Effect of antenatal and infant micronutrient supplementation on middle childhood and early adolescent development outcomes in Tanzania

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***Running Title*:** Micronutrient Supplementation and Development

Abstract

Background: There is growing evidence that nutritional interventions in the first 1,000 days of life may influence long-term health and development outcomes. Few studies have examined the effect of maternal and infant micronutrient supplementation on development outcomes in sub-Saharan Africa.

Methods: We conducted a follow-up study of two randomized trials of antenatal and infant micronutrient supplementation conducted in Dar es Salaam, Tanzania. We assessed the effect of maternal multiple micronutrient (MMN) supplementation in pregnancy on development of children at 11-14 years of age. We also examined the effect of infant zinc and MMN supplementation on development at 6-8 years of age. We use generalized linear models to assess standardized mean differences (SMDs) in general intelligence, executive function and mental health scores.

Results: We followed-up 446 children whose mothers were enrolled in the maternal MMN supplementation trial and 365 children who were enrolled in the infant zinc and MMN supplementation trial. We found no effect of maternal MMN supplementation on general intelligence (SMD: -0.03; 95% CI: -0.15, 0.09), executive function (SMD: 0.00; 95% CI: -0.11, 0.11) and mental health scores (SMD: 0.06; 95% CI: -0.10, 0.22). We also found no effect of either infant zinc or MMN supplementation on any of the three development domains (p-values >0.05).

Conclusions: We found that antenatal MMN supplementation and infant zinc and MMN supplementation did not have a large effect on development outcomes in middle childhood and early adolescence in Tanzania.

Introduction

It is estimated that 250 million children under the age of 5 years in low- and middle-income countries (LMICs) do not currently reach their full developmental potential (1). Suboptimal cognitive, language, motor and socioemotional development in LMICs is likely related to a combination of poverty-related biological, environmental, and psychosocial exposures (2). Developmental deficits during early childhood may persist and have a range of consequences across the life course including poor schooling achievement and reductions in lifetime earnings (3, 4). Therefore, interventions that promote early child development in LMICs may produce significant individual and societal benefit.

The first 1,000 days of life (conception through 2 years of age) represents a critical window of child growth and brain development. There is a relatively large body of observational evidence linking low birth weight and linear growth faltering with suboptimal cognitive and motor development (2, 5). Observational studies have also linked nutritional intake and status during pregnancy with early childhood with later developmental outcomes (6, 7). However, evidence on the effect of nutrition interventions during the first 1,000 days of life on short- and long-term development outcomes in LMICs is much more limited. Long-term follow-up studies of randomized trials of prenatal (maternal) multiple micronutrient (MMN) supplements in pregnancy conducted in Indonesia, China, and Nepal have noted null or mixed effects on development outcomes in middle childhood and early adolescence; however, there is some indication that MMN may provide greater benefits for girls and children born to mothers who were anemic in pregnancy (8-11). As for post-natal (infant) micronutrient supplementation, the most recent Cochrane Review on zinc supplementation, that included no trials from sub-Saharan Africa, found no effect on mental and psychomotor development scores (12). As a result, the evidence on the effect of maternal and infant micronutrient supplementation on development outcomes is mixed and is particularly limited in the population of mothers and infants in sub-Saharan Africa.

We present a long-term follow-up study of two randomized trials of maternal and child micronutrient supplementation conducted in Dar es Salaam, Tanzania. The first trial randomized HIV-uninfected pregnant women to daily MMN supplementation or placebo; we assessed development

outcomes of their children at 11-14 years of age (13). The second trial examined the effect of child zinc and MMN supplementation among HIV-uninfected infants; we followed-up these children at 6-8 years of age (14). In this report we examined the effect of the randomized supplementation regimens in each trial on general intelligence, executive function and on instruments reflecting mental health.

Materials and Methods

Study Population

The protocol for this long-term child development follow-up study has been fully detailed elsewhere (15). Briefly, we enrolled children from two randomized, double-blind trials of micronutrient supplementation conducted in Dar es Salaam, Tanzania: 1) a trial of maternal MMN supplementation in pregnancy (NCT00197548) and 2) a trial of infant zinc and MMN supplementation (NCT00197548) (13, 14).

The maternal multivitamin supplementation trial began enrollment in August 2001 and completed follow-up for the primary outcomes in February 2005 (13). The trial enrolled 8,428 HIV-uninfected pregnant women at 12-28 weeks gestation. Pregnant women were randomized to either a daily MMN or placebo regimen and were supplemented and followed up until 6 weeks postpartum. The MMN supplements contained 20 mg of vitamin B1, 20 mg of vitamin B2, 25 mg of vitamin B6, 100 mg of niacin, 50 µg of vitamin B12, 500 mg of vitamin C, 30 mg of vitamin E, and 0.8 mg of folic acid. These amounts were twice the recommended dietary allowance (RDA) for vitamin E and 6 to nearly 20 times the RDA for B vitamin complex and vitamin C (16). All participants received 60 mg iron and 0.25 mg folic acid (IFA) as standard of care.

The infant micronutrient supplementation trial began enrollment in July 2007 and completed follow-up for the primary outcomes in May 2011 (14). The trial enrolled 2,400 HIV-unexposed infants at 6 weeks of age and supplemented children to 18 months of age. Infants were randomized in a factorial design to receive a daily oral dose of one of four trial regimens: 1) zinc, 2) MMN, 3) zinc + MMN, or 4) placebo. Infants received one capsule per day from 6 weeks to 6 months of age and then two capsules per

day from 7 months of age to the end of follow-up at 18 months post-randomization. Infants in the zinc group received capsules that contained 5 mg of zinc. Infants in the multivitamin group received capsules that contained 60 mg of vitamin C, 8 mg of vitamin E, 0.5 mg of thiamine, 0.6 mg of riboflavin, 4 mg of niacin, 0.6 mg of vitamin B-6, 130 mg of folate, and 1 mg of vitamin B12. These doses were between 150% and 600% of the RDA or Adequate Intake (AI) for children 0-6 months of age and 200–400% of the RDA or AI for infants older than 6 months.

Child Development Follow-up Procedures and Assessments

The follow-up study was conducted from July 2015 – March 2017. All child participants of the maternal supplementation and child supplementation trials were eligible for recruitment into the follow-up study. Children of mothers who were enrolled in the maternal multivitamin supplementation trial were 11-14 years of age at the time of the follow-up study, while children enrolled in the infant zinc and multivitamin supplementation trial were 6-8 years of age. Written informed consent was sought from mothers or primary caregivers for all child participants; children were excluded from the study if the mother or primary caregiver did not consent for participation.

A full description of the child development test battery used in the follow-up study has been detailed elsewhere (15, 17). Briefly, we administered the East African Neurodevelopment Tools to children in both trials (17); the tests included the Atlantis, hand movements, footsteps, story completion, Kilifi Naming Test, Rey–Osterrieth complex figure (ROCF), go/no go test for sustained attention and response control (NOGO), shift, people search, literacy and numeracy tests. In addition, the Koh's Block Design Test and Verbal Fluency tests were conducted as assessments of general intelligence. We also administered the Strengths and Difficulties Questionnaire (SDQ) and the Behaviour Rating Inventory of Executive Function (BRIEF) to assess mental health. The study staff who administered the development assessment, the parents, and the children were blinded to their randomized trial group.

We assessed inter-rater reliability of each development test in a subgroup of 18 children by having two interviewers assess the same child at the same time. We conducted these inter-rater reliability

tests regularly at one month intervals during the full period of data collection. Kappa coefficients were used to capture the reliability of responses between interviewers for these 18 children and the results are presented in Supplemental Table 1. There was high agreement between interviewers for all tests (kappa coefficients >0.60), other than the Kilifi naming test (kappa coefficient: 0.42) and verbal fluency (kappa coefficient: 0.47) which had moderate reliability.

Statistical Methods

All primary statistical analyses were based on the intention-to-treat principle and were performed separately by maternal and infant supplementation trial. The development assessments were first grouped into three domains: general intelligence (Atlantis, Footsteps, Hand movement, Kilifi naming test, Koh's block design test, Story completion, and verbal fluency), executive function (Literacy, Numeracy, NOGO, People search, ROCF copy, ROCF recall, and Shift), and mental health (BRIEF and SDQ). Individual test scores were converted to z-scores and averaged to create a composite z-score for each of the three domains. This analytic method was used to reduce the risk of Type I errors due to multiple testing and has also been used by other studies (11). Prior to z-score conversion, all test scores were examined for skewness and those with a skewness value above 1 or below -1 were log-transformed. If the log-transformation reduced skewness, the log-transformed score was then converted to a z-score. All scores for which a lower score indicated a better performance were also multiplied by -1 before z-score conversion. All domain scores exceeding 5 standard deviations above or below the median were excluded from the analysis of the domain.

Generalized linear models with robust variances were used to determine the effect of randomized regimen on the general intelligence, executive function, and mental health development domain z-scores. Standardized mean differences (SMDs) and their 95% confidence intervals are presented for each domain. The primary analytic models were adjusted for child sex, age, and interviewer. As a sensitivity analysis, we additionally adjusted for sociodemographic characteristics including baseline maternal education, marital status, parity and household assets due to potential for imbalance by randomized regimen (even if

not statistically significant) and an independent relationship with development outcomes. We also explored whether there was any difference in individual test scores of each domain by randomized regimen using the non-parametric Kruskal–Wallis test. Due to evidence that the effect of maternal MMN supplementation in pregnancy on child development scores may be modified by child sex and maternal anemia status, we also present effect estimates for the maternal supplementation trial stratified by these variables (9, 11). In order to examine the risk of selection bias, we also compared characteristics of children and caregivers that were enrolled in the development follow-up study to those who did not participate. Missing data for covariates were retained in the analysis using the missing indicator method. All p-values were 2-sided and a p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using the SAS v 9.4 (SAS Institute, Cary, NC).

Results

A total of 8,428 pregnant women and 2,400 infants were enrolled in the parent maternal and child micronutrient supplementation trials, respectively. Figure 1 presents the participant flow for the main trials and the child development follow-up study. In the maternal MMN supplementation trial a total of 7,828 infants were alive at the end of the main trial follow-up period at 6 weeks of age; we enrolled 446 children at 11-14 years of age in the follow-up study. In the child zinc and MMN supplementation trial, 2,355 infants were alive at the end of the main trial follow-up at 2 years of age; we enrolled 365 children at 6-8 years of age in the follow-up study. We found that baseline characteristics between children enrolled in the development follow-up study were relatively similar to those who were not enrolled in both the maternal MMN and infant micronutrient supplementation trials (Supplemental Tables 2 and 3). Table 1 presents characteristics of child development follow-up study participants stratified by maternal and child supplementation trial. We examined potential imbalances in baseline characteristics by randomized treatment arm in each trial separately and found no indication of major imbalance between randomized arms in both trials (Supplemental Tables 4 and 5).

Effect of maternal MMN supplementation on development outcomes

The effect of maternal MMN supplementation on general intelligence, executive function and mental health z-scores at 11-14 years old is presented in Table 2. We found no effect of maternal MMN supplementation on any of the three development domains (p-values >0.05). In sensitivity analyses we also found no effect of maternal MMN after multivariate adjustment (Supplemental Table 6) or on individual test scores within the domains (Supplemental Table 7). In an exploratory analysis, we examined the effect of MMN on development outcomes stratified by maternal anemia status at trial enrollment in pregnancy and by child sex (Supplemental Table 8). There was some indication, although not statistically significant, that there may be a greater effect of MMN on mental health among pregnant women who were anemic at enrollment (SMD: 0.15; 95% CI: -0.07, 0.36) as compared to those who were not anemic (SMD: 0.06; 95% CI: -0.29, 0.42) (p-value for effect modification: 0.24). There was no indication that child sex modified the effect of MMN supplementation on development.

Effect of infant zinc and MMN supplementation on development outcomes

In the factorial designed infant supplementation trial, we found no evidence of interaction of infant zinc and MMN supplementation on the three development domains and therefore we present the study arms collapsed (p-values for interaction >0.05). We found no effect of infant zinc or MMN supplementation any development domain at 6-8 years of age (Table 3). We also found no effect of zinc or MMN supplementation on any development after multivariate adjustment (Supplemental Table 9) or on individual tests within the three domains (Supplemental Table 10).

Discussion

In this long-term follow-up study, we found no significant effect of maternal MMN supplementation in pregnancy on general intelligence, executive function or mental health of their children at 11-14 years of age. Similarly, we found no effect of infant zinc and MMN supplementation on these development domains at 6-8 years of age.

We did not identify an effect of maternal MMN supplementation on child development outcomes, which is in-line with the overall null findings in other follow-up studies (9, 10); however, there is also some evidence that MMN in pregnancy may provide child development benefits in some populations or subgroups of children (8, 9, 11). In a follow-up study conducted in Indonesia, children whose mothers received antenatal MMN supplementation scored a mean 0.11 standard deviations higher on procedural memory tests at 9-12 years of age as compared to children of mothers who received iron-folic acid alone (11). Additionally, this study found that children of anemic pregnant women who received MMN scored 0.18 standard deviations higher on general intelligence tests as compared to children of anemic pregnant women who received iron-folic acid alone (11). In our study, we found some indication in study that MMN may have a greater positive effect on mental health among children born to anemic mothers. This evidence suggests that MMN may provide greater benefit for mothers who are undernourished in pregnancy. Another recent study of maternal MMN in Nepal found no overall effect on child IQ at 12 years of age; however, girls whose mothers were randomized to MMN had significantly higher IQ (~3 IQ points) than girls of mothers who were randomized to iron-folic acid alone (9). There is also evidence that MMN supplementation in pregnancy may produce greater survival benefits for female as compared to male infants (18). As a result, further research on differences in the response to micronutrient supplementation in pregnancy by maternal nutritional status and sex are needed.

There are multiple mechanisms by which micronutrient supplements in pregnancy could influence child development outcomes. There is evidence that some vitamins and minerals, like vitamin B12, have a direct effect on brain development and function (19). A recent trial in India determined that children of mothers who received vitamin B12 supplementation in pregnancy had significantly higher scores on expressive language scores as compared to children of mothers who received placebo (20). There are also many indirect pathways through which micronutrients may potentially provide benefit, including increases in birthweight, reduction in risk of prematurity, and reductions in maternal and fetal inflammation that may subsequently influence child development (18, 21). In the primary report of the maternal supplementation trial, we found that antenatal MMN reduced the risk of low birth weight by

18%; low birth weight is a well-characterized predictor of suboptimal child cognitive development (13, 22, 23). Therefore, research is needed to determine which components of multivitamins may produce positive effects and also their mechanisms of action.

Prophylactic zinc supplementation for infants 6-24 months of age has been shown to reduce diarrhea incidence (24); however, the effect on child development outcomes remains equivocal (12). Diarrhea during infancy has been negatively linked with cognitive development; however, the effect for each additional diarrhea episode is suspected to be small (SMD <0.10) (25, 26). In the parent trial, we determined that infant zinc supplementation starting at 6 weeks of age reduced the risk of diarrhea during the 18-month follow-up period; however, in this follow-up study we found no significant effect on development outcomes at 6-8 years of age (14). The most recent Cochrane review determined there was no effect of infant zinc supplementation on mental development index (MDI) and psychomotor development index (PDI) scores of the Bayley Scales of Infant Development, although due to the small sample size the uncertainty in the estimates was large (12). As a result, larger studies of prophylactic zinc supplementation and child development will be needed to identify an effect size that may be 0.10 SD or less.

There is sparse evidence on the effect of infant MMN supplementation on development outcomes. The most recent meta-analysis identified six infant MMN trials that suggested there may be potential for benefit on mental development (SMD: 0.08; 95% CI: -0.01, 0.18), but the results were not statistically significant (27). Nevertheless, there is growing evidence that infant vitamin B12 supplementation, which was a component of our MMN supplements, may produce positive cognitive and motor effects. A recent randomized controlled trial of vitamin B12 and folic acid supplementation among Indian children aged 6–30 months found that children provided with both vitamin B12 and folic acid had better gross motor and problem solving functioning as compared to those who received placebo (27, 28). Overall, there are significant research gaps on the role of individual and combined micronutrient supplementation in development of infants and children.

There are a few limitations of this study. Foremost, we were only able to enroll 5% of the maternal supplementation trial cohort and 15% of the infant supplementation trial cohort and therefore our study is at risk of bias due to loss to follow-up. Although the measured baseline characteristics of study participants who were enrolled in the development follow-up study tended to be similar to participants who were not enrolled, we cannot empirically rule out the potential for selection bias. In addition, due to the small sample size of the follow-up study cohorts, we had limited power (<20%) to detect differences in child development that are likely for nutritional interventions in pregnancy and infancy (~0.1 standard deviations) (27). In addition, the full battery of development assessments used in our study has also not been directly validated for children in Tanzania and therefore there is a risk of non-differential misclassification for individual test and domain scores that would bias estimates to the null. As a result, studies examining the effect on objective measures of neuroanatomy and neurologic function may produce different results (29, 30).

We found that antenatal MMN supplementation and infant zinc and MMN supplementation did not have a large effect on general intelligence, executive function and mental health among Tanzanian children in middle childhood and early adolescence; however, we cannot rule out small to moderate beneficial or harmful effect. Integrated nutrition, environmental and stimulation interventions may produce larger positive effects on development of children in LMICs.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

WWF, CPD and KPM were the Principal Investigators of the parent trials. WWF, CPD, KPM, and RK contributed to conduct of the parent trials. TAS, IK, MH WWF, CPD and KPM designed the development follow-up study and obtained funding. KPM, RK, IK, MH, DCM, TAS, CPD, and WWF were involved in the adaptation and training of the development tool assessments used in the follow-up study. KPM and RK led field implementation of the follow-up study. CRS and AMD conducted the statistical analysis. CRS drafted the initial manuscript. All authors made significant contributions to editing the manuscript and all approved of the final manuscript for submission.

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Supplementary Information

Supplementary information is available at EJCN's website

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Table 1. Maternal and child characteristics of development follow-up study participants for the maternal supplementation [n=446] and infant supplementation [n=365] trial cohorts

	Maternal Supplementation Trial [n=446]	Infant Supplementation Trial [n=365]
Baseline maternal and socioeconomic characteristics		
Age, years		
< 20	22 (4.9)	13 (3.6)
20 – 24	106 (23.8)	88 (24.4)
25 – 29	181 (40.6)	129 (35.7)
≥ 30	137 (30.7)	131 (36.3)
Education, years		
None / did not complete primary	37 (8.1)	6 (1.7)
Primary	298 (63.2)	238 (65.8)
Secondary	106 (22.0)	99 (27.4)
Post-secondary	30 (6.7)	19 (5.2)
Married or living with partner	409 (91.7)	331 (91.7)
Prior pregnancies		
None	49 (11.0)	97 (26.7)
1 – 4	375 (84.1)	256 (70.5)
≥ 4	22 (4.9)	10 (2.8)
Household possessions[1]		
None	17 (3.8)	134 (37.0)
1 - 3	257 (57.6)	196 (54.1)
≥ 4	172 (38.6)	32 (8.8)
Child characteristics		
Age at development assessment		
6-8	0 (0)	365 (100.0)
11-14	446 (100.0)	0 (0)
Sex		
Male	226 (50.7)	191 (52.3)
Female	220 (49.3)	174 (47.7)
Low birth weight (<2500g)	27 (6.1)	6 (1.6)
Preterm (<37 weeks gestation)	67 (15.1)	34 (10.6)

[1]From a list that included a sofa, television, radio, refrigerator, and fan

Table 2. Effect of maternal multivitamin supplementation on general intelligence, executive function and mental health z-scores among children 11-14 years of age [n=446].

	General intelligence z-score (SD)	General intelligence SMD* (95% CI)	p-value	Executive function z-score (SD)	Executive function SMD* (95% CI)	p-value	Mental healt z-score (SD
Placebo [n=237]	0.00 (0.65)	Ref.		0.00 (0.60)	Ref.		-0.02 (0.87)
Multivitamins [n=209]	-0.01 (0.66)	-0.03 (-0.15, 0.09)	0.63	0.00 (0.58)	0.00 (-0.11, 0.11)	0.97	0.02 (0.89)

SMD = standardized mean difference
*Adjusted for child sex, age, and child development assessor

Table 3. Effect of infant zinc and multivitamin supplementation on general intelligence, executive function and mental health z-scores among children 6-8 years of age [n=365].

	General intelligence z-score (SD)	General intelligence SMD* (95% CI)	p-value	Executive function z-score (SD)	Executive function SMD* (95% CI)	p-value	Mental healt z-score (SD
No zinc [n=198]	0.00 (0.58)	Ref.		0.00 (0.59)	Ref.		-0.04 (0.90)
Zinc [n=167]	-0.01 (0.63)	0.02 (-0.09, 0.14)	0.71	0.00 (0.67)	0.03 (-0.10, 0.15)	0.69	0.04 (0.78)
No multivitamins [n=193]	0.00 (0.61)	Ref.		0.00 (0.51)	Ref.		-0.04 (0.78)
Multivitamins [n=172]	0.00 (0.59)	0.04 (-0.07, 0.16)	0.46	0.00 (0.64)	0.00 (-0.12, 0.13)	0.94	0.04 (0.93)

SMD = standardized mean difference
*Adjusted for child sex, age, and child development assessor

Supplemental Table 1. Inter-rater reliability by development assessment test (n=18)

Test	Kappa (95% CI)
Atlantis	1.00 (1.00, 1.00)
Footsteps	0.91 (0.83, 0.98)
Hand movements	0.87 (0.70, 1.00)
Kilifi naming test	0.42 (0.21, 0.64)
Koh's block design test	0.58 (0.36, 0.81)
Literacy	0.87 (0.70, 1.00)
Go/no go test for sustained attention and response control (NOGO)	1.00 (1.00, 1.00)
Numeracy	0.86 (0.68, 1.00)
People search	0.76 (0.56, 0.96)
Rey–Osterrieth complex figure copy	0.81 (0.61, 1.00)
Rey–Osterrieth complex figure recall	0.88 (0.72, 1.00)
Shift	0.88 (0.72, 1.00)
Story completion	0.94 (0.82, 1.00)
Verbal fluency	0.47 (0.23, 0.71)

Figure Legends

Figure 1. Flow chart of participation in child development follow-up study for maternal supplementation and child supplementation trial cohorts

Figure 1 Footnote. Maternal supplementation trial randomized pregnant women to receive multivitamins or placebo supplements from the second trimester of pregnancy to six week postpartum. Infant supplementation trial randomized infants to receive multivitamins and zinc, zinc only, multivitamins only, or placebo supplements from 6 weeks to 18 months of age.