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Multiple-micronutrient supplementation for women during pregnancy (Review)

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[Intervention Review]

Multiple-micronutrient supplementation for women during pregnancy

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ABSTRACT

Background

Multiple-micronutrient (MMN) deficiencies often coexist among women of reproductive age in low- and middle-income countries. They are exacerbated in pregnancy due to the increased demands of the developing fetus, leading to potentially adverse effects on the mother and baby. A consensus is yet to be reached regarding the replacement of iron and folic acid supplementation with MMNs. Since the last update of this Cochrane Review in 2017, evidence from several trials has become available. The findings of this review will be critical to inform policy on micronutrient supplementation in pregnancy.

Objectives

To evaluate the benefits of oral multiple-micronutrient supplementation during pregnancy on maternal, fetal and infant health outcomes.

Search methods

For this 2018 update, on 23 February 2018 we searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP), and reference lists of retrieved studies. We also contacted experts in the field for additional and ongoing trials.

Selection criteria

All prospective randomised controlled trials evaluating MMN supplementation with iron and folic acid during pregnancy and its effects on pregnancy outcomes were eligible, irrespective of language or the publication status of the trials. We included cluster-randomised trials, but excluded quasi-randomised trials. Trial reports that were published as abstracts were eligible.

Data collection and analysis

Two review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. We assessed the quality of the evidence using the GRADE approach.

Main results

We identified 21 trials (involving 142,496 women) as eligible for inclusion in this review, but only 20 trials (involving 141,849 women) contributed data. Of these 20 trials, 19 were conducted in low- and middle-income countries and compared MMN supplements with iron and folic acid to iron, with or without folic acid. One trial conducted in the UK compared MMN supplementation with placebo. In total, eight trials were cluster-randomised.

MMN with iron and folic acid versus iron, with or without folic acid (19 trials)

MMN supplementation probably led to a slight reduction in preterm births (average risk ratio (RR) 0.95, 95% confidence interval (CI) 0.90 to 1.01; 18 trials, 91,425 participants; moderate-quality evidence), and babies considered small-for-gestational age (SGA) (average RR 0.92, 95% CI 0.88 to 0.97; 17 trials; 57,348 participants; moderate-quality evidence), though the CI for the pooled effect for preterm births just crossed the line of no effect. MMN reduced the number of newborn infants identified as low birthweight (LBW) (average RR 0.88, 95% CI 0.85 to 0.91; 18 trials, 68,801 participants; high-quality evidence). We did not observe any differences between groups for perinatal mortality (average RR 1.00, 95% CI 0.90 to 1.11; 15 trials, 63,922 participants; high-quality evidence). MMN supplementation led to slightly fewer stillbirths (average RR 0.95, 95% CI 0.86 to 1.04; 17 trials, 97,927 participants; high-quality evidence) but, again, the CI for the pooled effect just crossed the line of no effect. MMN supplementation did not have an important effect on neonatal mortality (average RR 1.00, 95% CI 0.89 to 1.12; 14 trials, 80,964 participants; high-quality evidence). We observed little or no difference between groups for the other maternal and pregnancy outcomes: maternal anaemia in the third trimester (average RR 1.04, 95% CI 0.94 to 1.15; 9 trials, 5912 participants), maternal mortality (average RR 1.06, 95% CI 0.72 to 1.54; 6 trials, 106,275 participants), miscarriage (average RR 0.99, 95% CI 0.94 to 1.04; 12 trials, 100,565 participants), delivery via a caesarean section (average RR 1.13, 95% CI 0.99 to 1.29; 5 trials, 12,836 participants), and congenital anomalies (average RR 1.34, 95% CI 0.25 to 7.12; 2 trials, 1958 participants). However, MMN supplementation probably led to a reduction in very preterm births (average RR 0.81, 95% CI 0.71 to 0.93; 4 trials, 37,701 participants). We were unable to assess a number of prespecified, clinically important outcomes due to insufficient or non-available data.

When we assessed primary outcomes according to GRADE criteria, the quality of evidence for the review overall was moderate to high. We graded the following outcomes as high quality: LBW, perinatal mortality, stillbirth, and neonatal mortality. The outcomes of preterm birth and SGA we graded as moderate quality; both were downgraded for funnel plot asymmetry, indicating possible publication bias.

We carried out sensitivity analyses excluding trials with high levels of sample attrition (> 20%). We found that results were consistent with the main analyses for all outcomes. We explored heterogeneity through subgroup analyses by maternal height, maternal body mass index (BMI), timing of supplementation, dose of iron, and MMN supplement formulation (UNIMMAP versus non-UNIMMAP). There was a greater reduction in preterm births for women with low BMI and among those who took non-UNIMMAP supplements. We also observed subgroup differences for maternal BMI and maternal height for SGA, indicating greater impact among women with greater BMI and height. Though we found that MMN supplementation made little or no difference to perinatal mortality, the analysis demonstrated substantial statistical heterogeneity. We explored this heterogeneity using subgroup analysis and found differences for timing of supplementation, whereby higher impact was observed with later initiation of supplementation. For all other subgroup analyses, the findings were inconclusive.

MMN versus placebo (1 trial)
A single trial in the UK found little or no important effect of MMN supplementation on preterm births, SGA, or LBW but did find a reduction in maternal anaemia in the third trimester (RR 0.66, 95% CI 0.51 to 0.85), when compared to placebo. This trial did not measure our other outcomes.

Authors' conclusions

Our findings suggest a positive impact of MMN supplementation with iron and folic acid on several birth outcomes. MMN supplementation in pregnancy led to a reduction in babies considered LBW, and probably led to a reduction in babies considered SGA. In addition, MMN probably reduced preterm births. No important benefits or harms of MMN supplementation were found for mortality outcomes (stillbirths, perinatal and neonatal mortality). These findings may provide some basis to guide the replacement of iron and folic acid supplements with MMN supplements for pregnant women residing in low- and middle-income countries.

PLAIN LANGUAGE SUMMARY

Vitamin and mineral supplements for women during pregnancy

What is the issue?

In low- and middle-income countries, many women have poor diets and are deficient in nutrients and micronutrients that are required for good health. Micronutrients are vitamins and minerals that are needed by the body in very small quantities, but are important for normal functioning, growth and development. During pregnancy, these women often become more deficient because of the need to provide nutrition for the baby too, and this can negatively affect their health, along with the health of the baby.

Why is this important?

Combining multiple micronutrients into one supplement has been suggested as a cost-effective way to achieve multiple benefits for women during pregnancy. Micronutrient deficiencies are known to interact, and a greater effect may be achieved by multiple supplementation rather than single-nutrient supplementation. However, interactions could also lead to poor absorption of some of the nutrients. High doses of some nutrients may also cause harm to the mother or her baby.

What evidence did we find?

We searched Cochrane Pregnancy and Childbirth's Trials Register (23 February 2018). This systematic review included 21 trials (involving 142,496 women), but only 20 trials (involving 141,849 women) contributed data. The included trials compared pregnant women who

supplemented their diets with multiple micronutrients (including iron and folic acid) with pregnant women who received iron (with or without folic acid) or a placebo. Overall, we found that pregnant women who received multiple-micronutrient supplementation had fewer babies that were born too small (weighing less than 2500 g), fewer babies who were smaller in size than normal for their gestational age, and fewer births that occurred before week 37 of pregnancy. The evidence for the main outcomes of low birthweight and small-for-gestational age was found to be of high quality and moderate quality, respectively.

What does this mean?

These findings, which have been observed elsewhere, may provide a basis to guide the replacement of iron and folic acid supplements with multiple-micronutrient supplements for pregnant women in low- and middle-income countries.

Summary of findings for the main comparison. Multiple micronutrients compared to control (iron with or without folic acid) for women during pregnancy

Multiple micronutrients compared to control (iron with or without folic acid) for women during pregnancy

Patient or population: women during pregnancy
Setting: low- and middle-income countries
Intervention: multiple micronutrients
Comparison: control (iron with or without folic acid)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Quality of the evidence (GRADE)	Comments
	Risk with control (iron with or without folic acid)	Risk with multiple micronutrients				
Preterm births	Study population		RR 0.95 (0.90 to 1.01)	91,425 (18 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	
	197 per 1000	188 per 1000 (178 to 199)				
Small-for-gestational age	Study population		RR 0.92 (0.88 to 0.97)	57,348 (17 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	
	337 per 1000	310 per 1000 (296 to 327)				
Low birthweight	Study population		RR 0.88 (0.85 to 0.91)	68,801 (18 RCTs)	⊕⊕⊕⊕ **High**	
	212 per 1000	187 per 1000 (181 to 193)				
Perinatal mortality	Study population		RR 1.00 (0.90 to 1.11)	63,922 (15 RCTs)	⊕⊕⊕⊕ **High**	Raw event and participant data were unavailable for Ramakrishnan 2003 and West 2014, so have not been included in No of participants column.
	39 per 1000	39 per 1000 (35 to 43)				
Stillbirths	Study population		RR 0.95 (0.86 to 1.04)	97,927 (17 RCTs)	⊕⊕⊕⊕ **High**	
	30 per 1000	28 per 1000 (26 to 31)				

Neonatal mortality	Study population		RR 1.00 (0.89 to 1.12)	80,964 (14 RCTs)	⊕⊕⊕⊕ **High**	Raw event and participant data were unavailable for Bhutta 2009a and Fawzi 2007 so have not been included in No of participants column.
	29 per 1000	29 per 1000 (26 to 32)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Strong evidence of funnel plot asymmetry, indicating possible publication bias.

BACKGROUND

Description of the condition

Micronutrient deficiencies are common among women of reproductive age (15 to 49 years of age), especially those residing in low- and middle-income countries where diets often lack diversity and fortified foods are less available (Black 2013; FAO/WHO 2004). Infections and chronic illness can also contribute to micronutrient deficiencies by directly inhibiting nutrient absorption (Bailey 2015). Micronutrient deficiencies are exacerbated during pregnancy due to increased requirements of the growing fetus, placenta and maternal tissues. An inability to fulfil the increased demands results in potentially adverse effects on the mother and the fetus (Berti 2011). Additionally, there can be sustained intergenerational effects. Maternal malnutrition has been shown to affect both short-term and long-term outcomes for the offspring, including growth, neurodevelopment and cognition, and cardiometabolic, pulmonary, and immune function (Gernand 2016).

Up-to-date population-level estimates are largely lacking for individual micronutrients due to measurement and cost challenges associated with collecting these indicators (Gernand 2016). In addition, there are few data that have been disaggregated by age, parity, wealth status and other factors that can influence nutrition throughout pregnancy (Gernand 2016). However, we do know that anaemia due to iron deficiency is one of the most prevalent micronutrient deficiencies globally. According to 2013 estimates, the worldwide prevalence of prenatal iron-deficiency anaemia was 19.2% (95% confidence interval (CI) 17.1% to 21.5%; Black 2013). Anaemia during pregnancy has been found to be associated with increased risk of maternal mortality, perinatal mortality, and infants with low birthweight (LBW) (Allen 2001; Christian 2010; Haider 2013; Murray-Kolb 2013). Vitamin A is another important nutrient that, when deficient, can lead to night blindness. According to global estimates for the time period between 1995 and 2005, vitamin A deficiency, measured using night blindness and low serum retinol levels, affected 9.8 million (95% CI 8.7 to 10.8 million), and 19.1 million pregnant women (95% CI 9.30 to 29.0 million), respectively. This corresponds to 15.3% (95% CI 6.0% to 24.6%), of pregnant women being deficient in vitamin A (Black 2013). Deficiency of vitamin A has been associated with poor birth and mortality outcomes; however, supplementation with vitamin A during pregnancy has demonstrated no beneficial effect on these outcomes (McCauley 2015), but has been shown to reduce the risk of maternal anaemia, infection, and night blindness (McCauley 2015).

In the past decade, deficiency of vitamin D has also emerged as an important nutritional problem with high prevalence being reported in high-income, as well as low-income, populations (Datta 2002; Ginde 2010; Sachan 2005). Iodine deficiency, often measured by urinary iodine, is also common among pregnant women. The median urinary iodine level in a nationally representative sample of pregnant women in Nepal was reported to be 134 mcg/L (Benoist 2008), indicating insufficient iodine intake (Andersson 2007). Severe iodine deficiency during pregnancy results in pregnancy loss, mental retardation and cretinism (Dunn 1993). Although severe deficiency is now rare, mild to moderate deficiency continues to be a problem (Andersson 2007).

Deficiencies of other micronutrients are also common among pregnant women. According to the 2012 estimates, around 17% of the world's population have reduced dietary intake of zinc (Wessells 2012). Zinc deficiency has been associated with complications of pregnancy and delivery such as pre-eclampsia, premature rupture of membranes, and congenital abnormalities (Black 2001; Caulfield 1998). However, a review of trials of zinc supplementation showed a reduction in the risk of preterm birth only (Hess 2009; Ota 2015). Folic acid deficiency can lead to haematological consequences and congenital malformations; however, association with other birth outcomes is equivocal (Black 2001; De-Regil 2010). Concurrent deficiencies that could include vitamins A, D, E, riboflavin, B6, B12, folic acid, iron, and zinc have also been reported in studies conducted among pregnant women (Jiang 2005; Pathak 2004). Deficiencies in other minerals such as magnesium, selenium, copper and calcium may also potentially be associated with complications of pregnancy, childbirth or fetal development (Black 2001).

Description of the intervention

The World Health Organization (WHO) currently recommends iron and folic acid supplementation for women during pregnancy as part of routine antenatal care (WHO 2012). The recommended dose of iron ranges from 30 mg to 60 mg. In areas where anaemia is a severe public health problem, defined as a prevalence of 40% or higher, a daily dose of 60 mg of iron is preferred. The standard dose of 60 mg of iron was first recommended in 1959 and was based on maternal requirements during pregnancy (WHO 1959). Despite its provision as part of national antenatal care programmes for the last few decades in most low- and middle-income countries, compliance with the supplement is low. Gastrointestinal side-effects including constipation, nausea, vomiting, and diarrhoea are the most common complaints among women consuming high doses of iron (Oriji 2011; Seck 2008).

Supplementation with iron and folic acid during pregnancy has been found to be associated with reduction in the risk of maternal anaemia and infants with LBW (Haider 2013; Pena-Rosas 2015). To overcome other possible maternal micronutrient deficiencies, the United Nations Children's Fund (UNICEF), United Nations University (UNU) and the WHO, in 1999, agreed on the composition of a proposed multiple-micronutrient (MMN) tablet (UNICEF 1999). This UNIMMAP tablet provides one recommended daily allowance of vitamin A, vitamin B1, vitamin B2, niacin, vitamin B6, vitamin B12, folic acid, vitamin C, vitamin D, vitamin E, copper, selenium and iodine with 30 mg of iron and 15 mg of zinc for pregnant women. In contrast to the WHO recommendation, a lower dose of iron was recommended as the absorption of iron was expected to be enhanced due to vitamin C, vitamin A, and riboflavin, and given that the majority of pregnant women suffer from mild anaemia and the potential side-effects associated with higher doses of iron.

How the intervention might work

Vitamins and minerals play critical roles in cellular metabolism, growth and maintenance of normal functioning of the human body. They are also important in many enzymatic processes, signal transduction and transcription pathways (McArdle 1999; WHO 2004). Recent studies have suggested a possible benefit of multiple micronutrient supplementation for improving pregnancy outcomes through placental function, including modulation of inflammation and oxidative stress and vascular function (Owens 2015; Richard 2017). Deficiencies of these micronutrients rarely exist in isolation. Additionally, because of their role at various levels

in the biological pathways, it is difficult to assign a clinical or pre-clinical condition to the deficiency of a single micronutrient (McArdle 1999). Micronutrient deficiencies are also known to interact. Combining MMN in a single delivery mechanism has been suggested as a cost-effective way to achieve multiple benefits.

Why it is important to do this review

The interest of the global research community in eliminating micronutrient deficiencies stems from their significant negative impact on the health of women and infants. The health effects during the fetal life may also have consequences later as an adult. Several trials have demonstrated that supplementation with MMN during pregnancy reduces the risk of micronutrient deficiencies (Haider 2012). Findings from individual trials regarding the benefit on other maternal and pregnancy outcomes are inconsistent, as individual studies may not have statistical power to evaluate effects on these outcomes. Several meta-analyses have systematically reviewed and synthesised the evidence of the effect of supplementation with multiple micronutrients, with the first such synthesis of evidence being an earlier version of this Cochrane Review (Bhutta 2012; Haider 2006; Haider 2011; Haider 2012; Kawai 2011; Ramakrishnan 2012). On the basis of the evidence, supplementation with MMN during pregnancy has been recommended (Bhutta 2008; Bhutta 2013). However, a consensus is yet to be reached regarding the replacement of iron and folic acid supplementation with MMN. Since the last update of this Cochrane Review (Haider 2017), evidence from a few large trials has recently been made available, inclusion of which is critical to inform global policy.

This review updates a previously published Cochrane Review on MMN supplementation during pregnancy that had demonstrated positive effect of supplementation on birth outcomes (Haider 2017). The effects of supplementation with individual micronutrients during pregnancy have been evaluated in other Cochrane Reviews. The effect of MMN supplementation in HIV-infected pregnant women has been evaluated in another Cochrane Review (Siegfried 2012).

OBJECTIVES

To evaluate the benefits of oral multiple-micronutrient supplementation during pregnancy on maternal, fetal and infant health outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All prospective randomised controlled trials evaluating multiple micronutrient (MMN) supplementation during pregnancy and its effects on pregnancy outcomes were eligible, irrespective of language or publication status of the trials. Trial reports that were published as abstracts were eligible for inclusion. We included cluster-randomised trials, but excluded quasi-randomised trials.

Types of participants

Pregnant women. There was no limit on the length of gestation at the time of enrolment in the study. We excluded HIV-infected pregnant women from the review, as this population is at a greater risk of nutritional disorders compared to uninfected women. We also excluded studies recruiting women at high risk of nutritional disorders for other reasons. Another Cochrane Review has evaluated the effect of MMN supplementation in HIV-infected pregnant women (Siegfried 2012).

Types of interventions

Since WHO recommends use of iron and folic acid supplementation in women during pregnancy as a part of routine antenatal care, we evaluated the effect of MMN supplementation with iron and folic acid in pregnant women versus supplementation with iron, with or without folic acid. We also included trials comparing the outcomes of providing pregnant women with MMN supplements with iron and folic acid compared to placebo. The composition of MMN supplement by trial can be found in Table 1.

We excluded trials that used fewer than three micronutrients in the intervention group, regardless of their outcomes. There were no limits on the duration of supplementation.

We included the following specific comparisons in the review.

1. Multiple micronutrients with iron and folic acid versus control (iron with or without folic acid)
2. Multiple micronutrients with iron and folic acid versus control (placebo)

The review focuses on daily oral supplements. One trial (Biggs 2010), provided MMN twice weekly; we excluded data from this trial from the main results, but included them in the subgroup analysis for dose of iron to examine whether there are any notable differences when women are provided with a lower dose of iron throughout pregnancy (Biggs 2010 provided women with 120 mg per week compared to 210 mg or 420 mg per week in all other trials). We excluded trials examining parenteral MMN or food fortification with MMN.

Types of outcome measures

Primary outcomes

1. Preterm births (births before 37 weeks of gestation)
2. Small-for-gestational age (SGA) (as defined by the authors of the trials)
3. Low birthweight (LBW) (birthweight less than 2500 g)
4. Perinatal mortality
5. Stillbirths
6. Neonatal mortality

Secondary outcomes

1. Maternal anaemia (third trimester haemoglobin (Hb) < 110 g/L)
2. Maternal mortality
3. Miscarriage (loss of pregnancy before 28 weeks of gestation)
4. Premature rupture of membranes
5. Pre-eclampsia
6. Mode of delivery: caesarean section (not prespecified)
7. Macrosomia (not prespecified)
8. Placental abruption
9. Very preterm births (births before 34 weeks of gestation)
10. Neurodevelopmental delay (assessed using Bayley Scale of Infant Development (BSID) at six and 12 months of age)

11. Nutritional status of children (stunting, wasting and underweight at six, 12 and 24 months of age)
12. Cost of supplementation
13. Side-effects of MMN supplements
14. Congenital anomalies (including neural tube defects)
15. Maternal well-being or satisfaction

Search methods for identification of studies

The following search methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

For this update we searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (23 February 2018).

The Register is a database containing over 25,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review section (Included studies; Excluded studies; Studies awaiting classification; Ongoing studies).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports (24 February 2018) using the search methods detailed in Appendix 1.

Searching other resources

We searched reference lists of retrieved articles and key reviews. We contacted experts in the field for additional and ongoing trials.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see Haider 2017.

For this update, we used the following methods for assessing the reports that were identified as a result of the updated search.

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion.

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third review author. We entered data into Review Manager 5 software (Review Manager 2014), and checked them for accuracy.

When information regarding any of the above was unclear, we planned to contact authors of the original reports to provide further details.

Given some of the changes and data edits in the previous versions of this review, for this update, we re-extracted data for all primary and secondary outcomes for all included studies from the outset, not just those found from the most recent search.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We resolved any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);

- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered its likelihood to impact the findings. For cluster-randomised trials, we carefully considered recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomised trials (Higgins 2011a). We explored the impact of attrition bias through undertaking sensitivity analyses - see Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

For this update, we assessed the quality of the evidence using the GRADE approach as outlined in the GRADE Handbook (Schünemann 2013). We assessed the quality of the body of evidence relating to the following outcomes for the comparison of MMN versus iron and folic acid supplements:

1. Preterm births
2. SGA
3. LBW
4. Perinatal mortality
5. Stillbirths
6. Neonatal mortality

We used the GRADEpro Guideline Development Tool (GRADEpro GDT 2015), to import data from Review Manager 5.3 (Review Manager 2014), in order to create a 'Summary of findings' table. We produced a summary of the intervention effect and a measure of quality for each of the above outcomes using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence was downgraded from 'high quality' by one level for serious limitations (or by two levels for very serious), depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. We did not downgrade evidence for heterogeneity with an I^2 statistic value of less than 50% (Deeks 2017; Higgins 2003).

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio (RR) with 95% confidence intervals (CI).

Continuous data

We used the mean difference (MD) if outcomes were measured in the same way between trials. In future updates as appropriate, we plan to use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

If both adjusted and unadjusted effect estimates were provided in the primary report, we utilised the adjusted estimate. If only event and participant raw data were provided, we used these to calculate a relevant effect estimate (RR or MD) using the Review Manager 5 calculator function (Review Manager 2014). Where there were significant discrepancies between our re-extracted data and what had been reported in previous versions of this review, we contacted trial investigators for clarification.

Unit of analysis issues

Cluster-randomised trials

We included cluster-randomised trials (Christian 2003; Bhutta 2009a; Biggs 2010; SUMMIT 2008; Sunawang 2009; West 2014; Zagre 2007; Zeng 2008), in the analyses along with individually-randomised trials. We extracted cluster-adjusted effect estimates with their confidence intervals, which we analysed along with individually-randomised trials using the generic inverse variance method. If effect estimates were not cluster-adjusted, or if number of events was used to calculate the effect estimate for a given outcome, then we used the reported intracluster correlation coefficient (ICC) and average cluster size (M) to determine the design effect for a trial (1+(M-1)*ICC) (Higgins 2011a). Some trials reported the design effect, which we then applied to the number of events and sample size for dichotomous outcomes, and sample size only for continuous outcomes, to reduce cluster-randomised trial data to their effective sample size.

We had to adjust all reported estimates from each cluster-randomised trial, with the exception of Bhutta 2009a (all outcomes), Christian 2003 (all outcomes), SUMMIT 2008 (SGA, LBW, perinatal mortality, neonatal mortality, stillbirth, and maternal mortality), and West 2014 (preterm birth, SGA, LBW, perinatal mortality, neonatal mortality, and stillbirth). Details on reported ICCs and design effect by trial can be found in Table 2.

Trials with multiple intervention groups

For the majority of trials with multiple intervention groups, we selected one pair of interventions and excluded the others. This is one approach recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

We included trials with more than two intervention groups in the analysis after selecting the comparison groups (intervention and control groups) that satisfied the 'types of intervention' criterion and were relevant to the review. For Christian 2003, we included data from group 4 (MMN group with iron and folic acid) versus group 2 (control group iron with or without folic acid). We did not include groups 1 (folic acid with vitamin A) and 5 (vitamin A only), since they did not satisfy the inclusion criterion of the review. Further, group 3 (iron, folic acid, vitamin A, and zinc) did not include the majority of micronutrients being considered for inclusion in a MMN supplement for pregnant women and was also not comparable to the UNIMMAP formulation proposed by UNICEF, UNU, and WHO. For Kaestel 2005, we included group 1 (MMN with iron and folic acid) and group 3 (iron and folic acid) in the review. We selected the group with one recommended daily allowance, since the MMN supplement in group 1 was comparable to the UNIMMAP formulation. For Lui 2013, data from group 3 (MMN with iron and folic acid) versus group 2 (iron and folic acid) fitted the types of intervention criterion of the review and we included them in the analyses. Similarly, we included data for the comparison of groups 3 (MMN with iron and folic acid) versus 2 (iron and folic acid) for Zeng 2008. Group 1 in both Lui 2013 and Zeng 2008 had received folic acid only and did not satisfy the control definition of the review.

For Moore 2009, we included data from group 1 (iron and folic acid) versus group 2 (MMN with iron and folic acid). We excluded data from groups 3 (protein-energy plus iron and folic acid) and 4 (protein-energy plus MMN with iron and folic acid) due to the provision of a food-based supplement in both groups. For Biggs 2010, we included data from groups 1 (daily iron and folic acid) versus 3 (twice weekly MMN with iron and folic acid), though only for the purpose of the subgroup analysis looking at dose of iron. We excluded group 2 because they provided iron and folic acid twice weekly as opposed to daily.

If more than two intervention groups had met the eligibility criteria, we would have combined groups to create a single pair-wise comparison, as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We used this approach for Tofail 2008, where we combined early invitation and usual invitation to food groups to compare MMN with iron and folic acid to iron (30 mg) and folic acid.

Dealing with missing data

For included studies, we noted levels of attrition. We assessed the impact of including studies with high levels of missing data (> 20%) in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, that is, we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 (Higgins 2003), and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 statistic was greater than 30% and either a Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. If we identified substantial heterogeneity (above 30%), we explored it by pre-specified subgroup analysis (Deeks 2017).

Assessment of reporting biases

Where there are 10 or more studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually (Sterne 2017).

Data synthesis

We carried out statistical analysis using Review Manager 5 software (Review Manager 2014). We pooled together data from individually randomised and cluster-randomised trials during meta-analysis, using the generic inverse variance method, after appropriate adjustment of estimates from cluster-randomised trials, as noted above. In response to feedback received for the previous version of this review, we conducted all analyses using a random-effects model, given the clinical heterogeneity amongst the included trials. We treated the random-effects summary as the average of the range of possible treatment effects, and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials. We have presented the results as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2 statistic.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity at the outcome-level, we investigated it using subgroup analyses. We considered whether an overall summary was meaningful, and if it was, we used random-effects analysis to produce it.

We carried out the following subgroup analyses.

1. Timing of supplementation (categorised as either before or after 20 weeks of gestation)
2. Dose of iron in the MMN and control supplements (*15 to 20 mg versus 30 mg versus 60 mg of iron)
3. Baseline nutritional status of the mother, including body mass index (BMI < 20 kg/m^2 versus ≥ 20 kg/m^2) and height (< 154.9 cm versus ≥ 154.9 cm)
4. UNIMMAP versus **non-UNIMMAP MMN supplement formulation

*We used the 15 to 20 mg dosage range to allow us to incorporate the trial that provided 60 mg of iron to women twice weekly, which equates to about 17 mg iron daily.

**Variations on the UNIMMAP formulation (e.g. varying concentrations of micronutrients) would be included in the non-UNIMMAP group.

We assessed subgroup differences by interaction tests available within Review Manager 5 (Review Manager 2014). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value (Deeks 2017; Higgins 2003).

Sensitivity analysis

We carried out sensitivity analyses for all outcomes to explore the effect of risk of bias, as assessed by high attrition rates. We excluded trials at high risk of attrition bias (> 20% loss to follow up) from each analysis in order to assess whether this exclusion affected the overall result.

RESULTS

Description of studies

Results of the search

See: Figure 1

Figure 1. Study flow diagram

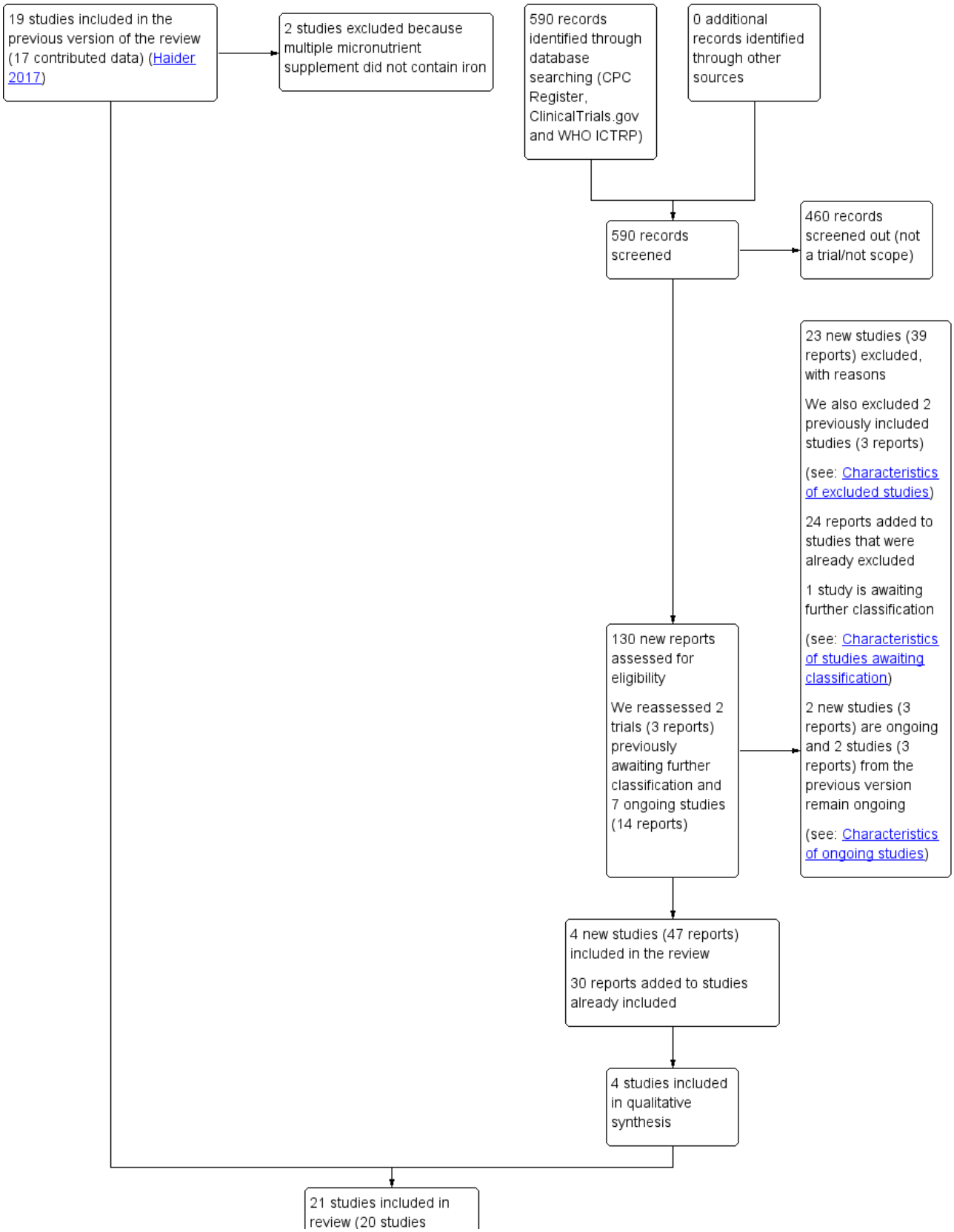
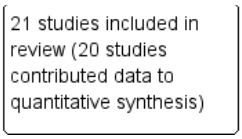


Figure 1. (Continued)



For this 2018 updated search, we retrieved and assessed 130 trial reports. We also reassessed the two studies (three reports) awaiting classification in the previous version of the review, and we checked the progress of the seven ongoing studies (14 reports).

We included four new trials in this update (Ashorn 2010; Biggs 2010; Dewey 2009; Moore 2009). We also added 30 new reports to trials already included.

We identified a total of 21 trials (involving 142,496 women) as eligible, of which 20 trials (involving 141,849 number of women) contributed data to the review.

We excluded 23 new studies (39 reports) and added 24 reports to studies that we had previously excluded. We also excluded two trials that we had included in the previous update (Hininger 2004; Theobald 1937), because the MMN supplement did not contain iron.

One study is awaiting classification (Gathwala 2012), due to missing group denominators. Two new studies (three reports) are ongoing (NCT03287882; Sumarmi 2015), in addition to NCT02190565 and Tu 2013 that have remained ongoing since the previous update. See Characteristics of ongoing studies for more information.

Included studies

We identified a total of 21 trials (involving 142,496 women) as eligible for inclusion in this review. Of these, one study (Sood 1975), presented data in a format that precluded its inclusion. Hence, this study did not contribute data to the analyses. A total of 141,849 women participated in the remaining 20 included trials (Ashorn 2010; Bhutta 2009a; Biggs 2010; Brough 2010; Christian 2003; Dewey 2009; Fawzi 2007; Friis 2004; Kaestel 2005; Lui 2013; Moore 2009; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; SUMMIT 2008; Sunawang 2009; Tofail 2008; West 2014; Zagre 2007; Zeng 2008), of which eight were cluster-randomised (Bhutta 2009a; Biggs 2010; Christian 2003; SUMMIT 2008; Sunawang 2009; West 2014; Zagre 2007; Zeng 2008). One trial was conducted in a high-income country (Brough 2010). Most of the outcomes were defined in the same way across different trials except for one trial that used different cut-offs for stillbirth and very preterm birth (West 2014), and three trials that used different cut-offs for miscarriage (Osrin 2005; West 2014; Zagre 2007). See Characteristics of included studies table for further details of included studies.

All trials reported sources of funding, with the exception of Sood 1975.

Seventeen trials included a statement of disclosure as to whether or not there was a potential conflict of interest related to the study (Ashorn 2010; Biggs 2010; Brough 2010; Christian 2003; Dewey 2009; Fawzi 2007; Friis 2004; Kaestel 2005; Lui 2013; Moore 2009; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; SUMMIT 2008; Tofail 2008; West 2014; Zeng 2008). Of these, there were 12 trials where all authors declared no conflict of interest (Biggs 2010; Brough 2010; Christian 2003; Fawzi 2007; Friis 2004; Kaestel 2005; Lui 2013; Moore 2009; Ramakrishnan 2003; Roberfroid 2008; SUMMIT 2008; Tofail 2008), and five studies where an author or several authors had indicated a conflict of interest (Ashorn 2010; Dewey 2009; Osrin 2005; West 2014; Zeng 2008). The remaining four studies did not provide a statement of disclosure, and therefore we could not assess potential conflicts of interest (Bhutta 2009a; Sood 1975; Sunawang 2009; Zagre 2007).

Participants

The 20 trials contributing data to the analyses included 141,849 pregnant women at varying gestational stages, ranging from early pregnancy to 36 weeks of gestation. Pregnant women with a haemoglobin (Hb) concentration of less than 80 g/L, with a serious medical condition or a complication of pregnancy such as cardiac disease, pneumonia and threatened abortion were not eligible for inclusion in the trials. Two trials (Ashorn 2010; Friis 2004), included a subgroup of pregnant women who were HIV-1-infected, but the data for these subgroups were excluded from the review. Baseline characteristics of the participants in the intervention and the control groups were comparable in the included trials except for minor differences in five trials (Christian 2003; Friis 2004; Ramakrishnan 2003; Roberfroid 2008; Zagre 2007). In Friis 2004, a higher proportion of primigravidae was found in the placebo group. In Ramakrishnan 2003, there was a higher proportion of single mothers and a lower mean BMI in the intervention group. In Christian 2003, more participants in the control group belonged to a specific ethnic background and owned land. In Roberfroid 2008, the Hb level was lower in the intervention group and the BMI was lower in the control group. In Zagre 2007, the intervention group had more households and preventive measures against malaria, whereas the placebo group had less education and more poverty.

Intervention

Seventeen trials assessed MMN supplementation versus control; iron with or without folic acid (Ashorn 2010; Bhutta 2009a; Biggs 2010; Christian 2003; Dewey 2009; Kaestel 2005; Lui 2013; Moore 2009; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; SUMMIT 2008; Sunawang 2009; Tofail 2008; West 2014; Zagre 2007; Zeng 2008). Two trials had a component of nutritional education along with MMN supplementation (Bhutta 2009a; Zagre 2007), and one trial had a food supplement co-intervention along with MMN supplementation (Tofail 2008). Three trials assessed MMN supplementation against a placebo (Brough 2010; Fawzi 2007; Friis 2004); however, in Fawzi 2007 and Friis 2004, all participants received iron and folic acid supplements. In Brough 2010, participants not taking folic acid received recommendations to take it daily.

The composition of the MMN supplement was different in all included trials. Eighteen trials included iron and folic acid in the MMN supplement (Ashorn 2010; Bhutta 2009a; Biggs 2010; Brough 2010; Christian 2003; Dewey 2009; Kaestel 2005; Lui 2013; Moore 2009; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; SUMMIT 2008; Sunawang 2009; Tofail 2008; West 2014; Zagre 2007; Zeng

2008). All supplements were given orally to the pregnant women throughout pregnancy from the time of enrolment, except for one trial where supplementation was started when the participants reached 14 weeks of gestation (Tofail 2008). The duration of supplementation varied because the time of enrolment differed across the trials. Six trials enrolled participants in the first trimester of pregnancy (Brough 2010; Christian 2003; Ramakrishnan 2003; Tofail 2008; West 2014; Zagre 2007). Two trials enrolled participants with a gestation of less than 16 weeks (Bhutta 2009a; Biggs 2010), four trials less than 20 weeks (Ashorn 2010; Dewey 2009; Lui 2013; Moore 2009), and one trial less than 28 weeks (Zeng 2008). Two trials enrolled participants in the second trimester (Osrin 2005; Sunawang 2009), one trial enrolled women in both the second and third trimester (Friis 2004), and two trials enrolled women who were less than 37 weeks of gestation (Fawzi 2007; Kaestel 2005). Two trials enrolled pregnant women irrespective of gestational age (Roberfroid 2008; SUMMIT 2008). Supplementation was given until delivery in 11 of the included trials (Bhutta 2009a; Brough 2010; Friis 2004; Kaestel 2005; Lui 2013; Moore 2009; Osrin 2005; Ramakrishnan 2003; Tofail 2008; Zagre 2007; Zeng 2008). Supplementation continued until four weeks after delivery in Sunawang 2009, six weeks after delivery in Fawzi 2007, 12 weeks after delivery in five trials (Biggs 2010; Christian 2003; Roberfroid 2008; SUMMIT 2008; West 2014), and for five weeks after a stillbirth or miscarriage in Christian 2003, and 24 weeks after delivery in two trials (Ashorn 2010; Biggs 2010). The frequency of MMN supplementation in all included trials was once daily, except for one trial where supplementation was provided six days a week (Ramakrishnan 2003), and another trial where supplementation was twice weekly (Biggs 2010).

Excluded studies

We excluded 117 trials from the review. Briefly, 32 trials evaluated the effects of a single or two micronutrients or compounds (Beazley 2002; Bergmann 2006; Carrasco 1962; Caulfield 1999; Chames 2002; Goldenberg 1995; Gopalan 2004; Hillman 1963; Holly 1955; Hossain 2014; Hunt 1983; Hunt 1985; Iannotti 2008; Lucia 2007; Ma 2008; Malvasi 2014; Marya 1987; Mathan 1979; Merialdi 1999; Muslimatun 2001; NCT01795131; Ochoa-Brust 2007; Robertson 1991; Sachdeva 1993; Sagaonkar 2009; Salzano 2001; Schmidt 2001; Semba 2000; Suharno 1993; Suprapto 2002; Tanumihardjo 2002; Zavaleta 2000). Fourteen trials did not satisfy the trial design criteria (ACTRN12616001449426; Aguayo 2005; Biswas 1984; Kubik 2004; Kynast 1986; Itam 2003; Menon 1962; Patimah 2013; Park 1999; People's League 1946; Pezzack 2014; Sun 2010; Thauvin 1992; Wijaya-Erhardt 2014), and six trials studied HIV-positive women (Arsenault 2010; Fawzi 1998; Khavari 2014; Merchant 2005; Olofin 2014; Webb 2009), and hence we excluded them from the review. Six trials gave MMN supplements to both groups of participants (Ahn 2006; Asemi 2014; Dawson 1987; Dawson 1998; Magon 2014; Taghizadeh 2014). Czeizel 1996, ICMR 2000, Cooper 2012, Gunaratna 2015, Khulan 2012 and Otoluwa 2017 evaluated supplementation in the periconceptional period, and Nguyen 2012 evaluated the effect of pre-conception supplementation. An 2001, Guldholt 1991, Graham 2007, Fleming 1986, and Wibowo 2012 assessed different doses of micronutrients; Agarwal 2012 evaluated different durations of the same micronutrients, while Feyi-Waboso 2005 and Nwagha 2010 evaluated parenteral infusion or injection. Ramirez-Velez 2011 did not contain an adequate comparison arm (they provided calcium in addition to ferrous sulphate and folic acid). Godfrey 2017 evaluated a drink enriched with micronutrients, probiotics and myo-inositol, Callaghan-Gillespie 2017 evaluated a food supplement (corn-soy blend) enriched with micronutrients, Fall 2006 evaluated a micronutrient-rich snack, Huang 2017 evaluated different maternal milk preparations, Nakano 2010 assessed the effect of chlorella tablets and Ling 1996 evaluated a herbal tonic. Li 2014 evaluated the effect of supplementation with folic acid and milk. Six excluded trials assessed the effect of fortification with MMN (Dieckmann 1944; Janmohamed 2016; Jarvenpaa 2007; Kureishy 2017; Tatala 2002; Vadillo-Ortega 2011). Twelve trials included high-risk women (Asemi 2015; Azami 2016; Christian 2003; Devi 2017; Gupta 2007; IRCT2015041321736N1; IRCT201704225623N109; ISRCTN83599025; NCT02802566; NCT02959125; Nossier 2015; Rumiris 2006). We excluded eight trials because they evaluated different forms of supplementation such as powder, tablet or spread (Choudhury 2012; Hambidge 2014; Huynh 2017; Lanou 2014; Young 2010); balanced energy protein supplementation (Huybregts 2009); weekly food provision (Wijaya-Erhardt 2011); or polyunsaturated fatty acids fortification in milk fortified with MMN (Mardones 2007). The cohort of an included trial (Tofail 2008), was later randomised to breastfeeding counselling or standard care groups measuring the impact on postnatal growth in children (Kabir 2009), and hence we excluded it. We excluded Leroy 2010 because it compared a traditional food-assisted maternal and child health and nutrition (MCHN) programme versus a newly designed approach to prevent malnutrition in children; Nguyen 2017 because it compared a nutrition-focused MNCH programme with a standard MNCH (antenatal care with standard nutrition counselling) programme. We excluded one abstract of a trial because it was a trial in women with alcohol consumption during pregnancy (Kable 2012). We excluded Coles 2015 because of the trial's quasi-randomised method of allocation to intervention and control arms. We excluded Dewey 2012 and Fernald 2016 because they evaluated the effects of lipid-based nutrient supplements.

We reclassified Hininger 2004 and Theobald 1937 from included to excluded for the 2018 update because the MMN supplement did not contain iron.

See the Characteristics of excluded studies table for more details.

One report comparing MMN supplementation versus iron folic acid remains awaiting assessment due to missing group denominators (Gathwala 2012).

Risk of bias in included studies

The risk of bias of the included studies was generally low with at least 50% of the judgements at 'low risk' for two domains (allocation concealment and incomplete outcome data) and at least 75% of judgements at 'low risk' for the remaining five domains. The domain with the highest risk of bias was incomplete outcome data (attrition bias), for which we have conducted a sensitivity analysis. It is unlikely that the evidence presented in this review is affected by the biases evaluated.

See Figure 2; Figure 3 and Characteristics of included studies table for further details on the risk of bias of the included studies.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

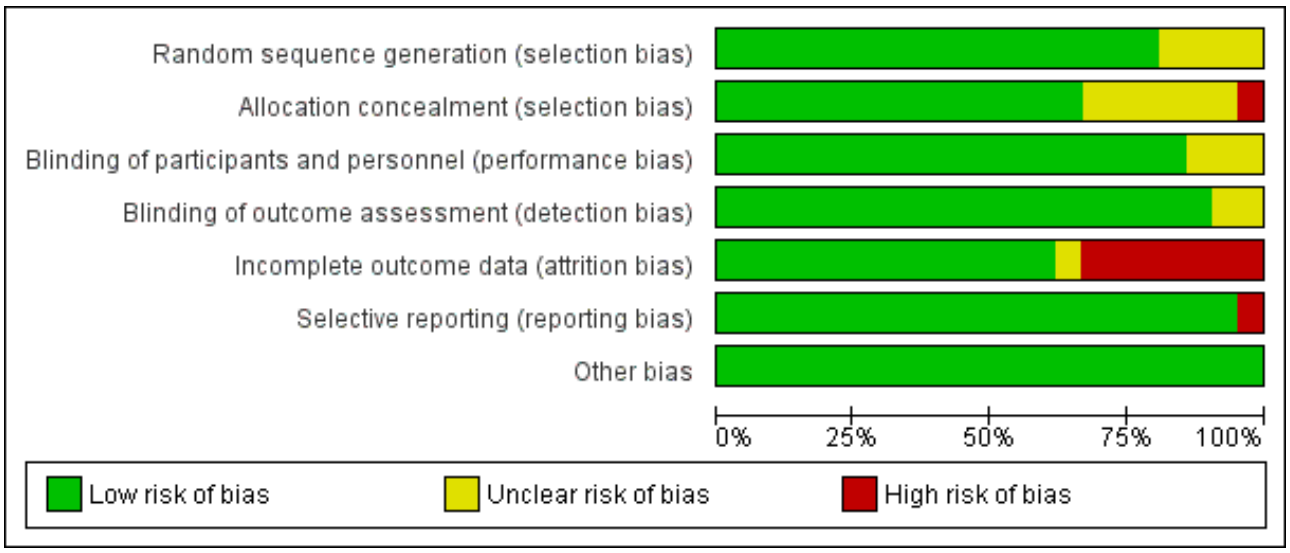


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study

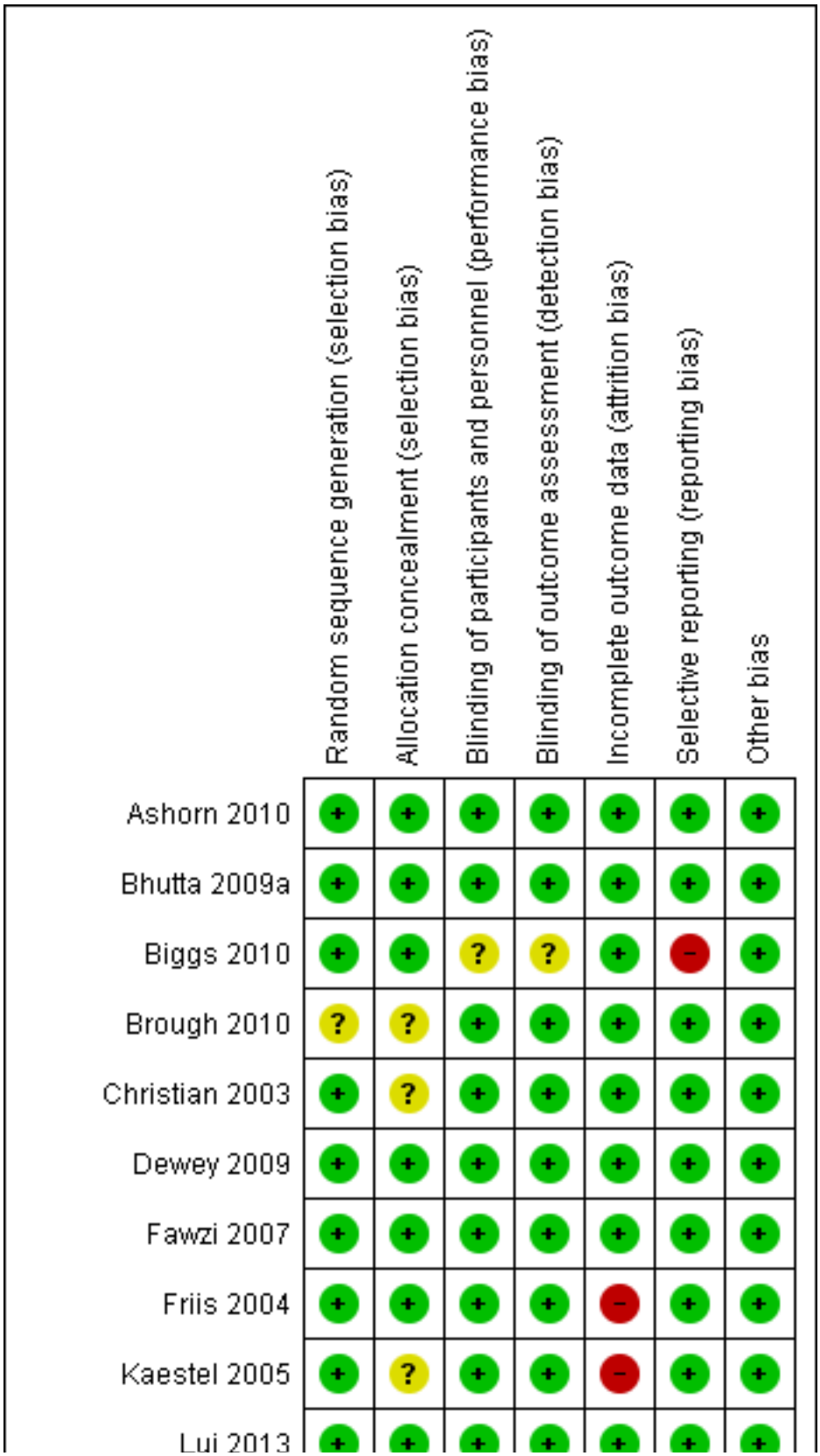
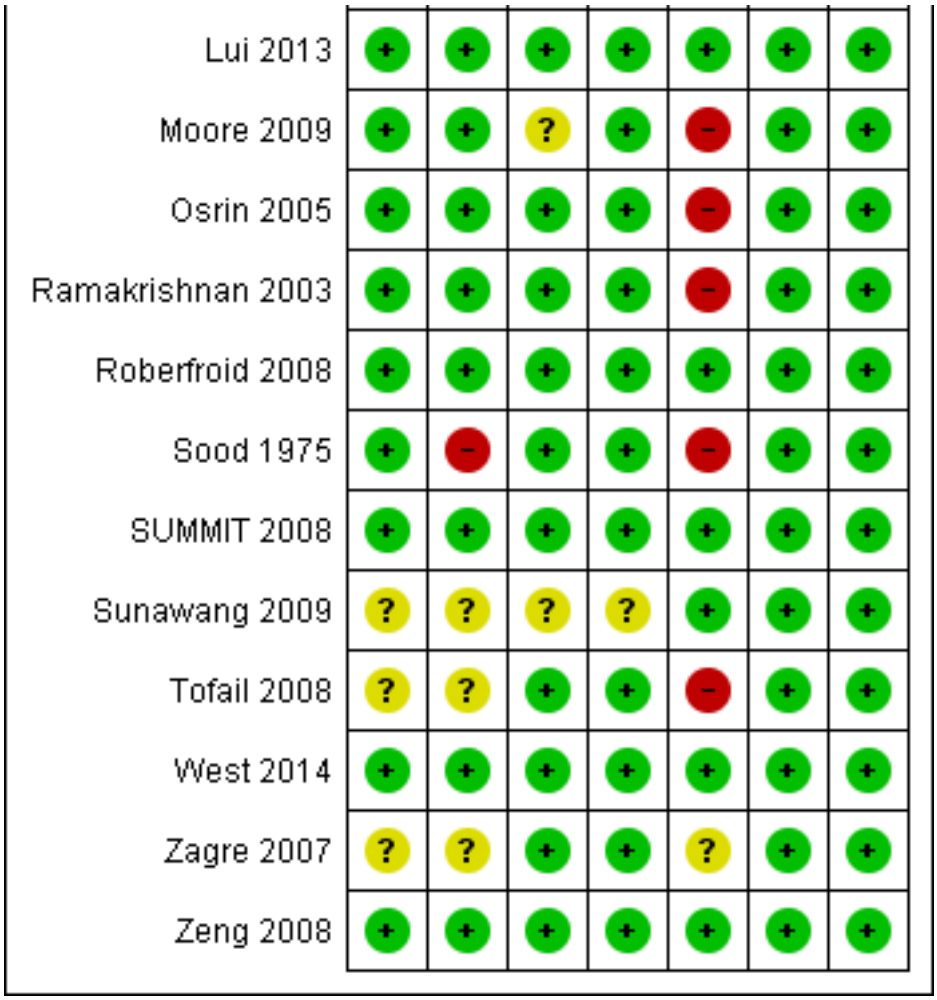


Figure 3. (Continued)



Allocation

The included trials were of variable risk of bias. Seventeen trials adequately randomised participants to the treatment groups (Ashorn 2010; Bhutta 2009a; Biggs 2010; Christian 2003; Dewey 2009; Fawzi 2007; Friis 2004; Kaestel 2005; Lui 2013; Moore 2009; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; Sood 1975; SUMMIT 2008; West 2014; Zeng 2008), whereas the remaining trials did not describe the method they used for generating the randomisation sequence in sufficient detail to permit judgement.

Fourteen trials concealed the allocation of participants to the intervention and control groups (Ashorn 2010; Bhutta 2009a; Biggs 2010; Dewey 2009; Fawzi 2007; Friis 2004; Lui 2013; Moore 2009; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; SUMMIT 2008; West 2014; Zeng 2008); it was unclear in six trials (Brough 2010; Christian 2003; Kaestel 2005; Sunawang 2009; Tofail 2008; Zagre 2007); whereas the remaining one trial probably did not conceal allocation (Sood 1975).

Blinding

Eighteen trials blinded the participants, personnel and outcome assessors to the treatment allocation (Ashorn 2010; Bhutta 2009a; Brough 2010; Christian 2003; Dewey 2009; Fawzi 2007; Friis 2004; Kaestel 2005; Lui 2013; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; Sood 1975; SUMMIT 2008; Tofail 2008; West 2014; Zagre 2007; Zeng 2008). However, Sunawang 2009 showed blinding of participants only and Moore 2009 indicated blinding of outcome assessors only. In Biggs 2010, it was not possible to blind the participants and personnel to the daily supplementation arm.

Incomplete outcome data

Loss to follow-up was less than 5% in four trials (Dewey 2009; Moore 2009; West 2014; Zeng 2008); between 5% to 9.9% in eight trials (Ashorn 2010; Biggs 2010; Christian 2003; Fawzi 2007; Lui 2013; Osrin 2005; Roberfroid 2008; SUMMIT 2008); and between 10% to 19.9% in four trials (Bhutta 2009a; Brough 2010; Sunawang 2009; Zagre 2007). In one trial (Zagre 2007), although attrition was less than 20% and they reported the reasons for attrition, the proportion of women who dropped out was significantly higher in the MMN versus the iron-folic acid group. In addition, they did not report exclusion data, so we have deemed this trial as 'unclear risk' of bias. Loss to follow-up was more than 20% in five trials (Friis 2004; Kaestel 2005; Ramakrishnan 2003; Sood 1975; Tofail 2008). In Osrin 2005, although attrition was 5% and they reported reasons for it, exclusion was 39.5% and without reported reasons, and so we assessed it as being at 'high risk'. Similarly, we assessed Moore 2009 to be 'high risk' because, although attrition was 4.8% and reasons for it were not reported, exclusion was 25.6% and reasons were

reported. All of the trials used intention-to-treat analysis except for two trials that used modified intention-to-treat analysis (Ashorn 2010; Biggs 2010).

Selective reporting

There was no indication of selective reporting in most of the included trials. One trial, however, did not present growth outcomes mentioned in the methods section in the results section of the paper, including weight-for-age and weight-for-length (Biggs 2010).

Other potential sources of bias

We did not identify any other potential sources of bias, including those related specifically to cluster design, in the included trials.

Effects of interventions

See: **Summary of findings for the main comparison** Multiple micronutrients compared to control (iron with or without folic acid) for women during pregnancy

Comparison 1: multiple micronutrients (MMN) versus control (all trials)

Twenty trials contributed data to this comparison. Nineteen out of 20 of these trials were carried out in low- and middle-income countries and compared MMN supplements containing iron and folic acid to iron, with or without folic acid. One trial carried out in the UK compared MMN with placebo and contributed data to only four outcomes. In view of the differences in the settings where trials were conducted, and considering the control group conditions, we have presented results separately in the forest plots and in the text below.

Multiple micronutrients (MMN) with iron and folic acid versus iron, with or without folic acid

In this comparison, we included 19 trials conducted in low- and middle-income countries that evaluated UNIMMAP or similar formulations of MMN supplement (Ashorn 2010; Bhutta 2009a; Biggs 2010; Christian 2003; Dewey 2009; Fawzi 2007; Friis 2004; Kaestel 2005; Lui 2013; Moore 2009; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; SUMMIT 2008; Sunawang 2009; Tofail 2008; West 2014; Zagre 2007; Zeng 2008). In two trials (Fawzi 2007; Friis 2004), women received iron and folic acid as separate supplements, and in one trial (Ramakrishnan 2003), women in the control group received iron only.

Primary outcomes

When we compared MMN supplementation against supplementation with iron with or without folic acid, there was probably a slight reduction in preterm births (average risk ratio (RR) 0.95, 95% confidence interval (CI) 0.90 to 1.01; studies = 18; random-effects, $Tau^2 = 0.00$, $I^2 = 49\%$; moderate-quality evidence; Analysis 1.1), although the confidence interval for the pooled effect estimate just crossed the line of no effect. MMN supplementation also probably reduced births that were considered small-for-gestational age (SGA) (average RR 0.92, 95% CI 0.88 to 0.97; studies = 17; random-effects, $Tau^2 = 0.00$, $I^2 = 39\%$; moderate-quality evidence; Analysis 1.2). MMN reduced births that were considered low birthweight (LBW) (average RR 0.88, 95% CI 0.85 to 0.91; studies = 18; random-effects, $Tau^2 = 0.00$, $I^2 = 0\%$; high-quality evidence; Analysis 1.3), and made little or no difference to perinatal mortality (average RR 1.00, 95% CI 0.90 to 1.11; studies = 15; random-effects, $Tau^2 = 0.01$, $I^2 = 42\%$; high-quality evidence; Analysis 1.4). Similar to preterm births, there was a slight reduction in stillbirths (average RR 0.95, 95% CI 0.86 to 1.04; studies = 17; random-effects, $Tau^2 = 0.00$, $I^2 = 12\%$; high-quality evidence; Analysis 1.5), though the confidence interval for the pooled effect estimate just crossed the line of no effect. MMN supplementation did not have an important effect on neonatal mortality (average RR 1.00, 95% CI 0.89 to 1.12; studies = 14; random-effects, $Tau^2 = 0.01$, $I^2 = 22\%$; high-quality evidence; Analysis 1.6). Visual inspection of funnel plots for all primary outcomes revealed no obvious funnel plot asymmetry (Figure 4; Figure 5; Figure 6; Figure 7), with the exception of preterm births (Figure 8), and SGA (Figure 9), where smaller studies appeared to report slightly more pronounced treatment effects.

Figure 4. Funnel plot of comparison 1. Multiple micronutrients vs control, outcome: 1.3 Low birthweight

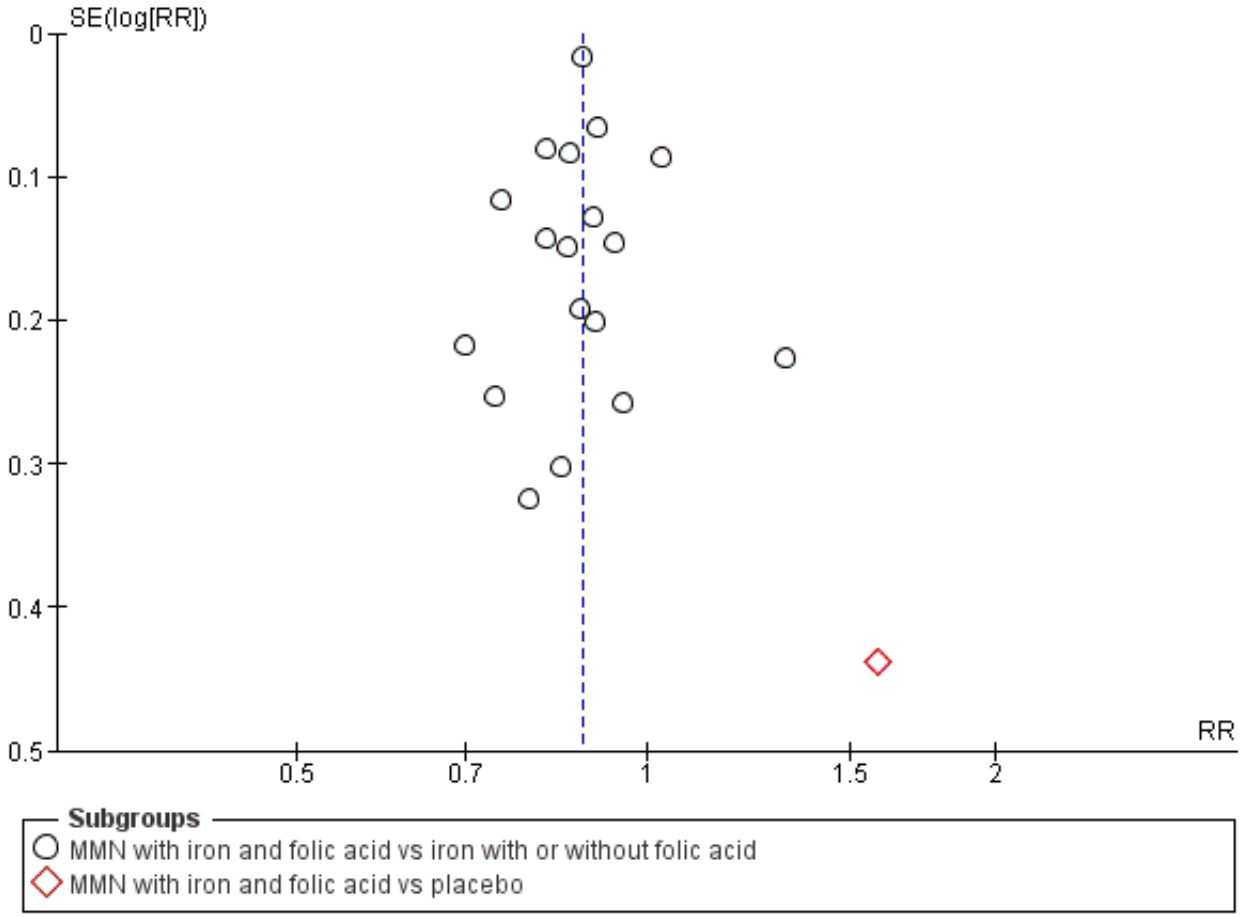


Figure 5. Funnel plot of comparison 1. Multiple micronutrients vs control, outcome: 1.4 Perinatal mortality

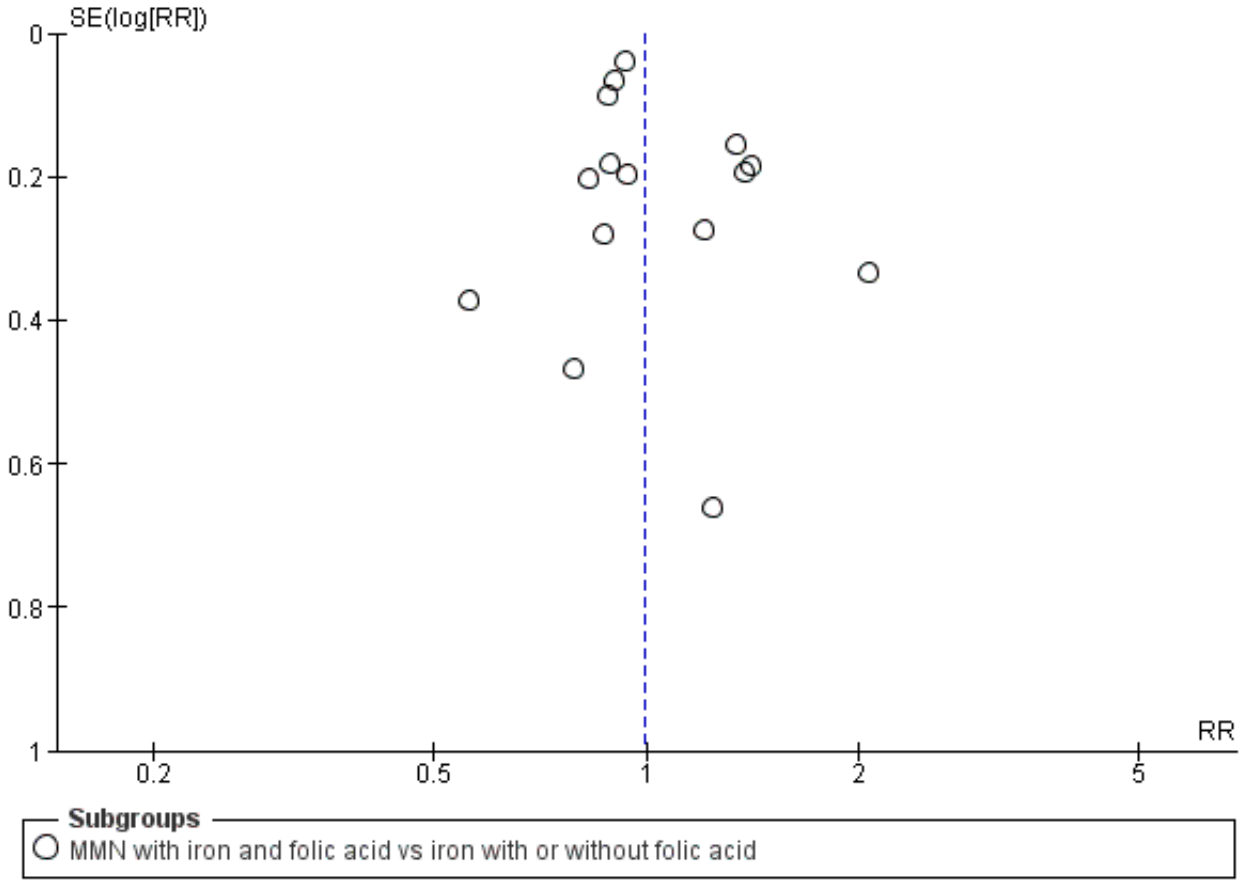


Figure 6. Funnel plot of comparison 1. Multiple micronutrients vs control, outcome: 1.5 Stillbirths

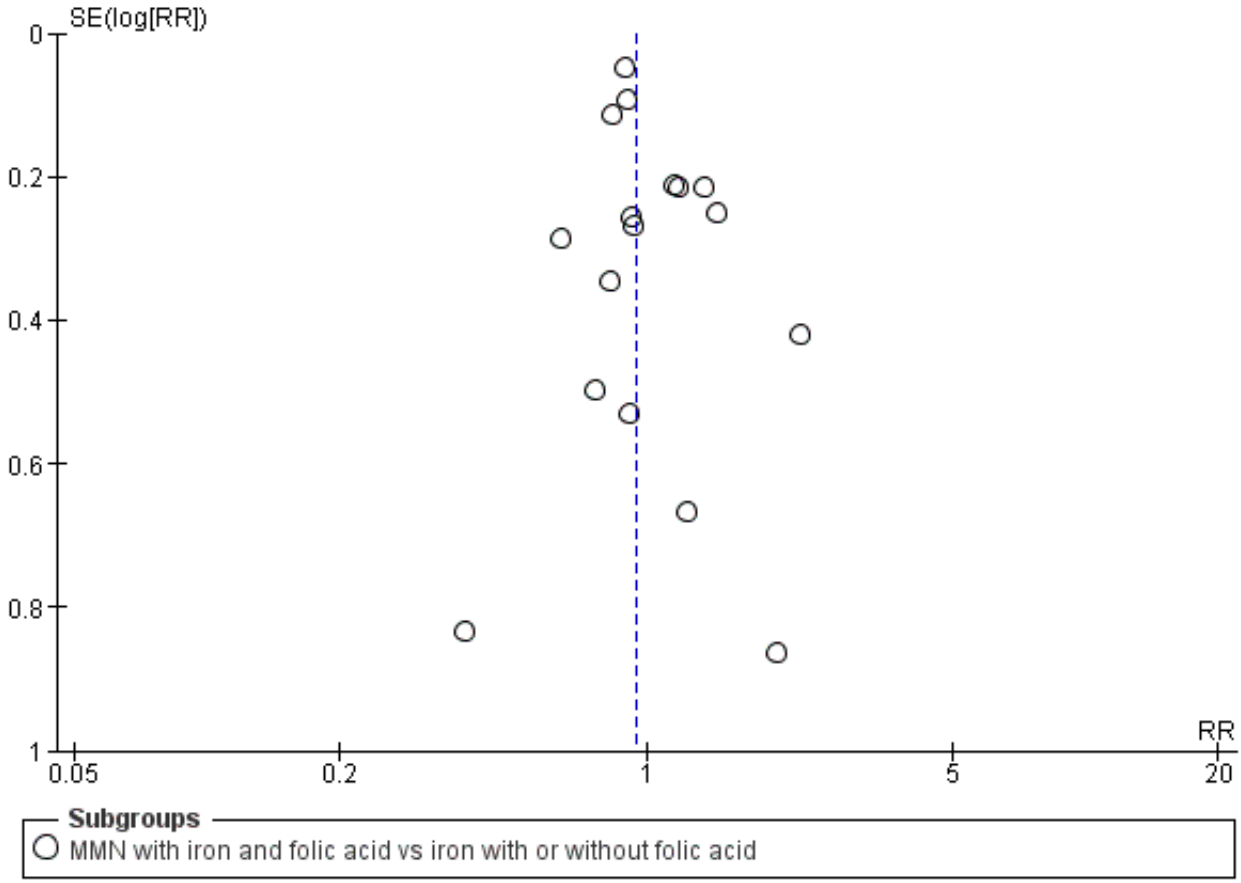


Figure 7. Funnel plot of comparison 1. Multiple micronutrients vs control, outcome: 1.6 Neonatal mortality

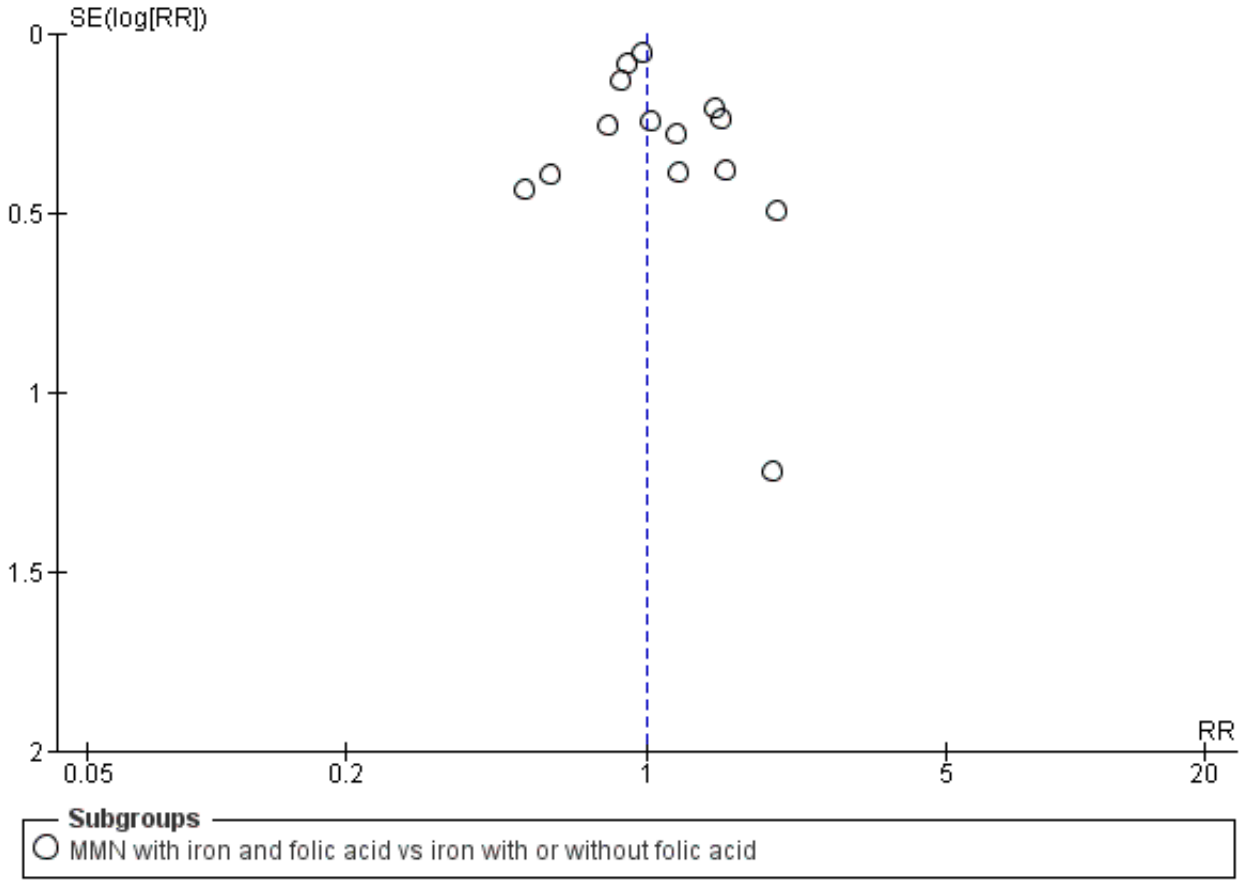


Figure 8. Funnel plot of comparison 1. Multiple micronutrients vs control, outcome: 1.1 Preterm births

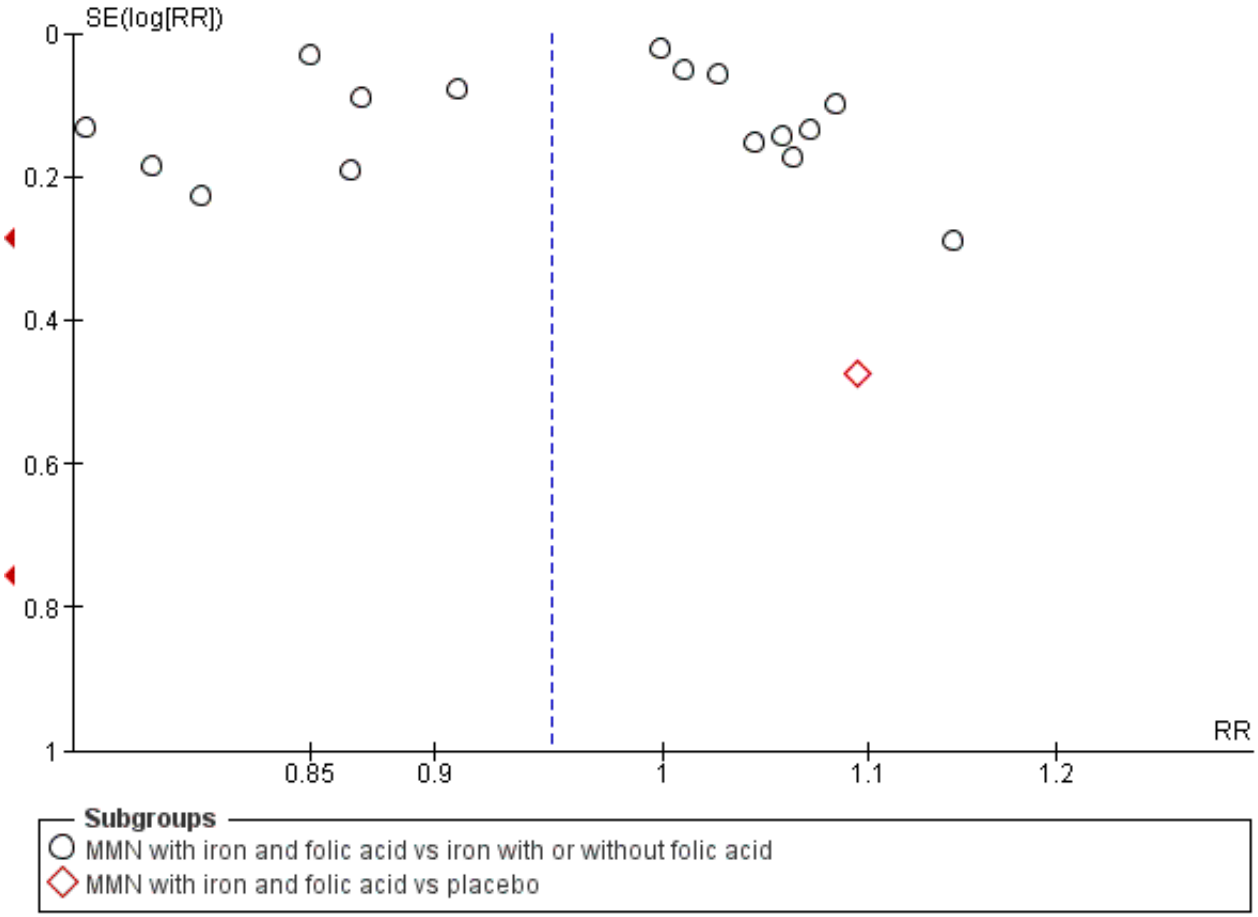
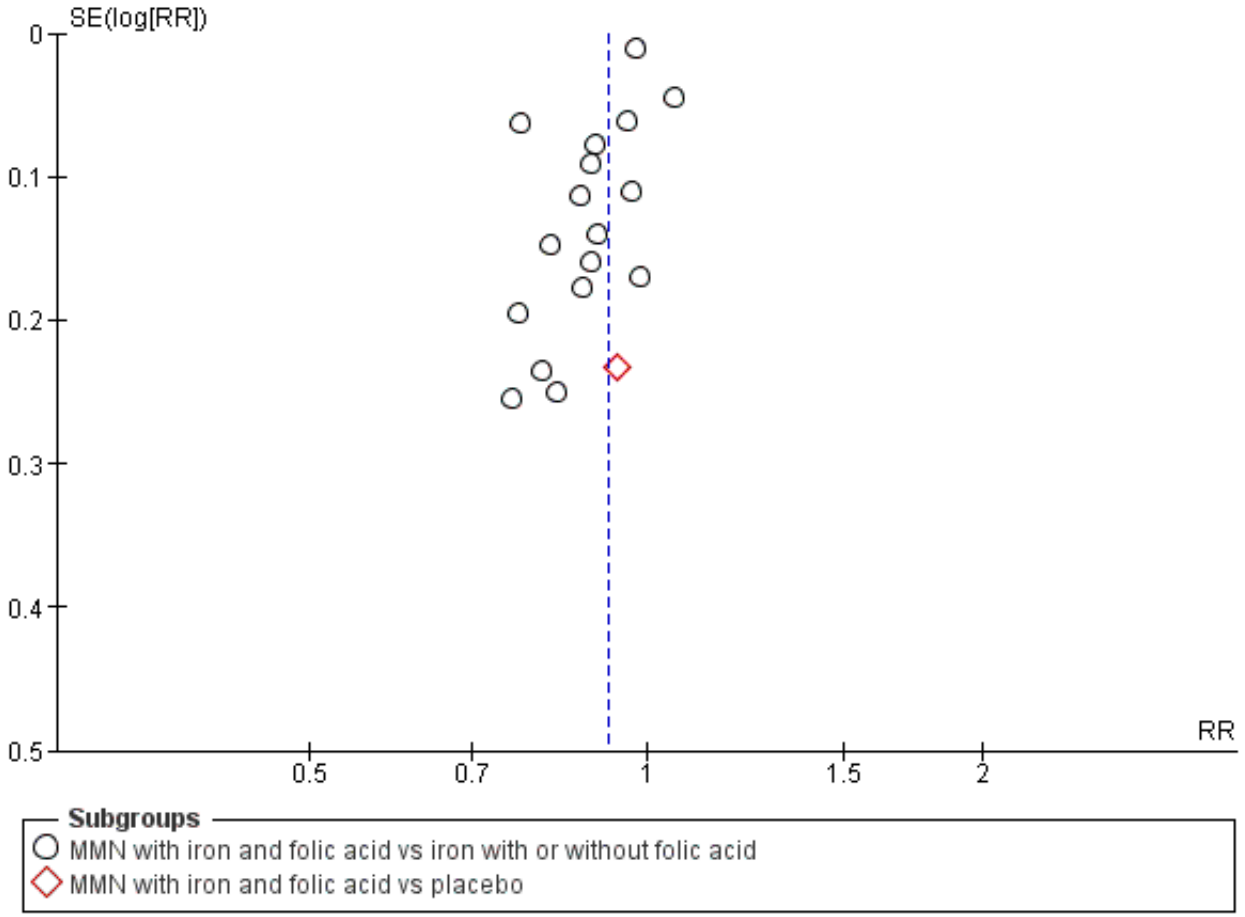


Figure 9. Funnel plot of comparison 1. Multiple micronutrients vs control, outcome: 1.2 Small-for-gestational age

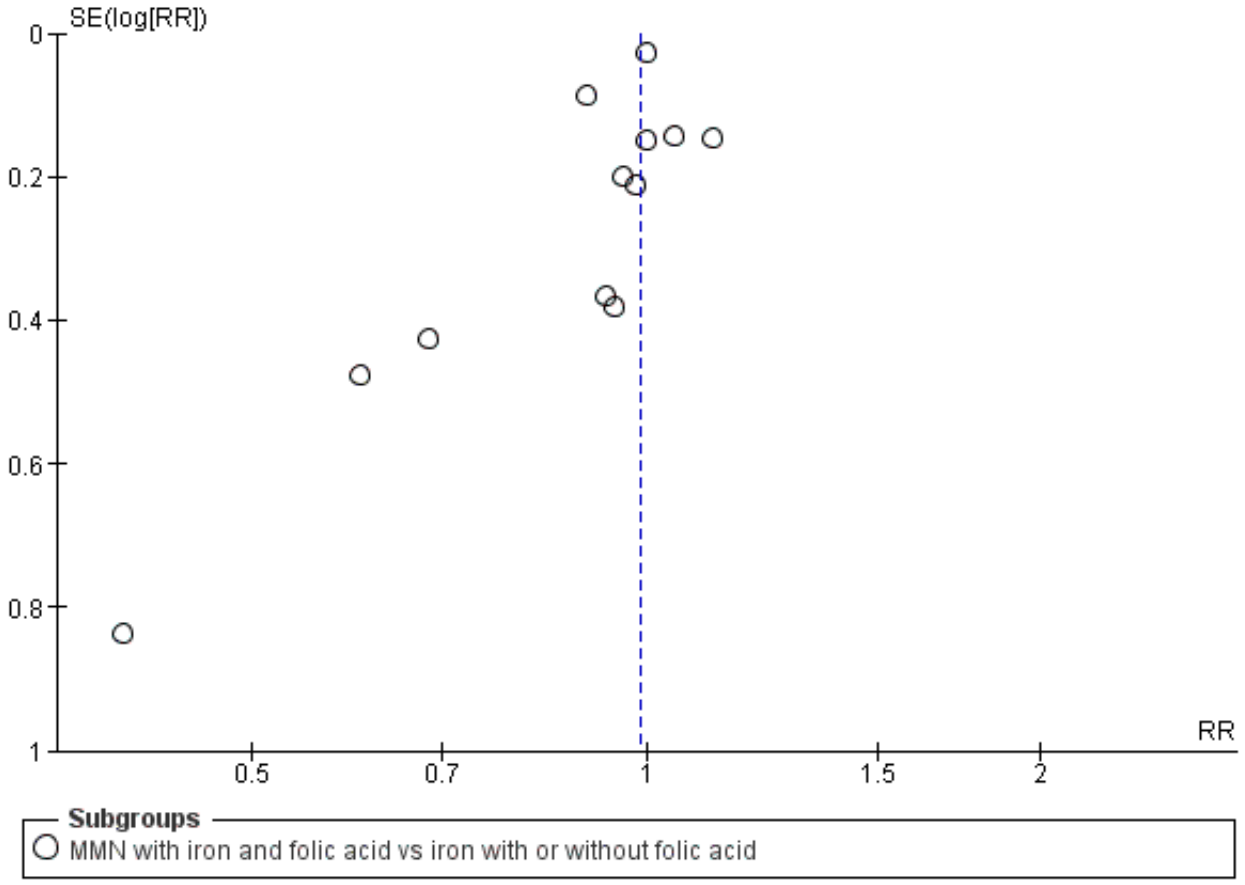


It should be noted that where none of the individual trial reports reported an outcome, then we obtained data from a separate supplement (Food and Nutrition Bulletin 2009), where possible. We took data for SGA estimates for the following trials from the Food and Nutrition Bulletin: Friis 2004; Kaestel 2005; Osrin 2005; Ramakrishnan 2003; Sunawang 2009; Tofail 2008; Zagre 2007. Similarly, we took data for preterm birth for the following trials: Kaestel 2005; Sunawang 2009; Tofail 2008; Zagre 2007; data for LBW for Tofail 2008; data for perinatal mortality for Sunawang 2009; and data for stillbirth for Kaestel 2005, from the same report.

Secondary outcomes

When we compared MMN supplementation to iron supplementation with or without folic acid, there was little or no difference between groups in: maternal anaemia in the third trimester (average RR 1.04, 95% CI 0.94 to 1.15; studies = 9; random-effects, Tau^2 = 0.01, I^2 = 50%; Analysis 1.7); maternal mortality (average RR 1.06, 95% CI 0.72 to 1.54; studies = 6; random-effects, Tau^2 = 0.00, I^2 = 0%; Analysis 1.8); miscarriage (average RR 0.99, 95% CI 0.94 to 1.04; studies = 12; random-effects, Tau^2 = 0.00, I^2 = 0%; Analysis 1.9); delivery via a caesarean section (average RR 1.13, 95% CI 0.99 to 1.29; studies = 5; random-effects, Tau^2 = 0.00, I^2 = 0%; Analysis 1.10); and congenital anomalies (average RR 1.34, 95% CI 0.25 to 7.12; studies = 2; random-effects, Tau^2 = 0.00, I^2 = 0%; Analysis 1.11). However, there was probably a reduction in very preterm births (average RR 0.81, 95% CI 0.71 to 0.93; studies = 4; random-effects, Tau^2 = 0.00, I^2 = 10%; Analysis 1.12). Of the secondary outcomes examined, only miscarriage had a sufficient amount of studies to create a funnel plot. Visual inspection of the funnel plot for this outcome (Figure 10), suggested that smaller studies reported more substantial treatment effects.

Figure 10. Funnel plot of comparison 1. Multiple micronutrients vs control, outcome: 1.9 Miscarriage (loss before 28 weeks)



There were a number of prespecified clinically important outcomes that we could not assess due to insufficient data from the included trials. These included the following outcomes, which only one or no trials measured, or which the trials presented in a format that precluded their inclusion in the analysis: premature rupture of membranes, pre-eclampsia, macrosomia (Roberfroid 2008), placental abruption, neurodevelopmental delay of infants (Zeng 2008), nutritional status of the children (Dewey 2009; Roberfroid 2008), cost of supplementation, side-effects of MMN supplementation (Lui 2013; Tofail 2008), and maternal well-being or satisfaction.

Multiple micronutrients (MMN) versus placebo

One trial conducted in the UK (Brough 2010), contributed data to this analysis. In this trial, women in the control group were advised to take folic acid. Brough 2010 randomised 402 women. Women receiving supplements were at reduced risk of anaemia in the third trimester (average RR 0.66, 95% CI 0.51 to 0.85; Analysis 1.7), but there were little or no differences between women receiving supplements and those in the placebo group for any of the other outcomes reported: preterm birth (average RR 1.09 95% CI 0.43 to 2.77; Analysis 1.1); SGA (average RR 0.94, 95% CI 0.60 to 1.48; Analysis 1.2); or LBW (average RR 1.58, 95% CI 0.67 to 3.72; Analysis 1.3).

Subgroup analysis (data shown in comparison 2) multiple micronutrients (MMN) with iron and folic acid versus iron with or without folic acid)

For the trials comparing MMN with iron and folic acid versus iron with or without folic acid (19 trials), we found substantial heterogeneity in the analyses for preterm birth, SGA, and perinatal mortality, and explored its presence through subgroup analyses.

For the outcome preterm birth, MMN supplementation probably led to fewer preterm births for women in a subgroup of trials with mean maternal BMI of less than 20 kg/m^2 (average RR 0.85, 95% CI 0.81 to 0.90; studies = 3), compared to women with a BMI of at least 20 kg/m^2 (average RR 0.99, 95% CI 0.96 to 1.03; studies = 15; the test for subgroup differences P < 0.00001, I^2 = 95.2%; Analysis 2.1). There were little or no differences among subgroups based on mean maternal height (Analysis 2.2), the timing of supplementation (Analysis 2.3), or the dose of iron (Analysis 2.4) (all P > 0.05). However, MMN supplementation probably led to fewer preterm births among women who took non-UNIMMAP supplements (average RR 0.89, 95% CI 0.82 to 0.98; studies = 8) compared to those who took UNIMMAP supplements (average RR 1.00, 95% CI 0.96 to 1.03; studies = 10; the test for subgroup differences P = 0.02, I^2 = 80.4%; Analysis 2.5).

For the outcome SGA, MMN supplementation probably led to fewer SGA births for women in a subgroup of trials with mean

maternal BMI of at least 20 kg/m² (average RR 0.88, 95% CI 0.83 to 0.93; studies = 14), but not for women with a mean maternal BMI of less than 20 kg/m² (average RR 1.00, 95% CI 0.92 to 1.08; studies = 3; test for subgroup differences P = 0.01, I^2 = 84.6%; Analysis 2.6). Similarly, we observed some differences between the subgroups of studies based on maternal height (Analysis 2.7). MMN supplementation probably reduced SGA births for women with a mean maternal height of at least 154.9 cm (average RR 0.85, 95% CI 0.79 to 0.91; studies = 9), and probably slightly reduced SGA births for women with a mean maternal height of less than 154.9 cm (average RR 0.98, 95% CI 0.96 to 1.00; studies = 8; test for subgroup differences P < 0.0001, I^2 = 93.7%; Analysis 2.7). There were little or no differences in SGA among subgroups based on timing of supplementation (Analysis 2.8), dose of iron (Analysis 2.9), or MMN supplement formulation (Analysis 2.10), when comparing MMN supplementation to iron with or without folic acid.

While we found that MMN supplementation made no difference to perinatal mortality as an outcome, the analysis demonstrated substantial statistical heterogeneity. However, subgroup analyses did not show clear differences based on mean maternal BMI (Analysis 2.11), mean maternal height (Analysis 2.12), dose of iron (Analysis 2.14) and MMN supplement formulation (Analysis 2.15) (all P > 0.05). However, we observed differences between subgroups based on the timing of supplementation. The reduction in perinatal mortality was probably higher in the subgroup with supplementation after 20 weeks (average RR 0.89, 95% CI 0.80 to 0.98; studies = 3) compared to the subgroup where women began supplementation before 20 weeks (average RR 1.09, 95% CI 0.92, 1.27; studies = 12; test for subgroup differences P = 0.04, I^2 = 76.5%; Analysis 2.13).

Sensitivity analysis (data shown in comparison 3) multiple micronutrients (MMN) with iron and folic acid versus iron, with or without folic acid

We undertook sensitivity analysis to study the effect of MMN supplementation on each outcome by excluding trials with loss to follow-up of more than 20% from the analyses (Friis 2004; Kaestel 2005; Ramakrishnan 2003; Tofail 2008). This exclusion did not significantly affect the findings for the outcomes.

DISCUSSION

Summary of main results

We identified 21 trials (involving 142,496 women) as eligible for inclusion in this review but only 20 trials (involving 141,849 women) contributed data to the review. This updated Cochrane Review summarises the current evidence on the effect of MMN supplementation during pregnancy on fetal, infant, and maternal outcomes. Overall, MMN supplementation with iron and folic acid versus supplementation with iron (with or without folic acid) showed an 8% reduction in the risk of SGA births (average risk ratio (RR) 0.92, 95% CI 0.88 to 0.97; moderate-quality evidence), and a 12% reduction in the risk of LBW (average RR 0.88, 95% CI 0.85 to 0.91; high-quality evidence). MMN supplementation slightly reduced the risk of both preterm births (average RR 0.95, 95% CI 0.90 to 1.01; 18 trials, moderate-quality evidence), and stillbirths (average RR 0.95, 95% CI 0.86 to 1.04; high-quality evidence), with the caveat that the confidence intervals for the pooled effects for both of these outcomes just crossed the line of no effect. We found that MMN supplementation did not have an important effect on perinatal mortality (average RR 1.00, 95% CI 0.90 to 1.11; high-quality evidence), and neonatal mortality (average RR 1.00, 95% CI 0.89 to 1.12; high-quality evidence). Of the secondary outcomes examined, we found that MMN supplementation reduced the risk of very preterm births by 19% (average RR 0.81, 95% CI 0.71 to 0.93). A summary of the main findings for trials comparing MMN with iron and folic acid versus iron with or without folic acid is presented in Summary of findings for the main comparison.

Overall completeness and applicability of evidence

This review included a total of 21 trials that evaluated the impact of MMN supplementation. The earliest trial was published in 1975 (Sood 1975), though this trial did not contribute data to the review because it reported its outcomes in a format that we could not use in the meta-analyses. An additional trial (Biggs 2010), did not contribute data to the main analyses because women received supplements twice-weekly as opposed to daily. All trials evaluating the UNIMMAP supplement (Bhutta 2009a; Kaestel 2005; Lui 2013; Osrin 2005; Roberfroid 2008; SUMMIT 2008; Sunawang 2009; Tofail 2008; Zagre 2007; Zeng 2008), proposed in 1999 by UNICEF, UNU, and WHO, started recruitment of participants as early as 2001 and we included them in the analysis along with trials that evaluated adapted-UNIMMAP formulations. Inclusion of these and older trials, identified as a result of an extensive search of literature published over the last several decades, represents overall completeness of evidence.

As iron/folic acid is recommended for pregnant women in low- and middle-income countries, we primarily evaluated the effect of adding additional micronutrients to the iron and folic acid supplement. The vast majority (95%) of the included trials were conducted in low- and middle-income countries, and included pregnant women at varying gestational stages, ranging from early pregnancy to 36 weeks of gestation.

In many low- and middle-income countries, fertility rates are high, alongside a high prevalence of maternal iron-deficiency anaemia and subclinical micronutrient deficiencies (Bhutta 2008). Studies have shown that a significant proportion of pregnant women suffer from multiple concurrent micronutrient deficiencies, especially throughout pregnancy when nutritional demands are increased. These deficiencies have been associated with a host of poor pregnancy outcomes including LBW, preterm, SGA, perinatal mortality, and maternal mortality (Allen 2001; Allen 2005; Christian 2010; De-Regil 2016; Dror 2011; Haider 2013; Keen 2003; MacKay 2001; Ota 2015). Increased risk of infection has also been postulated to be associated with anaemia, especially as a result of iron deficiency (Oppenheimer 2001). Our findings of improved LBW, SGA, and very preterm births, then, could be reflective of improved nutritional status of mothers and hence better resistance to maternal infections following MMN supplementation.

Maternal anthropometry pre-pregnancy and weight gain during pregnancy have also been associated with various neonatal and child outcomes. Maternal height is a relatively stable and easily measurable variable in the setting of low- and middle-income countries. Reviews have identified short maternal stature (short height) as an important determinant of intrauterine growth retardation and LBW (Kramer 2003; WHO 1995). Short maternal stature has been associated with an increased risk of child mortality, underweight infants, and stunting (Ozaltin 2010; Voigt 2010). Our subgroup analyses indicated that MMN

supplementation did not reduce SGA in women with poor nutritional status at baseline, defined as maternal height less than 154.9 cm and BMI less than 20 kg/m^2. However, MMN supplementation did reduce the risk of SGA babies among women with a mean maternal height of at least 154.9 cm. Similarly, MMN supplementation reduced the risk of SGA babies among women with a mean BMI of at least 20 kg/m^2. These findings should be interpreted with caution, but suggest a possible role of MMN in preventing SGA only among women with good nutritional status at baseline, and underscore an absence of similar effect in women with poor nutritional status at the time of conception. On the contrary, the findings for the subgroup analysis for preterm birth indicate a reduction among women with low BMI, but not among those with higher BMI. These differences further highlight the complex contribution of maternal malnutrition to fetal anthropometry and infant growth that relates to the intergenerational transfer of malnutrition. Though micronutrient supplementation has been implicated in improved child growth and survival, there is currently no evidence to suggest that maternal MMN supplementation during pregnancy improves child growth or survival when compared with iron/folic acid supplementation. Additional studies with long-term follow-up are required.

Quality of the evidence

We evaluated the quality of the available evidence by using the GRADE methodology as outlined in the GRADE Handbook. We created a 'Summary of findings' table for the primary outcomes of preterm birth, SGA, LBW, stillbirths, perinatal and neonatal mortality for Comparison 1: MMN with iron and folic acid versus iron with or without folic acid supplement.

When assessed according to GRADE criteria, the quality of evidence for the review's primary outcomes overall was moderate to high. We based pooled results for all primary outcomes on multiple randomised controlled trials with large sample sizes and precise estimates. For the comparison of MMN versus control (iron with or without folic acid) we graded the following outcomes as high quality: LBW, stillbirth, neonatal mortality, and perinatal mortality. The outcomes of preterm birth and SGA we graded as moderate quality; we downgraded both by one for funnel plot asymmetry, indicating possible publication bias.

Potential biases in the review process

This update of the review includes additional data published since the last update (2017). We conducted an extensive literature search to identify any additional studies since the last search. Two review authors independently conducted the screening of the updated search results, selection of eligible studies and data extraction. Two review authors also assessed the risk of bias. Given the application of the above Cochrane methodology, it is unlikely that the findings of this review are affected by biases in the review process.

Agreements and disagreements with other studies or reviews

The findings of reduction in SGA, LBW and very preterm risk as a result of MMN supplementation in the current review corroborate those of other systematic reviews and meta-analyses conducted since the first version of this Cochrane Review (Bhutta 2012; Kawai 2011; Margetts 2009; Ramakrishnan 2012). Another systematic review and meta-analysis (Christian 2015), also reports reduction in the risk of preterm births, LBW, and SGA; however, the effect on SGA is reported to be marginal (RR 0.91, 95% CI 0.84 to 1.00). This review included a smaller number of studies in the SGA analysis (studies = 7), as opposed to the current review (studies = 17), thereby explaining the difference between the estimates reported in the two reviews.

Another recent exercise (Smith 2017), used individual participant data from 17 randomised trials in low- and middle-income countries to perform a two-stage meta-analysis comparing MMN and iron-folic acid supplementation among pregnant women and identify potential modifiers of effect. Smith 2017 also found a reduction in LBW (random-effects RR 0.86, 95% CI 0.81 to 0.92), a slight reduction in SGA (random-effects RR 0.94, 95% CI 0.90 to 0.98), and some reduction in preterm births (random-effects RR 0.93, 95% CI 0.87 to 0.98). Similar to this review, there were no important survival benefits (or harms) noted. Smith 2017 also demonstrated a greater effect of MMN supplementation on preterm births among underweight women when compared to normal weight women and, although tests for heterogeneity were not significant, there appeared to be a trend towards higher impact on SGA for women with greater BMI and height, as we have also shown. Though we did not stratify data by anaemia status, authors found that MMN supplementation caused greater reductions in LBW, SGA, and six-month mortality among anaemic pregnant women when compared to those who were not anaemic. Taken together with the results of our subgroup analyses, this points to maternal nutritional status at baseline as a modifier of the effect of MMN supplementation for some important outcomes, and should instigate further studies to better elucidate these effects and the mechanisms behind them.

We found that MMN supplementation did not have an important effect on perinatal mortality, stillbirths, and neonatal mortality, which are similar to findings from earlier versions of this Cochrane Review and other systematic reviews and meta-analyses (Christian 2005; Haider 2011; Ronsmans 2009; Smith 2017). With the additional studies included in this 2018 update, RR estimates for perinatal mortality, stillbirths, and neonatal mortality declined from 1.01 (0.91 to 1.13), 0.97 (0.87 to 1.09), and 1.06 (0.92 to 1.22) to 1.00 (0.90 to 1.11), 0.95 (0.86 to 1.04), and 1.00 (0.89 to 1.12), respectively. Previously, concerns were raised regarding the possibly harmful effects of MMN supplements relating to risk of perinatal and neonatal mortality through increased birth asphyxia in heavier babies (Christian 2005). Indeed, the Smith 2017 analysis found a slightly increased risk of large-for-gestational-age births (defined by the Intergrowth standard) following MNN supplementation, but no indication of heightened risk of stillbirth or mortality. Two earlier trials conducted in Nepal (Christian 2003; Osrin 2005), both found no important increase in the risk of neonatal and perinatal mortality, though their pooled effect estimate showed an increase in the risk of these outcomes. This concern was questioned by other researchers in the field and has not been observed in other studies (Bhutta 2009b; Huffman 2005; Shrimpton 2005). Importantly, our current findings of no impact on neonatal mortality are supported by those of two MMN supplementation trials that were individually powered to evaluate an effect on early infant mortality (SUMMIT 2008; West 2014). The recent large trial in Bangladesh did not show an increase in neonatal or early infant mortality risk in the MMN supplementation group verus iron and folic acid (West 2014). The trial authors, however, in post-hoc analysis, report higher neonatal mortality among boys due to birth asphyxia (West 2014). This finding

should be interpreted with caution as the cause of death was ascertained by verbal autopsy with parents, which may result in misclassification of the underlying cause of death. Moreover, the trial was not powered to detect a statistically significant difference in cause-specific mortality by gender. Interestingly, Smith 2017 found about a 15% reduction in neonatal mortality for females babies but no effect for male babies, indicating that there may be a biological difference in the impact of MMN supplementation relating to sex. Previous work has suggested that this may be a function of birth complications relating to size, with greater length, weight, and head circumference typically being true of male babies (West 2014). However, Smith 2017 noted no sex-specific differences in stillbirths, indicating that other, potentially context-specific, mechanisms may be responsible for these differences. These findings warrants further research.

AUTHORS' CONCLUSIONS

Implications for practice

Our findings suggest a benefit in the use of multiple-micronutrient (MMN) supplements with iron and folic acid in low- and middle-income settings to improve low birthweight, small-for-gestational age, and possibly preterm births. We have also demonstrated that MMN supplementation does not have an important effect (neither beneficial nor harmful), on mortality outcomes, including stillbirths, perinatal, and neonatal mortality. These findings have been consistently observed in other systematic evaluations of evidence.

Implications for research

Based on results from our subgroup analyses, further research could be conducted to better understand how baseline nutritional status (maternal BMI and height) may affect pregnancy and birth outcomes following supplementation with MMN. Additionally, determining the optimal formulation for MMN supplements could have beneficial effects in practice. A greater understanding of the biological mechanisms through which MMN supplementation acts would be beneficial.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ashorn 2010

Methods	This was a randomised trial with 3 intervention groups conducted at 4 sites: a public district hospital (Mangochi), a semi private hospital (Malindi), and 2 public health centres (Lugwena and Namwera), in Mangochi District in southern Malawi. **Dates of study:** February 2011-December 2015
Participants	Participants (n = 1391) were pregnant women who were < 20 weeks of gestation confirmed by ultrasound, resided in the defined catchment area, were available during the study period, and signed or thumb-printed an informed consent form. Women who were < 15 years of age, needed frequent medical attention due to a chronic health condition, diagnosed with asthma treated with regular medication, had an illness warranting hospital referral, had a history of peanut allergy, anaphylaxis or serious allergic reaction to any substance, required emergency medical care, had pregnancy complications at enrolment (moderate-severe oedema, blood Hb concentration < 50 g/L, systolic BP > 160 mmHg or diastolic BP > 100 mmHg), participated in the iLiNS-DYAD-M trial during a previous pregnancy, or were concurrently participating in other clinical trials were excluded.
Interventions	1. IFA group (n = 463; 391 were HIV-ve) received a daily IFA tablet containing iron (60 mg) and folic acid (400 µg) during pregnancy, and a tablet containing calcium (200 mg/day) during the first 6 months of lactation. No supplementation was given to infants born to these women. 2. MMN group (n = 466; 414 were HIV-ve) received a daily MMN tablet during pregnancy and the first 6 months of lactation. The supplement consisted of vitamin A (800 µg retinol equivalents), vitamin B1 (2.8 mg), B2 (2.8 mg), B6 (3.8 mg), B12 (5.2 µg), vitamin C (100 mg), vitamin D (400 IU), vitamin E (20 mg), vitamin K (45 µg), niacin (36 mg), folic acid (400 µg), pantothenic acid (7 mg), iron (20 mg), zinc (30 mg), copper (4 mg), selenium (130 µg), iodine (250 µg) and manganese (2.6 mg). No supplementation was given to infants born to these women. 3. LNS group (n = 462; 395 were HIV-ve) received 20 g LNS daily during pregnancy and the first 6 months of lactation. The supplement consisted of the same micronutrients as the MMN supplement, in addition to calcium, phosphorus, potassium, magnesium, energy (118kcal/d) and macronutrients (protein and essential fatty acids). Infants born to these women received 20g of LNS daily from 6-18 months of age.
Outcomes	Birthweight, newborn length, newborn weight, head and arm circumference, pregnancy duration, maternal and newborn SAEs
Notes	All participants also received 2 doses of intermittent preventative malaria treatment with sulfadoxine-pyrimethamine (3 tablets of 500 mg sulfadoxine and 25 mg pyrimethamine orally). 1 dose was given at enrolment and the other between 28 and 34 weeks of gestation. In this review, the MMN group was used as the intervention group and the IFA group was used as the comparison group. HIV-ve data included in this review was obtained from personal correspondence with trial investigators. **Declarations of interest:** MZ worked as a director of research for Nutriset S.A.S., a company that produces and sells lipid-based nutrient supplements and also prepared the LNS supplements purchased for the current trial. The other authors declared no conflict of interest.

Ashorn 2010 *(Continued)*

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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A study statistician not involved in data collection generated 4 randomization code lists in blocks of 9 (one list for each of the 4 enrolment sites)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "a researcher not involved with the trial created individual randomisation slips (in blocks of 9) and packed them in sealed, numbered, opaque randomisation envelopes that were stored in numerical order. Eligible pregnant women were requested to choose 1 of the top 6 envelopes in the stack, and the contents of the envelope indicated her participant number and group allocation." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The IFA and MMN interventions were provided by using double-masked procedures—that is, the capsules looked identical, and neither the participants nor the research team members were aware of the nutrient contents of the supplement capsules." Comment: participants and caregivers were probably blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The data collectors who performed the anthropometric measurements or assessed other outcomes were not aware of group allocation. Researchers responsible for the data cleaning remained blind to the trial code until the database was fully cleaned." Comment: outcome assessors were probably blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition (until delivery) was 6.0% (and was balanced between treatment arms); reasons were not reported
Selective reporting (reporting bias)	Low risk	Comment: all outcomes presented in the methods section were reported in the paper.
Other bias	Low risk	Comment: no other bias was identified.

Bhutta 2009a

Methods	This cluster-randomised trial was conducted in urban and rural areas in Pakistan. **Dates of study:** not reported

Bhutta 2009a *(Continued)*

Participants	Pregnant women with gestational age < 16 weeks were eligible for enrolment. MMN group (n = 1148), IFA group (n = 1230)
Interventions	1. MMN group received vitamin A 800 mcg, D 200 IU, E 10 mg, C 70 mg, B1 1.4 mg, B2 1.4 mg, niacin 18 mg, B6 1.9 mg, B12 2.6 mg, folic acid 400 mcg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 mcg and iodine 150 mcg 2. IFA group received 60 mg iron and 400 mcg folic acid
Outcomes	Size at birth, gestational age at birth, perinatal mortality, maternal anaemia (Hb < 11 g/dl), mode of delivery (caesarean section) It should be noted that the data for SGA were obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
Notes	MMN and MMN + nutritional education groups were compared with IFA and IFA + nutritional education group. IFA given to all participants. Maternal malnutrition, vitamin A deficiency, anaemia and iron deficiency were common. 2 methods of community outreach were implemented that is, basic nutrition along with antenatal care messages and quarterly community-based group sessions conducted by CHWs and social scientist. There was no significant difference in baseline characteristics between 2 groups. Data for caesarean section were presented (intervention 18/743; control 22/832). Data were not included in the analysis as this was a cluster-RCT. **Declarations of interest:** not reported **Funding sources:** United Nations Children's Fund (UNICEF)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a cluster-based allocation strategy of supplements (either IF or MMN supplementation) by respective CHWs was implemented". Comment: probably done
Allocation concealment (selection bias)	Low risk	Comment: "allocated to either the IF or MMN supplements according to their respective location and allocation by the AKU Pharmacy". Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both tablets were identical in colour, shape and packaging" and "field staff (medical officers, CHWs, social scientists and data collection team) remained completely blinded as to the supplements allocation. All pregnant women were allocated a unique code and allocated a uniquely labelled and numerically coded specific supplement supply". Comment: participants and caregivers were probably blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both tablets were identical in colour, shape and packaging" and "field staff (medical officers, CHWs, social scientists and data collection team) remained completely blinded as to the supplements allocation". Comment: outcome assessors were probably blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition (15.8%) and exclusion (around 1%) along with their reasons were reported. Attrition and exclusions were balanced across the treatment arms.

Bhutta 2009a *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: results of all outcomes mentioned in methods section were presented in the paper
Other bias	Low risk	Comment: no other bias was identified, including cluster-design specific biases (recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomised trials)

Biggs 2010

Methods	This was a cluster-randomised trial comparing the impact of daily IFA, twice weekly IFA and twice weekly MMN for pregnant women on birthweight in Ha Nam province, Vietnam **Dates of study:** September 2010-2012
Participants	Participants (n = 1258) were pregnant women who were confirmed to be < 16 weeks of gestation, resided in trial communes (n = 104), were > 16 years of age, and were registered with the commune health station. Women with a high-risk pregnancy including those with a multi-fetal pregnancy (confirmed by palpation or ultrasound), a significant medical condition or severe anaemia (Hb concentration < 80 g/L) at enrolment were excluded.
Interventions	1. Daily IFA group (n = 426 participants; n = 34 communes) received an IFA tablet containing elemental iron (60 mg) and folic acid (0.4 mg), administered 7 days/week 2. Twice-weekly IFA group (n = 425 participants; n = 35 communes) received an IFA capsule containing elemental iron (60 mg) and folic acid (1.5 mg), administered as 2 capsules/week 3. Twice-weekly MMN group (n = 407 participants; n = 35 communes) received a MMN capsule containing elemental iron (60 mg), zinc (20 mg), iodine (300 µg), copper (4 mg), selenium (130 µg), vitamin A (1.6 mg), thiamine (2.8 mg), riboflavin (2.8 mg), niacin (36 mg), vitamin B6 (3.8 mg), B12 (5.2 µg), folic acid (1.5 mg), vitamin C (140 mg), vitamin D (400 IU) and vitamin E (20 mg), administered as 2 capsules/week All groups were provided supplements for the duration of the pregnancy until 3 months postpartum
Outcomes	Birthweight, maternal Hb and ferritin at 32 weeks, and infant length-for-age z-scores, Hb, ferritin, and infant cognitive development at 6 months of age
Notes	In the review, the twice-weekly MMN group was used as the intervention group and the daily IFA group was used as the comparison group. Since this review focuses on daily supplementation, outcomes from this study were omitted from the main analyses, however, they were included in the subgroup analyses. **Declarations of interest:** the trial authors declared no conflict of interest. **Funding sources:** National Health and Medical Research Coucil of Australia (Grant number 628751)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed by an independent statistician not involved in the study and blinded to the identity of the communes, using 'ralloc' in Stata (StataCorp)." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "Supplements were received from the manufacturing company in blister packs, with a code A, B, or C embossed on each blister pack. The intermittent IFA and MMN capsules were identical in both appearance and packaging.

Biggs 2010 *(Continued)*

		The manufacturing company confidentially notified the chairperson of the Data Monitoring and Safety Committee at the University of Melbourne of the allocation code, and the code was kept in a locked file cabinet at the University of Melbourne, Australia." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The investigators, field staff, and participants were blinded to the codes of the intermittent supplement groups throughout the study and during data analysis. Laboratory staff were unaware of the intervention groups. It was not possible to blind the field team to the daily supplementation arm, but participants were not informed about the dosing frequency of the intervention being given in other communes." Comment: participants and caregivers were probably not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The investigators, field staff, and participants were blinded to the codes of the intermittent supplement groups throughout the study and during data analysis. Laboratory staff were unaware of the intervention groups. It was not possible to blind the field team to the daily supplementation arm" and "The allocation code was broken at the completion of data analysis. An independent team undertook the BSID III assessments, and were blinded to the intervention arms." Comment: it is unclear whether outcome assessors were blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition (until delivery) was 7.2% and (and was balanced between treatment arms); reasons were reported
Selective reporting (reporting bias)	High risk	Comment: growths outcomes including weight-for-age, underweight, weight-for-length and wasted were mentioned in the methods section, however, results were not presented in the paper.
Other bias	Low risk	Comment: no other bias was identified, including cluster-design-specific biases (recruitment bias, baseline imbalance, loss of clusters, and comparability with individually randomised trials). Any incorrect analysis was corrected by adjustment for clustering within data reported in this review.

Brough 2010

Methods	This randomised trial was conducted in a socially deprived, multi-ethnic population in east London, United Kingdom. **Dates of study:** June 2002-May 2004
Participants	Participants included women aged ≥ 16 years with a singleton pregnancy. Exclusion criteria included a gestation of > 13 weeks of gestation, chronic disease or use of micronutrient supplements (excluding IFA). MMN group n = 207 and placebo n = 195
Interventions	Participants were randomised to receive either MMN supplements, known as Pregnacare, or a placebo comprising starch with an iron oxide coating. MMN supplement contained beta-carotene 3 mg, thiamin (as thiamin mononitrate, 3·6 mg) 3 mg, riboflavin 2 mg, niacin (as nicotinamide) 20 mg, vitamin B6 (as pyridoxine HCl) 10 mg, vitamin B12 (as cyanocobalamin) 6 mcg, folic acid 400 mcg, vitamin C (as ascorbic acid, 73 mg) 70 mg, vitamin D (as cholecalciferol, 200 IU) 5 mcg, vitamin E (as D-a-tocopheryl acid succinate, 21 mg) 20 mg, vitamin K 70 mcg, Fe (as ferrous fumarate, 63·3 mg) 20 mg, zinc (as zinc sul-

Brough 2010 *(Continued)*

	phate H_2O, 41 mg) 15 mg, Mg (as magnesium hydroxide, 372 mg) 150 mg, Iodine (as potassium iodide, 183 mg) 140 mcg and copper (as copper sulphate H_2O, 2·8 mg) 1 mg
Outcomes	Birthweight, preterm birth, SGA, head circumference, Hb
Notes	Women not using folic acid were also given 400 mcg folic acid to take daily until 12 weeks of gestation. There were no significant differences in age, height, weight, BMI or parity regarding treatment group allocation. **Declarations of interest:** the trial authors declared no conflict of interest. **Funding sources:** the Mother and Child Foundation, and Nutricia Research Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "a randomised, double-blind, placebo-controlled trial" and "Participants were randomised to receive either multiple-micronutrient supplements, known as Pregnacare, or a visually identical placebo". Comment: insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "a randomised, double-blind, placebo-controlled trial" Comment: insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants were randomised to receive either multiple micronutrient supplements, known as Pregnacare, or visually identical placebo comprising starch with an iron oxide coating. All tablets were provided by Vitabiotics (London, UK) and packaged to allow double blinding. Only Vitabiotics knew the code and it was not broken until statistical analysis had been completed". Comment: participants and caregivers were probably blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All tablets were provided by Vitabiotics (London, UK) and packaged to allow double blinding. Only Vitabiotics knew the code and it was not broken until statistical analysis had been completed". Comment: outcome assessors were probably blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (8.7%) and attrition (12.2%) were reported along with their reasons.
Selective reporting (reporting bias)	Low risk	Comment: results of all outcomes mentioned in methods were presented in the paper.
Other bias	Low risk	Comment: no other bias was identified.

Christian 2003

Methods	This was a double-blind cluster-randomised trial, carried out in rural Nepal. **Dates of study:** December 1998-April 2001

Christian 2003 *(Continued)*

Participants	A total of 4926 pregnant women were enrolled in the study. The women were randomised into 5 groups as follows: group 1 (n = 941), group 2 (n = 957), group 3 (n = 999), group 4 (n = 1050) and group 5 (n = 1051) Women who were currently pregnant or those who were breastfeeding an infant < 9 months old were excluded from the study. Also excluded were menopausal, sterilised or widowed women
Interventions	1. Group 1 received folic acid 400 mcg and vitamin A 2. Group 2 received folic acid 400 mcg, iron 60 mg as ferrous fumerate and vitamin A 3. Group 3 contained the same minerals as group 2 in addition to 30 mg of zinc as zinc sulphate 4. Group 4 received similar micronutrients as group 3 in addition to vitamin D 10 mcg, vitamin E 10 mg, vitamin B1 1.6 mg, vitamin B2 1.8 mg, niacin 20 mg, vitamin B6 2.2 mg, vitamin B12 2.6 mcg, vitamin C 100 mg, vitamin K 65 mcg, copper 2 mg and magnesium 100 mg 5. Group 5 (control group) received 1000 mcg of vitamin A only All supplements were given orally from the time of pregnancy detection until 12 weeks after a live birth or 5 weeks after a still birth or a miscarriage.
Outcomes	Preterm births, SGA (weight < 10 percentile of gestational age), LBW (< 2500 g), side-effects, fetal loss, perinatal mortality, neonatal mortality, 3-month infant mortality It should be noted that the data for SGA were obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
Notes	All women were offered 2 x 400 mg single-dose albendazole in the second and third trimester of pregnancy because of the high prevalence of hookworm infestation in this population. Hookworm infestation and vitamin A deficiency are one of the major causes of anaemia in this population. Due to this reason, vitamin A was given to all the participants including the control group. Baseline characteristics did not differ significantly among the various randomisation groups except for ethnicity and land holding. In this review, we used the group 4 data for the MMN group and group 2 data for the control group. All the estimates were adjusted for the cluster design and provided by the trial authors. **Declarations of interest:** the trial authors declared no conflict of interest. **Funding sources:** US Agency for International Development (USAID) and additional support from the Unicef Country Office, Kathmandu, Nepal, and the Bill and Melinda Gates Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done in blocks of five within each village development community by the senior study investigators, who drew numbered chips from a hat" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomisation was done in blocks of five within each village development community by the senior study investigators, who drew numbered chips from a hat" Comment: insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "participants, investigators, field staff and statisticians did not know supplement codes", "supplements, which were of identical shape, size, and color" and "code allocation was kept locked at the Johns Hopkins University, Baltimore".

Christian 2003 *(Continued)*

		Comment: participants and caregivers were blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "participants, investigators, field staff and statisticians did not know supplement codes" Comment: outcome assessors were blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (1.43%) and attrition (6.9%) were reported along with their reasons
Selective reporting (reporting bias)	Low risk	Comment: results of all outcomes mentioned in methods were presented in the various publications of this trial.
Other bias	Low risk	Comment: no other bias was identified, including cluster-design specific biases (recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomised trials).

Dewey 2009

Methods	This was a randomised trial with 3 intervention groups conducted in the Somanya-Kpong area of the Yilo Krobo and Lower Manya Krobo districts in southern Ghana. **Date of study:** December 2009-March 2014
Participants	Participants (n = 1320) were pregnant women who were ≥ 18 years of age and < 20 weeks of gestation confirmed by ultrasound. Women who were not residing in the target area, who intended to move within the next 2 years, had a known milk or peanut allergy, were unwilling to receive field workers or take the study supplement, were participating in another trial, or had an antenatal card indicating HIV infection, asthma, epilepsy, tuberculosis, or any malignancy were excluded.
Interventions	1. IFA group (n = 441) received a daily IFA tablet containing iron (60 mg) and folic acid (400 µg) during pregnancy, and a tablet containing calcium (200 mg/day) during the first 6 months of lactation. No supplementation was given to infants born to these women. 2. MMN group (n = 439) received a daily MMN tablet during pregnancy and the first 6 months of lactation. The supplement consisted of vitamin A (800 µg), vitamin B1 (2.8 mg), B2 (2.8 mg), B6 (3.8 mg), B12 (5.2 µg), vitamin C (100 mg), vitamin D (400 IU), vitamin E (20 mg), vitamin K (45 µg), niacin (36 mg), folic acid (400 µg), pantothenic acid (7 mg), iron (20 mg), zinc (30 mg), copper (4 mg), selenium (130 µg), iodine (250 µg) and manganese (2.6 mg). No supplementation was given to infants born to these women. 3. LNS group (n = 440) received 20g LNS daily during pregnancy and the first 6 months of lactation. The supplement consisted of the same micronutrients as the MMN supplement, in addition to calcium, phosphorus, potassium, magnesium, energy (118 kcal/d) and macronutrients (protein and essential fatty acids). Infants born to these women received 20 g of LNS daily from 6-18 months of age.
Outcomes	Primary outcomes were child length at birth and length-for-age Z-score (LAZ, based on WHO 2006 growth standards) at 18 months of age. Secondary outcomes included the following:

Dewey 2009 *(Continued)*

1. Maternal
   a. Anthropometric status (weight, BMI, mid-upper arm circumference and subscapular skin-fold thickness) at ~ 36 wk gestation and at 6, 12, and 18 months postpartum
   b. Pregnancy outcomes (birthweight, gestational age)
   c. Anemia, micronutrient (iron, vitamin A, B-vitamins, zinc) and essential fatty acid status, and malarial antigen at ~ 36 weeks' gestation and 6 months postpartum
   d. Total plasma cholesterol at ~ 36 weeks' gestation
   e. BP and urinary iodine, isoprostane (marker of oxidative stress) and 8-hydroxy-2'deoxyguanosine (8-OHdG) (marker of DNA damage) at 36 weeks' gestation
   f. Breast milk composition (EFA, vitamin A, B-vitamins, iodine) at 6 months postpartum
   g. Depressive symptoms (which may be related to EFA status) at 6 months postpartum
2. Child
   a. Anthropometric status (weight, length, head circumference and mid-upper arm circumference) at birth and 3, 6, 12 and 18 months
   b. Anaemia, micronutrient (iron, vitamin A, B-vitamins, iodine) and EFA status, and malarial antigen at 6 and 18 months
   c. Morbidity between 6 and 18 months
   d. Child feeding practices and maternal report of child sleep patterns at 6, 12 and 18 months
   e. Energy intake from complementary foods at 9 and 15 months
   f. Antibody response to measles vaccination at 12 months
   g. Achievement of 5 motor milestones (sitting without support, standing alone, walking with assistance, walking alone and running) and 4 other developmental milestones (pronouncing single words like mama or dada, waving goodbye, eating by self, drinking from a cup) from 0-18 months
   h. Neuro-behavioural development at 18 months of age

Notes	Temporary mislabelling of IFA and MMN capsules resulted in some women in the IFA (n = 92) and MMN (n = 85) groups receiving both IFA and MMN supplements during pregnancy. These women were excluded in the analysis of pregnancy outcomes. In this review, we used the MMN group as the intervention group and the IFA group as the comparison group. **Declarations of interest:** MZ was an employee of Nutriset S.A.S., which is a commercial producer of LNS products. The other trial authors declared no conflict of interest. **Funding sources:** Bill & Melinda Gates Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "women were randomly allocated into one of 3 groups by using a computer-generated scheme (SAS version 9.3; SAS Institute) in blocks of 9." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "Sheets bearing supplement allocations represented by 6 different color codes (3 for IFA and 3 for MMN) and an inscription “LNS” (for the LNS group) and numbered 1–1320 were placed in opaque envelopes and stacked in increasing order. At each enrolment, the study nurse shuffled the 9 topmost envelopes in the stack, and the woman picked one to reveal allocation. Allocation information was kept by the field supervisor (HO) in a password-protected file, which was shared with the study statistician (JMP) at UC Davis, who designed the randomisation scheme." Comment: probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Two individuals in Ghana who were independent of the research team color-coded the capsules by placing color stickers (which also included the letter P or L to indicate pregnancy or lactation) on the blister packs of IFA and

Dewey 2009 *(Continued)*

All outcomes		MMN, so that no investigator, study worker, or participant knew the identities of the capsules except by the colors." Comment: participants and caregivers were probably blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "none of the maternal or newborn anthropometrists was aware of the code allocations. Likewise, data analysts remained blinded until all preliminary analyses had been completed, and the allocation codes were broken." Comment: outcome assessors were probably blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (until delivery) was 20% (and was balanced between treatment arms); the reason was reported. Attrition (until delivery) was 4.4% and reasons were reported
Selective reporting (reporting bias)	Low risk	Comment: results of all outcomes mentioned in methods section were presented in the paper
Other bias	Low risk	Comment: no other bias was identified

Fawzi 2007

Methods	This was a double-blind trial in Dar es Salam, Tanzania. Pregnant women who attended antenatal clinics were included. **Dates of study:** August 2001-July 2004
Participants	Pregnant women who attended antenatal clinics, had a negative test for HIV infection, planned to stay in the city until delivery and for 1 year thereafter with gestational age between 12 and 27 weeks according to LMP were included. The study groups were similar with respect to baseline characteristics.
Interventions	1. Intervention group (n = 4214) received vitamin B1 20 mg, B2 20 mg, B6 25 mg, B12 50 µg, C 500 mg, E 30 mg niacin 100 mg, folic acid 0.8 mg 2. Control group (n = 4214) received placebo All women irrespective of group received daily iron (60 mg) and folic acid (0.25 mg). Women were randomly assigned to receive either MM or control from the time of enrolment until 6 weeks after delivery.
Outcomes	LBW (< 2500 g), preterm delivery (< 37 weeks of gestation), very LBW (< 2000 g), extremely preterm delivery (< 34 weeks of gestation), SGA (< 10th percentile for gestational age), fetal death, death in first 6 weeks, length, head circumference, placental weight, risk of caesarean section, maternal mortality, haematological status (Hb < 11 g/dL and < 8.5 g/dL, immune status (CD4 count < 775 per cubic mm, CD8 count < 480 per cubic mm and CD3 count < 1350 per cubic mm)
Notes	Malaria prophylaxis (sulphadoxine-pyrimethamine tablets) at 20 and 30 weeks of gestation was given to all. The study groups were similar with respect to baseline characteristics. **Declarations of interest:** the trial authors declared no conflict of interest. **Funding sources:** National Institute of Child Health and Human Development (NICHD R01 37701)

Risk of bias

Bias	Authors' judgement	Support for judgement

Fawzi 2007 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "A list was prepared according to a randomisation sequence in blocks of 20; at enrolment, each eligible women was assigned to the next numbered bottle" and computerised random number generator was used (personal communication) Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "Each eligible women was assigned to the next numbered bottle" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Active tablets and placebo were similar in shape, size and color and were packaged in identical coded bottles" and "Each eligible women was assigned to the next numbered bottle" Comment: participants and caregivers were blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "research assistants who assessed the study outcome were unaware of the intervention group" Comment: outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (0.5%) and attrition (5.4%) were reported with reasons in each arm.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper.
Other bias	Low risk	Comment: no other bias was identified.

Friis 2004

Methods	This trial was carried out in Zimbabwe. **Dates of study:** 1996-1997
Participants	Pregnant women who were between 22 and 36 weeks of gestation were eligible for enrolment. Participants (n =1669) were randomised into 2 groups, MMN group n = 837 and placebo n = 832. Out of the 1106 women that were followed, 725 were HIV-ve and 360 were HIV+ve.
Interventions	1. MMN group received daily supplementation of vitamin A 3000 mcg retinol equivalents, beta carotene 3.5 mg, thiamine 1.5 mg, riboflavin 1.6 mg, B6 2.2 mg, B12 4 mcg, niacin 17 mg, C 80 mg, D 10 mcg, E 10 mg, zinc 15 mg, copper 1.2 mcg and selenium 65 mcg 2. Placebo An IFA supplement was given separately as part of the routine antenatal care and was not part of the MMN tablet. Tablets were given from the day of enrolment until delivery.
Outcomes	Gestational age, birthweight, birth length, head circumference, preterm delivery (< 37 weeks of gestation), LBW (< 2500 g), IUGR-LBW (> 37 weeks' gestational age and < 2500 g birthweight). It should be noted that the data for SGA were obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.

Friis 2004 *(Continued)*

Notes	Study intervention was approximately the RDA for pregnant or lactating women, except for vitamin A for which a higher amount was given. Out of 1106 women who were followed, 725 were HIV-ve whereas 360 were HIV+ve and HIV status of 21 was indeterminate. We have used data of HIV-ve women only in this review. The intervention and the placebo groups were comparable at baseline except for the higher proportion of primigravida in the placebo group. **Declarations of interest:** the trial authors declared no conflict of interest. **Funding sources:** Council for Development Research, Danish International Development Assistance (to HF), the Danish Council for Medical Research (to HF), Southampton Insurance, Zimbabwe, the Foundation of 1870, BASF Health and Nutrition, the Hørslev Foundation, the Dagmar Marshall Foundation, the Sophus Jacobsens Foundation, and the Lily Benthine Lunds Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation to daily supplementation with multimicronutrient or identical-looking placebo tablets was based on simple blocked randomisation. The digits 0–5 in a computer-generated random sequence were replaced by 6 preassigned permuted blocks of 4: AABB, ABAB, ABBA, BABA, BBAA, and BAAB; the digits 6–9 were deleted". Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "Containers with 110 multimicronutrient or placebo tablets, which were coded A or B, respectively, were delivered by the manufacturer together with the code in 2 sealed envelopes. Duplicate containers, which corresponded to the random sequence, were consecutively numbered from 1 to 1800. The study participants were numbered consecutively at recruitment". Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind", "multimicronutrient or identical-looking placebo tablets" Comment: study participants and care providers were probably blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind", "multimicronutrient or identical-looking placebo tablets" Comment: investigators were probably blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was > 20% and reasons for it were reported. Exclusions were not reported in the trial
Selective reporting (reporting bias)	Low risk	Comment: all outcomes in the methods section were presented in the paper.
Other bias	Low risk	Comment: no other bias was identified.

Kaestel 2005

Methods	This trial was conducted in Guinea-Bissau

Kaestel 2005 *(Continued)*

	Dates of study: January 2001-October 2002
Participants	Pregnant women with < 37 weeks of gestation were eligible for enrolment. A total of 2100 women were randomised into 3 groups, MMN RDA group, MMN 2 RDA group and 60 mg iron 400 mcg folic acid group
Interventions	15 micronutrients were included in the supplement at RDA level, except for folic acid that was included at 400 mcg level. Supplement consisted of vitamin A 800 mcg, D 200 IU, E 10 mg, C 70 mg, B1 1.4 mg, B2 1.4 mg, niacin 18 mg, B6 1.9 mg, B12 2.6 mg, folic acid 400 mcg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 mcg and iodine 150 mcg 1. Intervention group (n = 1392) received MMN supplements (supplement RDA n = 695, supplement 2 RDA n = 697) 2. IFA group received folic acid 400 mcg and iron 60 mg n = 708
Outcomes	Size at birth, gestational age at birth, preterm birth (< 37 weeks of gestation), LBW (< 2500 g), miscarriage (fetal loss < 28 completed weeks of gestation), perinatal mortality (fetal loss between 28 weeks of gestation and first 7 days of life), neonatal mortality (deaths within the first 28 days of life), maternal Hb, anaemia (Hb < 100 g/L) and maternal death (death during pregnancy or within 42 days after termination of pregnancy), childhood mortality. It should be noted that the data for SGA were obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
Notes	Malaria is endemic but HIV prevalence is relatively low. IFA given to all participants. There was no significant difference in baseline characteristics between randomisation groups. We used the 1 RDA and control groups in this review. **Declarations of interest:** the trial authors declared no conflict of interest. **Funding sources:** the Royal Veterinary and Agricultural University, Denmark's Development Assistance (Danida), the Novo Nordisk Foundation, UNICEF, the Foundation of 1870, and Jakob & Olga Madsen's Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Simple block randomisation with a block size of 150 was managed as follows: at entry, the project midwife randomly drew 1 piece of coloured paper corresponding to the colour code on the tablet containers from envelopes with initially 50 pieces of each of the three colours" Comment: probably done.
Allocation concealment (selection bias)	Unclear risk	Quote: "at entry, the project midwife randomly drew one piece of coloured paper corresponding to the colour code on the tablet containers from envelopes with initially 50 pieces of each of the three colours" Comment: insufficient evidence to determine whether allocation was concealed following generation of the randomisation sequence.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "three identical-looking micronutrient supplements", "code was kept secret from study participants, study personnel, and data analysts until data cleaning and preliminary data analysis had been carried out." and "the health workers who collected outcome data after delivery did not have any knowledge of intervention group of the women" Comment: participants and caregivers were probably blinded to the treatment assignment.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "three identical-looking micronutrient supplements", "code was kept secret from study participants, study personnel, and data analysts until data

Kaestel 2005 *(Continued)*

All outcomes		cleaning and preliminary data analysis had been carried out." and "the health workers who collected outcome data after delivery did not have any knowledge of intervention group of the women" Comment: outcome assessors were probably blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Exclusion (3.1%) and attrition (20.4%) data were reported along with their reasons.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper.
Other bias	Low risk	Comment: no other bias was identified.

Lui 2013

Methods	This was a double-blind RCT conducted in 5 rural counties in Hebei Provinve, China **Dates of study:** May 2006-April 2009
Participants	Pregnant women who recorded dates of their menstruation for ≥ 2 months before they became pregnant, were nulliparous, ≥ 20 years old, < 20 weeks' gestation, legally competent, had not consumed micronutrient supplements other than folic acid in the prior 6 months, had a Hb level > 10.0 g/dL, resided in and received prenatal care in 1 of 5 counties, and consented to participate were eligible. 18,775 pregnant women with singleton pregnancies were randomised to group A (n = 6261), group B (n = 6252), and group C (n = 6262).
Interventions	The study had 3 arms. 1. Group A received folic acid 400 µg 2. Group B received folic acid 400 µg and iron 30 mg 3. Group C received the UNICEF formulation containing folic acid 400 µg, Fe 30 mg, vitamin A 800 µg, E 10 mg, D 5 mcg, C 70 mg, B1 1.4 mg, B2 1.4 mg, B6 1.9 mg, B12 2.6 µg, niacin 18 mg, Zn 15 mg, Cu 2 mg, iodine 150 µg, selenium 65 µg Supplements were take from enrolment until delivery.
Outcomes	Perinatal mortality, neonatal mortality, infant mortality, maternal Hb and anaemia at 24-28 weeks of gestation, gestational age at birth, preterm birth, LBW, birthweight, low weight for height, low weight for age, low height for age, infant anaemia, gastrointestinal side-effects (nausea, vomiting, or other mild gastrointestinal discomfort) at monthly visits
Notes	There were no significant differences at baseline between the groups Data for side-effects: 6% (n = 355) in the MMN group while 3.6% (n = 212) in the IFA group We used the estimates for the comparison of MMN vs. IFA groups in this review. **Declarations of interest:** the trial authors declared no conflict of interest **Funding sources:** supported by a co-operative agreement between Peking University Health Science Center and the Centers for Disease Control and Prevention.

Risk of bias

Bias	Authors' judgement	Support for judgement

Lui 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "A statistician external to the study randomly assigned ten 4-digit lot numbers to each of the 3 supplement types (masked to the formulation and allocation) and generated the assignment list for each county proportional to the expected number of participants; within each county and block, lot numbers were randomly assigned using RANUNI in SAS statistics software (SAS Institute Inc)" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "A statistician external to the study randomly assigned ten 4-digit lot numbers to each of the 3 supplement types (masked to the formulation and allocation)" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Aside from a pharmaceutical engineer who ensured allocation of lot numbers to the correct supplement formulations, all others (i.e., participants, local physicians, study personnel, and investigators) were masked to the identity of the supplements" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Treatment codes were broken after completion of the study and main analyses.", " double blind" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate (6.2%) was < 20% and reasons for attrition and exclusions were provided
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned were reported.
Other bias	Low risk	Comment: no other bias was identified.

Moore 2009

Methods	This was a randomised trial with 4 intervention groups investigating the effects of prenatal and infancy nutritional supplementation on infant immune development in the West Kiang region of the Gambia **Dates of study:** October 2009-September 2013
Participants	Participants (n = 875) were pregnant women who were 10-20 weeks of gestation confirmed by ultrasound. Women who were pregnant > 20 weeks of gestation on ultrasound assessment, enrolled in another Medical Research Council study, severely anaemic at booking (Hb < 7 g/dL), or reported the onset of menopause were excluded.
Interventions	The study had 4 pregnancy interventions given daily to participants from 12 weeks of gestation until delivery: 1. FeFol group received a daily tablet consisting of iron (60 mg) and folate (400 µg), representing the usual standard of care during pregnancy, as per Gambian Government guidelines (control group) 2. MMN group received a daily tablet consisting of 15 micronutrients. The supplement provided twice the RDA of all micronutrients, except for iron (60 mg) and folic acid (400 µg). The rest of the micronutrients included vitamin A (1600 µg retinol equivalents), vitamin D (400 IU), vitamin E (20 mg), vitamin C (140 mg), vitamin B1 (2.8 mg), B2 (2.8 mg), B6 (2.8 mg), B12 (5.2 µg), niacin (36 mg), zinc (30 mg), copper (4 mg), selenium (130 µg) and iodine (300 µg)

Moore 2009 *(Continued)*

	3. PE + FeFol group received a food-based supplement developed by Valid International, providing a comparable level of iron and folate to the FeFol-only arm, but with the addition of energy, protein and lipids 4. PE + MMN group received a micronutrient fortified food-based supplement also developed by Valid International, providing comparable levels of micronutrients to the MMN arm (including FeFol), in addition to the energy and protein and lipid content From 6 months of age, infants were further randomised to receive either a lipid-based nutritional supplement, with or without additional MMN, or placebo from 6-12 months of age
Outcomes	Thymic index at 1, 8, 24 and 52 weeks of age, antibody response to EPI vaccines (diphtheria, tetanus toxoid, HiB, measles) and cellular markers of immunity in a randomly selected subcohort of infants assessed at 12, 24 and 52 weeks of age. Subsidiary studies to the main trial will additionally assess the impact of supplementation on infant growth and development to 24 months of age.
Notes	In the review, the MMN group was used as the intervention group and the FeFol group was used as the comparison group. **Declarations of interest:** the trial authors declared no conflict of interest. **Funding sources:** UK Medical Research Council (MRC) (MC-A760-5QX00) and the UK Department for International Develop- ment (DFID) under the MRC/DFID Concordat agreement. WJ and SEM are funded by the UK MRC programme MC_UP_1005/1

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization into the trial is in blocks of 8, using an automated system, with the 8 groups reflecting the 8 combinations of prenatal and infancy supplements." Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "Allocation of each supplement combination to a number between 1 and 8 was performed by Dr Mathilde Savy (IRD, France), with this information passed directly to the supplement manufacturers. Each box of supplement is then distinguished by a number between 1 and 8. An additional hard copy of the code assignment is held in the safe in Keneba, accessible by the field station senior administrator and only at the request of the trial monitors." and "Using the automated allocation system, a member of the data office at MRC Keneba, independent to the trial analysis, allocates mother-infant pairs to their supplement codes and then generates printed labels for the supplement pots (including subject ID, name, and date of supplement period). Four members of the MRC Keneba field staff working on a different study then label the supplements using lists, by supplement allocation number (e.g. Group 1, women a, b, c etc.) provided by the data office." Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The antenatal arm of the trial is partly open, since it is not be possible to blind the field assistants or the women to the supplement type (tablet vs. LNS); all other investigators however will not know to which group the women belong." Comment: it is unclear whether participants and personnel were blinded to IFA and MMN groups.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "all other investigators however will not know to which group the women belong."

Moore 2009 *(Continued)*

		Comment: outcome assessors were probably blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Exclusion (until delivery) was 25.6% and reasons were reported. Attrition (until delivery) was 4.8% and reasons were not reported. Whether exclusion and attrition rates were balanced between treatment arms were not reported.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes in the methods section were presented in the paper.
Other bias	Low risk	Comment: no other bias was identified.

Osrin 2005

Methods	This study was undertaken in Nepal. All women attending a designated antenatal clinic at Janakpur zonal hospital were considered for enrolment. **Dates of study:** August 2002-July 2004
Participants	Women were eligible for enrolment if an ultrasound examination confirmed a singleton pregnancy, a gestational age between 12-20 completed weeks, no notable fetal abnormality, no existing maternal illness of a severity that could compromise the outcome of pregnancy; and the participant lived in an area of Dhanusha or the adjoining district of Mohattari accessible for home visits. Participants received supplements throughout pregnancy until delivery.
Interventions	1. MMN group (n = 600) received tablets containing vitamin A 800 mcg, vitamin E 10 mg, vitamin D 5 mcg, B1 1.4 mg, B2 1.4 mg, niacin 18 mg, B6 1.9 mg, B12 2.6 mcg, folic acid 400 mcg, vitamin C 70 mg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 mcg, and iodine 150 mcg. 2. Control group (n = 600) received tablets containing iron 60 mg and folic acid 400 mcg. There were 2 prespecified deviations from the protocol: if a participant's enrolment blood Hb concentration was < 70 g/L, she was given an extra 60 mg of iron daily, anthelmintic treatment, and her Hb was rechecked after 1 month; and if a participant described night blindness at any time, she was given 2000 ug of vitamin A daily and referred for medical follow up.
Outcomes	Birthweight, LBW (< 2500 g), gestational duration, preterm delivery (< 37 weeks of gestation), miscarriage, stillbirth, early and late neonatal death, infant length, head circumference. It should be noted that the data for SGA were obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
Notes	Infants were followed up to 3 months. Both groups of participants were comparable at baseline. There is a discrepancy in the number of neonatal deaths reported. Figure: 'Study profile' in the Devakumar 2014 Lancet publication (p e655) reports 12 neonatal deaths in the control group and Osrin 2005 reports 11 neonatal deaths in the control group. **Declarations of interest:** in the planning phase of the study, DO, SF, and AT attended an international principal investigators' meeting funded by the Micronutrient Initiative. After study completion, but before the paper was written, AV, DSM, and AT attended a second meeting funded by UNICEF. The other trial authors declared no conflict of interest. **Funding sources:** Wellcome Trust, UK

Risk of bias

Bias	Authors' judgement	Support for judgement

Osrin 2005 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomly allocated 1200 participant identification numbers by computer into two groups in permuted blocks of 50". Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "We did randomisation in advance of recruitment", "The allocation code was kept on file in Kathmandu and London. We allocated every identification number a supplement container to last throughout the trial. Containers were filled with either intervention or control tablets in Kathmandu by a team member who was otherwise uninvolved in the trial; these containers were then marked only with identification numbers and transported to the study centre in Janakpur" and "After screening, consent, and enrolment, one of us (YS) allocated participants sequential identification numbers and the corresponding supplement containers". Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The allocation code was kept on file in Kathmandu and London" and "Containers were filled with either intervention or control tablets in Kathmandu by a team member who was otherwise uninvolved in the trial; these containers were then marked only with identification numbers and transported to the study centre in Janakpur. Intervention and control supplements were manufactured to look, smell, and taste identical" Comment: participants and caregivers were probably blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The allocation code was kept on file in Kathmandu and London" and "Containers were filled with either intervention or control tablets in Kathmandu by a team member who was otherwise uninvolved in the trial; these containers were then marked only with identification numbers and transported to the study centre in Janakpur. Intervention and control supplements were manufactured to look, smell, and taste identical" Comment: outcome assessors were probably blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was 5% and reasons for it were reported. Exclusion was 39.5% and reasons were not reported.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper.
Other bias	Low risk	Comment: no other bias was identified.

Ramakrishnan 2003

Methods	This RCT was carried out in Mexico **Dates of study:** 1997-2000
Participants	Pregnant women who were < 13 weeks' pregnant, were not receiving MMN supplementation and who agreed to participate were included in the study. A total of 873 women were randomised into the MMN group (n = 435, mean age 23.09 ± 5.48) and the iron-only group (n = 438, mean age 23.00 ± 5.08).
Interventions	1. MMN group: tablets included the following vitamins and minerals: iron 60 mg as ferrous sulphate, folic acid 215 mcg, vitamin A 2150 IU, vitamin D3 309 IU, vitamin E 5.73 IU, thiamin 0.93 mg, riboflavin

Ramakrishnan 2003 *(Continued)*

	1.87 mg, niacin 15.5 mg, vitamin B6 1.94 mg, vitamin B12 2.04 mcg, vitamin C 66.5 mg, zinc 12.9 mg, magnesium 252 mg 2. Control group: given iron-only tablets with 60 mg of iron as iron sulphate All were given orally, from recruitment 6 days a week until delivery.
Outcomes	Preterm births (< 37 weeks of gestation), SGA (below the 10th percentile for birthweight-for-gestational age), LBW (< 2500 g), perinatal mortality, mean Hb concentration, mean serum ferritin It should be noted that the data for SGA were obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
Notes	Data on birth outcomes were only available for 656 pregnancies (MMN group n = 328 and control group, iron only n = 326). The 2 groups did not differ significantly in most of the characteristics at recruitment, except for marital status (more single mothers in MMN supplementation group) and mean BMI (significantly lower in the MMN supplementation group). **Declarations of interest:** the trial authors declared no conflict of interest. **Funding sources:** Thrasher Research Fund, United Nations Children's Fund (UNICEF) New York, Conacyt, and the Instituto Nacional de Salud Pública, Mexico

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was carried out by using 4 color-coded groups (2 per treatment) that were assigned a priori with the use of a computer-generated list". Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "Four colors were used to ensure masking and were assigned at random before the study began to a list of serial numbers from 1 to 1000" and "pregnant women were allocated to the pre-assigned color code as they were added to this list at the time of recruitment". Comment: probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All study personnel and investigators were blinded to the group assignment, the details of which were kept at Emory University and the INSP in sealed envelopes that were opened only after preliminary data analysis was completed". Comment: participants and caregivers were probably blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All study personnel and investigators were blinded to the group assignment, the details of which were kept at Emory University and the INSP in sealed envelopes that were opened only after preliminary data analysis was completed". Comment: outcome assessors were probably blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Exclusion was 5.2% but reasons for it were not reported. Attrition (26.2%) along with their reasons were reported.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the various publications of this trial.

Ramakrishnan 2003 *(Continued)*

Other bias	Low risk	Comment: no other bias was identified.

Roberfroid 2008

Methods	This was a factorial, double-blind, RCT conducted in the Hounde health district of Burkina Faso. **Dates of study:** March 2004-October 2006
Participants	Pregnant women irrespective of gestational age. Exclusion criterion was if women planned to leave area within 2 years
Interventions	1. Intervention group (n = 714) received vitamin A 800 mcg, D 200 IU, E 10 mg, B1 1.4 mg, B2 1.4 mg, niacin 18 mg, folic acid 400 mg, B6 1.9 mg, B12 2.6 mcg, C 70 mg, zinc 15 mg, iron 30 mg, copper 2 mg, selenium 65 mcg, iodine 150 mcg 2. Placebo group (n = 712) received folic acid 400 mcg and iron 60 mg
Outcomes	Stillbirths (fetal death between 28 weeks of gestation till birth), neonatal deaths, perinatal death, gestation age, preterm births (< 37 weeks of gestation), birthweight, LBW (< 2500 g), SGA (birthweight < 10 percentile of a reference population), LGA, birth length, Rohrer index, arm circumference, chest circumference, head circumference, Hb in cord blood, soluble serum transferrin receptor, stunting, wasting, underweight, and infant mortality during the first year of life. It should be noted that the data for SGA were obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
Notes	Supplement intake was observed directly and given till 3 months after delivery. Participants were also randomly assigned to receive either malaria chemoprophylaxis (300 mg chloroquine/week) or intermittent preventive treatment (1500 mg sulfadoxine and 75 mg pyrimethamine once in the second and third trimester). All participants received albendazole 400 mg during second and third trimester. Severely anaemic women received ferrous sulphate 200 mg and folic acid 0.25 mg twice daily for 3 months regardless of their allocation groups. The study groups were similar with respect to baseline characteristics except for small difference in Hb (lower in intervention group) and BMI (lower in control group). Stunting, wasting, underweight, and infant mortality during the first year of life were presented as hazard ratios and could not be included in the analysis of outcome using risk ratios. **Declarations of interest:** the trial authors declared no conflict of interest. **Funding sources:** Nutrition Third World and the Belgian Ministry of Development

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation scheme was generated by a computer program in permuted blocks of 4". Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "Randomization numbers were sealed in opaque envelopes. At each inclusion, the consulting physician opened the next sealed envelope and transmitted the randomisation number to a pharmacist managing the allocation sequence and the packaging of drugs in Center Muraz. The pharmacist was also blinded to the intervention. Individual plastic zip bags contained 31 tablets

Roberfroid 2008 *(Continued)*

		each and were labelled with the participant's name, address, and identification numbers only" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind", "Intervention and control micronutrient tablets were identical in appearance" and "code was kept secret from study participants and staff until completion of preliminary data analysis" and "Pharmacist was also blinded to the intervention". Comment: participants and caregivers were probably blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind", "Intervention and control micronutrient tablets were identical in appearance" and "code was kept secret from study participants and staff until completion of preliminary data analysis" and "Pharmacist was also blinded to the intervention". Comment: outcome assessors were probably blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 7.5% and reason for it was provided. Only 1 woman was excluded because of therapeutic abortion.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper.
Other bias	Low risk	Comment: no other bias was identified.

Sood 1975

Methods	Trial conducted in New Dehli and Tamil Nadu, India. **Dates of study:** not reported
Participants	Pregnant women with gestational age 22 ± 2 were eligible to participate in the trial. A total of 647 pregnant women participated in the trial. Women with chronic diseases like heart diseases, tuberculosis, leprosy, chronic diarrhoea and a Hb < 5 g/100 mL were excluded from the study.
Interventions	There were total of 7 study groups. 2 in the control group and 5 in the intervention group. 1. Intervention a. Intervention groups 1-4 received vitamin B12, folic acid and iron in a range of 30 to 240 mg b. Itervention group 5 received 120 mg of iron without vitamin B12 and folate 2. Control a. Control group 1 received placebo b. Control group 2 received vitamin B12 and folic acid alone Supplementation was given for 10-12 weeks.
Outcomes	Outcomes were improvement in maternal Hb/haematocrit, iron absorption from maternal gut, fetal birthweight, maternal and fetal Hb 3 months postpartum, hookworm infestation in mother and side-effects of supplementation
Notes	None of the outcomes were reported in a format that allowed inclusion of the data in this review. **Declarations of interest:** not reported

Sood 1975 *(Continued)*

Funding sources: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "By reference to previously prepared random tables the women were allocated to one of the two streams A or B" and "within each stratum subjects were allotted to final treatment groups according to a set of random numbers" Comment: probably done
Allocation concealment (selection bias)	High risk	Quote: "By reference to previously prepared random tables the women were allocated to one of the two streams A or B" and "within each stratum subjects were allotted to final treatment groups according to a, set of random numbers" Comment: probably not done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All the tablets had the same appearance and had the daily folic acid and iron dose divided into two tablets". Comment: participants, caregivers probably blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All the tablets had the same appearance and had the daily folic acid and iron dose divided into two tablets". Comment: outcome assessors probably blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was 30% and reasons for it were reported.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper
Other bias	Low risk	Comment: no other bias was identified

SUMMIT 2008

Methods	A double-blind cluster-randomised trial conducted at Lombok island of Indonesia. **Dates of study:** July 2001-April 2004
Participants	Pregnant women of any gestational age assessed by physical exam and reported LMP
Interventions	1. MMN group (n = 15,804)) received iron 30 mg, folic acid 400 mcg, vitamin A 800 mcg, D 200 IU, E 10 mg, C 70 mg, B1 1.4 mg, B6 1.9 mg, B12 2.6 mcg, zinc 15 mg, copper 2 mg, selenium 65 mcg, iodine 150 mcg and niacin 18 mg 2. Placebo group (n = 15,486) received iron 30 mg and folic acid 400 mcg
Outcomes	Early infant mortality (death within 12 weeks of birth), neonatal mortality (death within 28 days of birth), early neonatal mortality (death within 7 days of birth), late neonatal mortality (death between 7 and 28 days of birth), postneonatal mortality (death between 28 days and 12 weeks of birth), fetal loss, abortions (fetal loss before 28 weeks of gestation), still births (death between 28 weeks and before delivery), perinatal mortality (still birth or death within 7 days of birth), maternal mortality related to pregnancy up to 12 weeks postpartum, maternal cognition and mood, and child cognition (motor, cognitive and socioeconomic abilities) at 42 months of age.

SUMMIT 2008 *(Continued)*

	It should be noted that the data for SGA were obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
Notes	Women in both groups received supplements throughout pregnancy until 90 days postpartum. Intervention and placebo groups were comparable in terms of baseline characteristics. Study was stopped early due to insufficient funds **Declarations of interest:** the trial authors declared no conflict of interest. **Funding sources:** Turner Foundation, UNICEF, the Centre for Health and Human Development, and the United States Agency for International Development-Indonesia (grant no 497-G-00-01-00001-00)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before enrolment, midwife identification numbers were sequentially allocated to computer-generated, randomly permuted blocks of groups numbered one to eight, stratified by community health centre or village health clinic". Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "midwives at village health centres and community health centres were assigned midwife identification numbers" and "Before enrolment, midwife identification numbers were sequentially allocated to computer-generated, randomly permuted blocks of groups numbered one to eight, stratified by community health centre or village health clinic" Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All study scientists and personnel, government staff and enrolees were unaware of the allocation." and "The code to indicate which strip was IFA or MMN was known only by the manufacturing production manager and a quality control officer from UNICEF, Copenhagen, neither of whom had any connection to the study or its personnel". Comment: participants and caregivers were probably blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All study scientists and personnel, government staff and enrolees were unaware of the allocation." and "The code to indicate which strip was IFA or MMN was known only by the manufacturing production manager and a quality control officer from UNICEF, Copenhagen, neither of whom had any connection to the study or its personnel". Comment: outcome assessors were probably blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (25.2%) and attrition (5%) were reported along with their reasons.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper.
Other bias	Low risk	Comment: no other bias was identified, including cluster-design specific biases (recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomised trials).

Sunawang 2009

Methods	A cluster-randomised trial conducted in 2 subdistricts of Indramayu district of west Java province of Indonesia. **Dates of study:** May 2000-August 2003
Participants	Pregnant women irrespective of gestational age. Women suffering from diabetes mellitus, coronary heart disease and tuberculosis were excluded.
Interventions	1. Intervention group (n = 432) received RDA of 15 micronutrients according to the UNICEF/UNU/WHO recommended formula, including 30 mg of ferrous fumarate 2. Control group (n = 411) received ferrous sulphate 60 mg and folic acid 0.25 mg
Outcomes	Birthweight, birth length, head and chest circumference, Hb, serum ferritin, serum zinc, serum retinol and urinary Iodine, miscarriage, stillbirths, neonatal mortality It should be noted that the data for SGA were obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
Notes	Study groups were similar with respect to baseline characteristics. Supplements were given from the time of enrolment at 12-20 weeks' gestation and continued up to 30 days postpartum. **Declarations of interest:** not reported **Funding sources:** UNICEF Indonesia Office, Jakarta

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "We restructured the 157 hamlets into 160 dwelling clusters.", "these 160 clusters (and the pregnant women living within them) were randomly assigned into 4 blocks of 40 clusters each". Comment: method used for generating the randomisation sequence is not described in sufficient detail to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Comment:method used for allocation concealment is not described in sufficient detail to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "This study had a single-blind design, since the supplement for the treatment and control group looked different physically. However, participants residing in each cluster received the same supplement, so they were not aware that other participants from other clusters received a different supplement" Comment: study participants were blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: " This study had a single-blind design" Comment: blinding of outcome assessors probably not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (< 1%) and attrition (10.4%) were reported along with their reasons.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper.

Sunawang 2009 *(Continued)*

Other bias	Low risk	Comment: when considering cluster-design-specific biases, we found low risk of baseline imbalance, loss of clusters, and comparability with individually randomised trials. While participants may have been recruited after assignment of clusters (843 pregnant women enrolled after intensive surveillance), we found that this likely would not have led to recruitment bias because supplements were provided to both groups and pregnant women were similar (including mean gestational age at baseline). Any incorrect analysis was corrected by adjustment for clustering within data reported in this review.

Tofail 2008

Methods	The study was conducted in Matlab, a rural subdistrict in the east central plain of Bangladesh. **Dates of study:** November 2001-December 2003
Participants	Pregnant women with gestational age 6-8 weeks, Hb > equal to 80 g/L and no serious disease were eligible for enrolment.
Interventions	1. MMN group (n = 1224) received vitamin A 800 mcg, D 200 IU, E 10 mg, C 70 mg, B1 1.4 mg, B2 1.4 mg, niacin 18 mg, B6 1.9 mg, B12 2.6 mg, folic acid 400 mcg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 mcg and iodine 150 mcg 2. Other group received folic acid and iron (60 mg iron 400 mcg folic acid n = 1265 and 30 mg iron 400 mcg folic acid n = 1248)
Outcomes	Size at birth, gestational age at birth, perinatal mortality, maternal Hb at 30 weeks, birthweight, spontaneous abortions, infant mortality, motor development and behavioural development, infant micronutrient status, under 5 child mortality, BP and kidney function in children, child growth outcomes, and adverse effects It should be noted that the data for SGA were obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
Notes	Women were divided into 2 groups, that is, early food group and usual food group. Each food group was then divided into 3 subgroups of MMN and IFA groups. IFA given to all participants. There was no significant difference in baseline characteristics between randomisation groups. Maternal malnutrition was prevalent. Control group with 30 mg iron is included in this review. Data for child growth outcomes presented in a manner that precluded its inclusion in the analysis. Adverse effects included nausea (MMN supplementation 154/786, 30FeFA 126/763), vomiting (MMN 91/787, 30FeFA 54/762), loose motions (MMN 19/786, 30FeFA 18/763), heartburn (MMN 86/786, 30FeFA 83/763), and constipation (MMN 219/788, 30FeFA 227/762). Other trial (Gupta 2007) measuring this outcome presents data for all side-effects using a composite measure. Analyses for individual side-effects will be presented once additional trials are available. Cost data are published in Shaheen 2013 (see Tofail 2008 secondary reference). Stunting data relevant to this review are presented in Kahn 2013 (see Tofail 2008 secondary reference). The data for the Fe30F group are presented in Figure 1, a line graph, and we will contact the authors to clarify the exact numbers for inclusion in the next update. **Declarations of interest:** the trial authors declared no conflict of interest. **Funding sources:** The International Centre for Diarrheal Disease Research Bangladesh, the UK Medical Research Council, the Swedish Research Council, the UK Department for International Development, the Global Health Research Fund Japan, the Child Health and Nutrition Research Initiative, Uppsala University, the US Agency for International Development under the Cooperative Agreement #388-G-00-02-00125-00, the Australian International Development Agency, the Government of Bangladesh, the Canadian International Development Agency, The Kingdom of Saudi Arabia, the Government of

Tofail 2008 *(Continued)*

	the Netherlands, the Government of Sri Lanka, the Swedish International Development Cooperative Agency, and the Swiss Agency for Development and Cooperation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "individual randomisation was done in blocks of 12" and "After enrolment, women were randomly assigned to 6 intervention groups". Comment: method used for generating the randomisation sequence was not described in sufficient detail to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: method used for allocation concealment was not described in sufficient detail to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "pills were identical in appearance, and monthly supplies were provided in identical bottles", " the mothers were unaware of their micronutrient supplement" and "double masking was practiced" Comment: study participants and caregivers were blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "pills were identical in appearance, and monthly supplies were provided in identical bottles", "the testers were unaware of children's groups" and "double masking was practiced" Comment: outcome assessors were blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was (26%), reported along with their reasons.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper.
Other bias	Low risk	Comment: no other bias was identified.

West 2014

Methods	Community-based, cluster-randomised, double-blind trial to examine whether a daily antenatal and postnatal MMN supplement given to women will enhance newborn and infant survival and health and other birth outcomes in a rural setting in northwestern Bangladesh. **Dates of study:** January 2008-August 2012
Participants	Pregnant women, aged 12-45 years, consenting to participate were recruited (n = 45,000). Women not interviewed for consent within 12 consecutive weeks after being ascertained as pregnant by urine testing were excluded.
Interventions	1. Dietary supplement: MMN containing 15 micronutrients all at an RDA including: vitamin A (770 ug retinol equivalents, vitamin D (5 ug), vitamin E (15 mg), folic acid (600 ug), thiamin (1.4 mg), riboflavin (1.4 mg), niacin (18 mg), vitamin B-12 (2.6 mg), vitamin B-6 (1.9 mg), vitamin C (85 mg), iron (27 mg), zinc (12 mg), iodine (220 ug), copper (1000 ug), selenium (60 ug). 2. Control supplement contained iron (27 mg) - folic acid (600 ug) (providing the current standard of care during pregnancy). Mothers instructed to take 1 tablet per day, from the 1st trimester through 12 weeks postpartum.

West 2014 *(Continued)*

Outcomes	Infant mortality through 6 months of age, perinatal mortality, neonatal mortality, birth size (weight, length, circumferences), gestational age at birth, infant health outcomes, maternal morbidity, obstetric complications, body composition, nutritional status. Christian 2014, an additional report of this trial, reports length-for-age Z score and stunting at 1 and 3 months in an abstract.
Notes	The composition of the MMN supplement followed the UN MMN preparation, except with higher amounts as needed to meet the RDA from the Institute of Medicine. The substudy area was selected to be representative of the parent trial across a range of factors, including sociodemographic and geographic variations, which were evaluated during an earlier trial in the same area. **Declarations of interest:** Dr. West reported a grant from DSM awarded to the Program in Human Nutrition at Johns Hopkins Bloomberg School of Public Health and having given 2 scientific presentations in 2 consecutive years at DSM in Basel, Switzerland, with accommodations provided. Dr. Christian reported giving a presentation at DSM in Basel with accommodations provided. The other trial authors declared no conflict of interest. **Funding sources:** grant OPP614 (Global Controlof Micronutrient Deficiency) from the Bill and Melinda Gates Foundation and additional assistance was received from the Sight and Life Global Nutrition Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We used an in-house program (VBScript, Microsoft) that recognized 70 possible permutations for n=8 sectors and k=2 supplement allocations and 6 for the last block of n=4 sectors. Using this program, we randomized sectors within blocks to 1 of 2 codes such that each permutation had an equal probability of being chosen."
Allocation concealment (selection bias)	Low risk	Quote: "The resulting 2 lists of sectors were securely transmitted to field headquarters. One envelope with the code key was securely transmitted to the supplement producer and the other sealed in an envelope and secured at Johns Hopkins. At no time during the trial did study investigators or field or data management staff have access to the key."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double-masked", "Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)", "received daily supplementation, so treatment effect (still blinded due to the ongoing trial)" Comment: probably done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double-masked", "Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)", "received daily supplementation, so treatment effect (still blinded due to the ongoing trial)" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete information was not available as the main trial has not been published; however, attrition is reported to be < 20% (trial presentations).
Selective reporting (reporting bias)	Low risk	Comment: reports from the study are still being published

West 2014 *(Continued)*

Other bias	Low risk	Comment: no other bias was identified, including cluster-design specific biases (recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomised trials)

Zagre 2007

Methods	This study was a cluster-randomised, double-blind controlled programmatic study in rural Niger aiming to compare MMN supplementation versus iron and folic acid. **Dates of study:** not reported
Participants	Women residing in target villages and experiencing amenorrhoea for < 12 weeks were eligible for recruitment. All villages within the coverage of the 17 health centres of Mayahi district were included. Women with night blindness and/or signs of severe anaemia were excluded.
Interventions	1. MMN group (n = 1893) received vitamin A 800 mcg, D 200 IU, E 10 mg, C 70 mg, B1 1.4 mg, B2 1.4 mg, B3 18 mg, B6 1.9 mg, B12 2.6 mg, folic acid 400 mcg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 mcg, iodine 150 mcg. 2. Control (n = 1777) received IFA
Outcomes	Birthweight and incidence of LBW, miscarriage, stillbirth, maternal mortality It should be noted that the data for SGA were obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
Notes	Study participants received reproductive health services including malaria chemoprophylaxis, behaviour-change communication activities to increase awareness and adoption of better lifestyles (feeding and rest during pregnancy). Outreach prenatal care sessions were also conducted throughout intervention villages. Randomisation resulted in comparable groups for most baseline characteristics except for households and more preventive measures against malaria (more in MMN group) and less education and more poverty in IFA group. **Declarations of interest:** not reported **Funding sources:** UNICEF

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Villages - not individuals were randomly assigned to one treatment group or the other" Comment: method used for generating the randomisation sequence was not described in sufficient detail to permit judgement.
Allocation concealment (selection bias)	Unclear risk	Comment: method used for allocation concealment was not described to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Because the two supplements did not look identical and may have been recognizable, a coding system was put in place by the SONIPHAR pharmaceutical company in Niger. Six codes were assigned to the treatments: three for iron/folic acid and three for multimicronutrient supplements. SONIPHAR packaged the supplements in boxes with identical labelling except for the supplement code. Health workers, traditional midwives, and data collectors were

Zagre 2007 *(Continued)*

		informed that each supplement came in two sizes and colors, so that the code letter did not distinguish which supplement was used". Comment: participants and caregivers were probably blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Because the two supplements did not look identical and may have been recognizable, a coding system was put in place by the SONIPHAR pharmaceutical company in Niger. six codes were assigned to the treatments: three for iron/folic acid and three for multimicronutrient supplements. SONIPHAR packaged the supplements in boxes with identical labelling except for the supplement code. Health workers, traditional midwives, and data collectors were informed that each supplement came in two sizes and colors, so that the code letter did not distinguish which supplement was used". Comment: outcome assessors were probably blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition was 18%. Reasons for attrition were reported, and dropout was significantly higher in the MMN (25/1893 (1.3%)) versus IFA (8/1777 (0.5%)) group. Exclusion data were not reported.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper.
Other bias	Low risk	Comment: no other bias was identified, including cluster-design-specific biases (recruitment bias, baseline imbalance, loss of clusters, and comparability with individually randomised trials). Any incorrect analysis was corrected by adjustment for clustering within data reported in this review.

Zeng 2008

Methods	Community-based cluster-randomised trial conducted in 2 poor rural counties in Shaanxi province of north west China. **Dates of study:** August 2002-Feburary 2006
Participants	Pregnant women of < 28 weeks' gestation between August 2002 and January 2006. Pregnancy was confirmed using LMP and urine pregnancy test
Interventions	1. IFA group (n = 1912) received iron 60 mg and folic acid 0.4 mg 2. MMN group (n = 1899) received iron 30 mg, folic acid 0.4 mg, zinc 15 mg, copper 2 mg, selenium 0.65 mg, iodine 0.15 mg, vitamin A 0.8 mg, B1 1.4 mg, B2 1.4 mg, B6 1.9, B12 0.026 mg, D 0.05 mg, C 70 mg, E 10 mg, niacin 18 mg 3. Folic acid only group A (n = 2017) received folic acid 0.4 mg
Outcomes	Birthweight, LBW (< 2500 g), SGA (weight < 10 percentile for gestational age), preterm birth (< 37 weeks of gestation), very preterm birth (< 34 weeks of gestation), gestational age, birth length, head circumference, Hb, anaemia (Hb < 110 g/L in third trimester), neonatal deaths (death within 28 days of delivery), early neonatal deaths (death within 7 days of delivery), perinatal deaths (fetal death after 28 weeks of gestation plus early neonatal deaths); and mental and psychomotor development outcomes until 1 year of age by using the Bayley Scales of Infant Development, and growth outcomes (stunting, underweight, and wasting) in children in the first 30 months of life. It should be noted that the data for SGA were obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
Notes	For review purposes, we used the MMN and IFA groups. Intervention was administered until 6 weeks postpartum. Baseline characteristics at enrolment, and both cluster- and individual-level baseline

Zeng 2008 *(Continued)*

characteristics were balanced by treatment groups. Stunting, underweight, and wasting data presented as odds ratio and could not be included in the analysis.

Declarations of interest: MJD was consultant for UNICEF China UNICEF Pyongyang during the conduct of the trial. SC was nutrition consultant for UNICEF China from 2001-2002, and is now the liaison officer for UNICEF with the Ministry of Health.

Funding sources: United Nations Children's Fund (grant No YH101-H12/03) through a co-operative agreement between UNICEF and the Centers for Disease Control and Prevention, Atlanta, US, and the National Natural Science of Foundation of China (grant No 30271131), Beijing, China

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation schedule was generated off site with a pseudo-random number generator in SAS". Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation schedule was generated off site with a pseudo-random number generator in SAS version 6 (SAS Institute, Cary, NC). A treatment colour code was assigned to each village based on the treatment allocation schedule". Comment: probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind", "treatment colour code was assigned to each village based on the treatment allocation schedule. The treatment codes were opened only once all data had been collected and blinded analysis of the primary hypothesis was completed" and "were of identical appearance and packaged in blister packs" Comment: participants and caregivers were blinded to the treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "double blind", "treatment colour code was assigned to each village based on the treatment allocation schedule. The treatment codes were opened only once all data had been collected and blinded analysis of the primary hypothesis was completed" Comment: outcome assessors were blinded to the treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (4.8%) and attrition (2.3%) were reported along with their reasons
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper
Other bias	Low risk	Comment: no other bias was identified, including cluster-design-specific biases (recruitment bias, baseline imbalance, loss of clusters, and comparability with individually randomised trials). Investigators did not adjust for the cluster-randomised design in their sample size or outcome estimations, but this was corrected.

BMI: body mass index; **BP:** blood pressure; **CHW:** community health worker; **EPI:** Expanded Programme on Immunization; **FeFol:** iron folate; **Hb:** haemoglobin; **HIV-ve:** HIV-negative; **HIV+ve:** HIV-positive; **IF(A):** iron folic acid; **IU:** international unit; **IUGR:** intrauterine growth retardation; **LBW:** low birthweight; LGA: large-for-gestational age; **LMP:** last menstrual period; **LNS:** lipid-based nutrient supplement; **mcg:** microgram; **mg:** milligram; **Mg:** magnesium; **MMN:** multiple micronutrient; **PE:** protein energy; **RCT:** randomised controlled trial;

RDA: recommended daily allowance; **SAE:** serious adverse effects; **SGA:** small-for-gestational age; **UNICEF:** United Nations International Children's Emergency Fund; **UNU:** United Nations University; **WHO:** World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12616001449426	Protocol of a study that is not a RCT.
Agarwal 2012	Abstract only; similar micronutrients given for different durations.
Aguayo 2005	Not a RCT. Assessing acceptability of MMN supplements by pregnant and lactating women.
Ahn 2006	Comparing 2 MMN supplements.
An 2001	Compares different doses of iron (35 mg vs 60 mg).
Arsenault 2010	Includes HIV-1 positive women.
Asemi 2014	Single-blind trial comparing multivitamin vs multivitamin-mineral. Supplements differed in composition and dose.
Asemi 2015	Study population is women at high risk of pre-eclampsia.
Azami 2016	Study population is women with at least 1 risk factor for pre-eclampsia.
Beazley 2002	Assesses vitamin C and E supplementation only.
Bergmann 2006	Assesses docosahexaenoic acid and fructo-oligosaccharide.
Biswas 1984	Cross-over design, measuring only serum iron levels after single doses of different vitamin formulations.
Callaghan-Gillespie 2017	MMN is provided in the form of food supplements (fortified corn-soy blend).
Carrasco 1962	Study has assessed the impact of D-sorbitol on the absorption of MMNs in pregnant women.
Caulfield 1999	Only assesses zinc supplementation.
Chames 2002	Only assesses calcium supplementation.
Choudhury 2012	Comparing micronutrient powder (home fortification) containing iron, folic acid, vitamin C and zinc vs iron folic acid tablet to study impact on anaemia during pregnancy.
Christian 2009	Assesses the effectiveness of the standard of care (iron folic acid and single-dose mebendazole) for the treatment of severe anaemia (haemoglobin < 70 g/L) along with enhanced regimens.
Coles 2015	Investigators utilized a quasi-randomised method of allocation to intervention and control groups.
Cooper 2012	Evaluates periconceptional MMN supplementation only (no MMNs given during pregnancy) (same as Khulan 2012).
Czeizel 1996	Assesses periconceptional supplementation of 18 micronutrients against 4 micronutrients.
Dawson 1987	Assesses supplementation of 14 micronutrients against 11 micronutrients.
Dawson 1998	Assesses supplementation of different doses of 12 to 17 micronutrients.

Study	Reason for exclusion
Devi 2017	The study investigates the effect of supplemental high-quality protein (milk) and vitamin B12 on third-trimester methionine kinetics in pregnant women with low vitamin B12.
Dewey 2012	The study asesses the effect of LNS and child only micronutrient powder (MNP).
Dieckmann 1944	Fortification trial.
Fall 2006	This trial evaluates a micronutrient-rich snack containing vegetables, fruit, and milk.
Fawzi 1998	Includes pregnant women who are HIV-1 positive.
Fernald 2016	The study investigates the effect of various combined interventions including lipid-based supplementation on growth and development during pregnancy and early childhood. Does not study MMN supplements.
Feyi-Waboso 2005	Parenteral preparation.
Fleming 1986	Only assesses iron, folate and vitamin B in different combinations.
Godfrey 2017	Protocol of a study that investigates the effect of a micronutrient-enriched nutritional drink with probiotics and myo-inositol vs. a standard supplementation drink on the maintenance of healthy glucose metabolism in mothers and promotion of offspring health.
Goldenberg 1995	Only assesses zinc supplementation.
Gopalan 2004	Evaluates effect of soya oil.
Graham 2007	Study has looked at the impact of vitamin A fortified rice with and without iron and riboflavin supplementation in night-blinded women.
Guldholt 1991	Only assesses high-dose vs low-dose iron supplementation.
Gunaratna 2015	The study investigates the efficacy of pre-pregnancy multivitamins with IFA to reduce the prevalence of anemia during the periconceptional period.
Gupta 2007	Women with BMI < 18.5 and/or haemoglobin level of 7-9 g/dL were included.
Hambidge 2014	Protocol of a study comparing nutrition intervention (MMN fortified lipid-based supplement) in pre-conceptional and peri-conceptional stage.
Hillman 1963	Only assesses pyridoxine supplementation.
Hininger 2004	MMN supplement did not contain iron.
Holly 1955	Only assesses iron and cobalt supplementation.
Hossain 2014	Trial evaluates the effect of vitamin D supplementation. Both groups received iron and calcium.
Huang 2017	Protocol of a study that investigates at the effect of complex milk lipids and different maternal milk preparations during pregnancy.
Hunt 1983	Only assesses zinc supplementation.
Hunt 1985	Only assesses zinc supplementation.

Study	Reason for exclusion
Huybregts 2009	Assesses impact of balanced energy, protein dietary supplement.
Huynh 2017	The study compares maternal nutrient supplementation as a powder and breastfeeding support vs usual care (IFA).
Iannotti 2008	Only assesses zinc supplementation.
ICMR 2000	Assesses periconceptional supplementation of folic acid containing vitamins.
IRCT2015041321736N1	Protocol of a study that compares vitamin D injections every 2 weeks plus multi prenatal tablet including 400 units of vitamin D daily vs multi prenatal tablet only (control). Study population is women with vitamin D deficiency.
IRCT201704225623N109	Protocol of a study in which the study population is women with gestational diabetes.
ISRCTN83599025	Protocol of a study in which the intervention arm of the study includes pregnant women with nutrient deficiencies.
Itam 2003	Not a randomised trial.
Janmohamed 2016	This study assesses the effect of prenatal corn soya blend (CSB+) vs normal diet (control) on pregnancy outcomes.
Jarvenpaa 2007	Fortification trial.
Kabir 2009	This is the same cohort as Tofail 2008. However, all pregnant women were again randomised to breastfeeding counselling or a control (standard health message) group. Effect was evaluated on anthropometric outcomes in children.
Kable 2012	Trial in women consuming alcohol during pregnancy evaluating effect of MMNs in ameliorating the impact of prenatal alcohol exposure in infants.
Khavari 2014	The trial recruited HIV positive women.
Khulan 2012	Evaluates periconceptional MMN supplementation only (no MMNs given during pregnancy).
Kubik 2004	Original papers in Polish. Translated versions of the papers show that this study is not a randomised trial.
Kureishy 2017	Protocol of a study that assesses the effectiveness of food-based interventions: Wheat Soya Blend (WSB) for women during pregnancy and lactation, Wawa Mum for children 6-23 months, Micronutrient Powders (MNP) for children 24-59 months and Behaviour Change Communication vs. routine public health services (control) in preventing stunting in children under 5 years.
Kynast 1986	Study presented at a conference. Abstract does not indicate that it as a randomised trial.
Lanou 2014	Evaluated the effect of a lipid-based nutrient supplement LNS.
Leroy 2010	The study compares a traditional food assisted MCHN program vs a newly designed approach to prevent malnutrition in children.
Li 2014	The study evaluates the effect of supplementation with folic acid and milk.
Lindström 2011	Not an RCT of MMN versus iron and or folic acid. Describes prevalence of micronutrient deficiencies at baseline and its determinants.

Study	Reason for exclusion
Ling 1996	Evaluating the impact of traditional Chinese tonics with nutrients.
Lucia 2007	Evaluating impact of docosahexaenoic acid and fructo-oligosaccharide.
Ma 2008	Evaluating retinol and riboflavin supplementation.
Magon 2014	The trial evaluating the effect of use of fortified snacks during pregnancy. Both groups received the same micronutrients (i.e. iron, folic acid, beta-carotene, and calcium), however, the dose of micronutrients in the intervention group was higher than the control group.
Malvasi 2014	Study evaluating the effect of myoinositol, d-chiro inositol, folic acid and manganese during pregnancy on maternal blood pressure, glycaemic and cholesterol parameters. Inositol is not an essential nutrient.
Mardones 2007	Impact of fortification of fortified dairy product with polyunsaturated fatty acids.
Marya 1987	Only assesses calcium and vitamin D supplementation.
Mathan 1979	Assesses supplementation of vitamin C and protein.
Menon 1962	Not a RCT.
Merchant 2005	Includes pregnant women who are HIV-1 positive.
Merialdi 1999	Only assesses zinc supplementation.
Muslimatun 2001	Only assesses vitamin A supplementation.
Nakano 2010	The study assesses the effect of Chlorella tablets vs control (no supplements) on pregnancy anemia and pregnancy-induced hypertension. Does not study MMN supplements.
NCT01795131	Evaluated the effect of vitamin B12 only.
NCT02802566	Protocol of a study that investigates the efficacy of a BMI-based prenatal vitamin in decreasing markers of inflammation and oxidative stress in pregnancies complicated by obesity. Study population is obese (BMI > 30) women.
NCT02959125	Study population is women with anemia, mid upper arm circumference of less than 23.5 cm, or no weight gain
Nguyen 2012	Protocol of a study evaluating pre-conceptional MMN vs IFA supplements.
Nguyen 2017	The study compares a nutrition-focused Maternal, Neonatal, and Child Health (MNCH) program with a standard MNCH program.
Nossier 2015	Study population is women with low serum zinc level below the estimated median for gestational age.
Nwagha 2010	Micronutrients given via injection.
Ochoa-Brust 2007	Assesses impact of vitamin C only.
Olofin 2014	The trial included HIV-positive women.
Otoluwa 2017	Conference abstract; the study evaluates the effect MMN supplementation vs IFA in periconception period.

Study	Reason for exclusion
Park 1999	Semi-randomized study design does not satisfy the eligibility criteria of the review.
Patimah 2013	Not a randomised trial.
People's League 1946	Quasi-randomised trial. Women were divided into 2 groups by placing them alternately on separate lists.
Pezzack 2014	The study is a randomised cross-over trial that compares the fractional calcium absorption (FCA) from enteric coated (EC) calcium carbonate granules with non-EC granules in pregnant women.
Ramirez-Velez 2011	The comparator was not eligible. The control group received calcium in addition to ferrous sulphate and folic acid.
Robertson 1991	Only assesses zinc supplementation.
Rumiris 2006	Pregnant women with superoxidedismutase (SOD) levels below 1102 U/gHb included in the study.
Sachdeva 1993	Evaluated calcium supplementation.
Sagaonkar 2009	Comparison of 4 micronutrients with 3.
Salzano 2001	Evaluated supplementation with calcium and fatty acids (linoleic acid, mono and poly unsaturated fatty acids) vs control.
Schmidt 2001	Only assesses vitamin A supplementation.
Semba 2000	A trial of vitamin A supplementation in HIV-infected women.
Suharno 1993	Only assesses vitamin A supplementation.
Sun 2010	Quasi-randomised trial. Women were allocated to 4 groups in the order of enrolment.
Suprapto 2002	Only assesses vitamin A and riboflavin supplementation.
Taghizadeh 2014	Comparing 2 different MMN supplements (13 micronutrients vs 10 micronutrients).
Tanumihardjo 2002	Only assesses vitamin A and iron supplementation.
Tatala 2002	Fortification trial.
Thauvin 1992	Not a randomised trial.
Theobald 1937	MMN supplement did not contain iron.
Vadillo-Ortega 2011	Fortification trial
Webb 2009	Participants include HIV-positive women.
Wibowo 2012	Evaluating effect of milk fortified with different doses of minerals and vitamins.
Wijaya-Erhardt 2011	Evaluated weekly food provision (optimised diet) vs the control.
Wijaya-Erhardt 2014	Evaluated educational intervention using a pre-post design.

Study	Reason for exclusion
Young 2010	Study assessed the acceptability of a micronutrient powder (Sprinkles), a fortified food (Nutrivida), and tablets by the participants. All supplements has similar composition of micronutrients.
Zavaleta 2000	Only assesses zinc supplementation.

BMI: body mass index
IFA: iron and folic acid
LNS: lipid-based nutrient supplement
MMN: multiple micronutrient
RCT: randomised controlled trial
vs: versus

Characteristics of studies awaiting assessment *[ordered by study ID]*

Gathwala 2012

Methods	RCT
Participants	Pregnant women 12-14 weeks' gestation. Fetal malformation excluded. Total number randomised 560. Group denominators not stated
Interventions	MMN vs iron 100 mg and folic acid 500 mcg. MMN not described
Outcomes	Mean birthweight, LBW
Notes	No usable data due to missing group denominators. Trial authors contacted (g_gathwala@hotmail.com) in hopes of adding data in next update.

LBW: low birthweight; **MMN:** multiple micronutrient; **RCT:** randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT02190565

Trial name or title	Protocol identifier: NCT02190565 Supplementation with WellnessPack mama during pregnancy and lactation - a randomised double-blind, placebo-controlled study
Methods	Parallel, randomised, double-blind trial investigating food supplementation for the primary prevention of anaemia
Participants	Inclusion criteria: 1. Healthy pregnant women aged 18-40 years with a BMI above 18.5 and below 30 kg/m2 who visit prenatal clinics (midwife centres) to register 2. Nulliparous and multiparous women 3. The women must be able to understand verbal and written information in Swedish to give an informed consent to participate in the study Exclusion criteria: 1. Women < 18 or > 40 years old 2. Women with a BMI < 18.5 or > 30 kg/m2 3. Women with any form of anaemia as diagnosed at the first visit to the prenatal clinic 4. Women expecting ≥ 2 babies

NCT02190565 *(Continued)*

	5. Women who have undergone bariatric surgery 6. Women on medication with pharmaceuticals that could affect the result of the study, e.g. vitamin K antagonists 7. Women who are allergic to any of the components of WellnessPack mama, e.g. fish 8. Women who suffer from drug or alcohol abuse 9. Women who suffer from known severe eating disorders 10. Women who suffer from chronic diseases that could affect gastrointestinal absorption and metabolism 11. Women who want to continue or start using similar food supplements in addition to WellnessPack mama/placebo, unless recommended by a physician or midwife, will be excluded from the study Upon miscarriage or transfer to prenatal care specialist, the participant is excluded from the study.
Interventions	Placebo comparator: placebo Placebo consisting of 2 sham multivitamin and mineral tablets and 2 capsules of oil Active comparator: food supplement Food supplement consisting of fish oil (omega 3 fatty acids DHA and EPA) and multivitamin and mineral tablets with extra IFA Intervention: dietary supplement: food supplement
Outcomes	Primary outcome: prevalence of anaemia in active and placebo groups (time frame: pregnancy weeks 28-30) (Designated as safety issue: no) Blood will be analysed for Hb and ferritin values. We will compare how many women in each group (active vs placebo) are ordinated iron supplementation due to anaemia by mid-pregnancy. Secondary outcome: levels of nutritional biomarkers in maternal blood and breast milk (time frame: 6-10 weeks after delivery) (Designated as safety issue: no) Levels of nutritional biomarkers such as DHA and vitamin D in maternal blood and breast milk will be measured in active and placebo groups.
Starting date	October 2014-January 2016
Contact information	Professor Angelica Lindén Hirschberg: Angelica.Hirschberg.Linden@ki.se
Notes	Sudy sponsor: Oriflame Cosmetics AB. Collaborators: Karonlinska Institutet

NCT03287882

Trial name or title	Protocol identifier: NCT03287882 Prospective, cluster randomised effectiveness trial of multiple micronutrient supplementation and life skills education provided from preconception on health and nutrition outcomes of young, reproductive-age Pakistani women (15-24 years)
Methods	Parallel, randomised, double-blind trial investigating 1. impact of MMN supplementation from preconception and life skills education among women 15-18.9 years of age at enrolment on the prevalence of anaemia in a population setting 2. impact of MMN supplementation from preconception and life skills education among young women 15-24 years of age on the rate of LBW in a population setting
Participants	Inclusion criteria:

NCT03287882 *(Continued)*

	1. Minimum age at enrolment: 15 years 2. Maximum age at enrolment: 23 years 3. Any marital status 4. Intend to comply with study intervention and follow-up Exclusion criteria: 1. Women participating in other nutrition trials 2. Women who intend to leave the study area 3. Women who are already pregnant
Interventions	No Intervention: standard of care 1. Preconception period: none 2. Pregnancy period: daily iron (60 mg) and folic acid (400 µg) supplementation from confirmation of pregnancy; daily balanced energy protein supplements will additionally be provided to those participants who are underweight at the confirmation of pregnancy for the duration of the pregnancy 3. Postpartum period: daily iron and folic acid supplementation to 6 months postpartum Experimental: MMN supplementation (UNIMMAP composition) and life skills education 1. Preconception period: twice-weekly MMN supplementation and bi-monthly group session including life skill based education materials 2. Pregnancy period: daily MMN supplementation from confirmation of pregnancy; daily balanced energy protein supplements will additionally be provided to those participants who are underweight at the confirmation of pregnancy for the duration of the pregnancy 3. Postpartum period: daily MMN supplementation to 6 months postpartum
Outcomes	Primary outcomes: 1. anaemia status (time frame: 0, 12*, 24 months (*in subgroup only)) 2. LBW Secondary outcomes: 1. serum ferritin, serum transferrin receptor, hepcidin, serum retinol, serum 25(OH)D, alpha-glycolytic protein, C-reactive protein (women) (time frame: preconception (subgroup only): enrolment, 1 year, 2 years; pregnancy: 4-12 weeks, 32 weeks; postpartum: 1 week) 2. height (women) (time frame: preconception: enrolment, 6 months*, 1 year, 2 years (*in subgroup only); pregnancy: 4-12 weeks, 32 weeks; postpartum: 1 week, 6 months) 3. middle upper arm circumference (women) (time frame: preconception: enrolment, 6 months*, 1 year, 2 years (*in subgroup only); pregnancy: 4-12 weeks, 32 weeks; postpartum: 1 week, 6 months) 4. weight (women) (time frame: preconception: enrolment, 6 months*, 1 year, 2 years (*in subgroup only); pregnancy: 4-12 weeks, 32 weeks; postpartum: 1 week, 6 months) 5. gestational age (time frame: at birth) 6. preterm birth (time frame: at birth) 7. Stillbirth (time frame: at birth) 8. SGA (time frame: at birth) 9. birth size: length (time frame: within 24 hours of birth) 10. birth size: head circumference (time frame: within 24 hours of birth) 11. birth size: middle upper arm circumference (time frame: within 24 hours of birth) 12. birth size: weight (time frame: within 24 hours of birth) 13. birth defects (time frame: at birth) 14. infant growth: length (time frame: 1, 3, 6, 9, 12 months) 15. infant growth: head circumference (time frame: 1, 3, 6, 9, 12 months) 16. infant growth: middle upper arm circumference (time frame: 1, 3, 6, 9, 12 months)

NCT03287882 *(Continued)*

	17.infant growth: weight (time frame: 1, 3, 6, 9, 12 months) 18.age at marriage (time frame: enrolment, 1 year, 2 years) 19.completion of 10th grade education (time frame: enrolment, 1 year, 2 years) 20.use of sanitary pad during last menstrual period (time frame: enrolment, 1 year, 2 years) 21.dietary intake: 24-hour recall (subgroup of women) (time frame: preconception: enrolment; pregnancy: 4-12 weeks, 32 weeks)
Starting date	30 June 2017-30 April 2021
Contact information	Zulfiqar A Bhutta: zulfiqar.bhutta@aku.edu
Notes	

Sumarmi 2015

Trial name or title	Protocol identifier: TCTR20150614001 Preconceptional supplementation of multi micronutrients to improve maternal iron status and pregnancy outcomes: a randomized double blind community-based trial (Laduni)
Methods	Parallel, randomised, double-blind trial investigating the efficacy of MMN supplementation during preconception period on maternal iron status and pregnancy outcomes
Participants	Inclusion criteria: 1. Gender: female 2. Age limit: minimum 16 years, maximum 35 years 3. Not pregnant previously primigravida 4. Not suffering from chronic disease 5. Apparently healthy by physical examination and anamnese Exclusion criteria: 1. Initial Hb < 5g/dL
Interventions	Intervention: MMN group; participants received multinutrient capsule every 2 days, for 2-6 months before pregnancy and continued to receive multinutrient capsule daily during pregnancy (38 weeks). Comparator: placebo-IFA group; participants received placebo capsule every 2 days, for 2-6 months before pregnancy and received IFA daily during pregnancy (38 weeks)
Outcomes	Primary outcomes: birthweight, maternal iron status Secondary outcomes: maternal interleukin-12, maternal human placental lactogen, umbilical cord insulin-like growth factor-1
Starting date	21 March 2011-1 December 2014
Contact information	Sri Sumarmi: msrisumarmi@gmail.com
Notes	Asoociated conference abstract: Sumarmi 2017: Prolonging micronutrients supplementation 2-6 months prior to pregnancy significantly improves birthweight by increasing hPL production and controlling il-12 concentration: a randomised double blind controlled study

Tu 2013

Trial name or title	Effect of animal-source food supplement prior to and during pregnancy on birthweight and prematurity in rural Vietnam
Methods	Cluster-randomised trial recruiting women from 29 communes in Vietnam
Participants	Women recruited when registering for marriage
Interventions	1. Food supplement 5 days/week from marriage to term (˜18 months) 2. Food supplement 5 days/week from 16 weeks' gestation to term (˜5 months) 3. Routine prenatal care
Outcomes	The primary outcome is birthweight and the secondary outcome is the prevalence of prematurity. Other outcomes include maternal micronutrient status (iron, zinc, folic acid, vitamins A and B12), the incidence of infections; infant growth and infections from 0-6 months of age are also assessed. Maternal data and information are measured at recruitment, 16, and 34 weeks' gestation. Infant anthropometric status is measured at birth, 1, 3, and 6 months. Infant gestational age is assessed at birth to determine the prevalence of pre-term deliveries, and the mother's activity or physical work during pregnancy is also determined.
Starting date	Not stated
Contact information	N. Tu, Vietnam Nutrition Association, Hanoi, Vietnam. C. King, Children's Hospital Oakland Research Institute, Oakland, CA, USA
Notes	

BMI: body mass index; **DHA:** docosahexaenoic acid; **EPA:** eicosapentaenoic acid; **Hb:** haemoglobin; **IFA:** iron and folic acid; ITT: intention-to-treat; **LBW:** low birthweight; LNS: lipid-based nutrient supplement; mcg: microgram; **MMN:** multiple micronutrient; RDA: recommended daily allowance; SAE: serious adverse event; **SGA:** small-for-gestational-age

DATA AND ANALYSES

Comparison 1. Multiple micronutrients vs control

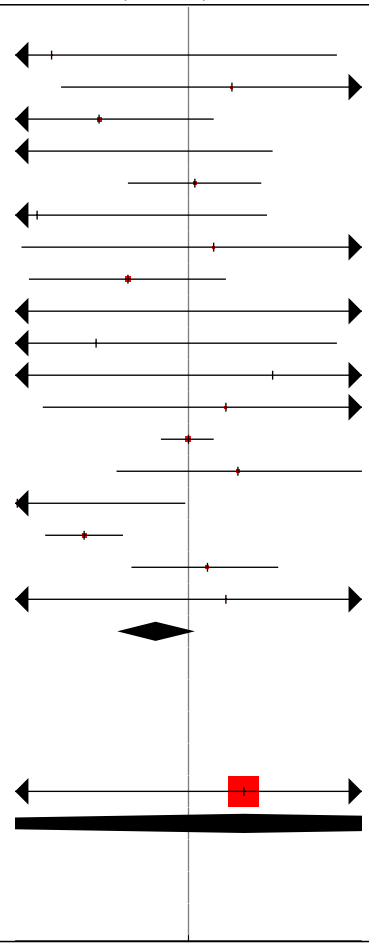
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm births	19		Risk Ratio (Random, 95% CI)	Subtotals only
1.1 MMN with iron and folic acid vs iron with or without folic acid	18		Risk Ratio (Random, 95% CI)	0.95 [0.90, 1.01]
1.2 MMN with iron and folic acid vs placebo	1		Risk Ratio (Random, 95% CI)	1.09 [0.43, 2.77]
2 Small-for-gestational age	18		Risk Ratio (Random, 95% CI)	Subtotals only
2.1 MMN with iron and folic acid vs iron with or without folic acid	17		Risk Ratio (Random, 95% CI)	0.92 [0.88, 0.97]
2.2 MMN with iron and folic acid vs placebo	1		Risk Ratio (Random, 95% CI)	0.94 [0.60, 1.48]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3 Low birthweight	19		Risk Ratio (Random, 95% CI)	Subtotals only
3.1 MMN with iron and folic acid vs iron with or without folic acid	18		Risk Ratio (Random, 95% CI)	0.88 [0.85, 0.91]
3.2 MMN with iron and folic acid vs placebo	1		Risk Ratio (Random, 95% CI)	1.58 [0.67, 3.72]
4 Perinatal mortality	15		Risk Ratio (Random, 95% CI)	Subtotals only
4.1 MMN with iron and folic acid vs iron with or without folic acid	15		Risk Ratio (Random, 95% CI)	1.00 [0.90, 1.11]
5 Stillbirths	17		Risk Ratio (Random, 95% CI)	Subtotals only
5.1 MMN with iron and folic acid vs iron with or without folic acid	17		Risk Ratio (Random, 95% CI)	0.95 [0.86, 1.04]
6 Neonatal mortality	14		Risk Ratio (Random, 95% CI)	Subtotals only
6.1 MMN with iron and folic acid vs iron with or without folic acid	14		Risk Ratio (Random, 95% CI)	1.00 [0.89, 1.12]
7 Maternal anaemia (third trimester Hb < 110 g/L)	10		Risk Ratio (Random, 95% CI)	Subtotals only
7.1 MMN with iron and folic acid vs iron with or without folic acid	9		Risk Ratio (Random, 95% CI)	1.04 [0.94, 1.15]
7.2 MMN with iron and folic acid vs placebo	1		Risk Ratio (Random, 95% CI)	0.66 [0.51, 0.85]
8 Maternal mortality	6		Risk Ratio (Random, 95% CI)	Subtotals only
8.1 MMN with iron and folic acid vs iron with or without folic acid	6		Risk Ratio (Random, 95% CI)	1.06 [0.72, 1.54]
9 Miscarriage (loss before 28 weeks)	12		Risk Ratio (Random, 95% CI)	Subtotals only
9.1 MMN with iron and folic acid vs iron with or without folic acid	12		Risk Ratio (Random, 95% CI)	0.99 [0.94, 1.04]
10 Mode of delivery: caesarean section	5		Risk Ratio (Random, 95% CI)	1.13 [0.99, 1.29]
10.1 MMN with iron and folic acid vs iron with or without folic acid	5		Risk Ratio (Random, 95% CI)	1.13 [0.99, 1.29]
11 Congenital anomalies	2		Risk Ratio (Random, 95% CI)	Subtotals only
11.1 MMN with iron and folic acid vs iron with or without folic acid	2		Risk Ratio (Random, 95% CI)	1.34 [0.25, 7.12]
12 Very preterm birth (before 34 weeks of gestation)	4		Risk Ratio (Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
12.1 MMN with iron and FA vs iron with or without folic acid	4		Risk Ratio (Random, 95% CI)	0.81 [0.71, 0.93]

Analysis 1.1. Comparison 1 Multiple micronutrients vs control, Outcome 1 Preterm births.

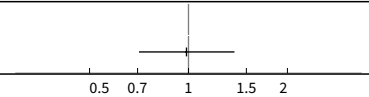
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 MMN with iron and folic acid vs iron with or without folic acid						
Ashorn 2010	0	0	-0.2 (0.228)		1.58%	0.81[0.52,1.26]
Bhutta 2009a	0	0	0.1 (0.136)		3.83%	1.07[0.82,1.4]
Christian 2003	0	0	-0.1 (0.09)		6.91%	0.87[0.73,1.04]
Dewey 2009	0	0	-0.4 (0.286)		1.03%	0.65[0.37,1.14]
Fawzi 2007	0	0	0 (0.053)		11.48%	1.01[0.91,1.12]
Friis 2004	0	0	-0.2 (0.185)		2.3%	0.79[0.55,1.13]
Kaestel 2005	0	0	0 (0.154)		3.13%	1.04[0.77,1.41]
Lui 2013	0	0	-0.1 (0.079)		8.04%	0.91[0.78,1.06]
Moore 2009	0	0	-0.4 (0.755)		0.16%	0.67[0.15,2.93]
Osrin 2005	0	0	-0.1 (0.191)		2.18%	0.87[0.6,1.26]
Ramakrishnan 2003	0	0	0.1 (0.288)		1.02%	1.14[0.65,2.01]
Roberfroid 2008	0	0	0.1 (0.144)		3.5%	1.06[0.8,1.4]
SUMMIT 2008	0	0	-0 (0.022)		16.41%	1[0.96,1.04]
Sunawang 2009	0	0	0.1 (0.098)		6.15%	1.08[0.89,1.31]
Tofail 2008	0	0	-0.3 (0.133)		3.95%	0.77[0.59,0.99]
West 2014	0	0	-0.2 (0.031)		15.1%	0.85[0.8,0.9]
Zagre 2007	0	0	0 (0.059)		10.64%	1.03[0.91,1.15]
Zeng 2008	0	0	0.1 (0.172)		2.59%	1.06[0.76,1.49]
Subtotal (95% CI)					**100%**	**0.95[0.9,1.01]**
Heterogeneity: Tau^2=0; Chi^2=33.16, df=17(P=0.01); I^2=48.73%						
Test for overall effect: Z=1.73(P=0.08)						
1.1.2 MMN with iron and folic acid vs placebo						
Brough 2010	0	0	0.1 (0.474)		100%	1.09[0.43,2.77]
Subtotal (95% CI)					**100%**	**1.09[0.43,2.77]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.19(P=0.85)						
Test for subgroup differences: Chi^2=0.09, df=1 (P=0.77), I^2=0%						



Favours MMN — Favours iron and/or folic

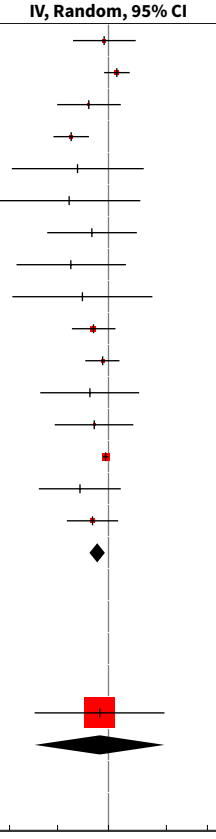
Analysis 1.2. Comparison 1 Multiple micronutrients vs control, Outcome 2 Small-for-gestational age.

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 MMN with iron and folic acid vs iron with or without folic acid						
Ashorn 2010	0	0	-0 (0.17)		2.35%	0.99[0.71,1.38]



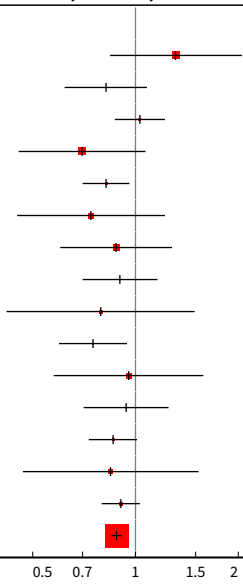
Favours MMN — Favours iron and/or folic

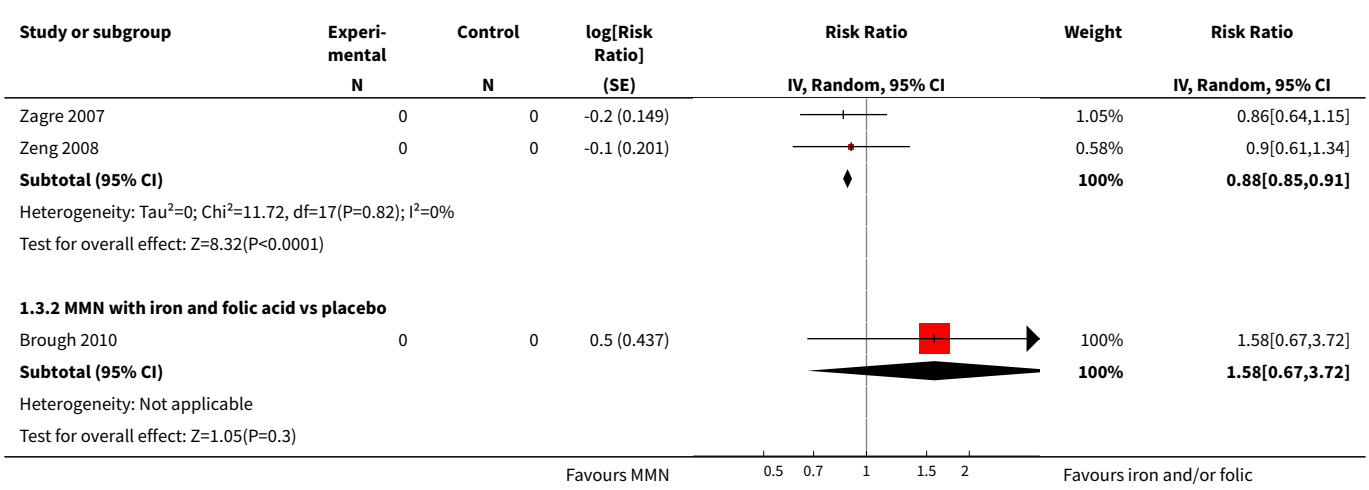
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Bhutta 2009a	0	0	-0 (0.111)		4.81%	0.97[0.78,1.21]
Christian 2003	0	0	0.1 (0.045)		14.11%	1.06[0.97,1.16]
Dewey 2009	0	0	-0.1 (0.113)		4.67%	0.87[0.7,1.09]
Fawzi 2007	0	0	-0.3 (0.063)		10.31%	0.77[0.68,0.87]
Friis 2004	0	0	-0.2 (0.236)		1.28%	0.81[0.51,1.28]
Kaestel 2005	0	0	-0.3 (0.255)		1.1%	0.76[0.46,1.25]
Moore 2009	0	0	-0.1 (0.16)		2.61%	0.89[0.65,1.22]
Osrin 2005	0	0	-0.3 (0.195)		1.83%	0.77[0.52,1.13]
Ramakrishnan 2003	0	0	-0.2 (0.25)		1.15%	0.83[0.51,1.36]
Roberfroid 2008	0	0	-0.1 (0.077)		8.14%	0.9[0.77,1.05]
SUMMIT 2008	0	0	-0 (0.062)		10.54%	0.96[0.85,1.08]
Sunawang 2009	0	0	-0.1 (0.178)		2.15%	0.88[0.62,1.24]
Tofail 2008	0	0	-0.1 (0.141)		3.25%	0.9[0.69,1.19]
West 2014	0	0	-0 (0.011)		22.2%	0.98[0.96,1]
Zagre 2007	0	0	-0.2 (0.147)		3.01%	0.82[0.61,1.09]
Zeng 2008	0	0	-0.1 (0.091)		6.48%	0.89[0.75,1.07]
Subtotal (95% CI)					**100%**	**0.92[0.88,0.97]**
Heterogeneity: Tau^2=0; Chi^2=26.25, df=16(P=0.05); I^2=39.05%						
Test for overall effect: Z=2.9(P=0)						
1.2.2 MMN with iron and folic acid vs placebo						
Brough 2010	0	0	-0.1 (0.233)		100%	0.94[0.6,1.48]
Subtotal (95% CI)					**100%**	**0.94[0.6,1.48]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%						
Test for overall effect: Z=0.26(P=0.79)						



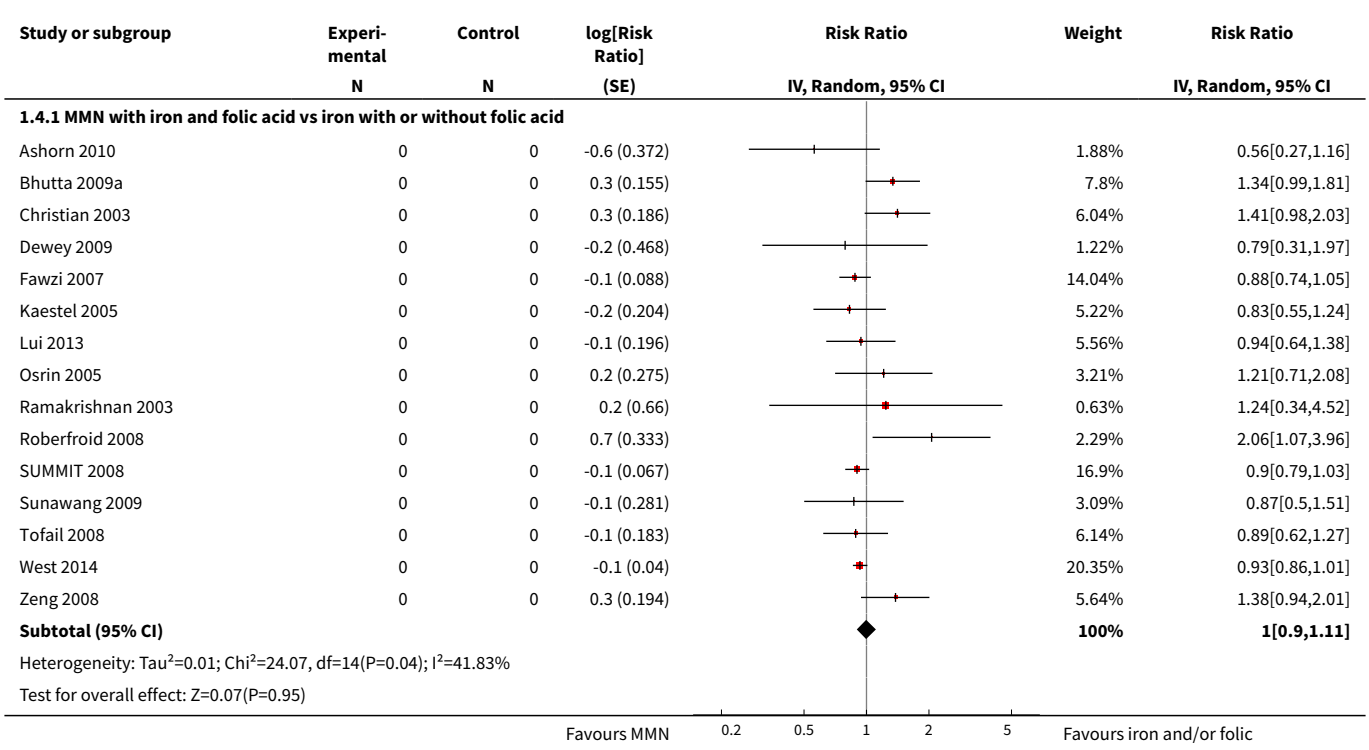
Analysis 1.3. Comparison 1 Multiple micronutrients vs control, Outcome 3 Low birthweight.

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.3.1 MMN with iron and folic acid vs iron with or without folic acid						
Ashorn 2010	0	0	0.3 (0.227)		0.46%	1.31[0.84,2.05]
Bhutta 2009a	0	0	-0.2 (0.143)		1.15%	0.82[0.62,1.08]
Christian 2003	0	0	0 (0.086)		3.16%	1.03[0.87,1.22]
Dewey 2009	0	0	-0.4 (0.218)		0.49%	0.7[0.45,1.07]
Fawzi 2007	0	0	-0.2 (0.081)		3.59%	0.82[0.7,0.96]
Friis 2004	0	0	-0.3 (0.254)		0.36%	0.74[0.45,1.22]
Kaestel 2005	0	0	-0.1 (0.192)		0.63%	0.88[0.6,1.28]
Lui 2013	0	0	-0.1 (0.128)		1.42%	0.9[0.7,1.16]
Moore 2009	0	0	-0.2 (0.324)		0.22%	0.79[0.42,1.49]
Osrin 2005	0	0	-0.3 (0.117)		1.72%	0.75[0.6,0.94]
Ramakrishnan 2003	0	0	-0 (0.258)		0.35%	0.96[0.58,1.58]
Roberfroid 2008	0	0	-0.1 (0.146)		1.09%	0.94[0.71,1.25]
SUMMIT 2008	0	0	-0.2 (0.084)		3.35%	0.86[0.73,1.01]
Sunawang 2009	0	0	-0.2 (0.302)		0.26%	0.85[0.47,1.53]
Tofail 2008	0	0	-0.1 (0.066)		5.45%	0.91[0.8,1.03]
West 2014	0	0	-0.1 (0.018)		74.66%	0.88[0.85,0.91]

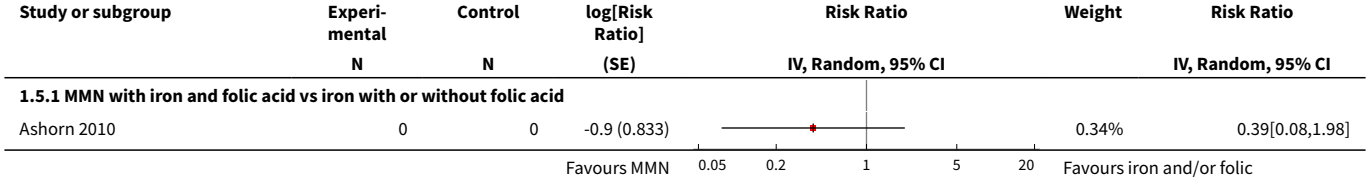




Analysis 1.4. Comparison 1 Multiple micronutrients vs control, Outcome 4 Perinatal mortality.



Analysis 1.5. Comparison 1 Multiple micronutrients vs control, Outcome 5 Stillbirths.



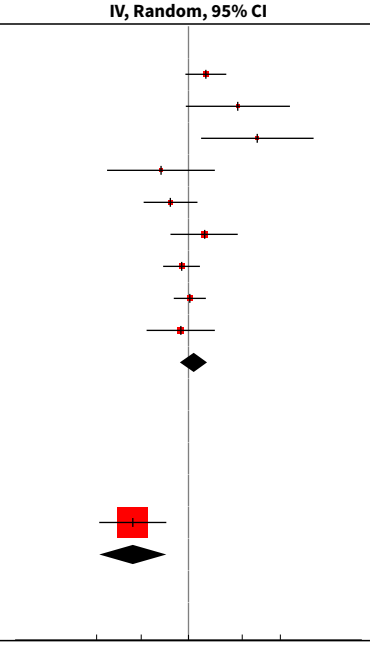
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Bhutta 2009a	0	0	0.1 (0.211)		4.85%	1.15[0.76,1.74]
Christian 2003	0	0	0.4 (0.251)		3.53%	1.44[0.88,2.36]
Dewey 2009	0	0	-0.3 (0.498)		0.94%	0.77[0.29,2.04]
Fawzi 2007	0	0	-0.2 (0.115)		13.41%	0.84[0.67,1.05]
Friis 2004	0	0	0.7 (0.863)		0.32%	1.98[0.37,10.76]
Kaestel 2005	0	0	-0.5 (0.287)		2.75%	0.64[0.36,1.12]
Lui 2013	0	0	-0.1 (0.268)		3.12%	0.93[0.55,1.57]
Osrin 2005	0	0	-0.2 (0.345)		1.93%	0.83[0.42,1.63]
Ramakrishnan 2003	0	0	0.2 (0.666)		0.53%	1.24[0.34,4.59]
Roberfroid 2008	0	0	0.8 (0.421)		1.31%	2.24[0.98,5.1]
SUMMIT 2008	0	0	-0.1 (0.093)		18.19%	0.9[0.75,1.08]
Sunawang 2009	0	0	-0.1 (0.529)		0.84%	0.91[0.32,2.56]
Tofail 2008	0	0	-0.1 (0.258)		3.37%	0.92[0.56,1.53]
West 2014	0	0	-0.1 (0.048)		35.22%	0.89[0.81,0.98]
Zagre 2007	0	0	0.2 (0.215)		4.7%	1.18[0.77,1.79]
Zeng 2008	0	0	0.3 (0.217)		4.64%	1.35[0.88,2.06]
Subtotal (95% CI)					**100%**	**0.95[0.86,1.04]**
Heterogeneity: Tau^2=0; Chi^2=18.24, df=16(P=0.31); I^2=12.27%						
Test for overall effect: Z=1.15(P=0.25)						

Analysis 1.6. Comparison 1 Multiple micronutrients vs control, Outcome 6 Neonatal mortality.

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.6.1 MMN with iron and folic acid vs iron with or without folic acid						
Ashorn 2010	0	0	-0.5 (0.396)		2.12%	0.6[0.28,1.3]
Bhutta 2009a	0	0	0.4 (0.212)		6.53%	1.44[0.95,2.18]
Christian 2003	0	0	0.4 (0.241)		5.27%	1.49[0.93,2.39]
Dewey 2009	0	0	0.7 (1.223)		0.23%	1.97[0.18,21.65]
Fawzi 2007	0	0	-0.1 (0.133)		13.22%	0.87[0.67,1.13]
Kaestel 2005	0	0	0.2 (0.283)		3.95%	1.17[0.67,2.03]
Lui 2013	0	0	-0.2 (0.256)		4.71%	0.81[0.49,1.34]
Osrin 2005	0	0	0.4 (0.382)		2.27%	1.53[0.72,3.23]
Roberfroid 2008	0	0	0.7 (0.497)		1.38%	2.02[0.76,5.35]
SUMMIT 2008	0	0	-0.1 (0.086)		21.62%	0.9[0.76,1.07]
Sunawang 2009	0	0	-0.7 (0.436)		1.77%	0.52[0.22,1.22]
Tofail 2008	0	0	0 (0.247)		5.05%	1.02[0.63,1.65]
West 2014	0	0	-0 (0.055)		29.71%	0.98[0.88,1.09]
Zeng 2008	0	0	0.2 (0.391)		2.17%	1.19[0.55,2.56]
Subtotal (95% CI)					**100%**	**1[0.89,1.12]**
Heterogeneity: Tau^2=0.01; Chi^2=16.76, df=13(P=0.21); I^2=22.44%						
Test for overall effect: Z=0.05(P=0.96)						

Analysis 1.7. Comparison 1 Multiple micronutrients vs control, Outcome 7 Maternal anaemia (third trimester Hb < 110 g/L).

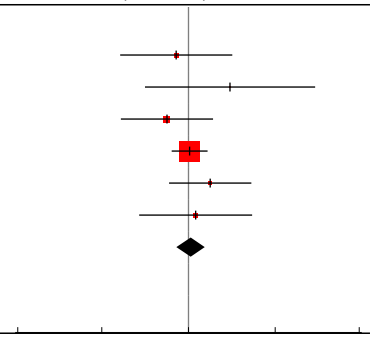
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.7.1 MMN with iron and folic acid vs iron with or without folic acid						
Ashorn 2010	0	0	0.1 (0.079)		16.13%	1.14[0.98,1.33]
Christian 2003	0	0	0.4 (0.2)		5.41%	1.45[0.98,2.15]
Dewey 2009	0	0	0.5 (0.216)		4.78%	1.68[1.1,2.57]
Moore 2009	0	0	-0.2 (0.208)		5.1%	0.81[0.54,1.22]
Osrin 2005	0	0	-0.1 (0.102)		12.92%	0.87[0.71,1.07]
Ramakrishnan 2003	0	0	0.1 (0.13)		9.95%	1.13[0.87,1.45]
Roberfroid 2008	0	0	-0.1 (0.072)		17.26%	0.95[0.83,1.09]
West 2014	0	0	0 (0.062)		18.7%	1.01[0.89,1.14]
Zeng 2008	0	0	-0.1 (0.132)		9.74%	0.94[0.73,1.22]
Subtotal (95% CI)					**100%**	**1.04[0.94,1.15]**
Heterogeneity: Tau²=0.01; Chi²=15.9, df=8(P=0.04); I²=49.7%						
Test for overall effect: Z=0.71(P=0.48)						
1.7.2 MMN with iron and folic acid vs placebo						
Brough 2010	0	0	-0.4 (0.129)		100%	0.66[0.51,0.85]
Subtotal (95% CI)					**100%**	**0.66[0.51,0.85]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.25(P=0)						



Favours MMN — Favours iron and/or folic

Analysis 1.8. Comparison 1 Multiple micronutrients vs control, Outcome 8 Maternal mortality.

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.8.1 MMN with iron and folic acid vs iron with or without folic acid						
Ashorn 2010	0	0	-0.3 (0.76)		6.42%	0.72[0.16,3.2]
Dewey 2009	0	0	1.1 (1.153)		2.79%	3.01[0.31,28.86]
Kaestel 2005	0	0	-0.6 (0.624)		9.54%	0.56[0.17,1.92]
SUMMIT 2008	0	0	0 (0.243)		62.98%	1.03[0.64,1.66]
West 2014	0	0	0.6 (0.558)		11.93%	1.78[0.6,5.31]
Zagre 2007	0	0	0.2 (0.765)		6.34%	1.21[0.27,5.42]
Subtotal (95% CI)					**100%**	**1.06[0.72,1.54]**
Heterogeneity: Tau²=0; Chi²=3, df=5(P=0.7); I²=0%						
Test for overall effect: Z=0.28(P=0.78)						



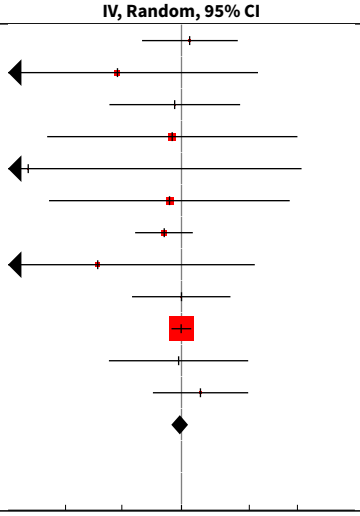
Favours MMN — Favours iron and/or folic

Analysis 1.9. Comparison 1 Multiple micronutrients vs control, Outcome 9 Miscarriage (loss before 28 weeks).

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.9.1 MMN with iron and folic acid vs iron with or without folic acid						

Favours MMN — Favours iron and/or folic

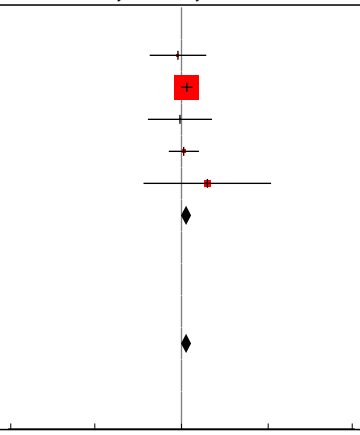
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Bhutta 2009a	0	0	0 (0.145)		3.19%	1.05[0.79,1.4]
Dewey 2009	0	0	-0.4 (0.427)		0.37%	0.68[0.3,1.58]
Fawzi 2007	0	0	-0 (0.199)		1.7%	0.96[0.65,1.42]
Kaestel 2005	0	0	-0.1 (0.381)		0.46%	0.95[0.45,2]
Osrin 2005	0	0	-0.9 (0.835)		0.1%	0.4[0.08,2.05]
Roberfroid 2008	0	0	-0.1 (0.368)		0.5%	0.93[0.45,1.91]
SUMMIT 2008	0	0	-0.1 (0.089)		8.51%	0.9[0.76,1.07]
Sunawang 2009	0	0	-0.5 (0.478)		0.29%	0.61[0.24,1.55]
Tofail 2008	0	0	0 (0.151)		2.96%	1[0.74,1.34]
West 2014	0	0	-0 (0.03)		77.28%	1[0.94,1.06]
Zagre 2007	0	0	-0 (0.213)		1.49%	0.98[0.65,1.49]
Zeng 2008	0	0	0.1 (0.146)		3.16%	1.12[0.84,1.49]
Subtotal (95% CI)					**100%**	**0.99[0.94,1.04]**
Heterogeneity: Tau²=0; Chi²=5.14, df=11(P=0.92); I²=0%						
Test for overall effect: Z=0.39(P=0.69)						



Favours MMN — Favours iron and/or folic

Analysis 1.10. Comparison 1 Multiple micronutrients vs control, Outcome 10 Mode of delivery: caesarean section.

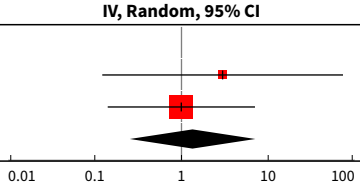
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.10.1 MMN with iron and folic acid vs iron with or without folic acid						
Bhutta 2009a	0	0	-0.1 (0.383)		3.27%	0.91[0.43,1.93]
Fawzi 2007	0	0	0.1 (0.076)		82%	1.15[0.99,1.34]
Friis 2004	0	0	-0 (0.434)		2.54%	0.96[0.41,2.25]
Osrin 2005	0	0	0.1 (0.204)		11.55%	1.06[0.71,1.59]
Roberfroid 2008	0	0	0.7 (0.864)		0.64%	1.99[0.37,10.81]
Subtotal (95% CI)					**100%**	**1.13[0.99,1.29]**
Heterogeneity: Tau²=0; Chi²=1.03, df=4(P=0.91); I²=0%						
Test for overall effect: Z=1.76(P=0.08)						
Total (95% CI)					**100%**	**1.13[0.99,1.29]**
Heterogeneity: Tau²=0; Chi²=1.03, df=4(P=0.91); I²=0%						
Test for overall effect: Z=1.76(P=0.08)						



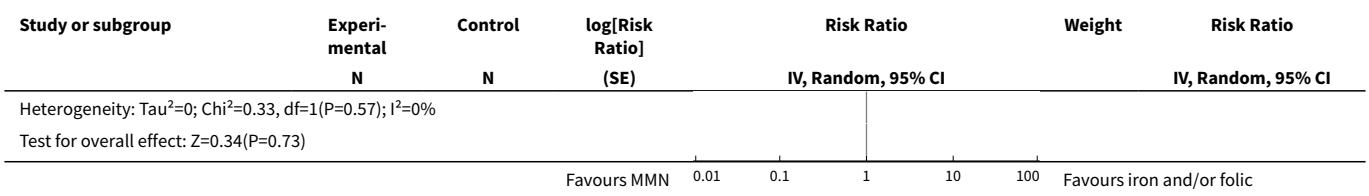
Favours MMN — Favours iron and/or folic

Analysis 1.11. Comparison 1 Multiple micronutrients vs control, Outcome 11 Congenital anomalies.

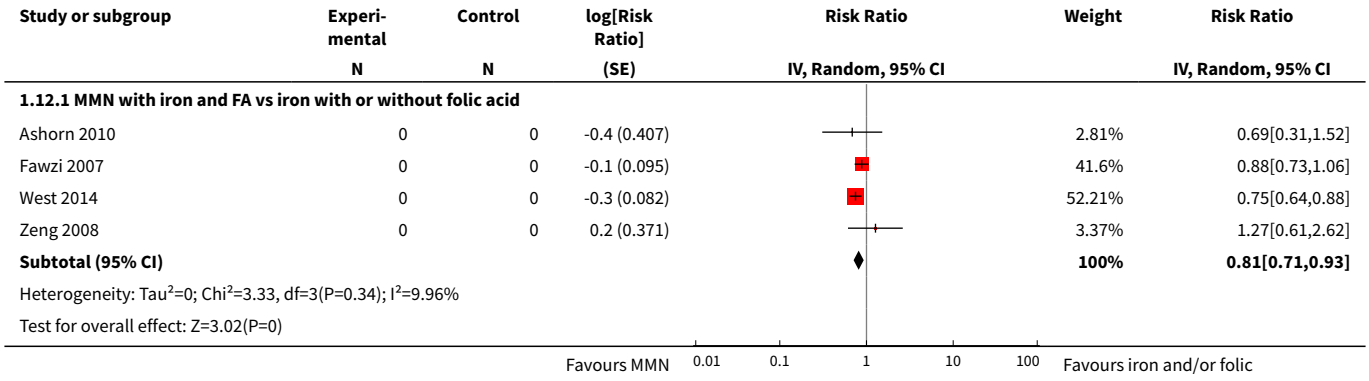
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
1.11.1 MMN with iron and folic acid vs iron with or without folic acid						
Dewey 2009	0	0	1.1 (1.631)		27.24%	2.98[0.12,72.88]
Osrin 2005	0	0	-0 (0.998)		72.76%	0.99[0.14,7.04]
Subtotal (95% CI)					**100%**	**1.34[0.25,7.12]**



Favours MMN — Favours iron and/or folic



Analysis 1.12. Comparison 1 Multiple micronutrients vs control, Outcome 12 Very preterm birth (before 34 weeks of gestation).



Comparison 2. Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid))

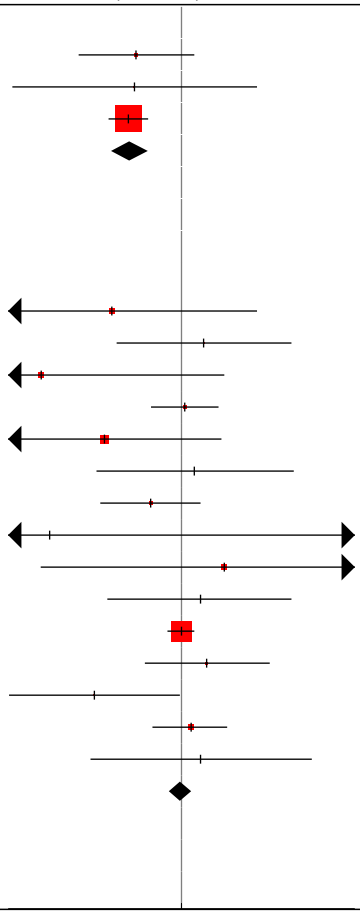
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm births: mean maternal BMI	18		Risk Ratio (Random, 95% CI)	Subtotals only
1.1 BMI < 20 kg/m^2	3		Risk Ratio (Random, 95% CI)	0.85 [0.81, 0.90]
1.2 BMI ≥ 20 kg/m^2	15		Risk Ratio (Random, 95% CI)	0.99 [0.96, 1.03]
2 Preterm births: mean maternal height	18		Risk Ratio (Random, 95% CI)	Subtotals only
2.1 Maternal height < 154.9 cm	8		Risk Ratio (Random, 95% CI)	0.93 [0.85, 1.03]
2.2 Maternal height ≥ 154.9 cm	10		Risk Ratio (Random, 95% CI)	0.99 [0.93, 1.05]
3 Preterm births: timing of supplementation	18		Risk Ratio (Random, 95% CI)	Subtotals only
3.1 Supplementation started before 20 weeks	14		Risk Ratio (Random, 95% CI)	0.93 [0.87, 1.00]
3.2 Supplementation after 20 weeks	4		Risk Ratio (Random, 95% CI)	1.00 [0.96, 1.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Preterm births: dose of iron	19		Risk Ratio (Random, 95% CI)	Subtotals only
4.1 MMN with 30 mg iron vs. supplement with 60 mg iron	6		Risk Ratio (Random, 95% CI)	1.05 [0.94, 1.17]
4.2 MMN with 60 mg iron vs. supplement with 60 mg iron	5		Risk Ratio (Random, 95% CI)	0.96 [0.88, 1.05]
4.3 MMN with 30 mg iron vs. supplement with 30 mg iron	5		Risk Ratio (Random, 95% CI)	0.92 [0.84, 1.02]
4.4 MMN with 15-20 mg iron vs. supplement with 60 mg iron	3		Risk Ratio (Random, 95% CI)	0.90 [0.64, 1.27]
5 Preterm births: MMN supplement formulation	18		Risk Ratio (Random, 95% CI)	Subtotals only
5.1 UNIMMAP formulation	10		Risk Ratio (Random, 95% CI)	1.00 [0.96, 1.03]
5.2 Non-UNIMMAP formulation	8		Risk Ratio (Random, 95% CI)	0.89 [0.82, 0.98]
6 Small-for-gestational age: mean maternal BMI	17		Risk Ratio (Random, 95% CI)	Subtotals only
6.1 BMI < 20 kg/m^2	3		Risk Ratio (Random, 95% CI)	1.00 [0.92, 1.08]
6.2 BMI ≥ 20 kg/m^2	14		Risk Ratio (Random, 95% CI)	0.88 [0.83, 0.93]
7 Small-for-gestational age: mean maternal height	17		Risk Ratio (Random, 95% CI)	Subtotals only
7.1 Maternal height < 154.9 cm	8		Risk Ratio (Random, 95% CI)	0.98 [0.96, 1.00]
7.2 Maternal height ≥ 154.9 cm	9		Risk Ratio (Random, 95% CI)	0.85 [0.79, 0.91]
8 Small-for-gestational age: timing of supplementation	17		Risk Ratio (Random, 95% CI)	Subtotals only
8.1 Supplementation started before 20 weeks	13		Risk Ratio (Random, 95% CI)	0.98 [0.96, 1.00]
8.2 Supplementation after 20 weeks	4		Risk Ratio (Random, 95% CI)	0.85 [0.72, 0.99]
9 Small-for-gestational age: dose of iron	17		Risk Ratio (Random, 95% CI)	Subtotals only
9.1 MMN with 30 mg iron vs. supplement with 60 mg iron	7		Risk Ratio (Random, 95% CI)	0.89 [0.81, 0.97]
9.2 MMN with 60 mg iron vs. supplement with 60 mg iron	5		Risk Ratio (Random, 95% CI)	0.88 [0.72, 1.08]
9.3 MMN with 30 mg iron vs. supplement with 30 mg iron	3		Risk Ratio (Random, 95% CI)	0.98 [0.96, 1.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.4 MMN with 20 mg iron vs. supplement with 60 mg iron	2		Risk Ratio (Random, 95% CI)	0.91 [0.75, 1.09]
10 Small-for-gestational age: MMN supplement formulation	17		Risk Ratio (Random, 95% CI)	Subtotals only
10.1 UNIMMAP formulation	9		Risk Ratio (Random, 95% CI)	0.91 [0.85, 0.98]
10.2 Non-UNIMMAP formulation	8		Risk Ratio (Random, 95% CI)	0.92 [0.84, 1.01]
11 Perinatal mortality: mean maternal BMI	15		Risk Ratio (Random, 95% CI)	Subtotals only
11.1 BMI < 20 kg/m^2	3		Risk Ratio (Random, 95% CI)	1.11 [0.82, 1.50]
11.2 BMI ≥ 20 kg/m^2	12		Risk Ratio (Random, 95% CI)	0.98 [0.86, 1.13]
12 Perinatal mortality: mean maternal height	15		Risk Ratio (Random, 95% CI)	Subtotals only
12.1 Maternal height < 154.9 cm	8		Risk Ratio (Random, 95% CI)	1.00 [0.89, 1.13]
12.2 Maternal height ≥ 154.9 cm	7		Risk Ratio (Random, 95% CI)	0.99 [0.78, 1.25]
13 Perinatal mortality: timing of supplementation	15		Risk Ratio (Random, 95% CI)	Subtotals only
13.1 Supplementation before 20 weeks	12		Risk Ratio (Random, 95% CI)	1.09 [0.92, 1.27]
13.2 Supplementation after 20 weeks	3		Risk Ratio (Random, 95% CI)	0.89 [0.80, 0.98]
14 Perinatal mortality: dose of iron	15		Risk Ratio (Random, 95% CI)	Subtotals only
14.1 MMN with 30 mg iron vs. supplement with 60 mg iron	6		Risk Ratio (Random, 95% CI)	1.20 [0.95, 1.51]
14.2 MMN with 60 mg iron vs. supplement with 60 mg iron	3		Risk Ratio (Random, 95% CI)	1.09 [0.74, 1.60]
14.3 MMN with 30 mg iron vs. supplement with 30 mg iron	4		Risk Ratio (Random, 95% CI)	0.92 [0.86, 0.98]
14.4 MMN with 20 mg iron vs. supplement with 60 mg iron	2		Risk Ratio (Random, 95% CI)	0.64 [0.36, 1.13]
15 Perinatal mortality: MMN supplement formulation	15		Risk Ratio (Random, 95% CI)	Subtotals only
15.1 UNIMMAP formulation	9		Risk Ratio (Random, 95% CI)	1.06 [0.89, 1.25]
15.2 Non-UNIMMAP formulation	6		Risk Ratio (Random, 95% CI)	0.94 [0.82, 1.09]

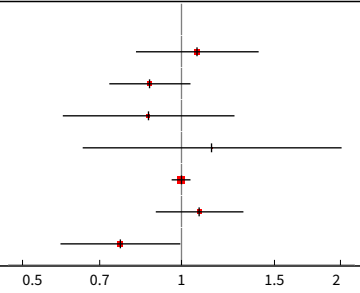
Analysis 2.1. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 1 Preterm births: mean maternal BMI.

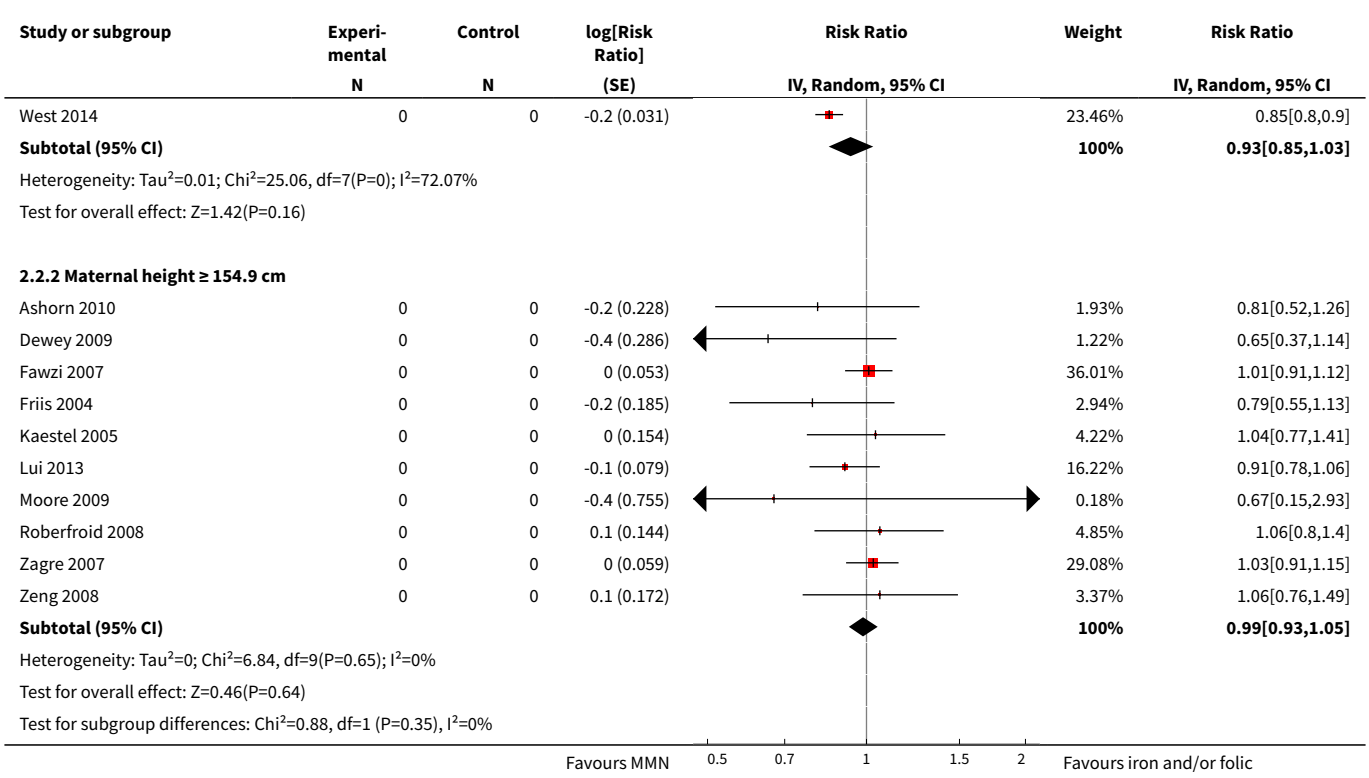
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 BMI < 20 kg/m2						
Christian 2003	0	0	-0.1 (0.09)		10.41%	0.87[0.73,1.04]
Osrin 2005	0	0	-0.1 (0.191)		2.3%	0.87[0.6,1.26]
West 2014	0	0	-0.2 (0.031)		87.3%	0.85[0.8,0.9]
Subtotal (95% CI)					**100%**	**0.85[0.81,0.9]**
Heterogeneity: Tau²=0; Chi²=0.07, df=2(P=0.97); I²=0%						
Test for overall effect: Z=5.53(P<0.0001)						
2.1.2 BMI ≥ 20 kg/m2						
Ashorn 2010	0	0	-0.2 (0.228)		0.58%	0.81[0.52,1.26]
Bhutta 2009a	0	0	0.1 (0.136)		1.64%	1.07[0.82,1.4]
Dewey 2009	0	0	-0.4 (0.286)		0.37%	0.65[0.37,1.14]
Fawzi 2007	0	0	0 (0.053)		10.86%	1.01[0.91,1.12]
Friis 2004	0	0	-0.2 (0.185)		0.89%	0.79[0.55,1.13]
Kaestel 2005	0	0	0 (0.154)		1.27%	1.04[0.77,1.41]
Lui 2013	0	0	-0.1 (0.079)		4.89%	0.91[0.78,1.06]
Moore 2009	0	0	-0.4 (0.755)		0.05%	0.67[0.15,2.93]
Ramakrishnan 2003	0	0	0.1 (0.288)		0.36%	1.14[0.65,2.01]
Roberfroid 2008	0	0	0.1 (0.144)		1.46%	1.06[0.8,1.4]
SUMMIT 2008	0	0	-0 (0.022)		63%	1[0.96,1.04]
Sunawang 2009	0	0	0.1 (0.098)		3.15%	1.08[0.89,1.31]
Tofail 2008	0	0	-0.3 (0.133)		1.7%	0.77[0.59,0.99]
Zagre 2007	0	0	0 (0.059)		8.77%	1.03[0.91,1.15]
Zeng 2008	0	0	0.1 (0.172)		1.02%	1.06[0.76,1.49]
Subtotal (95% CI)					**100%**	**0.99[0.96,1.03]**
Heterogeneity: Tau²=0; Chi²=12.09, df=14(P=0.6); I²=0%						
Test for overall effect: Z=0.3(P=0.77)						
Test for subgroup differences: Chi²=21.02, df=1 (P<0.0001), I²=95.24%						



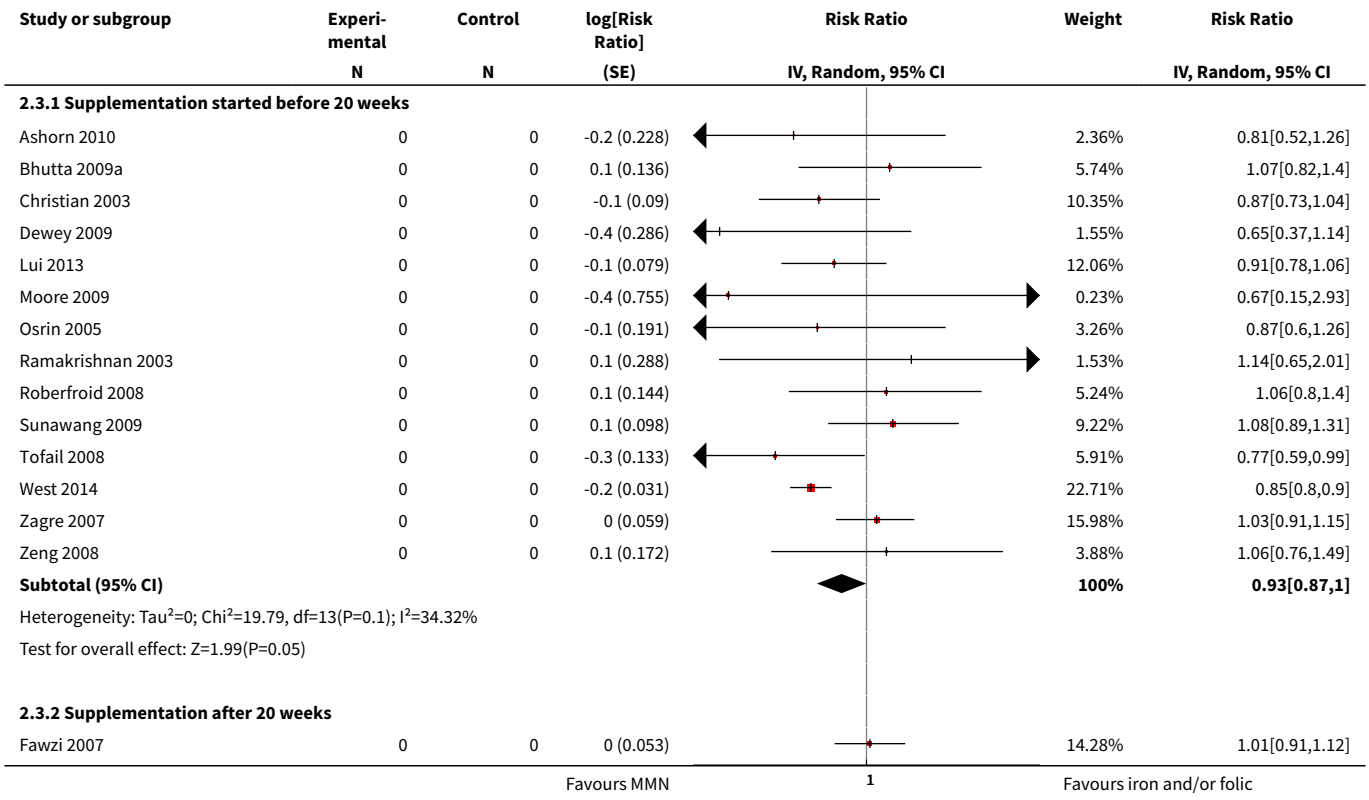
Analysis 2.2. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 2 Preterm births: mean maternal height.

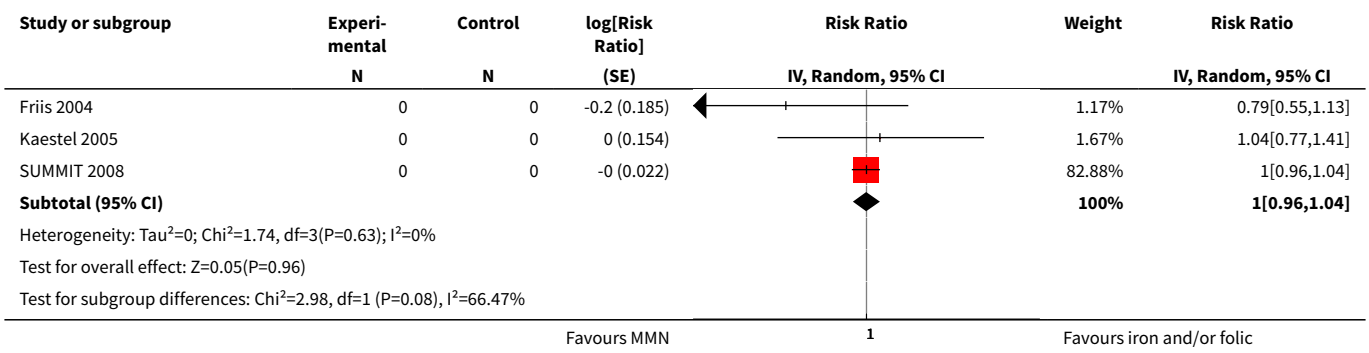
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
2.2.1 Maternal height < 154.9 cm						
Bhutta 2009a	0	0	0.1 (0.136)		8.65%	1.07[0.82,1.4]
Christian 2003	0	0	-0.1 (0.09)		13.87%	0.87[0.73,1.04]
Osrin 2005	0	0	-0.1 (0.191)		5.26%	0.87[0.6,1.26]
Ramakrishnan 2003	0	0	0.1 (0.288)		2.59%	1.14[0.65,2.01]
SUMMIT 2008	0	0	-0 (0.022)		24.6%	1[0.96,1.04]
Sunawang 2009	0	0	0.1 (0.098)		12.7%	1.08[0.89,1.31]
Tofail 2008	0	0	-0.3 (0.133)		8.86%	0.77[0.59,0.99]



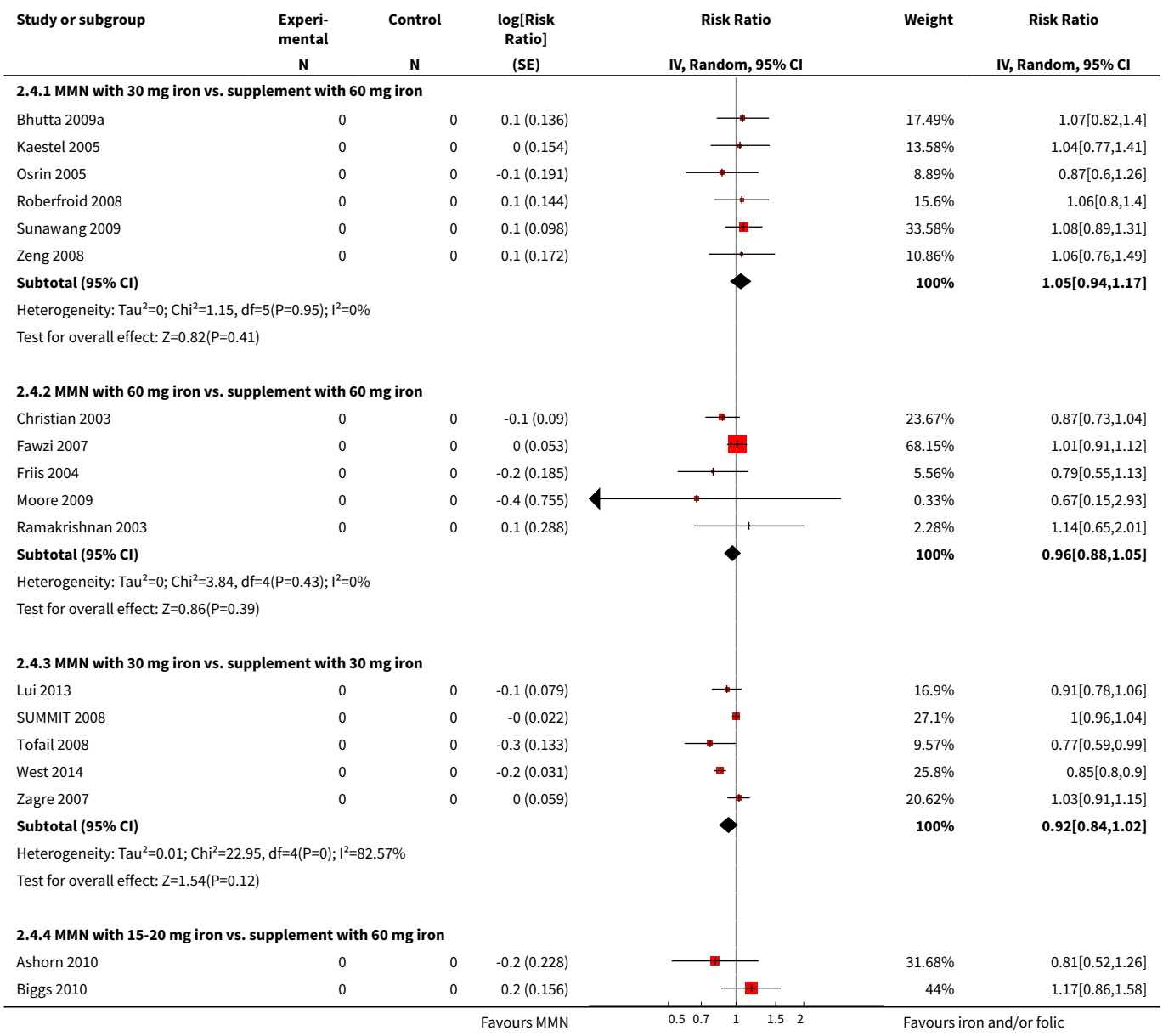


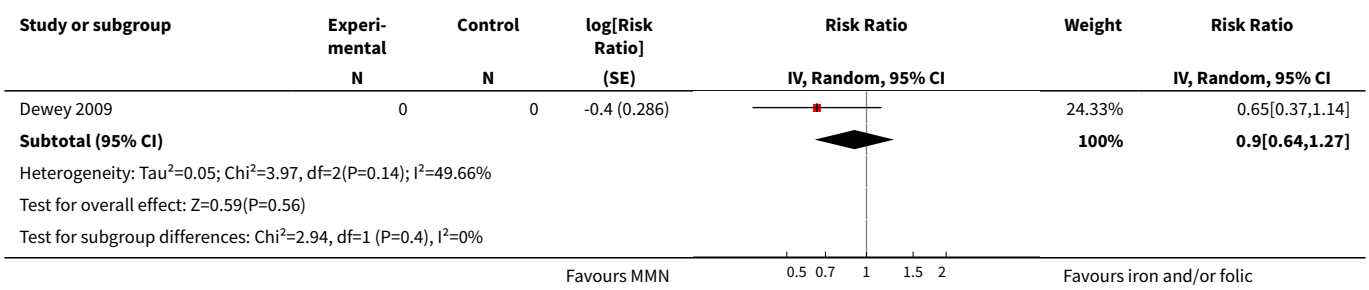
Analysis 2.3. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 3 Preterm births: timing of supplementation.



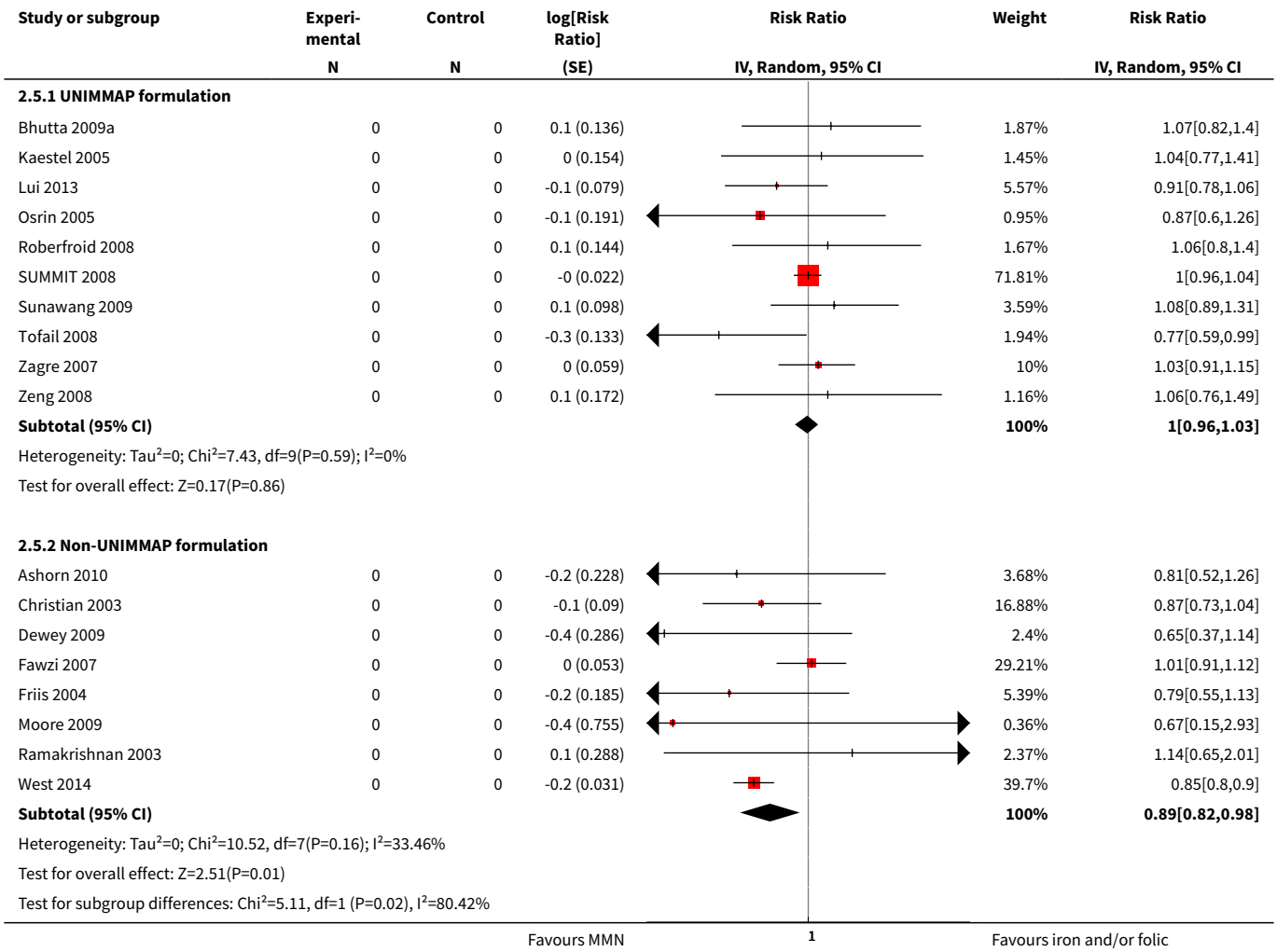


Analysis 2.4. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 4 Preterm births: dose of iron.



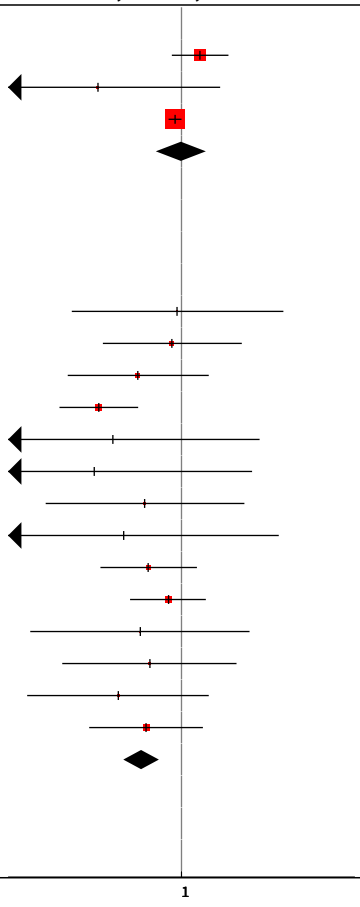


Analysis 2.5. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 5 Preterm births: MMN supplement formulation.



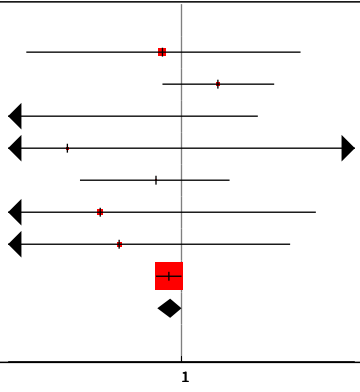
Analysis 2.6. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 6 Small-for-gestational age: mean maternal BMI.

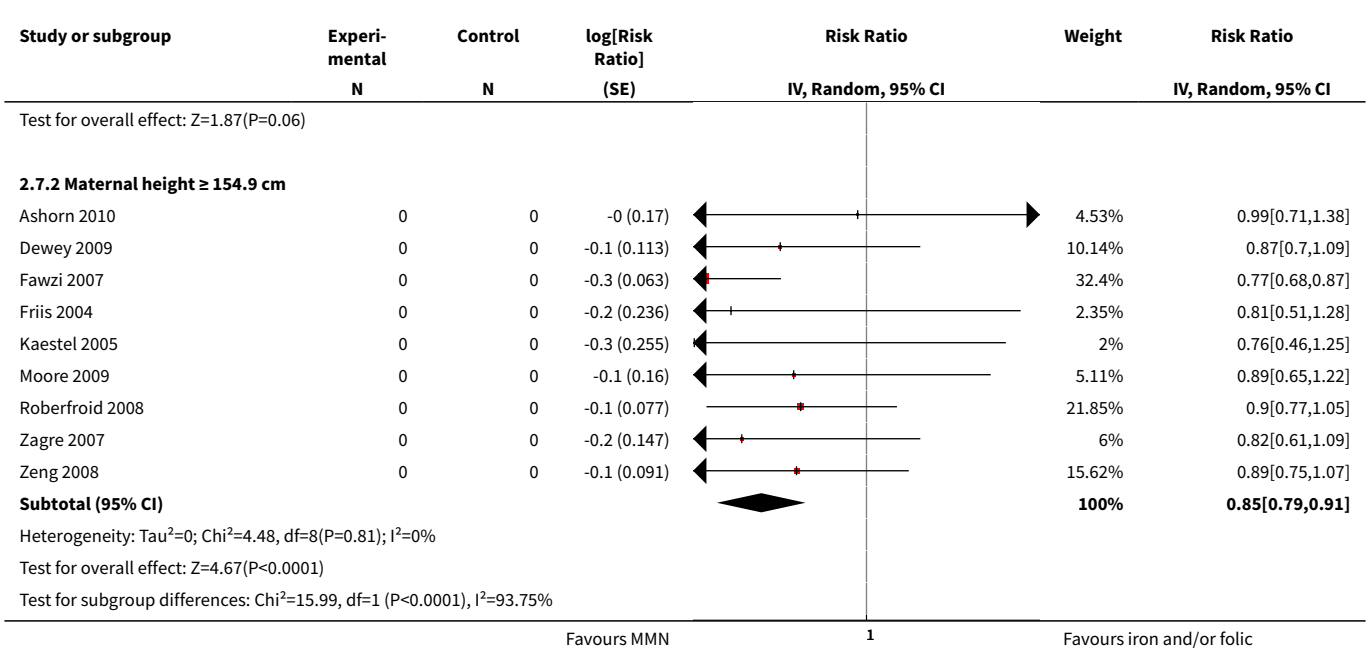
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
2.6.1 BMI < 20 kg/m2						
Christian 2003	0	0	0.1 (0.045)		35.08%	1.06[0.97,1.16]
Osrin 2005	0	0	-0.3 (0.195)		3.98%	0.77[0.52,1.13]
West 2014	0	0	-0 (0.011)		60.94%	0.98[0.96,1]
Subtotal (95% CI)					**100%**	**1[0.92,1.08]**
Heterogeneity: Tau²=0; Chi²=4.46, df=2(P=0.11); I²=55.16%						
Test for overall effect: Z=0.06(P=0.95)						
2.6.2 BMI ≥ 20 kg/m2						
Ashorn 2010	0	0	-0 (0.17)		2.88%	0.99[0.71,1.38]
Bhutta 2009a	0	0	-0 (0.111)		6.71%	0.97[0.78,1.21]
Dewey 2009	0	0	-0.1 (0.113)		6.46%	0.87[0.7,1.09]
Fawzi 2007	0	0	-0.3 (0.063)		20.63%	0.77[0.68,0.87]
Friis 2004	0	0	-0.2 (0.236)		1.5%	0.81[0.51,1.28]
Kaestel 2005	0	0	-0.3 (0.255)		1.28%	0.76[0.46,1.25]
Moore 2009	0	0	-0.1 (0.16)		3.25%	0.89[0.65,1.22]
Ramakrishnan 2003	0	0	-0.2 (0.25)		1.33%	0.83[0.51,1.36]
Roberfroid 2008	0	0	-0.1 (0.077)		13.91%	0.9[0.77,1.05]
SUMMIT 2008	0	0	-0 (0.062)		21.5%	0.96[0.85,1.08]
Sunawang 2009	0	0	-0.1 (0.178)		2.62%	0.88[0.62,1.24]
Tofail 2008	0	0	-0.1 (0.141)		4.18%	0.9[0.69,1.19]
Zagre 2007	0	0	-0.2 (0.147)		3.82%	0.82[0.61,1.09]
Zeng 2008	0	0	-0.1 (0.091)		9.95%	0.89[0.75,1.07]
Subtotal (95% CI)					**100%**	**0.88[0.83,0.93]**
Heterogeneity: Tau²=0; Chi²=8.56, df=13(P=0.81); I²=0%						
Test for overall effect: Z=4.45(P<0.0001)						
Test for subgroup differences: Chi²=6.49, df=1 (P=0.01), I²=84.59%						



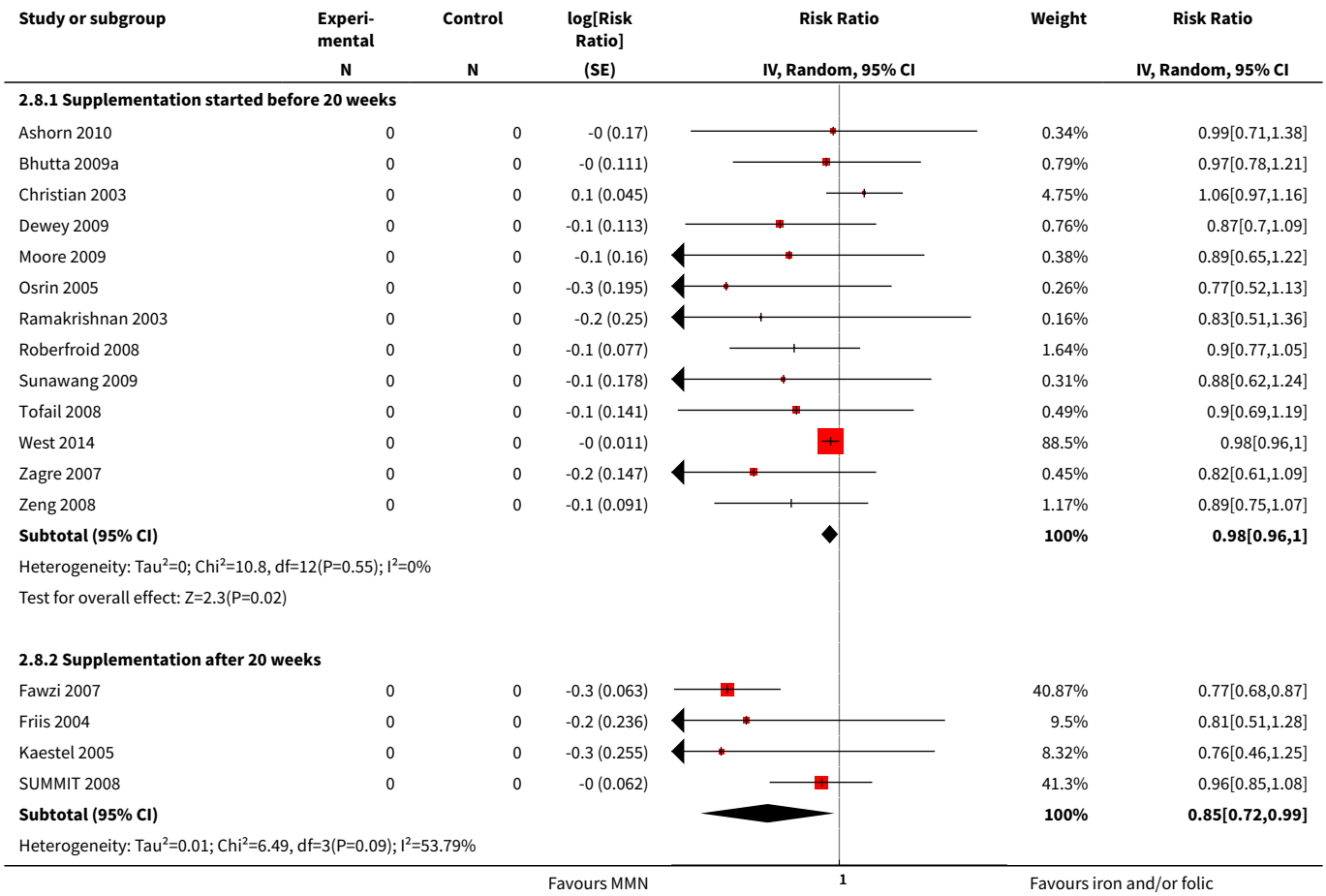
Analysis 2.7. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 7 Small-for-gestational age: mean maternal height.

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
2.7.1 Maternal height < 154.9 cm						
Bhutta 2009a	0	0	-0 (0.111)		0.81%	0.97[0.78,1.21]
Christian 2003	0	0	0.1 (0.045)		4.86%	1.06[0.97,1.16]
Osrin 2005	0	0	-0.3 (0.195)		0.26%	0.77[0.52,1.13]
Ramakrishnan 2003	0	0	-0.2 (0.25)		0.16%	0.83[0.51,1.36]
SUMMIT 2008	0	0	-0 (0.062)		2.59%	0.96[0.85,1.08]
Sunawang 2009	0	0	-0.1 (0.178)		0.31%	0.88[0.62,1.24]
Tofail 2008	0	0	-0.1 (0.141)		0.5%	0.9[0.69,1.19]
West 2014	0	0	-0 (0.011)		90.5%	0.98[0.96,1]
Subtotal (95% CI)					**100%**	**0.98[0.96,1]**
Heterogeneity: Tau²=0; Chi²=5.79, df=7(P=0.56); I²=0%						

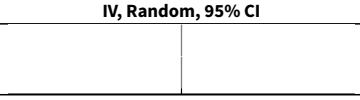




Analysis 2.8. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 8 Small-for-gestational age: timing of supplementation.

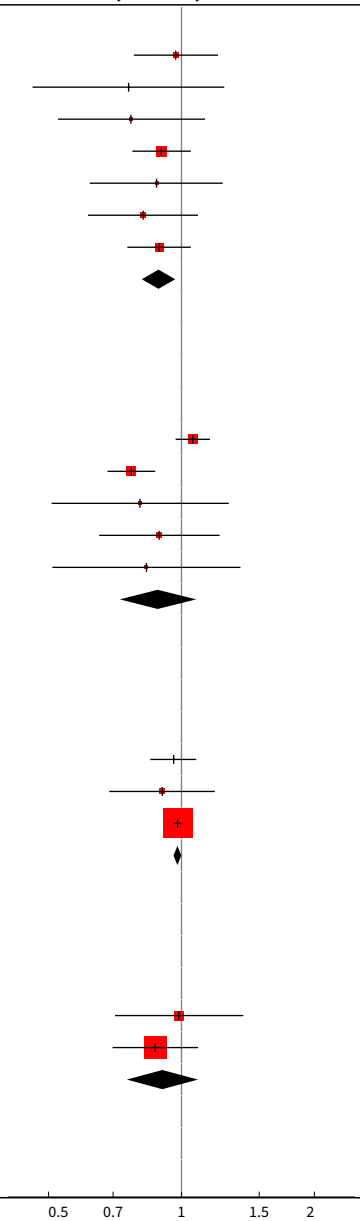


Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Test for overall effect: Z=2.1(P=0.04)						
Test for subgroup differences: Chi²=3.23, df=1 (P=0.07), I²=69.05%						



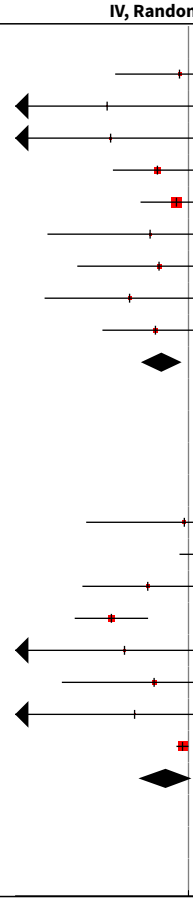
Analysis 2.9. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 9 Small-for-gestational age: dose of iron.

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
2.9.1 MMN with 30 mg iron vs. supplement with 60 mg iron						
Bhutta 2009a	0	0	-0 (0.111)		15.89%	0.97[0.78,1.21]
Kaestel 2005	0	0	-0.3 (0.255)		3.02%	0.76[0.46,1.25]
Osrin 2005	0	0	-0.3 (0.195)		5.19%	0.77[0.52,1.13]
Roberfroid 2008	0	0	-0.1 (0.077)		32.97%	0.9[0.77,1.05]
Sunawang 2009	0	0	-0.1 (0.178)		6.2%	0.88[0.62,1.24]
Zagre 2007	0	0	-0.2 (0.147)		9.06%	0.82[0.61,1.09]
Zeng 2008	0	0	-0.1 (0.084)		27.65%	0.89[0.75,1.05]
Subtotal (95% CI)					**100%**	**0.89[0.81,0.97]**
Heterogeneity: Tau²=0; Chi²=1.9, df=6(P=0.93); I²=0%						
Test for overall effect: Z=2.7(P=0.01)						
2.9.2 MMN with 60 mg iron vs. supplement with 60 mg iron						
Christian 2003	0	0	0.1 (0.045)		30.54%	1.06[0.97,1.16]
Fawzi 2007	0	0	-0.3 (0.063)		28.84%	0.77[0.68,0.87]
Friis 2004	0	0	-0.2 (0.236)		11.76%	0.81[0.51,1.28]
Moore 2009	0	0	-0.1 (0.16)		17.95%	0.89[0.65,1.22]
Ramakrishnan 2003	0	0	-0.2 (0.25)		10.9%	0.83[0.51,1.36]
Subtotal (95% CI)					**100%**	**0.88[0.72,1.08]**
Heterogeneity: Tau²=0.03; Chi²=17.72, df=4(P=0); I²=77.42%						
Test for overall effect: Z=1.23(P=0.22)						
2.9.3 MMN with 30 mg iron vs. supplement with 30 mg iron						
SUMMIT 2008	0	0	-0 (0.062)		2.76%	0.96[0.85,1.08]
Tofail 2008	0	0	-0.1 (0.141)		0.54%	0.9[0.69,1.19]
West 2014	0	0	-0 (0.011)		96.7%	0.98[0.96,1]
Subtotal (95% CI)					**100%**	**0.98[0.96,1]**
Heterogeneity: Tau²=0; Chi²=0.42, df=2(P=0.81); I²=0%						
Test for overall effect: Z=2.05(P=0.04)						
2.9.4 MMN with 20 mg iron vs. supplement with 60 mg iron						
Ashorn 2010	0	0	-0 (0.17)		30.86%	0.99[0.71,1.38]
Dewey 2009	0	0	-0.1 (0.113)		69.14%	0.87[0.7,1.09]
Subtotal (95% CI)					**100%**	**0.91[0.75,1.09]**
Heterogeneity: Tau²=0; Chi²=0.37, df=1(P=0.54); I²=0%						
Test for overall effect: Z=1.06(P=0.29)						
Test for subgroup differences: Chi²=6.21, df=1 (P=0.1), I²=51.71%						



Analysis 2.10. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 10 Small-for-gestational age: MMN supplement formulation.

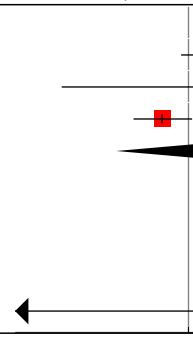
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
2.10.1 UNIMMAP formulation						
Bhutta 2009a	0	0	-0 (0.111)		10.14%	0.97[0.78,1.21]
Kaestel 2005	0	0	-0.3 (0.255)		1.93%	0.76[0.46,1.25]
Osrin 2005	0	0	-0.3 (0.195)		3.31%	0.77[0.52,1.13]
Roberfroid 2008	0	0	-0.1 (0.077)		21.03%	0.9[0.77,1.05]
SUMMIT 2008	0	0	-0 (0.062)		32.5%	0.96[0.85,1.08]
Sunawang 2009	0	0	-0.1 (0.178)		3.96%	0.88[0.62,1.24]
Tofail 2008	0	0	-0.1 (0.141)		6.31%	0.9[0.69,1.19]
Zagre 2007	0	0	-0.2 (0.147)		5.78%	0.82[0.61,1.09]
Zeng 2008	0	0	-0.1 (0.091)		15.04%	0.89[0.75,1.07]
Subtotal (95% CI)					**100%**	**0.91[0.85,0.98]**
Heterogeneity: Tau^2=0; Chi^2=2.95, df=8(P=0.94); I^2=0%						
Test for overall effect: Z=2.61(P=0.01)						
2.10.2 Non-UNIMMAP formulation						
Ashorn 2010	0	0	-0 (0.17)		5.98%	0.99[0.71,1.38]
Christian 2003	0	0	0.1 (0.045)		22.77%	1.06[0.97,1.16]
Dewey 2009	0	0	-0.1 (0.113)		10.67%	0.87[0.7,1.09]
Fawzi 2007	0	0	-0.3 (0.063)		18.86%	0.77[0.68,0.87]
Friis 2004	0	0	-0.2 (0.236)		3.44%	0.81[0.51,1.28]
Moore 2009	0	0	-0.1 (0.16)		6.57%	0.89[0.65,1.22]
Ramakrishnan 2003	0	0	-0.2 (0.25)		3.1%	0.83[0.51,1.36]
West 2014	0	0	-0 (0.011)		28.62%	0.98[0.96,1]
Subtotal (95% CI)					**100%**	**0.92[0.84,1.01]**
Heterogeneity: Tau^2=0.01; Chi^2=19.88, df=7(P=0.01); I^2=64.78%						
Test for overall effect: Z=1.68(P=0.09)						
Test for subgroup differences: Chi^2=0.06, df=1 (P=0.81), I^2=0%						



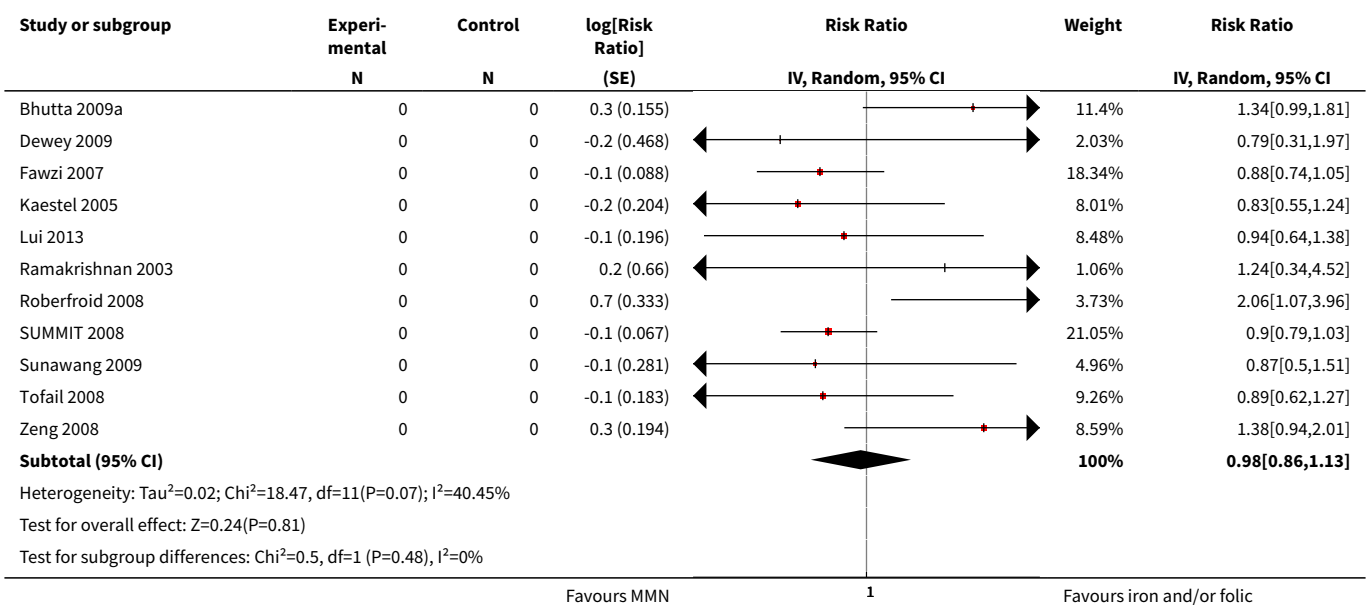
Favours MMN — Favours iron and/or folic

Analysis 2.11. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 11 Perinatal mortality: mean maternal BMI.

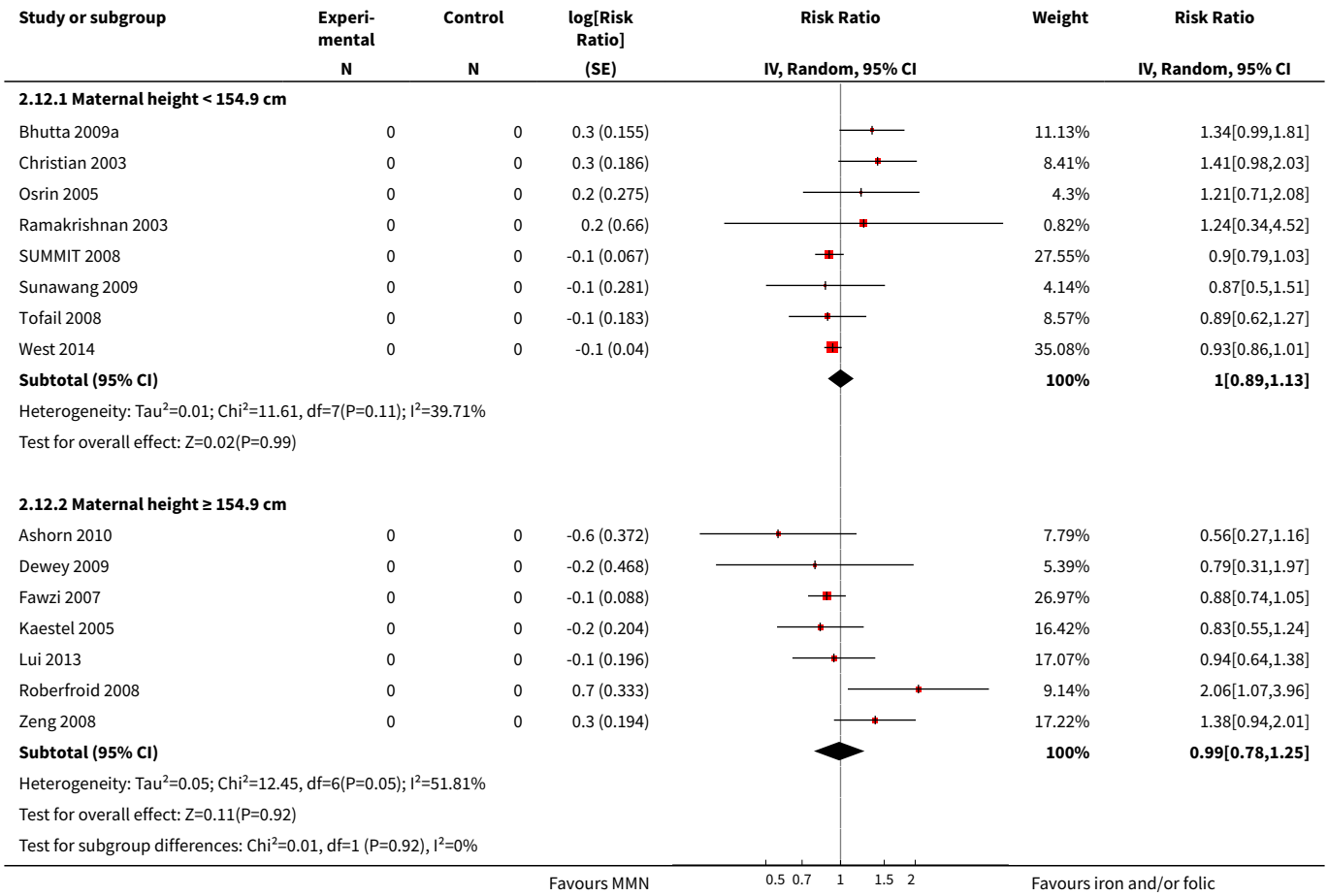
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
2.11.1 BMI < 20 kg/m²						
Christian 2003	0	0	0.3 (0.186)		29.7%	1.41[0.98,2.03]
Osrin 2005	0	0	0.2 (0.275)		19.52%	1.21[0.71,2.08]
West 2014	0	0	-0.1 (0.04)		50.78%	0.93[0.86,1.01]
Subtotal (95% CI)					**100%**	**1.11[0.82,1.5]**
Heterogeneity: Tau^2=0.04; Chi^2=5.59, df=2(P=0.06); I^2=64.21%						
Test for overall effect: Z=0.67(P=0.5)						
2.11.2 BMI ≥ 20 kg/m²						
Ashorn 2010	0	0	-0.6 (0.372)		3.09%	0.56[0.27,1.16]



Favours MMN — Favours iron and/or folic

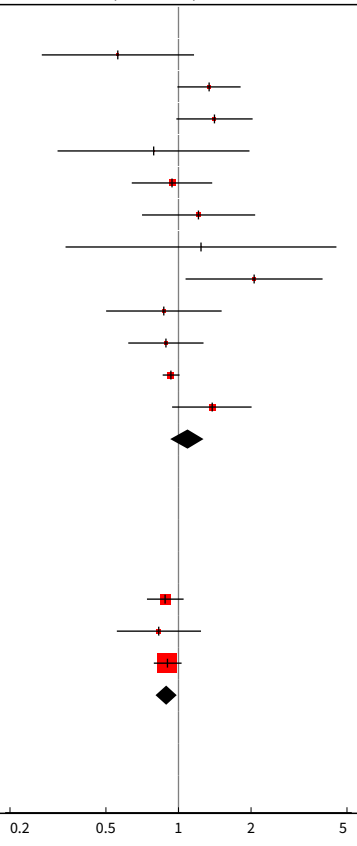


Analysis 2.12. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 12 Perinatal mortality: mean maternal height.



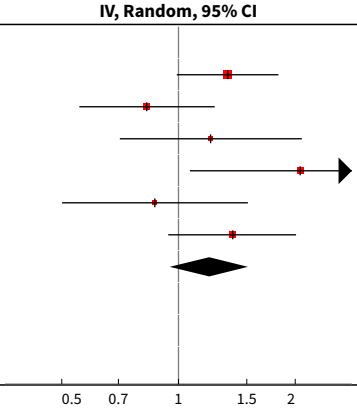
Analysis 2.13. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 13 Perinatal mortality: timing of supplementation.

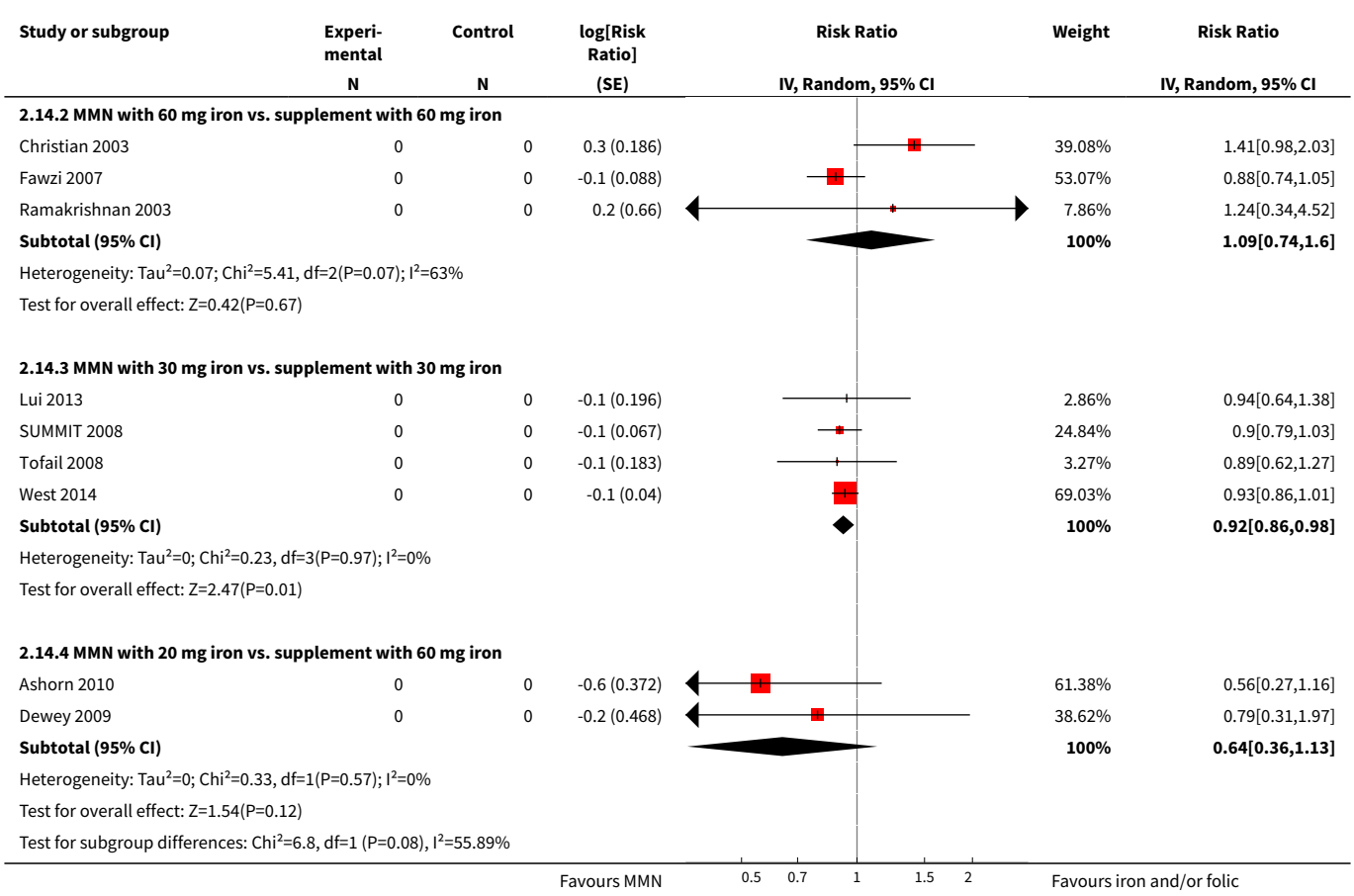
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
2.13.1 Supplementation before 20 weeks						
Ashorn 2010	0	0	-0.6 (0.372)		4%	0.56[0.27,1.16]
Bhutta 2009a	0	0	0.3 (0.155)		12.49%	1.34[0.99,1.81]
Christian 2003	0	0	0.3 (0.186)		10.44%	1.41[0.98,2.03]
Dewey 2009	0	0	-0.2 (0.468)		2.7%	0.79[0.31,1.97]
Lui 2013	0	0	-0.1 (0.196)		9.82%	0.94[0.64,1.38]
Osrin 2005	0	0	0.2 (0.275)		6.36%	1.21[0.71,2.08]
Ramakrishnan 2003	0	0	0.2 (0.66)		1.44%	1.24[0.34,4.52]
Roberfroid 2008	0	0	0.7 (0.333)		4.78%	2.06[1.07,3.96]
Sunawang 2009	0	0	-0.1 (0.281)		6.17%	0.87[0.5,1.51]
Tofail 2008	0	0	-0.1 (0.183)		10.57%	0.89[0.62,1.27]
West 2014	0	0	-0.1 (0.04)		21.3%	0.93[0.86,1.01]
Zeng 2008	0	0	0.3 (0.194)		9.93%	1.38[0.94,2.01]
Subtotal (95% CI)					**100%**	**1.09[0.92,1.27]**
Heterogeneity: Tau^2=0.03; Chi^2=21.45, df=11(P=0.03); I^2=48.72%						
Test for overall effect: Z=0.99(P=0.32)						
2.13.2 Supplementation after 20 weeks						
Fawzi 2007	0	0	-0.1 (0.088)		33.86%	0.88[0.74,1.05]
Kaestel 2005	0	0	-0.2 (0.204)		6.33%	0.83[0.55,1.24]
SUMMIT 2008	0	0	-0.1 (0.067)		59.81%	0.9[0.79,1.03]
Subtotal (95% CI)					**100%**	**0.89[0.8,0.98]**
Heterogeneity: Tau^2=0; Chi^2=0.17, df=2(P=0.92); I^2=0%						
Test for overall effect: Z=2.3(P=0.02)						
Test for subgroup differences: Chi^2=4.26, df=1 (P=0.04), I^2=76.53%						



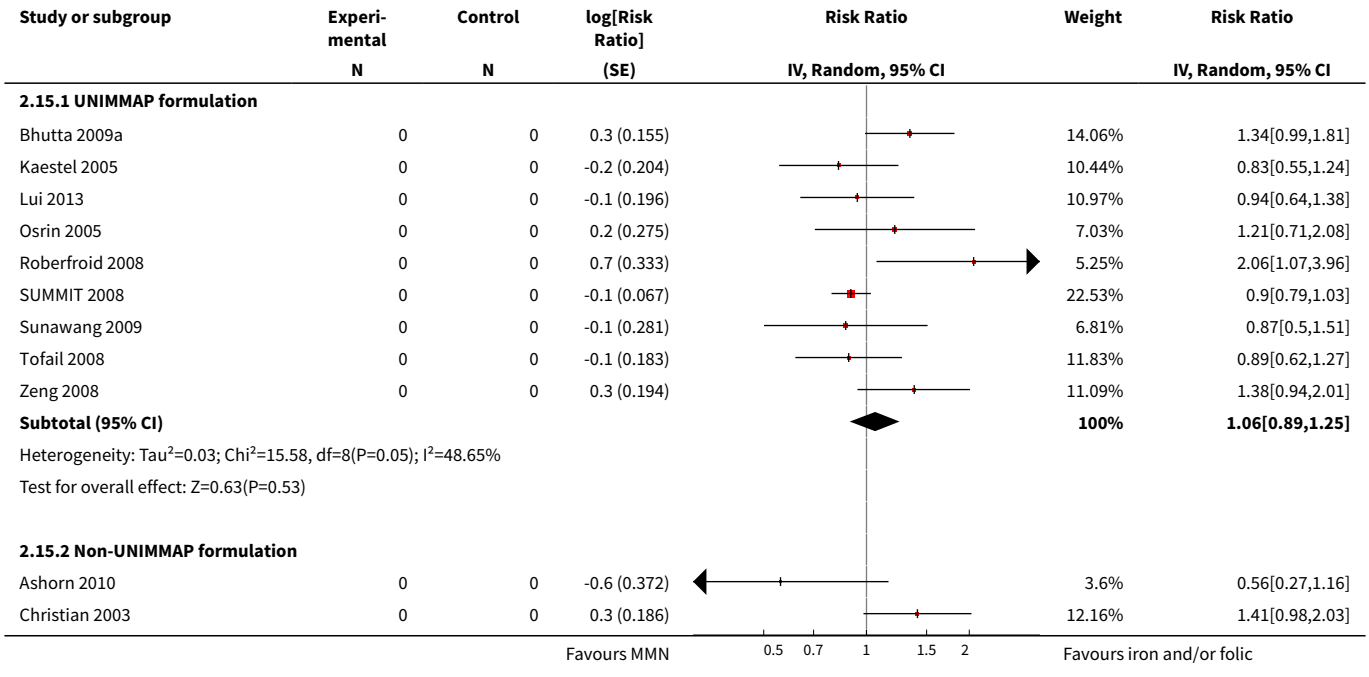
Analysis 2.14. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 14 Perinatal mortality: dose of iron.

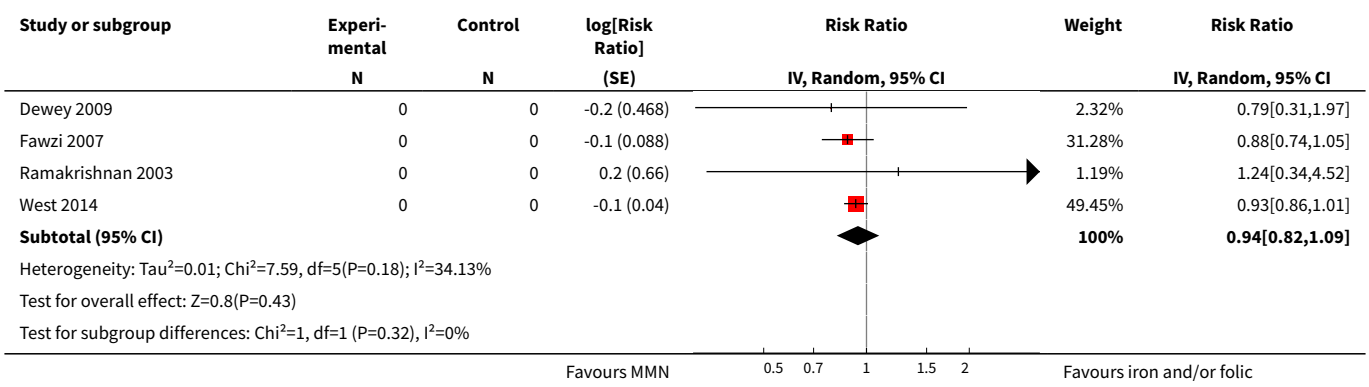
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
2.14.1 MMN with 30 mg iron vs. supplement with 60 mg iron						
Bhutta 2009a	0	0	0.3 (0.155)		25.09%	1.34[0.99,1.81]
Kaestel 2005	0	0	-0.2 (0.204)		19.06%	0.83[0.55,1.24]
Osrin 2005	0	0	0.2 (0.275)		13.09%	1.21[0.71,2.08]
Roberfroid 2008	0	0	0.7 (0.333)		9.89%	2.06[1.07,3.96]
Sunawang 2009	0	0	-0.1 (0.281)		12.71%	0.87[0.5,1.51]
Zeng 2008	0	0	0.3 (0.194)		20.16%	1.38[0.94,2.01]
Subtotal (95% CI)					**100%**	**1.2[0.95,1.51]**
Heterogeneity: Tau^2=0.03; Chi^2=8.27, df=5(P=0.14); I^2=39.56%						
Test for overall effect: Z=1.52(P=0.13)						





Analysis 2.15. Comparison 2 Subgroup analysis for primary outcomes (MMN with iron and folic acid vs iron with or without folic acid)), Outcome 15 Perinatal mortality: MMN supplement formulation.





Comparison 3. Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm births	14		Risk Ratio (Random, 95% CI)	0.96 [0.90, 1.02]
2 Small-for-gestational age	10		Risk Ratio (Random, 95% CI)	0.92 [0.85, 0.99]
3 Low birthweight	14		Risk Ratio (Random, 95% CI)	0.88 [0.85, 0.91]
4 Perinatal mortality	12		Risk Ratio (Random, 95% CI)	1.02 [0.91, 1.15]
5 Stillbirths	13		Risk Ratio (Random, 95% CI)	0.97 [0.86, 1.08]
6 Neonatal mortality	11		Risk Ratio (Random, 95% CI)	1.03 [0.88, 1.20]
7 Maternal anaemia (third trimester Hb < 110 g/L)	8		Risk Ratio (Random, 95% CI)	1.03 [0.92, 1.15]
8 Miscarriage (loss before 28 weeks)	9		Risk Ratio (Random, 95% CI)	0.99 [0.94, 1.04]
9 Maternal mortality	5		Risk Ratio (Random, 95% CI)	1.13 [0.76, 1.68]
10 Very preterm birth (before 34 weeks of gestation)	4		Risk Ratio (Random, 95% CI)	0.81 [0.71, 0.93]
11 Congenital anomalies	2		Risk Ratio (Random, 95% CI)	1.34 [0.25, 7.12]
12 Neurodevelopmental outcome: BSID scores	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 Mental development scores at 6 months of age: new subgroup	1	592	Mean Difference (IV, Random, 95% CI)	-0.02 [-6.75, 6.71]
12.2 Mental development scores at 12 months of age	1	572	Mean Difference (IV, Random, 95% CI)	1.21 [-5.04, 7.46]

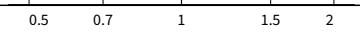
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.3 Psychomotor development scores ar 6 months of age	1	592	Mean Difference (IV, Random, 95% CI)	-0.16 [-3.89, 3.57]
12.4 Psychomotor development scores at 12 months of age	1	572	Mean Difference (IV, Random, 95% CI)	0.34 [-2.72, 3.40]
13 Mode of delivery: caesarean section	4		Risk Ratio (Random, 95% CI)	1.13 [0.99, 1.30]

Analysis 3.1. Comparison 3 Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up, Outcome 1 Preterm births.

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Ashorn 2010	0	0	-0.2 (0.228)		1.78%	0.81[0.52,1.26]
Bhutta 2009a	0	0	0.1 (0.136)		4.31%	1.07[0.82,1.4]
Christian 2003	0	0	-0.1 (0.09)		7.74%	0.87[0.73,1.04]
Dewey 2009	0	0	-0.4 (0.286)		1.17%	0.65[0.37,1.14]
Fawzi 2007	0	0	0 (0.053)		12.86%	1.01[0.91,1.12]
Lui 2013	0	0	-0.1 (0.079)		8.99%	0.91[0.78,1.06]
Moore 2009	0	0	-0.4 (0.755)		0.18%	0.67[0.15,2.93]
Osrin 2005	0	0	-0.1 (0.191)		2.45%	0.87[0.6,1.26]
Roberfroid 2008	0	0	0.1 (0.144)		3.94%	1.06[0.8,1.4]
SUMMIT 2008	0	0	-0 (0.022)		18.16%	1[0.96,1.04]
Sunawang 2009	0	0	0.1 (0.098)		6.9%	1.08[0.89,1.31]
West 2014	0	0	-0.2 (0.031)		16.74%	0.85[0.8,0.9]
Zagre 2007	0	0	0 (0.059)		11.87%	1.03[0.91,1.15]
Zeng 2008	0	0	0.1 (0.172)		2.92%	1.06[0.76,1.49]
Total (95% CI)					**100%**	**0.96[0.9,1.02]**

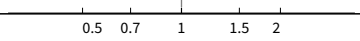
Heterogeneity: Tau²=0.01; Chi²=28.64, df=13(P=0.01); I²=54.62%

Test for overall effect: Z=1.35(P=0.18)

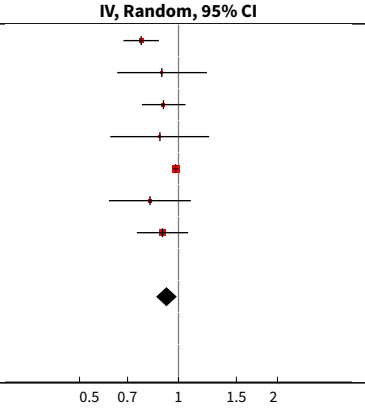


Analysis 3.2. Comparison 3 Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up, Outcome 2 Small-for-gestational age.

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Ashorn 2010	0	0	-0 (0.17)		3.96%	0.99[0.71,1.38]
Christian 2003	0	0	0.1 (0.045)		17.39%	1.06[0.97,1.16]
Dewey 2009	0	0	-0.1 (0.113)		7.34%	0.87[0.7,1.09]

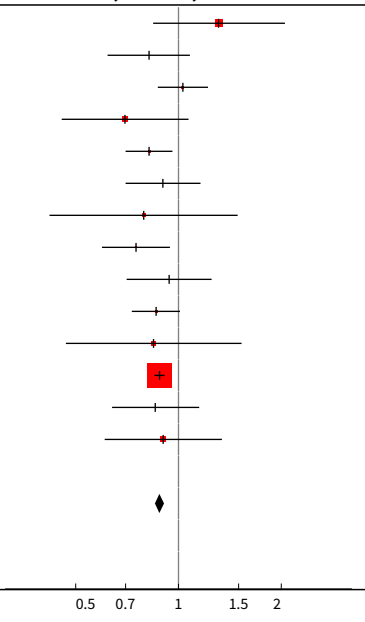


Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Fawzi 2007	0	0	-0.3 (0.063)		13.92%	0.77[0.68,0.87]
Moore 2009	0	0	-0.1 (0.16)		4.37%	0.89[0.65,1.22]
Roberfroid 2008	0	0	-0.1 (0.077)		11.63%	0.9[0.77,1.05]
Sunawang 2009	0	0	-0.1 (0.178)		3.65%	0.88[0.62,1.24]
West 2014	0	0	-0 (0.011)		23.08%	0.98[0.96,1]
Zagre 2007	0	0	-0.2 (0.147)		4.98%	0.82[0.61,1.09]
Zeng 2008	0	0	-0.1 (0.091)		9.68%	0.89[0.75,1.07]
Total (95% CI)					**100%**	**0.92[0.85,0.99]**
Heterogeneity: Tau²=0.01; Chi²=22.52, df=9(P=0.01); I²=60.03%						
Test for overall effect: Z=2.28(P=0.02)						



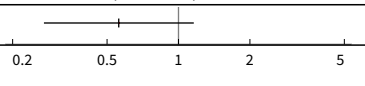
Analysis 3.3. Comparison 3 Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up, Outcome 3 Low birthweight.

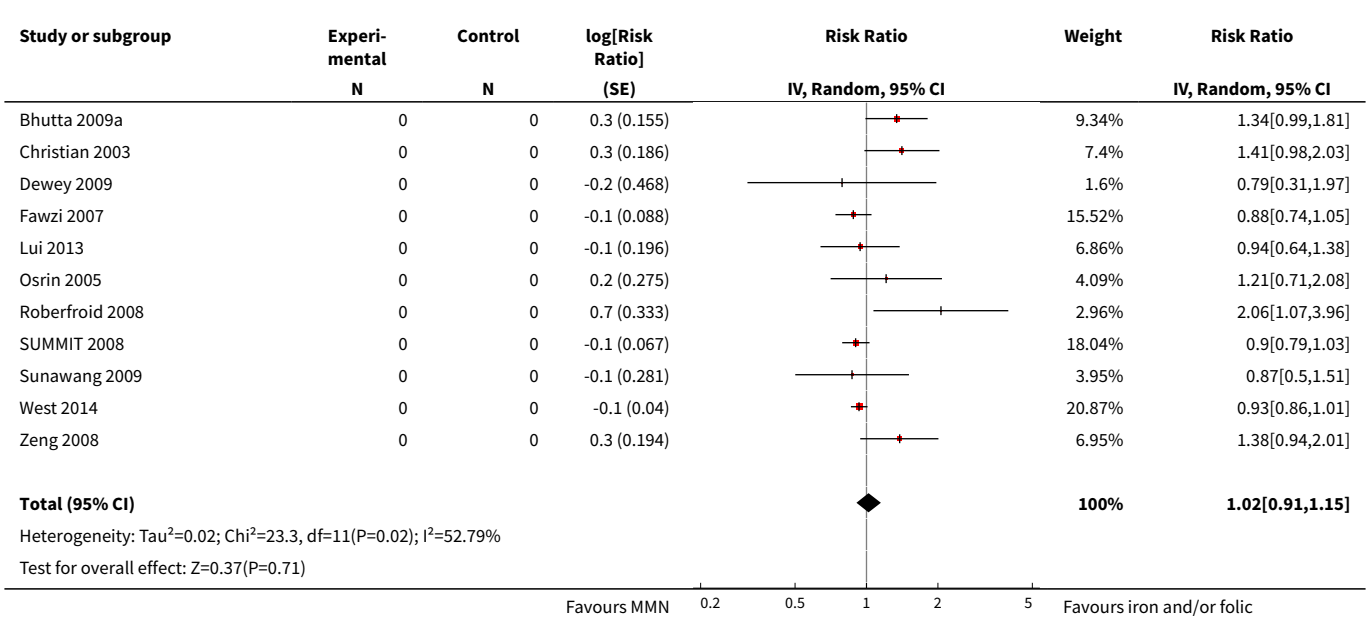
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Ashorn 2010	0	0	0.3 (0.227)		0.49%	1.31[0.84,2.05]
Bhutta 2009a	0	0	-0.2 (0.143)		1.23%	0.82[0.62,1.08]
Christian 2003	0	0	0 (0.086)		3.39%	1.03[0.87,1.22]
Dewey 2009	0	0	-0.4 (0.218)		0.53%	0.7[0.45,1.07]
Fawzi 2007	0	0	-0.2 (0.081)		3.85%	0.82[0.7,0.96]
Lui 2013	0	0	-0.1 (0.128)		1.53%	0.9[0.7,1.16]
Moore 2009	0	0	-0.2 (0.324)		0.24%	0.79[0.42,1.49]
Osrin 2005	0	0	-0.3 (0.117)		1.84%	0.75[0.6,0.94]
Roberfroid 2008	0	0	-0.1 (0.146)		1.17%	0.94[0.71,1.25]
SUMMIT 2008	0	0	-0.2 (0.084)		3.59%	0.86[0.73,1.01]
Sunawang 2009	0	0	-0.2 (0.302)		0.28%	0.85[0.47,1.53]
West 2014	0	0	-0.1 (0.018)		80.11%	0.88[0.85,0.91]
Zagre 2007	0	0	-0.2 (0.149)		1.13%	0.86[0.64,1.15]
Zeng 2008	0	0	-0.1 (0.201)		0.62%	0.9[0.61,1.34]
Total (95% CI)					**100%**	**0.88[0.85,0.91]**
Heterogeneity: Tau²=0; Chi²=10.96, df=13(P=0.61); I²=0%						
Test for overall effect: Z=8.11(P<0.0001)						



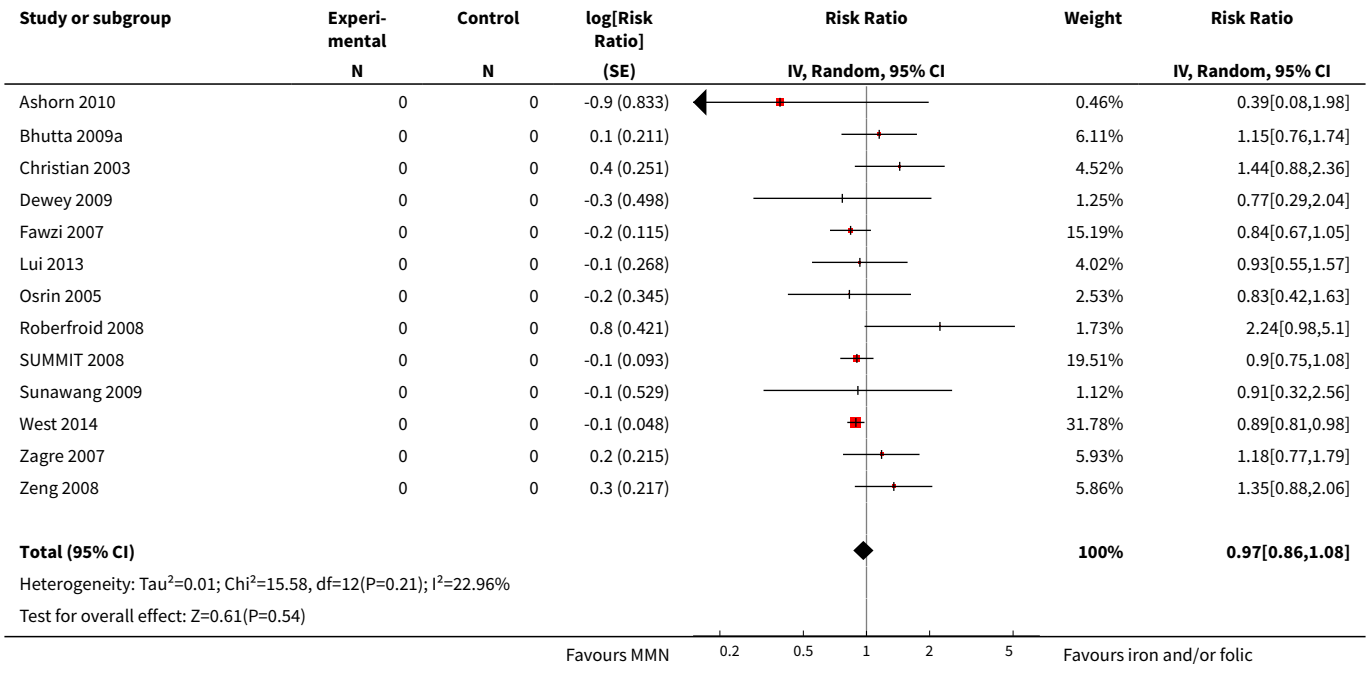
Analysis 3.4. Comparison 3 Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up, Outcome 4 Perinatal mortality.

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Ashorn 2010	0	0	-0.6 (0.372)		2.44%	0.56[0.27,1.16]



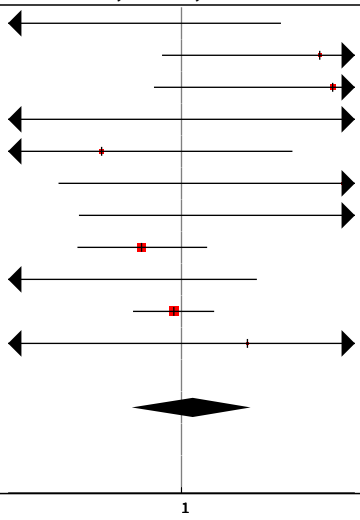


Analysis 3.5. Comparison 3 Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up, Outcome 5 Stillbirths.



Analysis 3.6. Comparison 3 Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up, Outcome 6 Neonatal mortality.

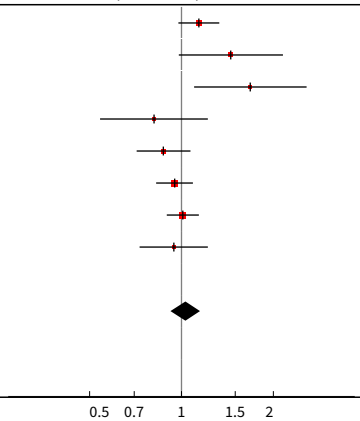
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Ashorn 2010	0	0	-0.5 (0.396)		3.65%	0.6[0.28,1.3]
Bhutta 2009a	0	0	0.4 (0.212)		10.19%	1.44[0.95,2.18]
Christian 2003	0	0	0.4 (0.241)		8.46%	1.49[0.93,2.39]
Dewey 2009	0	0	0.7 (1.223)		0.42%	1.97[0.18,21.65]
Lui 2013	0	0	-0.2 (0.256)		7.65%	0.81[0.49,1.34]
Osrin 2005	0	0	0.4 (0.382)		3.89%	1.53[0.72,3.23]
Roberfroid 2008	0	0	0.7 (0.497)		2.41%	2.02[0.76,5.35]
SUMMIT 2008	0	0	-0.1 (0.086)		25.51%	0.9[0.76,1.07]
Sunawang 2009	0	0	-0.7 (0.436)		3.07%	0.52[0.22,1.22]
West 2014	0	0	-0 (0.055)		31%	0.98[0.88,1.09]
Zeng 2008	0	0	0.2 (0.391)		3.74%	1.19[0.55,2.56]
Total (95% CI)					**100%**	**1.03[0.88,1.2]**
Heterogeneity: Tau^2=0.02; Chi^2=15.54, df=10(P=0.11); I^2=35.65%						
Test for overall effect: Z=0.32(P=0.75)						



Favours MMN — Favours iron and/or folic

Analysis 3.7. Comparison 3 Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up, Outcome 7 Maternal anaemia (third trimester Hb < 110 g/L).

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Ashorn 2010	0	0	0.1 (0.079)		17.67%	1.14[0.98,1.33]
Christian 2003	0	0	0.4 (0.2)		6.32%	1.45[0.98,2.15]
Dewey 2009	0	0	0.5 (0.216)		5.6%	1.68[1.1,2.57]
Moore 2009	0	0	-0.2 (0.208)		5.96%	0.81[0.54,1.22]
Osrin 2005	0	0	-0.1 (0.102)		14.41%	0.87[0.71,1.07]
Roberfroid 2008	0	0	-0.1 (0.072)		18.78%	0.95[0.83,1.09]
West 2014	0	0	0 (0.062)		20.19%	1.01[0.89,1.14]
Zeng 2008	0	0	-0.1 (0.132)		11.07%	0.94[0.73,1.22]
Total (95% CI)					**100%**	**1.03[0.92,1.15]**
Heterogeneity: Tau^2=0.01; Chi^2=15.32, df=7(P=0.03); I^2=54.32%						
Test for overall effect: Z=0.52(P=0.6)						



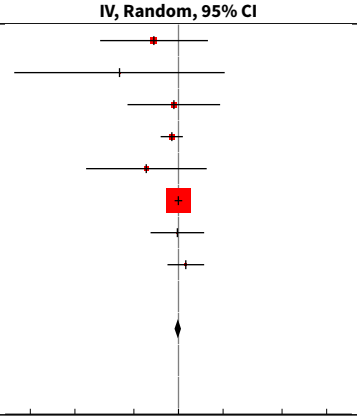
Favours MMN — Favours iron and/or folic

Analysis 3.8. Comparison 3 Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up, Outcome 8 Miscarriage (loss before 28 weeks).

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Bhutta 2009a	0	0	0 (0.145)		3.36%	1.05[0.79,1.4]

Favours MMN — Favours iron and/or folic

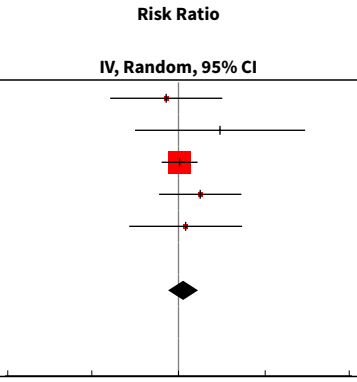
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Dewey 2009	0	0	-0.4 (0.427)		0.39%	0.68[0.3,1.58]
Osrin 2005	0	0	-0.9 (0.835)		0.1%	0.4[0.08,2.05]
Roberfroid 2008	0	0	-0.1 (0.368)		0.52%	0.93[0.45,1.91]
SUMMIT 2008	0	0	-0.1 (0.089)		8.97%	0.9[0.76,1.07]
Sunawang 2009	0	0	-0.5 (0.478)		0.31%	0.61[0.24,1.55]
West 2014	0	0	-0 (0.03)		81.45%	1[0.94,1.06]
Zagre 2007	0	0	-0 (0.213)		1.57%	0.98[0.65,1.49]
Zeng 2008	0	0	0.1 (0.146)		3.33%	1.12[0.84,1.49]
Total (95% CI)					**100%**	**0.99[0.94,1.04]**
Heterogeneity: Tau²=0; Chi²=5.1, df=8(P=0.75); I²=0%						
Test for overall effect: Z=0.37(P=0.71)						



Favours MMN — Favours iron and/or folic

Analysis 3.9. Comparison 3 Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up, Outcome 9 Maternal mortality.

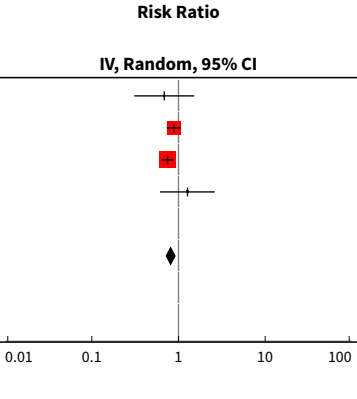
Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Ashorn 2010	0	0	-0.3 (0.76)		7.1%	0.72[0.16,3.2]
Dewey 2009	0	0	1.1 (1.153)		3.09%	3.01[0.31,28.86]
SUMMIT 2008	0	0	0 (0.243)		69.63%	1.03[0.64,1.66]
West 2014	0	0	0.6 (0.558)		13.19%	1.78[0.6,5.31]
Zagre 2007	0	0	0.2 (0.765)		7%	1.21[0.27,5.42]
Total (95% CI)					**100%**	**1.13[0.76,1.68]**
Heterogeneity: Tau²=0; Chi²=1.89, df=4(P=0.76); I²=0%						
Test for overall effect: Z=0.6(P=0.55)						



Favours MMN — Favours iron and/or folic

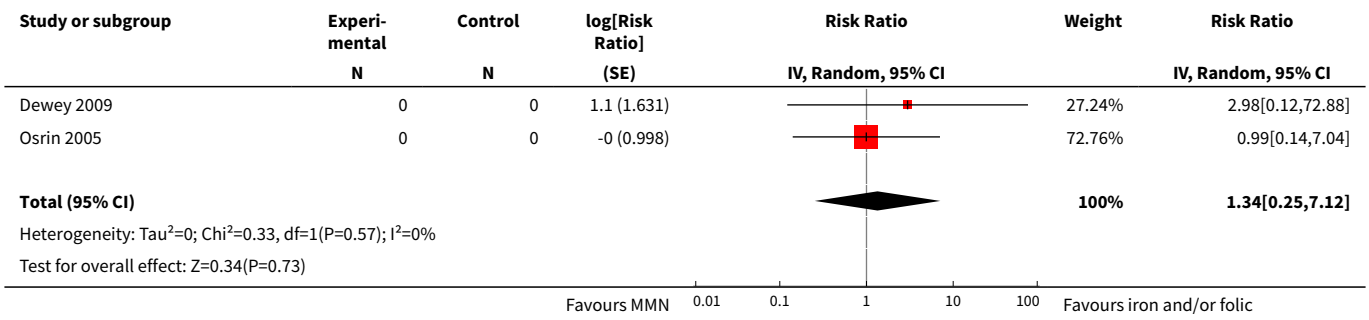
Analysis 3.10. Comparison 3 Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up, Outcome 10 Very preterm birth (before 34 weeks of gestation).

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Ashorn 2010	0	0	-0.4 (0.407)		2.81%	0.69[0.31,1.52]
Fawzi 2007	0	0	-0.1 (0.095)		41.6%	0.88[0.73,1.06]
West 2014	0	0	-0.3 (0.082)		52.21%	0.75[0.64,0.88]
Zeng 2008	0	0	0.2 (0.371)		3.37%	1.27[0.61,2.62]
Total (95% CI)					**100%**	**0.81[0.71,0.93]**
Heterogeneity: Tau²=0; Chi²=3.33, df=3(P=0.34); I²=9.96%						
Test for overall effect: Z=3.02(P=0)						

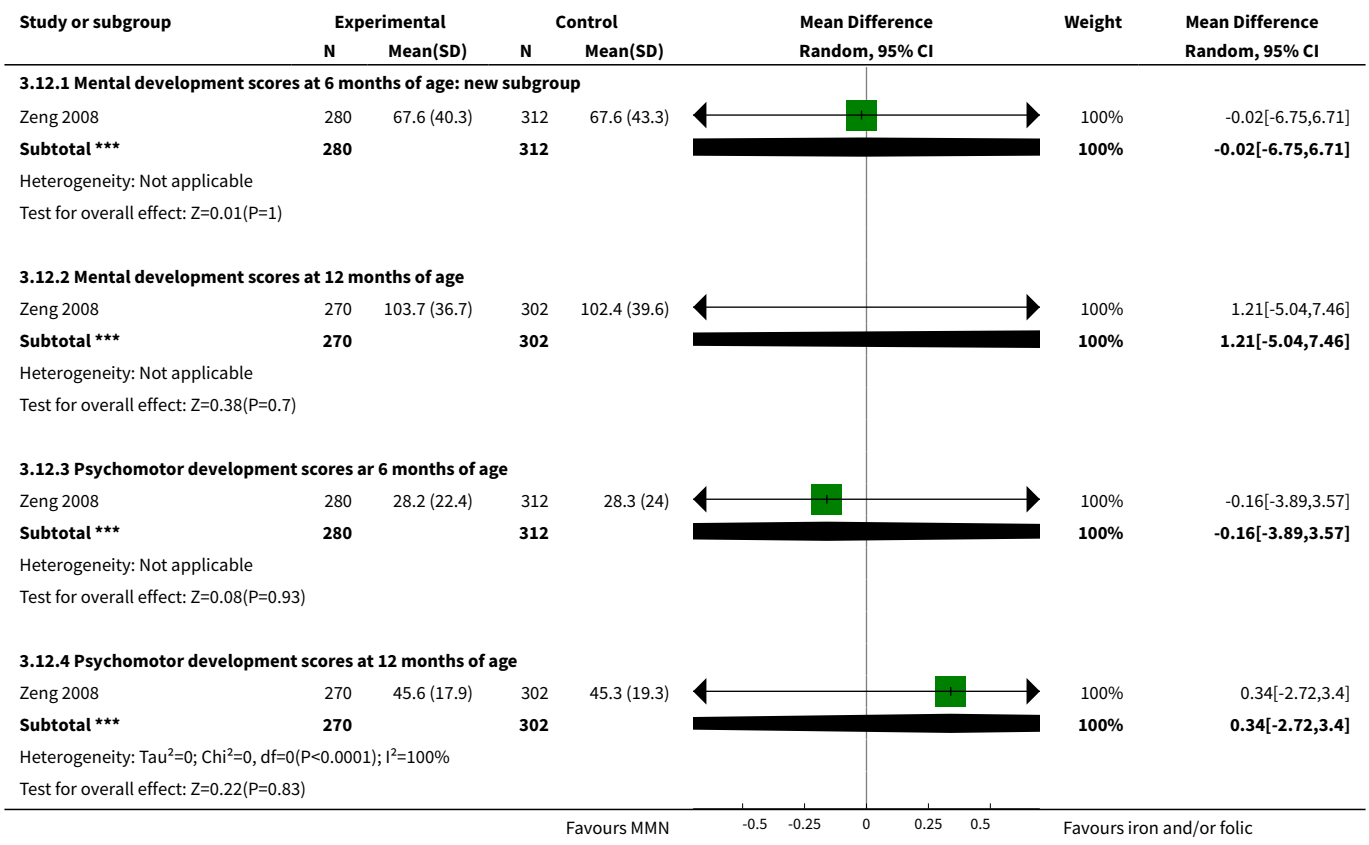


Favours MMN — Favours iron and/or folic

Analysis 3.11. Comparison 3 Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up, Outcome 11 Congenital anomalies.

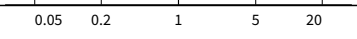


Analysis 3.12. Comparison 3 Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up, Outcome 12 Neurodevelopmental outcome: BSID scores.



Analysis 3.13. Comparison 3 Sensitivity analysis (all trials) excluding trials with > 20% loss to follow up, Outcome 13 Mode of delivery: caesarean section.

Study or subgroup	Experimental N	Control N	log[Risk Ratio] (SE)	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Bhutta 2009a	0	0	-0.1 (0.383)		3.36%	0.91[0.43,1.93]
Fawzi 2007	0	0	0.1 (0.076)		84.14%	1.15[0.99,1.34]
Osrin 2005	0	0	0.1 (0.204)		11.85%	1.06[0.71,1.59]
Roberfroid 2008	0	0	0.7 (0.864)		0.66%	1.99[0.37,10.81]
Total (95% CI)					**100%**	**1.13[0.99,1.3]**
Heterogeneity: Tau^2=0; Chi^2=0.88, df=3(P=0.83); I^2=0%						
Test for overall effect: Z=1.8(P=0.07)						



ADDITIONAL TABLES

Table 1. Micronutrients given to women in the intervention group

Study ID	Iron	Folic acid	Vit A	Be-ta-c	Vit C	Vit E	Vit E	Vit B1 (thi-amine)	Vit B2 (ri-boflavin)	Vit B3 (niacin)	Vit B5 (pan-tothenic acid)	Vit B6	Vit B12	Vit K	Cop-per	Se-le-ni-um	Zinc	Io-dine	Mag-ne-sium	Cal-ci-um	Bo-ron	Man-ganese
Ashorn 2010	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓				✓
Bhutta 2009a	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓				
Biggs 2010	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓				
Brough 2010	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓			
Christian 2003	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓		✓			
Dewey 2009	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓
Fawzi 2007	✓	✓			✓		✓	✓	✓	✓		✓	✓									
Friis 2004	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓					
Kaestel 2005	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓				
Lui 2013	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓				
Moore 2009	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓				
Osrin 2005	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓				
Ramakrishnan 2003	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓				✓		✓			
Roberfroid 2008	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓				
Sood 1975	✓	✓											✓									
SUMMIT 2008	✓	✓	✓		✓	✓	✓	✓		✓		✓	✓		✓	✓	✓	✓				
Sunawang 2009	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓				
Tofail 2008	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓				

Table 1. Micronutrients given to women in the intervention group *(Continued)*

West 2014	✓	✓	✓		✓	✓	✓	✓		✓	✓		✓	✓	✓	✓	
Zagre 2007	✓	✓	✓		✓	✓	✓	✓		✓	✓		✓	✓	✓	✓	
Zeng 2008	✓	✓	✓		✓	✓	✓	✓		✓	✓		✓	✓	✓	✓	

Table 2. Details on adjustments made for cluster-randomised controlled trials

Trial	Outcome(s)	Reported design effect	Reported ICC	Calculated M	Calculated design effect[a]
SUMMIT 2008	Preterm birth, miscarriage	1.2	-	-	-
Sunawang 2009	All	1.2	-	-	-
West 2014	Maternal anaemia, miscarriage, maternal mortality, very preterm birth	1.15	-	-	-
Zagre 2007	All	1.2	-	-	-
Zeng 2008	Preterm birth, very preterm birth	-	0.02	11	1.2
Zeng 2008	LBW	-	0.03	11	1.3
Zeng 2008	All other outcomes	-	0.03[b]	11	1.3
Biggs 2010	Maternal anaemia	-	0.03	12.1	1.3
Biggs 2010	All other outcomes	-	0	12.1	1.0

ICC: intracluster correlation coefficient; **M:** average cluster size

[a]Design effect = 1 + (M-1)*ICC.
[b]Zeng 2008 reported ICCs specific to gestational age and birthweight. For all other outcomes, we used the more conservative of the two ICCs (0.03) to calculate the design effect.

APPENDICES

Appendix 1. ICTRP and ClinicalTrials.gov - search methods

ICTRP

(We ran each line separately)

micronutrients AND pregnancy

vitamins AND pregnancy

multivitamins AND pregnancy

supplements AND pregnancy

supplementation AND pregnancy

multimicronutrients AND pregnancy

multi-micronutrients AND pregnancy

nutrients AND pregnancy

ClinicalTrials.gov

Advanced search

Interventional studies| pregnancy | micronutrients

Interventional studies| pregnancy | supplements

F E E D B A C K

Professor Caroline Fall, 31 May 2016

Summary

Our comments relate mainly to the stillbirth analysis. We believe a fixed-effect model is inappropriate for this analysis. While there was no statistical heterogeneity, the Cochrane handbook and the methods section of the review state that clinical (contextual) heterogeneity should be the main driver of the choice of model, rather than statistical heterogeneity. Contextual heterogeneity was evident in a number of aspects of these trials, including their design (individual or cluster randomized), interventions (composition of multiple micronutrient supplements and duration of supplementation), co-interventions (for example early or late food supplementation), comparison groups (iron alone, IFA, and different doses of these, especially iron), participants (geographic location, phenotype, and gestational age at randomization) and outcome definition (definition of stillbirths varied from ≥24 weeks to ≥28 weeks gestation, including or excluding multiple births). There is inconsistency in the use of fixed or random-effects models within the review; for example, for perinatal mortality (of which stillbirths form a sub-set, Analysis 1.4), including 12 of the 15 trials contributing to the stillbirth analysis, a random effects meta-analysis was used.

We think that three eligible trials have been omitted from the review (Ashorn 2015[1]; Hanieh 2013[2] [protocol of this trial is cited as Biggs 2011a]; and Adu-Afarwuah 2015[3] [protocol cited as Dewey 2011a). These are all listed in the review as 'ongoing trials', but they were published before the stated search date of March 2015. Inclusion of these trials makes little difference to the overall results, but a Cochrane review is expected to be complete.

The Methods section under "Unit of analysis issues" does not clearly define the strategy for comparisons in trials with factorial designs. Further, the comparisons made are unclear in places and inconsistent across studies. This issue potentially applies to 4 studies (Christian 2003; Kaestel 2005; Lui 2013; Zeng 2008), all of which had more than one eligible intervention and/or control group.

A reduction in stillbirths is the only direct benefit to health that has been reported as a result of multiple micronutrient supplements in pregnancy (as opposed to 'metric' outcomes like birth weight and rates of preterm birth), and is currently the only evidence sufficient to justify changing routine supplementation from IFA to MMN. A significant increase in birth weight might be expected to lead to significant health benefits (e.g.. reduced infant mortality) but until this review, there was no apparent effect of MMN supplementation in pregnancy on mortality. The soundness of the stillbirth evidence is therefore crucial to the policy review, and we believe that the evidence remains inconclusive.

Finally, we are curious to know how the review authors presented data for smallness for gestational age (SGA) as an outcome (Analysis 1.2) because data for SGA were not published for some of the trials.

(Summary of feedback from Harshpal Singh Sachdev, Delanjathan Devakumar, Caroline Fall, Clive Osmond, David Osrin, Jonathan Broad, Barrie Margetts, May 2016).

References

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2. Hanieh S, Ha TT, Simpson JA, Casey GJ, Khuong NC, Thoang DD, et al. The effect of intermittent antenatal iron supplementation on maternal and infant outcomes in rural Viet Nam: a cluster randomised trial. PLoS Med 2013; 10: e1001470.
3. Adu-Afarwuah S, Lartey A, Okronipa H, Ashorn P, Zeilani M, Peerson JM, et al. Lipid-based nutrient supplement increases the birth size of infants of primiparous women in Ghana. The American Journal of Clinical Nutrition 2015; 101: 835-46.

Reply

We would like to thank you and your colleagues for the detailed comments and queries on our review. We have made edits to the review to address the specific queries. We also plan to update this important review over the coming year, since the search will become out of date in March 2017.

1. Random-effects versus fixed-effect model – stillbirth analysis

Regarding the comment about the inconsistent use of fixed or random effects model in the review, please note we had not used these inconsistently. While we agree regarding the presence of contextual differences between the included trials, the decision to select fixed or random effects model for stillbirth analysis was based on the values of I^2, Tau^2 and/or p value, as per the methodological guidelines of Cochrane Pregnancy and Childbirth reviews: "We regarded heterogeneity as substantial if an I^2 was greater than 30% and either a Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity." We have taken on board your comments and

changed the stillbirth results to RR 0.97, 95% CI 0.87 to 1.09, using a random effects model. However, as our group statistician has advised, this is a very conservative approach and an interpretation of a possible reduction in stillbirth would also be valid.

2. Omission of trials

Regarding the omission of three eligible trials, namely Hanieh 2013, Ashorn 2015, and Adu-Afarwuah 2015, we consulted the Information Specialist of Cochrane Pregnancy and Childbirth. The Information Specialist has informed us that one of the trials, Adu-Afarwuah 2015 was not identified in the literature search conducted on 11th March 2015 – and had not been added to the Cochrane Pregnancy and Childbirth group trials register at that time. Regarding Ashorn 2015, this was in Ongoing studies, but has now been moved to Characteristics of studies awaiting classification. The review authors have requested additional data from the trial authors for Ashorn 2015, as stated in the notes section of the Characteristics of studies awaiting classification table. This trial included HIV+ patients: "This trial included women with a + HIV test: IFA = 15.6%; MMN 11.1% and LNS 14.4%. We have contacted authors to see if separate analyses for HIV- women are available." Hanieh 2013 had been assigned to another review on intermittent iron, but will be re-assessed at next update. The review authors will assess all three of these studies in the next update of this review.

3. Unit of analysis issues - Trials with multiple intervention groups

We appreciate that our methods section had not detailed clearly how unit of analysis issues for trials with multiple intervention groups had been dealt with. We have made edits to address this issue, as detailed in the Unit of analysis issues section for Christian 2003; Kaestel 2005; Lui 2013; Zeng 2008. For trials with multiple intervention groups, we selected one pair of interventions and excluded the others. This is one approach recommended by the Cochrane Handbook [16.5.4]. If more than two intervention groups had met the eligibility criteria, we would have combined groups to create a single pair-wise comparison as per [16.5.4] of the Cochrane Handbook.

4. **Source of data for Small for gestational age (SGA) Unit of analysis issues - Trials with multiple intervention groups**

We have spoken to the Research Associate, Cochrane Pregnancy and Childbirth, who helped with the last update. The SGA data for all but three trials, came from a separate report (Food and Nutrition Bulletin 2009). Only in three trials were we able to extract SGA data directly from the trial reports (Brough 2010; Fawzi 2007; West 2014).

(Reply from Batool A Haider, Zulfiqar A Bhutta, Philippa Middleton, March 2017).

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WHAT'S NEW

Date	Event	Description
19 July 2019	Amended	To clarify, for this 2019 update, we re-extracted data for all primary and secondary outcomes for all included studies from the outset, not just those found from the most recent search. Minor recalculations of cluster parameters resulted in slight differences in results in studies between this version and the previously pub-

Date	Event	Description
		lished version (Haider 2017) of this review. This has made very little difference to the overall results.

HISTORY

Protocol first published: Issue 3, 2004
Review first published: Issue 4, 2006

Date	Event	Description
23 February 2018	New citation required but conclusions have not changed	Along with the previous conclusions (which have not changed significantly), we found that multiple-micronutrient supplementation reduced the risk of very preterm birth when compared to iron, with or without folic acid.
23 February 2018	New search has been performed	Search updated and four additional studies added (Ashorn 2010; Biggs 2010; Dewey 2009; Moore 2009). Two previously included studies, Hininger 2004 and Theobald 1937, were reclassified from included to excluded for the 2018 update because the multiple-micronutrient supplement did not contain iron.
7 April 2017	Amended	Summary of amendments: 10 November 2015 We have corrected I^2 values for footnotes 1 and 2 in the Summary of findings table 1. 22 March 2016 We have corrected the stillbirth data for Friis 2004 and corrected the data for preterm birth, SGA, LBW, stillbirth, perinatal mortality, neonatal mortality, maternal anaemia, caesarian section, and miscarriage for Bhutta 2009a. 16 March 2017 Estimates for Christian 2003 trial were updated. In response to feedback received from Professor Caroline Fall, all analyses have now been changed to random-effects models, given the clinical heterogeneity amongst the included trials. The Unit of Analysis section has been updated to describe the inclusion of data from trials with more than two intervention groups. All feedback has been incorporated and addressed.
7 April 2017	New citation required but conclusions have not changed	There have been a number of cumulative amendments since the last published version in 2015. The overall conclusions remain unchanged.
22 March 2016	Amended	We have corrected the stillbirth data for Friis 2004 and corrected the data for preterm birth, SGA, LBW, stillbirth, perinatal mortality, neonatal mortality, maternal anaemia, caesarian section, and miscarriage for Bhutta 2009a.

Date	Event	Description
10 November 2015	Amended	We have corrected I^2 values for footnotes 1 and 2 in the Summary of findings table 1.
11 March 2015	New citation required and conclusions have changed	It is now explicit that the review focuses on oral supplements and trials examining parenteral provision of multiple micronutrients (MMN) or MMN via food fortification are now not included. The updated review includes 19 studies. There is now evidence to suggest that women who receive MMN are at lower risk of having a stillbirth.
11 March 2015	New search has been performed	Search updated and two new trials included (Lui 2013 and West 2014) and 51 new studies excluded. Six trials included in previous versions of the review have now been excluded: four trials assessed the effect of fortification with multiple micronutrients (MMN) (Dieckmann 1944; Jarvenpaa 2007; Tatala 2002; Vadillo-Ortega 2011) and two trials included high-risk women (Gupta 2007; Rumiris 2006). A 'Summary of findings' table has been added. Two new outcomes, mode of delivery and macrosomia, have been added to the review. The list of primary outcomes has been modified.
17 February 2012	New citation required but conclusions have not changed	Review updated. Conclusions not changed.
17 February 2012	New search has been performed	Search updated. For this update we have added 17 new included studies (Bhutta 2009a; Brough 2010; Fawzi 2007; Gupta 2007a; Hininger 2004a; Jarvenpaa 2007; Kaestel 2005; Roberfroid 2008; Rumiris 2006a; Sood 1975; SUMMIT 2008; Sunawang 2009; Theobald 1937a; Tofail 2008; Vadillo-Ortega 2011; Zagre 2007; Zeng 2008) and 15 new excluded studies. We have also identified six ongoing studies (Biggs 2011a; Cogswell 2006a; Dewey 2011a; Fall 2007a; Moore 2011a; West 2011a). This review is now comprised of 23 included studies; 64 excluded studies and six ongoing studies. The methods have been updated. Conclusions have not changed.
20 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Emily C Keats (ECK), Emily Tam (ET), Batool A Haider (BAH) and Zulfiqar A Bhutta (ZAB) undertook the current 2018 update of the 2017 Cochrane Review. ECK and ET undertook the revised analysis with input from BAH and ZAB. All authors approved the final version of this review.

ZAB was the principal investigator of Bhutta 2009a, and data extraction was undertaken by BAH for this trial. BAH created the comparisons, did the analysis and wrote the text of the review. ZAB provided guidance and approved the review.

DECLARATIONS OF INTEREST

Emily Keats: none

Batool A Haider: none

Emily Tam: none

Zulfiqar A Bhutta was the principal investigator of the UNIMAPP trial conducted in Pakistan (Bhutta 2009a). He was not involved in the screening and data extraction for this paper, which was conducted by other review authors acknowledged above. Dr Bhutta is also the recipient of a grant from the Bill & Melinda Gates Foundation to undertake an individual participant data analysis of nutrition interventions in adolescents and women during pregnancy.

SOURCES OF SUPPORT

Internal sources

- The Aga Khan University Hospital, Pakistan.

External sources

- Department for International Development, UK.
- United Nations Children's Fund (UNICEF), USA.
- UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Department of Reproductive Health and Research (RHR), World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated the methods to reflect the latest *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We merged the prespecified subgroup analysis 'duration of treatment' with another prespecified subgroup analysis 'gestational age at which supplementation was started' because it uses the same information. We also deleted a subgroup 'micronutrient interactions'. We have undertaken an additional subgroup analysis to look at UNIMMAP versus non-UNIMMAP formulation for the multiple micronutrient (MMN) supplement.

We have included two new secondary outcomes; these are macrosomia and mode of delivery. We have modified the list of primary outcomes so that it now includes some outcomes that were earlier included as secondary outcomes. We changed the primary and secondary outcomes to address issues identified in the recent literature, by experts in the field and given their importance from the policy perspective.

It is now explicit that the review focuses on oral supplements and trials examining parenteral provision of MMN or MMN via food fortification are now not included.

We added a 'Summary of findings' table.

For the 2018 update, we added in an additional search of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP).

For this update, we re-extracted data for all primary and secondary outcomes for all included studies from the outset, not just those found from the most recent search. Minor recalculations of cluster parameters resulted in slight differences in results in studies between this version and the previously published version (Haider 2017). This has made very little difference to the overall results. The data files corresponding to the changes are available from the authors on request.

NOTES

For this update, we re-extracted data for all primary and secondary outcomes for all included studies from the outset, not just those found from the most recent search. Minor recalculations of cluster parameters resulted in slight differences in results in studies between this version and the previously published version (Haider 2017). This has made very little difference to the overall results.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Drug Interactions; Folic Acid [*administration & dosage]; Infant, Small for Gestational Age; Iron, Dietary [*administration & dosage]; Micronutrients [*administration & dosage] [adverse effects] [deficiency]; Perinatal Mortality; Pregnancy Complications [*therapy]; Pregnancy Outcome; Premature Birth [epidemiology]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy