Effects of prenatal multiple micronutrient supplementation on growth and cognition through 2 y of age in rural Bangladesh: the JiVitA-3 Trial[1,2]

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ABSTRACT

Background: Childhood undernutrition may have prenatal origins, and the impact of prenatal interventions on postnatal growth is not well known.

Objective: We assessed the effects of prenatal multiple micronutrient (MM) supplementation on child growth and cognitive development.

Design: In a cluster-randomized controlled trial in rural Bangladesh, prenatal MM supplementation compared with iron-folic acid (IFA) supplementation was examined for its impact on growth assessed longitudinally from birth up to 24 mo of age (n = 8529) and, in a subsample (n = 734), on cognitive function at 24 mo of age by use of the Bayley scales of infant and toddler development–third edition test.

Results: Prevalence of stunting at birth [length for age z score (LAZ): <-2] was 31.9% in the MM and 35.7% in the IFA groups ($P < 0.001$); however, LAZ increased during the first 3–4 mo in both groups. With the use of a linear random-effects model, prenatal MM-exposed children sustained a higher mean predicted LAZ of ~0.10 at 1 and 3 mo and 0.06 at 6 mo of age compared with children in the IFA group. Supplementation reduced the prevalence of stunting at 1 (RR: 0.95; 95% CI: 0.92, 0.98) and 3 (RR: 0.91; 95% CI: 0.88, 0.94) mo of age. Differences between groups were absent by 6, 12, and 24 mo of age, when nearly 50% of children had stunted growth. Ponderal and linear growth velocities were somewhat slower from 3 to 12 mo of age in the MM group than in the IFA group, but not from 12 to 24 mo of age. There was no difference between groups on composite scores of cognition, language, and motor performance at 24 mo of age.

Conclusions: In this Bangladeshi trial, maternal pre- and postnatal MM supplementation resulted in improvements in LAZ and reduction in stunting through 3 mo of age, but not thereafter and had no impact on cognitive and motor function at 2 y. This trial was registered at clinicaltrials.gov as NCT000860470. *Am J Clin Nutr* 2016;104:1175–82.

Keywords: micronutrients, prenatal, children, growth, stunting, cognition

INTRODUCTION

The high burden of childhood undernutrition, especially stunting, continues to be a public health priority in many low-resource settings, although limited interventions exist (1, 2). Causes of stunting are multifactorial, but linear growth restriction begins early in fetal life. Maternal undernutrition during pregnancy (3) and fetal growth failure as reflected by a child being small for gestational age have been shown to contribute to the risk of stunting in the first 2 y of life (4). There is sufficient evidence from original randomized controlled trials in the past few decades that 3 nutritional interventions during pregnancy can improve birth weight and reduce the probability a child will be small for gestational age, as revealed in recent meta-analyses: supplementation with balanced protein-energy or food (5), iron-folic acid (IFA)[6] (6), and micronutrients (MMs) (7). Whether these prenatal interventions influence postnatal growth has been examined in studies that used single, cross-sectional follow-up assessments of the offspring born during the trials. Four such follow-up studies were combined in a meta-analysis to examine the effects of supplementation with prenatal MMs on height-for-age and weight-for-height z scores in children younger than 5 y; no impact on these anthropometric outcomes was found (8). Few studies, to our knowledge, have examined the impact of maternal interventions on patterns of postnatal growth over time. A study in Burkina Faso in which lipid-based nutrient supplements were used found inferior linear growth velocity in

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

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[6] Abbreviations used: IFA, iron-folic acid; LAZ, length-for-age z score; MM, multiple micronutrient; WAZ, weight-for-age z score; WLZ, weight-for-length z score.

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the supplement-versus-placebo arm, overriding the positive effect on birth length that was shown with supplementation (9). In a recent trial in Malawi, neither prenatal nor direct lipid-based supplementation had an impact on linear growth in children through 18 mo of age (10). In a study in Bangladesh, prenatal supplementation with MM compared with IFA resulted in higher rates of stunting when children were assessed at 54 mo of age (11); differential survival could have influenced this outcome, because the MMs intervention was shown to reduce postnatal mortality in the original trial (12).

In rural northwestern Bangladesh, we completed a large trial (NCT000860470) of MM compared with standard of care IFA prenatal supplementation and found significant improvements in the length of gestation that generated increases in size at birth and reductions in the risks of low birth weight, preterm birth, and stillbirth (13). We studied the growth of a sample of children born in this trial through the first 2 y of life and, in a smaller subset, assessed cognitive function at 24 mo of age. The purpose of this study was to examine the effect of maternal MM compared with IFA supplementation on postnatal linear and ponderal growth and on the prevalence of stunting and cognitive function at 24 mo of age.

METHODS

Study design and population

We conducted a double-blind, placebo-controlled cluster-randomized trial between 2008 and 2012 in rural northwestern Bangladesh to study the efficacy of a daily prenatal MM compared with a standard-of-care iron (27 mg) and folic acid (600 μg) supplement in improving 6-mo infant survival and birth outcomes [additional details are found in West et al. (13)]. The MM supplement contained a single recommended allowance of 13 MMs (13) in addition to the IFA at the same amount found in the control supplement. Pregnant women were enrolled soon after they were ascertained at a mean (SD) gestational age of 10.9 (4.9) wk through use of pregnancy surveillance and identification by a cadre of 596 local female workers to monitor monthly last menstrual period and to conduct urine-based testing for pregnancy among amenstrual women (13). After providing informed consent, pregnant women received weekly supplements targeted to their allocation group. Female workers replenished the coded supplements and monitored compliance and pregnancy outcome 1 time/wk. Supplementation was conducted through 3 mo postpartum. A separate team of trained data collectors and anthropometrists visited enrolled pregnant women at first and third trimester to collect interview-based data on diet, morbidity, antenatal health care, and work, and to conduct anthropometric measurements. At enrollment, women were interviewed about their household demographic and socioeconomic statuses, their husband's and their own education and occupation, and pregnancy history. Newborns were weighed and their length and midarm, head, and chest circumferences were measured within 72 h of birth. Subsequently, neonates and mothers were revisited at 1 and 3 mo to assess anthropometry in the infants and to elicit histories of complications in delivery and neonatal morbidity.

In October 2009, we added visits to conduct home-based assessments of infants at 6 and 12 mo of age. We assessed anthropometry, breastfeeding and complementary feeding practices, morbidity histories, treatments sought, and coverage for vaccinations and other health services. In April 2010, we added a 24-mo-of-age visit to the study to further assess anthropometry and interview mothers about the infants' weekly diet and morbidity history. Supplemental growth assessment protocols being introduced at times when substantial numbers of children had aged beyond the eligible 6-, 12-, and 24-mo ages specified caused some children not to be assessed for growth at and beyond 6 mo of age (**Figure 1**). This is important because the data are not missing because of bias in ascertaining eligible children but largely because of age ineligibility at the time the extended growth assessment protocol was implemented.

Anthropometry was assessed following standard methods. We measured weight to the nearest 10 g using an infant weight scale (model BD585, Tanita Corporation of America) that was checked daily for accuracy against standard weights. Supine length was taken with a locally developed length board standardized against the infant/child ShorrBoard (Weigh and Measure, LLC). Length and circumferential measures were obtained and recorded in triplicate and the median reading was used in the analysis. As a part of training the inter- and intraworker technical error of measurement for each dimension was set at 1.0% and 1.5%, respectively, and each anthropometrist met these benchmarks before the beginning and midway through the study.

In a substudy area, we brought 24-mo-old children ($n = 734$) to a central location to conduct an adapted Bayley scales of infant and toddler development–third edition (Bayley-III; Pearson) test translated into Bangla to assess domains of cognitive, language (expressive and receptive), and motor (fine and gross) skills. Although this standardized test was developed and normed for children in the United States, it has been used in many countries. In Bangladesh, the cultural adaptations to Bayley-III were made in studies conducted at the International Centre for Diarrhoeal Disease Research, Bangladesh. A few pictures were changed in the cognitive and language subtests to make them more culturally appropriate for use in Bangladesh (14). Training of psychological testers was provided by child development experts at the Child Development Center of the International Centre for Diarrhoeal Disease Research, Bangladesh; they also created the adapted version of the test we used. Three testers with master degrees in psychology were trained and achieved high interobserver (>0.90 intraclass correlation) reliability and test-retest (>0.80 intraclass correlation) reliability on each of the tests and subtests before they were certified to begin testing in the field. Throughout the data collection period, quality control was achieved through use of videotaped tests that were examined by one of the trainers, who provided feedback to the testers regarding test administration and scoring.

Statistical analysis

We used maternal trial allocation (MM compared with IFA) and children's age in months as explanatory variables. Outcomes included length-for-age z score (LAZ), weight-for-age z score (WAZ), and weight-for-length z score (WLZ) derived through use of the WHO international growth standards (15), weight (kilograms), and length (centimeters). Because each child was measured ≤6 times (at birth, 1, 3, 6, 12, and 24 mo), the data were clustered for each child. Because children were clustered within a sector, the data have a multilevel structure. We excluded

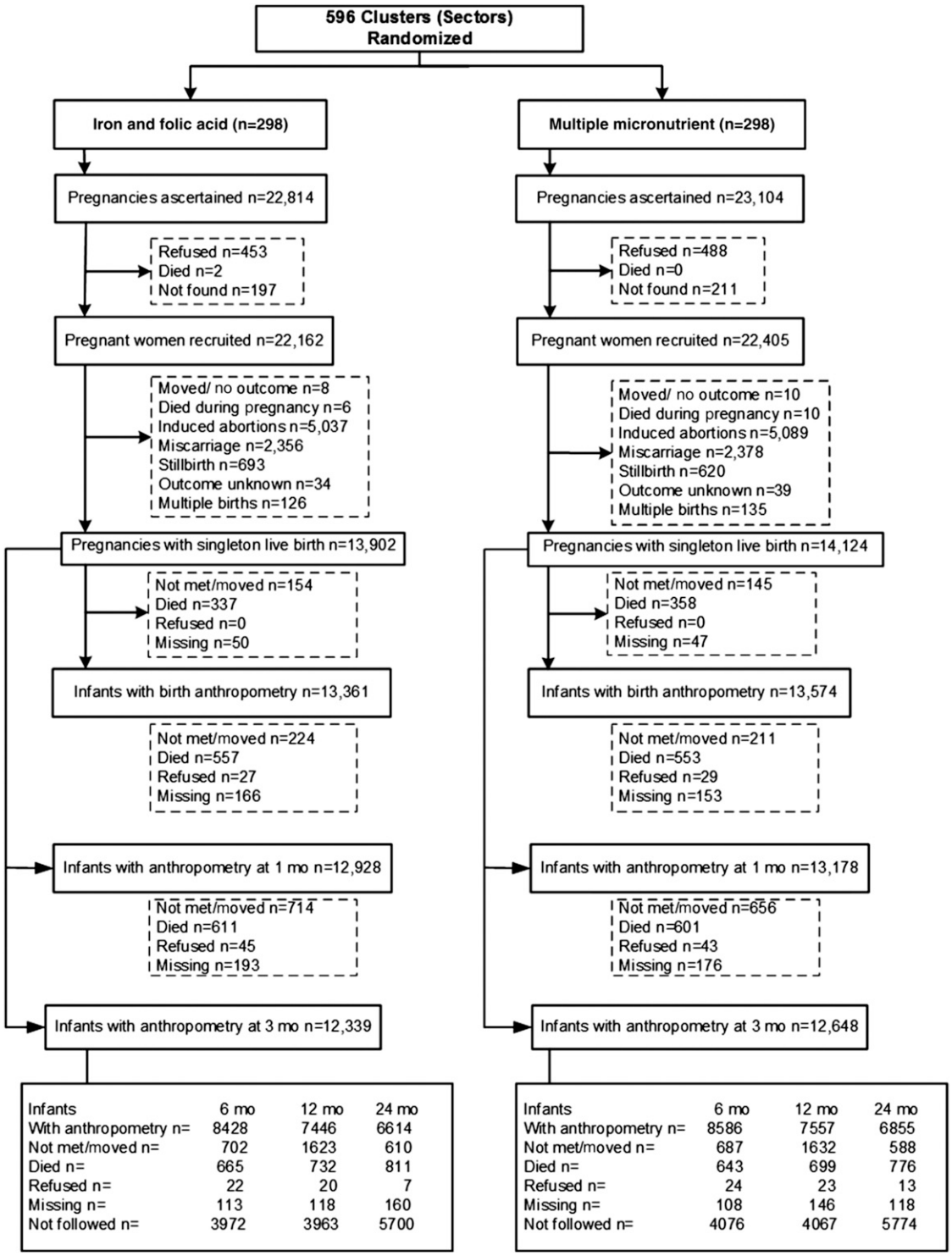

FIGURE 1 Study participation and follow-up by supplementation group. (Children not followed was by design because we started the post–6-mo-of-age follow-ups when some of the children had already reached ages 6 and 12 mo.)

records measured at 26 mo of age or later because of the scarcity of data in this interval.

Longitudinal data analysis was undertaken to examine treatment effects in 8529 children (4242 in the IFA group and 4287 in the MM group). This was the longitudinal sample for which weight data were available at all ages. For each of the outcome variables, we applied a linear mixed-effects model with a fourth-order polynomial. The fixed part of the model included an indicator variable for the treatment, with IFA serving as the reference group, age, age squared, third and fourth powers of age, and interaction terms between the treatment indicator and 4 age terms. We also tried third- and fifth-order polynomial models and a Loess model, but chose the fourth-order polynomial to allow enough flexibility to capture the characteristic of the data while

TABLE 1
Maternal characteristics and household living standards index at pregnancy enrollment and infant status at birth by supplement group[1]

	IFA (Total, n = 13,902)			MMs (Total, n = 14,124)		
	Variable, n	Numerator, n	Values	Variable, n	Numerator, n	Values
Maternal age, y	13,897			14,117		
<20		4750	34.2[2]		4749	33.6
20–29		7462	53.7		7526	53.3
≥30		1685	12.1		1842	13.1
Gestational age, wk	13,780			13,994		
7		3268	23.7		3364	24.1
8–12		6973	50.6		7115	50.8
≥13		3539	25.7		3515	25.1
Literacy	13,880	8788	63.3	14,109	8844	62.7
Education	13,876			14,106		
No class		3558	25.6		3665	26.0
Classes 1–4		1944	14.0		1961	13.9
Classes 5–9		7222	52.1		7312	51.8
Classes ≥10		1152	8.3		1168	9.3
Reproductive history						
Parity	13,881			14,110		
0		5363	38.6		5390	38.2
1–3		7900	56.9		8065	57.2
≥4		618	4.5		655	4.6
Fetal loss (≥1)[3]	9036	2693	29.8	9242	2788	30.2
Prior infant deaths (any)	8515	1900	22.3	8721	1984	22.8
Dietary intake: ≥3 times in past 7 d						
Any meat or liver	13,846	2118	15.3	14,082	2156	15.3
Any fish or seafood	13,846	8943	64.6	14,082	9158	65.0
Egg	13,846	2534	18.3	14,081	2544	18.1
Milk products	13,846	3608	26.1	14,082	3737	26.5
Yellow fruits and vegetables	13,845	2684	19.4	14,081	2786	19.8
Dark green leafy vegetables	13,846	3173	22.9	14,081	3184	22.6
Morbidity: Any in past 7 d						
Poor appetite	13,845	6032	43.6	14,083	6056	43.0
Nausea	13,846	6962	50.3	14,081	7025	49.9
Vomiting	13,843	3596	26.0	14082	3582	25.4
Low-grade fever*	13,843	4659	33.7	14,078	4511	32.0
Productive cough	13,844	1963	14.2	14,081	1980	14.1
Vaginal discharge	13,844	160	1.2	14,081	155	1.1
Tobacco or betel use in past 7 d						
Betel nut, chewing	13,844	9460	68.3	14,080	9641	68.5
Tobacco, chewing*	13,844	1359	9.8	14,077	1570	11.2
Height <150 cm	13,819	7250	52.5	14,062	7246	51.5
BMI <18.5 (kg/m^2)	13,813	5338	38.6	14,057	5564	39.6
Living standards index ≥−0.20859[4]	13,873	7130	51.4	14,099	7159	50.8
Infant characteristics						
Male	13,901	7100	51.1	14,121	7281	51.6
Fed colostrum	13,362	13,188	98.7	13,572	13,410	98.8
Place of delivery, home*	13,722	11,476	83.6	13,961	11,494	82.3
Stunting at birth[5]**	10,297	3680	35.7	10,416	3319	31.9
Wasting at birth[5]	8172	851	10.8	8529	881	10.0
Underweight at birth[5]**	10,523	3879	36.9	10,640	3412	32.1
Gestational age at birth, wk*		13,333	38.6 ± 3.1[6]		13,475	38.9 ± 2.9
Breastfeeding initiation, h		13,179	7.5 ± 15.0		13,373	7.4 ± 14.9

[1]*P < 0.05, **P < 0.001 through use of χ^2 or ANOVA. MM, multiple micronutrients.
[2]Values are percentages (all such values).
[3]Fetal loss includes induced abortions, miscarriages, and stillbirths among previously pregnant women,
[4]Median of the living standards index created through use of principal component analysis.
[5]Stunting defined as length-for-age z score <−2, wasting defined as weight-for-length z score <−2, underweight defined as weight-for-age z score <−2.
[6]Values are means ± SDs (all such values).

maintaining parsimony. In the random-effects portion, children were nested within a sector and the correlation structure was one of compound symmetry.

We first estimated treatment effects of MM over IFA supplementation for each outcome at birth, 1, 3, 6, 12, and 24 mo. These figures were obtained by calculating the differences of expected values between MM- and IFA-supplemented groups for the fixed-effects portion of the mixed models. We calculated 95% CIs of those treatment effects. Treatment effects also were estimated after adjusting for birth measurements. Similar results were found when treatment effects were estimated by use of simple cross-sectional comparisons by age. We also estimated the rates of change of each outcome and their SEs for both treatment groups for the periods 0–3, 3–6, 0–6, 6–12, and 12–24 mo by dividing the differences of the expected values of the outcome variable from the fixed-effects portion of the model between 2 measurements by the length of period. We also calculated the differences of these rates of change between treatment groups and their 95% CIs.

In addition, to estimate the risk reduction in stunting, we used generalized estimating equation (GEE) logistic regression analysis with a log link (to obtain RRs) that involved an exchangeable correlation structure and an indicator variable for the supplement allocation, with IFA as the referent category. For testing differences in scores by supplement group on the composite cognitive, language, and motor performance scores, we used GEE linear regression analysis. Normative scaled scores were derived from raw scores based on the age of the child. All of the mixed-effects data analyses were conducted using the linear and nonlinear mixed effects package in R version 3.0.2 (R Foundation). The GEE regression models were run in SAS version 9.2 (SAS Institute).

RESULTS

Figure 1 provides the number of pregnancies, live births, and infants studied for anthropometry from birth through 24 mo of age by maternal supplementation group. Early losses were caused largely by infant deaths, whereas later losses were the result of families having moved out of the study area. Follow-ups after 3 mo did not commence until some children had aged beyond 6, 12, and 24 mo, which explained the higher but comparable loss-to-follow-up by group at these ages. In all, 8529 children had at least their weight taken at each of the visits. Most maternal and household characteristics at enrollment and status of infants at birth did not differ between groups, although low-grade fever and use of chewing tobacco in the past 7 d was significantly different between the 2 groups (**Table 1**). At birth, gestational age was higher and prevalence of stunting and underweight but not of wasting was lower in the MM group than in the control arm of IFA.

From birth to ~5 mo of age, predicted LAZ increased in both groups, with a trend for the increase being higher in the MM group than in the IFA control group (**Figure 2**); linear growth faltering began after 5 mo of age, reaching its nadir by 20 mo. Before adjustment for size at birth indicators, the MM group was significantly higher than the IFA group through 6 mo for LAZ and WAZ and through 1 mo for WLZ (**Table 2**). After adjusting for the birth difference, the difference at early ages between the 2 groups become nonsignificant for most measures of size. At 12 and 24 mo the adjusted difference in these indicators reversed, with lower LAZ being observed in the MM group than the IFA group. WLZ scores were lower in the unadjusted analysis through 1 mo of age, but in the adjusted analysis they were incrementally lower at each of the ages in the MM group than the IFA group.

Mean (SD) LAZ, WLZ, and WAZ and prevalence of stunting, wasting, and underweight by age of assessment in the longitudinal sample are provided in **Supplemental Tables 1 and 2**. By age 24 mo the mean LAZ was −2.0 in both groups, and the prevalence of stunting was ~50%. Children born to MM- compared with IFA-supplemented mothers exhibited a lower risk (RRR) of stunting and underweight at 1 and 3 mo of age, although by 6 mo this difference was no longer detectable (**Table 3**). The difference also was not seen at the later ages of 12 and 24 mo (data not shown). The risk of wasting was lower in the MM group at 1 mo of age but not thereafter.

Growth velocities presented as rates of weight, length, and head circumference gain per month declined with age and were not different by treatment group and lower by a small magnitude (6–7 g for weight, 0.02 cm for length, and 0.01 cm for head circumference per month) in the intervention compared with the control group, albeit statistically significant (**Table 4**). Cognitive, language, and motor performance composite scores did not differ between the 2 groups (**Table 5**).

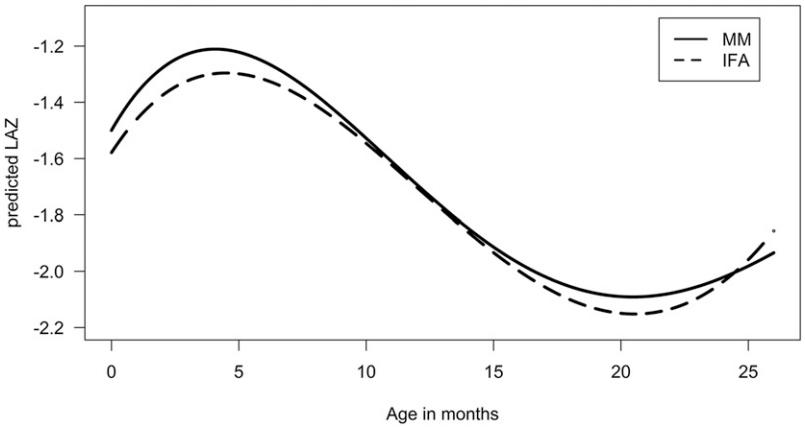

FIGURE 2 Predicted length-for-age *z* scores from birth until 24 mo of age by prenatal MM compared with IFA supplementation group by use of a linear mixed-effects model with a fourth-order polynomial (n = ~8529). IFA, iron-folic acid; LAZ, length-for-age *z* score; MM, multiple micronutrient.

TABLE 2
Predicted z score differences by age between MM and IFA supplementation groups before and after adjustment for difference at birth[1]

	Unadjusted difference[2]		Adjusted difference for size at birth[2]	
	Predicted	95% CI	Predicted	95% CI
LAZ				
At birth	0.08	(0.02, 0.13)	—	
1 mo	0.09	(0.04, 0.14)	0.01	(−0.00, 0.03)
3 mo	0.10	(0.04, 0.15)	0.02	(−0.02, 0.05)
6 mo	0.06	(0.01, 0.12)	−0.02	(−0.05, 0.02)
12 mo	0.01	(−0.04, 0.06)	−0.07	(−0.10, −0.04)
24 mo	0.01	(−0.06, 0.09)	−0.06	(−0.13, 0.00)
WAZ				
At birth	0.11	(0.06, 0.16)	—	
1 mo	0.11	(0.06, 0.15)	−0.00	(−0.02, 0.01)
3 mo	0.09	(0.04, 0.13)	−0.02	(−0.06, 0.01)
6 mo	0.04	(0.00, 0.09)	−0.07	(−0.10, −0.03)
12 mo	−0.01	(−0.06, 0.04)	−0.12	(−0.15, −0.09)
24 mo	0.01	(−0.06, 0.07)	−0.10	(−0.16, −0.04)
WLZ				
At birth	0.08	(0.04, 0.13)	—	
1 mo	0.05	(0.01, 0.09)	−0.03	(−0.06, −0.01)
3 mo	0.01	(−0.03, 0.05)	−0.07	(−0.12, −0.03)
6 mo	−0.01	(−005, 0.03)	−0.09	(−0.14, −0.04)
12 mo	−0.01	(−0.06, 0.03)	−0.10	(−0.14, −0.05)
24 mo	−0.03	(−0.11, 0.04)	−0.12	(−0.20, −0.03)

[1] n = ~8529. IFA, iron-folic acid; LAZ, length-for-age z score; MM, multiple micronutrient; WAZ, weight-for-age z score; WLZ, weight-for-length z score.

[2] Linear mixed-effects model with a fourth-order polynomial; predicted differences and 95% CIs were obtained by calculating differences of expected values between the MM group and the IFA group (MN-IFA) for the fixed-effects part of the mixed models. Adjusted predicted differences were estimated by including each indicator at birth in the model.

TABLE 3
Effect of MM supplementation on anthropometric outcomes[1]

Approximate age, mo	Stunting	Wasting	Underweight
1	0.95 (0.92, 0.98)	0.88 (0.79, 0.98)	0.90 (0.88, 0.93)
3	0.91 (0.88, 0.94)	0.96 (0.86, 1.06)	0.92 (0.88, 0.95)
6	0.97 (0.92, 1.02)	1.02 (0.90, 1.16)	1.01 (0.96, 1.06)

[1] n = ~8529. Values are RRs (95% CIs). Estimated with GEE logistic regression analysis with a log link, adjusted for differences in anthropometric indicators at birth and age of assessment at follow-up. GEE, generalized estimating equation; MM, multiple micronutrient.

DISCUSSION

In rural Bangladesh we found that prenatal MM supplementation, which led to an incremental increase in size at birth, attributed to longer gestational age, had a small effect on postnatal LAZ and stunting through 3 mo of age, but not beyond this point. The prevalence of stunting and underweight at 3 mo of age was lower by 8–9% in the intervention group relative to the control group after adjusting for the supplementation effect at birth. From 6 mo and beyond, growth velocities uniformly declined with age in both groups, although linear growth began decelerating slightly earlier in MM supplement–exposed than IFA supplement–exposed infants between 3 and 12 mo of age. There was some evidence of difference at birth being reversed during the period between 3 and 12 mo of age, with growth velocity becoming slower in the MM group compared with the control group. This, however, should be interpreted in light of the prenatal supplementation effects that resulted in a substantial increase in gestational age at birth (0.3 wk), which led to an increase in size at birth (13). Because the children born in the MM supplement group were slightly older, they may have exhibited growth deceleration at a slightly earlier age postnatally than children in the IFA group. As such, during the period from 3 to 12 mo of age, the rate of change in LAZ appeared to be slightly but statistically significantly lower in the intervention group relative to the control group. This stems in part from the use of the WHO growth standards, which do not take into account gestational age at birth, and we acknowledge this as a limitation of our study. The tendency toward a lower WLZ in the first 6 mo could result from the MM-supplemented infants having sustained greater length at birth into the postnatal period. The same infants may be expected to become slightly thinner by virtue of being somewhat longer, at least for a short time, in the absence of a difference in their exposure, except possibly through elevated amounts of MMs through breast milk.

Irrespective of maternal supplement allocation, both groups of infants accelerated in their linear growth in the first 3 to 4 mo of life, which was interpreted as their exhibiting catch-up growth. Mean z scores across all 3 indicators of length, weight, and weight-for-length improved in early infancy, reached a peak at 3–4 mo of age, and were followed by a steady decline against the referent, which continued through ~20 mo of age; after this point z scores appeared to increase. This growth trajectory, found through use of longitudinal data, is somewhat different from the attained growth curves described for 54 Demographic Health Surveys based on cross-sectional data; here, this early improvement in z scores through 3–4 mo of age is not as evident (16). Exclusive breastfeeding in the first 6 mo of life is critical, but we found rates of exclusivity in this population of ~65% up to 3 mo, which declined to ~20–25% by 6 mo of age (17). This may be a factor in influencing the dramatic deceleration in growth that is observed and may be related to improper and early introduction of complementary foods, which can result in increased morbidity and subsequent growth faltering (18). It is worth noting that the MM supplementation continued in the postpartum period through 3 mo (13).

Few studies, to our knowledge, have examined the impact of prenatal MM supplementation on child growth. One trial of MM supplementation compared with iron alone in periurban Mexico found no effect on height, weight, and head circumference of children at 24-mo follow-up (19). To date, only one study has shown any benefit of prenatal MM supplementation on children's anthropometry beyond birth. This study, conducted in Nepal, also showed substantial improvements in birth weight from the intervention (20), similar to our parent trial. At follow-up, children of mothers who were randomly assigned to receive the MM supplement had higher WAZ z scores and head circumferences at 2 y of age (21); however, when followed up at 8.5 y of age, the same cohort did not differ in their weight, height, or BMI by supplementation group (22), suggesting that the early differences were not sustained.

The American Journal of Clinical Nutrition

TABLE 4
Rate of weight, length, and head circumference gain per month within different age intervals in the first 2 y of life by maternal supplementation group[1]

	0–3 mo		3–6 mo		6–12 mo		12–24 mo	
Indicator	IFA	MM	IFA	MM	IFA	MM	IFA	MM
Weight, kg/mo								
Rate (SE)	0.861 (0.003)	0.863 (0.003)	0.475 (0.002)	0.470 (0.002)	0.190 (0.001)	0.183 (0.001)	0.144 (0.001)	0.143 (0.001)
Diff (95% CI)	0.002 (−0.007, 0.010)		−0.006 (−0.011, −0.001)		−0.007 (−0.011, −0.003)		−0.001 (−0.004, 0.003)	
Length, cm/mo								
Rate (SE)	3.619 (0.010)	3.634 (0.010)	2.065 (0.006)	2.049 (0.006)	1.087 (0.004)	1.068 (0.004)	0.848 (0.004)	0.846 (0.004)
Diff (95% CI)	0.015 (−0.012, 0.041)		−0.016 (−0.032, 0.000)		−0.019 (−0.030, −0.008)		−0.003 (−0.014, 0.009)	
Head circumference, cm/mo								
Rate (SE)	1.950 (0.005)	1.936 (0.005)	0.913 (0.003)	0.899 (0.003)	0.329 (0.002)	0.319 (0.002)	0.216 (0.002)	0.216 (0.002)
Diff (95% CI)	−0.015 (−0.030, 0.000)		−0.014 (−0.023, −0.0060)		−0.010 (−0.016, −0.004)		0.000 (−0.006, 0.0060)	

[1] n = ~8529. The estimated rates of change and their SEs for the period of 0–3, 3–6, 6–12, and 12–24 mo were obtained by dividing the differences between 2 measurements of the expected values of the outcome variable from the fixed-effects part of the mixed-effects model by the length of period. Also calculated were the differences of these rates of changes between treatment groups and their 95% CIs. Diff, difference; IFA, iron-folic acid; MM, multiple micronutrient.

TABLE 5
Performance on the Bayley-III at 24 mo of age by supplementation group[1]

Index[2]	IFA (n = 384)	MM (n = 348)	Difference (95% CI)[3]	P[3]
Cognitive	76.5 ± 7.8[4]	76.2 ± 7.0	−0.32 (−1.33, 0.68)	0.52
Language	85.2 ± 10.0	85.3± 8.9	0.04 (−1.70, 1.78)	0.97
Motor	90.7 ± 7.8	90.1 ± 7.4	−0.60 (−1.58, 0.37)	0.22

[1] GEE, generalized estimating equation; IFA, iron-folic acid; MM, multiple micronutrient.

[2] All 3 indexes were composite scores derived from raw scores. n = 1 each missing in IFA and MM groups.

[3] Estimated with GEE linear regression analysis in the MM compared with IFA.

[4] Values are means ± SDs (all such values).

A meta-analysis involving 4 studies found the mean difference in height-for-age and weight-for-height z scores between the prenatal MM supplementation group compared with control group, assessed any time at postnatal age younger than 5 y, to be 0.01 (95% CI: −0.07, 0.10) and 0.05 (95% CI: −0.03, 0.14), respectively (8). In a randomized controlled trial in Burkina Faso of a lipid-based nutritional supplement (containing small amounts of energy and protein in addition to MMs) compared with a "control" receiving a MM supplement, linear growth velocity did not differ, and the previously noted difference in size at birth leveled off during infancy (9).

Prenatal supplementation did not affect cognitive function assessed at 24 mo of age through use of Bayley scales of infant and toddler cognitive, language, and motor function. Few studies, to our knowledge, have examined the impact of prenatal MM supplementation on childhood cognitive function. In rural Nepal, we assessed neurocognitive outcomes in a cohort of children 7–9 y of age born to women who participated in a prenatal MM supplementation trial and found that IFA but not MMs (including IFA) enhanced aspects of intellectual, motor, and executive functioning (23). A trial in Indonesia showed that prenatal MM supplementation benefited subgroups of children born to undernourished and anemic mothers, but found no overall domain or function to be affected (24). It is likely that the Bayley-III test is not sufficiently sensitive to discern cognitive and motor differences in early childhood, although the lack of difference in anthropometry parallels these findings.

Our large sample allowed us to look at patterns of growth using a longitudinal analytic approach to discern differences between prenatal supplementation groups. The randomized design allowed growth differences between groups to be interpreted within a causal framework. Undernutrition is common in this Bangladeshi population, and without intervention, growth deceleration that begins from ~4–6 mo of age becomes rapid through nearly 24 mo of age. In a recent study conducted in this same population, we showed that complementary year-long, daily, ready-to-use food supplementation, beginning at 6 mo of age, can improve growth velocity and reduce stunting prevalence at 18 mo by 4–6% (17). At 6 mo of age, when supplementation commenced, however, 25% of children already were classified as having stunted growth. The first 6 mo of life may be a critical period for enhancing postnatal growth and preventing growth faltering, but breastfeeding-promotion interventions in

a systematic review and meta-analysis of 35 studies reported no impact on child growth (25).

In conclusion, a prenatal intervention of MM supplementation resulted in many benefits to newborns and in birth outcomes, as was shown in a recent meta-analysis (7). The difference in size at birth was sustained through 3 mo of age, and stunting and underweight were reduced at 3 mo of age. Although the tempo of linear growth was not different in subsequent months related to prenatal supplementation, an early-life programming effect cannot be ruled out. Prenatal MM supplementation conveys a fetal life and possibly an early postnatal life health advantage to offspring in undernourished rural settings and should be considered for programmatic use in low- and middle-income countries. Given the high burden of growth failure and stunting in this region of Bangladesh, complementary food supplementation to promote growth beginning at ∼6 mo of age (17) may help mitigate linear growth stunting in the first 1000 d of life.

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