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Nutrient supplementation during the first 1000 days and growth of infants born to pregnant adolescents

Kathryn G. Dewey,[1] (iD) Susana L. Matias,[1] Malay K. Mridha,[1,2] and Charles D. Arnold[1] (iD)

[1]Department of Nutrition, University of California, Davis, California. [2]BRAC James P Grant School of Public Health, BRAC University, Dhaka, Bangladesh

Address for correspondence: Kathryn G. Dewey, Department of Nutrition, University of California, One Shields Ave., Davis, CA 95616. kgdewey@ucdavis.edu

Few studies have evaluated the impact of nutritional supplementation among pregnant adolescents. We examined the effects of the Rang Din Nutrition Study (RDNS) interventions on children born to mothers <20 years of age. The RDNS was a cluster-randomized effectiveness trial with four arms: (1) women and children both received small-quantity lipid-based nutrient supplements (LNS-LNS), (2) women received iron and folic acid (IFA) and children received LNS (IFA-LNS), (3) women received IFA and children received micronutrient powder (MNP) (IFA-MNP), and (4) women received IFA and children received no supplements (IFA-Control). We enrolled 4011 women at <20 weeks gestation; 1552 were adolescents. Among adolescents, prenatal LNS reduced newborn stunting by 25% and small head size by 28% and had a marginally significant effect on newborn wasting, compared with IFA. Low birth weight and preterm birth were reduced only among adolescents with lower food security. Effects on subsequent growth status were observed only among female children in the LNS-LNS group: less stunting at 18 months (versus IFA-MNP) and lower prevalence of small head circumference and wasting at 24 months (versus IFA-Control). Initiatives targeting pregnant adolescents in similar settings should consider inclusion of small-quantity LNS, particularly for adolescents living in food-insecure households.

Keywords: prenatal nutrition; low birth weight; stunting; lipid-based nutrient supplements; child growth

Introduction

More than 10% of total births globally occur to girls 15–19 years of age.[1] Adolescents may be at higher nutritional risk than adults, which could compromise pregnancy outcomes and subsequent growth of infants born to pregnant adolescents. For example, in a recent survey of women within the first 6 months postpartum in Bangladesh, the percentage of mothers with low body mass index (BMI; <18.5 kg/m^2) was 30% in adolescents versus 19% in adults, and infants born to adolescent mothers had significantly lower weight-for-age and length-for-age than infants of adult mothers.[2] Moreover, the competition for nutrients between a mother who is still growing and her fetus may contribute to fetal growth restriction.[3] Pregnant adolescents have a higher risk for low birth weight (LBW) and preterm delivery compared with adults.[1,4,5] The combination of low prepregnancy BMI and young maternal

age could be particularly risky, given that low BMI is also related to small-for-gestational age (SGA) at birth.[6]

There is very little evidence regarding the effects of prenatal nutritional supplementation interventions for pregnant adolescents[7] apart from three studies of zinc supplementation in the United States[8,9] and Chile;[10] four studies of supplementation with calcium (or dairy products) in the United States,[11,12] Ecuador,[13] and Brazil;[14] one study of energy-protein supplementation in the United States;[15] and one study in Malawi comparing groups given supplements with similar energy and protein, but differing in micronutrient content.[16] In a pooled analysis of 17 trials of prenatal multiple micronutrient supplements,[17] younger women (<20 years of age) did not respond differently than adult women in terms of effects on birth outcomes. However, there could be differential response to

food-based supplements, particularly if adolescents have lower BMIs than adults.

We conducted a secondary analysis of data from the Rang Din Nutrition Study (RDNS) in Bangladesh to examine effects of prenatal nutritional supplementation among pregnant adolescents. The RDNS was a cluster-randomized effectiveness trial, designed to evaluate the impact of nutrition interventions during the "1000 days" window on nutritional status of pregnant and lactating women and on growth, nutritional status, and development of their children.[18,19] We focused on the first 1000 days because nutritional insults and growth faltering during this time period are associated with serious long-term adverse consequences.[20,21] Of the pregnant women enrolled in the study, almost 40% were adolescents (<20 years of age). We previously reported an interaction between maternal age and intervention group with respect to the risk of newborn stunting, with larger effects of prenatal small-quantity lipid-based nutrient supplements (LNS) among adolescents than among women ≥20 years of age.[18] The objectives of the analyses reported herein are to examine the effects of the intervention within the subgroup of adolescent mothers with respect to birth outcomes and child growth status at 18–24 months, and to explore whether the effects of the intervention differed by child sex or household food security.

Methods

Study design and data collection
The RDNS was a longitudinal, cluster-randomized effectiveness trial with four arms: (1) Comprehensive LNS arm, in which the women received LNS during pregnancy and the first 6 months postpartum, and their children received LNS from 6 to 24 months of age (LNS-LNS group); (2) Child-only LNS arm, in which the women received one tablet of 60 mg iron and 400 μg folic acid (IFA) daily during pregnancy and every alternate day during the first 3 months postpartum, and their children received LNS from 6 to 24 months of age (IFA-LNS group); (3) Child-only micronutrient powder (MNP) arm, in which the 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 (IFA-MNP

group); and (4) Control arm, in which the women received IFA daily during pregnancy and every alternate day during the first 3 months postpartum, and their children received no supplements (IFA-Control group). Details of LNS, IFA, and MNP supplement composition are provided elsewhere.[18,19] Briefly, LNS for women was formulated based on nutrient requirements for pregnant and lactating women, and LNS for children was based on nutrient needs between 6 and 24 months of age.[18,19,22] LNS ingredients included soybean oil, powdered milk, peanut paste, sugar, and multiple micronutrients, and the dose for both women and children was 20 g/day (118 kcal/day). The dose of IFA was based on WHO recommendations.[23] MNP was produced by Renata Ltd. in Bangladesh and had the same nutrient composition as the MNP being scaled-up in Bangladesh by BRAC.

The RDNS was conducted by three partners: UC Davis; icddr,b; and LAMB (a local NGO responsible for supplement distribution). It was conducted in two subdistricts in northwest Bangladesh: Badarganj and Chirirbandar, in one of the poorest regions of Bangladesh, with 52% of the population being illiterate. We implemented the study in 64 clusters (16 per arm), with a cluster defined as the supervision area of a LAMB community health worker. Eligibility criteria included gestational age ≤20 weeks and no plans to move out of the study area during the following 3 years. At enrollment, women were interviewed to collect data on socioeconomic status, diet, food security, and knowledge, attitudes, and practices relevant to nutrition. They were invited to the local LAMB clinic within 1 week, where anthropometric assessments were done (all women) and blood and urine were collected (subsample). Follow up occurred at 36 weeks gestation, ≤72 h of childbirth, 42 days postpartum, and 6, 12, 18, and 24 months postpartum. The study protocol was approved by the institutional review boards of UCD, icddr,b, and LAMB, and registered at clinicaltrials.gov (NCT01715038).

At each postnatal follow-up contact, trained anthropometrists measured child weight to the nearest 0.05 kg (infant scale, Seca® 876), length to the nearest 0.5 cm (ShorrBoard®, Weigh and Measure LLC), and head circumference to the nearest 0.5 cm (Shorrtape®, Shorr Productions, Olney, MD), using procedures described previously.[18,19] For infants measured between 3 and 14 days after

delivery, we back-calculated the weight, length, and head circumference at birth as described elsewhere.[18] We used WHO 2006 Child Growth Standards to determine Z-scores for length-for-age (LAZ), body mass index-for-age (BMIZ), weight-for-length (WLZ), and head circumference-for-age (HCZ).[24] Extreme observations for Z-scores were truncated at 4 units from the sample median.

Gestational age was calculated based on the first day of the last menstrual period, elicited through maternal recall with the aid of Gregorian, Bengali, and Arabic calendars; antenatal cards; and ultrasound reports. Using the Household Food Insecurity Access Scale (HFIAS)[25] to assess food insecurity, we categorized participants into four levels: severe food insecurity, moderate food insecurity, mild food insecurity, and food security. We also used a continuous variable, the HFIAS score, with higher scores indicating greater food insecurity. A variable named "season at enrollment" was created to approximate seasonality by using 2-month time intervals, 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 season calendar. Using principal components analysis, we calculated an asset ownership index from a set of 19 questions about household ownership of selected items (e.g., televisions, irrigation pumps, tables, bicycles, sewing machines, and other goods). A composite categorical variable for household air quality was based on the presence of smokers in the household as well as cooking location, method, fuel, and time; the variable included five categories ranging from best to worst. A composite variable for housing quality was based on electricity in the home and quality of building materials for roofing, walls, and flooring.

Data analysis

The birth outcomes included in this secondary analysis are preterm birth (<37 weeks gestation), LBW (<2500 g), stunting (birth LAZ < −2), wasting (birth BMIZ < −2), small head circumference (birth HCZ < −2), and small for gestational age (SGA, defined as <10th percentile for the INTER-GROWTH reference[26]). Child growth outcomes at 18 and 24 months included stunting (LAZ < −2), wasting (WLZ < −2), and small head circumference (HCZ < −2).

The primary analysis was by complete case intention-to-treat. That is, results were analyzed according to the group to which participants were assigned regardless of any protocol violations. Data on participants who were lost to follow-up because of death, travel from the study site, or refusal to continue with the study were included in the analysis, if available.

We first tested the null hypothesis of no difference between intervention groups using mixed model logistic regression. For birth outcomes, there were two intervention groups, LNS versus IFA. For child growth outcomes, there were four intervention groups: LNS-LNS, IFA-LNS, IFA-MNP, and IFA-Control. The analysis took into account that randomization occurred at the cluster level, stratified by location. Location variables were subdistrict (two subdistricts were represented in this study, out of 492 subdistricts in Bangladesh) and union (the lowest administrative unit in Bangladesh). Thus, all models included random effects of cluster nested within intervention arm and union nested within subdistrict. Nesting of clusters within intervention arm is also explicitly accounted for in the random effect statement. For the four-group analyses of child growth outcomes at 18–24 months, if the global null hypothesis was rejected at 0.05 level, then we performed post-hoc pairwise comparisons of intervention groups using the Tukey–Kramer adjustment.[27]

Then, we repeated all analyses with adjustment for prespecified covariates (gestational age at enrollment, years since menarche, maternal age, education, BMI, height, nulliparity, air quality, garbage disposal method, latrine quality, housing quality, asset ownership index, food security score, child sex, and season at enrollment). Only covariates significantly associated with an outcome at 10% level of significance in a bivariate analysis were included in the final adjusted analysis. This means we may have different sets of covariates for each outcome.

All intervention group comparison tests were two-sided, at a 5% level of significance.

We examined the potential effect modification by child sex and household food security by using interaction terms in the logistic regression model, one at a time. These two potential effect modifiers were chosen based on findings in the full sample.[18,19] Significant interactions ($P < 0.10$) were further examined with stratified analyses
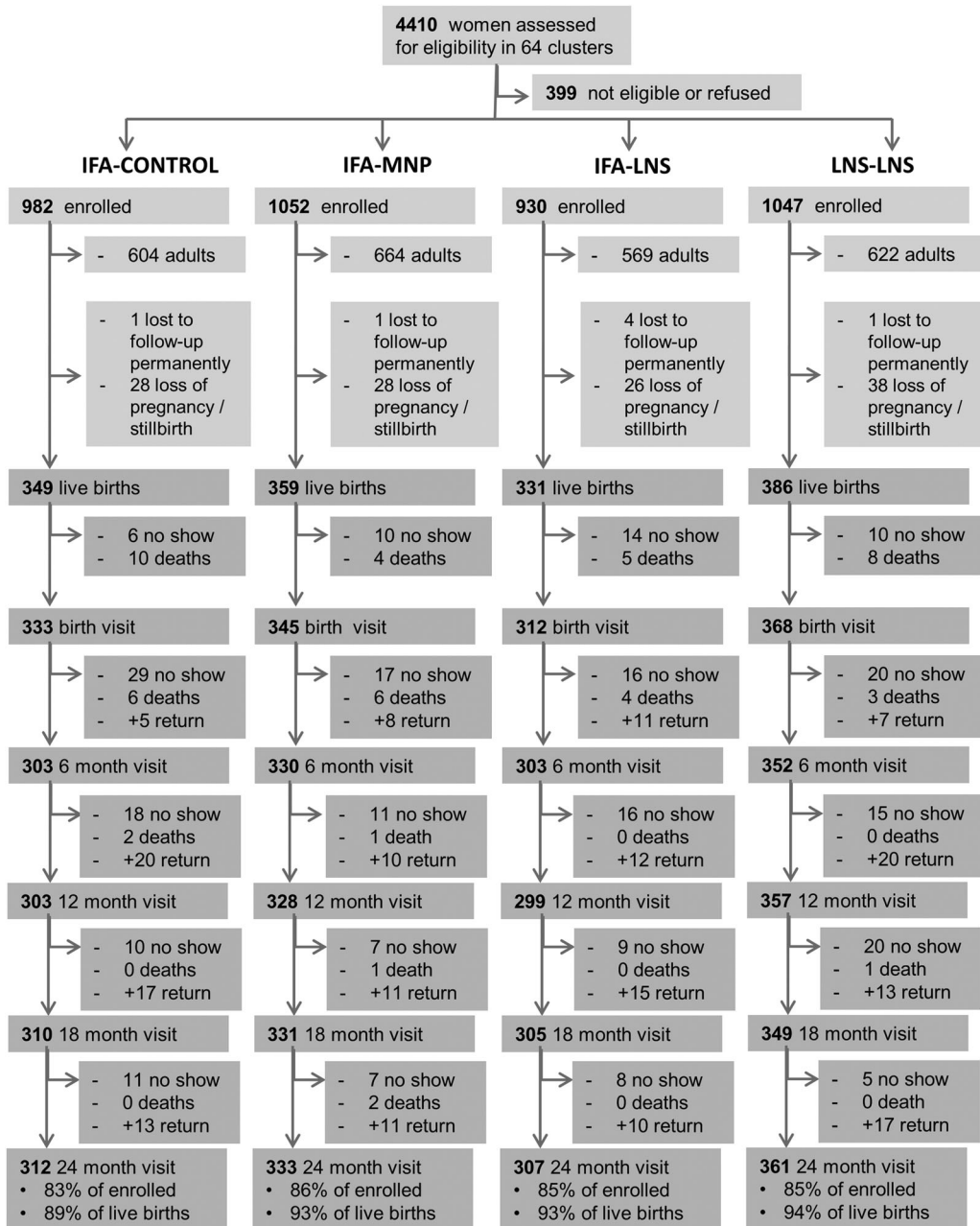
Figure 1. Participation flow diagram.

in order to understand the nature of the effect modification.

Results

In total, 4011 women were enrolled between October 15, 2011 and August 31, 2012, of whom 1552 (39%) were <20 years of age. Among the adolescent participants, 1425 live births occurred between January 15, 2012 and May 5, 2013 to those remaining in the study, and we have birth anthropometry data for 1358 infants. At 24 months of age, anthropometric data were obtained for 1313 children. Figure 1

Table 1. Baseline characteristics of pregnant adolescents enrolled[a]

Variable	LNS-LNS (n = 425)	IFA-LNS (n = 361)	IFA-MNP (n = 388)	IFA-Control (n = 378)
Age (years)	17.3 ± 1.3	17.4 ± 1.3	17.5 ± 1.3	17.4 ± 1.3
Years of formal education	6.5 ± 2.4	6.3 ± 2.9	6.4 ± 2.8	6.6 ± 2.7
Height (cm)	150.6 ± 5.6	150.1 ± 5.0	150.2 ± 5.5	150.3 ± 5.4
BMI (adjusted to 96 days of gestation, kg/m^2)	19.3 ± 2.1	19.6 ± 2.3	19.3 ± 2.1	19.3 ± 2.2
Low BMI (<18.5, n (%))	160 (37.7)	128 (35.5)	135 (34.8)	146 (38.6)
Gestational age at enrollment (weeks)	12.9 ± 3.6	13.2 ± 3.8	13.1 ± 3.7	13.0 ± 3.7
Nulliparous (n (%))	341 (80.4)	293 (81.2)	305 (78.8)	300 (79.6)
Food insecure (n (%))	190 (44.7)	173 (47.9)	183 (47.2)	191 (50.5)
Sanitation (n (%))				
No toilet	113 (26.6)	92 (25.5)	116 (29.9)	87 (23.0)
Latrine	274 (64.5)	233 (64.5)	224 (57.7)	242 (64.0)
Flushing toilet	38 (8.9)	36 (10.0)	48 (12.4)	49 (13.0)

[a]Mean ± SD unless otherwise indicated; there were no significant differences in baseline characteristics among intervention groups.

illustrates the number of participants for whom we have data on birth outcomes and subsequent child growth status.

Baseline characteristics of the pregnant adolescents are shown in Table 1 by intervention group. Mean (SD) age was 17.4 (1.3) years. Participants had an average of 6–7 years of formal education. Mean BMI was 19.3 kg/m^2, and 36% were underweight (BMI < 18.5 kg/m^2). Average gestational age at enrollment was 13 weeks and 80% were nulliparous. Nearly half of the households were categorized as food insecure, and more than a quarter had no toilet or latrine. Baseline characteristics were balanced across intervention groups.

Birth outcomes

Table 2 shows that there were no significant differences between the prenatal LNS and IFA groups with regard to preterm delivery, LBW, or SGA. However, there were significant differences in new-

born stunting and small head circumference and a marginally significant difference in newborn wasting. Compared with the IFA group, the LNS group exhibited a 25% reduction in newborn stunting and a 28% reduction in small head circumference. Adjustment for covariates other than union and cluster did not alter these findings (data not shown).

There was a significant interaction between intervention group and child sex with regard to LBW (*P*-for-interaction = 0.058): among female infants, the percentage with LBW was 42.4% in the LNS group versus 52.4% in the IFA group (*P* = 0.065), whereas among males, the percentages were 44.2% versus 40.2% (*P* = 0.425). There was no significant interaction between intervention group and child sex with respect to preterm delivery, stunting, small head circumference, wasting, or SGA.

Food security modified the effect of the intervention on LBW, stunting, and preterm delivery (Fig. 2), but not small head circumference, newborn

Table 2. Dichotomous birth outcomes, by intervention group, among adolescents[a]

Outcome variable	LNS (n = 360)	IFA (n = 974)	Relative risk	Odds ratio (95% CI)	P value
Preterm delivery	11.7%	13.8%	0.85	0.83 (0.57–1.21)	0.321
Low birth weight	43.3%	46.3%	0.94	0.89 (0.69–1.15)	0.373
Stunting	20.0%	26.9%	0.75	0.69 (0.51–0.93)	0.018
Small head size	20.8%	28.8%	0.72	0.65 (0.49–0.88)	0.005
Low BMI Z-score	33.6%	39.0%	0.86	0.79 (0.61–1.03)	0.080
Small for gestational age	67.3%	68.6%	0.98	0.94 (0.71–1.26)	0.693

[a]*P* values for analyses are based on logistic regression, accounting for random effects of union (nested within subdistrict) and cluster, but not adjusted for other covariates. Intracluster correlation coefficient was zero for the primary outcomes.
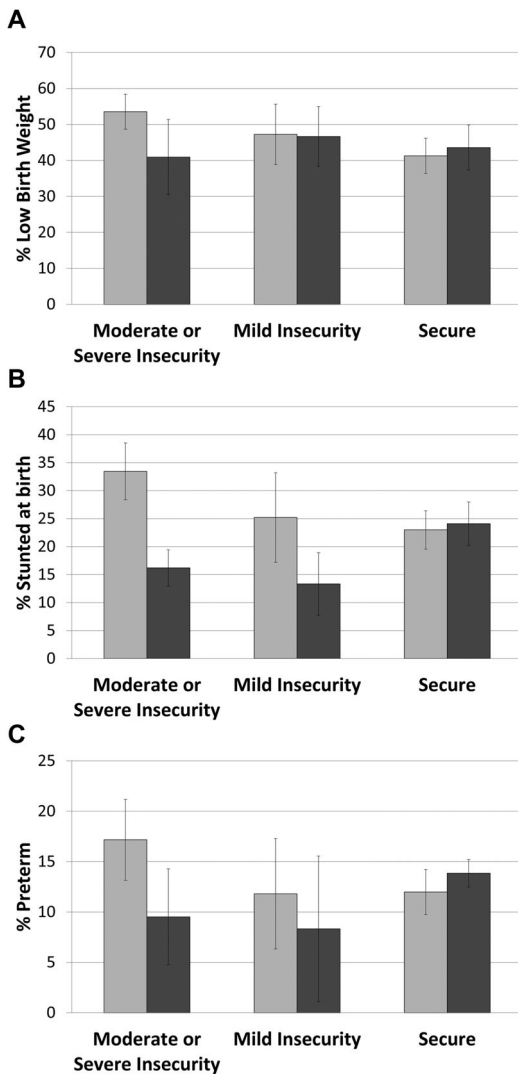
wasting, or SGA. For LBW, stunting, and preterm birth, the effect of LNS during pregnancy was more evident among adolescents from households with food insecurity than among those from households reported to be food secure. Among those with moderate to severe food insecurity, LNS during pregnancy reduced LBW by 24%, newborn stunting by 51%, and preterm birth by 56%.

Child growth outcomes at 18–24 months

Table 3 shows that there were no significant differences between intervention groups in stunting, wasting, or small head circumference at 18 or 24 months. Adjustment for covariates other than union and cluster did not alter these findings (data not shown).

Significant interactions were detected between intervention group and child sex. At 18 months, stunting prevalence was lower in the LNS-LNS group compared with the IFA-MNP group among girls (24.8% versus 40.9%, respectively) but not among boys (Fig. 3A). At 24 months, the same trend was evident but was no longer significant (Fig. 3B). Small head circumference at 24 months (but not at 18 months) was significantly less common in the LNS-LNS group than in the IFA-Control and IFA-MNP groups among girls (32.9% versus 52.5% and 49.7%, respectively), whereas no group differences were detected among boys (Fig. 3C). Finally, Figure 3D shows that there was less wasting in the LNS-LNS group compared with the IFA-Control group among girls at 24 months (but not at 18 months), whereas there were no group differences among boys.

There were no significant interactions between intervention group and household food security with regard to child growth outcomes at 18–24 months.

Discussion

In this cohort of pregnant adolescents, prenatal small-quantity LNS did not lead to significant reductions in LBW, SGA, or preterm birth, but it reduced newborn stunting by 25% and small head size by 28% and had a marginally significant effect on newborn wasting, compared with IFA. The effects on newborn stunting were particularly strong among adolescents with lower food security. In adolescents with lower food security, prenatal LNS also reduced LBW and preterm birth.

Figure 2. Percentages of low birth weight (A), stunting at birth (B), and preterm birth (C), by food security and intervention group, among children of adolescent mothers. IFA = light gray; LNS = dark gray. Sample sizes: moderate or severe insecurity, IFA = 338 and LNS = 105; mild insecurity, IFA = 127 and LNS = 60; food secure, IFA = 509 and LNS = 195. For % low birth weight, *P* for interaction with continuous food security = 0.0173; within those with moderate or severe food insecurity, LNS versus IFA, *P* = 0.0276, OR = 0.60 (0.38–0.95). For % stunting at birth, *P* for interaction with continuous food security = 0.003; within those with moderate or severe food insecurity, LNS versus IFA, *P* = 0.001, OR = 0.39 (0.22–0.68); within those with mild food insecurity, *P* = 0.074, OR = 0.46 (0.20–1.08). For preterm birth, *P* for interaction with continuous food security = 0.069; within those with moderate or severe food insecurity, LNS versus IFA, *P* = 0.062, OR = 0.50 (0.25–1.04). *P* values account for the random effects of union (nested within subdistrict) and cluster, but are not adjusted for other covariates, as further adjustment did not alter these results.

Table 3. Dichotomous growth outcomes at 18 and 24 months, by intervention group, among children of adolescent mothers[a]

Outcome variable	Survey visit	LNS-LNS (n = 361)	IFA-LNS (n = 307)	IFA-MNP (n = 333)	IFA-Control (n = 312)	P value
Stunting	18 months	36.1%	36.4%	42.9%	38.1%	0.176
		0.90 (0.58–1.38)	0.92 (0.59–1.44)	1.25 (0.81–1.92)	ref.	
	24 months	42.1%	43.0%	48.1%	44.9%	0.426
		0.89 (0.59–1.35)	0.93 (0.60–1.42)	1.14 (0.75–1.73)	ref.	
Small head size	18 months	35.5%	38.7%	39.9%	36.1%	0.626
		0.97 (0.63–1.51)	1.12 (0.71–1.74)	1.17 (0.76–1.81)	ref.	
	24 months	41.0%	41.7%	46.6%	45.2%	0.391
		0.85 (0.56–1.28)	0.87 (0.56–1.33)	1.07 (0.70–1.63)	ref.	
Wasting	18 months	16.6%	14.8%	18.2%	20.0%	0.383
		0.79 (0.45–1.38)	0.69 (0.38–1.24)	0.89 (0.51–1.55)	ref.	
	24 months	12.5%	11.8%	12.0%	16.4%	0.363
		0.72 (0.38–1.39)	0.67 (0.34–1.34)	0.69 (0.36–1.35)	ref.	

[a]P values for analyses are based on logistic regression, accounting for random effects of union (nested within subdistrict) and cluster but not adjusted for other covariates. Intracluster correlation coefficient was zero for the primary outcomes. Results are presented as prevalence, OR (95% CI).

In the four-group analyses of child growth status at 18–24 months, there were no significant main effects of intervention group with regard to child stunting, wasting, or small head circumference, but among female children, the group that received both maternal and child LNS (LNS-LNS group) exhibited reductions in stunting at 18 months (compared with the IFA-MNP group) and in small head circumference and wasting at 24 months (compared with the IFA-Control group).

The 25% reduction in newborn stunting and 28% reduction in small head circumference among infants of adolescent mothers who received LNS are larger effects than observed in the entire study population (18% reduction in stunting and 16% reduction in small head circumference[18]), suggesting that infants of pregnant adolescents have a greater potential to respond to this intervention than infants of adult women in this setting. More than a third of the adolescents in this cohort were underweight in early pregnancy, and the combination of low BMI and young maternal age may have made them particularly vulnerable to adverse birth outcomes and hence more likely to benefit from a food-based intervention that supplied both micro- and macronutrients.

Among the pregnant adolescents with moderate to severe food insecurity, prenatal LNS reduced LBW by 24%, newborn stunting by 51%, and preterm birth by 56%. In the entire study population (both adolescents and adults), food security modified the effect of prenatal LNS on nearly all of the birth outcomes,[18] so these findings within the subset of adolescents are consistent with those results. Women in food-insecure households are more likely to suffer from both macro- and micronutrient deficiencies during pregnancy, which could explain their greater response to prenatal LNS. By contrast, household food insecurity did not modify the effect of the pre- plus postnatal RDNS interventions on child growth status at 18–24 months, either in the entire study population[19] or in the children of this subset of adolescent mothers. Thus, it would appear that food insecurity affects the potential to respond to such interventions during the prenatal period but not thereafter.

The intervention group differences in anthropometric outcomes at 24 months among the female children of adolescent mothers, but not among the male children, warrant further investigation. Within the IFA-Control group, female children appeared to have a higher risk of small head size (Fig. 3C) and wasting (Fig. 3D) than male children, even though the rate of stunting was very similar between females and males (Fig. 3B). This suggests that there was greater potential to benefit from LNS among the female children, with respect to head circumference and wasting. The interaction between
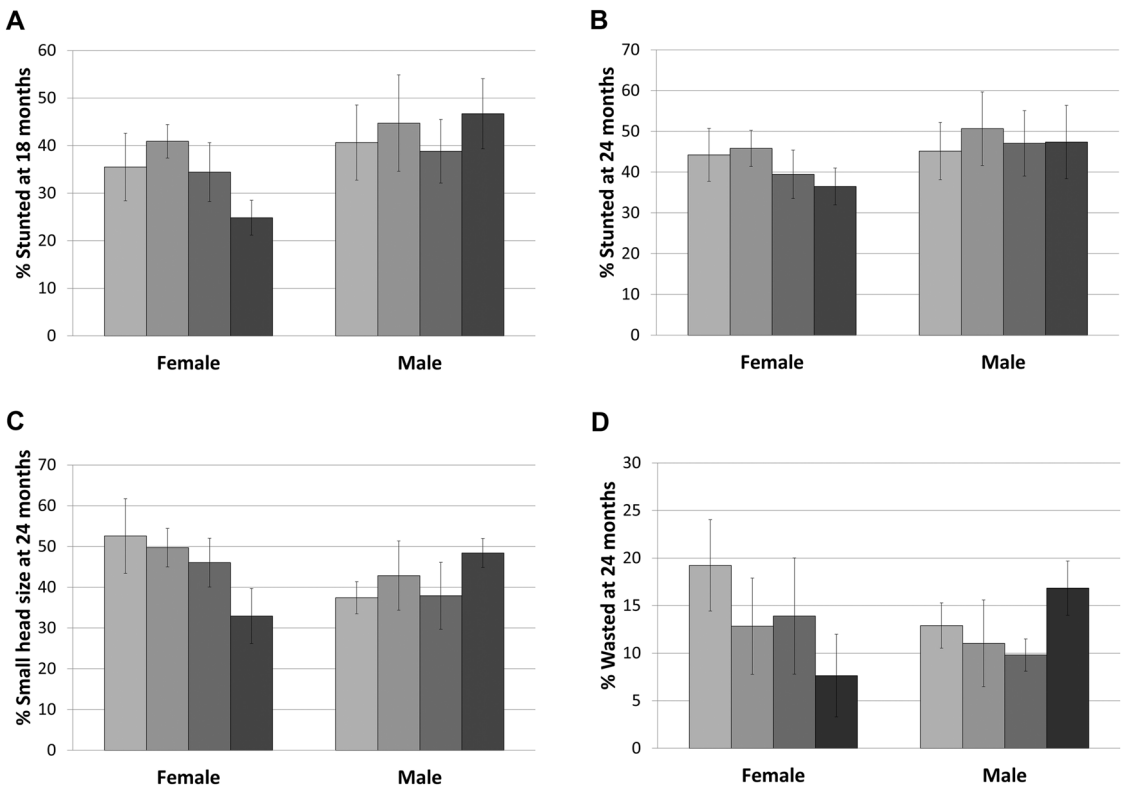
Figure 3. Stunting at 18 months (A), stunting at 24 months (B), small head size at 24 months (C), and wasting at 24 months (D), by sex and intervention group, among children of adolescent mothers. IFA-Control = light gray; IFA-MNP = medium-light gray; IFA-LNS = medium gray; LNS-LNS = dark gray. Sample sizes: (A) females: IFA-Control = 155, IFA-MNP = 176, IFA-LNS = 151, and LNS-LNS = 165; males: IFA-Control = 155, IFA-MNP = 152, IFA-LNS = 152, and LNS-LNS = 182; (B) females: IFA-Control = 156, IFA-MNP = 179, IFA-LNS = 152, and LNS-LNS = 170; males: IFA-Control = 155, IFA-MNP = 154, IFA-LNS = 153, LNS-LNS = 190; (C) females: IFA-Control = 156, IFA-MNP = 179, IFA-LNS = 152, and LNS-LNS = 170; males: IFA-Control = 155, IFA-MNP = 154, IFA-LNS = 153, and LNS-LNS = 190; (D) females: IFA-Control = 156, IFA-MNP = 179, IFA-LNS = 151, and LNS-LNS = 170; males: IFA-Control = 155, IFA-MNP = 154, IFA-LNS = 153, and LNS-LNS = 190. For (A), *P* for interaction = 0.033; within females, LNS-LNS versus IFA-MNP, *P* = 0.014, OR = 0.48 (0.26–0.89). For (B), *P* for interaction = 0.799; within females, LNS-LNS versus IFA-MNP, *P* = 0.086, OR = 0.68 (0.38, 1.22). For (C), *P* for interaction = 0.002; within females, LNS-LNS versus IFA-MNP, *P* = 0.015, OR = 0.49 (0.27–0.90); LNS-LNS versus IFA-Control, *P* = 0.007, OR = 0.28 (0.24–0.84). For (D), *P* for interaction = 0.030; within females, LNS-LNS versus IFA-Control, *P* = 0.064, OR = 0.36 (0.12–1.04). *P* values account for the random effects of union (nested within subdistrict) and cluster, but are not adjusted for other covariates, as further adjustment did not alter these results.

child sex and intervention group, with regard to head circumference, was also observed within the entire study population.[19] The potential biological mechanisms that underlie the greater response among girls require further research.

There are few previously published studies regarding the effects of nutritional supplementation interventions targeting pregnant adolescents, and thus little evidence against which to compare our results. Three studies investigated the effects of prenatal zinc supplementation among pregnant adolescents, two in the United States[8,9] and one

in Chile.[10] The U.S. studies showed no effect of 20 mg/day zinc on birth weight, but in one of those studies[8] there was a reduction in preterm birth among adolescents who entered the study with normal weight status, though not among those who were under- or overweight at enrollment. The study in Chile was conducted in poor urban communities and showed significant effects of 30 mg/day zinc supplementation on the prevalence of LBW and preterm birth. The prenatal LNS used in the RDNS contained 30 mg of zinc, so this may have contributed to the effects we

observed on birth outcomes. Four studies investigated the effects of prenatal supplementation with 2000 mg/day calcium,[11,13] 600 mg/day calcium plus 200 IU/day vitamin D,[14] 1200 mg/day calcium with orange juice,[12] or 1200 mg/day calcium from dairy products.[12] Two of these studies, in Ecuador[13] and the United States,[12] showed no effect of calcium or calcium with orange juice on birth weight, but there was a beneficial effect of calcium on the incidence of preterm delivery and LBW in an earlier U.S. study,[11] a positive effect of calcium plus vitamin D on fetal weight in Brazil,[14] and a positive effect of dairy products on birth weight in the later U.S. study.[12] It is possible that the calcium content of the prenatal LNS used in our trial contributed to the positive effects on birth outcomes, but the amount of calcium provided (280 mg) was well below the doses used in the above studies. With regard to balanced energy-protein supplementation, we found only one trial among pregnant adolescents, which was conducted in a cohort of 157 disadvantaged African-Americans in the United States[15] and demonstrated a significant effect on mean birth weight compared with a no-supplementation control group. One recent study in Malawi compared groups of moderately malnourished pregnant adolescents given supplements with similar energy and protein but differing in micronutrient content, and did not observe any group differences in infant outcomes.[16] A recent systematic review[7] concluded that there is a major gap in the evidence regarding effects of nutritional interventions for pregnant adolescents, highlighting the need for further research.

The strengths of this study include the randomized design of the intervention, a low rate of attrition, and the relatively large sample of adolescent mothers. The study is limited by the inability to blind participants to the supplements received, given the very different physical appearance and taste of the LNS, IFA, and MNP. This paper reports secondary analyses and thus the results should be interpreted with caution. In particular, replication in similar settings of the findings from the exploratory analyses of effect modification by food insecurity and child sex is necessary.

We conclude that initiatives targeting pregnant adolescents in similar settings should consider inclusion of small-quantity LNS, particularly for the most vulnerable subgroups, such as adolescents living in food-insecure households. During the postnatal period, our results suggest that female children of adolescent mothers have greater potential to respond to LNS than male children, with regard to linear growth status and head circumference, which could have important implications in terms of subsequent height and development. Further research is needed to confirm these findings in other populations, and to document the long-term consequences of nutritional interventions during the first 1000 days among children of adolescent mothers.

Author contributions

K.G.D., S.L.M., and M.K.M. designed the research. M.K.M. supervised data collection. C.D.A. performed the statistical analysis. K.G.D. was the principal investigator for the overall project, supervised

the statistical analysis, wrote the first draft of the manuscript, and had primary responsibility for final content. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

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