Effects of prenatal nutritional supplements on gestational weight gain in low- and middle-income countries: a meta-analysis of individual participant data

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Short running head: nutrient supplements and gestational weight gain

Abbreviations

BMI	Body mass index
GWG	Gestational weight gain
IOM	Institute of Medicine
LMICs	Low- and middle-income countries
LNS	Lipid-based nutrient supplements
MMS	Multiple micronutrient supplements
WMD	Weighted mean difference

Keywords: Multiple micronutrient supplements; Small-quantity lipid-based nutrient supplements; Gestational weight gain; Randomized controlled trials; Meta-analysis; Low- and middle-income countries

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ABSTRACT

Background: Gestational weight gain (GWG) below or above the Institute of Medicine (IOM) recommendations has been associated with adverse perinatal outcomes. Few studies have examined the effect of prenatal nutrient supplementations on GWG in low- and middle-income countries (LMICs).

Objective: To investigate the effects of multiple micronutrient supplements (MMS) and small-quantity lipid-based nutrient supplements (LNS) on GWG in LMICs.

Methods A two-stage meta-analysis of individual participant data was conducted to examine the effects of MMS (45,507 women from 14 trials) and small-quantity LNS (6,237 women from 4 trials) on GWG compared to iron and folic acid supplements only. Percent adequacy of GWG and total weight gain at delivery were calculated according to the IOM 2009 guidelines. Binary outcomes included severely inadequate (percent adequacy < 70%), inadequate (< 90%), and excessive (>125%) GWG. Results from individual trials were pooled using fixed-effects inverse-variance models. Heterogeneity was examined using I^2, stratified analysis, and meta-regression.

Results MMS resulted in a greater percent adequacy of GWG (weighted mean difference (WMD): 0.86%; 95% CI: 0.28%,1.44%; P < 0.01) and higher GWG at delivery (WMD: 209 g; 95% CI: 139, 280; P < 0.01) than among those in the control arm. Women who received MMS had a 2.9% reduced risk of severely inadequate GWG (RR: 0.971; 95% CI: 0.956, 0.987; P < 0.01). No association was found between small-quantity LNS and GWG percent adequacy (WMD: 1.51%; 95% CI: -0.38%, 3.40%; P = 0.21). Neither MMS nor small-quantity LNS was associated with excessive GWG.

Conclusions Maternal MMS was associated with a greater GWG percent adequacy and total GWG at delivery compared to iron and folic acid only. This finding is consistent with previous results on birth outcomes and will inform policy development and local recommendation of switching routine prenatal iron and folic acid supplements to MMS.

INTRODUCTION

Pregnancy is characterized by multiple metabolic changes with additional requirements for nutrients and energy intake. As pregnancy progresses, the maternal basal metabolic rate continues to increase, reaching 10-20% more than non-pregnancy levels (1). Maternal weight gain is small and primarily due to fat deposition and placental development during the first trimester. The fastest weight gain occurs in the second trimester, with a slightly decreasing rate during the third trimester. Weight gain in the later trimesters is more related to fetal growth as well as maternal fat stores and total body water accretion (2). Overall approximately 50% of total gestational weight gain (GWG) during pregnancy is attributed to the fetoplacental unit (fetus, placental, amniotic fluid, and gravid uterus), another 25% is attributed to increases in blood volume, extravascular fluid, and breast tissue, and the remaining 25% to maternal fat stores (1, 2).

Undernutrition is common among women in low- and middle-income countries (LMICs) (3). Pregnant women in these settings are often at higher risk of multiple micronutrient deficiencies due to food insecurity, low dietary diversity, and the increased demands of the developing fetus (4, 5). Currently, the widely available prenatal multiple micronutrient supplements (MMS) product is the United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) tablet, which contains 15 micronutrients including 30 mg of iron and 0.4 mg of folic acid. Data from previous meta-analyses have shown that, compared to iron and folic acid supplements, prenatal MMS decreases the risk of low birthweight and small-for-gestational-age birth (6, 7), and particularly benefit infants born to underweight or anemic women (6).

Prenatal small-quantity lipid-based nutrient supplements (LNS), providing approximately 120 kcal/day, offer another strategy for delivering not only vitamins and minerals, but also essential fatty acids and macronutrients not incorporated in MMS tablets. Two meta-analyses reported that prenatal LNS, including those providing much more than 120 kcal/day, significantly increased birthweight and length and reduced the risk of small for gestational age birth (8, 9). However, meta-analysis focused on the effect of small-quantity LNS is lacking.

Gestational weight gain (GWG) is widely used as an indicator of the adequacy of nutrition during pregnancy. Inadequate GWG has been consistently associated with adverse birth outcomes such as prematurity (10-12), small for gestational age birth (12-14), low birthweight (10, 12-15), and infant mortality (16). On the other hand, excessive GWG has been associated with increased risks of large for gestational age, macrosomia, cesarean delivery, gestational diabetes, and subsequent maternal obesity (17, 18). Demographic surveillance data from sub-Saharan Africa and India suggest that average weight gain among pregnant women is only around 60% of the recommended amount for normal-weight women (19). A more recent modeling analysis using Demographic and Health Surveys data revealed inadequate GWG in most LMICs and regions (20).

Since weight gain during pregnancy is often monitored in prenatal clinical care, it is a modifiable risk factor for adverse birth and maternal outcomes. However, few existing randomized controlled trials have been designed to examine the effect of prenatal nutritional supplements on GWG (21-23), and direct evidence of the effect on GWG is limited. We conducted a systematic review and meta-analysis using individual participant data from randomized controlled trials to examine the effects of MMS and small-quantity LNS on GWG among pregnant women in LMICs. We further aimed to identify potential modifiers of the effect of these nutritional supplements on GWG.

METHODS

Identification of eligible trials and individual participants

We conducted a systematic search using PubMed, Embase, and Web of Science to identify randomized controlled trials among pregnant women published after January 2000 up to December 2021 **(Supplemental material: Search strategy)**. Study-level inclusion criteria included: 1) randomized controlled trials of prenatal nutrient supplements from LMICs, including trials of MMS or small-quantity LNS; and 2) studies that had measured maternal weight during pregnancy. Trials conducted exclusively among pregnant women with a health condition, such as anemia, human immunodeficiency virus, or diabetes, were excluded. We also reviewed the references of the included trials and previous systematic reviews to identify additional relevant studies. Study protocol was developed with pre-defined outcome metrics and analysis plan while we were conducting literature search and screening.

We contacted the principal investigators of all identified trials to seek collaboration and data sharing. For those who agreed to participate in this individual participant data meta-analyses, the Knowledge Integration (Ki) team at the Bill & Melinda Gates Foundation and study principal investigators executed data contributor agreements with the corresponding institutions. Once data were obtained from each trial, we checked data completeness and mapped all the variables we had requested. All data queries were resolved with individual principal investigators, and there was no critical issue regarding data integrity. In order to facilitate pooling of data across trials, data items were recoded into a common format, classifications of participant characteristics and their disease/condition status were standardized, and variables were named consistently across studies. We further applied individual-level criteria to identify eligible individual participants, including: 1) singleton pregnancies, 2) at least one weight measurement in the second or third trimesters, 3) known gestational ages at the time of weight measurements, and 4) availability of maternal height measure. Data from pregnancies that resulted in stillbirths or neonatal deaths were included. The balance across intervention and controls arms with respect to baseline subject characteristic were checked for each trial separately.

Estimation of pre-pregnancy weight and BMI

An accurate assessment of GWG during pregnancy requires a pre-pregnancy weight measure, which is often unavailable in epidemiologic studies. In this analysis, we used first-trimester weight as a proxy for maternal pre-pregnancy weight. Overall, 60% of pregnant women included in the analysis had pre-pregnancy weight or weight measured in the first trimester. We developed an imputation model for women who did not have observed pre-pregnancy or first-trimester weight measure to impute their first-trimester weight using weights measured later during pregnancy. The details of the model development, selection, and validation have been published elsewhere (24). Briefly, mixed-effects models and restricted cubic splines were used to impute weight at 9 weeks of gestation. We chose to impute weight at 9 weeks because it is consistent with the first available weight measure during pregnancy used in the INTERGROWTH-21st Study, an international research project that developed GWG standards among pre-pregnancy normal-weight women (25). The availability of an observed pre-pregnancy or first-trimester weight measure and the average of total number of weight measures during pregnancy by trials are presented **Supplemental Table 1**. Body mass index (BMI) was calculated by dividing pre-pregnancy (observed) or first-trimester weight (observed or imputed) in kilograms by the square of height in meters. For women aged ≥ 20 years old, we used the World Health Organization (WHO) BMI cutoffs to define underweight (BMI < 18.5 kg/m^2), normal weight (18.5 ≤ BMI < 25.0 kg/m^2), overweight (25.0 ≤ BMI < 30.0 kg/m^2), and obesity (BMI ≥ 30.0 kg/m^2) (26). For adolescent women (< 20 years old), we used the WHO adolescent growth reference to define underweight (BMI-for-age Z-score: < -2), normal weight (BMI-for-age Z-score: -2 to < 1), overweight (BMI-for-age Z-score: 1 to < 2), and obesity (BMI-for-age Z-score: ≥ 2) (27).

Outcome metrics

Percent adequacy of GWG

First, GWG at the time of last weight measure during pregnancy was calculated for each woman by subtracting pre-pregnancy or first-trimester weight from the last available weight measurement during

pregnancy. Second, following the Institute of Medicine (IOM) 2009 recommendation (2), we estimated the expected weight gain for each woman at the time of their last observed weight measure using the following formula:

Recommended GWG = expected first-trimester weight gain/13.86(13.86-gestation age at first observed or imputed weight measurement) + [(gestational age at the last weight measurement – 13.86 weeks)* × *recommended rate of GWG for the second and third trimester by BMI category based on IOM guidelines].*

We assumed that the expected first-trimester weight gain was 2 kg for underweight and normal-weight women, 1 kg for overweight women, and 0.5 kg for women with obesity (22). The recommended rates of GWG for the second and third trimesters were 0.51, 0.42, 0.28, and 0.22 kg per week for women with underweight, normal weight, overweight, and obesity, respectively (2).

Finally, the percent adequacy of GWG was calculated by dividing the observed GWG at the time of the last weight measurement by the expected GWG for that week of gestation based on the IOM recommendations, multiplied by 100. This continuous outcome is independent of gestational age at the time of weight measure and has been employed previously (22).

Severely inadequate, inadequate, and excessive GWG

The percent adequacy of GWG defined as above was considered adequate between 90% and 125%. The cut points 90% and 125% correspond to the lower and upper limits of the recommended total weight gain during pregnancy by IOM guideline (2). Severely inadequate GWG was defined as percent adequacy of GWG < 70%, inadequate GWG as percent adequacy of GWG < 90%, and excessive GWG as percent adequacy of GWG >125% (22).

Estimated total GWG at delivery

The median time interval between last weight measurement and delivery was 6.0 (interquartile range: 3.2, 8.4) weeks. The total GWG at delivery was estimated by multiplying the percent adequacy of GWG (estimated above) by the IOM-recommended GWG at delivery, which was calculated based on the gestational age at delivery and BMI category for each individual woman.

Statistical analysis

Within each trial, we used multiple linear regression models to examine the association between MMS or small-quantity-LNS and continuous outcomes, including percent adequacy of GWG and estimated total GWG at delivery. Mean differences in percent adequacy and estimated total GWG and their 95% confidence intervals (CIs) were reported for continuous outcomes. We used modified Poisson regression with robust variance estimation to estimate the association between MMS or small-quantity-LNS versus iron and folic acid only and binary outcomes, including severely inadequate, inadequate, and excessive GWG. Risk ratios (RRs) and 95% CIs were reported for binary outcomes. For cluster randomized controlled trials, compound symmetry correlation structure was used to account for the fact that clusters were randomized instead of individual participants. For factorial design trials with MMS and another intervention, the interaction test between the two interventions was examined within each trial first, and if no interaction was found, all intervention arms were collapsed based on whether MMS was received.

To identify potential subgroups of women who might experience a greater effect from MMS or small-quantity LNS, we conducted stratified analyses by categories of the following factors for each trial: 1) pre-pregnancy BMI (underweight, normal-weight, overweight or obese); 2) adherence to the assigned regimen (< 90% or ≥ 90%); 3) maternal age (< 20 yrs, 20-29 yrs, and ≥ 30 yrs); 4) gestational age at randomization (< 20 wks or ≥ 20 wks); 5) parity (0 or ≥ 1); 6) maternal education level (< 8 yrs or ≥ 8 yrs); 7) maternal anemia status (< 11.0 g/dL or ≥11.0 g/dL); 8) maternal height (< 150 cm or ≥ 150cm); and 9) infant sex (male or female). These factors and their cut points were selected based on their inclusion in existing literature, data availability, and distribution in the current analysis. Individual data on

pill count or intervention uptake of the assigned regimen from each trial were collected, and adherence was assessed by dividing the amount of regimen consumed by the amount distributed to each woman during the overall study period. Mean differences for continuous outcomes and their corresponding 95% CIs were estimated by subgroups within each trial.

After analyses were completed for each trial, fixed-effect inverse-variance meta-analyses were conducted to pool study-specific overall and subgroup effects. Heterogeneity across trials was assessed using the I^2 statistic, with thresholds of < 30%, 30-60%, and > 60% considered low, moderate, and high heterogeneity, respectively. Meta-regression analysis was used to examine the statistical difference in the effect of MMS or small-quantity LNS on GWG across categories of potential effect modifiers with $P < 0.05$ considered as indicative of effect modification.

As a secondary analysis, we calculated GWG z-score using the INTERGROWTH-21 maternal weight gain standards (25) and further examined the association of this z-score with MMS and small-quantity LNS among normal-weight women.

Random-effect meta-analyses were conducted as a sensitivity analysis for continuous outcomes. To evaluate whether our results were driven by the JiVitA-3 trial (28) due to its large sample size, or the Women First trial (29) due to the provision of extra calories by its study design, we conducted sensitivity analysis for GWG percent adequacy excluding these two trials. In another sensitivity analysis, we excluded pregnant women who had the last weight measure in the second trimester and restricted our analysis to those who had the final weight measure in the third trimester. In a similar analysis, we restricted our analysis to women who had imputed first-trimester weight to evaluate the potential bias by use of the imputation.

All individual trials were approved by their respective ethics committees. Two-tailed p-values < 0.05 were considered significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute) and Stata version 16.

RESULTS

General characteristics of the included studies

A summary of the characteristics of each trial included in the analysis is shown in **Table 1**. We identified 17 randomized controlled trials that met our eligibility criteria, and 16 of them with a combined sample size of 50,927 pregnant women were included in this analysis (22, 23, 28-41) **(Supplemental material: PRISMA IPD flow diagram)**. For interventions, 12 of 16 trials included had an MMS arm, 2 trials had a small-quantity LNS arm, and another 2 trials had both MMS and small-quantity LNS arms. The only eligible trial not included in the analysis due to non-response to invitation had an MMS arm (42). In all trials, women in the control arm were provided daily supplementation of iron with (n=15) or without folic acid (n=1) by the study team or had access to prenatal supplementation from local health services. Of the included trials, six were cluster-randomized (23, 28, 30, 37, 38, 40) and the remainder were individually randomized. Pregnant women were enrolled before or at 20 weeks of gestation in 14 of 16 trials. The participants' characteristics and cumulative incidence of binary outcomes by trial are presented in **Supplemental Table 2** for the analysis of MMS and **Supplemental Table 3** for the analysis of small-quantity LNS. We updated our search in August 2022 and did not find any new eligible trial published.

Continuous outcomes: percent adequacy and total GWG

The mean GWG percent adequacy was 77%, ranging from 60% to 107% across the 16 trials included in the analysis. Pregnant women who received maternal MMS had greater percent adequacy of GWG and estimated total GWG at delivery than those in the control arm (**Table 2**). Study-specific results demonstrated that in nine of the 14 trials, MMS had positive effects on percent adequacy of GWG. The weighted mean difference (WMD) from fixed-effects meta-analyses was 0.86% (95% CI: 0.28%, 1.44%; I^2 =13.3%) (**Figure 1)** and the WMD in estimated total GWG at delivery was 209 g (95% CI: 139, 280; I^2 =52.5%) (**Figure 2)**.

Individual data from four trials of small-quantity LNS were included in the analysis. In the study-specific analysis, maternal small-quantity LNS was positively associated with GWG percent adequacy in

three of the four trials, and two of them were statistically significant. The overall WMD from the fixed effects meta-analysis comparing women who received small-quantity LNS with those in the control arm was 1.51% (95% CI: -0.38%, 3.40%; $I^2 = 69.5\%$) (**Table 2, Figure 3**). For estimated absolute GWG at delivery, the WMD from the fixed-effect meta-analysis between women who received small-quantity LNS and those in the control arm was 152 g (95% CI: -71, 376; $I^2 = 42.2\%$) **(Table 2, Figure 4)**. Random effects meta-analysis produced similar results on the effect of MMS or small-quantity LNS on continuous outcomes **(Table 2)**.

Binary outcomes: severely inadequate, inadequate, and excessive GWG

On average, 70% of women in the analysis had inadequate GWG and 45% had severely inadequate GWG. Compared to women in the control arm, women in the MMS arm had a 2.9% reduced risk of severely inadequate GWG (fixed effect RR: 0.971; 95% CI: 0.956, 0.987, $I^2 = 57.6\%$) and a 1.4% reduced risk of inadequate GWG (RR: 0.986; 95% CI: 0.978, 0.995, $I^2 = 48.4\%$). No significant association was found between MMS and risks of excessive (RR: 1.042; 95% CI: 0.975, 1.113) GWG **(Table 3 and Supplemental Figures 1, 2, 3)**. There were no significant associations of maternal small-quantity LNS with the risk of severely inadequate (fixed effect RR: 0.952; 95% CI: 0.903, 1.005), inadequate (RR: 0.992; 95% CI: 0.962, 1.022), or excessive (RR: 1.131; 95% CI: 0.970, 1.318) GWG **(Table 3 and Supplemental Figures 4, 5, 6)**. Results from random-effects meta-analysis were similar to those from fixed-effects meta-analysis **(Table 3)**.

Potential effect modifiers

Adherence to the assigned regimen modified the effect of MMS on percent adequacy of GWG. Maternal MMS was associated with greater percentage adequacy of GWG among women with adherence of 90% or more (WMD: 1.4%; 95% CI: 0.6%, 2.1%), but not among women with adherence less than 90% (WMD: 0.1%; 95% CI: -0.9%, 1.1%; P for interaction = 0.04) **(Table 4)**. Maternal MMS had a greater effect on percentage adequacy of GWG among women enrolled at 20 weeks of gestation age or

later (WMD: 2.3%; 95% CI: 0.8%, 3.7%) than those enrolled earlier (WMD: 0.7%; 95% CI: 0.1%, 1.3%; P for interaction = 0.054).

We found that small-quantity LNS increased percent adequacy of GWG among women with overweight and obesity (WMD: 15.5%; 95% CI: 7.0%, 23.9%), but not among underweight (-0.2%; 95% CI: -3.4%, 2.9%) and normal-weight women (0.6%; 95% CI: -1.4%, 2.6%, P for interaction = 0.04) **(Table 4)**. Also, small-quantity LNS increased percent adequacy of GWG among women with height shorter than 150 cm (WMD: 5.3%; 95% CI: 2.7%, 7.9%), but not among taller women (WMD: -1.2%; 95% CI -3.6%, 1.3%; P for interaction < 0.001) **(Table 4**). We did not find any other factors that modified the effect of MMS or small-quantity LNS on GWG.

Results from secondary and sensitivity analyses

No association was found between the INTERGROWTH-21 GWG z-score and MMS or small-quantity LNS among normal-weight women **(Supplemental Figures 7 and 8)**. With more than 23,000 study subjects, the JiVtA-3 trial from Bangladesh had a much larger sample size than other trials and was weighted heavily in the meta-analysis. In a sensitivity analysis excluding this trial, we found that MMS was still associated with GWG percent adequacy with a WMD of 1.06% (95% CI: 0.10%, 2.02%) **(Supplemental Figure 9**). Similarly, we conducted a sensitivity analysis excluding the Women First trial from the meta-analysis because it was not a typical small-quantity LNS trial since individuals in the intervention arm who were underweight or had weight gain that did not meet expectation received additional daily lipid-based protein-energy supplement. The result in GWG percent adequacy remained non-significant with a WMD of 0.47% (95% CI: -1.63%, 2.56%) (**Supplemental Figure 10**).

There were 3,148 (6.2%) women for whom the last weight measure was in the second trimester. In sensitivity analysis, we removed these women and restricted our analysis to those who had weight measures in the third trimester. The significant association between MMS and GWG percent adequacy persisted (**Supplemental Figure 11**), as did the lack of association between small-quantity LNS and GWG percent adequacy (**Supplemental Figure 12**). When we restricted our analysis to women with

imputed first-trimester weight, point effect estimates for MMS (**Supplemental Figure 13**) and small-quantity LNS (**Supplemental Figure 14**) were not materially different from their original estimates and not significant.

DISCUSSION

In these meta-analyses using individual participant data, mean GWG percent adequacy according to the IOM recommendation was 77%; 45% of pregnant women had severely inadequate GWG and 70% had inadequate GWG. MMS increased GWG percent adequacy and total weight gain at delivery and reduced the risks of severely inadequate and inadequate GWG. The beneficial effect of maternal MMS was only observed among those with ≥ 90% adherence to the assigned regimen. Only 4 eligible trials were identified to examine the effect of small-quantity LNS on GWG. No association was found in the overall analysis, but small-quantity LNS was associated with greater GWG adequacy in the subgroups of women with overweight or obesity and those with height < 150 cm. Neither MMS nor small-quantity LNS was associated with excessive GWG.

Our estimate that 70% of pregnant women had inadequate GWG in the current analysis is consistent with the previous findings from similar settings. In a recently published meta-analysis of studies conducted among pregnant women in sub-Saharan Africa, the percentage of inadequate gestational weight gain was greater than 50% in 9 of 16 studies (43). Using data from Demographic and Health Surveys, Wang et al (20) reported that the mean estimated GWG did not meet the minimum recommendation by the IOM in most developing regions and countries. Data from individual studies indicated inadequate GWG among 74% of pregnant women in Bangladesh (14) and 52% in Tanzania (44). In the current meta-analysis, we found that prenatal MMS was associated with a 209-gram increase in total GWG at delivery and a 1.4% reduced risk of inadequate GWG. Although the effect size seems small, given the high proportion (~70%) of inadequate GWG in LMICs, the small reduction in risk would correspond to shifting 1% of total number of pregnant women in these settings from inadequate GWG to adequate GWG. With the expectation that the fetus constitutes 27% of GWG (45), we estimate that 55

gram of the 209-gram increase in GWG would be fetal growth and manifest as higher birthweight, a number consistent with previously reported effect sizes of MMS on birthweight from individual trials (28, 30, 32, 33, 46).

Previous randomized controlled trials in pregnant women have focused on the effect of MMS on birth outcomes, rather than GWG. Several meta-analyses have been conducted to assess the effect of prenatal MMS on birth outcomes (6, 47-49), and it has consistently been shown that the provision of MMS reduced the risk of low birthweight and small-for-gestational-age birth (8, 9). In response to the new evidence from randomized controlled trials, in 2020, the WHO updated their guidelines on prenatal nutritional interventions and recommended the use of MMS in the context of rigorous implementation research to establish the impact of switching from iron and folic acid supplements to MMS containing iron and folic acid (50). Our findings that MMS increases GWG and reduces the risks of severely inadequate GWG compared to iron and folic acid provide further evidence supporting the WHO's updated recommendation. This position is further reinforced by the results of a systematic review of over 1.3 million pregnancies reporting that inadequate weight gain was associated with an increased risk of small-for-gestational-age births and preterm birth (18). Since birth outcomes have long been prioritized over maternal outcomes, more efforts should be made in future research to study the determinants and consequences of maternal outcomes of pregnancy.

There are several plausible mechanisms through which prenatal micronutrient supplements can impact GWG. First, nutritional supplements may reduce the risk of infections and morbidities during pregnancy (51, 52). Micronutrients included in the prenatal supplements might help improve immune function, increase iron absorption, and reduce the risks of anemia, pre-eclampsia, and eclampsia during pregnancy (53, 54). Second, supplementation with micronutrients may improve appetite, leading to increases in food intake by influencing gut microbiome as well as peptide hormone levels and neurotransmitters that affect satiety and appetite (55, 56). Third, micronutrients included in the supplements directly improve fetal development and growth, thereby leading to greater GWG (57, 58). For example, iron, zinc, vitamin C, and B-vitamins are involved in protein and energy metabolism, DNA

and RNA synthesis, and cell division (59-62); further, antioxidants, including vitamins C and E, protect against free radical generation and damage caused by increased oxidative stress during pregnancy (63, 64), which has been associated with adverse pregnancy outcomes, including low birthweight and preterm birth (65, 66).

Small-quantity LNS was provided as the intervention supplement in 4 trials included in the analysis. However, it should be noted that women enrolled in the intervention arm of the Women First trial received an extra daily lipid-based protein-energy supplement, which provided 300 Kcal and 11 g protein per day, if they had a BMI < 20 kg/m^2 at any time during the study period or had weight gain in the second or third trimester less than the IOM guidelines (29). To avoid the possibility that our pooled results were driven by the Women First trial, in sensitivity analyses, we excluded this trial from the meta-analysis and found that the results attenuated towards the null and remained statistically nonsignificant. Consistent with the previous meta-analysis published in 2018 (8), we did not find an association between small-quantity LNS and GWG with participant data from two more trials included (29, 36). However, we found that small-quantity LNS was associated with a greater adequacy of GWG in the subgroup of women with overweight or obesity and the subgroup with short height (less than 150 cm). Women with overweight or obesity have lower GWG recommendation than women with underweight or normal weight according to IOM guideline, this may at least partially explain why the effect of small-quantity LNS on GWG percent adequacy, which was assessed based IOM recommendation, was greater in this subgroup. Women with short height might tend to have low socioeconomic status and suffer from long-term undernutrition and concurrent nutritional deprivation (67, 68), and thereby potentially benefit more in GWG from the prenatal small-quantity LNS. As a highly nutrient-dense supplement, LNS could be a good source of macronutrients and micronutrients for malnourished pregnant women in LMICs. The effect of medium quantity LNS and other balanced energy protein interventions among pregnant women in food insecurity contexts warrants further research (69).

Our study has several strengths. It is the first individual participant data meta-analysis to synthesize the effect of nutrient supplementation on GWG. Although weight gain during pregnancy is

widely used in prenatal clinics as an indicator of the adequacy of maternal nutrition, it is often not reported as one of the primary outcomes in randomized controlled trials among pregnant women. By contacting each principal investigator for their originally collected data, we were able to include trials from 14 LMICs. Furthermore, our analysis is the first meta-analysis to examine the effect of small-quantity LNS, which provides less than 120 kcal per day, on GWG among pregnant women. Although most of the energy is supplied from fat, the energy contents of different types of LNS vary widely. Previous meta-analyses usually included LNS trials in which larger quantities of energy were provided (8, 9). By confining our analysis to trials of small-quantity LNS, our pooled results were more likely to reflect the effect of the multiple micronutrients plus essential fatty acids included in the LNS.

Limitations of these analyses should be noted. First, a direct measure of GWG during the entire pregnancy period was not always available because of the lack of pre-pregnancy weight and large variance in gestational age at enrollment and last weight measure before delivery. To overcome this limitation, we estimated early pregnancy weight at 9 weeks of gestation for women without weight measure in the first trimester by applying a validated statistical modeling approach to their individual weight measures during pregnancy. We then developed several GWG outcome metrics including GWG percent adequacy and estimated total GWG at delivery according to the IOM GWG guideline. We further calculated GWG Z-score by applying the INTERGROWTH-21st GWG standards in normal-weight women (25), and obtained similar results when we examined the association of GWG Z-score with MMS and small-quantity LNS among normal-weight women, indicating that our findings are robust. However, random or systematic measurement errors in weight and gestational age during pregnancy and their influence on the results could not be ruled out. Second, we were not able to examine whether food insecurity was an effect modifier of the associations between prenatal nutrient supplements and GWG given limited data on food insecurity. We did perform stratified analysis by baseline BMI categories and found that baseline BMI modified the effect of small-quantity LNS, but not MMS, on GWG adequacy. Third, even with two more trials included compared to the previous meta-analysis on LNS, our sample size is still relatively small, and this may have limited our power to detect the effect of small-quantity

LNS on GWG among underweight and normal weight women.

In conclusion, by using individual participant data we conducted a two-stage meta-analysis and found that the provision of prenatal MMS increases GWG compared to iron and folic acid supplements only in LMICs. Given that previous trials of maternal MMS have been mainly focused on birth outcomes, our result on GWG might help to explain and further understand its beneficial effect on birth outcomes observed previously. This finding provides additional evidence to support the recently updated WHO guidelines on prenatal MMS and lends support to switching prenatal supplements to MMS instead of iron and folic acid alone. The contribution of LNS of different quantities and balanced energy protein supplements to GWG and birth outcomes warrants further study.

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The authors' contributions: EL, DQ, AMD, NP, MW, and WWF designed the study (project conception, development of overall research plan, and study oversight) with substantial input from technical advisory group members (PC, KGD, GK, SHK, and TA). All members of GWG Pooling Project Consortium contributed data, provided feedback on the study methods and interpretation of the findings, and critically reviewed the manuscript for important intellectual content. VS, BB, and DQ provided technical support and coordination for data collection, data management and harmonization. DQ, EL, AMD, and NP had access to the pooled data. EL led the statistical analysis, drafted and revised the manuscript. EL and WWF have the primary responsibility for the final content. All authors reviewed and contributed to the final manuscript.

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Declaration of interests

We declare no competing interests.

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Table 1. Characteristics of 16 trials of MMS or small-quantity LNS included in the meta-analysis of the effect of prenatal nutritional supplements on GWG[1]

Author, publication year	Country	Years of study	Control arm	Intervention arm(s)	Number of Participants included in analysis	Weeks of gestation at enrollment, median	BMI [2], kg/m^2, median	Adherence (%), median
Christian, 2003 [3]	Nepal	1998-2001	60mg iron+400 µg folic acid/day+1000 µg Vitamin A,	MMS	1193	9.6	18.9	93.7
Friis, 2004	Zimbabwe	1996-1997	60 mg iron + 400 µg folic acid/day	MMS	415	26.0	22.0	80.0
Osrin, 2005	Nepal	2002-2004	60 mg iron + 400 µg folic acid/day	MMS	1,108	15.9	19.2	98.1
Ramakrishnan, 2005	Mexico	1997-2000	60 mg iron/day	MMS	353	9.0	23.3	95.0
Fawzi, 2007	Tanzania	2001-2004	60 mg of iron + 250 µg folic acid/day	MMS	7,421	21.6	22.5	96.4
Zeng, 2008 [3]	China	2002-2006	60 mg iron + 400 µg folic acid/day	MMS	2,653	13.6	20.1	98.7
Roberfroid, 2008	Burkina Faso	2004-2006	60 mg iron + 400 µg folic acid/day	MMS	1,091	15.7	20.0	84.3
Bhutta, 2009 [3]	Pakistan	2002-2004	60 mg iron + 400 µg folic acid/day	MMS	1,507	12.9	20.6	81.4
Persson, 2012 [4]	Bangladesh	2001-2003	60 mg iron + 400 µg folic acid/day	MMS	2,329	9.0	19.7	70.0
Moore, 2012 [4]	The Gambia	2010-2012	60 mg iron + 400 µg folic acid/day	MMS	803	13.4	20.4	87.9
West, 2014 [3]	Bangladesh	2008-2012	27mg iron +600 µg folic acid/day	MMS	23,577	9.7	18.8	95.0

Author, publication year	Country	Years of study	Control arm	Intervention arm(s)	Number of Participants included in analysis	Weeks of gestation at enrollment, median	BMI [2], kg/m^2, median	Adherence (%), median
Ashorn, 2015	Malawi	2011-2013	60 mg iron + 400 µg folic acid/day	MMS; small-quantity LNS	1,321	17.1	20.8	92.1
Matias, 2016 [3]	Bangladesh	2011-2012	60 mg iron + 400 µg folic acid/day	small-quantity LNS	3,343	13.4	19.5	80.0
Adu-Afarwuah, 2017	Ghana	2009-2011	60 mg iron + 400 µg folic acid/day	MMS; small-quantity LNS	1,114	15.9	23.1	80.9
Hambidge, 2019 [5]	Guatemala, India, and Pakistan	2013-2014	Iron+ folic acid.	small-quantity LNS	1,277	12.0	21.0	88.0
Isanaka, 2021 [3]	Niger	2014-2019	60 mg iron + 400 µg folic acid/day	MMS	1422	11.0	21.1	85.4

[1]MMS, multiple micronutrient supplements; LNS, lipid-based nutrient supplements; GWG, gestational weight gain;

[2] BMI, body mass index, observed during the first trimester or imputed for 9 weeks of gestation.

[3] Cluster-randomized trial

[4] Randomized controlled trial with factorial design, and intervention arms were collapsed based on MMS received or not.

[5] Data from the Democratic Republic of the Congo were excluded due to missing gestational age data. The pre-conceptional supplementation arm was excluded as the analysis focused on prenatal supplementation during pregnancy.

Table 2. The effect of prenatal nutritional supplements on percent adequacy of GWG and estimated total GWG at delivery[1]

		Intervention	
Outcome		**MMS [2]**	**small-quantity LNS [3]**
Percent Adequacy [4], %	Number of studies	14	4
	Number of participants, total	45,507	6,237
	Number of participants, by intervention/control arms	22,940/22,567	2,335/3,902
	WMD[5] (95% CI) [5], Fixed-effects	0.86 (0.28, 1.44)	1.51 (-0.38, 3.40)
	WMD (95% CI) [5], Random-effects	0.90 (0.08, 1.71)	2.55 (-1.42, 6.52)
	I^2 (%) [6]	13.3	69.5
	P for heterogeneity	0.31	0.02
Total GWG [1], gram	Number of studies	14	4
	Number of participants	45,455	6,026
	Number of participants, by intervention/control arms	22,914/22,541	2,287/3,739
	WMD (95% CI) [5], Fixed-effects	209 (139, 280)	152 (-71,376)
	WMD (95% CI) [5], Random-effects	186 (43, 329)	203 (-123,529)
	I^2 (%) [6]	52.5	42.2
	P for heterogeneity	0.01	0.16

[1] GWG, gestational weight gain;
[2] MMS, multiple micronutrient supplements;
[3] LNS, lipid-based nutrient supplements;
[4] The percent adequacy of GWG was calculated by dividing the actual GWG at the last weight measure during pregnancy by the recommended GWG according to the Institute of Medicine (IOM) 2009 guideline, multiplied by 100.
[5] WMD(95% CI), weighted mean difference(95% confidence interval).
[6] I^2(%), statistic index used to assess heterogeneity across trials, with thresholds of < 30%, 30-60%, and > 60% considered low, moderate, and high heterogeneity.
MMS, multiple micronutrient supplements; LNS, lipid-based nutrient supplements.

Table 3. The effect of prenatal nutritional supplements on the risk of severely inadequate, inadequate, and excessive GWG[1].

		Intervention	
Outcome		**MMS [2]**	**small-quantity LNS [3]**
Severely inadequate	Number of studies	14	4
	Number of participants, total	45,507	6,237
	Number of participants, by intervention/control arms	22,940/22,567	2,335/3,902
	RR (95% CI) [4], Fixed-effects	0.971 (0.956, 0.987)	0.952 (0.903, 1.005)
	RR (95% CI) [4], Random-effects	0.959 (0.922, 0.997)	0.935 (0.829, 1.055)
	I^2(%) [5]	57.6	71.1
	P for heterogeneity	<0.01	0.02
Inadequate	Number of studies	14	4
	Number of participants, total	45,507	6,237
	Number of participants, by intervention/control arms	22,940/22,567	2,335/3,902
	RR (95% CI) [4], Fixed-effects	0.986 (0.978, 0.995)	0.992 (0.962, 1.022)
	RR (95% CI) [4], Random-effects	0.982 (0.963, 1.002)	0.976 (0.927, 1.028)
	I^2(%) [5]	48.4	46.8
	P for heterogeneity	0.02	0.13
Excessive	Number of studies	14	4
	Number of participants, total	45,507	6,237
	Number of participants, by intervention/control arms	22,940/22,567	2,335/3,902
	RR (95% CI) [4], Fixed-effects	1.042 (0.975, 1.113)	1.131 (0.970, 1.318)
	RR (95% CI) [4], Random-effects	1.032 (0.944, 1.127)	1.127 (0.946, 1.342)
	I^2(%) [5]	18.3	15.6
	P for heterogeneity	0.25	0.31

[1] GWG, gestational weight gain; The percent adequacy of GWG was calculated by dividing the actual GWG at the last weight measure during pregnancy by the recommended GWG according to the Institute of Medicine (IOM) 2009 guideline, multiplied by 100. Severely inadequate GWG was defined as % adequacy < 70, inadequate GWG as % adequacy < 90, and excessive GWG as % adequacy >125.
[2] MMS, multiple micronutrient supplements;

[3] LNS, lipid-based nutrient supplements;
[4] RR(95%CI), risk ratio(95% confidence interval).
[5] I^2(%), statistic index used to assess heterogeneity across trials, with thresholds of < 30%, 30-60%, and > 60% considered low, moderate, and high heterogeneity.

Table 4. The effect of prenatal nutrient supplements on percent adequacy GWG [1], by potential modifiers

	MMS [2](14 trials)			small-quantity LNS [3](4 trials)		
Subgroup	n	WMD (95% CI) [4]	P for interaction [5]	n	WMD (95% CI) [4]	P for interaction [5]
Estimated pre-pregnancy BMI [6] (kg/m^2)			0.48			0.04
<18.5	10,330	1.6 (0.7, 2.5)		1,116	-0.2(-3.4, 2.9)	
18.5-<25.0	31,671	0.8 (0.1, 1.4)		4,423	0.6 (-1.4, 2.6)	
≥25.0	3,506	2.8 (-0.1, 5.7)		698	15.5 (7.0, 23.9)	
Maternal adherence to regimen (%)			0.04			0.98
<90	16,208	0.1 (-0.9, 1.1)		1,265	-2.0 (-7.2, 3.2)	
≥90	25,421	1.4 (0.6, 2.1)		999	-2.1 (-6.3, 2.1)	
Maternal age (years)			0.79			0.44
<20	10,659	0.8(-0.3, 1.8)		1,657	9.1(-3.7,21.9)	
20-29	26,970	0.9 (0.1, 1.6)		3,289	2.7 (-1.9, 7.2)	
≥30	7,812	1.0 (-0.5, 2.4)		783	8.1 (2.9, 13.3)	
Gestational age at enrolment (weeks)			0.054			0.15
<20	37,922	0.7 (0.1, 1.3)		5,779	1.7 (-0.3, 3.6)	
≥20	7,252	2.3 (0.8, 3.7)		240	-4.7 (-13.2, 3.8)	
Parity			0.99			0.13
0	16,983	01.1 (-0.3, 2.5)		870	-3.0 (-9.3, 3.4)	
≥1	27,025	1.0 (0.2, 1.7)		3,671	2.3 (-1.4, 6.1)	
Maternal education(years)			0.51			0.89
<8	29,703	0.9 (0.2, 1.6)		4,027	1.8 (-0.9, 4.5)	
≥8	14,109	10.7 (-26.3,47.8)		2,206	1.9 (-3.8, 7.7)	
Maternal hemoglobin at enrolment (g/dl)			0.79			0.52
<11.0	7,402	0.4 (-1.7, 2.5)		1,506	2.4 (-1.1, 6.0)	
≥11.0	7,001	0.3 (-1.3, 1.9)		1,947	5.0 (-0.5, 10.5)	
Maternal height (cm)			0.26			<0.001
<150	16,754	0.5 (-0.3, 1.3)		2,348	5.3 (2.7, 7.9)	
≥150	28,753	1.2 (0.4, 1.9)		3,889	-1.2 (-3.6, 1.3)	
Infant sex						0.65
Female	21,881	1.0 (-0.3, 2.4)	0.66	2,947	1.2(-1.8, 4.3)	
Male	23,154	0.7 (-0.1, 1.5)		2,960	3.2 (-1.7, 8.1)	

[1] GWG, gestational weight gain; the percent adequacy of GWG was calculated by dividing the actual GWG at the last weight measure during pregnancy by the recommended GWG according to the Institute of Medicine (IOM) 2009 guideline, multiplied by 100.
[2] MMS, multiple micronutrient supplements;
[3] LNS, lipid-based nutrient supplements;
[4] WMD(95% CI), weighted mean difference(95% confidence interval);
[5] P value for interaction was obtained from meta-regression analysis
[6] BMI, body mass index, observed during the first trimester or imputed for 9 weeks of gestation.

Figure 1. The effect of MMS on the percent adequacy of GWG. MMS, multiple micronutrient supplements; GWG, gestational weight gain; percent adequacy of GWG was calculated by dividing the actual GWG at the last weight measure during pregnancy by the recommended GWG according to the Institute of Medicine (IOM) 2009 guideline, multiplied by 100. The sample size by MMS/control arms for each trial is 648/545, 210/205, 559/549, 176/177, 3701/3704, 535/556, 1323/1330, 713/794, 409/394, 1156/1173, 11994/11583, 443/447, 375/370, 682/740, respectively.

Figure 2. The effect of MMS on estimated total GWG at delivery. MMS, multiple micronutrient supplements; GWG, gestational weight gain; The total GWG at delivery was estimated by multiplying the percent adequacy of GWG by the IOM-recommended GWG at delivery, which was calculated based on the gestational age at delivery and BMI category for each individual woman. The sample size by MMS/control arms for each trial is 648/545, 210/205, 559/549, 176/177, 3701/3704, 526/549, 1323/1330, 696/775, 409/394, 1156/1173, 11994/11583, 443/447, 375/370, 682/740, respectively.

Figure 3. The effect of small-quantity LNS on the percent adequacy of GWG. LNS, lipid-based nutrient supplements; GWG, gestational weight gain; percent adequacy of GWG was calculated by dividing the actual GWG at the last weight measure during pregnancy by the recommended GWG according to the Institute of Medicine (IOM) 2009 guideline, multiplied by 100. The sample size by small-quantity LNS/control arms for each trial is 431/447, 865/2478, 369/370, 670/607, respectively.

Figure 4. The effect of small-quantity LNS on estimated total GWG at delivery. LNS, lipid-based nutrient supplements; GWG, gestational weight gain; The total GWG at delivery was estimated by multiplying the percent adequacy of GWG by the IOM-recommended GWG at delivery, which was calculated based on the gestational age at delivery and BMI category for each individual woman. The sample size by small-quantity LNS/control arms for each trial is 431/447, 817/2315, 369/370, 670/607, respectively.