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Multiple-micronutrient supplementation for women during pregnancy (Review)

Haider BA, Bhutta ZA

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[Intervention Review]

Multiple-micronutrient supplementation for women during pregnancy

Batool A Haider[1], Zulfiqar A Bhutta[2]

[1]Department of Global Health and Population, Harvard School of Public Health, Boston, MA, USA. [2]Centre for Global Child Health, Hospital for Sick Children, Toronto, Canada

Contact address: Zulfiqar A Bhutta, Centre for Global Child Health, Hospital for Sick Children, Toronto, ON, M5G A04, Canada. Zulfiqar.bhutta@sickkids.ca, zulfiqar.bhutta@aku.edu.

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ABSTRACT

Background

Multiple-micronutrient (MMN) deficiencies often coexist among women of reproductive age in low- to middle-income countries. They are exacerbated in pregnancy due to the increased demands, leading to potentially adverse effects on the mother and developing fetus. Though supplementation with MMNs has been recommended earlier because of the evidence of impact on pregnancy outcomes, 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, evidence from a few large trials has recently been made available, the inclusion of which is critical to inform policy.

Objectives

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

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (11 March 2015) and reference lists of retrieved articles and key reviews. 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 the pregnancy outcome were eligible, irrespective of language or the publication status of the trials. We included cluster-randomised trials, but quasi-randomised trials were excluded.

Data collection and analysis

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

Main results

Nineteen trials (involving 138,538 women) were identified as eligible for inclusion in this review but only 17 trials (involving 137,791 women) contributed data to the review. Fifteen of these 17 trials were carried out in low and middle-income countries and compared

MMN supplements with iron and folic acid versus iron with or without folic acid. Two trials carried out in the UK compared MMN with a placebo.

MMN with iron and folic acid versus iron, with or without folic acid (15 trials): MMN resulted in a significant decrease in the number of newborn infants identified as low birthweight (LBW) (average risk ratio (RR) 0.88, 95% confidence interval (CI) 0.85 to 0.91; *high-quality evidence*) or small-for-gestational age (SGA) (average RR 0.92, 95% CI 0.86 to 0.98; *moderate-quality evidence*). No significant differences were shown for other maternal and pregnancy outcomes: preterm births (average RR 0.96, 95% CI 0.90 to 1.03; *high-quality evidence*), stillbirth (average RR 0.97, 95% CI 0.87, 1.09; *high-quality evidence*), maternal anaemia in the third trimester (average RR 1.03, 95% CI 0.85 to 1.24), miscarriage (average RR 0.91, 95% CI 0.80 to 1.03), maternal mortality (average RR 0.97, 95% CI 0.63 to 1.48), perinatal mortality (average RR 1.01, 95% CI 0.91 to 1.13; *high-quality evidence)*, neonatal mortality (average RR 1.06, 95% CI 0.92 to 1.22; *high-quality evidence*), or risk of delivery via a caesarean section (average RR 1.04; 95% CI 0.74 to 1.46).

A number of prespecified, clinically important outcomes could not be assessed due to insufficient or non-available data. Single trials reported results for: very preterm birth < 34 weeks, macrosomia, side-effects of supplements, nutritional status of children, and congenital anomalies including neural tube defects and neurodevelopmental outcome: Bayley Scales of Infant Development (BSID) scores. None of these trials reported pre-eclampsia, placental abruption, premature rupture of membranes, cost of supplementation, and maternal well-being or satisfaction.

When assessed according to GRADE criteria, the quality of evidence for the review's primary outcomes overall was good. Pooled results for primary outcomes were based on multiple trials with large sample sizes and precise estimates. The following outcomes were graded to be as of high quality: preterm birth, LBW, perinatal mortality, stillbirth and neonatal mortality. The outcome of SGA was graded to be of moderate quality, with evidence downgraded by one for funnel plot asymmetry and potential publication bias.

We carried out sensitivity analysis excluding trials with high levels of sample attrition (> 20%); results were consistent with the main analysis except for the findings for SGA (average RR 0.91, 95% CI 0.84 to 1.00). We explored heterogeneity through subgroup analyses by maternal height and body mass index (BMI), timing of supplementation and dose of iron. Subgroup differences were observed for maternal BMI for the outcome preterm birth, with significant findings among women with low BMI. Subgroup differences were also observed for maternal BMI and maternal height for the outcome SGA, indicating a significant impact among women with higher maternal BMI and height. The overall analysis of perinatal mortality, although showed a non-significant effect of MMN supplements versus iron with or without folic acid, was found to have substantial statistical heterogeneity. Subgroup differences were observed for timing of supplementation for this outcome, indicating a significantly higher impact with late initiation of supplementation. The findings between subgroups for other primary outcomes were inconclusive.

MMN versus placebo (two trials): A single trial in the UK found no clear differences between groups for preterm birth, SGA, LBW or maternal anaemia in the third trimester. A second trial reported the number of women with pre-eclampsia; there was no evidence of a difference between groups. Other outcomes were not reported.

Authors' conclusions

Our findings support the effect of MMN supplements with iron and folic acid in improving some birth outcomes. Overall, pregnant women who received MMN supplementation had fewer low birthweight babies and small-for-gestational-age babies. The findings, consistently observed in several systematic evaluations of evidence, provide a basis to guide the replacement of iron and folic acid with MMN supplements containing iron and folic acid for pregnant women in low and middle-income countries where MMN deficiencies are common among women of reproductive age. Efforts could focus on the integration of this intervention in maternal nutrition and antenatal care programs in low and middle-income countries.

PLAIN LANGUAGE SUMMARY

Multiple-micronutrient supplementation 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 which 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, with the need to provide nutrition for the baby too, and this can impact on their health and that of their babies.

Why is this important?

Combining multiple micronutrients 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, although interactions may 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 (11 March 2015). This systematic review included 19 trials involving 138,538 women, but only 17 trials involving 137,791 women contributed data. The included trials compared pregnant women who supplemented their diets with multiple micronutrients with iron and folic acid with pregnant women who received a placebo or supplementation with iron, with or without folic acid. Overall, pregnant women who received multiple-micronutrient supplementation had fewer low birthweight babies and small-for-gestational-age babies than pregnant women who received only iron, with or without folic acid. The evidence for the main outcomes was found to be of high quality.

What does this mean?

These findings, consistently observed in several other systematic reviews of evidence, provide a strong basis to guide the replacement of iron and folic acid with multiple-micronutrient supplements for pregnant women in low- and middle-income countries countries where multiple-micronutrient deficiencies are prevalent among women.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Multiple micronutrients compared with control (iron and/or folic acid) for women during pregnancy

Patient or population: Pregnant women
Settings: Trials took place in Bangladesh (2), Burkina Faso, China (2), Guinea-Bissau, India, Indonesia (3), Mexico, Nepal (2), Niger, Pakistan, Tanzania and Zimbabwe.
Intervention: Multiple micronutrients
Comparison: Control (iron with or without folic acid)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Median control group risk (iron and/or folic acid)	Multiple micronutrients				
Preterm births	Moderate		average RR 0.96 (0.90 to 1.03)	90892 (15 RCTs)	⊕⊕⊕⊕ HIGH	Denominators have been taken from individual trial reports or from a series of articles published in the FNB supplement (Fall 2009). Where different denominators are stated in different reports, we have taken the larger Both the participant totals and the median control group risk are for illustrative purposes only. In the majority of the trials in this review, the final risk ratio presented will not

						correspond with raw event and participant data due to adjustments made for the effects of cluster design
	183 per 1000	176 per 1000 (163 to 187)				
Small-for-gestational age	Moderate		average RR 0.92 (0.86 to 0.98)	67036 (14 RCTs)	⊕⊕⊕◯ MODERATE [1]	
	118 per 1000	105 per 1000 (98 to 113)				
Low birthweight	Moderate		average RR 0.88 (0.85 to 0.91)	70044 (15 RCTs)	⊕⊕⊕⊕ HIGH	
	136 per 1000	120 per 1000 (117 to 124)				
Perinatal mortality	Moderate		average RR 1.01 (0.91 to 1.13)	94780 (12 RCTs)	⊕⊕⊕⊕ HIGH [2]	
	40 per 1000	37 per 1000 (34 to 40)				
Stillbirths	Moderate		average RR 0.97 (0.87 to 1.09)	98808 (15 RCTs)	⊕⊕⊕⊕ HIGH	
	31 per 1000	28 per 1000 (26 to 30)				
Neonatal mortality	Moderate		average RR 1.06 (0.92 to 1.22)	83103 (11 RCTs)	⊕⊕⊕⊕ HIGH	
	31 per 1000	30 per 1000 (28 to 33)				

*The basis for the **assumed risk** is the median control group risk. This rate has been calculated from event and participant raw data, where available. If we found no raw event and participant data in published reports, these trials were not included in the calculation of the median control group risk. We have labelled this risk moderate because it is the median of a range of control group rates

The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the control group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Statistical heterogeneity I^2 = 43%. We have not downgraded evidence for heterogeneity. There is evidence of funnel plot asymmetry for this outcome (-1).
[2]Statistical heterogeneity I^2 = 45%. We have not downgraded evidence for heterogeneity.

BACKGROUND

Description of the condition

Micronutrient deficiencies are common among women of reproductive age (15 to 49 years of age) (Black 2013). Women in low- and middle-income countries often have limited intake of animal products, fruits, vegetables and fortified foods resulting in multiple-micronutrient (MMN) deficiencies (FAO/WHO 2004; Huffman 1998). Pregnant women are at an increased risk of multiple deficiencies. These deficiencies are exacerbated during pregnancy because of the increased requirements of the growing fetus, placenta and maternal tissues. An inability to fulfil the increased requirements/demands results in potentially adverse effects on the mother and the fetus (Berti 2011).

Anaemia due to iron deficiency is one of the most prevalent micronutrient deficiencies globally. According to 2011 estimates, the worldwide prevalence of anaemia in pregnant women was 38% (95% confidence interval 33% to 43%), translating into 32 (28 to 36) million pregnant women globally (Stevens 2013). More than 50% of these cases were due to iron deficiency in regions where fewer other causes were present. The majority of these women live in south Asia, and central and west Africa (Stevens 2013). Anaemia during pregnancy has been found to be associated with increased risk of infants with low birthweight (LBW) (Haider 2013). It is also associated with an increased risk of maternal mortality (Murray-Kolb 2013). Vitamin A deficiency is another important nutritional deficiency that leads to night blindness. According to the 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 7.8% and 15.3% of pregnant women in populations at risk of vitamin A deficiency globally (WHO 2009). Deficiency of vitamin A was indicated to be associated with poor birth and mortality outcomes; however, supplementation with vitamin A during pregnancy has demonstrated no beneficial effect on these outcomes (Edmond 2012; Tielsch 2008).

In the past decade, deficiency of vitamin D has also emerged as an important nutritional problem as women of reproductive age and those pregnant have been found to have low levels of vitamin D. High prevalence has not only been reported in studies conducted in low-income countries but also from high-income countries (Datta 2002; Ginde 2010; Sachan 2005). Iodine deficiency is also common among pregnant women. National surveys in several countries found lower than normal urinary iodine levels in 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, congenital abnormalities in some studies (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 have also been reported in studies conducted among pregnant women (Jiang 2005; Pathak 2004). These include deficiencies of vitamins A, D, E, riboflavin, B6, B12, folic acid, iron and zinc. Deficiencies of other minerals such as magnesium, selenium, copper and calcium have also been 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 the 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 programs for the last few decades in most low and middle-income countries, the compliance with the supplement is low. The gastrointestinal side-effects including constipation, nausea, vomiting, and diarrhoea are the most common complaints among women consuming high dose 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. These are also important in many enzymatic processes, signal transduction and transcription pathways (McArdle 1999; WHO 2004). 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 research community globally in eliminating these deficiencies is because of their significant impact on the health of the 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). The findings of the individual trials regarding the benefit on other maternal and pregnancy outcomes are inconsistent as the individual studies may not have statistical power to evaluate statistically significant effects on these outcomes. Several meta-analyses have systematically reviewed and synthesised the evidence of the effect of supplementation with these 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 2012a). 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 at regarding the replacement of iron and folic acid supplementation with MMN. Since the last update of this Cochrane review (Haider 2012), 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 2012). 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 (MMN) supplementation during pregnancy on maternal, fetal and infant 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 the pregnancy outcome were eligible, irrespective of language or publication status of the trials. We included cluster-randomised trials, but quasi-randomised trials were excluded.

Types of participants

Pregnant women. There was no limit on the length of gestation at the time of enrolment in the study. HIV-infected pregnant women were excluded 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. The effect of MMN supplementation in HIV-infected pregnant women has been evaluated in another Cochrane review (Siegfried 2012).

Types of interventions

Since WHO recommends use of iron 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. Studies comparing the outcomes of providing pregnant women with MMN supplements with iron and folic acid compared to placebo was also included

We evaluated the effects of micronutrients that were different in the two groups and not any co-interventions. Trials that used fewer than three micronutrients in the intervention group were excluded regardless of their outcomes. There were no limits on the duration of supplementation.

The following specific comparisons were included in the review.

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

The review focuses on daily oral supplements; trials examining parenteral MMN or food fortification with MMN are not included.

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

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (11 March 2015).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator 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.

Details of the 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 can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

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 2012.

For this update, the following methods were used 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 the Cochrane Pregnancy and Childbirth Group.

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 the third review author. Data were entered into Review Manager software (RevMan 2014) and checked for accuracy.

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

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 2011). Any disagreement was resolved 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 *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We explored the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

For this update, the quality of the evidence was assessed using the GRADE approach as outlined in the GRADE Handbook. 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. Small-for-gestational age (SGA)
3. Low birthweight (LBW)
4. Perinatal mortality
5. Stillbirths
6. Neonatal mortality

We used the GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create a 'Summary of findings' table. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced 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 value of less than 60%, though we have noted moderate heterogeneity in the footnotes of the 'Summary of findings' table.

Measures of treatment effect

Dichotomous data

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

Continuous data

We used the mean difference 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.

Unit of analysis issues

Cluster-randomised trials

We included cluster-randomised trials in the analyses along with individually-randomised trials. We extracted cluster-adjusted effect estimates with their confidence intervals, which were analysed along with individually-randomised trials using the generic inverse variance method.

Trials with multiple intervention groups

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].

Trials with more than two intervention groups were included 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, data for group 4 (MMN group with iron and folic acid) versus group 2 (control group iron with or without folic acid) were included. Groups 1 (folic acid with vitamin A) and 5 (vitamin A only) were not included 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, groups 1 (MMN with iron and folic acid) and group 3 (iron and folic acid) were included in the review. The group with one RDA was selected since the MMN supplement in group 1 was comparable to the UNIMMAP formulation. For Lui 2013, data for groups 3 (MMN with iron and folic acid) versus group 2 (iron and folic acid) fit the types of intervention criterion of the review and were included in the analyses. Similarly, data for the comparison of groups 3 (MMN with iron and folic acid) versus 2 (iron and folic acid) were included 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.

If more than two intervention groups had met the eligibility criteria, we would have combined groups to create a single pair-wise comparison [16.5.4] the Cochrane Handbook.

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, analyses were carried out, as far as possible, on an intention-to-treat basis, i.e. 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 and Chi^2 statistics. 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. If we identified substantial heterogeneity (above 30%), we explored it by pre-specified subgroup analysis.

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.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average 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. If we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity 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 (30 mg versus 60 mg of iron)
3. Baseline nutritional status of the mother (including body mass index (BMI) and height)

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2014). We reported the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We carried out sensitivity analyses to explore the effect of trial quality assessed by high attrition rates, with poor quality studies being excluded from the analyses in order to assess whether this made any difference to the overall result.

RESULTS

Description of studies

Results of the search

For the 2015 update, 81 new reports were assessed for inclusion. We included two new trials in this update (Lui 2013; West 2014). Nineteen trials (involving 138,538 women) were identified as eligible for inclusion in this review but only 17 trials (involving 137,791 women) contributed data to the review. We excluded 97 trials. Two trials are in the Studies awaiting classification section (Ashorn 2015; Gathwala 2012). We have contacted authors to see if separate analyses for HIV- women are available in one trial (Ashorn 2015) and are seeking clarification on missing group denominators in the second trial (Gathwala 2012). There are seven ongoing trials (Biggs 2011; Dewey 2011; Hirschberg 2014; Moore 2011; Mridha 2014; Ramakrishnan 2012; Tu 2013). *See* Characteristics of ongoing studies for more information.

Included studies

A total of 19 trials (involving 138,538 women) were identified as eligible for inclusion in this review. Of these, two studies (Hininger 2004; Sood 1975) either did not report outcomes that were of interest in this review or presented data in a format that precluded their inclusion. Hence, these studies did not contribute data to the analyses. A total of 137,791 women participated in the remaining 17 included trials (Bhutta 2009a; Brough 2010; Christian 2003; Fawzi 2007; Friis 2004; Kaestel 2005; Lui 2013; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; SUMMIT 2008; Sunawang 2009; Theobald 1937; Tofail 2008; West 2014; Zagre 2007; Zeng 2008), of which seven were cluster-randomised (Bhutta 2009a; Christian 2003; SUMMIT 2008; Sunawang 2009; West 2014; Zagre 2007; Zeng 2008). Three trials were conducted in developed countries (Brough 2010; Hininger 2004; Theobald 1937). Most of the outcomes were defined in the same way across different trials except for anaemia for which different cut-offs were used in two trials (Fawzi 2007; Zeng 2008). *See* the Characteristics of included studies table for further details of included studies.

Participants

The 17 included trials contributing data to the analysis included 137,791 pregnant women at varying gestational stages, ranging from early pregnancy to 36 weeks of gestation. Pregnant women with a haemoglobin (Hb) 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. One trial (Friis 2004) included a subgroup of pregnant women who were HIV-1 infected but the data for this subgroup were not included in 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); and these characteristics were not reported in one trial (Theobald 1937). In Friis 2004, a higher proportion of primigravidae were 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

Fourteen trials assessed MMN supplementation versus control (Bhutta 2009a; Christian 2003; Fawzi 2007; Kaestel 2005; Lui 2013; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; SUMMIT 2008; Sunawang 2009; Tofail 2008; West 2014; Zagre 2007; Zeng 2008). Two trials also had a component of nutritional education along with supplementation (Bhutta 2009a; Zagre 2007). Three supplementation trials assessed MMN 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 were asked to take it daily.

The composition of the MMN supplement was different in all included trials. Fourteen trials included iron and folic acid in the MMN supplement (Bhutta 2009a; Brough 2010; Christian 2003; Kaestel 2005; Lui 2013; 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. However, the duration of supplementation varied because the time of enrolment differed across the trials. Seven trials enrolled participants in the first trimester of pregnancy (Brough 2010; Christian 2003; Ramakrishnan 2003; Roberfroid 2008; Tofail 2008; West 2014; Zagre 2007). One trial enrolled participants with a gestation of less than 20 weeks (Lui 2013), and another less than 28 weeks (Zeng 2008). Three trials enrolled participants in the second trimester (Bhutta 2009a; Osrin 2005; Sunawang 2009), one trial enrolled women in both second and third trimester (Friis 2004), while three trials enrolled pregnant women who were less than 37 weeks' gestation (Fawzi 2007; Kaestel 2005; SUMMIT 2008). Supplementation was given until delivery in 10 of the included trials (Bhutta 2009a; Brough 2010; Lui 2013; Friis 2004; Kaestel 2005; Osrin 2005; Ramakrishnan 2003; Tofail 2008; Zagre 2007; Zeng 2008). Supplementation continued until four weeks after delivery in one trial (Sunawang 2009), six weeks after delivery in the Fawzi 2007 trial, 12 weeks after delivery in four trials (Christian 2003; Roberfroid 2008; SUMMIT 2008; West 2014), and for five weeks after a stillbirth or miscarriage (Christian 2003).

Excluded studies

Ninety-seven trials were excluded from the review. Briefly, 36 trials evaluated the effects of a single or two micronutrients or compounds (Beazley 2002; Bergmann 2006; Carrasco 1962; Caulfield 1999; Caulfield 1999a; Chames 2002; Goldenberg 1995; Gopalan 2004; Hillman 1963; Holly 1955; Hossain 2014; Hunt 1983; Hunt 1984; Hunt 1985; Iannotti 2008; Lucia 2007; Ma 2008; Malvasi 2014; Marya 1987; Mathan 1979; Merialdi 1999; Muslimatun 2001a; Muslimatun 2001b; Ochoa-Brust 2007; Raqib 2013; Robertson 1991; Sachdeva 1993; Sagaonkar 2009; Salzano 2001; Schmidt 2001; Schmidt 2002; Semba 2000; Semba 2001; Suharno 1993; Suprapto 2002; Tanumihardjo 2002; Zavaleta 2000). Twelve trials did not satisfy the study design criteria (Aguayo 2005; Biswas 1984; Kubik 2004; Kynast 1986; Itam 2003; Menon 1962; Patimah 2013; Park 1999; People's League 1946; Sun 2010; Thauvin 1992; Wijaya-Erhardt 2014), and five trials studied HIV-positive women (Fawzi 1998; Khavari 2014; Merchant 2005; Olofin 2014; Webb 2009) and hence were excluded from the review. In four trials, MMN supplements were given to both groups of patients (Asemi 2014; Dawson 1987; Dawson 1998; Magon 2014). Czeizel 1996, ICMR 2000, Cooper 2012, and Khulan 2012 evaluated supplementation in the periconceptional period, and Nguyen 2012 evaluated the effect of preconception 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 compared nine versus three micronutrients, and Ling 1996 evaluated a herbal tonic. Li 2014 evaluated the effect of supplementation with folic acid and milk. Four excluded trials assessed the effect of fortification with MMN (Dieckmann 1944; Jarvenpaa 2007; Tatala 2002; Vadillo-Ortega 2011). Two trials included high-risk women (Gupta 2007; Rumiris 2006). Eight trials were excluded because they evaluated the acceptability of different forms of supplementation such as powder, tablet or spread (Choudhury 2012; Hambidge 2014; Lanou 2014; Young 2010); balanced energy protein supplementation (Huybregts 2009; Huybregts 2013); weekly food provision (Wijaya-Erhardt 2011); or polyunsaturated fatty acids fortification in milk fortified with MMN (Mardones 2007). The cohort of an included study (Tofail 2008) was later randomised to breastfeeding counselling or standard care groups measuring the impact on postnatal growth in children (Kabir 2009) and hence was excluded. Leroy 2010 was excluded because it compared a traditional food assisted MCHN program versus a newly designed approach to prevent malnutrition in children. One abstract of a trial was excluded because it was a trial in women with alcohol consumption during pregnancy (Kable 2012).

Fall 2007 was moved from ongoing to excluded for the 2015 update because it is not a trial of supplementation.

See the Characteristics of excluded studies table for more details.

One abstract comparing MMN supplements versus iron folic acid

remains in awaiting assessment due to missing group denominators (Gathwala 2012).

Risk of bias in included studies

The methodological quality of the included studies was generally good with at least 50% of the judgements at "low risk" for the various domains. It is unlikely that the evidence presented in this review is affected by the biases evaluated.
See Figure 1; Figure 2 and Characteristics of included studies table for further details on the methodological quality of the included studies.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

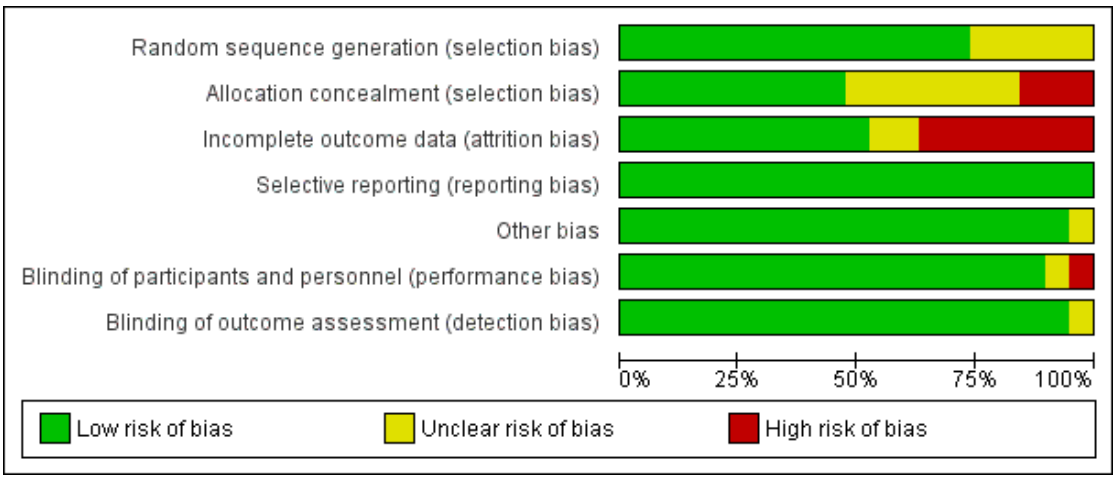
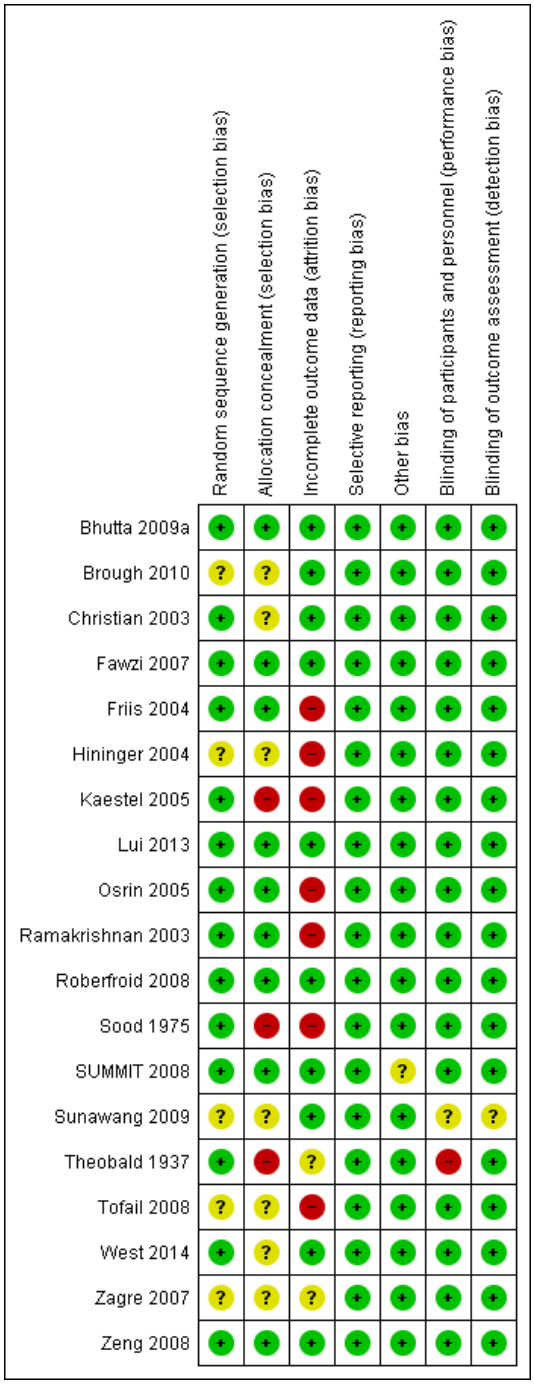


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The included trials were of variable methodological quality. Participants were adequately randomised to the treatment groups in 14 trials (Bhutta 2009a; Christian 2003; Lui 2013;Fawzi 2007; Friis 2004; Kaestel 2005; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; Sood 1975; SUMMIT 2008; Theobald 1937; West 2014; Zeng 2008), whereas the method used for generating the randomisation sequence was not described in sufficient detail in the remaining studies to permit judgement.

Allocation of participants in to the intervention and control groups was concealed in nine trials (Bhutta 2009a; Fawzi 2007; Friis 2004; Lui 2013; Ramakrishnan 2003; Roberfroid 2008; SUMMIT 2008; Zeng 2008); it was unclear in seven trials (Brough 2010; Christian 2003; Hininger 2004; Sunawang 2009; Tofail 2008; West 2014; Zagre 2007); whereas allocation was not probably concealed in the remaining three trials (Kaestel 2005; Sood 1975; Theobald 1937).

Blinding

In two trials (Bhutta 2009a; Tofail 2008), the participants and the outcome assessors were blinded to the treatment allocation. Another 15 trials showed blinding of the participants, caregivers and the outcome assessors (Brough 2010; Christian 2003; Fawzi 2007; Friis 2004; Hininger 2004; Kaestel 2005; Lui 2013; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; SUMMIT 2008; Tofail 2008; West 2014; Zagre 2007; Zeng 2008). However, Sunawang 2009 showed blinding of participants only and Theobald 1937 indicated blinding only of outcome assessors.

Incomplete outcome data

Loss to follow-up was less than 5% in two trials (West 2014; Zeng 2008); between 5% to 9.9% in six trials (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). It was more than 20% in six trials (Friis 2004; Hininger 2004; Kaestel 2005; Ramakrishnan 2003; Sood 1975; Tofail 2008); and not reported in Theobald 1937. In Osrin 2005, although attrition was 5% and reasons for it were reported, exclusion was 39.5% and reasons were not reported and so it has been assessed as being at "high risk". Intention-to-treat analysis was used in all of the trials. In this review, an intention-to-treat analysis was conducted for all outcome measures.

Selective reporting

There was no indication of selective reporting in any of the included trials. All outcomes mentioned in the methods section or the protocol were presented in the various published papers of the trials.

Other potential sources of bias

No other potential sources of bias were identified in most of the included trials.

Effects of interventions

See: **Summary of findings for the main comparison** Multiple micronutrients compared with control (iron and/or folic acid) for women during pregnancy

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

Seventeen trials contributed data to this comparison, however, 15 of these 17 trials were carried out in low- and middle-income countries and compared MMN supplements with iron and folic acid versus iron, with or without folic acid. Two trials carried out in the UK compared MMN with a placebo and contributed data to a very limited number of outcomes. In view of the differences in the settings where trials were conducted, and the in 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 15 trials conducted in low and middle-income countries and evaluating UNIMMAP or similar formulations (Bhutta 2009a; Christian 2003; Fawzi 2007; Friis 2004; Kaestel 2005; Lui 2013; 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 MMN supplementation was compared against iron with or without folic acid supplementation, there was a reduction in small-for-gestational age (SGA) (average risk ratio (RR) 0.92, 95% confidence interval (CI) 0.86 to 0.98; studies = 14; random-effects, $Tau^2 = 0.00$, $I^2 = 48\%$; *moderate-quality evidence;* Analysis 1.2) and low birthweight (LBW) (average RR 0.88, 95% CI 0.85 to 0.91; studies = 15; *high-quality evidence;* Analysis 1.3). No differences were observed between groups for the other primary outcomes:

preterm births (average RR 0.96, 95% CI 0.90 to 1.03; studies = 15; random-effects, Tau² = 0.01, I² = 52%; *high-quality evidence;* Analysis 1.1), perinatal mortality (average RR 1.01, 95% CI 0.91 to 1.13; studies = 13; random-effects, Tau² = 0.01, I² = 46%; *high-quality evidence;* Analysis 1.4), stillbirth (average RR 0.97, 95% CI 0.87 to 1.09; studies = 15; random-effects, Tau² = 0.01, I² = 26%; *high-quality evidence;* Analysis 1.5), and neonatal mortality (average RR 1.06, 95% CI 0.92 to 1.22; studies = 11; random-effects, Tau² = 0.01, I² = 31%; *high-quality evidence;* Analysis 1.6). It should be noted that the data for SGA for the following trials (Bhutta 2009a; Christian 2003; Friis 2004; Kaestel 2005; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; SUMMIT 2008; Sunawang 2009; Tofail 2008; Zagre 2007; Zeng 2008) was obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial reports. For this data from the Food and Nutrition Bulletin 2009, the following were excluded: "*women known to be HIV-positive, women known to have multiple pregnancy, fetal losses before 28 weeks, stillbirths, infants with gestational age at delivery < 189 or > 314 days, and babies measured > 72 hours after birth. Only one pregnancy (the earliest) was included for each mother.*"

Secondary outcomes

MMN supplementation when compared against iron, with or without, folic acid showed no significant impact on maternal anaemia in the third trimester (average RR 1.03, 95% CI 0.85 to 1.24; studies = four; random-effects, Tau² = 0.02, I² = 54%; Analysis 1.7). Similarly, no statistically significant difference was seen for the outcomes of miscarriage (average RR 0.91, 95% CI 0.80 to 1.03; studies = eight; random-effects, Tau² = 0.00, I² = 0%; Analysis 1.8), delivery via a caesarean section (average RR 1.04, 95% CI 0.74 to 1.46; studies = four; random-effects, Tau² = 0.00, I² = 0%; Analysis 1.13), and maternal mortality (average RR 0.97, 95% CI 0.63 to 1.48; studies = three; random-effects, Tau² = 0.00, I² = 0%; Analysis 1.9).

A number of prespecified clinically important outcomes could not be assessed due to insufficient data from the included trials. These included the following outcomes, which were measured either only in one trial or in none, or were presented in a format which precluded their inclusion in the analysis: placental abruption, congenital anomalies including neural tube defects (Osrin 2005), pre-eclampsia, very preterm birth (Zeng 2008), side-effects of MMN supplementation (Lui 2013; Tofail 2008), and neurodevelopmental delay (Zeng 2008). Additional important outcomes are: macrosomia (Roberfroid 2008), cost of supplementation, maternal well-being or satisfaction, and nutritional status of the children (Roberfroid 2008).

Multiple micronutrients (MMN) versus placebo

Two trials conducted in the UK (Brough 2010; Theobald 1937) contributed data; in the Brough 2010 trial women in the control group were advised to take folic acid. The Theobald 1937 trial contributed data to one outcome only, and showed no clear differences between groups for pre-eclampsia (average RR 0.67, 95% CI 0.12 to 3.74; Analysis 1.14). In the Brough 2010 trial, 402 women were randomised; women receiving supplements were at reduced risk of anaemia in the third trimester (average RR 0.46, 95% CI 0.29 to 0.73; Analysis 1.7), but there were no clear differences between women receiving supplements and those in the placebo group for any of the other outcomes reported; preterm birth (average RR1.10, 95% CI 0.41 to 2.95; Analysis 1.1); SGA (average RR 0.93, 95% CI 0.53 to1.63; Analysis 1.2); or LBW (average RR 1.63, 95% CI 0.66 to 4.03; 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 MNN with iron and folic acid versus iron with or without folic acid (15 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 led to fewer preterm births for women in a subgroup of trials with mean maternal BMI of less than 20 kg/m² (average RR 0.85, 95% CI 0.80 to 0.90; studies = four), but not for women with a higher BMI (average RR 1.02, 95% CI 0.97 to 1.07; studies = 11); the test for subgroup differences was significant P < 0.00001, I² = 95.6%) Analysis 2.1. There were no group differences for the subgroups based on the timing of supplementation (Analysis 2.3), maternal height (Analysis 2.2), or for dose of iron for the outcome of preterm birth (Analysis 2.4) (all p>0.05).

Subgroup analysis based on mean maternal BMI showed that the effect of MMN on SGA as compared to iron, with or without folic acid, was significant for the subgroup of trials with mean maternal BMI of at least 20 kg/m² (average RR 0.86, 95% CI 0.81 to 0.92; studies = 10), while it was non-significant for the subgroup with mean maternal BMI of less than 20 kg/m² (average RR 1.00, 95% CI 0.95 to 1.05; studies = four; test for subgroup differences P = 0.001, I² = 90.7%) Analysis 2.5. Similarly, a significant difference was observed between the subgroup of studies based on maternal height (Analysis 2.8). The effect on SGA was significant in the subgroup with mean maternal height of at least 154.9 cm, while it was not significant in the subgroup with mean maternal height of less than 154.9 cm (average RR 0.82, 95% CI 0.76 to 0.89; studies = six) versus (average RR 0.99, 95% CI 0.97 to 1.01; studies = eight; test for subgroup differences P < 0.0001, I² = 94.6%), Analysis 2.8. Finally, the subgroup differences by the timing of supplementation and different doses of iron were tested and found tobe non-significant (both p>0.05) (Analysis 2.7, Analysis 2.6, respectively).

The overall analysis of perinatal mortality, although showing a non-significant effect of MMN supplements versus iron with or

without folic acid, was found to have substantial statistical heterogeneity. Tests for subgroup differences did not show clear differences between subgroups based on mean maternal BMI, mean maternal height, and dose of iron (all P >0.05). However, statistically significant differences were observed between subgroups based on the timing of supplementation. The reduction in perinatal mortality was significantly higher in the subgroup with supplementation after 20 weeks (average RR 0.88, 95% CI 0.80, 0.97; studies = three), while it was non-significant in the subgroup with supplementation before 20 weeks (average RR 1.13, 95% CI 0.96, 1.33; studies = ten), Analysis 2.11.

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

Sensitivity analysis was undertaken to study the effect of MMN supplementation on various outcomes by excluding trials with loss to follow-up of more than 20% (Friis 2004; Kaestel 2005; Ramakrishnan 2003; Tofail 2008) from the analyses. This exclusion did not affect the significance of the findings for the outcomes.

DISCUSSION

Summary of main results

Nineteen trials (involving 138,538 women) were identified as eligible for inclusion in this review. However, only 17 trials (involving 137,791 women) contributed data to the review. This update summarises the current evidence on the effect of multiple-micronutrients (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 a 8% reduction in the risk of small-for-gestational age (SGA) births and a 12% reduction in the risk of low birthweight (LBW). A summary of the main findings for trials comparing MMN with iron and folic acid verus 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 19 trials evaluating the effect of MMN supplementation but only 17 contributed data. Trials conducted as early as 1937 were included in the review. All trials evaluating UNIMMAP supplement proposed in 1999 by UNICEF, UNU, and WHO and starting recruitment of participants as early as 2001 were included in the analysis. 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 with folic acid are 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. Most 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. Pregnant women with serious medical conditions, such as, cardiac disease or respiratory infections, were excluded from the trials.

Comparison 1: multiple micronutrients (MMN) with iron and folic acid versus control (iron with or without folic acid) resulted in a significant decrease in the number of newborn infants identified as LBW or SGA. No significant differences were shown for other maternal and pregnancy outcomes: preterm births, maternal anaemia in the third trimester, miscarriage, maternal mortality, perinatal mortality, stillbirth, neonatal mortality, or risk of delivery via a caesarean section. A number of prespecified, clinically important outcomes could not be assessed due to insufficient or non-available data. Single trials reported results for: very preterm birth < 34 weeks, macrosomia, side-effects of supplements, nutritional status of children, and congenital anomalies including neural tube defects and neurodevelopmental outcome: Bayley Scales of Infant Development (BSID) scores. No trial reported pre-eclampsia, placental abruption, premature rupture of membranes, cost of supplementation, and maternal well-being or satisfaction.

Supplementation with MMN with iron and folic acid versus iron with or without folic acid reduced the risk of LBW and SGA. One of the postulated pathways for this finding is through an increase in birthweight; higher birthweight resulting in lower proportion of LBW and SGA births. Most of the studies included in these analyses demonstrated an increase in birthweight as a result of supplementation with MMN. During pregnancy, the increase in weight of the fetus occurs during the third trimester and this is a potential window of opportunity to improve birthweight. Importantly, a major proportion of women in these studies were taking supplements in the third trimester as several studies recruited pregnant women in the first trimester with supplementation starting in the second trimester; whereas the others recruited almost 80% of their participants by the end of the second trimester. This provides support to the postulated pathway as the intervention was in place much before the beginning of third trimester. Furthermore, since MMN supplementation did not show an impact on preterm birth, which is an underlying cause of LBW, this finding cannot be attributed to a longer duration of gestation.

Most of the studies included in this review were undertaken in low and middle-income countries with high fertility rates, low maternal body mass index (BMI), a high prevalence of iron-deficiency anaemia, and frequent subclinical micronutrient deficien-

cies (Bhutta 2008). Studies have shown that a significant proportion of pregnant women suffer from MMN deficiencies at the same time. These have been associated with poor pregnancy outcomes including LBW (Allen 2005; Keen 2003). Anaemia, especially as a result of iron deficiency, which is frequent in these women, is also possibly associated with an increased risk of infections (Oppenheimer 2001). Whilst the objective of the review was not to measure impact on the immune status or maternal infections, our findings of a significant impact on LBW and SGA as a result of MMN supplementation could be through improved nutritional status and hence better immune system and resistance to maternal infections.

Maternal anthropometry pre-pregnancy and weight gain during pregnancy have also been associated with various neonatal and child outcomes. Maternal height seems to be a stable and easily measurable variable in the setting of low and middle-income countries. Reviews have identified short maternal stature as an important determinant of intrauterine growth retardation and LBW (Kramer 2003; WHO 1995). Short maternal stature (short height) has been found to be significantly associated with an increased risk of child mortality, underweight infants and stunting (Ozaltin 2010; Voigt 2010). Our subgroup analyses indicate that MMN failed to show a significant effect on the SGA outcome in women with poor nutritional status at baseline, defined as maternal height less than 154.9 cm and BMI less than 20 kg/m². MMN showed a significant reduction in SGA babies among women with a mean maternal height at least 154.9 cm as compared to iron with or without folic acid, whereas the effect was non-significant among women with a mean height less than 154.9 cm. Similarly, MMN micronutrients showed a significant reduction in SGA babies among women with a mean BMI at least 20 kg/m², whereas a non-significant effect among those women with a mean BMI less than 20 kg/m². These findings should be interpreted with caution but suggest a possible role of MMN in preventing SGA, but only in women with good nutritional status at baseline, and an absence of similar effects 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 significant effect among women with low BMI but not among those with higher BMI. These differences could be explained by the different underlying causes and mechanisms leading to poor outcomes. The findings further highlight the contribution of maternal malnutrition to poor fetal anthropometry and stunting later in childhood, resulting in an intergenerational transfer of malnutrition. Though supplementation has been suggested to improve child growth and survival, there is currently no evidence that maternal MMN supplementation during pregnancy, compared to iron and folic acid, improves child growth or survival and studies with long-term follow-up are required.

We could not assess a number of prespecified, clinically important outcomes in this review due to insufficient or non-available data. These include placental abruption, congenital anomalies including neural tube defects, premature rupture of membranes, macrosomia, neurodevelopmental delay, very preterm births, macrosomia, cost of supplementation, side-effects of supplements, maternal well-being or satisfaction, and nutritional status or growth during childhood.

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 high. Pooled results for all primary outcomes were based on multiple trials with large sample sizes and precise estimates. For the comparison of MMN versus control (iron and/or folic acid) the following outcomes were graded to be as of high quality: preterm birth, low LBW, perinatal mortality, stillbirth and neonatal mortality. The outcome of SGA was graded to be of moderate quality, downgraded once for funnel plot asymmetry and potential publication bias.

Potential biases in the review process

This update of the review includes additional data published since the last update. An extensive literature search was conducted to identify any additional studies since the last search. The screening of the updated search, selection of eligible studies and data extraction were conducted independently by two review authors. The risk of bias was also assessed by two review authors. 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 significant findings of reduction in the SGA and LBW 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 2012a). A recent systematic review and meta-analysis also reports reduction in the LBW and SGA risk; however, the effect on SGA is reported to be marginally significant (Christian 2015). This review included a smaller number of studies in the SGA analysis (studies = seven) as opposed to the current review (studies = 14), thereby explaining the difference between the estimates reported in the two reviews.

We did not find a significant effect of MMN supplements on perinatal mortality, stillbirth, and neonatal mortality in the main analyses, which are similar to the earlier version of this Cochrane review and other systematic reviews (Haider 2011; Ronsmans 2009). Christian 2015 also observed similar findings for neonatal mortality. Previously, concerns were raised regarding the possible harmful effect of MMN supplements by increasing the risk of perinatal and neonatal mortality through increased birth asphyxia in heavier babies (Christian 2005). Two earlier trials conducted in Nepal by Christian et al and Osrin et al, both had found a non-significant increase in the risk of neonatal and perinatal mortality, but their pooled effect estimate showed a significant increase in the risk of these outcomes (Christian 2003; Osrin 2005). 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 authors, in post-hoc analysis, however 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.

The finding suggesting an increase in the risk of neonatal mortality in some settings is likely due to the absence of skilled care at delivery and the poor standard of care in the health systems in low and middle-income countries, where the majority of births take place at home without the supervision of skilled attendants. This was also observed in a systematic review of MMN supplementation performed using the Child Health Epidemiology Research Group (CHERG) methodology (Walker 2010). While the current review showed no overall increase in the neonatal mortality risk as a result of MMN supplementation, a significantly increased risk was observed in the subgroup of populations with the majority of births at home while no effect was seen where the majority of births took place in health facilities (Haider 2011). This finding may be relevant to efforts to improve maternal nutrition and weight gain during pregnancy (and by inference fetal size) in settings where maternal care during pregnancy and childbirth may be sub optimal. We would recommend the use of MMN supplements in pregnancy principally in settings where skilled maternal care during childbirth and facility-based births can be provided.

As noted earlier, the composition of the MMN supplements differed in several of the included trials (Table 1), and use of folic acid alone or iron with folic acid remains a standard recommendation for pregnant women in many countries globally. In order to identify the effect of a single micronutrient on pregnancy outcomes, each additional micronutrient should be evaluated against a placebo in women receiving iron with folic acid. This would, however, only be of value in populations with single or limited micronutrient deficiencies.

AUTHORS' CONCLUSIONS

Implications for practice

Our findings support the effect of multiple-micronutrient (MMN) supplements with iron and folic acid in improving birth outcomes. These findings have been consistently observed in several systematic evaluations of evidence and provide a strong basis to guide the replacement of iron and folic acid with MMN supplements for pregnant women in low and middle-income countries where deficiencies of MMNs exist.

Implications for research

Efforts should focus on the integration of this intervention in maternal nutrition and antenatal care programs in low and middle-income countries where MMN deficiencies are common among women of reproductive age.

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As part of the prepublication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser (2015 update).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bhutta 2009a

Methods	This cluster-randomised trial was conducted in urban and rural areas in Pakistan
Participants	Pregnant women with gestational age < 16 weeks were eligible for enrolment. MMN group (n = 1148), iron folic acid group (n = 1230)
Interventions	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 Iron folic acid 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 was 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 iron folic acid and iron folic acid + nutritional education group. Iron folic acid 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). It was not included in the analysis as this was a cluster RCT

Risk of bias ***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.
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 bal-

Bhutta 2009a (*Continued*)

		anced across the treatment arms
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.
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

Brough 2010

Methods	This randomised trial was conducted in a socially deprived, multi-ethnic population in east London, United Kingdom
Participants	Participants included women aged 16 years or older with a singleton pregnancy. Exclusion criteria included a gestation of greater than 13 weeks of gestation, chronic disease or use of micronutrient supplements (excluding folic acid and iron). 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) 10mg, 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 sulphate 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

Brough 2010 (*Continued*)

	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

Risk of bias ***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.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (8.7%) and attrition (12.2%) was 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.
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

Christian 2003

Methods	This was a double-blind cluster-randomised trial, carried out in rural Nepal from December 1998 to April 2001
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 less than 9 months old were excluded from the study. Also excluded were menopausal, sterilised or widowed women
Interventions	Group 1 received folic acid 400 mcg and vitamin A. Group 2 received folic acid 400 mcg, iron 60 mg as ferrous fumerate and vitamin A Group 3 contained the same minerals as group 2 in addition to 30 mg of zinc as zinc sulphate 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 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 was obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
Notes	All women were offered 2, 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 authors

Christian 2003 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization 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: "Randomization 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.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (1.43%) and attrition (6.9%) was 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.
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". 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

Fawzi 2007

Methods	This was a double-blind trial in Dar es Salam, Tanzania. Pregnant women who attended antenatal clinics between August 2001 and July 2004 were included
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	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. Control group (n = 4214) received placebo. 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	All women irrespective of group received iron 60 mg and folic acid 0.25 mg. 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

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A list was prepared according to a randomization 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.
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.

Fawzi 2007 (*Continued*)

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.

Friis 2004

Methods	This trial was carried out in Zimbabwe in 1996-1997.
Participants	Pregnant women who were between 22 and 36 weeks of gestation were eligible for enrolment. Participants 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	MMN group received daily supplementation of vitamin A 3000 mcg RE, 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 while the other group received a placebo. An iron folic acid 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 was obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
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

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Friis 2004 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "Allocation to daily supplementation with multimicronutrient or identical-looking placebo tablets was based on simple blocked randomization. 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.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was > 20% and reasons for it were reported. Exclusions were not reported in the study
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.
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

Hininger 2004

Methods	A double-blind, randomised placebo-controlled trial. The study was conducted at Obstetric Departments of Grenoble and Lyon Hospitals in France
Participants	A total of 100 apparently healthy women receiving prenatal care between 12 and 16 weeks of gestation were enrolled
Interventions	The intervention group received a MMN supplement and the control group received a placebo. The MMN supplement contained vitamin C (60 mg), b-carotene (4.8 mg), vitamin E (10 mg), thiamin (1.4 mg), riboflavin (1.6 mg), niacin (15 mg), pantothenic acid (6 mg), folic acid (200 mg), cobalamin (1 mg), Zn (15mg as citrate), Mg (87.5 mg as glycerophosphate), Ca (100 mg as carbonate). The supplement was given for an average of 14 ± 2 weeks of gestation till delivery
Outcomes	Effect of MMN supplementation on maternal blood vitamin concentrations, mineral and trace element concentrations and oxidative stress indexes concentrations. Maternal weight gain, gestational age of baby at birth, birthweight and head circumference were also assessed
Notes	The MMN supplement was iron-free, due to its oxidative potential effect. Baseline characteristics and vitamin mineral status of the enrolled participants were comparable in both groups. Outcomes measured were presented in a format that precluded its inclusion in this review

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Pregnant women were randomly assigned" and "randomized, placebo-controlled trial" Comment: method used to generate the randomisation sequence is not described in sufficient detail to permit judgement
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Reasons for attrition (35%) were not described in the study. There were no exclusions 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.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The subjects, the hospital staff and the investigators were blinded to the coding scheme until analyses of the data were

Hininger 2004 (*Continued*)

		completed". Comment: participants and caregivers were blinded to the treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The subjects, the hospital staff and the investigators were blinded to the coding scheme until analyses of the data were completed". Comment: outcome assessors were blinded to the treatment assignment

Kaestel 2005

Methods	This study was conducted in Guinea-Bissau.
Participants	Pregnant women with less than 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. Intervention group (n = 1392) received MMN supplements (supplement RDA n = 695, supplement 2 RDA n = 697) while the other 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 before 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 was 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. Iron folic acid 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

Risk of bias ***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 ran-

		domly 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)	High 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: probably not done.
Incomplete outcome data (attrition bias) All outcomes	High risk	Exclusion (3.1%) and attrition (20.4%) data was 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.
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) 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: outcome assessors were probably blinded to the treatment assignment

Lui 2013

Methods	This was a double -blind randomised controlled trial conducted in five rural counties in Hebei Provinve, China. Women were enrolled from May 2006 to April 2009
Participants	Pregnant women who recorded dates of their menstruation for 2 or more months before they became pregnant, were nulliparous, at least 20 years old, not more than 20 weeks' gestation, legally competent, had not consumed micronutrient supplements other than folic acid in the prior 6 months, had a Hb level greater than 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 has 3 arms. Group A received folic acid 400 μg, group B received folic acid 400 μg and iron 30 mg, and 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 to 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 iron folic acid group We used the estimates for the comparison of MMN vs. IFA groups in this review

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
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)"

Lui 2013 (*Continued*)

		Comment: probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rate (6.2%) was less than 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.
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.

Osrin 2005

Methods	This study was undertaken in Nepal. All women attending a designated antenatal clinic at Janakpur zonal hospital were considered for enrolment
Participants	Women were eligible for enrolment if an ultrasound examination confirmed a singleton pregnancy, a gestational age between 12 to 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	The 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. 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 less than 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

Osrin 2005 (*Continued*)

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 was 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.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
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.
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.

Osrin 2005 (*Continued*)

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

Ramakrishnan 2003

Methods	This randomised controlled trial was carried out during 1997-2000 in Mexico
Participants	Pregnant women who were less than 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	MMN 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 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. The controls were 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

Ramakrishnan 2003 (*Continued*)

	It should be noted that the data for SGA was 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)

Risk of bias ***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.
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
Other bias	Low risk	Comment: no other bias was identified.
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

Roberfroid 2008

Methods	This was a factorial, double-blind, randomised controlled trial from March 2004 to October 2006 in the Hounde health district of Burkina Faso
Participants	Pregnant women irrespective of gestational age. Exclusion criterion was if women planned to leave area within 2 years
Interventions	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. 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 less than 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 was obtained from a separate report (Food and Nutrition Bulletin 2009) and not from the individual trial report.
Notes	Supplement intake was observed directly and were given till 3 months after delivery. Participants were also randomly assigned to receive either malaria chemoprophylaxis (300 mg cholorquine/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

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Quote: "The randomization 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 each and were labelled with the participant's name, address, and identification numbers only" Comment: probably done.
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.
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 proba-

		bly blinded to the treatment assignment

Sood 1975

Methods	Trial conducted in New Dehli and Tamil Nadu, India.
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 of the control groups received placebo and other received vitamin B12 and folic acid alone. 4 intervention groups received vitamin B12, folic acid and iron in a range of 30 to 240 mg. The fifth intervention group received 120 mg of iron without vitamin B12 and folate. 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

Risk of bias ***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.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was 30% and reasons for it were reported.

Sood 1975 (*Continued*)

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.
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

SUMMIT 2008

Methods	A double-blind cluster-randomised trial conducted at Lombok island of Indonesia between July 1, 2001 and April 1, 2004
Participants	Pregnant women of any gestational age assessed by physical exam and reported LMP
Interventions	MMN group (n = 15804)) 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. 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 It should be noted that the data for SGA was 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.

Risk of bias	***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.
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	Unclear risk	Study was stopped early due to insufficient funds.
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 pro-

		duction 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

Sunawang 2009

Methods	A cluster-randomised trial conducted in 2 subdistricts of Indramayu district of west Java province of Indonesia from May 2000 till August 2003
Participants	Pregnant women irrespective of gestational age. Women suffering from diabetes mellitus, coronary heart disease and tuberculosis were excluded
Interventions	Intervention group (n = 432) received RDA of 15 micronutrients according to the UNICEF/UNU/WHO recommended formula, including 30 mg of ferrous fumarate. 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 was 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

Risk of bias ***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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (< 1%) and attrition (10.4%) were reported along with their reasons

Sunawang 2009 (*Continued*)

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.
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

Theobald 1937

Methods	This study was conducted at St. Mary Abbots hospital, London during 1936
Participants	Pregnant women less than 24 weeks of gestation. No baseline characteristics comparison was performed
Interventions	Intervention group (n = 50) received calcium lactate 20 grains, vitamin A 11,000 IU, D 450 IU. Placebo group did not receive any intervention
Outcomes	Albuminuria + hypertension, hypertension, albuminuria, hyperemeses, oedema, headache, cramps, insomnia
Notes	There was no proof that all the patients in intervention took capsules (vitamin A and D) and tablets (calcium lactate) regularly. Outcomes included in this study were not of review interest

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "An equal number of blue and white beads were placed in a box. Each women accepted for the experiment was asked to draw a bead from the box. Those who drew blue beads were placed in group

Theobald 1937 (*Continued*)

		A while those who drew white beads were placed in group B." Comment: probably done.
Allocation concealment (selection bias)	High risk	Comment: probably not done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No exclusion and attrition 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.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "participants were divided into 2 groups, the intervention group received extra vitamins and the control did not receive any intervention" Comment: probably not blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "symptoms were recorded by independent antenatal officers who had no knowledge as to which patients were receiving the additional substances". Comment: outcome assessors were blinded to the treatment assignment

Tofail 2008

Methods	The study was conducted in Matlab, a rural subdistrict in the east central plain of Bangladesh from November 2001 till December 2003
Participants	Pregnant women with gestational age 6-8 weeks, Hb greater than equal to 80 g/L and no serious disease were eligible for enrolment
Interventions	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, while the 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, blood pressure and kidney function in children, child growth outcomes, and adverse effects It should be noted that the data for SGA was 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 divided into 3 subgroups of MMN and iron folic acid groups. Iron folic acid 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 which 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. Stunting data relevant to this review are presented in Kahn 2013. 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

Risk of bias ***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 to permit judgement
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.
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 care-

Tofail 2008 (*Continued*)

		givers 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

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
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	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). 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
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 2014a 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

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomized", "study area was divided into 596 sectors of comparable size that were

West 2014 (*Continued*)

		used as units of randomization". Comment: probably done.
Allocation concealment (selection bias)	Unclear risk	Quote: "cluster-randomized", "Allocation: Randomized". Comment: insufficient information to permit judgement.
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.
Other bias	Low risk	Comment: no other bias was identified.
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.

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
Participants	Women residing in target villages and experiencing amenorrhoea for less than 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	Micronutrient 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. Control (n = 1777) received iron and folic acid

Zagre 2007 (*Continued*)

Outcomes	Birthweight and incidence of LBW, miscarriage, stillbirth, maternal mortality It should be noted that the data for SGA was 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, behavior 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 iron/folic acid group

Risk of bias ***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
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition was 18%. Reasons for attrition were reported. 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.
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

Zeng 2008

Methods	Community-based cluster-randomised trial conducted in 2 poor rural counties in Shaanxi province of north west China between August 2002 and January 2006
Participants	Pregnant women of less than 28 weeks' gestation between August 2002 and January 2006. Pregnancy was confirmed using last menstrual period (LMP) and urine pregnancy test
Interventions	Group A (n = 2017) received folic acid 0.4 mg. Group B (n = 1912) received iron 60 mg and folic acid 0.4 mg. Group C (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
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 was obtained from a separate report (Food and

Zeng 2008 (*Continued*)

	Nutrition Bulletin 2009) and not from the individual trial report.
Notes	For review purpose, MMN and iron folate groups are used. Intervention was administered till 6 weeks postpartum. Baseline characteristics at enrolment and both cluster and individual level baseline characteristics were balanced by treatment groups. Stunting, underweight, and wasting data presented as odds ratio and could not be included in the analysis

Risk of bias ***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.
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.
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

BMI: body mass index
Hb: haemoglobin
HIV: human immunodeficiency virus
IU: international unit
IUGR: intrauterine growth retardation
LBW: low birthweight
LGA: large-for-gestational age
LMP: last menstrual period
mcg: microgram
mg: milligram
Mg: magnesium
MMN: multiple micronutrient
RCT: randomised controlled trial
RDA: recommended daily allowance
SGA: small-for-gestational age

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

Study	Reason for exclusion
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
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

(*Continued*)

Carrasco 1962	Study has assessed the impact of D-sorbitol on the absorption of MMNs in pregnant women
Caulfield 1999	Only assesses zinc supplementation.
Caulfield 1999a	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
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
Dieckmann 1944	Fortification trial.
Fall 2007	This is not a trial evaluating micronutrient supplementation
Fawzi 1998	Includes pregnant women who are HIV-1 positive.
Feyi-Waboso 2005	Parenteral preparation.
Fleming 1986	Only assesses iron, folate and vitamin B in different combinations
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.
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

(*Continued*)

Hillman 1963	Only assesses pyridoxine supplementation.
Holly 1955	Only assesses iron and cobalt supplementation.
Hossain 2014	Trial evaluates the effect of vitamin D supplementation. Both groups received iron and calcium
Hunt 1983	Only assesses zinc supplementation.
Hunt 1984	Only assesses zinc supplementation.
Hunt 1985	Only assesses zinc supplementation.
Huybregts 2009	Assesses impact of balanced energy, protein dietary supplement
Huybregts 2013	Trial compares prenatal LNS vs MMN. Follow-up of primary trial excluded (Huybregts 2009).
Iannotti 2008	Only assesses zinc supplementation.
ICMR 2000	Assesses periconceptional supplementation of folic acid containing vitamins
Itam 2003	Not a randomised trial.
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
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	Describing prevalence of micronutrient deficiencies at baseline and its determinants

(*Continued*)

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 2001a	Only assesses vitamin A supplementation.
Muslimatun 2001b	Evaluates vitamin A supplementation.
Nguyen 2012	Protocol of a study evaluating pre-conceptional MMN vs IFA supplements
Nwagha 2010	Micronutrients given via injection.
Ochoa-Brust 2007	Assesses impact of vitamin C only.
Olofin 2014	The trial included HIV-positive women.
Park 1999	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
Ramirez-Velez 2011	Intervention group receives 9 micronutrients and control group receives 3 micronutrients
Raqib 2013	Evaluated the effect of vitamin B12 only.

(*Continued*)

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.
Schmidt 2002	Only assesses vitamin A supplementation.
Semba 2000	A trial of vitamin A supplementation in HIV-infected women.
Semba 2001	Only assesses vitamin A supplementation.
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.
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.
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

(*Continued*)

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]*

Ashorn 2015

Methods	Parallel randomised trial recruiting at 4 sites in Malawi. Setting: 1 public district hospital (Mangochi), 1 semiprivate hospital (Malindi), and 2 public health centres (Lungwena and Namwera) in Mangochi District, southern Malawi
Participants	Inclusion: ultrasound-confirmed pregnancy of no more than 20 completed gestation weeks, residence in the defined catchment area, availability during the period of the study, and signed or thumb-printed informed consent Exclusion: age younger than 15 years, need for frequent medical attention due to a chronic health condition, diagnosed asthma treated with regular medication, severe illness warranting hospital referral, history of allergy toward peanuts, history of anaphylaxis or serious allergic reaction to any substance, requiring emergency medical care, pregnancy complications evident at enrolment visit (moderate to severe edema, blood Hb concentration, 50 g/L, systolic blood pressure .160 mm Hg or diastolic blood pressure .100 mm Hg), earlier participation in the iLiNS-DYAD-M trial (during a previous pregnancy), or concurrent participation in any other clinical trial 1391 women randomised. (IFA - 463; MMN 466; LNS - 462). Lost to follow-up (IFA 26; MMN 32; LNS 26). Group demographic characteristics similar.
Interventions	Intervention: Group 1: IFA - 1 capsule containing 60 mg iron and 400 mcg folic acid and 2 doses of intermittent preventive malaria treatment with sulfadoxine-pyrimethamine Group 2: MMN - malaria treatment as above plus 1 capsule containing IFA and 16 micronutrients Group 3: LNS - malaria treatment as above and sachets of SQ-LNS containing the same micronutrients as group 2 plus 4 additional minerals, protein and fat (118 kcal) All supplements to be taken daily. Follow-up until 6 weeks postpartum. Data collectors delivered supplements fortnightly. Participants were invited to antennal care visits at the clinic at 32 and 36 weeks and 1-2 weeks postpartum. Participants were given mobile phones and airtime so that they could inform of deliveries outside of clinics
Outcomes	Primary outcomes: birthweight and newborn length (within 6 weeks of birth). Secondary outcomes: newborn weight, head circumference, mid-upper arm circumference (MUAC), and the duration of pregnancy, as well as the incidence of maternal or newborn SAEs. Several other maternal and infant outcomes are reported

Ashorn 2015 (*Continued*)

Notes	Due to testing of LNS products for a bacteria, 160 pregnant women in the LNS group missed out their supplement for 1-20 days during August 2012. 127 of these women were provided with IFA tablets at this time, while 33 were not available for contact Adverse events were recorded separately and monitored, and a study physician determined if the participant should continue with the allocated supplement Analysis modified ITT = participants with missing data for an outcome were excluded from analysis of that outcome 12 twin pregnancies were excluded from all analyses. 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. Authors have agreed to provide these data for inclusion in the next update of this review

Gathwala 2012

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

MMN: multiple micronutrient

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

Biggs 2011

Trial name or title	A randomised controlled trial to compare the impact on birthweight of daily iron folic acid, twice weekly iron folic acid and twice weekly multiple-micronutrient supplementation for pregnant women in Ha Nam province, Vietnam
Methods	Randomised controlled trial. Communes agreeing to participate in the study will be randomly assigned to 1 of the 3 treatment arms. The commune was chosen as the cluster unit of randomisation to reduce the likelihood of interactions between the intervention groups. All eligible women in each commune will be invited to participate in the study. The pharmaceutical manufacturer and the Chairman of the DSMC will retain the allocation code
Participants	Healthy pregnant women 16 weeks' gestation or less were included. Women with complicated pregnancies (e.g. twins, diabetes, other medical conditions), or Hb $\leq$ 8.0 will be excluded

Biggs 2011 (*Continued*)

Interventions	Study has 3 arms. Group 1 will receive elemental iron 60 mg and folic acid 1.5 mg taken orally twice weekly, group 2 will receive multiple micronutrients (modified 2xUNIMAPP) taken orally twice weekly, and group 3 will receive elemental iron 60 mg and folic acid 0.4 mg taken orally once daily. All supplements will be provided for the duration of pregnancy and 3 months postpartum
Outcomes	Birthweight, maternal Hb and ferritin, infant cognitive development, infant height, Hb
Starting date	September 2010.
Contact information	Beverley-Ann Biggs Department of Medicine Royal Melbourne Hospital Parkville, Victoria, 3050 Australia. Tel # 61383443256 Email: babiggs@unimelbi.edu.au
Notes	

Dewey 2011

Trial name or title	ILINS-DYAD - Ghana population. Protocol identifier: NCT00970866. Dewey 2011 title (abstract): Efficacy of Lipid-Based Nutrient Supplements (LNS) for pregnant and lactating women and their Infants
Methods	This study will be a community-based, randomised controlled trial with 3 intervention groups
Participants	Inclusion criteria 1. At least 18 years of age. 2. No more than 20 weeks of gestation. 3. Given antenatal cards of the Ghana Health Service. 4. Completed the initial routine antenatal examination at the clinics. 5. HIV negative or status unknown (as from the antenatal card). 6. Free from chronic disease, e.g. malignancy requiring frequent medical attention (as from the antenatal card). 7. Residing in the Manya Krobo or Yilo Krobo district. 8. Prepared to sign an informed consent. 9. Living in the area throughout the duration of the study. 10. Acceptance of home visitors. Exclusion criteria 1. Known asthmatic or history of allergy towards peanut or milk products. 2. Concurrent participation in another clinical trial. 3. Severe illness warranting hospital referral.

Dewey 2011 (*Continued*)

Interventions	1. Dietary supplement: iron and folic acid (IFA): pregnant women will receive 1 (1) iron (60 mg) and folic acid (400 mcg) (IFA) tablet daily during pregnancy, and a tablet containing calcium (Ca) only (akin to a placebo) during lactation; there will be no supplementation for infants born to the women. The Fe/FA tablets will be taken each day with water after meals 2. Dietary supplement: multiple micronutrient (MMN) group. Pregnant women will receive 1 (1) multiple-micronutrient tablet daily during pregnancy and the first 6 months of lactation; there will be no supplementation for infants born to the women. The MMN tablets will be taken each day with water after meals 3. Dietary supplement: lipid-based nutrient supplements (LNS) group. Pregnant women will receive 20 g of LNS-P&L daily during pregnancy and the first 6 months of lactation, whilst infants born to the women will receive 20 g of LNS-20 g daily from 6 to 18 months of age
Outcomes	Primary outcome is child length at birth, length-for-age Z-score (LAZ, based on WHO 2006 growth standards) at 18 months of age Secondary outcomes include the following. i. Maternal 1. 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. 2. Pregnancy outcomes (birthweight, gestational age). 3. Anemia, micronutrient (iron, vitamin A, B-vitamins, zinc) and EFA status, and malarial antigen at ~ 36 wk gestation and 6 mo postpartum. 4. Total plasma cholesterol at ~ 36 wk gestation. 5. Blood pressure and urinary iodine, isoprostane (marker of oxidative stress) and 8-hydroxy-2'deoxyguanosine (8-OHdG) (marker of DNA damage) at 36 wk gestation. 6. Breast milk composition (EFA, vitamin A, B-vitamins, iodine) at 6 mo postpartum. 7. Depressive symptoms (which may be related to EFA status) at 6 mo postpartum. ii. Child 1. Anthropometric status (weight, length, head circumference and mid-upper arm circumference) at birth and 3, 6, 12 and 18 mo. 2. Anaemia, micronutrient (iron, vitamin A, B-vitamins, iodine) and EFA status, and malarial antigen at 6 and 18 months. 3. Morbidity between 6 and 18 months. 4. Child feeding practices and maternal report of child sleep patterns at 6, 12 and 18 months. 5. Energy intake from complementary foods at 9 and 15 months. 6. Antibody response to measles vaccination at 12 months. 7. 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 to 18 months. 8. Neuro-behavioural development at 18 months of age.
Starting date	November 2009.
Contact information	Kathryn G Dewey, UC Davis
Notes	Sample size = 864. For the 2015 update of this review, we identified 3 further reports related to the ILINS-DYAD Ghana trial: Adu-Afarwuah 2013, Adu-Afarwuah 2014 and Oaks 2014. These reports are abstracts; the full report of pregnancy outcome data has not yet been published

Hirschberg 2014

Trial name or title	Protocol identifier: NCT02190565. Supplementation with WellnessPack mama during pregnancy and lactation - a randomized 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 body mass index (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 below the age of 18 or above 40 years old. 2. Women with a BMI below 18.5 or above 30 kg/m2. 3. Women with any form of anaemia as diagnosed at the first visit to the prenatal clinic. 4. Women expecting 2 or more babies. 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 iron and folic acid 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

Moore 2011

Trial name or title	Investigating the effects of prenatal and infancy nutritional supplementation on infant immune development in The Gambia: The Early Nutrition and Immune Development (ENID) Trial
Methods	A randomised trial to investigate the effects of prenatal and infancy nutritional supplementation on infant immune development
Participants	Women (aged 18 to 45 years) resident in rural Kiang West Region, the Gambia, with pregnancy confirmed by urine test and ultrasound examination and with gestational age approximately 10-20 weeks will be recruited. Women currently enrolled in another MRC study or current pregnancy (beyond 20 weeks on ultrasound assessment), with severe anaemia (Hb less than 7 g/dL), reported onset of menopause will be excluded
Interventions	4 pregnancy interventions, to be given daily from 12 weeks' gestation until delivery: 1. FeFol: Iron-folate, 60 mg iron 400 µg folate, representing the usual standard of care during pregnancy, as per Gambian Government guidelines (control group). 2. MMN: multiple micronutrients. A combination of 15 micronutrients, specifically designed for use during pregnancy, and as formulated by UNICEF. A single tablet provides the recommended dietary allowance (RDA) for each micronutrient, but we will supplement women in this arm of the trial with 2 daily MMN tablets. 3. PE + FeFol: protein-energy and iron-folate. 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: protein-energy and multiple micronutrients. A micronutrient fortified food-based supplement also developed by Valid International, and 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 will further be randomised to receive either a lipid-based nutritional supplement, with or without additional MMN, or placebo from 6 to 12 months of age
Outcomes	Primary outcomes: 1. Thymic index at 1, 8, 24 and 52 weeks of age. 2. Antibody response to EPI vaccines (diphtheria, tetanus toxoid, HiB, measles) Secondary outcomes: cellular markers of immunity in a randomly selected subcohort of infants, stratified by treatment group. The secondary outcome measurements will be assessed when the infants are 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
Starting date	October 1, 2009.
Contact information	Sophie Moore MRC Keneba MRC Laboratories Fajara, Banjul Gambia PO Box 273 Email: smoore@mrc.gm

Moore 2011 (*Continued*)

Notes	800 mother-infant pairs.

Mridha 2014

Trial name or title	Rang-Din Nutrition Study. Mridha 2014 (abstract) title: Lipid-based nutrient supplements for pregnant women reduce newborn stunting in Bangladesh Protocol identifier: NCT01715038. Harding 2014 documents trial methods and compliance.
Methods	Cluster-randomised effectiveness trial
Participants	4011 pregnant women recruited. Inclusion criteria 1. Gestational age $\leq$ 20 weeks. 2. Planning to remain in the study area during pregnancy and the following 3 years (i.e. a permanent resident of the study area). Exclusion criteria 1. Pregnancy identified and registered in the CHDP program before the beginning of the enrolment.
Interventions	1. Experimental: Comprehensive "Comprehensive" LNS: LNS-PLW provided daily to mothers during pregnancy and postpartum lactation (a total of at least 11 months, starting by 20 weeks' gestation and ending at 6 months postpartum) and LNS developed for infants and young children (LNS-child) provided daily to their infants (beginning at 6 months of age for a period of 18 months i.e. from 6-24 months of age) 2. Experimental: child-only LNS "Child-only" LNS: daily LNS-child supplementation of the child starting at 6 months of age and ending at 24 months of age (18 months total). Women will be provided with iron and folic acid (IFA) tablets during pregnancy and for 3 months postpartum 3. Experimental: child-only MNP "Child-only" MNP: daily MNP supplementation of the child starting at 6 months of age and ending at 24 months of age (18 months total). Women will be provided with iron and folic acid (IFA) tablets during pregnancy and for 3 months postpartum 4. Active comparator: control: IFA. Control: no additional nutrient supplementation for the child will be provided through the study, but the regular nutrition education and visits provided by the program frontline staff will continue. Women will be provided with IFA tablets during pregnancy and for 3 months postpartum
Outcomes	Primary outcome measures: 1. Birthweight [Time Frame: Within 48 hours (or back calculated from later measurements).] [Designated as safety issue: No]. Birthweight of the infants (women who received LNS-PLW vs. women who received IFA tablets). Pre-defined tests for interaction will be done for: baseline maternal characteristics (age, height, BMI, education, primiparity, food insecurity, wealth and gestational age at enrolment), time of year when outcome was assessed and child sex 2. Birth length [Time Frame: Within 48 hours (or back calculated from later measurements)] [Designated as safety issue: No]. Birth length of the infants (women who received LNS-PLW vs. women who received IFA tablets). Pre-defined tests for interaction will be done for: baseline maternal characteristics (age, height, BMI,

	education, primiparity, food insecurity, wealth and gestational age at enrolment), time of year when outcome was assessed and sex of child 3. Child linear growth status at 24 months [Time Frame: 24 months] [Designated as safety issue: No]. Linear growth (the "comprehensive" LNS approach vs. the "child-only" LNS approach vs. "child-only" MNP) vis-à-vis one another and vis-à-vis the control group. Pre-defined tests for interaction will be done for: baseline maternal characteristics (age, height, BMI, education, primiparity, food insecurity, wealth and gestational age at enrolment), time of year when outcome was assessed and sex of child Secondary outcome measures: There are many additional maternal and neonatal outcomes listed on the protocol
Starting date	October 2011 - April 2015.
Contact information	Kathryn Dewey, University of California, Davis.
Notes	Study sponsors: University of California, Davis US Agency for International Development Family Health International 360 International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) World Mission Prayer League (LAMB) FANTA

Ramakrishnan 2012

Trial name or title	Impact of pre-pregnancy micronutrient supplementation on maternal and child outcomes Protocol identifier: NCT01665378. Setting: Vietnam.
Methods	Parallel, double-blind randomised trial.
Participants	Inclusion criteria: 1. 18-35 years old. 2. Currently married. 3. Intends to live in the study area for the next 24 months. 4. Plans to have children in the next year. 5. Agrees to participate with informed consent. Exclusion criteria: 1. Currently pregnant. 2. Delivered in the previous 6 months. 3. Regularly consumed IFA or MM supplements in the past 2 months. 4. Severe anaemia (Hb < 7 g/L). 5. History of high-risk pregnancy including abruptio placenta, placenta previa, gestational diabetes, pregnancy-induced hypertension, coagulation disorders, thrombocytopenia or chronic vascular, renal or systemic disease and drug use. Chronic haematological diseases, hereditary defects of red cells or Hb.
Interventions	Arms 1 and 2: experimental: multiple micronutrients. Multiple micronutrient groups receive: vitamin A (μg) 800 vitamin D (IU) 600 vitamin E (mg) 10 vitamin C (mg) 70 thiamine (mg) 1.4 riboflavin (mg) 1.4 niacin (mg) 18 vitamin B6 (mg) 1.9 vitamin B12 (μg) 2.6 folic acid (μg)* 2800 Iron (mg)* 60 zinc (mg) 15 copper (mg) 2 selenium (μg) 65 iodine (μg) 150

Ramakrishnan 2012 (*Continued*)

	Arm 3 and 4: active comparator: iron and folic acid. Iron and folic acid groups receive: iron (60 mg) and folic acid (2800 μg), based on current WHO recommendations for WRA Arm 5 and 6: placebo comparator: folic acid. Folic acid groups receive: 2800 μg FA once a week during the pre-pregnancy period
Outcomes	Primary outcomes: 1. Birth Size [Time Frame: At birth] [Designated as safety issue: No] Infants' weight, length and head circumference will be measured as early as possible within 24 hours after birth using standard procedures. All measurements will be obtained in duplicate by the same data collector. Weight-for-age and length-for-age z scores will be calculated using the 2006 WHO reference data 2. Gestational Age [Time Frame: At birth] [Designated as safety issue: No] Gestational age will be calculated based on the date of last menstrual period. This method has been shown to be reliable in previous work and we expect precise estimates since we will be visiting women weekly from baseline during the pre-pregnancy period and will exclude women who may be have delivered in the past 6 months Secondary outcomes: Maternal and infant iron status.
Starting date	October 2011 - September 2014.
Contact information	Dr. Usha Ramakrishnan, Emory University.
Notes	Sponsor: Emory University. Collaborator: MicroNutrient Initiative.

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	I) Food supplement 5 days/week from marriage to term (~18 months) II) Food supplement 5 days/week from 16 weeks' gestation to term (~5 months) III) 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.

Tu 2013 (*Continued*)

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
LNS: lipid-based nutrient supplement
mcg: microgram
MMN: multiple micronutrient
RDA: recommended daily allowance
SAE: serious adverse event

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	16		Risk Ratio (Random, 95% CI)	Subtotals only
1.1 MMN with iron and folic acid vs iron with or without folic acid	15		Risk Ratio (Random, 95% CI)	0.96 [0.90, 1.03]
1.2 MMN with iron and folic acid vs placebo	1		Risk Ratio (Random, 95% CI)	1.10 [0.41, 2.95]
2 Small-for-gestational age	15		Risk Ratio (Random, 95% CI)	Subtotals only
2.1 MMN with iron and folic acid vs iron with or without folic acid	14		Risk Ratio (Random, 95% CI)	0.92 [0.86, 0.98]
2.2 MMN with iron and folic acid vs placebo	1		Risk Ratio (Random, 95% CI)	0.93 [0.53, 1.63]
3 Low birthweight	16		Risk Ratio (Random, 95% CI)	Subtotals only
3.1 MMN with iron and folic acid vs iron with or without folic acid	15		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)	1.63 [0.66, 4.03]
4 Perinatal mortality	13		Risk Ratio (Random, 95% CI)	Subtotals only
4.1 MMN with iron and folic acid vs iron with or without folic acid	13		Risk Ratio (Random, 95% CI)	1.01 [0.91, 1.13]
5 Stillbirths	15		Risk Ratio (Random, 95% CI)	Subtotals only
5.1 MMN with iron and folic acid vs iron with or without folic acid	15		Risk Ratio (Random, 95% CI)	0.97 [0.87, 1.09]
6 Neonatal mortality	11		Risk Ratio (Random, 95% CI)	1.06 [0.92, 1.22]
6.1 MMN with iron and folic acid vs iron with or without folic acid	11		Risk Ratio (Random, 95% CI)	1.06 [0.92, 1.22]
7 Maternal anaemia (third trimester Hb <110 g/L)	5		Risk Ratio (Random, 95% CI)	Subtotals only
7.1 MMN with iron and folic acid vs iron with or without folic acid	4		Risk Ratio (Random, 95% CI)	1.03 [0.85, 1.24]
7.2 MMN with iron and folic acid vs placebo	1		Risk Ratio (Random, 95% CI)	0.46 [0.29, 0.73]
8 Miscarriage (loss before 28 weeks)	8		Risk Ratio (Random, 95% CI)	Subtotals only
8.1 MMN with iron and folic acid vs iron with or without folic acid	8		Risk Ratio (Random, 95% CI)	0.91 [0.80, 1.03]

9 Maternal mortality	3		Risk Ratio (Random, 95% CI)	Subtotals only
9.1 MMN with iron and folic acid vs iron with or without folic acid	3		Risk Ratio (Random, 95% CI)	0.97 [0.63, 1.48]
10 Very preterm birth (before 34 weeks of gestation)	1		Risk Ratio (Random, 95% CI)	Subtotals only
10.1 MMN with iron and FA vs iron with or without folic acid	1		Risk Ratio (Random, 95% CI)	1.30 [0.67, 2.54]
11 Congenital anomalies	1		Risk Ratio (Random, 95% CI)	Subtotals only
11.1 MMN with iron and folic acid vs iron with or without folic acid	1		Risk Ratio (Random, 95% CI)	0.99 [0.14, 7.00]
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	770	Mean Difference (IV, Random, 95% CI)	-0.02 [-6.78, 6.74]
12.2 Mental development scores at 12 months of age	1	744	Mean Difference (IV, Random, 95% CI)	1.21 [-5.06, 7.48]
12.3 Psychomotor development scores ar 6 months of age	1	770	Mean Difference (IV, Random, 95% CI)	-0.16 [-3.91, 3.59]
12.4 Psychomotor development scores at 12 months of age	1	744	Mean Difference (IV, Random, 95% CI)	0.34 [-2.73, 3.41]
13 Mode of delivery: caesarean section	4		Risk Ratio (Random, 95% CI)	1.04 [0.74, 1.46]
13.1 MMN with iron and folic acid vs iron with or without folic acid	4		Risk Ratio (Random, 95% CI)	1.04 [0.74, 1.46]
14 Pre-eclampsia	1		Risk Ratio (Random, 95% CI)	0.67 [0.12, 3.74]

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	15		Risk Ratio (Random, 95% CI)	Subtotals only
1.1 BMI < 20 kg/m^2	4		Risk Ratio (Random, 95% CI)	0.85 [0.80, 0.90]
1.2 BMI ≥ 20 kg/m^2	11		Risk Ratio (Random, 95% CI)	1.02 [0.97, 1.07]
2 Preterm births: mean maternal height	15		Risk Ratio (Random, 95% CI)	Subtotals only
2.1 Maternal height < 154.9 cm	8		Risk Ratio (Random, 95% CI)	0.94 [0.84, 1.06]
2.2 Maternal height ≥ 154.9 cm	7		Risk Ratio (Random, 95% CI)	0.99 [0.93, 1.06]

3 Preterm births: timing of supplementation	15	Risk Ratio (Random, 95% CI)	Subtotals only
3.1 Supplementation started before 20 weeks	11	Risk Ratio (Random, 95% CI)	0.94 [0.87, 1.01]
3.2 Supplementation after 20 weeks	4	Risk Ratio (Random, 95% CI)	1.03 [0.96, 1.10]
4 Preterm births: dose of iron	15	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 [0.92, 1.19]
4.2 MMN with 60 mg iron vs. supplement with 60 mg iron	4	Risk Ratio (Random, 95% CI)	0.95 [0.85, 1.06]
4.3 MMN with 30 mg iron vs. supplement with 30 mg iron	5	Risk Ratio (Random, 95% CI)	0.93 [0.83, 1.05]
5 Small-for-gestational age: mean maternal BMI	14	Risk Ratio (Random, 95% CI)	Subtotals only
5.1 BMI < 20 kg/m^2	4	Risk Ratio (Random, 95% CI)	1.00 [0.95, 1.05]
5.2 BMI ≥ 20 kg/m^2	10	Risk Ratio (Random, 95% CI)	0.86 [0.81, 0.92]
6 Small-for-gestational age: dose of iron	14	Risk Ratio (Random, 95% CI)	Subtotals only
6.1 MMN with 30 mg iron vs. supplement with 60 mg iron	6	Risk Ratio (Random, 95% CI)	0.88 [0.79, 0.98]
6.2 MMN with 60 mg iron vs. supplement with 60 mg iron	4	Risk Ratio (Random, 95% CI)	0.89 [0.72, 1.11]
6.3 MMN with 30 mg iron vs. supplement with 30 mg iron	4	Risk Ratio (Random, 95% CI)	0.99 [0.97, 1.01]
7 Small-for-gestational age: timing of supplementation	14	Risk Ratio (Random, 95% CI)	Subtotals only
7.1 Supplementation started before 20 weeks	10	Risk Ratio (Random, 95% CI)	0.97 [0.93, 1.02]
7.2 Supplementation after 20 weeks	4	Risk Ratio (Random, 95% CI)	0.85 [0.75, 0.98]
8 Small-for-gestational age: mean maternal height	14	Risk Ratio (Random, 95% CI)	Subtotals only
8.1 Maternal height < 154.9 cm	8	Risk Ratio (Random, 95% CI)	0.99 [0.97, 1.01]
8.2 Maternal height ≥ 154.9 cm	6	Risk Ratio (Random, 95% CI)	0.82 [0.76, 0.89]
9 Perinatal mortality: mean maternal BMI	13	Risk Ratio (Random, 95% CI)	Subtotals only
9.1 BMI < 20 kg/m^2	4	Risk Ratio (Random, 95% CI)	1.05 [0.85, 1.29]
9.2 BMI ≥ 20 kg/m^2	9	Risk Ratio (Random, 95% CI)	1.02 [0.87, 1.19]
10 Perinatal mortality: mean maternal height	13	Risk Ratio (Random, 95% CI)	Subtotals only
10.1 Maternal height < 154.9 cm	8	Risk Ratio (Random, 95% CI)	1.01 [0.89, 1.14]
10.2 Maternal height ≥ 154.9 cm	5	Risk Ratio (Random, 95% CI)	1.04 [0.81, 1.34]
11 Perinatal mortality: timing of supplementation	13	Risk Ratio (Random, 95% CI)	Subtotals only
11.1 Supplementation before 20 weeks	10	Risk Ratio (Random, 95% CI)	1.13 [0.96, 1.33]

11.2 Supplementation after 20 weeks	3	Risk Ratio (Random, 95% CI)	0.88 [0.80, 0.97]
12 Perinatal mortality: dose of iron	13	Risk Ratio (Random, 95% CI)	Subtotals only
12.1 MMN with 30 mg iron vs. supplement with 60 mg iron	6	Risk Ratio (Random, 95% CI)	1.19 [0.95, 1.48]
12.2 MMN with 60 mg iron vs. supplement with 60 mg iron	3	Risk Ratio (Random, 95% CI)	1.08 [0.71, 1.63]
12.3 MMN with 30 mg iron vs. supplement with 30 mg iron	4	Risk Ratio (Random, 95% CI)	0.92 [0.87, 0.99]

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	10		Risk Ratio (Random, 95% CI)	0.97 [0.90, 1.04]
2 Small-for-gestational age	8		Risk Ratio (Random, 95% CI)	0.91 [0.84, 1.00]
3 Low birthweight	11		Risk Ratio (Random, 95% CI)	0.88 [0.85, 0.91]
4 Perinatal mortality	10		Risk Ratio (Random, 95% CI)	1.04 [0.92, 1.17]
5 Stillbirths	11		Risk Ratio (Random, 95% CI)	0.98 [0.88, 1.09]
6 Neonatal mortality	11		Risk Ratio (Random, 95% CI)	1.06 [0.92, 1.22]
7 Maternal anaemia (third trimester Hb <110 g/L)	3		Risk Ratio (Random, 95% CI)	1.01 [0.79, 1.29]
8 Miscarriage (loss before 28 weeks)	6		Risk Ratio (Random, 95% CI)	0.92 [0.81, 1.05]
9 Maternal mortality	2		Risk Ratio (Random, 95% CI)	1.05 [0.66, 1.64]
10 Very preterm birth (before 34 weeks of gestation)	1		Risk Ratio (Random, 95% CI)	1.30 [0.67, 2.54]
11 Congenital anomalies	1		Risk Ratio (Random, 95% CI)	0.99 [0.14, 7.00]
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	770	Mean Difference (IV, Random, 95% CI)	-0.02 [-6.78, 6.74]
12.2 Mental development scores at 12 months of age	1	744	Mean Difference (IV, Random, 95% CI)	1.21 [-5.06, 7.48]
12.3 Psychomotor development scores ar 6 months of age	1	770	Mean Difference (IV, Random, 95% CI)	-0.16 [-3.91, 3.59]
12.4 Psychomotor development scores at 12 months of age	1	744	Mean Difference (IV, Random, 95% CI)	0.34 [-2.73, 3.41]
13 Mode of delivery: caesarean section	4		Risk Ratio (Random, 95% CI)	1.04 [0.74, 1.46]

ADDITIONAL TABLES

Table 1. Micronutrients given to women in the intervention group

Study ID	Iron	Folic acid	Vit A	Beta-carot	Vit C	Vit D	Vit E	Vit B1	Vit B2	Vit B3	Vit B6	Vit B12	Vit K	Cop-per	Se-le-nium	Zinc	Io-dine	Mag-ne-sium	Cal-cium	Phos pho-rus	Bi-otin	Potas sium	Man-ganese
Bhut 2009	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓						
Brou 2010	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓					
Chri tian 2003	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓					
Cogs 2013	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓						
Fawz 2007	✓	✓						✓	✓	✓	✓	✓											
Friis 2004	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓							
Hini 2004		✓		✓	✓		✓	✓	✓	✓	✓	✓		✓		✓		✓					
Kaes tel 2005	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓						
Os-rin 2005	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓						
Ra-maku ish-nan	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓				✓		✓					

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

200																						
Robe froid 2008	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓					
Sood 1975	✓	✓										✓										
SUM MIT 2008	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓		✓	✓	✓	✓					
Suna 2009	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓		✓	✓	✓	✓					
Thec 1937			✓			✓													✓			
To-fail 2008	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓					
West 2014	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓					
Za-gre 2007	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓					
Zeng 2008	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓					

FEEDBACK

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 2011]; and Adu-Afarwuah 2015[3] [protocol cited as Dewey 2011). 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 (eg. 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

1. Ashorn P, Alho L, Ashorn U, Cheung YB, Dewey KG, Harjunmaa U, et al. The impact of lipid-based nutrient supplement provision to pregnant women on newborn size in rural Malawi: a randomized controlled trial. The American Journal of Clinical Nutrition 2015; 101: 387-97.
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

Tau² was greater than zero, or there was a low P value (less than 0.10) in the Chi² 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).

Contributors

Harshpal Singh Sachdev MD, Senior Consultant in Pediatrics and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research, New Delhi, India

Delanjathan Devakumar PhD, NIHR Clinical Lecturer in Public Health, Institute for Global Health, Faculty of Population Health Sciences, University College London, London, UK

Caroline Fall DM, Professor of International Paediatric Epidemiology, MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK

Clive Osmond PhD, Professor of Biostatistics, MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK

David Osrin PhD, Professor of Global Health, Institute for Global Health, Faculty of Population Health Sciences, University College London, London, UK

Jonathan Broad MBChB, Honorary research fellow, University of Bristol, Academic Foundation Doctor, Peninsula Deanery

Barrie Margetts PhD, Emeritus Professor, Population Health Sciences Research Group, Faculty of Medicine, University of Southampton, Southampton, UK

Batool A Haider, Researcher, Department of Global Health and Population, Harvard School of Public Health, Boston, MA, USA

Zulfiqar A Bhutta, Robert Harding Chair in Global Child Health & Policy, Centre for Global Child Health, Hospital for Sick Children, Toronto, Canada

Philippa Middleton, Editor, Australian Satellite of Cochrane Pregnancy and Childbirth/Principal Research Fellow, Healthy Mothers, Babies and Children, South Australian Health and Medical Research Institute, Women's and Children's Hospital, Adelaide, Australia

WHAT'S NEW

Last assessed as up-to-date: 11 March 2015.

Date	Event	Description
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 for the main comparison. 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

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 4, 2006

Date	Event	Description
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.
10 November 2015	Amended	We have corrected I^2 values for footnotes 1 and 2 in the Summary of findings for the main comparison.

(*Continued*)

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
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
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 2004; Jarvenpaa 2007; Kaestel 2005; Roberfroid 2008; Rumiris 2006a; Sood 1975; SUMMIT 2008; Sunawang 2009; Theobald 1937; Tofail 2008; Vadillo-Ortega 2011; Zagre 2007; Zeng 2008) and 15 new excluded studies. We have also identified six ongoing studies (Biggs 2011; Cogswell 2006a; Dewey 2011; Fall 2007a; Moore 2011; 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.
17 February 2012	New citation required but conclusions have not changed	Review updated. Conclusions not changed.
20 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Batool A Haider (BAH) and Zulfiqar A Bhutta (ZAB) undertook the current 2015 update of the 2012 Cochrane Review. BAH undertook the revised analysis with input from ZAB. Both authors approved the final version of the review.

ZAB was the principal investigator of Bhutta 2009a, and data extraction was undertaken by BAH and Arjumand Rizvi 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

Batool A Haider: 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.

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

The methods have been updated to reflect the latest *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The prespecified subgroup analysis 'duration of treatment' has been merged 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'.

Two new secondary outcomes have been included; these are macrosomia and mode of delivery. The list of primary outcomes has been modified so that it now includes some outcomes that were earlier included as secondary outcomes. The changes to the primary and secondary outcomes have been made 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 multiple micronutrients (MMN) or MMN via food fortification are now not included.

A 'Summary of findings' table has been added.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; Drug Interactions; Folic Acid [*administration & dosage]; Iron, Dietary [*administration & dosage]; Micronutrients [*administration & dosage; adverse effects; deficiency]; Pregnancy Complications [*therapy]; Pregnancy Outcome; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy