFA-MNP groups had higher motor development z-scores than those in the IFA-Control group, but no group difference was observed among children from households with greater home stimulation (Figure 12).

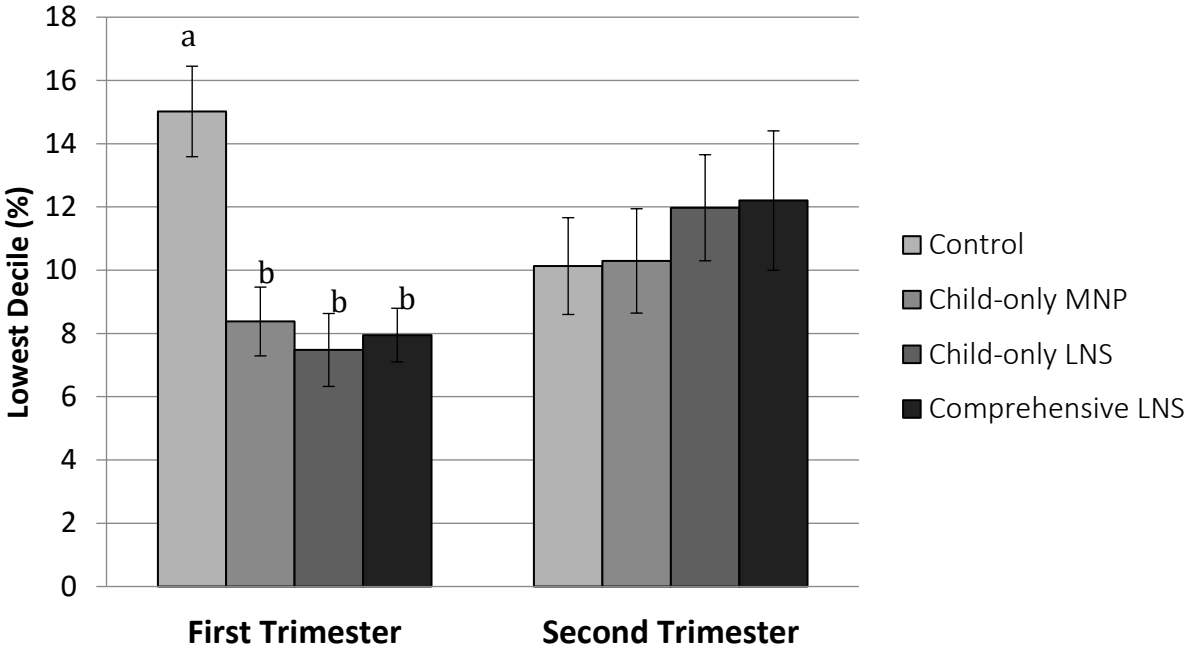
Figure 12. Motor Development Z-Score at 24 Months, Stratified by FCI Score



P for interaction with FCI score: p <0.0001
Below FCI Median:
Control vs Child-only MNP, p=0.022
Control vs Comprehensive LNS, p=0.007
Groups that do not share a common letter differ, p < 0.05

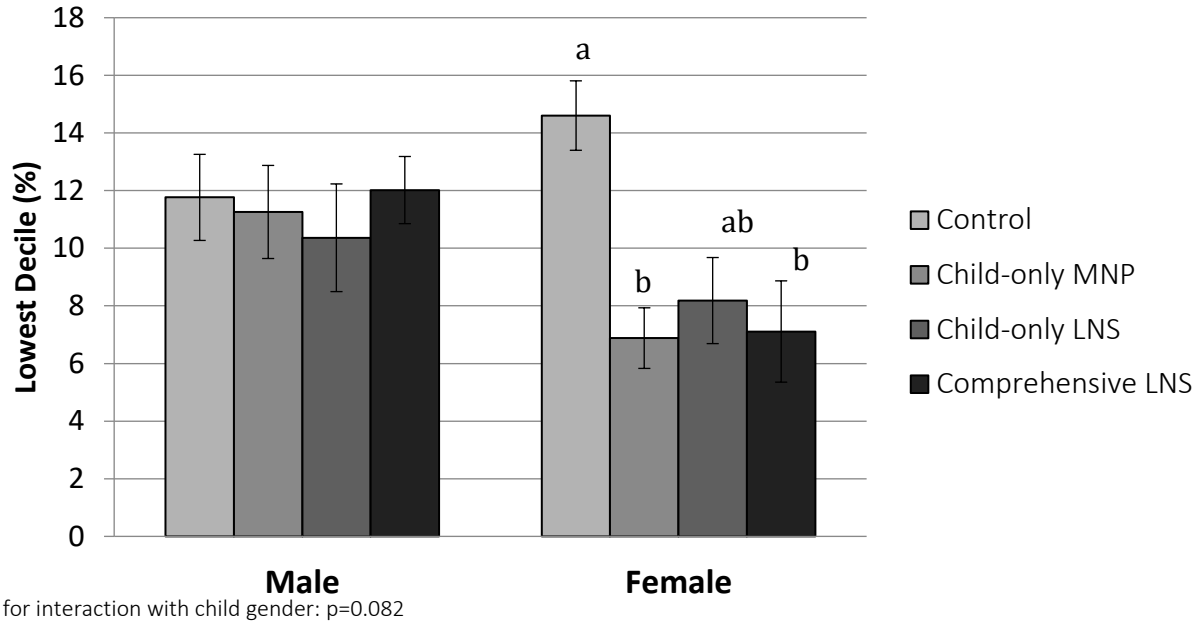
Gestational age at enrollment, child's sex, and asset score modified the effect of intervention group on language comprehension. For the percentage in the lowest decile, group differences were evident in children whose mothers were enrolled in their first trimester of pregnancy, but not among children of those enrolled later in pregnancy (Figure 13). A similar pattern was observed for the percentage in the lowest quartile for language comprehension (p=0.011 for interaction with gestational age) and for language comprehension z-score (p=0.004 for interaction with gestational age). Group differences were observed in the percentage of children in the lowest quartile from households with an asset score below the median, but not from households with higher asset scores (Figure 14). Also, group differences in the percentage in the lowest decile were observed among female children, but not among males (Figure 15).

Figure 13. Percentage of Children in the Lowest Decile for Language Comprehension at 24 Months, Stratified by Trimester of Enrollment



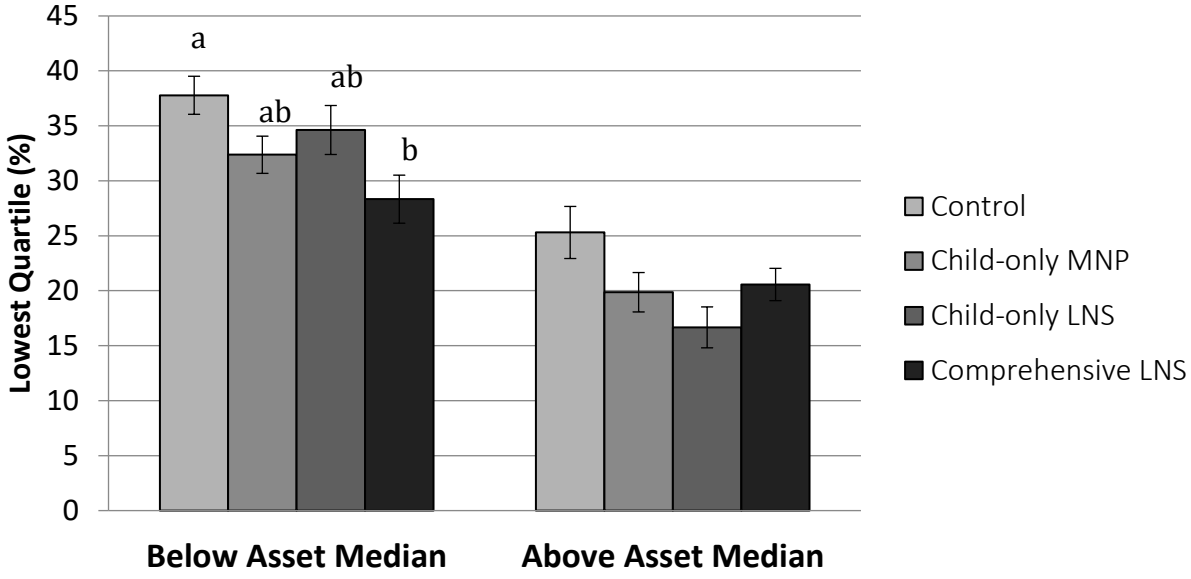
P for interaction with continuous gestational age: p=0.014
Among women enrolled during their first trimester:
Control vs Comprehensive LNS, p=0.006
Control vs Child-only LNS, p=0.009
Control vs Child-only MNP, p=0.014
Groups that do not share a common letter differ, $p < 0.05$

Figure 14. Percentage of Children in the Lowest Decile for Language Comprehension at 24 Months, Stratified by Child Gender



P for interaction with child gender: p=0.082
Among female children:
Control vs Comprehensive LNS, p=0.022
Control vs Child-only MNP, p=0.007
Groups that do not share a common letter differ, p < 0.05

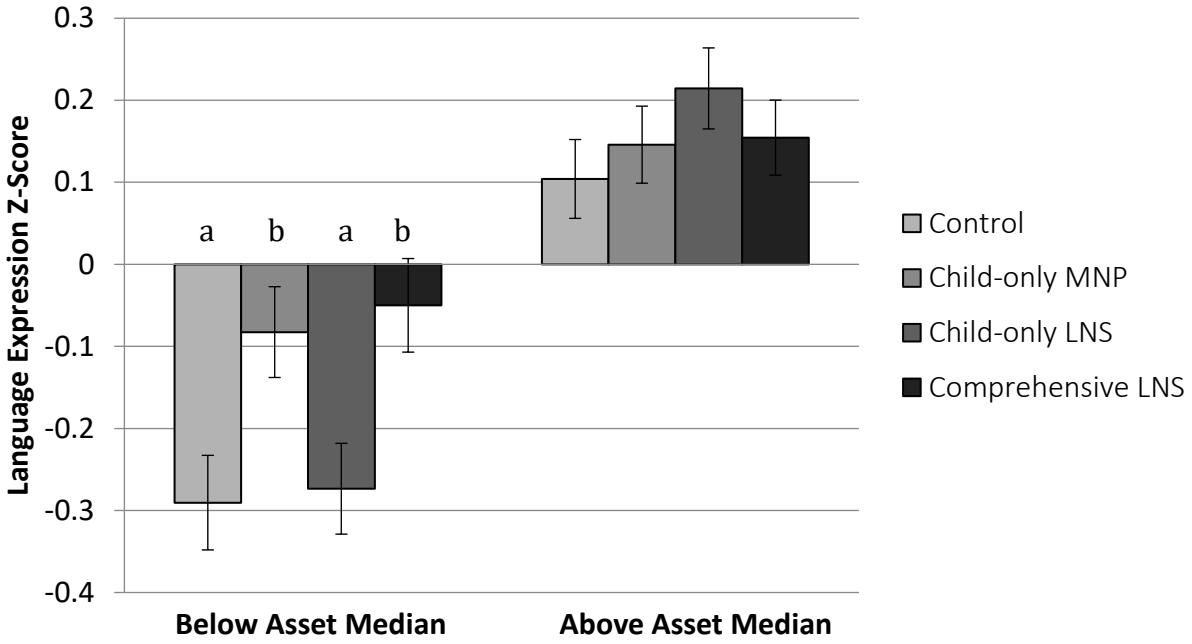
Figure 15. Percentage of Children in the Lowest Quartile for Language Comprehension at 24 Months, Stratified by Asset Score



P for interaction with continuous asset score: p=0.019
Below Asset Median: Control vs Comprehensive LNS, p=0.027
Groups that do not share a common letter differ, p < 0.05

For expressive language z-score, differences between intervention groups were evident in children from households with lower asset scores, but not among those from households with higher asset scores (Figure 16).

Figure 16. Language Expression Z-Score at 24 Months, Stratified by Asset Score



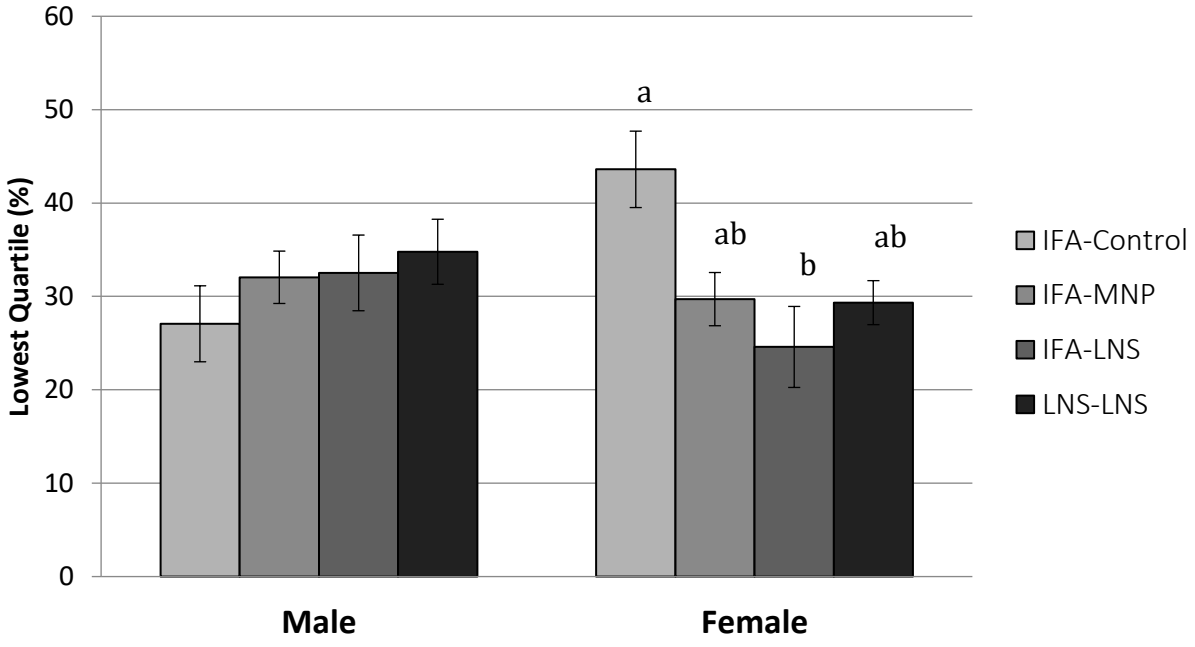
P for interaction with continuous asset score: p=0.019
Below Asset Median:

Control vs Child-only MNP, p=0.015	Control vs Comprehensive LNS, p=0.004
Child-only LNS vs Child-only MNP, p=0.031	Child-only LNS vs Comprehensive LNS, p=0.010

Groups that do not share a common letter differ, P < 0.05

Child's sex also modified the effect of the intervention on the proportion of correct responses in the executive function task, with significant differences by intervention group in the percentage of children in the lowest quartile among females, but not among males (Figure 17).

Figure 17. Percentage of Children in the Lowest Quartile for Executive Function (A-not-B Total Correct) at 24 Months, Stratified by Child Gender



P for interaction with child gender: p=0.017
Among females: IFA-Control vs IFA-LNS, p=0.024
Groups that do not share a common letter differ, P < 0.05

Table 10. Developmental Z-Scores at 24 Months, by Intervention Group (n = 3,379)[a]

	Comprehensive LNS (LNS-LNS)	Child LNS (IFA-LNS)	Child MNP (IFA-MNP)	Control (IFA-Control)	P-value
Motor z-score[b]	0.04 ± 0.74[c,d]	0.03 ± 0.95[c,d]	0.04 ± 0.92[c]	-0.11 ± 1.32[d]	0.028
Comprehensive language z-score[e]	0.05 ± 0.97[c]	0.03 ± 0.99[c]	0.04 ± 0.98[c]	-0.13 ± 1.05[d]	0.003
Expressive language z-score[f]	0.08 ± 1.00[c]	0.00 ± 1.02[c,d]	0.02 ± 0.98[c]	-0.11 ± 0.99[d]	0.003
Personal-social z-score	0.03 ± 0.89	-0.01 ± 1.00	0.05 ± 0.92	-0.08 ± 1.18	0.146
A-not-B correct z-score	0.00 ± 1.05	0.07 ± 0.97	0.00 ± 0.95	-0.07 ± 1.02	0.467
A-not-B perseverative errors z-score	-0.08 ± 0.98	-0.04 ± 0.98	0.04 ± 0.98	0.08 ± 1.06	0.233

[a] Values are means ± SD
[b] IFA-MNP vs IFA-Control, p=0.048
[c,d] Groups that do not share a common superscript differ significantly from each other (p < 0.05)
[e] LNS-LNS vs IFA-Control, p=0.008; IFA-LNS vs IFA-Control, p=0.022; IFA-MNP vs IFA-Control, p=0.009
[f] LNS-LNS vs IFA-Control, p=0.035; IFA-MNP vs IFA-Control, p=0.002

Table 11. Dichotomous Developmental Outcomes (Lowest Quartile and Decile) at 24 Months, by Intervention Group (n = 3,379)[a]

		Comprehensive LNS (LNS-LNS)	Child LNS (IFA-LNS)	Child MNP (IFA-MNP)	Control (IFA-Control)	P-value
Motor	Lowest quartile	28.3%	27.8%	27.9%	32.7%	0.141
		0.81 (0.59, 1.10)	0.78 (0.57, 1.07)	0.80 (0.59, 1.09)	--	
		0.87	0.84	0.86	--	
	Lowest decile	10.6%	11.1%	10.8%	13.0%	0.444
		0.79 (0.52, 1.22)	0.83 (0.54, 1.29)	0.80 (0.52, 1.23)	--	
		0.82	0.85	0.82	--	
Comprehensive language	Lowest quartile	24.6%[b]	25.5%[b]	26.2%[b,c]	31.6%[c]	0.009
		0.70 (0.53, 0.94)	0.74 (0.55, 1.00)	0.77 (0.58, 1.02)	--	
		0.78	0.81	0.83	--	
	Lowest decile	9.7%[b,c]	9.2%[b]	9.2%[b]	13.5%[c]	0.012
		0.66 (0.44, 1.00)	0.65 (0.42, 1.00)	0.64 (0.42, 0.97)	--	
		0.70	0.68	0.67	--	
Expressive language	Lowest quartile	23.4%	27.8%	25.5%	28.3%	0.094
		0.77 (0.58, 1.04)	0.98 (0.73, 1.31)	0.87 (0.65, 1.16)	--	
		0.83	0.98	0.90	--	
	Lowest decile	10.8%	10.8%	9.4%	11.8%	0.650
		0.90 (0.54, 1.51)	0.93 (0.55, 1.57)	0.78 (0.46, 1.32)	--	
		0.91	0.94	0.80	--	
Personal-social	Lowest quartile[d]	27.8%[b,c]	29.0%[b]	23.1%[c]	28.6%[b,c]	0.040
		0.96 (0.71, 1.30)	1.03 (0.75, 1.40)	0.75 (0.55, 1.03)	--	
		0.97	1.02	0.81	--	
	Lowest decile	11.2%	12.2%	11.0%	13.9%	0.305
		0.78 (0.51, 1.18)	0.88 (0.57, 1.34)	0.77 (0.50, 1.17)	--	
		0.80	0.88	0.79	--	
A-not-B correct	Lowest quartile	31.9%	28.3%	30.9%	35.3%	0.394
		0.86 (0.53, 1.38)	0.72 (0.44, 1.20)	0.82 (0.51, 1.31)	--	
		0.90	0.80	0.87	--	
	Lowest decile	17.4%	15.4%	15.9%	18.4%	0.748
		0.92 (0.51, 1.65)	0.79 (0.42, 1.48)	0.83 (0.46, 1.50)	--	
		0.94	0.84	0.86	--	

[a] Results presented as prevalence, OR (95% CI), RR

[b,c] Groups that do not share a common superscript differ significantly from each other ($p < 0.05$)

[d] IFA-LNS vs IFA-MNP, OR=1.37 (1.00, 1.89), RR=1.26

3.5 Impact on Child Hemoglobin and Micronutrient Status

3.5.1 Hemoglobin and Iron Status at 18 Months

This section presents results on the effect of the interventions on child hemoglobin and iron outcomes, measured at 18 months of age (endpoint for biochemical outcomes) and described in section 2.6.3.

A total of 1,346 mothers were randomly selected at enrollment for their children to be in the biochemical sub-sample. Of those, hemoglobin and iron biomarker data were available for 1,128 children (294 in the LNS-LNS group, 260 in the IFA-LNS group, 300 in the IFA-MNP group, and 274 in the IFA-Control group). This subsample represented 34% of the total number of children in the study at 18 months of age. Children included in the analysis did not differ from those not included with respect to the baseline characteristics of their mothers and households (data not shown), except for gestational age at enrollment, which was 12.9 (3.7) weeks for women whose children were included in these analyses and 13.2 (3.8) weeks for those not included (p=0.03).

Hemoglobin and Anemia

Table 12 shows that there were significant differences among intervention groups in hemoglobin concentration (p=0.001) in children at 18 months. Pairwise tests between the groups indicated that the LNS-LNS, IFA-LNS, and IFA-MNP groups all differed (positively) from the IFA-Control group, although the mean hemoglobin concentration among children in the IFA-MNP group was only marginally higher than in the IFA-Control group. In adjusted analyses (including season at birth, tube-well iron content quintile, and gestational age at enrollment), only the mean hemoglobin concentration among children in the LNS-LNS remained significantly higher than in the IFA-Control group (data not shown).

The prevalence of anemia was significantly different among intervention groups (p=0.008) (Table 13). Pairwise comparisons indicated that children in the LNS-LNS group had a lower rate of anemia than those in the IFA-Control group. Adjustment for pre-determined covariates yielded similar results (data not shown).

Ferritin

At 18 months, there were significant differences among intervention groups in ferritin levels, with or without correction for inflammation (Table 12). Pairwise tests between the groups indicated that the LNS-LNS, IFA-LNS, and IFA-MNP groups all had higher ferritin concentrations than the IFA-Control group.

The proportions of children with low ferritin at 18 months (Table 13) differed significantly among intervention groups (p<0.001 for both uncorrected and inflammation-corrected values). Pairwise comparisons indicated lower proportions of children with low ferritin in the LNS-LNS, IFA-LNS, and IFA-MNP groups than in the IFA-Control group, although the difference between the IFA-MNP and IFA-Control groups did not reach statistical significance when ferritin values were uncorrected (p=0.063).

Adjustment for pre-determined covariates (including season at birth, tube-well iron content quintile, and child sex for uncorrected ferritin; and season at birth, tube-well iron content quintile, child sex, maternal height, and primiparity for inflammation-corrected ferritin) yielded similar results, with the exception that the difference in the proportion of children with low ferritin (based on uncorrected values) became statistically significant between the IFA-MNP and the IFA-Control groups (data not shown).

sTfR

Overall, there were significant differences among intervention groups in sTfR concentrations (Table 12). Pairwise tests between the groups indicated that the LNS-LNS, IFA-LNS, and IFA-MNP groups all differed (lower concentrations, indicating higher iron status) from the IFA-Control group. In addition, the LNS-LNS group had lower values than the IFA-MNP group (p=0.032).

Adjustment for pre-determined covariates (including maternal education, maternal height, season at birth, and child's sex) yielded similar results, except for the difference in sTfR concentrations between the LNS-LNS and the IFA-MNP groups, which was attenuated (p=0.083) (data not shown).

There were significant differences among groups in the proportions of children with high sTfR (Table 13) at 18 months. Pairwise comparisons indicated a lower prevalence of high sTfR in the LNS-LNS group than in the IFA-MNP and the IFA-Control groups. Adjustment for pre-determined covariates yielded similar results (data not shown).

Iron Deficiency

Table 13 shows that there were significant differences in the prevalence of iron deficiency (ID) among intervention groups (p<0.001). Pairwise tests between the groups indicated that the prevalence in the LNS-LNS group was lower than in the IFA-Control and the IFA-MNP groups (p=0.012).

Adjustment for pre-determined covariates (including maternal height, gestational age at enrollment, season at birth, tube-well iron content quintile, and child's sex) yielded similar results, except that the prevalence of ID (based on uncorrected values) was significantly lower in the LNS-LNS than in the IFA-LNS group (data not shown).

Iron Deficiency Anemia

Overall, there were significant differences among intervention groups in the prevalence of iron deficiency anemia (IDA) (Table 13). Pairwise tests between the groups indicated that the LNS-LNS, IFA-LNS, and IFA-MNP groups all differed (lower prevalence) from the IFA-Control group, regardless of whether the values used were uncorrected or inflammation-corrected.

Adjustment for pre-determined covariates did not change these results (data not shown).

Table 12. Hemoglobin, Ferritin, Corrected Ferritin, and sTfR at 18 Months, by Intervention Group[a]

	Comprehensive LNS (LNS-LNS)	Child LNS (IFA-LNS)	Child MNP (IFA-MNP)	Control (IFA-Control)	P-value
Hemoglobin (g/L)[b]	117.3 ± 13.0[c]	115.5 ± 12.5[c]	115.2 ± 12.5[c,d]	112.3 ± 13.5[d]	0.001
Ferritin (µ/L)[f,g]	36.6 ± 1.9[c]	40.1 ± 1.9[c]	38.1 ± 2.0[c]	25.3 ± 2.1[d]	<0.001
Corrected ferritin (µ/L)[f,h]	33.6 ± 1.9[c]	35.7 ± 1.9[c]	33.5 ± 1.9[c]	22.6 ± 2.0[d]	<0.001
sTfR (mg/L)[f,i]	7.9 ± 1.3[c]	8.4 ± 1.4[c,d]	8.5 ± 1.4[d]	9.5 ± 1.5[e]	<0.001

[a] Values are means (or geometric means) ± SD

[b] LNS-LNS vs. IFA-Control, p<0.001; IFA-LNS vs. IFA-Control, p=0.034

[c,d,e] Groups that do not share a common superscript differ significantly from each other (p < 0.05)

[f] Hypothesis testing was conducted with transformed (natural logarithm) values; estimates were calculated by back transformation.

[g] LNS-LNS vs. IFA-Control, p<0.001; IFA-LNS vs. IFA-Control, p<0.001; IFA-MNP vs. IFA-Control, p<0.001

[h] Values were corrected for presence of inflammation. LNS-LNS vs. IFA-Control, p<0.001; IFA-LNS vs. IFA-Control, p<0.001; IFA-MNP vs. IFA-Control, p<0.001

[i] LNS-LNS vs. IFA-Control, p<0.001; IFA-LNS vs. IFA-Control, p=0.001; IFA-MNP vs. IFA-Control, p=0.001; LNS-LNS vs. IFA-MNP, p=0.032

Table 13. Prevalence of Anemia, Low Ferritin, High sTfR, ID and IDA at 18 Months, by Intervention Group[a]

		Comprehensive LNS (LNS-LNS)	Child LNS (IFA-LNS)	Child MNP (IFA-MNP)	Control (IFA-Control)	P-value
Anemia (Hb<110 g/L)[b]		25.9[c]	29.7[c,d]	31.0[c,d]	42.3[d]	0.008
		0.45 (0.24, 0.83)	0.57 (0.31, 1.06)	0.58 (0.32, 1.06)	--	
		0.58	0.70	0.70	--	
Low ferritin (<12.0 µg/L)	Uncorrected[e]	3.7[c]	4.2[c]	7.0[c,d]	13.5[d]	<0.001
		0.25 (0.10, 0.64)	0.28 (0.11, 0.73)	0.48 (0.22, 1. 03)	--	
		0.28	0.32	0.52	--	
	Corrected[f,g]	5.8[c]	5.4[c]	7.3[c]	18.3[d]	<0.001
		0.27 (0.13, 0.60)	0.25 (0.11, 0.59)	0.35 (0.17, 0.73)	--	
		0.32	0.28	0.41	--	
High sTfR (>8.3 mg/L)[h]		34.0[c]	44.6[c,d]	46.7[d]	52.6[d]	<0.001
		0.47 (0.29, 0.73)	0.73 (0.46, 1.15)	0.79 (0.51, 1.23)	--	
		0.65	0.85	0.89	--	
ID (ferritin<12.0 µg/L or sTfR>8.3 mg/L)	Uncorrected[i]	35.4[c]	45.4[c,d]	48.3[d]	54.7[d]	<0.001
		0.45 (0.29, 0.71)	0.69 (0.43, 1.09)	0.77 (0.50, 1.20)	--	
		0.65	0.83	0.88	--	
	Corrected[f,j]	35.4[c]	46.2[c,d]	48.3[d]	55.1[d]	<0.001
		0.45 (0.28, 0.70)	0.70 (0.44, 1.11)	0.76 (0.49, 1.19)	--	
		0.64	0.83	0.88	--	
IDA (ID and Hb<110 g/L)	Uncorrected[k]	13.6[c]	16.6[c]	18.0[c]	29.9[d]	<0.001
		0.37 (0.20, 0.67)	0.46 (0.25, 0.85)	0.51 (0.29, 0.90)	--	
		0.44	0.55	0.59	--	
	Corrected[f,l]	12.6[c]	15.8[c]	16.7[c]	29.6[d]	<0.001
		0.34 (0.18, 0.65)	0.44 (0.23, 0.85)	0.47 (0.25, 0.87)	--	
		0.42	0.51	0.55	--	

[a] Results presented as prevalence (%), OR (95% CI), RR
[b] LNS-LNS vs. IFA-Control, p=0.006
[c,d] Groups that do not share a common superscript differ significantly from each other ($p < 0.05$)
[e] LNS-LNS vs. IFA-Control, p=0.001; IFA-LNS vs. IFA-Control, p=0.004
[f] Based on values that were corrected for presence of inflammation
[g] LNS-LNS vs. IFA-Control, p<0.001; IFA-LNS vs. IFA-Control, p<0.001; IFA-MNP vs. IFA-Control, p=0.002
[h] LNS-LNS vs. IFA-Control, p<0.001; LNS-LNS vs. IFA-MNP, p=0.014
[i] LNS-LNS vs. IFA-Control, p<0.001; LNS-LNS vs. IFA-MNP, p=0.012
[j] LNS-LNS vs. IFA-Control, p<0.001; LNS-LNS vs. IFA-MNP, p=0.012
[k] LNS-LNS vs. IFA-Control, p<0.001; IFA-LNS vs. IFA-Control, p=0.007; IFA-MNP vs. IFA-Control, p=0.014
[l] LNS-LNS vs. IFA-Control, p<0.001; IFA-LNS vs. IFA-Control, p=0.008; IFA-MNP vs. IFA-Control, p=0.010

3.5.2 Vitamin A Status

This section reports results of the effect of the interventions on child vitamin A status measured at 18 months of age.

Vitamin A Status at 18 Months

A total of 1,346 mothers were randomly selected at enrollment for the analysis of their children's vitamin A status. Of those, RBP data were available for 1,110 children (292 in the LNS-LNS group, 251 in the IFA-LNS group, 297 in the IFA-MNP group, and 270 in the IFA-Control group). This subsample represented 33% of the total number of children in the study at 18 months of age. Children included in the analysis did not differ from those not included with respect to the baseline characteristics of their mothers and households (data not shown), except for gestational age at enrollment, which was 12.9 (3.8) weeks for women whose children were included in these analyses and 13.2 (3.8) weeks for those not included (p=0.04).

At 18 months, there were no significant differences between groups in RBP concentration, with or without correcting for the presence of inflammation (Table 14). With respect to prevalence of low vitamin A status (Table 15), there were significant differences between the groups (p = 0.025) when values were not corrected for inflammation. Pairwise tests indicated that the prevalence of low vitamin A status was lower in the LNS-LNS group than in the IFA-MNP group (55.5% vs 68.4%; p = 0.025). However, when the values were corrected for the presence of inflammation, there were no significant group differences. There were no group differences with respect to the prevalence of vitamin A deficiency, with or without correcting for inflammation.

Effect Modification

Only one of the interactions examined was significant: maternal BMI modified the effect of the intervention on the prevalence of vitamin A deficiency. However, this was observed only when RBP values were not corrected for inflammation, so these results are not reported.

Table 14. RBP Concentration at 18 Months, by Intervention Group (n=1,110)

Child outcomes[1]	Comprehensive LNS (LNS-LNS)	Child LNS (IFA-LNS)	Child MNP (IFA-MNP)	Control (IFA-Control)	P-value
RBP (µmol/L)[3]	1.13 ± 0.26	1.10 ± 0.28	1.09 ± 0.26	1.10 ± 0.30	0.215
Corrected RBP (µmol/L)[2,3]	1.19 ± 0.24	1.18 ± 0.26	1.17 ± 0.24	1.17 ± 0.28	0.616

[1] Mean ± SD

[2] Values were corrected for the presence of inflammation

[3] Hypothesis testing was conducted with transformed (natural logarithm) values; estimates were calculated by back transformation

Table 15. Prevalence of Low Vitamin A Status and Vitamin A Deficiency and Relative Risk at 18 Months, by Intervention Group (n=1,110)

Child outcomes[a]		Comprehensive LNS (LNS-LNS)	Child LNS (IFA-LNS)	Child MNP (IFA-MNP)	Control (IFA-Control)	P-value
Low vitamin A status (RBP<1.17 µmol/L)	Uncorrected[b]	55.5% [c]	61.4% [c,d]	68.4% [d]	60.7% [a,b]	0.025
		0.80 (0.21, 1.27)	1.02 (0.63, 1.66)	1.39 (0.87, 2.23)	--	
		0.88	1.01	1.24	--	
	Corrected[e]	50.0%	55.4%	55.2%	56.3%	0.435
		0.77 (0.49, 1.22)	0.59 (0.31, 1.11)	0.56 (0.31, 1.04)	--	
		0.87	0.98	0.98	--	
Vitamin A deficiency (RBP<0.83 µmol/L)	Uncorrected	13.7%	17.5%	15.5%	20.3%	0.207
		0.63 (0.34, 1.15)	0.84 (0.46, 1.52)	0.72 (0.40, 1.28)	--	
		0.68	0.86	0.75	--	
	Corrected[e]	8.6%	9.6%	8.8%	13.0%	0.289
		0.63 (0.30, 1.31)	0.71 (0.34, 1.49)	0.64 (0.31, 1.33)	--	
		0.66	0.74	0.68	--	

[a] Results presented as prevalence, RR

[b] LNS-LNS vs. IFA-MNP, p=0.013

[c,d] Groups that do not share a common superscript differ significantly from each other ($p < 0.05$)

[e] Based on values that were corrected for the presence of inflammation

3.6 Postnatal Health Care Expenditures

This section reports results on the effects of the intervention on household health care-seeking behavior and on health care expenditures for study children. Results are reported independently by survey round for two reasons. First, the survey questionnaire only collected recall information for approximately half the intervention period, not the entire study period. Second, we could more readily exclude households with missing or unknown health care expenditure information from a single round than from the entire sample. Thus, presenting results by round allowed us to maintain a larger dataset.

3.6.1 Health Care-Seeking Behavior from 6–24 Months of Age

Health care-seeking data, defined as the number of visits to a health facility for whatever reason by study children within 3 months prior to the interview date, were available for all 3,371 households for each round (6, 12, 18, and 24 months). Covariate-adjusted mean numbers of visits by treatment arm and survey round are presented in Figure 18.

There were no statistically significant differences among study groups (LNS-LNS, IFA-LNS, IFA-MNP, IFA-Control) in the number of visits to health facilities in any given round. The average number of visits for the entire sample was 2.5 at ages 3–6 months (first survey round); 2.7 at ages 9–12 months (second survey round); 2.4 at ages 15–18 months (third survey round); and 2.1 at ages 21–24 months (fourth and

final survey round). This corresponded to an average of approximately 1 visit every 5–6 weeks, and was significantly lower in the last round compared to the first.[2]

Several household covariates were associated with care-seeking behavior ($p < 0.05$) in expected ways. The household asset index was positively associated with the number of care-seeking visits in every round except at 24 months. Household food security was also positively associated with the number of care-seeking visits in every round (i.e., more secure households reported more visits). The number of other children under 5 in the household was negatively associated with the number of care-seeking visits in every round; joint and nuclear households did not differ in the number of care-seeking visits when controlling for the total number of children under 5. Maternal age (in all rounds except at 24 months) and education (in all rounds) were positively associated with the number of child health care visits, but paternal education was not associated with care-seeking behavior in any round.

3.6.2 Health Care Expenditures from 6–24 Months of Age

Health care expenditure data (in takas, 70tk=US$1[3]) were available for 3,236 households at the 6-month visit; 3,069 households at the 12-month visit; 3,142 households at the 18-month visit; and 3,236 households at the 24-month visit. Covariate-adjusted mean household child health care expenditures by treatment arm and survey round are presented in Figure 19.

There were no statistically significant differences between study groups in the amount of money spent on health care for study children during any round. Mean expenditures (for the entire sample) per child per round were 435tk (US$6.2) at 3–6 months; 389tk (US$5.56) at 9–12 months; 355tk (US$5.07) at 15–18 months; and 278tk (US$3.97) at 21–24 months. In terms of US dollars, expenditures decreased from a little over $2/month for newborn infants to about $1.30/month for children 21–24 months.[4] The decrease in expenditures across rounds was statistically significant when we compared the 6-month and 24-month visits. This mirrors the trend of decreasing expenditures with child age (Figure 19).

As with numbers of visits, health expenditures on study children were correlated with household and parental characteristics in expected ways. However, associations with expenditures were weaker and estimates were less precise than between household and parental characteristics and the number of care-seeking visits. The household asset index was positively associated with health care expenditures in all rounds, but in some cases, the associations were marginally significant and household food insecurity was not significantly associated with expenditures in any round. Parental education (maternal at 6 months and 18 months; paternal at 24 months) and maternal age (at 18 months) were significantly associated with expenditures in some rounds, but not others; no clear pattern of the direction of these associations emerged over time.

3.6.3 Time Lost by Caregivers for Child Health Care from 6–24 Months of Age

We measured household time lost by caregivers due to child sickness as the numbers of days in which the respondent or another family member were unable to perform their regular duties to care for the study child during illness. Household data were available for all 3,371 households (all rounds) on time spent by

[2] For each health care-seeking and health care expenditure outcome, we tested whether the mean from the first round was equal to the mean from the last round, accounting for clustering of treatment assignment. We did this because all the outcomes trended in only one direction (downward) across age. Testing the first and last rounds maximized power while retaining comparability across rounds.

[3] This exchange rate is an approximation over the study period. Exchange rates have hovered between 70 and 80 takas/US$ since 2013.

[4] Recall windows were 3 months, and so we divided the mean difference by 3 to generate a monthly rate.

any household member on caring for sick children. Covariate-adjusted mean number of days lost to sick child care are presented by treatment arm and survey round (Figure 20).

The mean amount of time spent tending to sick children (for the entire sample) was 1.3 days at 3–6 months; 1.2 days at 9–12 months; 0.9 days at 15–18 months; and 0.6 days at 21–24 months. Again, comparing the first and last rounds, there was a statistically significant decline.

There was one statistically significant group difference in the amount of time spent tending to sick children: in the round covering 21–24 months (final survey round), households in the control arm spent significantly less time on care for their sick children than did households in the IFA-MNP group (d = 0.26 days, p=.007). All other comparisons and rounds showed no significant differences.

Maternal age was positively associated (marginally, in some rounds) with time spent tending to sick children in all rounds and maternal education was positively associated with time spent on sick child care in the 12-month and 18-month rounds. Higher food insecurity was significantly associated with less time spent on sick child care in the 12-month round. In general, estimates of associations with time spent on sick child care were less precise than for the number of clinic visits and health care expenditures.

Figure 18. Number of Health Care-Seeking Visits for Study Children 6 to 24 Months

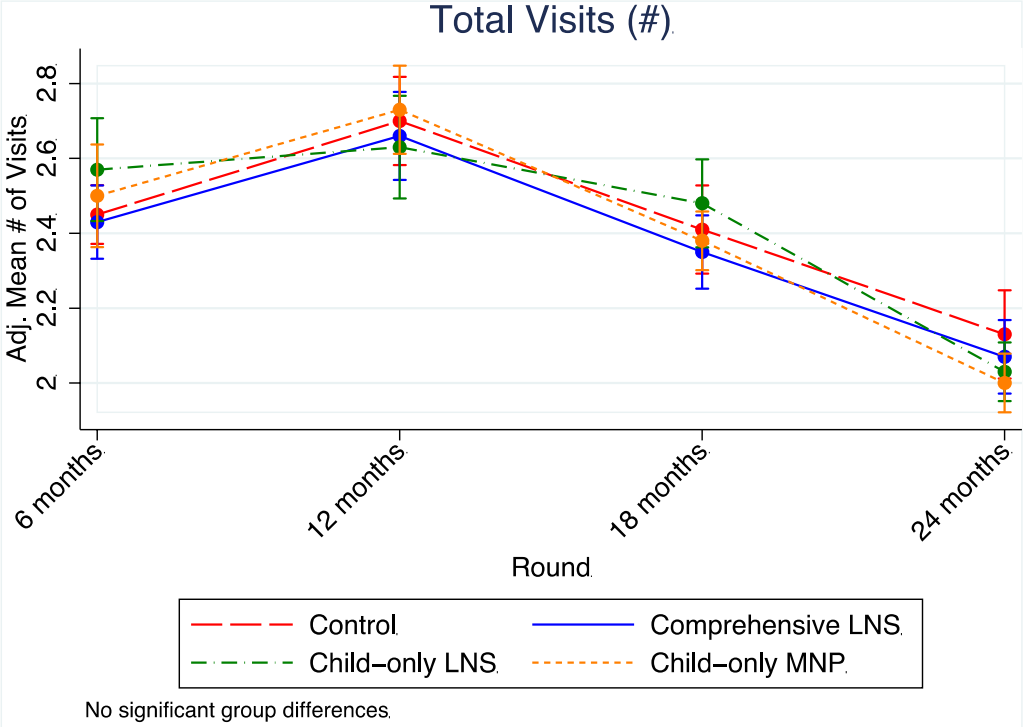


Figure 19. Expenditures on Health Care for Study Children 6 to 24 Months

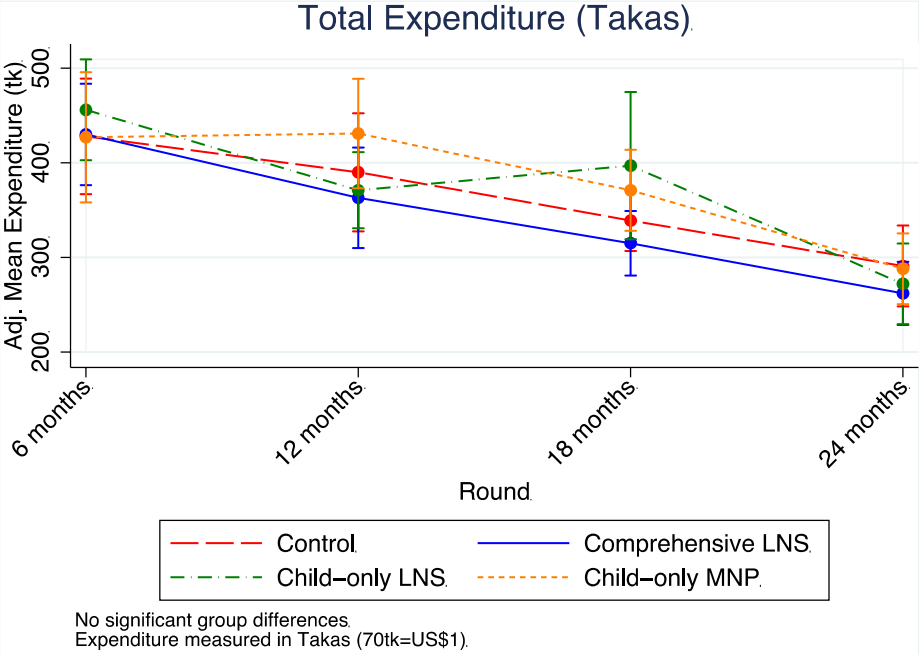
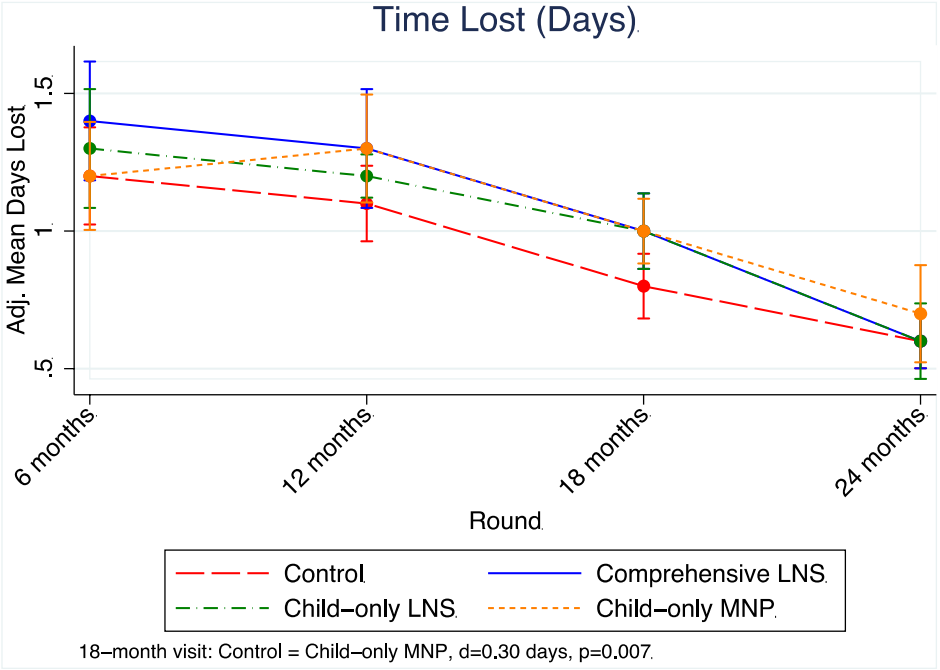


Figure 20. Amount of Time Lost by Household Members to Care for Sick Children 6 to 24 Months



4. Discussion

4.1 Child Growth

There were significant positive effects of small-quantity LNS on the primary outcome, LAZ at 24 months. Pairwise comparisons between intervention groups showed the greatest difference in LAZ between children in the Comprehensive LNS and Child MNP groups (+0.13 Z). This difference was already apparent by 6 months of age and was *not* due to reduced growth in the MNP group between 6 and 24 months. By 24 months, only the Comprehensive LNS group differed significantly from any of the other groups, but the mean LAZ scores at 24 months for the Comprehensive LNS and Child LNS groups were very similar (-1.72 vs. -1.73). Even though mean LAZ at birth was slighter greater in the Comprehensive LNS group (+0.09 Z), the Child LNS group achieved the same mean length by 24 months. Significant differences in stunting prevalence were evident at 18 months, when there was a 20% reduction in stunting in the Comprehensive LNS group compared to the MNP group (7.8 percentage points). By 24 months, the difference in stunting prevalence between those two groups was 5.2 percentage points, but was not statistically significant.

There were also positive effects of LNS on HCZ, with a significant difference of 0.15 Z between the Comprehensive LNS and Control groups at 24 months. The difference between these two groups in the prevalence of small head size (< -2 Z) at 24 months was marginally significant overall (11% reduction), but highly significant among girls (33% reduction).

Although we did not hypothesize differences in WLZ or wasting, there was a significant effect of LNS on these outcomes at 18 months (but not at 24 months), with a significant pairwise difference between the Child LNS and Control groups. Wasting at 18 months was reduced by 27% in the Child LNS group (and by a non-significant 20% in the Comprehensive LNS group).

There was no effect of maternal LNS-PL vs. IFA on postnatal growth from birth to 6 months. From 6 to 24 months, there was a small but significant increase in the length and head circumference of children given LNS, as compared to the controls (though the difference in attained size at 24 months was already largely present at birth in the Comprehensive LNS group). There was no effect of MNP on the postnatal growth rate.

In comparable intervention trials using small-quantity LNS (SQ-LNS), supplementation generally ended at 18 months. In Malawi, no impact on linear growth was observed with postnatal supplementation (Maleta et al. 2015) or with combined pre- and postnatal supplementation (Ashorn et al. 2015). By contrast, in Ghana, combined pre- and postnatal small-quantity LNS supplementation increased linear growth (+0.28 LAZ) and reduced stunting (by 41%, or 6.2 percentage points, from 15.1% in the control group to 8.9% in the SQ-LNS group) (Adu-Afarwuah et al. 2016). In the JiVita-4 efficacy trial conducted in the same area of Bangladesh as the RDNS (Christian et al. 2015), there was a small but significant effect of three different formulations of postnatal small/medium-quantity LNS on LAZ at 18 months (+0.07–0.10 Z) and a reduction in stunting of 5–6 percentage points with two of these LNS formulations, in comparison to a control group that received nutrition counseling only. In the RDNS, the effects of combined pre- and postnatal SQ-LNS on linear growth and stunting at 18 months were similar to the impact of postnatal supplementation seen in the JiVita-4 trial (Table 16).

Table 16. Comparison of Effect of LNS on Linear Growth Outcomes at 18 Months in the RDNS and JiVita-4 Trials

Outcome	RDNS	JiVita-4
LAZ at 6 months (Control)	-1.3	-1.3
LAZ at 18 months (Control)	-1.7	-1.9
Effect of LNS intervention (LAZ difference at 18 months)	+0.05 (Child-only LNS vs Control) +0.06 (Comprehensive LNS vs Control) +0.12 (Child-only LNS vs Child-only MNP) +0.13 (Comprehensive LNS vs Child-only MNP)	+0.10 (Plumpy'doz vs Control) +0.08 (Chickpea LNS vs Control) +0.07 (Rice-lentil LNS vs Control)
Prevalence of stunting at 18 months	35.2% Control 38.6% Child-only MNP 34.1% Child-only LNS 30.8% Comprehensive LNS	44.2% Control 40.3% Plumpy'doz 39.1% Chickpea LNS 43.7% Rice-lentil LNS
Reduction in stunting prevalence at 18 months (percentage point difference compared to control group)	-4.4 (Comprehensive LNS vs Control) -7.8 (Comprehensive LNS vs Child-only MNP)	-5.0 (Plumpy'doz) -6.2 (Chickpea LNS) -2.2 (Rice-lentil LNS)

4.2 Child Development

The RDNS intervention had significant positive effects on child development at 24 months, with the most consistent effects observed in language development.

4.2.1 Motor Development

Motor development scores differed significantly by intervention group. Pairwise tests showed that the Child MNP group had higher mean scores than the Control group, though mean scores were very similar among the three intervention groups (Comprehensive LNS, Child LNS, and Child MNP). The proportion of children in the lowest quartile and lowest decile for motor development scores did not differ by intervention group.

In two efficacy trials conducted in Africa (one in Malawi, n=869, and the other in Ghana, n=1,320), in which pregnant women were provided with either IFA, multiple micronutrients, or LNS, and the children of women in the LNS group also received LNS from 6 to 18 months, no significant group differences were observed in motor development scores or the proportion of children in the lowest decile or lowest

quartile at 18 months (Prado et al. 2016a; Prado et al. 2016b). However, the study designs (including duration of supplementation) and the children's age at final measurement were not the same as in the RDNS.

Subgroup analysis in the RDNS sample indicated that among households with low home stimulation scores, children in the Child MNP and Comprehensive LNS groups had higher motor development scores than those in the Control group. No group differences were observed among children from households with high home stimulation scores. These findings highlight the potential of MNP and LNS to benefit children who may be at high risk of motor development delays.

4.2.2 Language Development

Consistent beneficial effects of the interventions were observed on children's language development. Children in all three intervention groups had higher scores in comprehensive language, and those in the Comprehensive LNS and Child MNP groups had higher scores in expressive language, when compared to those in the Control group. For comprehensive language, there were lower proportions of children in the Comprehensive LNS and Child LNS groups in the lowest quartile, and in the Child LNS and Child MNP groups in the lowest decile, when compared to the Control group. No differences in the proportion of children in the lowest decile or quartile were observed for expressive language. These results differed from those reported in the Africa trials using a very similar language tool with younger (18-month-old) children, where no significant effects were observed (Prado et al. 2016a; Prado et al. 2016b). The older age of the children in the RDNS may explain these conflicting results, given that increasing (almost explosive) language development occurs during the first 2–3 years of life, potentially making any supplementation effects more evident in older children.

Several characteristics modified the effect of the intervention on language development. Among children whose mothers were enrolled early in their pregnancies, those in the intervention groups (in particular the Comprehensive LNS and Child LNS groups) had better receptive language performance than those in the Control group. Women who enrolled early in their pregnancies may have differed in ways that enhanced the effect of the intervention, for instance in their level of health awareness. It is also possible that this result is due to chance.

The household asset index, a proxy for SES, also modified the effect of the intervention on language. Among children from households with an asset score below the median, the Comprehensive LNS group had a lower proportion of children in the lowest quartile, and those in the Comprehensive LNS and Child MNP groups had higher expressive language scores than those in the Control group. No differences were observed among children from households with higher asset scores. Low SES is a well-known risk factor for poor developmental outcomes (Grantham-McGregor, et al. 2007), affecting language, in particular (Farah et al. 2006). Thus, this result may indicate that pre-and postnatal LNS supplementation and postnatal MNP supplementation are particularly beneficial among children at high risk of poor language development.

Among female children, the Comprehensive LNS and Child MNP groups had lower proportions in the lowest decile for comprehensive language compared to the Control group, while no differences were observed among males. These results are quite interesting given that the effect of the intervention on the proportion of children with small head circumference was also observed among females, but not males.

4.2.3 Personal-Social Development

We did not observe any significant group differences in personal-social development scores. These results are consistent with those reported in the Africa trials at 18 months, although the socioemotional tool used in those trials was different (Prado et al. 2016a; Prado et al. 2016b). With regard to the categorical outcomes, the Child LNS group had a higher proportion of children in the lowest quartile, compared to the Child MNP group; no other significant differences were observed.

4.2.4 Executive Function

No significant differences among groups were observed for children's executive function at 24 months of age. Similar results were reported in the Malawi and Ghana trials at 18 months of age, using the same executive function task (i.e., A-not-B task) (Prado et al. 2016a; Prado et al. 2016b). Brain development of the prefrontal cortex, which is responsible for higher cognitive functions such as executive function, peaks during the first and second years of life, but significant development still occurs after the first 2 years (Thompson and Nelson 2001). Thus, it is possible that any benefits of nutritional supplementation will become evident at a later age. Another potential explanation for these results may relate to the difficulty of measuring executive function in young children, and furthermore, from a rural area.

However, we did observe a lower proportion of children in the lowest quartile in the Child LNS vs. Control group among females. Sex differences, favoring girls, have been observed in executive function tasks among older children (Wiebe et al. 2008).

4.3 Child Hemoglobin and Micronutrient Status

The RDNS intervention had significant positive effects on all child hemoglobin and iron status outcomes at 18 months, with the Comprehensive LNS group showing the strongest and most consistent effects.

Systematic reviews have indicated that home fortification with MNP (including 5–15 micronutrients) is an effective strategy for reducing anemia (De-Regil et al. 2013) and iron deficiency (ID) (De-Regil et al. 2013; Dewey et al. 2009) in infants and young children, with an overall (relative) reduction in anemia and ID prevalence of 31% (RR:0.69, 95% CI:0.60–0.78) and 51% (RR: 0.49, 95% CI:0.35–0.67), respectively (De-Regil et al. 2013). In our study, the Child MNP and Child LNS groups showed similar (relative) reductions in anemia when compared to the Control group (30% and 27% in the Child LNS and Child MNP groups, respectively) indicating that LNS was as effective as MNP for anemia reduction. The relative reduction in anemia among children in the Comprehensive LNS group was even greater (39%), although not significantly different from the other two intervention groups. These results suggest that starting LNS supplementation prenatally may provide an additional benefit for anemia reduction in children. It is noteworthy that the women in the Comprehensive LNS group received less iron during pregnancy (20 mg/d) than those in the other groups (60 mg/d), yet their children had the highest hemoglobin concentrations at 18 months.

Provision of MNP (12.5 mg of iron) to Cambodian infants and young children from 6 to 18 months resulted in higher ferritin levels, when compared to those given placebo (Giovannini et al. 2006). In Ghana, LNS (9 mg of iron) and MNP (12.5 mg of iron) supplementation from 6 to 12 months of age resulted in greater ferritin and lower sTfR, when compared to a no-intervention group (Adu-Afarwuah et al. 2008). To our knowledge, there are no published results of the effects of LNS provided both pre- and postnatally on children's iron status.

In our study, the interventions reduced ID (inflammation-corrected) by 12% (Child MNP), 16% (Child LNS), and 36% (Comprehensive LNS). Although none of these reductions was as large as reported in the systematic review by De-Regil et al. (2013), the Comprehensive LNS approach appears to be the most

efficacious for reducing ID in this population, as it was the only intervention that resulted in a significantly lower prevalence (vs. the Control group).

With regard to iron deficiency anemia (IDA), all three interventions resulted in larger relative reductions than those observed for ID: the interventions reduced IDA (inflammation-corrected) by 44% (Child MNP), 47% (Child LNS), and 57% (Comprehensive LNS). De-Regil et al. (2013) did not report meta-analysis results for IDA.

With regard to vitamin A status, average retinol-binding protein (RBP) concentration and prevalence of vitamin A deficiency did not differ significantly between groups, with or without correcting for inflammation. Low vitamin A prevalence was higher in the MNP group compared to the Comprehensive LNS group when the values were not corrected for inflammation, but not when using corrected values; this was because the prevalence of inflammation was somewhat higher in the MNP group, not because there was a true difference in vitamin A status. The prevalence of vitamin A deficiency (defined as RBP < 0.83 µmol/L) in the RDNS at 18 months of age (13% in the Control group after correcting for inflammation) was lower than the prevalence (defined as serum retinol < 0.70 µmol/L) among rural preschool children (6–59 months of age) in the most recent National Micronutrient Status Survey (NMSS) of Bangladesh (20.5% after correcting for inflammation; NMSS 2013). Our data revealed that a large proportion of RDNS children in all groups received large-dose vitamin A supplements (76% to 81% between 6 and 12 months; 79% to 82% between 12 and 18 months). Therefore, the lack of differences in vitamin A status between the intervention groups may be explained by the high coverage of vitamin A supplements as part of the Expanded Program on Immunization Plus of the Government of Bangladesh.

4.4 Health Care Expenditures

Economic theory is ambiguous about the potential effect of treatment with nutritional supplements on the time and out-of-pocket expenditures that households allocate to their children (Dupas, 2011). For example, the biological effects of treatment may directly affect observable short-term health outcomes, and thus influence health care seeking decisions. Under this scenario, LNS supplementation could affect either the *observed* frequency or severity of child illnesses, thereby triggering changes in care-seeking behavior and/or health care expenditures for the child. Also, *expected* LNS treatment effects can influence household health care-seeking behaviors. For example, if households expect that their children will be healthier than they otherwise would have been (due to their consumption of LNS), they may be more or less likely to seek treatment for their children, and/or more or less inclined towards expensive treatments when they do seek care. Our analysis examines the net effects of both biological and behavioral mechanisms to help answer an important economic and policy question regarding the links between health and demand for health care: does improvement in early-life nutritional status increase or decrease health care demand for young children?

We found only one statistically significant group difference in any health care-seeking behavior category after adjusting p-values for multiple-comparisons: Control group households spent less time caring for sick children than those in the Child-only MNP group.[5] Despite the lack of consistent patterns in measurable treatment effects, the results provide important insights into household health care seeking behaviors.

In order to determine whether and/or how households adapted health care-seeking decision-making, we examined the number of times households took their children to seek medical care. We found no significant group differences in the number of times households took children to seek medical care,

[5] Because of the number of comparisons, we would expect at least one statistically significant result purely by chance, even if there was no treatment effect.

indicating that households in our sample did not strongly adapt their health care-seeking behaviors in response to treatment. These estimates were fairly precise, with standard errors of less than 0.1 visits per round for dichotomous variables across the treatment groups.

Despite a lack of group differences in number of visits, expenditures at each visit still may have changed if households adjusted *how much* they spent (or were willing to spend) on treatments when they sought care for sick children. In order to address this possibility, we tested for group differences in total health care expenditures for care-seeking visits. We found no statistically significant differences in total health care expenditure across treatment groups, and standard errors were reasonably small (approximately 10% of total expenditure, relative to the control) for dichotomous variables across the treatment groups.

One final decision available to households is the amount of time spent tending to sick children. To test for group differences, we examined mean household time spent on caring for sick children by treatment group. This consisted of the total time when *any* household member could not perform her/his regular duties because s/he was occupied providing care to a sick child, including time spent going to/from health care facilities. We found one significant difference across the study groups, between the Control and the Child MNP groups, but only in the 18-month round. We did not consider this particularly strong evidence of any effect of the intervention on household decision-making. However, we noted that Control group participants reported losing relatively little time to tend to sick children in every round, on average. Again, standard errors were fairly small (between 0.1 and 0.2 days lost per round, or 3-month window) for dichotomous variables across the treatment groups.

While, we did not find evidence of any effects of LNS treatment on any of our primary health care outcomes we did find evidence that our health care expenditure measures were sufficiently precise to capture other important associations: expenditures varied in expected ways along key socioeconomic dimensions, including parental age and education as well as household asset and food security indices. In addition, our confidence intervals were sufficiently precise to rule out very large effects of treatment on health care-seeking behavior, health care expenditures, and time lost by caregivers on child health care. We thus concluded that broad provision of LNS is unlikely to have strong effects on the health care-seeking decisions of families in similarly poor, rural households.

4.5 Strengths and Limitations

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 more than 4,000 women, who were representative of the target population, 3) a low rate of attrition (mostly due to travel out of the study area rather than refusal to participate), and 4) use of well-trained and standardized anthropometrists, who performed measurements according to WHO guidelines.

Among the limitations were a disruption (beyond our control) in the supply of LNS-PL for a period of 10 weeks, which compromised our ability to investigate the full potential of Comprehensive LNS as an intervention. Second, it was not possible to blind the participants 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 relied on reported health care expenditures, time lost due to illnesses, and supplement consumption (to assess adherence), instead of direct observation, so these data may have been reported inaccurately. Finally, we examined effects within several targeted subgroups, and the effect modification results need to be interpreted with caution due to the number of hypotheses being tested.

4.6 Conclusions

Significant, though modest, increases in linear growth and head size (and reductions in stunting at 18 months), were achieved in the RDNS, with the Comprehensive LNS group showing the largest differences in comparison to the Control group (for head size) and the Child MNP group (for linear growth). All three intervention groups exhibited significant improvements in child development at 24 months, with the most consistent effects observed in language development. This suggests that the micronutrients provided by both LNS and MNP can have a positive impact on development, whereas the growth response was evident only among children who received the additional macro- and micronutrients provided in LNS. All three intervention groups also exhibited significant improvements in child hemoglobin and iron status at 18 months, with the Comprehensive LNS group showing the strongest and most consistent differences relative to the Control group. By contrast, there were no differences in vitamin A status between the intervention groups, probably because most children in the groups were already receiving high-dose vitamin A supplements on a regular basis. There was no evidence that the interventions altered health care-seeking behaviors for the study children, measured in terms of number of visits to health care providers, total expenditures, and time lost to tend to sick children.

Because this study was conducted within a community-based health program, the findings should be relevant to programs targeting similar populations. The programmatic implications depend on the goals of decision-makers. If the goal is to improve child growth, provision of both pre- and postnatal LNS appears to be the most effective approach, but also the costliest. By contrast, MNP had no growth-promoting effect in the RDNS, which is consistent with results of systematic reviews (DeRegil et al. 2013; Salam et al. 2013). This has important policy implications because MNP distribution is being scaled-up nationally in Bangladesh and in other countries (Home Fortification Technical Advisory Group 2016), mainly to reduce anemia. Although enhanced formulations of MNP with 22 micronutrients may promote growth in low birth weight infants (Shafique et al. 2015), their efficacy and effectiveness for the general infant population have not been tested. Moreover, replicating the amounts of micronutrients that are provided via LNS may require two sachets of MNP per day (Olney et al. 2012), which may increase costs and compromise adherence, while failing to address the potential need for macronutrients such as essential fatty acids and high-quality protein. It should be noted that postnatal growth faltering in this study and in others (Hess et al. 2015; Christian et al. 2015) was still evident (though reduced), despite provision of fortified supplements. Thus, the impact of fortified supplements like LNS should continue to be evaluated in the context of comprehensive strategies that target multiple causes of poor growth (Dewey 2016).

If the goal of program planners is to reduce iron-deficiency anemia or improve child development (but not growth), all three interventions tested in the RDNS appear to be effective, though anemia reduction was greatest in the Comprehensive LNS group. An important question to consider is, to what extent can the effects of these interventions on growth and development be sustained beyond the intervention period? Data from a follow-up of the RDNS cohort, undertaken when the children were 40–52 months of age, will help answer this question.

5. References

Abubakar, A.; Holding, P.; Van Baar, A.; Newton, C.; Van de Vijver, F.; Espy, K. 2013. "The performance of children prenatally exposed to HIV on the a-not-b task in Kilifi, Kenya: a preliminary study." *International Journal of Environmental Research and Public Health*. 10: 4132.

Adu-Afarwuah, S.; Lartey, A.; Brown, K.; Zlotkin, S.; Briend, A.; Dewey, K. 2008. "Home fortification of complementary foods with micronutrient supplements is well accepted and has positive effects on infant iron status in Ghana." *American Journal of Clinical Nutrition*. 87: 929–38.

Adu-Afarwuah, S.; Lartey, A.; Okronipa, H.; Ashorn, P.; Peerson, J.M.; et al. 2016. "Small-quantity lipid-based nutrient supplements provided to women during pregnancy and 6 mo postpartum, and to their infants from 6 mo of age, increases child linear growth status by18 mo of age in semi-urban Ghana: a randomized controlled trial." *American Journal of Clinical Nutrition*. 104(3): 797–808

Arimond, M., et al. 2013. "Considerations in developing lipid-based nutrient supplements for prevention of undernutrition: experience from the international lipid-based nutrient supplements (iLiNS) project." *Maternal and Child Nutrition*. 11 Suppl 4: 31–61.

Ashorn, P.; Alho, L.; Ashorn, U.; Cheung, Y.B.; Dewey, K.G.; et al. 2015. "Supplementation of maternal diets during pregnancy and for 6 months postpartum and infant diets thereafter with small-quantity lipid-based nutrient supplements does not promote child growth by 18 months of age in rural Malawi: a randomized controlled trial." (Abstract). *Journal of Nutrition*. 145(6): 1345–53.

Bangladesh Bureau of Statistics. 2011a. "Community Report. Rangpur Zila." *Bangladesh Population and Housing Census.* Available at http://203.112.218.66/PageWebMenuContent.aspx?MenuKey=480.

Bangladesh Bureau of Statistics. 2011b. "Community Report. Dinajpur Zila." *Bangladesh Population and Housing Census.* Available at http://203.112.218.66/PageWebMenuContent.aspx?MenuKey=474.

Bogard, J.R.; Hother, A.L.; Saha, M.; Bose, S.; Kabir, H.; et al. 2015. "Inclusion of small indigenous fish improves nutritional quality during the first 1000 days." *Food Nutrition Bulletin.* 36(3): 276–289.

Caldwell, B.M. and Bradley, R.H. 2003. *Home Observation for Measurement of the Environment: Administration Manual*. Tempe, AZ: Family & Human Dynamics Research Institute, Arizona State University.

CDC. 2014. "Cronobacter." 02/12/2014 [cited 2014 06/06]. Available at: http://www.cdc.gov/cronobacter/technical.html.

Christian, P.; Shaikh, S.; Shamim, A.A.; Mehra, S.; Wu, L.; Mitra, M.; et al. 2015. "Effect of fortified complementary food supplementation on child growth in rural Bangladesh: a cluster-randomized trial." *International Journal of Epidemiology*. 44(6): 1862–76.

Coates, J. and Swindale, A. 2007. *Household Food Insecurity Access Scale (HFIAS) for Measurement of Household Food Access: Indicator Guide (v. 3)*. Washington, DC: FHI 360/FANTA.

Dewey, K.; Yang, Z.; Boy, E. 2009. "Systematic review and meta-analysis of home fortification of complementary foods." *Maternal Child Nutrition*. 5:283–321.

Dewey, K.G. 2016. "Reducing stunting by improving maternal, infant and young child nutrition in regions such as South Asia: evidence, challenges and opportunities." *Maternal Child Nutrition*. 12 Suppl 1: 27–38.

Dewey, Kathryn G.; Mridha, Malay K.; Matias, Susana L.; Cummins, Joseph R.; Peerson, Janet M.; et al. 2016. *Effectiveness of a Lipid-Based Nutrient Supplement (LNS) Intervention on Pregnancy and Birth Outcomes in Bangladesh*. Washington, DC: FHI 360/FANTA.

Dupas, P. 2011. "Health behavior in developing countries." *Annual Review of Economics. 3*(1): 425–449.

Engle-Stone, R.; et al. 2011. "Plasma retinol binding protein predicts plasma retinol concentration in both infected and uninfected Cameroonian women and children." *Journal of Nutrition.* 141: 2233–2241.

Erhardt, J.G.; et al. 2004. "Combined measurement of ferritin, soluble transferrin receptor, retinol binding protein, and c-reactive protein by an inexpensive, sensitive, and simple sandwich enzyme-linked immunosorbent assay technique." *Journal of Nutrition.* 134: 3127–3132.

Espy, K.A.; Kaufmann, P.M.; McDiarmid, M.D.; Glisky, M.L. 1999. "Executive functioning in preschool children: performance on a-not-b and other delayed response format tasks." *Brain and Cognition*. 41:178–99.

Farah, M.J.; Shera, D.M.; Savage, J.H.; Betancourt, L.; Giannetta, J.M.; et al. 2006. "Childhood poverty: specific associations with neurocognitive development." *Brain Research*. 1110: 166–74.

Fenson, L.; Marchman, V.A.; Thal, D.J.; Dale, P.S.; Reznick, J.S.; Bates, E. 2007. *MacArthur-Bates Communicative Development Inventories: User's Guide and Technical Manual, Second Edition*. Baltimore: Brookes Publishing.

Fiedler, J.L.; Lividini, K.; Bermudez, O.I. 2015. "Estimating the impact of vitamin A-fortified vegetable oil in Bangladesh in the absence of dietary assessment data." *Public Health Nutritition.* 18(3): 414–420.

Giovannini, M.; Sala, D.; Usuelli, M.; Livio, L.; Francescato, G. 2006. "Double-blind, placebo-controlled trial comparing effects of supplementation with two different combinations of micronutrients delivered as sprinkles on growth, anemia, and iron deficiency in Cambodian infants." *Journal of Pediatric Gastroenterology and Nutrition*. 42: 306–12.

Grantham-McGregor, S.; Cheung, Y.B.; Cueto, S.; Glewwe, P.; Richter, L.; Strupp, B. 2007. "Developmental potential in the first 5 years for children in developing countries." *The Lancet*. 369: 60–70.

Hamadani, J.; Baker-Henningham, H.; Tofail, F.; Mehrin, F.; Huda, S.; Grantham-McGregor, S. 2010. "The vailidity and reliability of mothers' report language development in one year old children in a large survey in Bangladesh." *Food and Nutrition Bulletin* 31: S198–S206.

Hamadani, J.D.; Tofail, F.; Hilaly, A.; Huda, S.N.; Engle, P.; Grantham-McGregor, S.M. 2010. "Use of family care indicators and their relationship with child development in Bangladesh." *Journal of Health, Population, and Nutrition*. 28(1): 23–33.

Hess, S.Y.; Abbeddou, S.; Jimenez, E.Y.; Some, J.W.; Vosti, S.A.; et al. 2015. "Small-quantity lipid-based nutrient supplements, regardless of their zinc content, increase growth and reduce the prevalence of stunting and wasting in young burkinabe children: a cluster-randomized trial." *PLoS One*. 10:e0122242.

Home Fortification Technical Advisory Group (HF-TAG) website: http://www.hftag.org/, accessed September 8, 2016.

Lazzerini, M. 2013. "Commentary on 'Home fortification of foods with multiple micronutrient powders for health and nutrition in children under two years of age.'" *Evidence-Based Child Health*. 8:112–201.

Maleta, K.M.; Phuka, J.; Alho, L.; Cheung, Y.B.; Dewey, K.G.; et al. 2015. "Provision of 10–40 g/d lipid-based nutrient supplements from 6 to 18 months of age does not prevent linear growth faltering in Malawi." *Journal of Nutrition*. doi:10.3945/jn.114.208181 [epub ahead of print].

McNutt, L.A.; Wu, C.; Xue, X; Hafner, J.P. 2003. "Estimating the relative risk in cohort studies and clinical trials of common outcomes." *American Journal of Epidemiology*. 157(10): 940–943.

Nampijja, M.; Apule, B.; Lule, S.; Akurut, H.; Muhangi, L.; et al. 2012. "Effects of maternal worm infections and anthelminthic treatment during pregnancy on infant motor and neurocognitive functioning." *Journal of the International Neuropsychological Society*. 18: 1019–30.

National Institute of Population Research and Training (NIPORT); Mitra and Associates; and ICF International. 2013. *Bangladesh Demographic and Health Survey 2011*. Dhaka, Bangladesh, and Calverton, MD: NIPORT, Mitra and Associates, and ICF International.

National Institute of Population Research and Training (NIPORT), Mitra and Associates, and ICF International. 2016. *Bangladesh Demographic and Health Survey 2014*. Dhaka, Bangladesh, and Rockville, MD: NIPORT, Mitra and Associates, and ICF International.

NMSS. 2013. *National Micronutrients Status Survey 2011–12*. Dhaka, Bangladesh: icddr,b, UNICEF, Bangladesh, GAIN, Institute of Public Health Nutrition.

Olney, D.; Arriola, R.; Carranza, R.; Leroy, J.; Richter, S.; et al. 2012. *Report of Formative Research Conducted in Alta Verapaz, Guatemala, to Help Inform the Health-Strengthening Activities and the Social and Behavior Change Communication Strategy That Will Be Implemented through Mercy Corps PM2A Program – PROCOMIDA*. Washington, DC: FHI 360/FANTA.

Prado, E.L.; Abubakar, A.A.; Abbeddou, S.; Jimenez, E.Y.; Somé, J.W.; et al.. 2014. "Extending the developmental milestones checklist for use in a different context in Sub-Saharan Africa." *Acta Paediatrica*. 103: 447–54.

Prado, E.L.; Maleta, K.; Ashorn, P.; Ashorn, U.; Vosti, S.A.; et al. 2016 a. "Effects of maternal and child lipid-based nutrient supplements on infant development: a randomized trial in Malawi." *American Journal of Clinical Nutrition*. 103: 784–93.

Prado, E.; Adu-Afarwuah, S.; Lartey, A.; Ocansey, E.; Ashorn, P.; et al. 2016 b. "Effects of pre- and post-natal lipid-based nutrient supplements on infant development in a randomized trial in Ghana." *Early Human Development*. 99: 43–51.

Rahman, A.S.; Ahmed, T.; Ahmed, F.; Alam, M.S.; Wahed, M.A.; Sack, D.A. 2015. "Double-blind cluster randomised controlled trial of wheat flour chapatti fortified with micronutrients on the status of vitamin A and iron in school-aged children in rural Bangladesh." *Maternal Child Nutrition*. 11 Suppl 4: 120–131.

Salam R.A.; MacPhail, C.; Das, J.K.; Bhutta Z.A. 2013. "Effectiveness of micronutrient powders (MNP) in women and children." *BMC Public Health*. 13 Suppl 3: S22.

Sebayang, S.K.; et al. 2012. "Determinants of low birthweight, small-for-gestational-Aage and preterm birth in Lombok, Indonesia: analyses of the birthweight cohort of the SUMMIT trial." *Tropical Medicine and International Health*. 17(8): 938–950.

Shafique, S.; Sellen, D.W.; Lou, W.; Jalal, C.S.; Jolly S.P.; Zlotkin, S.H. 2016. "Mineral- and vitamin-enhanced micronutrient powder reduces stunting in full-term low-birth-weight infants receiving nutrition, health, and hygiene education: a 2 × 2 factorial, cluster-randomized trial in Bangladesh." *American Journal Clinical Nutrition*. 103(5): 1357–1369.

Su, T.T.; Kouyaté, B.; Flessa, S. 2006. "Catastrophic household expenditure for health care in a low-income society: a study from Nouna District, Burkina Faso." *Bulletin of the World Health Organization.* 84(1): 21–27.

Thompson, R.A. and Nelson, C.A. 2001. "Developmental science and the media: Early brain development." *American Psychologist* 56(1): 5–15.

Thurnham, D.I.; et al. 2010. "Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: a meta-analysis." *American Journal of Clinical Nutrition*. 92(3): 546–555.

Walker, S.P.; Wachs, T.D.; Gardner, J.M.; Lozoff, B.; Wasserman, G.A.; et al. 2007. "Child development: risk factors for adverse outcomes in developing countries." *Lancet*. 369(9556): 145–157.

WHO. 2001. *Iron Deficiency Anemia. Assessment, Prevention and Control. A guide for programme managers*. Geneva, Switzerland: WHO.

WHO. 2006. *WHO Child Growth Standards. Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age. Methods and Development 2006.* Geneva, Switzerland: WHO.

WHO. 2011. *Child Growth Standards. WHO Anthro* (version 3.2.2 , January 2011) and macros. Available at: http://www.who.int/childgrowth/software/en/ (accessed 06/06 2014).

WHO. 2011. *Hemoglobin concentrations for the diagnosis of anemia and assessment of severity*. Vitamin and Mineral Nutrition Information System. WHO/NMH/NHD/MNM/11.1. Geneva, Switzerland: WHO.

WHO. 2012. *WHO Guideline: Daily Iron and Folic Acid Supplementation in Pregnant Women.* Geneva, Switzerland: WHO.

Wiebe, S.A.; Espy, K.A.; Charak, D. 2008. "Using confirmatory factor analysis to understand executive control in preschool children: I. latent structure." *Developmental Psychology*. 44(2): 575–587.

Xu, K.; Saksenaa, P.; Holly, A. 2011. "The determinants of health expenditure: a country-level panel data analysis." Working Paper. Geneva, Switzerland: WHO-RDI.

Appendix 1. Health Education Messages Regarding LNS-C (Sonamoni) and MNP (Pustikona), and Standard Infant and Young Child Feeding Messages in the LAMB CHDP

The following messages were written in Bangla on the back of each Rang-Din Nutrition Study participant's registration card and recalled by the caregiver or read to the community health worker (CHW) at each supplement distribution date. Caregivers receiving Sonamoni for their children were instructed as below (and these messages were written on the label of the Sonamoni container). Similarly, caregivers receiving Pustikona for their children were instructed as below.

Sonamoni Messages

1. Sonamoni is a special food just for children 6–24 months of age. Sonamoni contains edible oil, milk powder, peanut, sugar, mineral and vitamin mix, maltodextrin, and lecithin.
2. Give your child 2 packets of Sonamoni every day after your child completes 6 months and continue until your child is 24 months old. Provide one packet in the morning and one packet at night. It should not replace breast milk. Infants should receive only breast milk for the first 6 months of life. Breastfeeding should be continued along with other infant foods afterwards. Give your baby meat, fish, eggs, fruits and vegetables whenever you can. Babies need these foods even if they receive Sonamoni.
3. Do not give your child more than two packets of Sonamoni in a day. If you forget to give Sonamoni for a day, you do not need to give your child more than two packets of Sonamoni the next day.
4. Mix the entire packet of Sonanomi with 2–3 spoonfuls of an already-prepared food that you would normally feed your child. Do not cook the supplement with the food. Feed your child the whole mixture of food and Sonanomi at a time.
5. Store the packets of Sonamoni in the container provided, out of the reach of small children. Store Sonamoni in a cool and dry place.
6. Please bring the Sonamoni container and registration card each time you get a monthly supply of Sonamoni.
7. We do not expect any side effects after you feed your child Sonamoni. However, if there are any side-effects (such as vomiting, stomach pain, skin rashes, wheezing, or difficulty breathing), please inform the VHV or CHW in your area.
8. If your child is fed Sonamoni, there is no need for any other vitamin and mineral tablets or capsules.
9. If your child has a serious health condition or is hospitalized, please inform the VHV or CHW in your area.

Pustikona Messages

1. Pushtikona is a special food only for children 6–60 months of age. Pushtikona contains mineral and vitamin mix and maltodextrin.
2. Mix 1 packet of Pushtikona with your child's food every day after your child completes 6 months and continue until your child is 24 months old. It should not replace breast milk. Infants should receive only breast milk for the first 6 months of life. Breastfeeding should be continued along with other infant foods afterwards. Give your baby meat, fish, eggs, fruits and vegetables whenever you can. Babies need these foods even if they receive Pushtikona.

3. Do not give your child more than one packet of Pushtikona in a day. If you forget to give Pushtikona for a day, you do not need to give your child more than one packet of Pushtikona the next day.
4. Mix the entire packet of Pushtikona with 2–3 spoonfuls of an already-prepared food that you would normally feed your child. Do not cook the supplement with the food. Feed your child the whole mixture of food and Pushtikona at a time. Do not mix Pushtikona with extremely hot food or with highly liquid food.
5. Store the packets of Pushtikona in the ziplock bag provided, out of the reach of small children. Store Pushtikona in a cool and dry place.
6. Please bring the ziplock bag and the registration card each time you get a monthly supply of Pushtikona.
7. We do not expect any side effects after you feed your child Pushtikona. Your child's stool may become darker, but this is not harmful. However, if there are any other side-effects (such as vomiting, stomach pain, skin rashes, wheezing, or difficulty breathing), please inform the VHV or CHW in your area.
8. If your child is fed Pushtikona, there is no need for any other vitamin and mineral tablets or capsules.
9. If your child has a serious health condition or is hospitalized, please inform the VHV or CHW in your area.

Standard Infant and Young Child Feeding Messages Given to All Participants in the LAMB CHDP Program

For newborn: Begin breastfeeding within one hour of birth, continue breastfeeding only (no other liquids and water) for six months;

For children 181 days to 8 months: Introduce local family foods; half of a 250 ml bowl or bati of semi-solid or solid food two times a day, along with continued breastfeeding;

For children 9-11 months: Rapidly increase amount of food to a half of a 250 ml bowl or bati of food three times a day, plus two snacks, along with continued breastfeeding;

For children 12-23 months: Rapidly increase food to one full 250 ml bowl or bati of food three times a day, plus two snacks, along with continued br.

Appendix 2: Selection of Subset for Child Biochemical Outcomes

	Comprehensive LNS	Child-only LNS	Child-only MNP	Control	Total
Selected (at baseline) for inclusion in biochemical subset	353	311	329	353	1346
Vitamin A data available for children at 18 months of age	297	251	292	270	1110
Hb and iron data available for children at 18 months of age	294	260	300	274	1128