Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries

Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: an individual patient data meta-analysis of 17 randomized trials

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Running Title: Effect modifiers of maternal micronutrient supplements

Abstract

Background: Randomized trials indicate maternal multiple micronutrient supplementation (MMS) decreases the risk of low birthweight and potentially improves other infant health outcomes. However, heterogeneity across studies suggests influence from effect modifiers.

Methods: We performed a two-stage individual patient data (IPD) meta-analysis of 17 randomized controlled trials (including 112,953 pregnancies) conducted in 14 low- and middle-income countries (LMICs) to identify individual-level modifiers of the effect of MMS on stillbirth, birth outcomes, and infant mortality. Study-specific estimates were generated, and we pooled subgroup estimates using fixed effects models.

Findings: MMS provided significantly greater reductions in neonatal mortality for female (RR: 0·85; 95% CI: 0·75-0·96) as compared to male neonates (RR: 1·06; 95% CI: 0·95-1·17) (p-value for interaction: 0·007). MMS resulted in greater reductions in low birthweight (RR 0·81; 95% CI: 0·74-0·89; p-value for interaction: 0·049), small-for-gestational age births (RR 0·92; 95% CI: 0·87-0·97; p-value for interaction: 0·03), and six-month mortality (RR: 0·71; 95% CI: 0·60-0·86; p-value for interaction: 0·04) among anemic (hemoglobin <110g/L) as compared with non-anemic pregnant women. MMS also had a greater impact on preterm births among underweight pregnant women (body mass index <18·5kg/m^2) (RR: 0·84; 95% CI: 0·78-0·91; p-value for interaction: 0·01). Initiation of MMS prior to 20 weeks gestation provided greater reductions in preterm birth (RR 0·89; 95% CI: 0·85-0·93; p-value for interaction: 0·03). In general, the survival and birth outcome effects of MMS were greater with high adherence (≥95%) to supplementation. MMS did not significantly increase the risk of neonatal, six month, or infant mortality, nor stillbirth, overall or in any of the 26 subgroups examined.

Interpretation: Antenatal MMS improved survival for female infants and provided greater birth outcome benefits for infants born to undernourished and anemic pregnant women. Early initiation in pregnancy and high adherence to MMS also provided greater overall benefits. Mechanisms to explain differences in the effect of antenatal MMS on infant health by sex remains to be understood.

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Research in Context

Evidence before this study: Micronutrient deficiencies are common among pregnant women in low- and middle-income countries (LMICs). However, debate persists regarding the current World Health Organization (WHO) recommendation to provide pregnant women with iron-folic acid (IFA) supplementation alone, rather than multiple micronutrient supplements (MMS) containing other essential micronutrients in addition to iron-folic acid during routine antenatal care. Over the past two decades, more than 20 randomized trials have examined the effect of MMS during pregnancy, compared to IFA-alone, on maternal and child health outcomes. The 2017 Cochrane review and meta-analysis determined that provision of daily oral MMS reduced the risk of low birthweight (<2500g) and small-for-gestational-age (SGA) births, but had no overall effect on perinatal and neonatal mortality as compared to IFA-alone.

The recently-updated 2016 WHO antenatal care (ANC) recommendations acknowledged that policymakers in populations with a high prevalence of nutritional deficiencies may wish to provide MMS. However, WHO ~~declined to make a global recommendation for~~ does not universally recommend MMS, noting: 'There is some evidence of additional benefit of MMN supplements containing 13–15 different micronutrients (including iron and folic acid) over iron and folic acid supplements alone, but there is also some evidence of risk, and some important gaps in the evidence.'

Added value of this study: The primary objective of this study was to conduct a comprehensive two-stage individual patient data meta-analysis to identify factors which may alter the impact of MMS on stillbirth, birth outcomes, and infant mortality using data from 17 randomized controlled trials conducted in LMICs. This study is the most detailed approach to analyzing the existing MMS trial data to date. Previous meta-analyses identified overall benefits of MMS in terms of birth size, but we contribute that specific subgroups experience mortality benefits - notably female infants. Women with indicators of malnutrition during pregnancy also had greater reductions in low birthweight, preterm, and small-for-gestational-age births with MMS. We found no evidence that MMS significantly increased the risk of stillbirth or neonatal, six month, or infant mortality, neither overall or in any of the 26 examined subgroups.

Implications of the available evidence: This novel analysis identified subgroups of mothers and infants that may benefit the most from MMS. ~~Additionally, we found no significant evidence of harm in any subgroup.~~

Introduction

Micronutrient deficiencies are common among women in low- and middle-income countries (LMICs) primarily due to inadequate dietary intake and limited diversity of fruits, vegetables, animal protein, and fortified foods.[1] The burden and severity of micronutrient deficiencies are exacerbated during pregnancy due to increased demands of both the mother and the growing fetus.[2] It is well established that iron-deficiency anemia in pregnancy can lead to decreased birthweight, and insufficient folate levels in the periconceptional period increases the risk of neural tube defects and other adverse outcomes.[3-5] Deficiencies in other micronutrients including vitamins A, B-complex, D, E, zinc, calcium, copper, magnesium, selenium and iodine are also prevalent in LMICs and may lead to poor pregnancy, fetal growth, and child health outcomes.[3,6-8] As such, maternal multiple micronutrient supplementation (MMS) including iron-folic acid is a potential intervention to improve maternal and child health as compared to iron-folic acid supplementation (IFA) alone.

The 2017 Cochrane systematic review and meta-analysis which examined the effect of maternal MMS in pregnancy on infant mortality identified nineteen randomized controlled trials and pooled data from 17 of these studies.[6] Provision of MMS in combination with iron-folic acid during pregnancy reduced the risk of ~~stillbirth (relative risk (RR): 0.92, 95% confidence interval (CI) 0.86 to 0.99),~~ low birthweight (<2500g) (RR: 0·88, 95% CI 0·85 to 0·91) and small-for-gestational-age (SGA) births (RR: 0·92, 95% CI 0·86 to 0·98), but had no significant effect on perinatal (RR: 1.01, 95% CI 0·91 to 1·13) and neonatal mortality (RR: 1.06, 95% CI 0·92 to 1·22) as compared to iron-folic acid supplementation alone.[6] There was moderate heterogeneity, as measured by I^2, of the effect of MMS on some birth outcomes across published trials but substantial heterogeneity for perinatal mortality. A previously published pooled analysis of 12 MMS trials also indicated the effect of MMS on birthweight may be greater in pregnant women with higher body mass index (BMI).[9]

In 2016 the World Health Organization (WHO) reviewed their antenatal care (ANC) recommendations and acknowledged that policymakers in populations with a high prevalence of nutritional deficiencies may wish to provide MMS containing iron and folic-acid. However, ~~WHO declined to make a global recommendation for~~ WHO did not universally recommend MMS, noting that there was evidence of benefit but also some evidence of harm ~~associated with MMS~~.[10] ~~A contributing factor to the WHO statement regarding the possibility of harm was an exploratory subgroup meta-analysis of trials that used 60mg iron and 400µg folic acid control groups which found MMS potentially increased risk of neonatal mortality (6 trials; RR 1.22; 95% CI: 0.95-1.57)[10-16]. Of note, in the WHO subgroup analysis, all but one trial used a higher dose iron in the control arm as compared to the MMS arm; higher dose iron may independently effect birth outcomes and infant mortality.~~ The existing data also precluded definitive conclusions if any subgroups experience greater benefits or harm due to MMS. The primary objective of our study was to examine potential effect modifiers which might alter the impact of maternal MMS on stillbirth, birth outcomes, and infant mortality through an individual patient data (IPD) meta-analysis of randomized controlled trials conducted in LMICs. The study intended to identify subgroups of pregnant women and infants who may experience greater benefit or harm due to MMS and explore potential mechanisms that may have led to heterogeneity across randomized trials.

Methods

We conducted a two-stage individual patient data meta-analysis (IPD). First, we identified potential studies for inclusion through a review of recent meta-analyses.[6,11,12] We updated this list of potential studies using the search strategy employed by the 2015 Cochrane review to identify randomized controlled trials published through July 20, 2015.[6] We also reviewed the references of included trials and systematic reviews; there were no language restrictions.

Eligible studies (i) were randomized controlled trials of multiple micronutrient supplements for pregnant women, containing at least three micronutrients, (ii) were conducted in LMICs as defined by the World

Bank, (iii) included a control group that had received iron and folic acid supplements as part of the trial or as standard of care, (iv) whose authors presented data on birth outcomes, stillbirth, or infant mortality, and (v) whose authors agreed to participate in this new IPD study. We excluded trials or trial arms that used lipid-based micronutrient supplements and micronutrient-fortified powders as these provided additional calories and nutrients which might have independent effects on outcomes of interest.

All outcomes, subgroups, and statistical methods were defined *a priori*. Outcomes of interest included: stillbirth, early neonatal (≤7 days age), neonatal (≤28 days age), 6-month (≤180 days age), and infant (≤365 days age) mortality. Birth outcomes included: birthweight, very low birthweight (<2000g), low birth weight (<2500g), early preterm (<34 weeks gestation), preterm (<37 weeks gestation), SGA (<10th percentile of weight-for-gestational-age and sex as defined by Oken[13] and Intergrowth[14] standards), and large-for-gestational age (LGA) birth (>90th percentile as defined by Oken[13] and Intergrowth[14] standards). Births <33 or >43 completed weeks gestation were excluded from Intergrowth[14] analyses as SGA and LGA cut-offs are not defined for these gestational ages.

We assessed the effect of MMS on all outcomes within the following subgroups selected based on biologic plausibility and inclusion in previous meta-analyses: gestational age at randomization (trimesters and <20 weeks vs. ≥20 weeks), parity (1 child vs. ≥2 children), maternal age (<18 years vs. ≥18 years and <20 years vs. ≥20 years), maternal underweight at randomization (body mass index (BMI) <18·5 kg/m^2 vs. ≥18·5 kg/m^2), maternal anemia at randomization (<110 g/L vs. ≥110 g/L), maternal stature (<150 cm vs. ≥150 cm), maternal education (none vs. ≥1 year), infant sex (male vs. female), and adherence to multivitamin regimen (≥95% vs. <95%). We examined the effect of MMS on stillbirth and mortality outcomes by the presence of a skilled birth attendant (SBA) at delivery (yes vs. no).

We contacted principal investigators of each study and invited them to participate in this study. Eight trials provided individual-level data to the Harvard T.H. Chan investigators (ERS and CRS) and nine

independently conducted the subgroup analyses in accordance with the study protocol and using the same statistical analysis code. We calculated non-parametric relative risk or mean difference estimates and corresponding 95% confidence intervals for individually randomized trials. We calculated estimates and 95% confidence intervals for cluster randomized trials utilizing methods consistent with the primary published paper.

We pooled study-specific relative risk and mean difference estimates using fixed effects models using STATA version 14 METAN command. We excluded trials which did not contribute at least one subject to all strata within a subgroup analysis. Heterogeneity within strata was quantified using the I^2 test statistic and corresponding p value, while heterogeneity between subgroups was assessed with the $\chi 2$ test for heterogeneity. We qualitatively assessed study quality.[15] As a sensitivity analysis for individual subgroup effects, we generated pooled subgroup estimates using random effects models; we also examined overall and subgroup effects separately for trials using the same dose of iron in the MMS and comparison arm and again for the trials using a lower dose iron in the MMS arm than the comparison arm In addition, we conducted an influence analysis for significant results whereby we present pooled estimates omitting each study, one at a time (results presented in Appendix E, pp218-220).[16] To assess publication bias and small study effects we visually inspected funnel-plots (results presented in Appendix F, pp221-224). All individual trials were approved by their respective ethics committees. The pooling study protocol was approved by the Harvard T. H. Chan School of Public Health IRB (15-2969). There was no funding source for this study.

Results

We identified 19 randomized controlled trials which met our inclusion criteria, 17 of which participated in this meta-analysis.[17-33] Two did not participate.[34,35] A summary of trials included in the meta-analysis is presented in Table 1. The trials included 112,953 pregnant women and study-specific sample size ranged from 200[22] to 44,567[31], with two studies contributing more than two-thirds of total participants.[26,31] Eight

trials used the United Nations multiple micronutrient preparation (UNIMMAP) (MMS formulations in AppendixA-pp1)[20,21,23,26-30]. All trials used MMS preparations that included at least 8 micronutrients in addition to iron-folic acid. The prevalence of effect modifiers and cumulative incidence of study outcomes by trial are presented in Appendix A (pp3-4). All trials were graded low or moderate risk of bias (AppendixA-pp2). Funnel plots did not provide clear evidence of publication bias or small study effects (Appendix F, pp221-224).

In Figure 1 we present subgroup-specific pooled effect sized for the following outcomes: stillbirth, neonatal mortality, infant mortality outcomes, low birth weight, preterm, and SGA births by the Oken standard. Forest plots for all subgroup meta-analyses are presented in Appendix B (pp5-205). Table 2 presents the effect of MMS on stillbirth, neonatal mortality, mortality to six months, and infant mortality stratified by potential effect modifiers. We did not identify any factors which significantly modified the effect of MMS on stillbirth among all trials. In meta-analyses including all live births, there was no overall effect of MMS on mortality at any time point; however, there were several subgroups for which MMS provided significant survival benefits. We found sex modified the effect of MMS on survival in the early neonatal, neonatal, and infant periods (p-values for heterogeneity: 0·047, 0·007, 0·04) (Table 2 and Appendix B pp23). MMS significantly reduced the risk of neonatal mortality by 15% among females (95% CI: 4-25%) with a similar magnitude of reduction for early neonatal, six months, and infant mortality. Significant mortality benefits of MMS for females were also found at all-time points in random effects sensitivity analyses (Appendix C pp206). MMS provided significantly greater six-month mortality reduction among anemic pregnant women (RR: 0·71; 95% CI: 0·60-0·86) as compared to non-anemic pregnant women (RR: 0·93; 95% CI: 0·78-1·11) (p-value for heterogeneity: 0·04). Maternal adherence to the intervention also modified the effect of MMS on infant mortality, with survival benefits for infants born to women reporting >95% adherence to the supplements (Table 2). There was no subgroup which experienced significantly increased risk of stillbirth or neonatal, six month, or infant mortality in both fixed and random effects meta-analyses (Table 2 and Appendix C pp206).

Among all live births, MMS significantly reduced the risk of very low birthweight (<2000 g), low birthweight (<2500 g), early preterm (<34 weeks), preterm (<37 weeks), and SGA (Oken or Intergrowth standards) (Table 3 and Appendix B pp80, pp122). We also found MMS significantly increased the risk of being born LGA by the Intergrowth standard (RR: 1·11; 95% CI: 1·04-1·19) (Appendix B pp150). There was no evidence that infant sex modified the effect of MMS on low birthweight, prematurity, or SGA births. MMS had a greater impact on reducing the risk of low birthweight (RR 0·81; 95% CI: 0·74-0·89) and SGA by Oken standard (RR 0·92; 95% CI: 0·87-0·97) among anemic as compared to non-anemic pregnant women (p values for heterogeneity: 0·049 and 0·03) (Table 3). Maternal BMI modified the effect of MMS on several birth outcomes. MMS reduced the risk of being born early preterm and preterm with greater magnitude among pregnant women with a BMI <18·5 kg/m^2 compared to non-underweight pregnant women (Table 3, Appendix B pp86). Maternal BMI also modified the risk of having an LGA birth based on the Oken standard (p value for heterogeneity = 0·045); with non-underweight women (BMI ≥18·5 kg/m^2) having a greater increase in risk of LGA (Table 4).

Gestational age at MMS initiation modified the effect of supplementation. Women initiating MMS <20 weeks gestation had greater reductions in the risk of preterm birth (RR 0·89; 95% CI: 0·85-0·93) (p value for heterogeneity 0·03) (Table 3). However, MMS provided greater reductions in the risk of SGA birth by Oken standard among women initiating supplementation after 20 weeks (RR 0·91; 95% CI: 0·86-0·96) (p value heterogeneity 0·004) (Table 3). MMS initiation before or after 20 weeks gestation conferred similar benefits in reducing the risk of low birthweight (Table 3).

As a sensitivity analysis, we stratified studies by whether or not they used the same dose of iron in the MMS and IFA arms. We present overall (Supplemental Table 7, Appendix D pp208) and subgroup estimates (Supplemental Tables 8-16, Appendix D pp209-217) of the impact of MMS for trials using the

same dose of iron in the MMS and IFA-alone arms, and for trials using a lower dose iron in the MMS arm than the IFA-alone arm (all used ≤30mg iron for MMS and 60mg iron for IFA-alone). The results for trials using the same dose of iron in both arms revealed benefits of MMS and were consistent with the primary analysis. In contrast, some subgroups given MMS with low dose iron (≤30mg) observed higher stillbirth and neonatal mortality than IFA-alone with 60mg iron. Specifically, MMS containing lower dose iron than the IFA comparison arm was found to increase: stillbirth among first pregnancies, early neonatal mortality among women who initiated supplementation before 20 weeks gestation, early neonatal and neonatal mortality among women with <95% adherence, and early neonatal mortality for multigravidae.

Discussion

This comprehensive individual patient data meta-analysis found that MMS including iron-folic acid reduced the risk of low birthweight, preterm birth, and being born SGA across all included trials, and we identified several factors that modified the impact of MMS on infant survival and birth outcomes. The effect of MMS on mortality was modified by infant sex. Survival benefits were significantly greater for female than for male infants. However, sex did not modify the effect of MMS on low birthweight, preterm, or SGA births. MMS also resulted in greater reductions in the risk of six-month mortality, low birthweight, and SGA births among anemic as compared to non-anemic pregnant women. Similarly, MMS provided greater reductions in risk of being born preterm or early preterm among underweight as compared to non-underweight women. Starting MMS before 20 weeks gestation reduced the risk of preterm birth, but there were also beneficial effects of MMS on SGA and low birthweight births among women initiating MMS after 20 weeks. In general, the mortality and birth outcome effects of MMS were greater for women with ≥95% adherence to supplementation. We did not identify any subgroup for which MMS significantly elevated the risk of stillbirth or neonatal, six month, or infant mortality.

The effect of MMS on mortality was modified by infant sex. MMS consistently reduced mortality by approximately 15% among females during the first year of life, but we did not observe significant benefits

among males. The biological mechanisms leading to these sex differences are not clear. Christian, West, and colleagues have previously proposed that sex differences in the mortality effect of MMS may be explained by differences in birth size by sex.[31,36] Males have greater length, head circumference, and birth weight on average as compared to females, and increased birth size due to MMS may lead to greater birth complications among males.[37] However, we found no sex differences in the effect of MMS on stillbirth which suggests that effect modification by sex may operate through other mechanisms or vary with the population context. The burden of infections and leading causes of mortality have been shown to vary by infant sex[38,39]; additional information on the causes and timing of deaths within trials may help clarify why MMS appears to be more beneficial for female infants. Nevertheless, we do not recommend programs considering implementation of MMS target only pregnant women carrying female fetuses as both male and female newborns experience birthweight benefits and small positive survival benefits are possible among males.

MMS had greater impact on birth outcomes among women with poor nutritional status, as indicated by anemia or low BMI, at the start of supplementation as initially reported in the SUMMIT study.[26] Anemic women experienced greater reductions in the risk of low birthweight, SGA birth, and mortality to six months than non-anemic pregnant women. The effect of MMS on preterm birth was also greater for pregnant women who had a BMI <18·5 kg/m^2 at the start of supplementation. These findings indicate that iron-folic acid alone is likely an insufficient intervention for anemic pregnant women and justifies continued focus on anemia and low BMI as key effect modifiers for nutrition interventions in pregnancy. A recent MMS trial conducted in China among non- and mildly-anemic women (not included in our meta-analysis) found no effect of MMS on perinatal mortality and a non-significant 10% reduction in low birthweight.[34] These findings are consistent with our non-anemic subgroup results, which showed no effect of MMS on early neonatal, neonatal, or infant mortality and an 8% (95% CI: 2-15%) reduction in low birthweight.

Due to the clustering of protein-energy and micronutrient deficiencies, we cannot directly examine whether improvement in maternal hemoglobin status mediated a greater impact of MMS on low birthweight among anemic women. Anemia may be a proxy for deficiencies of micronutrients included in MMS, as well as numerous other factors including maternal infection.[40,41] A previous meta-analysis found that multiple micronutrient supplements (which included iron) had a similar effect on hemoglobin and anemia compared with iron alone or iron with folic acid.[42] Notably, some trials included in our meta-analysis and the anemia meta-analysis used higher dose iron in the control arm than the MMS arm, which may have attenuated the hemoglobin, mortality, and birth outcome effects of MMS, particularly among anemic pregnant women.[20,21,27-29,32,33,35,42] Despite this, we still find a larger effect of MMS among anemic than for non-anemic pregnant women. There are several hemoglobin independent pathways by which MMS might improve birth outcomes[5], including reductions in maternal and fetal inflammation[43], improvements in oxidative metabolism and placental function[44,45], and altered maternal endocrine effects.[46] Although the biological mechanisms through which MMS provides benefits are unclear, our meta-analysis indicates that the population-level benefits for birth outcomes are likely to be greater in settings with high rates of maternal nutritional deficiencies. It is also important to note that in the MINIMat trial women who received both early food supplementation and MMS had the lowest rate of infant mortality[30]; combined macronutrient and micronutrient interventions may produce even greater effects in settings with high rates of maternal malnutrition.

We did not identify any subgroup which experienced significantly elevated risk of stillbirth or mortality at any time point in the primary analysis. MMS trial reports have raised concerns that increased birth size due to MMS may increase the risk of cephalopelvic disproportion and neonatal asphyxia, particularly among women of small stature.[17,31] We found that MMS indeed increased the risk of LGA births (as defined by the Intergrowth standard[14]), which could hypothetically increase the risk of maternal-fetal disproportion and related birth complications. However, we found no indication that mothers whose

height was <150 cm had increased risk of stillbirth or mortality at any time point. As such, alternative interpretations or mechanisms to explain no overall effect of MMS on mortality should be explored.

We also provide evidence that iron dosage influences the observed effect of MMS on stillbirth and mortality. Specifically, the sensitivity analyses revealed benefits and no significant harmful effects overall or in any subgroup among trials that used the same dose of iron in the MMS and IFA-alone arms. In contrast, the sensitivity analyses also suggested that MMS with low dose iron (≤30mg) may result in a higher observed stillbirth and mortality in some subgroups when compared to IFA-alone with 60mg iron. The most recent Cochrane review found similar effect modification by iron dose on perinatal mortality.[6] Furthermore, the WHO ANC guidelines noted the potential for harmful effects of MMS on neonatal mortality among a subgroup analysis in which 5 out of 6 trials used low dose iron (≤30mg) in the MMS arm and 60mg iron in the IFA-alone arm.[10] Taken together, our analyses and others indicate that both iron and multiple micronutrients have beneficial effects and that multiple micronutrients together with IFA may provide even greater benefits than IFA alone. Accordingly, countries and programs considering implementation of MMS should use a formulation with an iron dose similar to what they currently utilize; for example, MMS that contains 60mg iron should be considered in settings where 60mg IFA is currently implemented.

Notwithstanding the large sample size and consistency of our findings, there are several limitations to our meta-analysis. First, due to the number of subgroup analyses performed, there is an inflated risk of type 1 errors inherent to the number of heterogeneity tests presented. However, our findings as a whole exceed those that would be expected by chance. We observed that 13 out of 70 tests for heterogeneity for mortality outcomes were significant (probability of occurring by chance alone <0.01%). There is also low probability that of finding 26 out of 146 subgroups experienced significant survival benefits (<0.01%) and that no subgroups out of 146 had increased mortality risk (2.5%) if we assume there was no true effect of MMS on mortality in any subgroup. Second, as previously discussed, some trials used a higher dose of

iron in the control arm as compared with the MMS arm, and our sensitivity analysis suggests that inclusion of these trials resulted in attenuation of the effect of MMS because control group subjects may have experienced benefits from additional iron.[20,21,27-29,32,33] ~~We did not present sensitivity analyses restricting to trials using identical iron doses in control and MMS arms since this would double the number of statistical tests resulting in even greater risk of type 1 errors.~~ Third, the JiVitA-3[31] and SUMMIT[26] trials are weighted heavily in many of the subgroup strata due to their large sample sizes and high event rates. Our sensitivity analyses show that sex differences in the effect of MMS on neonatal mortality are robust to excluding either of these studies (Appendix E, p218-220). However, the stronger benefit of MMS on 6 month mortality among infants born to anemic women is driven by the SUMMIT study, and the stronger benefit of MMS on preterm birth among infants born to underweight women and infant mortality among male infants, are driven by JiVitA-3 (Appendix E, pp218-220). Fourth, we were unable to examine HIV as a potential effect modifier since only two trials included both HIV-infected and HIV-uninfected women. Nevertheless, there was no indication that the effect of MMS varied by maternal HIV status in these studies.[19,32] Lastly, although our analysis identified several maternal and child factors which alter the effect of MMS on mortality and birth outcomes, we can provide only limited insight into the biological mechanisms through which MMS may operate. As poor socioeconomic status, significant barriers to health services, and nutritional deficiencies often coexist, the effect modifiers we examined in this analysis (*e.g.* skilled birth attendants, maternal underweight, and maternal anemia) have overlap as indicators of underlying adversity. Even so, the factors identified in this paper indicate subgroups which may experience the greatest benefits from MMS, regardless of the mechanisms through which MMS operates.

Our IPD meta-analysis that included data from more than 112,000 pregnancies in 14 LMICs determined that MMS reduced mortality among female infants, and although MMS increased birthweight and reduced preterm among all infants, the greatest effects were for those born to pregnant women with nutritional deficiency as indicated by anemia or low BMI. Based on the included data and methods of this

IPD meta-analysis, we also found none of the 26 subgroups, or the population overall, showed MMS significantly increased the risk of stillbirth or neonatal, six-month, or infant mortality. A systematic review which examined the long-term health effects found no significant evidence that MMS improved child growth, body composition, blood pressure, respiratory, or cognitive outcomes as compared to iron folic-acid alone.[47] However, a recently published long-term follow-up study of SUMMIT found that MMS significantly improved procedural memory and produced better scores on 18 out of 21 cognitive tests administered to Indonesian children at 9-12 years of age.[48] This new evidence suggests that WHO may wish to reevaluate the balance of benefits and harms of universal MMS in their ANC recommendations. Programs and LMICs considering implementation of MMS have the opportunity to simultaneously expand coverage of early ANC attendance and MMS including iron-folic acid, while also improving the quality of ANC counseling and services to produce population-level infant health benefits which may be greater than any of these strategies in isolation. Packaging MMS with effective ANC interventions for coordinated delivery is consistent with the Sustainable Development Goals (SDGs) which emphasize identification of synergies that have the potential for rapid impact.[49]

Contributors: ERS, CRS, AS, WF designed the study (project conception, development of overall research plan, and study oversight). All authors contributed input and reviewed the study protocol and assisted or completed statistical analyses for their respective trials. ERS, LW, CRS developed statistical program code for trial-specific analyses. ERS and CRS pooled the data and conducted the meta-analyses. ERS, CRS drafted the initial paper. All authors reviewed and contributed to the final manuscript. ERS, CRS have primary responsibility for final content.

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Table 1. Description of studies

Study	Location	Years of Study	Study Design*	N	Study Population
Fawzi 1998	Dar es Salaam, Tanzania	1995-1997	RCT	1075	HIV-infected pregnant women 12-27 weeks gestation
Christian 2003	Sarlahi, Nepal	1998-2001	cRCT	4926	Pregnant women
Ramakrishnan 2003	Cuernavaca, Mexico	1997-2000	RCT	873	Pregnant women <13 weeks gestation
Friis 2004	Harare, Zimbabwe	1996-1997	RCT	1669	Pregnant women 22-36 weeks gestation including 725 HIV-infected women
Kaestel 2005	Bissau, Guinea Bissau	2001-2002	RCT	2100	Pregnant women <37 weeks gestation
Osrin 2005	Dhanusha and Mahottari Districts, Nepal	2002-2004	RCT	1200	Singleton pregnant women between 12-20 weeks gestation
Gupta 2007	East Delhi, India	2002-2003	RCT	200	Pregnant women with BMI <18.5 kg/m^2, 24-32 weeks gestation
Zagre 2007	Maradi, Niger	2004-2006	cRCT	2902	Pregnant women <28 weeks gestation
Fawzi 2007	Dar es Salaam, Tanzania	2001-2004	RCT	8468	HIV-uninfected pregnant women of 12-27 weeks gestation
Shankar 2008	Lombok island, Indonesia	2001-2004	cRCT	31290	Pregnant women (34% first, 43% second, and 23% third trimester)
Zeng 2008	Shaanxi Province, China	2002-2006	cRCT	3811	Pregnant women (folic acid only arm excluded)
Roberfroid 2008	Hounde health district, Burkina Faso	2004-2006	RCT	1426	Pregnant women
Bhutta 2009	Bilal colony, Karachi, Kot Diji, Sindh, Pakistan	2002-2004	cRCT	2378	Pregnant women <16 weeks gestation
Persson 2012	Matlab, Bangladesh	2001-2003	RCT	4436	Pregnant women between 6-8 weeks gestation
West 2014	Gaibandha and Rangpur, Bangladesh	2007-2012	cRCT	44567	Pregnant women (79% <13 weeks gestation)
Ashorn 2015	Mangochi District, Malawi	2011-2013	RCT	929	Pregnant women <20 weeks gestation (excluding lipid-based nutrient supplement arm)
Adu-Afarwuah 2015	Somanya-Kpong, Ghana	2009-2011	RCT	703	Pregnant women <20 weeks gestation (excluding lipid-based nutrient supplement arm)

* Randomized Control Trial (RCT). Cluster Randomized Control Trial (cRCT).

Table 2. The effect of MMS on stillbirth, neonatal mortality, mortality to six months, and infant mortality stratified by potential effect modifiers.

	Stillbirth			Neonatal Mortality (≤28 days)			Mortality to Six Months			Infant Mortality (≤365 days)		
	N[1]	Relative risk (95% CI)	p value heterogeneity	N[1]	Relative risk (95% CI)	p value heterogeneity	N[1]	Relative risk (95% CI)	p value heterogeneity	N[1]	Relative risk (95% CI)	p value heterogeneity
Overall-Fixed Effects	16	0.92 (0.86-0.99)	-	12	0.98 (0.90-1.05)	-	9	0.93 (0.85-1.00)	-	8	0.97 (0.88-1.06)	-
Overall-Random Effects		0.97 (0.85-1.11)			0.99 (0.89-1.09)			0.93 (0.86-1.00)			0.97 (0.88-1.06)	
Infant Sex												
Male	16	0.92 (0.82-1.03)	0.88	12	1.06 (0.95-1.17)	0.007	9	0.98 (0.89-1.09)	0.06	8	1.05 (0.93-1.18)	0.04
Female		0.91 (0.80-1.03)			0.85 (0.75-0.96)			0.85 (0.75-0.95)			0.87 (0.77-0.99)	
Gestational Age at Enrollment												
<20 Weeks	10	0.97 (0.89-1.06)	0.05	10	0.99 (0.90-1.09)	0.60	7	0.96 (0.87-1.05)	0.10	7	0.98 (0.89-1.07)	0.57
≥ 20 Weeks		0.81 (0.70-0.95)			0.94 (0.81-1.10)			0.82 (0.69-0.96)			0.89 (0.64-1.23)	
Maternal adherence to regimen												
< 95% Adherence	11	0.92 (0.83-1.01)	0.96	9	1.05 (0.94-1.17)	0.05	6	0.98 (0.88-1.09)	0.11	5	1.06 (0.94-1.20)	0.02
≥ 95% Adherence		0.92 (0.85-0.99)			0.88 (0.77-1.01)			0.85 (0.74-0.97)			0.85 (0.74-0.97)	
Maternal Age												
< 20 years	16	0.99 (0.85-1.16)	0.26	9	0.95 (0.83-1.10)	0.51	8	0.96 (0.84-1.09)	0.68	8	0.98 (0.86-1.13)	0.87
≥ 20 years		0.90 (0.83-0.97)			1.01 (0.92-1.12)			0.92 (0.84-1.02)			0.97 (0.87-1.09)	
Parity												
First birth	15	1.01 (0.90-1.14)	0.06	12	0.93 (0.83-1.04)	0.26	9	0.94 (0.84-1.04)	0.76	8	0.97 (0.85-1.10)	0.87
Second + birth		0.88 (0.80-0.96)			1.02 (0.91-1.14)			0.92 (0.82-1.02)			0.96 (0.85-1.08)	
Maternal Underweight at enrollment												
BMI <18.5	12	0.90 (0.78-1.04)	0.53	11	1.01 (0.86-1.20)	0.61	8	0.96 (0.83-1.12)	0.60	7	0.97 (0.84-1.13)	0.95
BMI ≥18.5		0.95 (0.87-1.04)			0.96 (0.88-1.06)			0.92 (0.84-1.01)			0.98 (0.88-1.09)	
Maternal stature												
Height <150 cm	14	0.96 (0.86-1.08)	0.38	10	0.97 (0.86-1.08)	0.98	7	0.92 (0.83-1.02)	0.84	6	0.98 (0.87-1.11)	0.58
Height ≥150 cm		0.90 (0.81-1.00)			0.96 (0.86-1.08)			0.91 (0.81-1.02)			0.93 (0.81-1.06)	
Maternal hemoglobin at enrollment												
Anemic <110 g/L	13	0.79 (0.66-0.94)	0.16	10	0.87 (0.73-1.03)	0.54	8	0.71 (0.60-0.86)	0.04	7	1.00 (0.73-1.30)	0.95
Non-anemic ≥110 g/L		0.94 (0.79-1.12)			0.94 (0.79-1.11)			0.93 (0.78-1.11)			1.01 (0.79-1.30)	
Maternal education												
None	14	0.95 (0.83-1.09)	0.62	12	1.13 (0.97-1.31)	0.02	8	0.99 (0.86-1.13)	0.22	7	1.02 (0.88-1.18)	0.24
≥1 year formal education		0.91 (0.84-1.00)			0.92 (0.83-1.01)			0.89 (0.81-0.98)			0.92 (0.82-1.02)	
Skilled birth attendant												
Yes	10	0.87 (0.78-0.97)	0.09	10	1.00 (0.91-1.11)	0.23	7	1.00 (0.90-1.11)	0.01	6	1.06 (0.95-1.20)	0.006
No		1.01 (0.88-1.15)			0.91 (0.80-1.03)			0.82 (0.74-0.92)			0.82 (0.71-0.95)	

[1] N Number of studies included in subgroup analysis

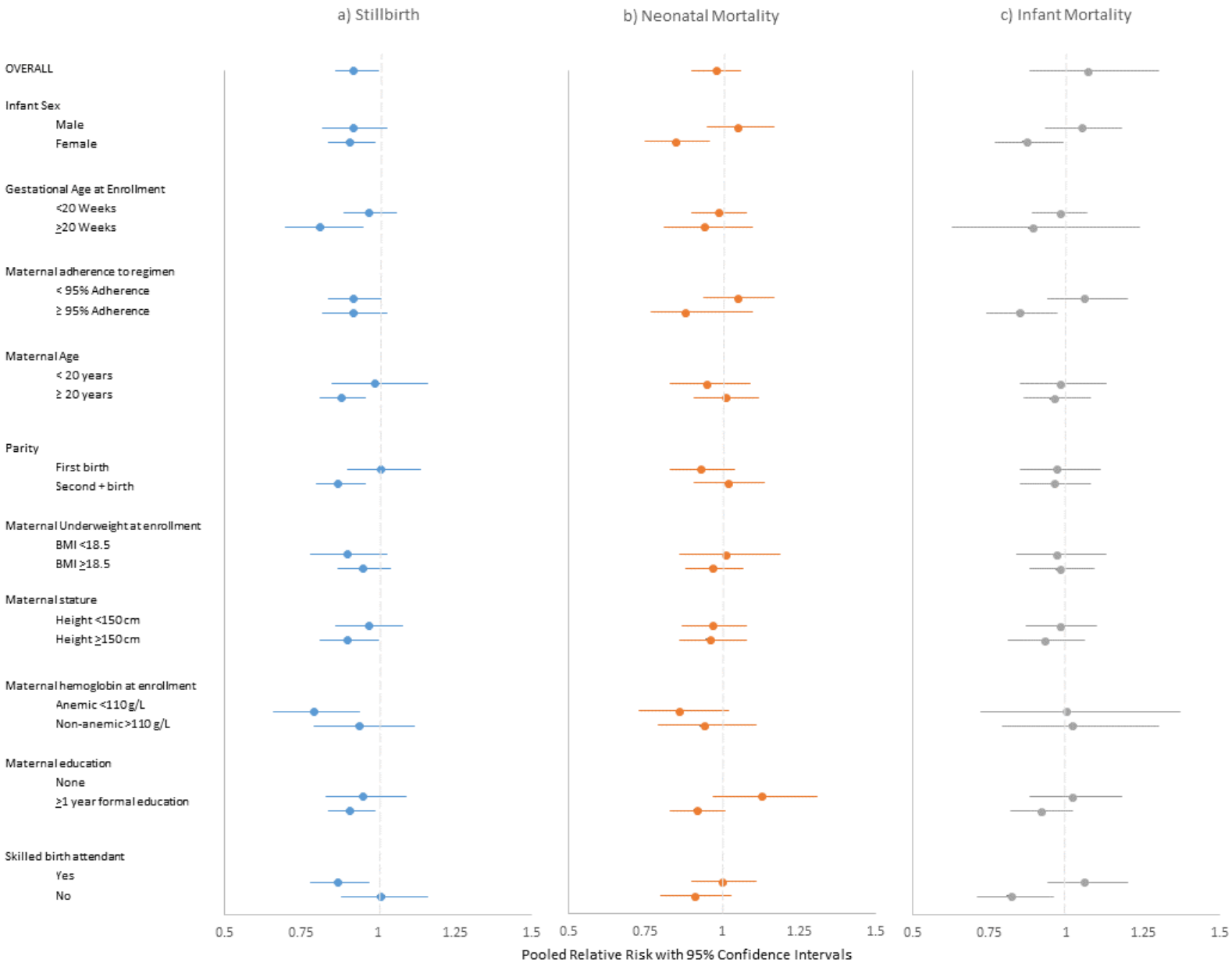
Table 3. The effect of MMS on low birthweight (<2500 g), preterm birth (<37 weeks), small-for-gestational-age (SGA) (<10th percentile Oken), large-for-gestational-age (LGA) (>90th percentile Oken) - stratified by potential effect modifiers

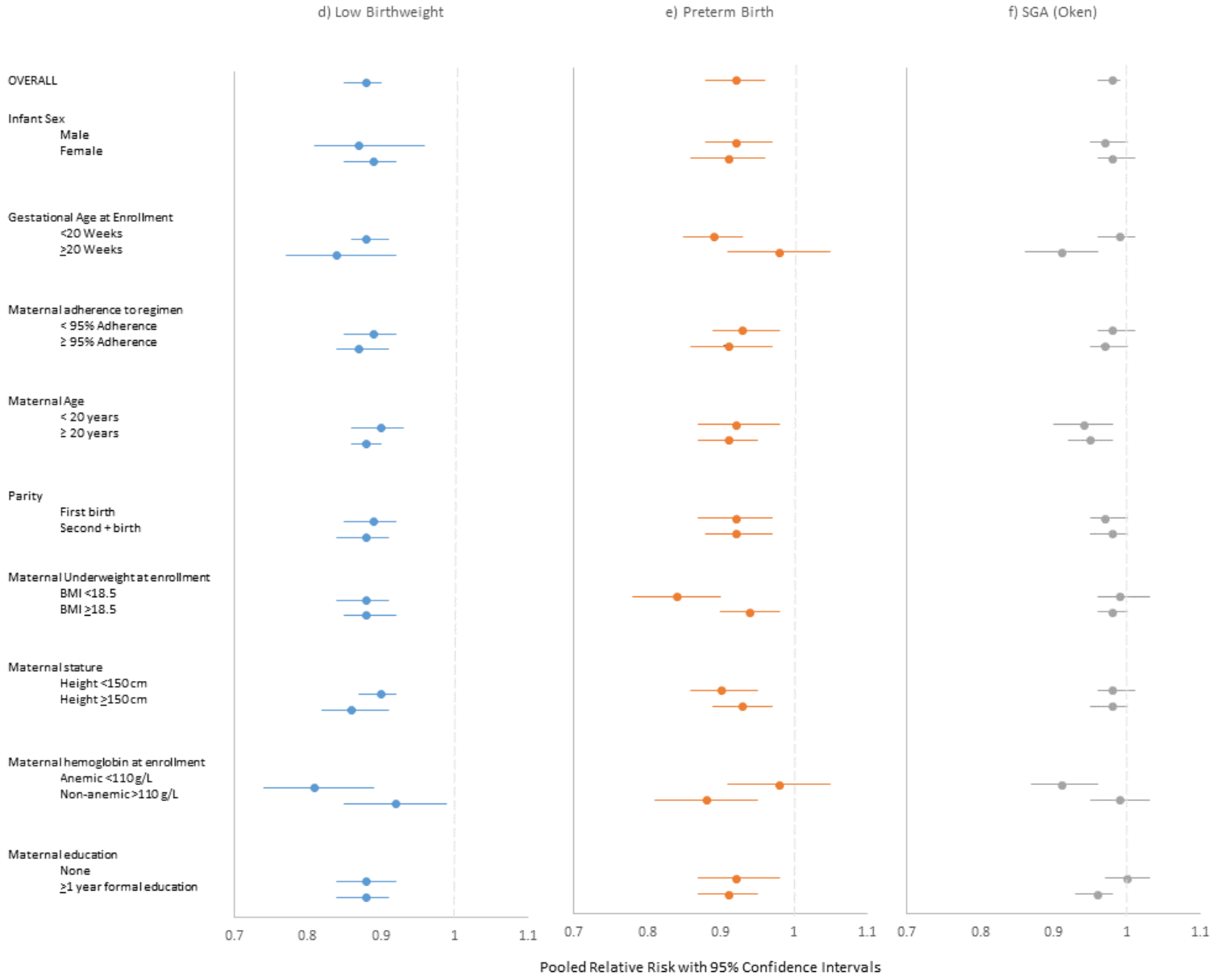
	Low Birthweight (<2500g)			Preterm (<37 weeks)			SGA (Oken)			LGA (Oken)		
	N[1]	Relative risk (95% CI)	p value heterogeneity	N[1]	Relative risk (95% CI)	p value heterogeneity	N[1]	Relative risk (95% CI)	p value heterogeneity	N[1]	Relative risk (95% CI)	p value heterogeneity
Overall-Fixed Effects	17	0.88 (0.85-0.90)	-	16	0.92 (0.88-0.95)	-	16	0.97 (0.96-0.99)	-	13	1.05 (0.95-1.15)	-
Overall-Random Effects		0.86 (0.81-0.92)			0.93 (0.87-0.98)			0.94 (0.90-0.98)			1.04 (0.92-1.18)	
Infant Sex												
Male	17	0.87 (0.83-0.91)	0.48	15	0.93 (0.88-0.97)	0.63	15	0.97 (0.95-1.00)	0.62	12	1.11 (0.98-1.25)	0.18
Female		0.89 (0.86-0.92)			0.91 (0.86-0.96)			0.98 (0.96-1.01)			0.98 (0.86-1.12)	
Gestational Age at Enrollment												
<20 Weeks	13	0.88 (0.86-0.91)	0.32	11	0.89 (0.85-0.93)	0.03	12	0.99 (0.97-1.01)	0.004	8	0.99 (0.86-1.13)	0.09
≥20 Weeks		0.84 (0.77-0.92)			1.00 (0.94-1.08)			0.91 (0.86-0.96)			1.18 (1.02-1.37)	
Maternal adherence to regimen												
< 95% Adherence	12	0.89 (0.85-0.92)	0.61	10	0.93 (0.88-0.97)	0.62	11	0.98 (0.96-1.01)	0.43	8	1.03 (0.90-1.18)	0.88
≥ 95% Adherence		0.87 (0.84-0.91)			0.90 (0.85-0.96)			0.97 (0.94-1.00)			1.05 (0.90-1.22)	
Maternal Age												
< 20 years	15	0.90 (0.86-0.93)	0.85	15	0.92 (0.87-0.98)	0.82	16	0.98 (0.95-1.00)	0.70	11	0.98 (0.79-1.22)	0.51
≥ 20 years		0.90 (0.88-0.92)			0.92 (0.88-0.96)			0.97 (0.94-0.99)			1.06 (0.96-1.18)	
Parity												
First birth	16	0.88 (0.85-0.92)	0.88	14	0.91 (0.86-0.96)	0.63	15	0.98 (0.95-1.00)	0.94	10	0.94 (0.78-1.12)	0.09
Second + birth		0.88 (0.85-0.92)			0.92 (0.88-0.97)			0.97 (0.95-1.00)			1.12 (1.00-1.25)	
Maternal Underweight at enrollment												
BMI <18.5	16	0.88 (0.84-0.91)	0.80	13	0.84 (0.78-0.91)	0.01	16	1.00 (0.96-1.03)	0.20	8	0.77 (0.57-1.05)	0.045
BMI ≥18.5		0.88 (0.85-0.92)			0.94 (0.90-0.98)			0.97 (0.95-0.99)			1.08 (0.97-1.21)	
Maternal stature												
Height <150 cm	16	0.90 (0.87-0.93)	0.16	15	0.91 (0.86-0.96)	0.58	16	0.99 (0.96-1.01)	0.27	10	0.93 (0.78-1.12)	0.17
Height ≥150 cm		0.86 (0.82-0.90)			0.92 (0.88-0.97)			0.97 (0.96-0.99)			1.09 (0.97-1.22)	
Maternal hemoglobin at enrollment												
Anemic <110 g/L	14	0.81 (0.74-0.89)	0.049	12	0.98 (0.91-1.05)	0.05	13	0.92 (0.87-0.97)	0.03	9	1.25 (1.06-1.49)	0.09
Non-anemic ≥110 g/L		0.91 (0.85-0.98)			0.88 (0.81-0.95)			0.99 (0.95-1.03)			0.99 (0.80-1.22)	
Maternal education												
None	16	0.88 (0.84-0.93)	0.75	14	0.92 (0.87-0.98)	0.64	15	1.00 (0.97-1.03)	0.049	9	1.07 (0.88-1.29)	0.75
≥1 year formal education		0.87 (0.84-0.91)			0.90 (0.87-0.95)			0.96 (0.94-0.98)			1.03 (0.92-1.16)	

[1] N Number of studies included in subgroup analysis

Figure Titles.

Figure 1. Summary forest plots for the effect of MMS containing iron-folic acid compared to iron-folic acid alone on a) stillbirth, b) neonatal mortality, c) infant mortality, d) low birthweight, e) preterm birth, and f) SGA by the Oken standard - stratified by modifiers of interest.


a) Stillbirth
b) Neonatal Mortality
c) Infant Mortality
OVERALL
Infant Sex
Male
Female
Gestational Age at Enrollment
<20 Weeks
≥20 Weeks
Maternal adherence to regimen
< 95% Adherence
≥ 95% Adherence
Maternal Age
< 20 years
≥ 20 years
Parity
First birth
Second + birth
Maternal Underweight at enrollment
BMI <18.5
BMI ≥18.5
Maternal stature
Height <150 cm
Height ≥150 cm
Maternal hemoglobin at enrollment
Anemic <110 g/L
Non-anemic >110 g/L
Maternal education
None
≥1 year formal education
Skilled birth attendant
Yes
No
0.5
0.75
1
1.25
1.5
Pooled Relative Risk with 95% Confidence Intervals


d) Low Birthweight
e) Preterm Birth
f) SGA (Oken)
OVERALL
Infant Sex
Male
Female
Gestational Age at Enrollment
<20 Weeks
≥20 Weeks
Maternal adherence to regimen
< 95% Adherence
≥ 95% Adherence
Maternal Age
< 20 years
≥ 20 years
Parity
First birth
Second + birth
Maternal Underweight at enrollment
BMI <18.5
BMI ≥18.5
Maternal stature
Height <150 cm
Height ≥150 cm
Maternal hemoglobin at enrollment
Anemic <110 g/L
Non-anemic >110 g/L
Maternal education
None
≥1 year formal education
0.7
0.8
0.9
1
1.1
Pooled Relative Risk with 95% Confidence Intervals