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Original Research Article

Dietary diversity as a modifier of the effect of supplementation with multiple micronutrients during pregnancy on low birth weight in a randomized controlled trial in Bangladesh

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A B S T R A C T

Background: Meta-analysis of trials of multiple micronutrient supplements (MMS) compared with iron-folic acid (IFA) suggests an overall benefit of 12% on low birth weight (LBW).

Objectives: Building on prior work showing that MMS is more effective in anemic and higher body mass index females; this paper explores whether dietary quality modifies the effect of MMS on birth weight.

Methods: A 7-day food frequency questionnaire was administered in late pregnancy to 19,160 pregnant participants in the JiVitA-3 cluster-randomized controlled trial of MMS compared with IFA supplementation in Bangladesh. A 10-item dietary diversity score (DDS) was created by summing the number of food groups consumed ≥4 times per week. Risk ratios (RRs) and 95% confidence intervals (CIs) for the effect of MMS compared with IFA on LBW were estimated by DDS. The interaction between DDS and MMS was tested using a generalized estimating equations log-binomial regression model to account for the cluster randomization. Point estimates and 95% CI for the effect of MMS on LBW were estimated at each DDS. Models were adjusted for confounders. We used $P < 0.1$ to determine the statistical significance of the interaction.

Results: The median DDS was 3 (interquartile range: 2, 4), and 18.6% of pregnant women had a score ≥ 5. The fully adjusted protective effect of MMS on LBW was inversely associated with dietary diversity [MMS×DDS RR: 1.02 (95% CI: 1.00, 1.04), *P*-interaction = 0.05]. The effect was greatest at the lowest DDS [DDS= 1, RR LBW: 0.86 (0.81, 0.91)] and decreased at higher scores [DDS = 7, RR: 0.92 (0.84, 1.00)].

Conclusions: In rural Bangladesh, where maternal dietary diversity was generally low, MMS (compared with IFA) supplementation had the strongest effect on reducing low birth weight among pregnant females with the least diverse diet, possibly reflecting the additional benefit of supplementation in this vulnerable group.

This trial was registered at clinicaltrials.gov as NCT00860470.

Keywords: Multiple Micronutrient Supplements, Dietary Diversity, Maternal Nutrition, Bangladesh, Nutritional Epidemiology

Introduction

Maternal nutrition is an important predictor of fetal and neonatal growth and development [1], but it can be difficult to meet nutritional needs due to the increased physiological demands of pregnancy [2]. This is particularly true in low- and middle-income contexts where females can enter pregnancy with substantial pre-existing nutritional deficits [3].

The WHO recommends iron and folic acid (IFA) supplementation for pregnant females as iron-deficiency anemia is common in pregnancy [4,5]. Recognizing the added benefit of multiple micronutrient supplements (MMS) on birth outcomes [6–8] and the additional nutrient requirements of pregnancy, countries are increasingly piloting the replacement of IFA with MMS [9]. The UNICEF United Nations

Abbreviations: ASF, animal source foods; BMI, body mass index; DDS, dietary diversity score; FFQ, food frequency questionnaire; IFA, iron-folic acid; IQR, interquartile range; LBW, low birth weight; MDD-W, minimum dietary diversity—females; MMS, multiple micronutrient supplements; RR, relative risk; SD, standard deviation; UNIMMAP, United Nations International Multiple Micronutrient Antenatal Preparation.

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International Multiple Micronutrient Antenatal Preparation ("UNIMMAP") MMS formulation includes 15 vitamins and minerals essential for prenatal health [10]. MMS offers additional benefits beyond supplementation with IFA alone, including reduced incidence of low birth weight (LBW) [7]. The movement toward MMS aligns with WHO's recent updates to its antenatal care guidelines, which recommend MMS in the context of rigorous research [11].

Systematic reviews and meta-analyses have demonstrated that the benefits of MMS can vary based on both maternal and infant characteristics. For example, the effect of MMS on birth weight was greater among adolescent females than older females [7], and MMS was also more efficacious among females with low body mass index (BMI) and anemia [12] in an individual participant data meta-analysis. The effect modification observed by these indicators of females' nutritional status suggests that MMS's effectiveness might be influenced by maternal diet quality; however, this question has not been directly examined.

Diet quality can be operationalized in several ways, notably as dietary variety or diversity [13]. Dietary diversity can also function as a proxy for micronutrient adequacy [14], as in the minimum dietary diversity for women (MDD-W) indicator [15]. The MDD-W is an easy-to-use indicator calculated by summing the total of 10 food groups consumed over the preceding 24-hour period and dichotomized using a cut-off of 5 of 10 food groups [16]. A validation study of nonpregnant, nonlactating females found that it captured a 60% mean probability of adequacy for 11 micronutrients [17].

Northwest Bangladesh is a region with limited dietary diversity and micronutrient adequacy [18] and was the site of the JiVitA-3 trial, one of the largest MMS efficacy trials to date. Trial investigators reported a 12% average reduction in the relative risk of LBW among pregnant females receiving MMS as compared with IFA [19]. Dietary intake data using a 7-day food frequency questionnaire (FFQ) were also collected at baseline and late pregnancy for the JiVitA-3 participants.

It can be hypothesized that the benefit of MMS on birth outcomes is achieved through filling maternal nutrient intake deficits in pregnancy. The data from JiVitA-3 offer the opportunity to test whether the effect of MMS in reducing LBW differs by the degree of lack of dietary diversity during pregnancy, thereby strengthening the role of micronutrient deficiencies in the etiology of adverse birth outcomes.

Methods

This secondary analysis used data from the JiVitA-3 double-blind, cluster-randomized controlled trial (n = 28,516 live births) conducted from 2008 to 2012 in the rural Gaibandha and Rangpur districts of northwestern Bangladesh. Although full details of the trial have been published previously [19], briefly, 596 sectors served as clusters and were randomized to receive either MMS or IFA (as control). Within these communities, married females of reproductive age were enumerated and consenting females were enrolled in the study for pregnancy monitoring. Exclusion criteria included age younger than 12 or older than 45 years, living separately from the husband, and nonconsent. Participants were visited every 5 weeks and those who missed a menstrual period were administered a pregnancy test; test-positive pregnant females were enrolled in the trial, whereupon they received one of the 2 supplements—a daily dose of either the UNIMMAP MMS or a combined tablet of 27 mg iron and 600 μg folic acid. The participant's age, pregnancy history, anthropometry, household assets, and education were collected at this initial visit. To capture typical diet during the pregnancy period, trial participants were administered 2 7-day FFQ; 1 in early pregnancy and 1 at ~32 weeks of gestation. The FFQ contained information on 32 micronutrient-rich foods commonly consumed in the project area. Within 72 hours of birth, birth outcome data, including infant anthropometry, were collected. In addition to being followed throughout their pregnancies, participants received follow-up until 6 months postpartum.

Inclusion criteria for this analysis consisted of trial participants with singleton live births, infant anthropometry collected within the 72-hour window, completed late pregnancy FFQ, and complete covariates for maternal age, maternal BMI, parity, maternal education, and maternal socioeconomic status (SES). Only the late pregnancy visit FFQ data were incorporated in the subsequent analyses, as late pregnancy dietary intake was considered both more correlated with birth weight, as it is when females' nutrient needs are highest [20], as well as being more representative of a woman's pregnancy diet given the impact of nausea and food aversions in early pregnancy. Because this choice might possibly affect conclusions, we conducted sensitivity analyses, repeating our analytical process to examine the effects when using only the early pregnancy FFQ as well as the mean of the early and late period; these results are included in the Supplemental Materials.

Because we used dietary data collected in late pregnancy, we wished to test whether consumption was similar across randomized treatment assignments (MMS compared with IFA). To test this, we examined whether the frequency of intake of any of the 32 late pregnancy FFQ food items differed between participants who had consumed MMS and those who had consumed IFA. A Mann-Whitney U-test with a Bonferroni correction ($P = 0.05/32 = 0.00156$) was applied to account for multiple comparisons.

For each woman in the analysis, a dietary diversity score (DDS) was created using food groups from the MDD-W, the most well-studied dietary diversity index [21]. The DDS comprises 10 food groups (grains, roots, and tubers; pulses; nuts; dairy; meat, poultry, and fish; eggs; dark green leafy vegetables; other vitamin A-rich fruits and vegetables; and other vegetables); all foods from the JiVitA FFQ were categorized into one of these 10 MDD-W food groups.

The MDD-W was originally developed for use with 24-hour dietary recall data, with participants scoring a "1" for a food group if they consumed >15 g of any food within that group within the preceding 24-hour period [17]. Because data in this analysis were drawn from a 7-day FFQ, each category was scored as a "1" if foods were consumed ≥ 4 times in the past week, based on the logic that if a food was consumed 4 or more times in the last 7 day, this represented a >50% chance of that food being captured in any given 24-hour period. Rice consumption was not included in the JiVitA FFQ as it is nearly universal and shows little variability in this population [18,22,23]. Therefore, a score of "1" was assigned to all participants for the "Grains, Roots, and Tubers" food group.

The final DDS used for the remainder of this paper was calculated as the sum of the number of 10 food group categories that had been scored as "1". A dichotomous index was also produced, with the cut-off at <5 and ≥5 out of the 10 food groups, to assess what proportion of participants had achieved the definition of minimum dietary diversity, as with the MDD-W.

Risk ratios (RRs) and 95% confidence intervals (CIs) for the effect of MMS on LBW in the presence of the DDS and with the DDS × MMS interaction were estimated using log-binomial regression with robust variance estimation and an exchangeable correlation to take into account the geographical clustering of participants by sector. Multivariable

models were adjusted for known sources of MMS effect heterogeneity, including infant sex (male/female), maternal age (<18, 18–35, or >35 y), maternal parity (0, 1, or ≥2 births), maternal BMI (<18.5, 18.5–<20, 20–<22.5, 22.5–<25.0, 25.0–<27.5, or ≥27.5 kg/m^2), maternal SES (continuous, derived within sample using the previously validated Living Standards Index [24]), and maternal education (0, 1-4, 5-9, or >9 y). Categories for maternal age, parity, and BMI were based on established criteria associated with increased risk of a LBW infant [25].

Four logistic regression models were analyzed using generalized estimating equations to account for geographical clustering of the data. The outcome for each analysis was LBW. The following 5 models were analyzed: *1*) an unadjusted model with only the DDS term; *2*) an unadjusted model with both the MMS and the DDS; *3*) a fully adjusted model, which included all the covariates but without the interaction term; *4*) a fully adjusted model that also included the MMS × DDS interaction; *5*) a model that included an interaction between the MMS × the dichotomous DDS measure.

The Wald test was used to test the statistical significance of the interaction terms in both models 4 and 5. For model 4, point estimates of the effect of MMS as compared with IFA on LBW across all 10 levels of the DDS were generated and plotted. A 10% alpha level was used to determine the significance of the interaction term.

The minimum detectable interaction effect was calculated in advance of the analysis. Using the sample size of 19,136 participants, the prevalence of the 10 levels of dietary diversity within this sample, the random assignment of MMS to 50% of the sample, the relative risk of MMS as compared with IFA on LBW in the JiVitA 3 trial (RR = 0.88, with a SE of 0.02), and using alpha = 0.10 and beta = 0.80, we calculated that we could detect a minimum relative risk of interaction of 1.01 (or 0.99 for the inverse).

Given our threshold for food group consumption had not been previously validated, and considering the novelty of applying the MDD-W approach to 7-day food frequency data, we conducted multiple sensitivity analyses. Specifically, we varied the number of days of consumption per week that were required to score "1" in a given food category—our baseline number was 4 or more times per week, but we also reanalyzed the data using 3 or more times per week and 7 or more times per week to assess how this choice affected our conclusions. We additionally applied alternative cut-offs for minimum dietary diversity such as 6 or 7 out of 10 food groups, rather than the 5 out of 10 applied in our main analysis. These sensitivity analyses did not affect our conclusions, so we are presenting all results based on the 4 days/week scoring criterion.

The JiVitA-3 study protocol and amendments were approved by the Johns Hopkins Bloomberg School of Public Health institutional review board and the Bangladesh Medical Research Council (clinicaltrials.gov Identifier: NCT00860470, trial protocol in supplement 1 and amended trial protocol in supplement 2). An international data and safety monitoring board annually reviewed the trial, procedures, and findings on primary and selected secondary outcomes. Oral informed consent was provided by study participants. No incentives were offered for study participation. All

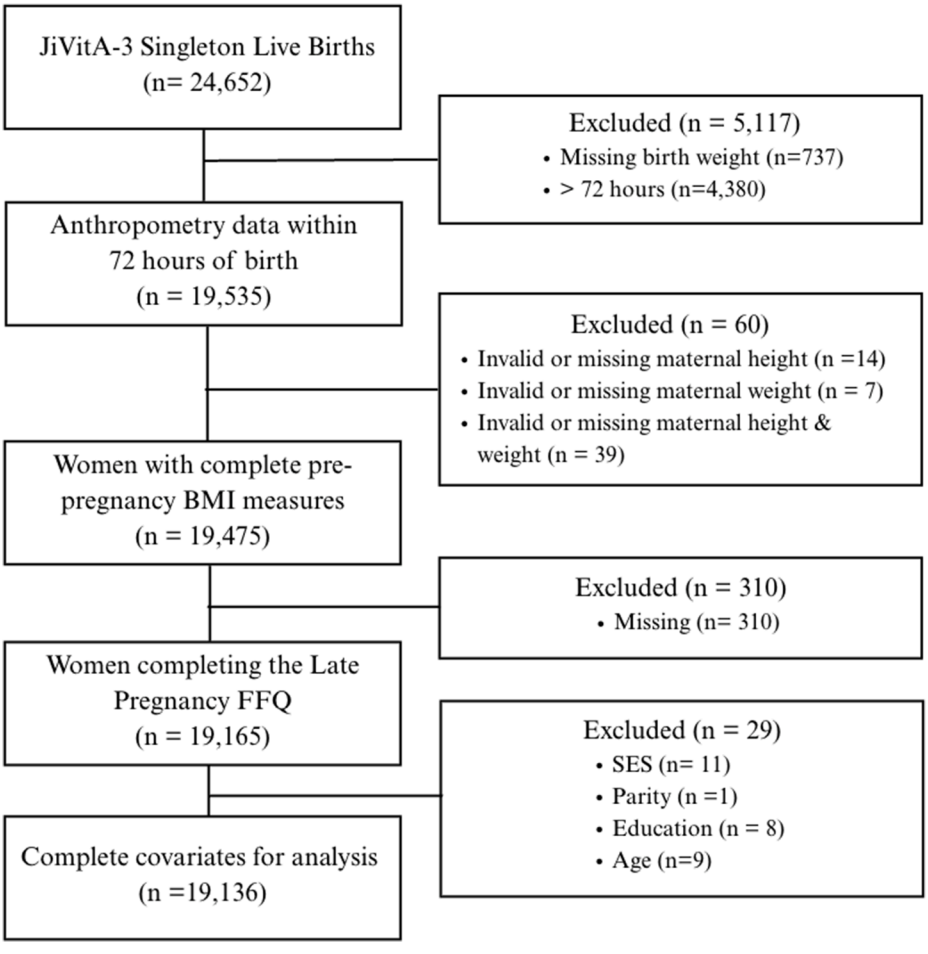


FIGURE 1. Study flow diagram. BMI, body mass index; FFQ, food frequency questionnaire; SES, socioeconomic status.

statistical analyses were conducted in R Studio version 2024.12.0+467.

Results

A total of 19,136 pregnant females contributed data to this analysis; individuals were included if they had experienced singleton live births (n = 24,652, or 86% of the trial sample), with anthropometry collected within 72 hours of birth (n = 19,535, 68.5%), had complete prepregnancy BMI measures (n = 19,475, 68.3%), and had completed the late pregnancy FFQ (n = 19,165, 67.2%), as well as having all other complete covariates for the analysis (n = 19,136, 67.1%) (Figure 1). Characteristics of the population, disaggregated by DDS, are presented in Table 1. Thirty-four percent of participants with a DDS below the minimum diversity cut-off of 5 food groups had multiple prior children (as compared with 27% of females above the 5 food group cut-off), 31% were uneducated (as compared with 16%), and 43% had low BMI (as compared with 36%).

The distribution of food groups contributing to the DDS was right-skewed (Supplemental Figure 1). Consumption of nuts was almost universally zero; both dairy and eggs were consumed either very infrequently or once per week. More variety was seen in the meat, poultry, and fish group, driven primarily by widespread consumption of fish, which was reported at least once in 7 day by >87% of the sample, with 44% reporting consuming >4 times per week. Similarly, the other vegetables group exhibited a wider distribution of consumption, again driven primarily by high frequency consumption of one food item—in this case eggplant, which accounted for 55.2% of the servings captured in the category.

To determine whether MMS had differentially altered participants' frequency of consumption compared with IFA, we compared the frequency of consumption of the 32 JiVitA FFQ food items in late pregnancy between the MMS and IFA arms (MMS n = 9279, IFA n = 9080) and found no differences across the 32 items using a Bonferroni-adjusted P (data not shown).

When each food group category was scored using the modified scoring criteria to account for 7-day compared with 24-hour data (using 4 or more as compared with <4 times per week) the 2 food groups that had the highest proportion of adequate consumption were meat, poultry, and fish (74.2%) and other vegetables (66.5%) (Supplemental Table 1).

We calculated a median DDS of 3 (interquartile range (IQR): 2, 4) and a mean of 3.37 (standard deviation (SD) = 1.35) across the entire sample and the proportion of females achieving the minimum diversity cut-off was 18.4%. The prevalence of the 10 DDS from 1 to 10 was: 1 = 5.6%, 2 = 21.3%, 3 = 32.3%, 4 =22.4%, 5 =11.6%, 6 =4.6%, 7 = 1.7%, 8 = 0.5%, 9 = 0.1%, and 10 = 0.01%. In sensitivity analyses using either the early pregnancy FFQ data or the average of early and late pregnancy FFQ data, we saw lower mean and median DDS and lower prevalence of adequate dietary diversity (Supplemental Table 2).

Across the 4 regression models, the effect of the DDS remained relatively constant, with a 1 level increase in dietary diversity

TABLE 1
Characteristics of analytic sample by dietary diversity score above and below the 5-group cut-off.

	Low dietary diversity (<5 food groups) n = 15,585 (81.4%)	Adequate dietary diversity (≥5 food groups) n = 3551 (18.6%)	Total n = 19,160
Parity			
Nulliparous	4906 (31.5%)	1391 (39.2%)	6297 (33%)
One previous child	5389 (34.6%)	1204 (33.9%)	6593 (34.5%)
More than 1 child	5290 (33.9%)	956 (26.98%)	6246 (32.5%)
Education			
No education	4765 (30.6%)	583 (16.4%)	5338 (27.9%)
Primary education	2489 (16.0%)	358 (10.1%)	2847 (14.9%)
Ninth grade education	5928 (38.0%)	1272 (35.8%)	7200 (37.6%)
More than ninth grade	2403 (15.4%)	1338 (37.7%)	3741 (19.6%)
Body Mass Index (BMI)			
Below 18.5 kg/m^2	6697 (43.0%)	1279 (36.0%)	7976 (41.7%)
18.5 ≤ BMI < 20 kg/m^2	4362 (28.0%)	989 (27.9%)	5351 (27.9%)
20 ≤ BMI < 22.5 kg/m^2	3466 (22.2%)	862 (24.3%)	4314 (22.6%)
22.5 ≤ BMI < 25 kg/m^2	804 (5.2%)	304 (8.6%)	1105 (5.8%)
25 ≤ BMI < 27.5 kg/m^2	192 (1.2%)	87 (2.5%)	279 (1.5%)
> 27.5 kg/m^2	64 (0.4%)	30 (0.8%)	93 (0.5%)
Age			
< 18 y old	2259 (14.5%)	535 (15.1%)	27,940 (14.6%)
18–35 y old	12,907 (82.8%)	2919 (82.2%)	1,582,756 (82.7%)
> 35 y old	419 (2.7%)	97 (2.7%)	5165 (2.7%)
Living standards index			
Mean (SD)	−0.19 (0.86)	0.45 (1.08)	−0.07 (0.94)
Median (IQR)	−0.34 (−0.81, 0.26)	0.28 (–0.40, 1.14)	−0.25 (−0.75, 0.42)
Dietary diversity score (DDS)			
Mean (SD)	2.88 (0.89)	5.53 (0.81)	3.37 (1.36)
Median (IQR)	3 (2–4)	5 (5–6)	3 (2–4)
Treatment allocation			
IFA	7684 (49.3%)	1741 (49.0%)	9425 (49.3%)
MMS	7901 (50.7%)	1810 (51.0%)	9711 (50.7%)

Statistics are presented as n (%) unless otherwise noted.
BMI, body mass index; DDS, dietary diversity score; IFA, iron-folic acid; MMS, multiple micronutrient supplements.

TABLE 2
Regression coefficients for the relative risk of LBW in the MMS compared with IFA arms using the baseline DDS scoring approach[1].

	Model 1: DDS only unadjusted	Model 2: DDS + MMS unadjusted	Model 3: DDS + MMS adjusted[2]	Model 4: DDS × MMS interaction adjusted[2]
DDS	0.96 (0.95, 0.97)	0.96 (0.95, 0.97)	0.99 (0.98, 1.00)	0.98 (0.96, 0.99)
MMS		0.88 (0.86, 0.91)	0.88 (0.85, 0.91)	0.81 (0.75, 0.89)
DDS × MMS				1.02 (1.00, 1.04)
				P-interaction = 0.05

Abbreviations: DDS, dietary diversity score; IFA, iron-folic acid; LBW, low birth weight; MMS, multiple micronutrient supplements, RR, relative risk.
[1] Relative risks were estimated from generalized estimating equations - generalized linear models (GEE GLM) log-binomial regressions with exchangeable correlation structures; the Wald Test was used to determine the significance of the interaction terms. Total sample size was 19,160 pregnant females.
[2] Adjusted for infant sex (male/female), maternal age (<18, 18–35, >35 years), maternal parity (0, 1, ≳2 births), maternal body mass index (<18.5, 18.5–<20, 20–<22.5, 22.5–<25.0, 25.0–<27.5, ≳27.5 kg/m^2), maternal socioeconomic status (continuous, derived within sample using the Living Standards Index, and maternal education (0, 1–4, 5–9, >9 y).

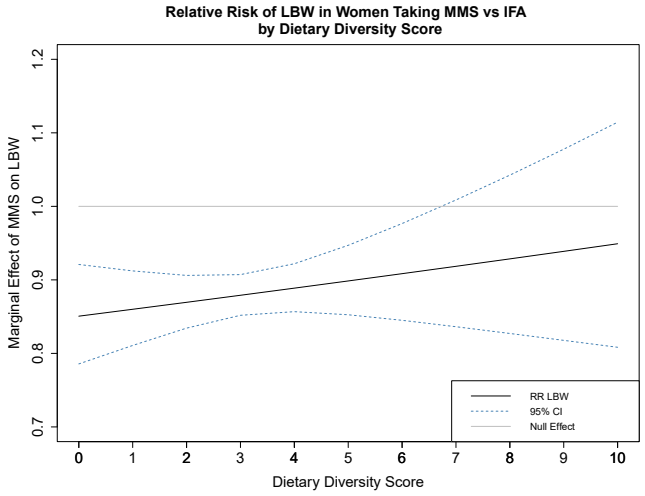


FIGURE 2. Changes in the relative risk of LBW in participants taking MMS compared with IFA by dietary diversity score; RR LBW calculated based on GEE regression coefficients for each level of DDS; SEs at each DDS level were calculated using the delta method. –CI, confidence interval; DDS, dietary diversity score; GEE, generalized estimating equations; IFA, iron-folic acid; LBW, low birth weight; MMS, multiple micronutrient supplements, RR, relative risk.

corresponding to an ~2–4% reduction in the risk of LBW comparing MMS to IFA (Table 2). The unadjusted risk reduction of MMS as compared with IFA on LBW was 0.88 (0.86, 0.91). When introducing the MMS × DDS interaction, the effect of MMS in reducing the risk of LBW increased. In the final adjusted model with the interaction, MMS led to an ~19% risk reduction [RR = 0.81 (0.75, 0.89)] of LBW as compared with IFA. The MMS × DDS interaction was significant in both unadjusted and adjusted models, with a final adjusted interaction term of 1.02 (1.00, 1.04), *P*-interaction = 0.05 (Table 2), suggesting that as dietary diversity increases, the effectiveness of MMS declines (Figure 2). For example, at DDS = 1, the relative risk of LBW due to MMS as compared with IFA was 0.83 (0.78, 0.89), at level 4 it was 0.90 (0.86, 0.93), and at level 7 it was 0.96 (0.88, 1.06). Wide CIs were observed for participants with DDS ≥ 6, limiting the ability to draw inference at higher levels.

The interaction effect was not detectable using the dichotomous DDS indicator. In the final adjusted model, the MMS × dichotomized DDS interaction term was measured at 1.04 (0.97, 1.11), *P*-interaction = 0.316.

Sensitivity analyses revealed a similar interaction term ($P < 0.10$) when using the average of early and late pregnancy FFQ data but not for the early pregnancy data alone; the dichotomous indicator of minimum diversity was not significant when using either of these alternate time points (Supplemental Table 3).

Our sensitivity analyses also revealed that findings were robust to the use of different scoring thresholds for food group categories (using a frequency of 3 or 7 instead of 4 times per week to score a "1" in a given food group category). When the threshold was decreased to 3 or less, >30% of participants met the minimum dietary diversity cut-off. However, the overall size and direction of the DDS and MMS × DDS effect remained the same, with the statistical significance of the interaction term decreasing slightly in the fully adjusted model 4 [MMS × DDS: 1.02 (1.00, 1.04), *P*-interaction = 0.06] (Supplemental Table 4). Conversely, when the frequency of consumption scoring threshold was raised to 7 or more times weekly, the number of participants achieving minimum dietary diversity declined markedly: only 5.5% of participants met the cut-off of 5 food groups consumed, and the overall magnitude of the DDS and MMS × DDS interaction terms as well as their statistical significance level increased [in the fully adjusted interaction model (model 4) MMS × DDS: 1.03 (1.00, 1.06), *P*-interaction = 0.027] (Supplemental Table 5).

Finally, when applying alternative cut-offs for achieving minimum dietary diversity, at a cut-off of ≥ 6 food groups, 6.8% of participants would be characterized as achieving minimum dietary diversity, and with a cut-off of ≥7 food groups, only 2.2% of participants would achieve minimum dietary diversity.

In sum, across models, scoring thresholds, and sensitivity analyses, the modifying effect of dietary diversity on the effect of MMS compared with IFA on LBW remained consistent.

Discussion

This analysis demonstrated that dietary diversity modified the effect of MMS on LBW, with greater effects among participants with lower DDS in late pregnancy, in a context where overall dietary diversity was poor.

Populations with lower DDS are likely to consume micronutrient inadequate diets; indeed, the MDD-W indicator was validated to measure this [17]. MMS may have helped compensate for these deficiencies, explaining its impact on the risk of LBW when compared with IFA in this rural Bangladeshi population [19]. Although the single recommended dietary allowance in MMS may not fully compensate

for this population's substantial micronutrient deficits [3], our findings suggest that MMS exerted a disproportionate benefit among mothers with monotonous and likely more micronutrient deficient diets.

Notably, this interaction effect was not significant when dietary diversity was analyzed as a dichotomous indicator rather than as a continuous, 10-point score. This is unsurprising given that the diets of over 80% of the participants in our study population did not exceed the conventional adequate dietary diversity cut-off, and only 2 of >9000 participants scored the maximum of 10. Dichotomization reduces statistical power and can obscure gradations in relative risk [26], limitations previously noted when comparing the MDD-W to a continuous DDS [27].

Beyond assessing a population's nutrient adequacy—the accepted function of the MDD-W [14] and the related child dietary diversity index [28]—our results suggest that maternal DDS in late pregnancy may also help predict "responsiveness" to micronutrient supplementation in regard to reduction in LBW of the offspring. Although targeting MMS is likely unnecessary, given its low and comparable cost relative to IFA [29], these findings highlight its utility in populations with persistently poor diets, and responsiveness of other outcomes to MMS should be examined.

This analysis also provides insight into the diets of the JiVitA-3 study participants. Participants routinely consumed grains/roots/tubers and eggplant, but intake of animal source foods was limited. Fish, historically a key animal source protein within the Bangladeshi diet due to family fish ponds [30], was widely consumed; however, egg and milk were consumed only moderately, yogurt, goat, and poultry were eaten infrequently, and nuts were very rarely consumed. This is probably due to the economic constraints of rural Bangladeshi families [31]. These constraints may also explain why the MMS and IFA groups showed no dietary differences in late pregnancy, despite the hypothesized stimulatory effect of MMS on appetite [32,33]. Limited resources and restricted agency may have constrained participants' ability to consume more food [34,35].

Our analysis also underscores the proequity role of MMS, as lower DDS identified a generally at-risk population, with lower education and socioeconomic status and higher health risks. Previous research in Bangladesh has described the ability of maternal MMS supplementation to reduce equity-related gaps in infant and child mortality [36], and our results suggest it may similarly mitigate disparities in birth outcomes.

Indeed, the limited dietary diversity seen in this sample may help define the types of populations with chronically poor dietary intakes where MMS could have the greatest impact. The monotonous, poor diets of rural Bangladesh highlight the underlying risk in this population and the value of MMS. This benefit is likely generalizable to other remote, resource-limited settings in Bangladesh, where dietary diversity is similarly low, as well as rural regions of Sub-Saharan Africa [37,38], areas with strong seasonal variation in food availability [39], and other rural parts of the Indo-Gangetic plain [40,41].

It remains unclear, however, whether dietary diversity would exhibit effect modification in settings where more varied diets are the norm. In our analysis, the effect of MMS attenuated and lost statistical significance when participants consumed 6 or more food groups ≥4 times per week. However, given the small number of participants in our sample who were able to achieve this level of dietary variety, we cannot assess the precision of any effect at the higher end of the dietary diversity spectrum.

This analysis has several strengths. It leverages data from one of the largest MMS trials ever conducted, which enrolled nearly all pregnant females in a population of 650,000 over a 4-y period. The large sample size coupled with ample dietary data from multiple time points in gestation allows for the characterization of diet over time and for an analysis of interaction effects, which is often not possible in small studies. Such analyses help clarify the mechanisms by which MMS produces its impact on birth weight.

Limitations also exist. The original, MDD-W indicator was validated against mean probability of nutrient adequacy using 24-hour recall data [16], whereas this analysis used a 7-day FFQ approach that has not been validated. Additionally, the JiVitA-3 FFQ focused on frequently consumed, micronutrient-rich foods, potentially leading to underestimates of consumption of certain food groups. This may explain why our levels of adequate diet from the dichotomized DDS and average DDS are somewhat lower than those reported in other studies conducted—albeit later in time—among pregnant females in Bangladesh [27,42]. However, this bias is unlikely to be differential across intervention arms, and therefore should not impact our final conclusions.

We have attempted to address many of these concerns in our sensitivity analyses, examining the robustness of our findings when incorporating data collected at alternative time points, using alternative scoring approaches, or applying different minimum dietary diversity cut-offs. Also, comparing our main results with those using dietary data from early pregnancy or averaged across late and early pregnancy supports our hypothesis that late pregnancy consumption might be more crucial in determining birth outcomes; the interaction effect when using dietary data averaged across both time points, representing diet throughout pregnancy, largely mirrored that seen when using late pregnancy data alone. Adjusting the dietary diversity cut-off to a more lenient threshold (thrice-weekly consumption) weakened statistical significance but maintained the direction and magnitude of the effect. A stricter threshold (daily consumption) strengthened the detected effect but may not be realistic for this population. Across scoring approaches and when using average pregnancy intake, dietary diversity remained a statistically significant effect modifier, reinforcing the robustness and reliability of our conclusions.

We believe further replication of these findings is warranted, including examining the relationship between dietary diversity and MMS effectiveness on LBW relative to IFA in other study samples with different dietary patterns, including outside of South Asia. It would also be pertinent to examine whether effect heterogeneity is evident for other outcomes that MMS has been shown to impact, including preterm birth, small-for-gestational age, and stillbirth [7]. Examining these issues will require more widespread integration of dietary modules into micronutrient supplementation studies and the re-examination of existing data sets, such as has been done in this analysis using the JiVitA-3 trial and the outcome of LBW.

Additionally, validating these findings in more diverse samples would allow us to determine whether MMS truly shows a null effect at higher levels of dietary quality, given our limited sample size of females consuming a more diverse diet. Beyond low- and middle-income countries, micronutrient supplementation is broadly encouraged for females in high-income contexts, where it has been noted that achieving minimum dietary diversity levels that can meet the increased micronutrient requirements remains challenging in pregnancy [43].

We acknowledge that MMS is one of many strategies to address micronutrient deficiencies in pregnancy. Food fortification, the promotion of healthy and diverse diets, as well as rising levels of

economic welfare, a trend that has already been evidenced in Bangladesh [44], will also be crucial. However, prior work from Bangladesh has shown that, given current income levels, diverse diets are not affordable for >40% of the population [45]. Similarly, fortification and dietary improvement are longer-term processes that will not benefit pregnant females currently living in rural, under-resourced settings with extremely low levels of dietary quality measured in this analysis. For these populations, MMS does and will continue to play a crucial role in the near-term, particularly given the time-limited, high-need period of pregnancy and the life-long impacts of antenatal nutritional deprivation [46].

Author contributions

The authors' responsibilities were as follows – KPW, PC: designed the research; HA, SS, AAS: conducted the research; MdB: analyzed data; MdB, ALT-L, PC: wrote the paper; MdB, ALT-L: had primary responsibility for final content; and all authors: read and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

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Data availability

Data described in the manuscript, code book, and analytic code will be made available on request pending application and approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2025.07.007.

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