Multiple-micronutrient supplementation for women during pregnancy (Review)

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[Intervention Review]

Multiple-micronutrient supplementation for women during pregnancy

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Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 11, 2012.
Review content assessed as up-to-date: 17 February 2012.

Citation: Haider BA, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No.: CD004905. DOI: 10.1002/14651858.CD004905.pub3.

ABSTRACT

Background

Multiple-micronutrient deficiencies often coexist in low- to middle-income countries. They are exacerbated in pregnancy due to the increased demands, leading to potentially adverse effects on the mother. Substantive evidence regarding the effectiveness of multiple-micronutrient supplements (MMS) during pregnancy is not available.

Objectives

To evaluate the benefits to both mother and infant of multiple-micronutrient supplements in pregnancy and to assess the risk of adverse events as a result of supplementation.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (17 February 2012) 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 multiple-micronutrient supplementation during pregnancy and its effects on the pregnancy outcome, irrespective of language or 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 trial quality. Two review authors independently extracted the data. Data were checked for accuracy.

Main results

Twenty-three trials (involving 76,532 women) were identified as eligible for inclusion in this review but only 21 trials (involving 75,785 women) contributed data to the review.

When compared with iron and folate supplementation, MMS resulted in a statistically significant decrease in the number of low birthweight babies (risk ratio (RR) 0.89; 95% confidence interval (CI) 0.83 to 0.94) and small-for-gestational age (SGA) babies (RR

0.87; 95% CI 0.81 to 0.95). No statistically significant differences were shown for other maternal and pregnancy outcomes: preterm births RR 0.99 (95% CI 0.96 to 1.02), miscarriage RR 0.90 (95% CI 0.79 to 1.02), maternal mortality RR 0.97 (95% CI 0.63 to 1.48), perinatal mortality RR 0.99 (95% CI 0.84 to 1.16), stillbirths RR 0.96 (95% CI 0.86 to 1.07) and neonatal mortality RR 1.01 (95% CI 0.89 to 1.15).

A number of prespecified clinically important outcomes could not be assessed due to insufficient or non-available data. These include placental abruption, congenital anomalies including neural tube defects, premature rupture of membranes, neurodevelopmental delay, very preterm births, cost of supplementation, side-effects of supplements, maternal well being or satisfaction, and nutritional status of children.

Authors' conclusions

Though multiple micronutrients have been found to have a significant beneficial impact on SGA and low birthweight babies, we still need more evidence to guide a universal policy change and to suggest replacement of routine iron and folate supplementation with a MMS. Future trials should be adequately powered to evaluate the effects on mortality and other morbidity outcomes. Trials should also assess the effect of variability between different combinations and dosages of micronutrients, keeping within the safe recommended levels. In regions with deficiency of a single micronutrient, evaluation of each micronutrient against a placebo in women already receiving iron with folic acid would be especially useful in justifying the inclusion of that micronutrient in routine antenatal care.

PLAIN LANGUAGE SUMMARY

Multiple-micronutrient supplementation for women during pregnancy

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. Combining multiple micronutrients has been suggested as a cost-effective way to achieve multiple benefits for the 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. Overall, multiple-micronutrient supplementation reduced the number of low birthweight and small-for-gestational age babies when compared with supplementation with two or less micronutrients, iron and folic acid supplements, no supplementation or a placebo. This review included 23 studies (involving 76,532 women) but only 21 trials (involving 75,785 women) contributed data. However, more evidence of effect is needed, particularly for determining any adverse effects including placental abruption, premature rupture of the membranes, neural tube defects and other congenital abnormalities, neurodevelopmental delay, very preterm births and side-effects of the supplements.

BACKGROUND

Description of the condition

Micronutrients are vitamins and minerals required in minute amounts for normal functioning, growth and development. Women in low-income countries often consume inadequate levels of micronutrients due to limited intake of animal products, fruits, vegetables and fortified foods (Huffman 1998). The resulting micronutrient deficiencies are exacerbated in pregnancy leading to potentially adverse effects on the mother such as anaemia, hypertension, complications of labour and even death (Ramakrishnan 1999). At least 50 million pregnant women in low-income countries are anaemic, primarily due to iron deficiency (Stoltzfus 1995). Vitamin A deficiency affects millions of women and children worldwide. A study carried out in Nepal showed that 20% of pregnant women and 27% of postpartum women were vitamin A deficient (West 1997). Approximately 100 million women of reproductive age suffer from iodine deficiency (Leslie 1991). An estimated 82% of pregnant women worldwide have inadequate in-

takes of zinc to meet the normative needs of pregnancy (Caulfield 1998). In Egypt, suboptimal vitamin B6 status has been observed among more than one-third of breastfeeding women based on low breastmilk concentrations (Kirksey 1994). Low serum vitamin B12 has been observed among pregnant and lactating women in Mexico, and low breastmilk vitamin B12 was reported in Kenya (Allen 1993).

Micronutrient status plays an important role in pregnancy and birth outcomes. Iron deficiency results in anaemia, which may increase the risk of death from haemorrhage after delivery although its effects on fetal development and birth outcomes are still unclear. Folic acid deficiency can lead to haematological consequences, pregnancy complications and congenital malformations but, again, the association with other birth outcomes is equivocal (Black 2001). A clinical trial by Botto et al has demonstrated a protective effect of multivitamin supplements and folic acid against neural tube defects and other defects such as orofacial clefts and some heart defects, although the evidence is not as consistent or as strong as with neural tube defects (Botto 2002). This was further investigated by Lumley et al and periconceptional folate supplementation was found to have a strong protective effect against neural tube defects (De-Regil 2010).

Severe iodine deficiency results in pregnancy loss, mental retardation and cretinism (Dunn 1993) but little is known for other outcomes, especially with marginal iodine deficiency (Ramakrishnan 1999). 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). Magnesium deficiency especially has been linked with pre-eclampsia and preterm delivery (Chein 1996).

Vitamin A deficiency in pregnancy is known to result in night blindness, to increase the risk of maternal mortality, and is associated with premature birth, intrauterine growth retardation, low birthweight and abruptio placentae (Ladipo 2000). A study from Nepal (West 1999) showed that weekly vitamin A supplementation reduced maternal mortality by 40%. West et al in 1997 (West 1997) showed that maternal mortality in Nepal decreased by about half in women who received vitamin A for at least three months before and during pregnancy (UNICEF 1998; West 1997). It was also found that the prevalence of iron-deficiency anaemia in pregnancy was reduced from 76% in controls to 69% among those receiving vitamin A (Stoltzfus 1997).

Zinc deficiency has been associated with complications of pregnancy and delivery such as pre-eclampsia and premature rupture of membranes in some but not all studies (Caulfield 1998), as well as with growth retardation, congenital abnormalities and retarded neurobehavioural and immunological development in the fetus (Black 2001). Ramakrishnan 1999 states that there is strong evidence, primarily from high-income countries, that zinc, calcium and magnesium supplementation could improve birthweight, prematurity and hypertension particularly in high-risk groups. Improving maternal iron intake during pregnancy has been shown in Peru to improve the iron status of newborns (O'Brien 2003).

Description of the intervention

In 1999, the United Nations Children's Fund (UNICEF), United Nations University (UNU) and World Health Organization (WHO) agreed on the composition of a proposed multiple-micronutrient tablet providing 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. However, according to the guidelines provided by the National Research Council in 1989, 15 mg of zinc for pregnant and lactating women is based on a dietary availability of zinc of approximately 20%. If dietary availability is only 10%, as is the case in many low-income to middle-income countries, the nutritional requirements of zinc might be much higher.

When multiple supplements were provided to HIV-positive pregnant women in Tanzania, the risk of low birthweight decreased by 44% and preterm births by 39% (Fawzi 1998). There is a published review assessing the effect of micronutrient supplementation in HIV-infected children and adults (Irlam 2010). In pregnant women in Indonesia, daily supplements of vitamin A (retinol) with iron (elemental iron) increased haemoglobin and had a greater impact on reducing anaemia than iron alone (Suharno 1992; Suharno 1993). While absorption of both zinc and iron are inhibited when combined (O'Brien 2003), improvements in both iron and zinc status were found among pregnant women receiving supplements in Peru (Caulfield 1997). It was shown by Scholl that the risk of low birthweight was reduced approximately two-fold with multivitamin supplement use during the first and second trimester of pregnancy, although it appeared that this effect was due to an associated two-fold reduction in the risk of preterm delivery. On the other hand, a large Hungarian trial of micronutrient supplementation (Czeizel 1996) found no significant effect on the rate of fetal deaths, low birthweight and preterm births in singletons.

How the intervention might work

Some authors have questioned the effectiveness of multiple-micronutrient supplements due to possible interactions among nutrients that can result in their impaired absorption (Argiratos 1994). Studies have shown that high doses of iron impair the absorption of zinc, and vice versa. The risk of interaction is larger when the nutrients are provided as supplements (Sandstrom 2001). Manganese affects iron absorption in a way that indicates that the intestine cannot differentiate between manganese and iron (Rossander 1991). Similarly, high-dose zinc supplements (50 mg per day for 10 weeks) reduce indices for iron and copper status (Yadrick 1989). Calcium was shown to have a negative effect on iron absorption (Hallberg 1991).

Vitamin C is a strong promoter of dietary iron absorption (Hallberg 1986). However, long-term vitamin C supplementation may impair the absorption of copper and thereby counteract the positive effect on iron absorption. These effects of vitamin C on copper are not conclusive (Jacob 1987). Vitamin C affects selenium availability both positively and negatively depending on the chemical form and dietary conditions (Lavender 1987).

Recent studies suggest that vitamin A and beta-carotene can enhance non-haemal iron absorption. Another issue is that frequencies of supplementation and dose levels may not be compatible (Mason 2001). Supplements may result in excess levels and cause harm; for example, high doses of vitamin A in pregnant women increases the risk of teratogenicity. An excess of vitamin E in adult humans (Bell 1989) causes impaired leukocyte function, increased bleeding, inhibition of platelet prostaglandin synthesis and of platelet aggregation. Iron deficiency as well as iron overload seem to involve a degree of oxidative stress. A vitamin C excess has been reported to cause serious cardiovascular disturbances in iron-overloaded patients (McLaran 1982). High doses of vitamin C (500 mg per day) plus iron can cause certain oxidative base modifications in DNA extracted from leucocytes of healthy human donors (Rehman 1998), however the significance of this is unknown.

Authors argue that a poor pregnancy outcome is the result of a multiplicity of factors and cannot be corrected by 'a narrow pharmaceutical shortcut'; instead, they call for an overall improvement in antenatal care and dietary diversification (Gopalan 2002). The effectiveness of already existing worldwide conventional iron or folate supplementation programs for pregnant women has been questioned (Yip 1996). These programs suffer from limited coverage and poor compliance, and their limitation to the duration of the pregnancy provides an insufficient time period in which to reduce iron deficiency.

Why it is important to do this review

Multiple-micronutrient deficiencies often coexist and there is an increased interest in evaluating the benefit of multiple-micronutrient supplements in pregnancy. Consideration that there may be multiple deficiencies in the populations of low-income to middle-income countries and that it is difficult to evaluate the effects of all of the potentially important micronutrients, as well as their possible interactions, have lead some to conclude that a multivitamin mineral supplement should be given during pregnancy (UNICEF 1999).

Combining multiple micronutrients in a single delivery mechanism has been suggested as a cost-effective way to achieve multiple benefits (Alnwick 1998; Yip 1997). Moreover, micronutrient deficiencies are known to interact and a greater effect may be achieved by multiple supplementation rather than single nutrient supplementation. Clearly, substantial evidence is required before multiple-micronutrient supplementation programs are implemented on a global scale (Bhutta 2009b). In this review we are looking at supplementation with three or more micronutrients. Other relevant information can be found in the trials conducted on individual vitamins and minerals and their effects.

OBJECTIVES

To evaluate the benefits to both mother and infant of multiple-micronutrient supplements in pregnancy and to assess the risk of adverse events as a result of supplementation.

METHODS

Criteria for considering studies for this review

Types of studies

All prospective randomised controlled trials evaluating multiple-micronutrient supplementation during pregnancy and its effects on the pregnancy outcome, 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-positive women were excluded from the review.

Types of interventions

Studies comparing the outcomes of providing pregnant women with multiple-micronutrient supplements containing three or more micronutrients compared with placebo, no supplementation, or supplementation with two or less micronutrients. We evaluated the effects of micronutrients that were different in the two groups and not any co-interventions. We compared multiple-micronutrient supplements containing at least three micronutrients with supplements with two or less, or none, as iron with folic acid or folic acid alone are standard recommendations for pregnant women in many countries. Trials that used fewer than three supplements in the intervention group were excluded regardless of their outcome. There were no limits on the duration of supplementation. Since WHO recommends use of iron folic acid supplementation in women during pregnancy as a part of routine antenatal care, we also evaluated the effect of multiple-micronutrient supplementation versus supplementation with iron and folic acid.

Types of outcome measures

Primary outcomes

1. Preterm births (births before 37 weeks of gestation)
2. Small-for-gestational age (as defined by the authors of the trials)
3. Low birthweight (birthweight less than 2500 grams)
4. Premature rupture of membranes
5. Pre-eclampsia
6. Miscarriage (loss of pregnancy before 28 weeks of gestation)
7. Maternal mortality
8. Perinatal mortality
9. Stillbirths
10. Neonatal mortality

Secondary outcomes

1. Maternal anaemia
2. Neurodevelopmental delay (assessed using Bayley Scale of Infant Development at six and 12 months of age)
3. Placental abruption
4. Very preterm births (births before 34 weeks of gestation)
5. Cost of supplementation
6. Side-effects of supplements
7. Congenital anomalies (including neural tube defects)
8. Maternal well being or satisfaction
9. Nutritional status of children (stunting, wasting and underweight at 6, 12 and 24 months of age)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (17 February 2012).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

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

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, 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 restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, *see* Appendix 1. For this update we used the following methods when assessing the trials identified by the updated search.

Selection of studies

The review authors independently assessed for inclusion all potential studies that were 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, the review authors extracted the data using the agreed form. We resolved discrepancies through discussion. Data were entered into Review Manager software (RevMan 2011) and checked for accuracy.

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

Assessment of risk of bias in included studies

The 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.

(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); or
- unclear risk of bias.

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

We described for each included study the methods used to conceal allocation to interventions prior to assignment and to assess 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) Blinding of participants, personnel and outcome assessors (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 studies to be at low risk of bias if they were blinded, or if we judged that the lack of blinding would be 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;
- low, high or unclear risk of bias for outcome assessors.

(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 state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total number of 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 is reported, or was supplied by the trial authors, we 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 the 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 prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's prespecified outcomes have been reported; one or more of the reported primary outcomes were not prespecified; 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) Overall risk of bias

We made explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We explored the impact of the level of bias through undertaking Sensitivity analysis.

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we used mean difference when outcomes were measured in the same way between trials.

Unit of analysis issues

Cluster-randomised trials

There were six cluster-randomised trials included in this review (Bhutta 2009a; Christian 2003; SUMMIT 2008; Sunawang 2009; Zagre 2007; Zeng 2008). We used the generic inverse variance method to include cluster-randomised trials. We adjusted the standard errors of their estimates using the methods described in the *Handbook*, using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or we used cluster-

adjusted estimates. If we identified both cluster-randomised trials and individually randomised trials, we synthesised the relevant information. We considered it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of the intervention and the choice of randomisation unit was considered to be unlikely.

Dealing with missing data

For included studies, we noted levels of attrition. We explored the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes we carried out analyses, as far as possible, on an intention-to-treat basis, that is we attempted to include all participants randomised to each group in the analyses. All participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. 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 T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if I^2 was greater than 50% and either T^2 was greater than zero or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

Where there were 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 and proposed formal tests for funnel plot asymmetry. As our dichotomous outcomes measured effects of intervention as risk ratios, we used visual assessment of funnel plots. If asymmetry was suggested by a visual assessment, we performed exploratory analyses to investigate it. For future review updates, we propose the test by Egger 1997.

Data synthesis

We analysed the data using Review Manager (RevMan 2011) and generated risk ratios with 95% confidence intervals for the dichotomous outcomes. We used fixed-effect model meta-analysis for combining data where trials were examining similar interventions and the trials' populations and methods were judged sufficiently similar. Where we suspected methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials, we used random-effects model meta-analysis.

Subgroup analysis and investigation of heterogeneity

Statistical heterogeneity among the trials was measured by visually inspecting the forest plots and calculating the T^2, I^2 and Chi^2 statistics. Clinical heterogeneity was assessed for those outcomes for which available the literature indicated the presence of clinical diversity. We prespecified the following subgroup analyses to investigate statistical or clinical heterogeneity for primary outcomes:

1. gestational age at which the supplementation was initiated, duration of supplementation;
2. dosage of the micronutrients in the supplement;
3. baseline nutritional status of the mother (including body mass index (BMI), height and micronutrient levels).

Differences between subgroups were assessed by interaction tests and the P values.

Sensitivity analysis

Sensitivity analysis was undertaken to study the effect of multiple-micronutrient supplementation on various outcomes by excluding trials in which the method of randomisation, allocation concealment or blinding was not achieved, or trials with a large loss to follow up (greater than 20%).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

Twenty-three trials (involving 76,532 women) were identified as eligible for inclusion in this review but only 21 trials (involving 75,785 women) contributed data to the review. Sixty-four trials were excluded. There were six ongoing trials (Biggs 2011; Cogswell 2006; Dewey 2011; Fall 2007; Moore 2011; West 2011), *see* Characteristics of ongoing studies for more information.

Included studies

A total of 23 trials (involving 76,532 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 included studies did not contribute data to the analyses. A total of 75,785 women participated in the remaining 21 included trials (Bhutta 2009a; Brough 2010; Christian 2003; Dieckmann 1943; Fawzi 2007;

Friis 2004; Gupta 2007; Jarvenpaa 2007; Kaestel 2005; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; Rumiris 2006; SUMMIT 2008; Sunawang 2009; Tatala 2002; Theobald 1937; Tofail 2008; Vadillo-Ortega 2011; Zagre 2007; Zeng 2008) of which six were cluster-randomised (Bhutta 2009a; Christian 2003; SUMMIT 2008; Sunawang 2009; Zagre 2007; Zeng 2008). Most of the outcomes were defined in the same way across different trials except for miscarriage, which was defined differently in one trial (Dieckmann 1943) and hence did not allow inclusion of data from this trial. Two trials used different cut-offs to define anaemia (Fawzi 2007; Zeng 2008). *See* the Characteristics of included studies table for further details of included studies.

Participants

The 21 included trials contributing data to the analysis included 75,785 women at varying gestational stages, ranging from early pregnancy to 36 weeks of gestation. Pregnant women with a haemoglobin 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. However, Vadillo-Ortega 2011 recruited women who were at high risk for pre-eclampsia. One trial (Friis 2004) included a subgroup of pregnant women who were HIV-1 infected but their data have not been included in this 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 haemoglobin 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 multiple-micronutrient supplementation versus supplementation with two or less micronutrients (Bhutta 2009a; Christian 2003; Dieckmann 1943; Fawzi 2007; Gupta 2007; Kaestel 2005; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; Rumiris 2006; SUMMIT 2008; Sunawang 2009; Tofail 2008; Zagre 2007; Zeng 2008). Another two trials had a component of nutritional education along with supplementation (Bhutta 2009a; Zagre 2007) whereas four trials assessed multiple micronutrients against a placebo (Brough 2010; Friis 2004; Theobald 1937; Vadillo-Ortega 2011). Two included trials assessed the impact of fortification with multiple micronutrients, Tatala 2002 used a fortified beverage mix and Jarvenpaa 2007 used fortified mineral water. The composition of the multiple-micronutrient supplement was different in all included trials. 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. Eight trials enrolled participants in the first trimester of pregnancy (Brough 2010; Christian 2003; Dieckmann 1943; Ramakrishnan 2003; Roberfroid 2008; Rumiris 2006; Tofail 2008; Zagre 2007). One trial enrolled participants with gestation of less than 28 weeks (Zeng 2008). Three trials enrolled participants in the second trimester (Bhutta 2009a; Osrin 2005; Sunawang 2009), three trials enrolled women in both second and third trimester (Friis 2004; Gupta 2007; Vadillo-Ortega 2011), whereas three trials enrolled pregnant women who were less than 37 weeks' gestation (Fawzi 2007; Kaestel 2005; SUMMIT 2008). Supplementation was given until delivery in 13 of the included trials (Bhutta 2009a; Brough 2010; Dieckmann 1943; Friis 2004; Gupta 2007; Kaestel 2005; Osrin 2005; Ramakrishnan 2003; Rumiris 2006; Tofail 2008; Vadillo-Ortega 2011; 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 three trials (Christian 2003; Roberfroid 2008; SUMMIT 2008) and for five weeks after a stillbirth or miscarriage (Christian 2003).

Excluded studies

Sixty trials were excluded from the review. Briefly, 33 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; Hunt 1983; Hunt 1984; Hunt 1985; Iannotti 2008; Lucia 2007; Ma 2008; Marya 1987; Mathan 1979; Merialdi 1999; Muslimatun 2001a; Muslimatun 2001b; Ochoa-Brust 2007; Robertson 1991; Sachdeva 1993; Sagaonkar 2009; Schmidt 2001; Schmidt 2002; Semba 2000; Semba 2001; Suharno 1993; Suprapto 2002; Tanumihardjo 2002; Zavaleta 2000), nine trials did not satisfy the study design criteria (Aguayo 2005; Biswas 1984; Kubik 2004; Kynast 1986; Menon 1962; Park 1999; People's League 1946; Sun 2010; Thauvin 1992) and three trials were in HIV-positive women (Fawzi 1998; Merchant 2005; Webb 2009) and hence were excluded from the review. Czeizel 1996 and ICMR 2000 evaluated supplementation in the periconceptional period; An 2001, Guldholt 1991, Graham 2007 and Fleming 1986 assessed different doses of micronutrients; Feyi-Waboso 2005 evaluated parenteral infusion; Dawson 1987 and Dawson 1998 assessed the impact of supplementation with more than 11 micronutrients; Ramirez-Velez 2011 compared nine versus three micronutrients; and Ling 1996 evaluated a herbal

tonic; hence they were not found to be eligible. Four trials were excluded because they evaluated the acceptability of different forms of supplementation such as powder, tablet or spread (Young 2010); balanced energy protein supplementation (Huybregts 2009); or polyunsaturated fatty acids fortification in milk fortified with multiple micronutrients (Mardones 2007). The cohort of an included study (Tofail 2008) was later randomised to breastfeeding counselling or standard care groups measuring impact on postnatal growth in children (Kabir 2009) and was hence excluded.
See the Characteristics of excluded studies table for more details.

Risk of bias in included studies

The included trials were of variable methodological quality. Participants were adequately randomised to the treatment groups in 15 trials (Bhutta 2009a; Christian 2003; Fawzi 2007; Friis 2004; Gupta 2007; Kaestel 2005; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; Rumiris 2006; Sood 1975; SUMMIT 2008; Theobald 1937; Vadillo-Ortega 2011; 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 10 trials (Bhutta 2009a; Fawzi 2007; Friis 2004; Gupta 2007; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; SUMMIT 2008; Vadillo-Ortega 2011; Zeng 2008); it was unclear in 10 trials (Brough 2010; Christian 2003; Dieckmann 1943; Hininger 2004; Jarvenpaa 2007; Rumiris 2006; Sunawang 2009; Tatala 2002; Tofail 2008; Zagre 2007); whereas allocation was not probably concealed in the remaining three trials (Kaestel 2005; Sood 1975; Theobald 1937).
In two trials (Bhutta 2009a; Tofail 2008), the participants and the outcome assessors were blinded to the treatment allocation. Another 14 trials showed blinding of the participants, caregivers and the outcome assessors (Brough 2010; Christian 2003; Fawzi 2007; Friis 2004; Gupta 2007; Kaestel 2005; Osrin 2005; Ramakrishnan 2003; Roberfroid 2008; Rumiris 2006; SUMMIT 2008; Vadillo-Ortega 2011; Zagre 2007; Zeng 2008). However, Tatala 2002 showed blinding of participants and caregivers; and Sunawang 2009 showed blinding of participants only. Jarvenpaa 2007 was a double blind trial but it was not clear as to who was blinded; and blinding was not stated in the text of Dieckmann 1943.
Loss to follow up was less than 5% in two trials (Rumiris 2006; Zeng 2008); between 5% to 9.9% in five trials (Christian 2003; Fawzi 2007; Osrin 2005; Roberfroid 2008; SUMMIT 2008); and between 10% to 19.9% in six trials (Bhutta 2009a; Brough 2010; Sunawang 2009; Tatala 2002; Vadillo-Ortega 2011; Zagre 2007). It was more than 20% in seven trials (Friis 2004; Gupta 2007; Hininger 2004; Kaestel 2005; Ramakrishnan 2003; Sood 1975; Tofail 2008); and not reported in three trials (Dieckmann 1943; Jarvenpaa 2007; Theobald 1937). The method of randomisation and allocation concealment was not stated in the text of one trial (Dieckmann 1943). 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. *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.

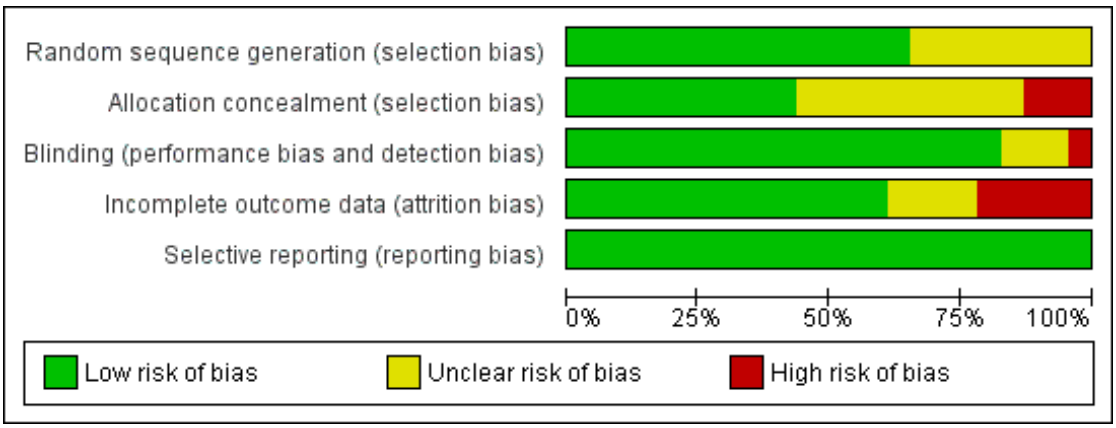
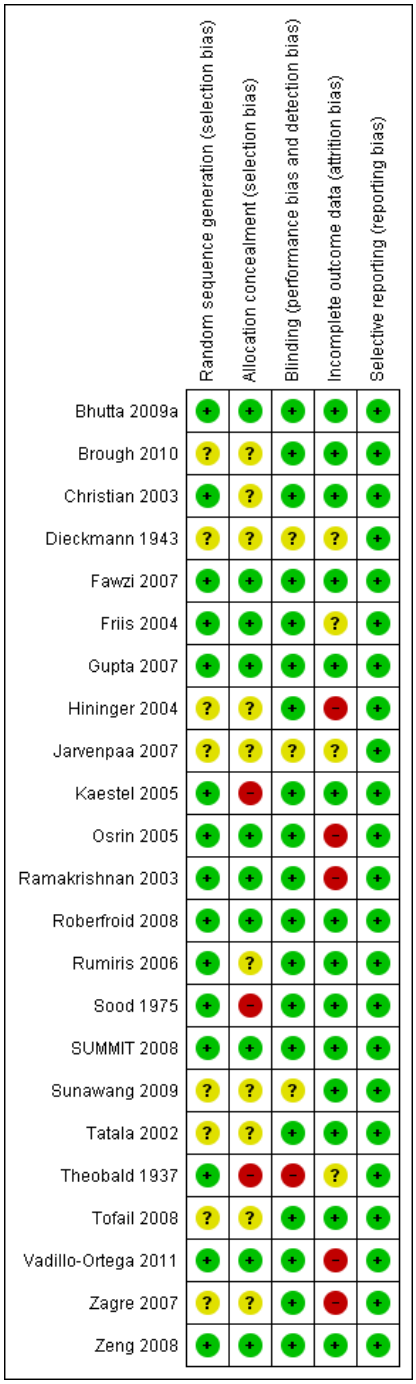


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

Primary outcome

1. Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

When compared with supplementation of two or less micronutrients, no supplementation or a placebo, multiple-micronutrient supplementation resulted in a statistically significant decrease in the number of low birthweight (LBW) infants (risk ratio (RR) 0.86; 95% confidence interval (CI) 0.80 to 0.91; 15 studies; Analysis 1.6) and small-for-gestational age (SGA) babies (RR 0.87; 95% CI 0.83 to 0.92; 15 studies; Analysis 1.2). No statistically significant differences were shown for the outcomes of preterm birth (RR 0.99; 95% CI 0.97 to 1.02; 17 studies; Analysis 1.1), miscarriage (RR 0.90; 95% CI 0.79 to 1.02; eight studies; Analysis 1.11), pre-eclampsia (RR 0.47; 95% CI 0.22 to 1.03; four studies; Analysis 1.10), maternal mortality (RR 0.97; 95% CI 0.63 to 1.48; three studies; Analysis 1.12), perinatal mortality (RR 0.96; 95% CI 0.84 to 1.10; 12 studies; Analysis 1.13), stillbirths (RR 0.95; 95% CI 0.85 to 1.06; 13 studies; Analysis 1.14) and neonatal mortality (RR 1.01; 95% CI 0.89 to 1.16; 10 studies; Analysis 1.15).

Subgroup analysis

We performed subgroup analyses to assess the effect of clinical diversity of participants on SGA and LBW. For SGA, the pooled effect of multiple micronutrients was more pronounced for studies with women having a mean BMI at least 20 kg/m² (RR 0.85; 95% CI 0.80 to 0.91; 11 studies; Analysis 1.3) as compared to studies of women with a mean BMI less than 20 kg/m² (RR 0.90; 95% CI 0.83 to 0.98), however the difference between subgroups was not statistically significant (P = 0.31). Similar effects were noted for a mean maternal height at least 154.9 cm (RR 0.82; 95% CI 0.76 to 0.89; seven studies; Analysis 1.4) as compared to a mean maternal height less than 154.9 cm (RR 0.91; 95% CI 0.85 to 0.98; eight studies; Analysis 1.4) (P = 0.07); and the duration of supplementation and gestational week at which supplementation was initiated (after 20 weeks RR 0.83; 95% CI 0.76 to 0.91 versus before 20 weeks RR 0.90; 95% CI 0.84 to 0.96; P = 0.22; Analysis 1.5). The effects of multiple micronutrients on LBW in various subgroups were also similar: mean BMI less than 20 kg/m² (average RR 0.78; 95% CI 0.65 to 0.93; four studies; random-effects, T^2 = 0.02, I^2 = 60%) versus mean BMI at least 20 kg/m² (RR 0.88; 95% CI 0.81 to 0.96; 10 studies) (P = 0.20; Analysis 1.7); mean maternal height less than 154.9 cm (average RR 0.86; 95% CI 0.76 to 0.98; eight studies; random-effects, T^2= 0.02, I^2= 53%) versus maternal height at least 154.9 cm (RR 0.86; 95% CI 0.77 to 0.95; seven studies) (P = 0.93, Analysis 1.8); and gestational week at which supplementation was initiated before 20 weeks (RR 0.88; 95% CI 0.81 to 0.95; 10 studies) versus after 20 weeks (RR 0.82; 95% CI 0.75 to 0.91; 5 studies) (P = 0.31, Analysis 1.9).

2. Multiple micronutrients versus iron folate only

When multiple-micronutrient supplementation was compared with iron and folic acid supplementation, the effect on the outcomes SGA (RR 0.87; 95% CI 0.81 to 0.95; 14 studies; Analysis 2.2) and LBW (RR 0.89; 95% CI 0.83 to 0.94; 14 studies; Analysis 2.6) remained significant. Non-significant differences were shown for the other primary outcomes: preterm births (RR 0.99; 95% CI 0.96 to 1.02; 15 studies; Analysis 2.1), miscarriage (RR 0.90; 95% CI 0.79 to 1.02; eight studies; Analysis 2.11), maternal mortality (RR 0.97; 95% CI 0.63 to 1.48; three studies; Analysis 2.12); and perinatal mortality (average RR 0.99; 95% CI 0.84 to 1.16; 11 studies; random-effects, T^2 = 0.03, I^2 = 56%; Analysis 2.13), stillbirths (RR 0.96; 95% CI 0.86 to 1.07; 13 studies; Analysis 2.17) and neonatal mortality (RR 1.01; 95% CI 0.89 to 1.15; nine studies; Analysis 2.18).

Subgroup analysis

The effect of multiple-micronutrient supplementation as compared to iron and folic acid on the outcomes of SGA and LBW were also evaluated in various prespecified subgroups. Subgroup analysis based on mean maternal BMI showed that the effect of multiple micronutrients on SGA as compared to iron and folic acid was significant for women with mean BMI at least 20 kg/m² (RR 0.85; 95% CI 0.79 to 0.91; 10 studies) whereas it was non-significant for women with mean BMI less than 20 kg/m² (average RR 0.86; 95% CI 0.69 to 1.08; four studies; random-effects, T^2 = 0.03, I^2 = 65%) (P = 0.91; Analysis 2.3). Similar effects were observed for subgroups according to maternal height: mean maternal height at least 154.9 cm (RR 0.82; 95% CI 0.76 to 0.89; six studies) and less than 154.9 cm (RR 0.97; 95% CI 0.90 to 1.04) (P = 0.004; Analysis 2.4); and gestation week at which supplementation was initiated: after 20 weeks (RR 0.83; 95% CI 0.76 to 0.91; five studies) and before 20 weeks (RR 0.94; 95% CI 0.88 to 1.01; nine studies) (P = 0.04; Analysis 2.5). Effects of intervention on LBW for various subgroups were as follows: BMI less than 20 kg/m² (average RR 0.80; 95% CI 0.62 to 1.02; four studies; random-effects, T^2 = 0.05, I^2 = 79%) and BMI at least 20 kg/m² (RR 0.88; 95% CI 0.81 to 0.96; 10 studies) (P = 0.44; Analysis 2.7); maternal height less than 154.9 cm (average RR 0.90; 95% CI 0.77 to 1.04; eight studies; random-effects, T^2 = 0.03, I^2 = 63%) and maternal height at least 154.9 cm (RR 0.85;

95% CI 0.76 to 0.94; six studies) (P = 0.56; Analysis 2.8); and gestational week at initiation of supplementation before 20 weeks (RR 0.93; 95% CI 0.86 to 1.02; nine studies) and after 20 weeks (RR 0.82; 95% CI 0.75 to 0.91; five studies) (P = 0.05; Analysis 2.9).

The results for perinatal mortality were found to be heterogeneous (Chi² = 22.47, df = 10, P = 0.01; I² = 56%). Heterogeneity was investigated using subgroup analyses: BMI less than 20 kg/m² (RR 1.19; 95% CI 0.94 to 1.50; three trials) and BMI at least 20 kg/m² (average RR 0.93; 95% CI 0.78 to 1.11; eight studies; random-effects, T^2 = 0.03, I^2 = 56%) (P = 0.10; Analysis 2.14); maternal height less than 154.9 cm (RR 0.95; 95% CI 0.77 to 1.17; seven studies) and maternal height at least 154.9 cm (average RR 1.08; 95% CI 0.79 to 1.50; four studies; random-effects, T^2 = 0.07, I^2 = 71%) (P = 0.49; Analysis 2.15); and gestational week at initiation of supplementation before 20 weeks (average RR 1.09; 95% CI 0.84 to 1.42; eight studies; random-effects, T^2 = 0.08, I^2 = 57%) and after 20 weeks (RR 0.88; 95% CI 0.80 to 0.97; three studies) (P = 0.14; Analysis 2.16).

Analyses for the outcomes of preterm birth, LBW, SGA, stillbirths and perinatal mortality contained more than 10 studies (range 12 to 16). Funnel plots for the assessment of reporting bias did not reveal any substantial asymmetry (Figure 3; Figure 4; Figure 5; Figure 6; Figure 7).

Figure 3. Funnel plot of comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), outcome: 1.1 Preterm births.

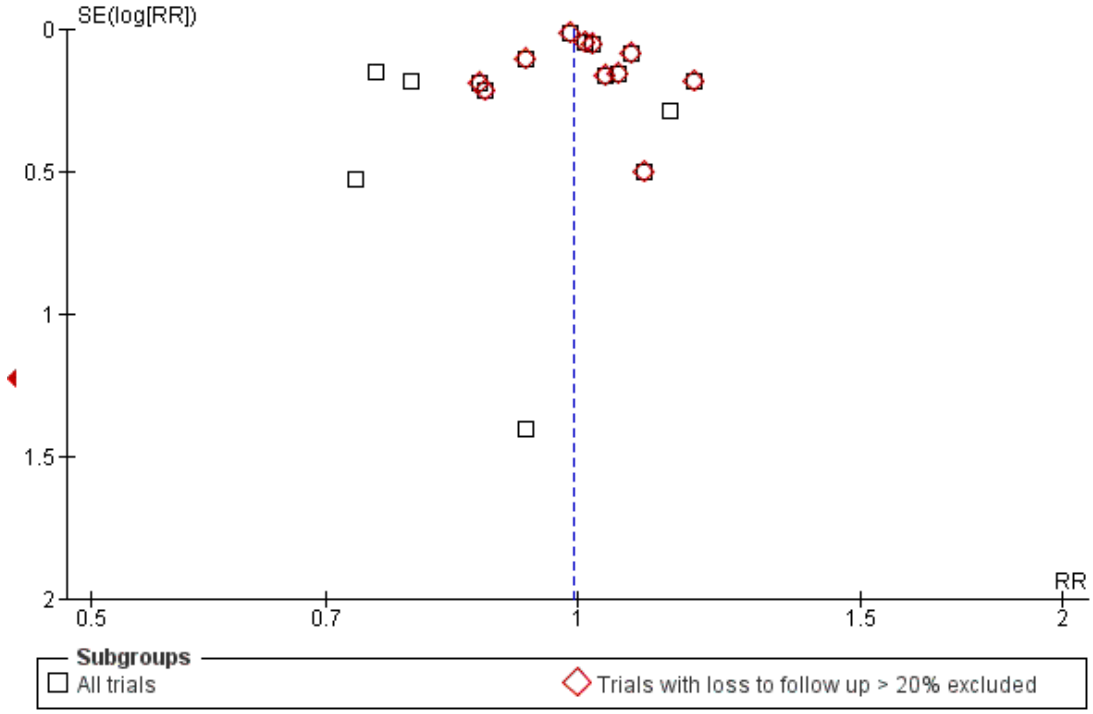


Figure 4. Funnel plot of comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), outcome: 1.2 Small-for-gestational age.

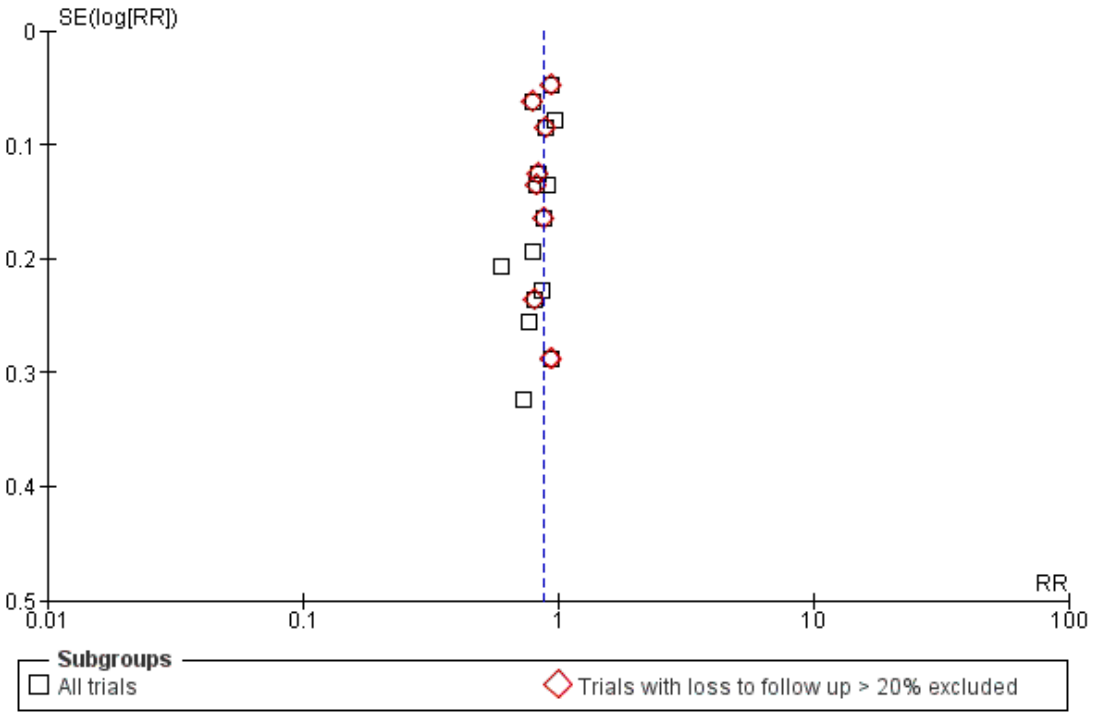


Figure 5. Funnel plot of comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), outcome: 1.6 Low birthweight.

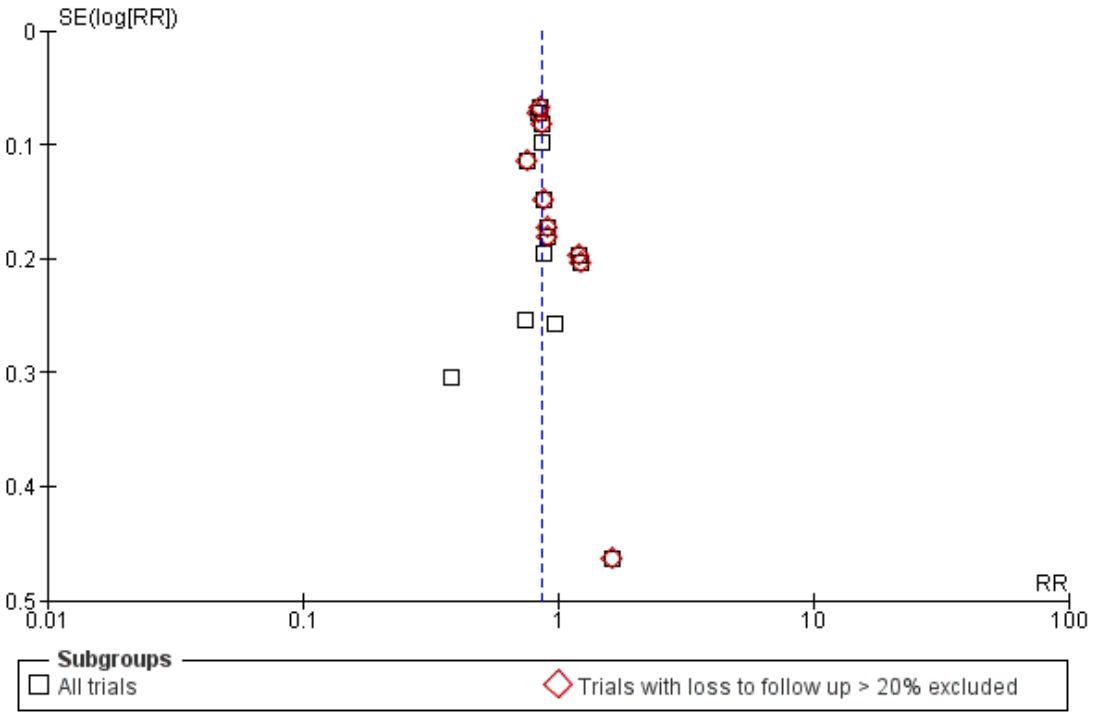


Figure 6. Funnel plot of comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), outcome: 1.13 Perinatal mortality.

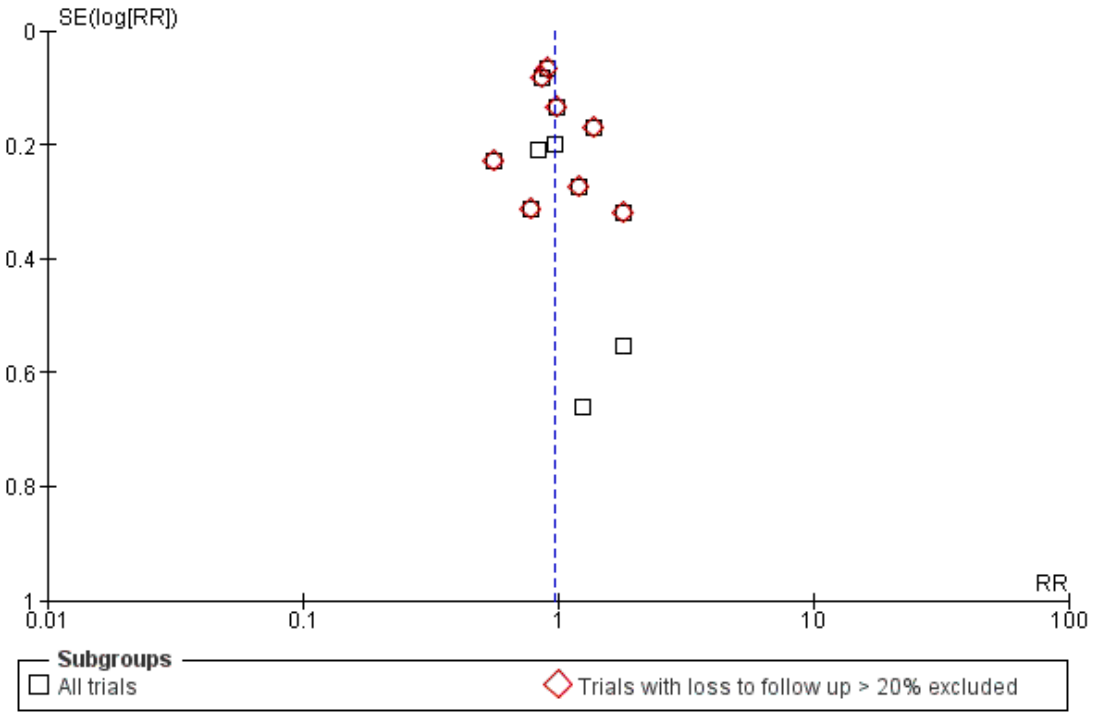
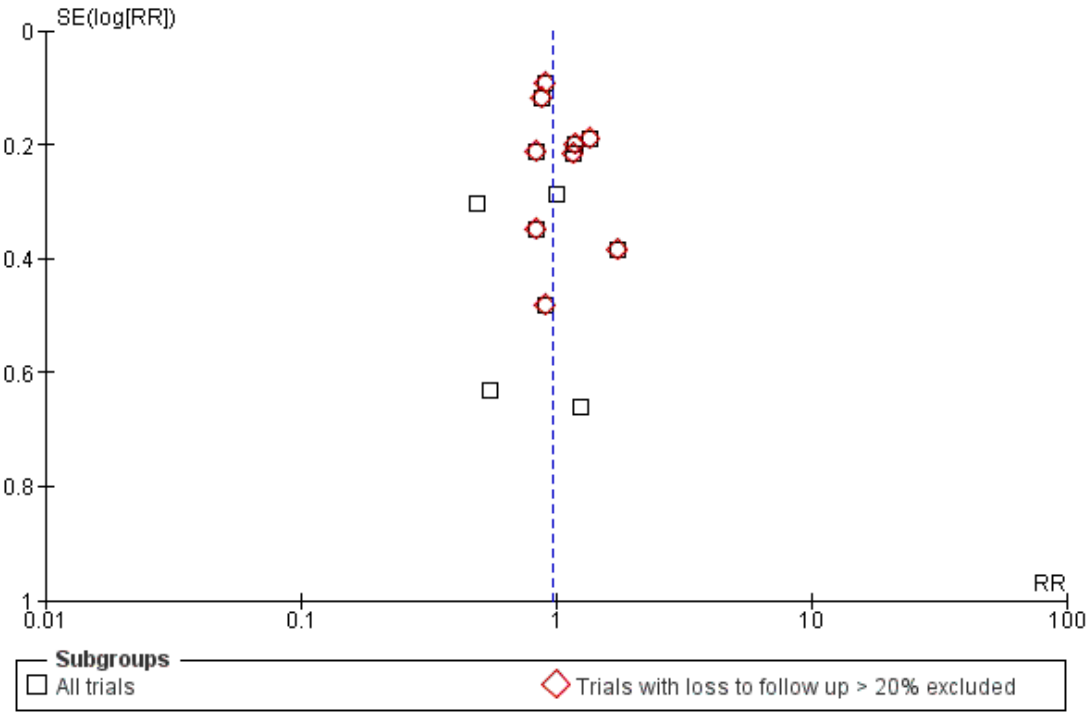


Figure 7. Funnel plot of comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), outcome: 1.14 Stillbirths.



Our review found only two trials of fortification with multiple micronutrients (Jarvenpaa 2007; Tatala 2002) and hence the independent effect of studies utilising a fortification strategy could not be evaluated. No trial measured effects on premature rupture of membranes.

Secondary outcomes

Multiple-micronutrient supplementation when compared with supplementation of two or less micronutrients, no supplementation or a placebo showed a statistically significant decrease in maternal anaemia in the third trimester (average RR 0.81; 95% CI 0.66 to 0.98; eight trials; random-effects, T^2 = 0.05, I^2 = 70%; Analysis 1.16). However, the result was not significant when multiple micronutrients were compared with iron and folic acid (RR 0.96; 95% CI 0.86 to 1.07; six trials; Analysis 2.19).

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: placental abruption (Dieckmann 1943), congenital anomalies including neural tube defects (Osrin 2005), side-effects of multiple-micronutrient supplementation (Gupta 2007), neurodevelopmental delay (Zeng 2008), cost of supplementation, maternal well being or satisfaction, and nutritional status of the children.

Sensitivity analysis

Sensitivity analysis was undertaken to study the effect of multiple-micronutrient supplementation on various outcomes by excluding trials in which the methods of randomisation, allocation concealment and blinding were not stated in the text (Dieckmann 1943). However, the overall effect estimate and the CI were not sensitive to this change. Similarly, trials with losses to follow up of more than 20% were excluded (Friis 2004; Gupta 2007; Kaestel 2005; Ramakrishnan 2003; Tofail 2008) from the analyses of LBW and SGA and this exclusion did not affect the estimates.

DISCUSSION

This updated review is now comprised of Twenty-three included studies (involving 76,532 women) but only 21 trials (involving 75,785 women) contributed data towards our analyses.

Whether to use a multiple-micronutrient supplement or iron folate or no supplements during pregnancy is a very important clinical question due to its effects on the fetus and the mother. This updated review has incorporated a further 13 recent studies. From the 22 included studies, 12 studies used the multiple-micronutrient supplement UNIMAPP formulation by UNICEF and six studies used other combinations of these micronutrients. Overall, multiple-micronutrient supplementation showed a significant effect on small-for-gestational age (SGA) and low birthweight (LBW) outcomes when compared to supplementation with two or less micronutrients, no supplementation or a placebo. Comparison of the multiple-micronutrient supplementation with iron and folate showed similar beneficial effects on SGA and LBW outcomes. These findings corroborate those of recent systematic reviews, the review commissioned by UNICEF/WHO/SCN of 12 UNIMAPP trials (Fall 2009; Margetts 2009) and a systematic review using Child Health Epidemiology Reference Group (CHERG) rules for the Lives Saved Tool (LiST) (Haider 2011).

Multiple micronutrients were found to reduce the SGA births by 10% and LBW babies by 11% as compared to iron folate supplements. They failed to show a significant impact on any of the other outcomes of pregnancy. One of the postulated pathways for the significant impact on these two outcomes is through an increase in birthweight, with higher birthweight resulting in a lower proportion of LBW babies and also reducing the proportion of SGA births. This is supported by the evidence of an impact on birthweight in the supplemented group as compared to iron and folic acid in most of the included studies wherein the major proportion of pregnant women were taking supplements in the third trimester, which is a period of significant increase in fetal weight. Among the included studies, several studies recruited pregnant women in the first trimester with supplementation starting from the second trimester; whereas the other trials recruited almost 80% of their participants by the end of the second trimester, and with only two trials (Friis 2004; Gupta 2007) recruiting after 22 or 24 months of gestation. This further supports the postulated pathway as the intervention was in place much before the beginning of third trimester, a possible window of opportunity to improve fetal weight. Furthermore, the significant effect does not seem to be the result of increasing the duration of gestation as multiple micronutrients failed to have a significant impact on preterm births.

Most of the studies included in this review were undertaken in developing countries with high fertility rates, low maternal body mass index (BMI), a high prevalence of iron deficiency anaemia, and frequent subclinical micronutrient deficiencies (Bhutta 2008). Studies have shown that a significant proportion of pregnant women suffer from multiple micronutrient 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 births as a result of multiple-micronutrients supplementation could be through improved nutritional status and hence better immune system and resistance to maternal infections.

Maternal anthropometry prepregnancy and weight gain during pregnancy have also been implicated in various neonatal and child outcomes. Maternal height seems to be a stable and easily measurable variable in the setting of developing 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 multiple micronutrients 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/m^2. Multiple micronutrients showed an 18% reduction in SGA babies among women with a mean maternal height at least 154.9 cm as compared to iron folate, whereas the effect was found to be non-significant among women with a mean height less than 154.9 cm. Similarly, multiple micronutrients showed a 15% reduction in SGA babies among women with a mean BMI at least 20 kg/m^2 whereas the effect was non-significant among those women with a mean BMI less than 20 kg/m^2. These findings should be interpreted with caution but suggest a possible role of multiple micronutrients in preventing poor pregnancy outcomes 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. This further highlights the contribution of maternal malnutrition to poor fetal anthropometry and stunting later in childhood, resulting in an intergenerational transfer of malnutrition.

We failed to find a significant effect of the multiple micronutrients on the outcomes of perinatal mortality, stillbirths and neonatal mortality. Our earlier review, which included data from nine studies, had also failed to show an impact on these pregnancy outcomes. These findings corroborate those from recent reviews (Haider 2011; Ronsmans 2009). It can be hypothesised that a reduction in fetal growth restriction and SGA babies may contribute indirectly to improved infant survival. Recent reviews indicate that poor fetal growth results in a higher risk of neonatal mortality through neonatal infections such as sepsis, diarrhoea and pneumonia; and through birth asphyxia (Black 2008). This review update did not find a significant effect of multiple micronutrients on neonatal mortality. It is important to note that of the studies conducted so far, only the Indonesian SUMMIT trial was sufficiently powered to evaluate an effect on early infant mortality (SUMMIT 2008). There is controversy regarding the possible harmful effect of multiple-micronutrient supplements by increasing the risk of

perinatal and neonatal mortality through increased birth asphyxia in heavier babies (Christian 2005). Two trials conducted in Nepal by Christian et al and Osrin et al both 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). However, this concern has been questioned by other researchers in the field and has not been observed in other studies (Bhutta 2009b; Huffman 2005; Shrimpton 2005). The multiple-micronutrient supplementation review using CHERG methodology also found no significant increase in the risk of neonatal mortality as a result of this intervention. The increased risk may be related to the absence of skilled care at delivery and the standard of care in the health systems. This is also supported by the finding of a significant increase in the subgroup of populations where the majority of births occurred at home, and no effect where skilled birth care was available and the majority of births took place in facilities (Haider 2011).

As noted earlier, the composition of the multiple-micronutrient supplements was different in all included trials (Table 1), and use of folic acid alone or iron with folic acid is a standard recommendation for pregnant women in many countries globally. In order to identify the effect of a micronutrient on pregnancy outcomes and to justify its inclusion in routine antenatal care, each micronutrient should be evaluated against a placebo in women receiving iron with folic acid. This can especially prove useful for countries or regions with deficiencies of single micronutrients.

AUTHORS' CONCLUSIONS

Implications for practice

Whilst multiple micronutrients have been found to have a significant impact on small-for-gestational age and low birthweight outcomes, more evidence is needed to guide a universal policy change and to suggest replacement of routine iron and folate supplementation with a multiple-micronutrient supplement. There is also insufficient evidence regarding adverse effects and to make any conclusions that multiple-micronutrient supplementation during pregnancy is harmful to the mother or the fetus.

Implications for research

Further trials with larger sample sizes are needed to evaluate effects on mortality and other morbidity outcomes. Trials that are adequately powered to evaluate effects on mortality outcomes are needed urgently. Trials should assess the effect of variability between different combinations and dosages, keeping within the safe recommended levels. Additionally, data should be collected on outcomes which would allow an assessment of the risk of excess supplementation, potential adverse interactions between the micronutrients, and the other outcomes that we failed to assess in this review.

ACKNOWLEDGEMENTS

This review was prepared in part during the Fellowship Programme organised by the Cochrane Infectious Diseases Group in July 2003 and March 2005. The Department for International Development (UK) supports this programme through the Effective Health Care Research Programme Consortium at the Liverpool Tropical School of Medicine. The views expressed are not necessarily those of the Department for International Development.

We would like to thank Ms Lynn Hampson for her assistance with the literature search, and Professor James Neilson who provided support and guidance for the review.

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.

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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. Multiple-micronutrient groups (n = 1148), iron folic acid group (n = 1230)
Interventions	Multiple-micronutrient 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 groups received 60 mg iron and 400 mcg folic acid
Outcomes	Size at birth, gestational age at birth, perinatal mortality and maternal anaemia (Hb < 11 g/ dl)
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

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 MMS) by respective CHWs was implemented" Comment: probably done.
Allocation concealment (selection bias)	Low risk	Comment: "allocated to either the IF or MMN supplements according to their respective location and allocation by the AKU Pharmacy" Comment: probably done.
Blinding (performance bias and 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. All pregnant women were allocated a unique code and allocated a

Bhutta 2009a (*Continued*)

		uniquely labelled and numerically coded specific supplement supply." Comment: participants, caregivers and outcome assessors were probably blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition (15.8%) and exclusion (around 1%) along with their reasons were reported. Attrition and exclusions were balanced across the treatment arms
Selective reporting (reporting bias)	Low risk	Comment: results of all outcomes mentioned in methods section were presented in the paper

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 sulfate H_2O, 41 mg) 15 mg, Mg (as magnesium hydroxide, 372 mg) 150 mg, Iodine (as potassium iodide, 183 mg) 140mcg and copper (as copper sulfate 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		
Bias	**Authors' judgement**	**Support for judgement**

Brough 2010 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "a randomised, double-blind, placebo-controlled trial" and "Participants were randomised to receive either multiple-micronutrient supplements, known as Pregnacare, or a visually identical placebo" Comment: insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Quote: "a randomised, double-blind, placebo-controlled trial" Comment: insufficient information to permit judgement.
Blinding (performance bias and detection 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, caregivers and outcome assessors were probably blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (8.7%) and attrition (12.2%) 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

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

Christian 2003 (*Continued*)

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. The control 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
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 anemia in this population. Due to this reason, vitamin A was given to all the participants including the control group. For the purpose of the review, the multiple-micronutrient group includes groups 2, 3 and 4 whereas the control group includes groups 1 and 5. Baseline characteristics did not differ significantly among the various randomisation groups except for ethnicity and land holding In this review, we have used the comparisons of MMN vs iron folate vitamin A groups and MMN vs folate vitamin A group and have calculated estimates adjusted for the cluster design

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.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "participants, investigators, field staff and statisticians did not know supplement codes", "supplements, which were of

Christian 2003 (*Continued*)

		identical shape, size, and color" and "code allocation was kept locked at the Johns Hopkins University, Baltimore" Comment: participants, caregivers and outcome assessors were blinded to the treatment assignment
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

Dieckmann 1943

Methods	The study was carried out by the Department of Obstetrics and Gynecology, The University of Chicago and the Chicago Lying-in Hospital, USA
Participants	A total of 554 women were selected at random and assigned to 4 groups, group 1 control (n = 175, mean age = 25.5), group 2 received a cereal containing calcium, phosphorus and iron (n = 179, mean age = 25.5), group 3 received vitamin A and D (n = 98, mean age = 25.3) whereas group 4 received cereal along with vitamin A and D (n = 102, mean age = 24.4). These groups received treatment throughout pregnancy. The groups were comparable at baseline
Interventions	Intervention group (groups 2 and 4) received 100 gm of cereal containing calcium 0.78 gm, phosphorus 0.62 gm and iron 30 mg, but, on an average, 30-50 gm of cereal was consumed each day. The women were also given vitamin A 39,900 IU and vitamin D 5500 IU daily. Other group (groups 1 and 3) is the control
Outcomes	Haemoglobin, serum calcium, phosphorus and protein, preterm birth, toxaemia in pregnancy, pregnancy loss, perinatal mortality, anemia and placental abruption
Notes	For the purpose of the review, MMN group includes groups 2 and 4 whereas the control group includes groups 1 and 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "groups were selected at random". Comment: insufficient information about the sequence generation process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement.

Dieckmann 1943 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no attrition and exclusion reported.
Selective reporting (reporting bias)	Low risk	Comment: outcomes mentioned in the objectives and methods were presented in the paper

Fawzi 2007

Methods	It 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	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 iron and folic acid. 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), small for gestational age (< 10th percentile for gestational age), fetal death, death in first 6 weeks, length, head circumference, placental weight, risk of caesarean section, maternal mortality, haematologic 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

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)

Fawzi 2007 (*Continued*)

		Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "Each eligible women was assigned to the next numbered bottle" Comment: probably done.
Blinding (performance bias and detection 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 "research assistants who assessed the study outcome were unaware of the intervention group" and "Each eligible women was assigned to the next numbered bottle" Comment: participants, caregivers and outcome assessors were blinded to the treatment assignment
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

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, multi-micronutrient 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	Multi-micronutrient 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 multi-micronutrient 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)
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 that 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation to daily supplementation with multimicronutrient or identical-looking placebo tablets was based on simple blocked 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.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double blind", "multimicronutrient or identical-looking placebo tablets" Comment: study participants, care providers and investigators were probably blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear 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

Gupta 2007

Methods	The study was conducted in a tertiary care hospital of East Delhi, India from May 1, 2002 to April 30, 2003
Participants	Pregnant women of any gravidity with gestational ages between 24 to 32 weeks, carrying a singleton pregnancy, having BMI < 18.5 and/or haemoglobin level of 7-9 g/dl. Exclusion criteria included chronic hypertension, renal disease, heart disease, diabetes mellitus, urinary tract infection, tuberculosis, smoking, alcohol intake or chronic intake of other drugs and women already taking iron and folic acid or other micronutrients supplements
Interventions	Micronutrient supplements (n = 99) included vitamin A 1500 IU, vitamin B1 1 mg, vitamin B2 1.5 mg, vitamin B6 1 mg, vitamin B12 1microg, vitamin C 50 mg, vitamin D3 200 IU, vitamin E 7.5 mg, calcium pentothenate 5 mg, folic acid 0.15 mg, nicotinamide 20 mg, biotin 30 microg, zinc 15 mg, potassium iodide 0.15 mg, ferrous fumarate 10 mg, magnesium oxide 100 mg, manganese sulfate 2.5 mg, copper 2 mg, cacium 162 mg, phosphorus 125 mg, potassium 40 mg, chloride 36.3 mg, chromium 25 microg, molybdenum 25 microg, sodium selenate 30 microg, nickel 5 microg, silicon dioxide 2 mg, vanadium 10 microg, boron 150 microg. Placebo (n = 101) consisted of calcium with chocolate flavor and colour. All subjects received iron and folic acid supplementations
Outcomes	Birthweight, length and mid-arm circumference at birth, incidence of LBW (< 2500 g), small for gestational age infants, early neonatal morbidity, adverse effects of supplementation (nausea, vomiting, diarrhoea, abdominal pain, and anorexia)
Notes	Only women residing within 5 kilometers of the hospital and planning to deliver in the hospital were enrolled. Baseline characteristics of the enrolled subjects were comparable in both groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were first allocated (by computer generated random sequence) to be in 1 of 10 blocks of 20 subjects each. These blocks were coded as 1 to 10 in random manner. Of 1 to 10, 5 blocks were randomly assigned to receive the placebo and rest to receive multimicronutrient tablets.. " Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "Allocation was concealed by the use of sealed envelopes." Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind", "The caregiver and the subject were blinded regarding the content of the tablet being given. Randomiza-

Gupta 2007 (*Continued*)

		tion, coding, allocation concealment, and blinding was performed by one of us (R. K.), and the drugs were dispensed by another (M.R.)", "code key was opened only after the intervention, data collection, follow-up, and tabulation were finished" and "The same observer (M.R.) obtained all of the measurements" Comment: study participants, care providers and outcome assessor were probably blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (38.4%) and attrition (27%) were mentioned in the study along with their reasons
Selective reporting (reporting bias)	Low risk	Comment: all outcomes in the methods section were presented in the paper

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 (87.5mg as glycerophosphate), Ca (100 mg as carbonate). The supplement was give 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 subjects were comparable in both groups. Outcomes measured were presented in a format that precluded its inclusion in this review

Risk of bias

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

Hininger 2004 (*Continued*)

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.
Blinding (performance bias and 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: participants, caregivers and outcome assessors were blinded to the treatment assignment
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

Jarvenpaa 2007

Methods	A randomised, controlled, double blind, parallel group intervention study in Oulu, Finland
Participants	72 pregnant women during the 11th week of gestation were recruited from 2 healthcare units. The study had an initial 2-week run-in period, followed by an 8-week intervention period
Interventions	Participants consumed 1000 ml fortified or normal mineral water per day. Fortified mineral water (n = 40) contained potassium 141 mg, magnesium 53 mg, calcium 800 mg, sodium 6 mg, vitamin B6 1.5 mg, vitamin B12 2.1 mcg, folic acid 470 mcg and vitamin D 5 mcg; and normal mineral water (n = 32) contained potassium 141 mg, magnesium 53 mg, calcium 32 mg and sodium 6 mg
Outcomes	Mean homocysteine concentration, serum folate, vitamin B12, erythrocyte folate concentrations, biparietal measurement, head circumference, blood pressure of the mother, preeclampsia, delivery complications, and the weight and Apgar score of the baby
Notes	No significant differences in the baseline characteristics of participants

Risk of bias

Jarvenpaa 2007 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At baseline, subjects were randomly assigned into either the intervention or the control group" and "randomized, controlled, double-blind" 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.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind". Comment: insufficient information to identify who was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No attrition or exclusion for the primary outcomes reported.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes in the methods section were presented in the paper

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, multiple-micronutrient RDA group, multiple-micronutrient 2 RDA group and 60 mg iron 400 mcg folic acid group
Interventions	Fifteen 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 multiple-micronutrient 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 haemoglobin, anemia (Hb < 100 g/L) and maternal death (death during pregnancy or within 42 days after termination of pregnancy), childhood mortality

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 RDA and control groups in this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Simple block randomisation with a block size of 150 was managed as follows: at entry, the project midwife randomly drew 1 piece of coloured paper corresponding to the colour code on the tablet containers from envelopes with initially 50 pieces of each of the three colours" Comment: probably done.
Allocation concealment (selection bias)	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.
Blinding (performance bias and 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: participants, caregivers and outcome assessors were probably blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low 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

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 multi-micronutrient 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 haemoglobin concentration was less than 70 g/L, she was given an extra 60 mg of iron daily, anthelmintic treatment, and her haemoglobin was rechecked after 1 month; and if a participant described night blindness at any time, she was given 2000 ug of vitamin A daily and referred for medical follow up
Outcomes	Birthweight, LBW (< 2500 g), gestational duration, preterm delivery (< 37 weeks of gestation), miscarriage, stillbirth, early and late neonatal death, infant length, head circumference
Notes	Infants were followed up to 3 months. Both groups of participants were comparable at baseline

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

Osrin 2005 (*Continued*)

		centre in Janakpur" and "After screening, consent, and enrolment, one of us (YS) allocated participants sequential identification numbers and the corresponding supplement containers" Comment: probably done.
Blinding (performance bias and 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: participants, caregivers and outcome assessors were probably blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was 5% and reasons for it were reported. Exclusion was 39.5% and reasons were not reported
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper

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 multiple-micronutrient supplementation and who agreed to participate were included in the study. A total of 873 women were randomised into the multiple-micronutrient group (n = 435, mean age 23.09 ± 5.48) and the iron only group (n = 438, mean age 23.00 ± 5.08)
Interventions	Multi-micronutrient 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

Ramakrishnan 2003 (*Continued*)

Outcomes	Preterm births (< 37 weeks of gestation), small-for-gestational age (below the 10th percentile for birthweight-for-gestational age), LBW (< 2500 g), perinatal mortality, mean haemoglobin concentration, mean serum ferritin
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 multiple-micronutrient supplementation group) and mean body mass index (significantly lower in the multiple-micronutrient supplementation group)

Risk of bias

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

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), small-for-gestational age (birthweight less than 10 percentile of a reference population), large-for-gestational age, birth length, Rohrer index, arm circumference, chest circumference, head circumference, haemoglobin in cord blood, soluble serum transferrin receptor
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 haemoglobin (lower in intervention group) and body mass index (lower in control group)

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 partic-

		ipant's name, address, and identification numbers only" Comment: probably done.
Blinding (performance bias and 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: participants, caregivers and outcome assessors were probably blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 7.5% and reason for it was provided. Only 1 woman was excluded because of therapeutic abortion
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper

Rumiris 2006

Methods	The study was conducted at Obstetrics and Gynecology department, University of Indonesia in Jakarta, Indonesia between March 2003 and June 2004
Participants	Pregnant women between 8 and 12 weeks of gestation with superoxidedismutase (SOD) levels below 1102 U/gHb who consulted at antenatal clinics. Exclusion criteria were history of current use of antihypertensives and diuretics, use of vitamin C > 150 mg and/or E > 75 IU per day, known placental abnormalities, current pregnancy as a result of in vitro fertilisation, regular use of platelets active drugs or non-steroidal anti-inflammatory drugs, known fetal abnormalities, documented uterine bleeding within a week of screening, uterine malformation and history of medical complications
Interventions	MMN group (n = 29) received vitamin A 1000 IU, B6 2.2 mg, B12 2.2 μg, C 200 mg, E 400 IU, folic acid 400 μg, N-acetylcysteine 200 mg, copper 2 mg, zinc 15 mg, mangnese 0.5 mg, ferrous 30 mg, calcium 800 mg and selenium 100 μg. Placebo group (n = 31) received ferrous 30 mg, folic acid 400 μg and sucrose
Outcomes	Pre-eclampsia, abortion, hypertension, IUGR and intrauterine fetal death
Notes	Participants were assigned on individual basis to MMN or to placebo. Low antioxidant status was defined as SOD < 1102 U/gHb No significant differences between control and supplementation groups were apparent in terms of the recorded clinical and demographic variables

Rumiris 2006 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomized according to a computer generated random number sequence by an independent party who had no conflict of interest in the study. " Comment: probably done.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information to permit judgement.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Treatments allocations were blinded to both investigator and patient until the study was finished." and "placebo's size and appearance were matched with those of antioxidants and contained only sucrose." Comment: participants, caregivers and outcome assessors were probably blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition (n = 0) was reported.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper

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 haemoglobin < 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 haemoglobin/haematocrit, iron absorption from maternal gut, fetal birthweight, maternal and fetal haemoglobin 3 months post-partum, 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

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "By reference to previously prepared random tables the women were allocated to one of the two streams A or B" and "within each stratum subjects were allotted to final treatment groups according to a set of random numbers" Comment: probably done.
Allocation concealment (selection bias)	High risk	Quote: "By reference to previously prepared random tables the women were allocated to one of the two streams A or B" and "within each stratum subjects were allotted to final treatment groups according to a, set of random numbers" Comment: probably not done.
Blinding (performance bias and 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: participants, caregivers and outcome assessors probably blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 30% and reasons for it were reported.
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper

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 = 15486) 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
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Before enrolment, midwife identification numbers were sequentially allocated to computer-generated, randomly permuted blocks of groups numbered one to eight, stratified by community health centre or village health clinic." Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "midwives at village health centres and community health centres were assigned midwife identification numbers" and "Before enrolment, midwife identification numbers were sequentially allocated to computer-generated, randomly permuted blocks of groups numbered one to eight, stratified by community health centre or village health clinic." Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "All study scientists and personnel, government staff and enrolees were unaware of the allocation." and "The code

		to indicate which strip was IFA or MMN was known only by the manufacturing production manager and a quality control officer from UNICEF, Copenhagen, neither of whom had any connection to the study or its personnel." Comment: participants, caregivers and outcome assessors were probably blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (25.2%) and attrition (5%) were reported along with their reasons
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper

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, hemoglobin, serum ferritin, serum zinc, serum retinol and urinary Iodine, miscarriage, stillbirths, neonatal mortality
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

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

Sunawang 2009 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Comment:method used for allocation concealment is not described in sufficient detail to permit judgement
Blinding (performance bias and detection 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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (<1%) and attrition (10.4%) were reported along with their reasons
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper

Tatala 2002

Methods	The study was conducted in Tanzania. Participant enrolment took place during 2 weeks in August of 1999 and post-intervention evaluations were conducted 8 weeks after enrolment
Participants	Pregnant women between 12-34 weeks of gestation were eligible for enrolment. Exclusion criteria included a pregnancy less than 12 weeks or more than 34 weeks on uterine palpation, a haemoglobin concentration of less than 80 g/L or a serious medical condition, or a complication of pregnancy such as cardiac disease, pneumonia and threatened abortion
Interventions	Micronutrient-fortified powder beverage mix (n = 227) included iron 10.8 mg, vitamin A 1050 RE, iodine 90 mcg, zinc 10.5 mg, vitamin C 14 mg, riboflavin 1.2 mg, folic acid 280 mcg, vitamin B 12 6 mcg, vitamin B 6 1.4 mg, niacin 10 mg and vitamin E 21 mg. The nonfortified beverage mix to the control group (n = 212) served as a placebo
Outcomes	Anemia, iron-deficiency anemia, change in hemoglobin, vitamin A status and thyroid stimulating hormone
Notes	All women received elemental iron 60 mg and folic acid 500 mcg. Women who were found to have parasitic infection were treated with a single dose to albendazole 400 mg. The intervention and the placebo groups were comparable at baseline. Prevalence of parasitic infestation was low. Malaria was endemic
Risk of bias	

Tatala 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At each of the six study centers, a block randomization (10 subjects in each block) was used to assign women". Comment: method used for generating the randomisation sequence was not described in sufficient detail to permit judgement
Allocation concealment (selection bias)	Unclear risk	Comment: method used for allocation concealment was not described in sufficient detail to permit judgement
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "nonfortified beverage mix of identical appearance, color and taste was packaged in similar, but different colored, 25-g packets and served as the placebo" and "double-blind effectiveness trial" Comment: participants and providers were probably blinded to the treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions (21.4%) and attrition (19.6%) 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

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, edema, 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

Theobald 1937 (*Continued*)

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 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.
Blinding (performance bias and detection bias) All outcomes	High 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 but participants and investigators were probably not blinded
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

Tofail 2008

Methods	The study was conducted in Matlab, a rural subdistrict in the east central plain of Bangladesh from May 2002 till December 2003
Participants	Pregnant women with gestational age 6-8 weeks, haemoglobin greater than equal to 80 g/L and no serious disease were eligible for enrolment
Interventions	Multiple-micronutrient 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 haemoglobin, motor development and behavioural development, infant micronutrient status

Tofail 2008 (*Continued*)

Notes	Women were divided into 2 groups, that is, early food group and usual food group. Each food group was divided into 3 subgroup 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

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 enrollment, 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
Blinding (performance bias and 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; the mothers were unaware of their micronutrient supplement" and "double masking was practiced" Comment: study participants, caregivers and outcome assessors were blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low 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

Vadillo-Ortega 2011

Methods	This study was conducted in Mexico city between 2001 and 2005
Participants	Pregnant women between 14 and 32 weeks of gestation, at high risk of pre-eclampsia (either a personal history of pre-eclampsia or pre-eclampsia in a first degree relative), who were receiving prenatal care at the Instituto Nacional de Perinatologia Isidro Espinosa de los Reyes in Mexico City between January 2001 and December 2005 were eligible.

	We included eligible participants who agreed to have their prenatal care and delivery at the institution and provide informed consent. Exclusion criteria included patients with multiple gestation, known major fetal anomalies, diabetes mellitus or gestational diabetes, pre-existing hypertension, pre-existing renal disease, collagen vascular disease, cancer or strong family history of cancer in first degree relatives, and pre-existing maternal disease needing drug treatment
Interventions	Participants were randomly assigned to receive one of the three treatments. Intervention group (n=228) was the L-arginine plus antioxidant vitamins group which received total fat 2 g, cholesterol 10 mg, total carbohydrates 19 g, protein 9 g containing 3.3 g of L-arginine, sodium 65 mg, potassium 100 mg, vitamin C 250 mg, vitamin E 200 IU, niacin 25 mg, vitamin B6 2 mg, vitamin B 12 4.8 mcg, folate 200 mcg.. Each participant in the L-arginine plus antioxidant vitamins group received two bars a day. Participants in the antioxidant vitamins alone group (n=222) received two bars a day devoid of L-arginine but containing antioxidant vitamins. Participants in the placebo group (n=222) received two placebo bars a day devoid of L-arginine and antioxidant vitamins. Bars were consumed until the day of delivery
Outcomes	Pre-eclampsia (defined as as hypertension (systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg, or both) and proteinuria (>300 mg/24 hours) presenting after 20 weeks of gestation in women known to be previously normotensive), mild and severe preeclampsia, eclampsia (defined as non-epileptic convulsions., eclampsia, neonatal end points, including preterm birth (born before 37 weeks of gestation), birth weight, small for gestational age (according to institutional charts), and Apgar scores
Notes	All women were screened for gestational diabetes at week 14 and again at week 24 of gestation, according to the institutional protocol. If a woman was diagnosed as having gestational diabetes after randomisation she would discontinue taking bars because of the aforementioned safety concerns. However, these women were included in the data analysis The treatment groups were well balanced with regards to baseline characteristics We used antioxidant vitamin and placebo groups in our review. Data for pre-eclampsia were presented together with eclampsia and were not included in the analysis. Data for pre-eclampsia only will be requested from the authors. Data for the outcomes of placental abruption and SGA is not presented in the paper

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The principal investigator made the assignment centrally after the patient had given informed consent, by using a computer generated code in random size blocks with concealment of allocation by sealed envelopes" Comment: probably done.

Vadillo-Ortega 2011 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "The principal investigator made the assignment centrally after the patient had given informed consent, by using a computer generated code in random size blocks with concealment of allocation by sealed envelopes" Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The bars were packaged in similar envelopes that made them indistinguishable by appearance, and they were flavoured such that they had the same taste irrespective of composition " and "Only the principal investigator knew the group codes" Comment: study participants, care givers and outcome assessors were probably blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Exclusion (9.8%) and attrition (8.3%) 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

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 amenorrhea for less than 12 weeks were eligible for recruitment. All villages within the coverage of the 17 health centers of Mayahi district were included. Women with night blindness and/or signs of severe anemia 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
Outcomes	Birthweight and incidence of LBW, miscarriage, stillbirth, maternal mortality
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 MMS group)

	and less education and more poverty in iron/folic acid group	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Villages - not individuals were randomly assigned to one treatment group or the other." Comment: method used for generating the randomisation sequence was not described in sufficient detail to permit judgement
Allocation concealment (selection bias)	Unclear risk	Comment: method used for allocation concealment was not described to permit judgement
Blinding (performance bias and 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 labeling 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: participants, caregivers and outcome assessors were probably blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was 18%. Reasons for attrition were reported. Exclusion data was not reported
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper

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), small for gestational age (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, haemoglobin, 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
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 In this review, we have used the comparisons of MMN versus iron folate and have calculated and used estimates unadjusted for the cluster design

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation schedule was generated off site with a pseudo-random number generator in SAS" Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation schedule was generated off site with a pseudo-random number generator in SAS version 6 (SAS Institute, Cary, NC). A treatment colour code was assigned to each village based on the treatment allocation schedule." Comment: probably done.
Blinding (performance bias and 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 com-

		pleted" and "were of identical appearance and packaged in blister packs" Comment: participants, caregivers and outcome assessors were blinded to the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusion (4.8%) and attrition (2.3%) were reported along with their reasons
Selective reporting (reporting bias)	Low risk	Comment: all outcomes mentioned in the methods section were presented in the paper

BMI: basal metabolic index
Hb: haemoglobin
HIV: human immunodeficiency virus
IU: international unit
IUGR: intrauterine growth retardation
LBW: low birthweight
mcg: microgram
mg: milligram
MMN: multiple micronutrient
RDA: recommended daily allowance
SGA: small-for-gestational age

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

Study	Reason for exclusion
Aguayo 2005	Not a RCT. Assessing acceptability of multiple micronutrient supplements by pregnant and lactating women
Ahn 2006	Comparing 2 multiple-micronutrient supplements.
An 2001	Compares different doses of iron (35 mg versus 60 mg).
Arsenault 2010	Includes HIV-1 positive women.
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
Carrasco 1962	Study has assessed the impact of D-sorbitol on the absorption of multiple micronutrients in pregnant women

(*Continued*)

Caulfield 1999	Only assesses zinc supplementation.
Caulfield 1999a	Only assesses zinc supplementation.
Chames 2002	Only assesses calcium supplementation.
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
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
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 versus low-dose iron supplementation
Hillman 1963	Only assesses pyridoxine supplementation.
Holly 1955	Only assesses iron and cobalt supplementation.
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
Iannotti 2008	Only assesses zinc supplementation.
ICMR 2000	Assesses periconceptional supplementation of folic acid containing vitamins

(*Continued*)

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
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
Lindström 2011	Describing prevalence of micronutrient deficiencies at baseline and its determinants
Ling 1996	Evaluating the impact of traditional Chinese tonics with nutrients
Lucia 2007	Evaluating impact of docosahexaenoic acid and fructo-oligosccharide
Ma 2008	Evaluating retinol and riboflavin supplementation.
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.
Ochoa-Brust 2007	Assesses impact of vitamin C only.
Park 1999	Study design does not satisfy the eligibility criteria of the review
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
Robertson 1991	Only assesses zinc supplementation.
Sachdeva 1993	Evaluates calcium supplementation.
Sagaonkar 2009	Comparison of 4 micronutrients with 3.
Schmidt 2001	Only assesses vitamin A supplementation.

(*Continued*)

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.
Tanumihardjo 2002	Only assesses vitamin A and iron supplementation.
Thauvin 1992	Not a randomised trial.
Webb 2009	Participants include HIV-positive women.
Young 2010	Study assessed the acceptability of a micronutrient powder (Sprinkles), a fortified food (Nutrivida), and tablets by the participants. All supplements has similar composition of micronutrients
Zavaleta 2000	Only assesses zinc supplementation.

RCT: randomised controlled trial

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 haemoglobin $\leq$ 8.0 will be excluded
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

Biggs 2011 (*Continued*)

	provided for the duration of pregnancy and three months postpartum
Outcomes	Birth weight, maternal haemoglobin and ferritin, infant cognitive development, infant height, haemoglobin
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	

Cogswell 2006

Trial name or title	Impact of Iron/Folic Acid Versus Multimicronutrient Versus Folic Acid Supplements During Pregnancy on Mortality, Morbidity, and Complications During Pregnancy, Labor, and Delivery: A Randomised Controlled Trial in China
Methods	This is a double blind randomised controlled trial, comparing folic acid, folic acid plus iron and multi-micronutrient supplements. Infants of women who receive daily prenatal supplements that contain 400 μg folic acid alone, will be compared with infants of women who receive daily supplements that contain 30 mg iron and 400 μg folic acid. Infants of women who receive daily supplements that contain 30 mg iron and 400 μg folic acid will be compared with infants of women who receive a daily supplement containing 30 mg iron, 400 μg folic acid and other vitamins and minerals (UNICEF formulation). Pregnant women living in study counties that is, Laoting, Mancheng, Fengrun, Xianghe, Yuansh will be assessed for enrollment
Participants	Pregnant women less than 20 weeks of gestation. Exclusion criteria include more than 20 weeks' gestation at enrollment, previous live birth, haemoglobin < 10 g/dl in 1st trimester and < 9.5 g/dl in 2nd trimester at enrolment, current use of iron or other vitamin or mineral supplements (except folic acid), age < 20 years, under treatment for anaemia at enrollment. refuse to participate
Interventions	The study has 3 arms. Group A (active comparator) will receive folic acid 400 μg. Group B (experimental) will receive folic acid 400 μg and iron 30 mg and Group C (experimental multiple-micronutrient supplement) will receive 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
Outcomes	Primary outcome measures: perinatal mortality, gastrointestinal side-effects at monthly visits. Secondary outcome measures: maternal anaemia, Infant gestation age at birth, low birthweight, low weight for height, low weight for age, low height for age, infant anaemia
Starting date	May 2006

Cogswell 2006 (*Continued*)

Contact information	Zuguo Mei, MD, MPH 770-488-5864 ZMei@cdc.gov Mary E Cogswell, DrPH, RN 404-498-3901 MCogswell@cdc.gov
Notes	

Dewey 2011

Trial name or title	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 three intervention groups
Participants	Inclusion criteria • At least 18 years of age • No more than 20 wk of gestation • Given Ante-natal Cards of the Ghana Health Service • Completed the initial routine ante-natal examination at the clinics • HIV negative or status unknown (as from the Ante-natal card) • Free from chronic disease e.g. malignancy requiring frequent medical attention (as from the Ante-natal card) • Residing in the Manya Krobo or Yilo Krobo district • Prepared to sign an informed consent • Living in the area throughout the duration of the study • Acceptance of home visitors Exclusion criteria • Known asthmatic or history of allergy towards peanut or milk products • Concurrent participation in another clinical trial • Severe illness warranting hospital referral
Interventions	1. Dietary supplement: Iron and Folic Acid (IFA):Pregnant women will receive one (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 one (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-20gM daily from 6 to 18 mo 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 • Anthropometric status (weight, BMI, mid-upper arm circumference and subscapular skin-fold thickness) at ~ 36 wk gestation and at 6, 12, and 18 mo postpartum • Pregnancy outcomes (birth weight, gestational age) • Anemia, micronutrient (iron, vitamin A, B-vitamins, zinc) and EFA status, and malarial antigen at ~ 36 wk gestation and 6 mo postpartum

Dewey 2011 (*Continued*)

	• Total plasma cholesterol at ~ 36 wk gestation • 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 • Breast milk composition (EFA, vitamin A, B-vitamins, iodine) at 6 mo postpartum • Depressive symptoms (which may be related to EFA status) at 6 mo postpartum ii. Child • Anthropometric status (weight, length, head circumference and mid-upper arm circumference) at birth and 3, 6, 12 and 18 mo • Anaemia, micronutrient (iron, vitamin A, B-vitamins, iodine) and EFA status, and malarial antigen at 6 and 18 mo • Morbidity between 6 and 18 mo • Child feeding practices and maternal report of child sleep patterns at 6, 12 and 18 mo • Energy intake from complementary foods at 9 and 15 mo • Antibody response to measles vaccination at 12 mo • Achievement of five motor milestones (sitting without support, standing alone, walking with assistance, walking alone and running) and four other developmental milestones (pronouncing single words like mama or dada, waving goodbye, eating by self, drinking from a cup) from 0 to 18 mo • Neuro-behavioural development at 18 mo of age
Starting date	November 2009
Contact information	Kathryn G Dewey, UC Davis
Notes	sample size = 864

Fall 2007

Trial name or title	Mumbai Maternal Diet Study: randomised controlled trial of micronutrient-dense food before and during pregnancy to prevent low birthweight
Methods	This is randomised controlled trial. Women meeting inclusion criteria will be recruited and randomised to 1 of 4 groups, to receive 1 of 2 interventions. Supplementation will be supervised. Field staff will record menstrual dates, in order to detect pregnancy as early as possible. Women who become pregnant will have investigations during pregnancy, including blood samples and ultrasound scans
Participants	Married women of age between 15-35, living in slum communities in Bandra and Khar districts of Mumbai served by the Women of India Network (WIN) primary healthcare clinics, not pregnant at recruitment, not using any permanent form of contraception, Intending to have more children and planning any future deliveries in Mumbai. Exclusion criteria include unmarried women living outside the study area, outside the age range specified, currently pregnant (these may become eligible after delivery), women who have undergone sterilisation surgery, or whose husbands have had a vasectomy, women not planning further pregnancies and women planning further deliveries outside Mumbai
Interventions	A daily food-based supplement made from vegetables, fruit, and milk, of differing micronutrient content
Outcomes	Primary outcome measures: birthweight, infant mortality. Secondary outcome measures: maternal micronutrient status, maternal infection load, maternal immune status, fetal losses (miscarriages and stillbirths), newborn body composition, newborn immune function

Fall 2007 (*Continued*)

Starting date	January 9, 2006
Contact information	Dr Caroline Fall MRC Epidemiology Resource Centre Southampton General Hospital University of Southampton Tremona Road, Southampton, SO16 6YD, United Kingdom Tel # +44 (0)2380 777624
Notes	

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 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 (haemoglobin (Hb) less than 7 g/dL), reported onset of menopause will be excluded
Interventions	Four 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 two 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 a nutrient enriched weaning food fortificant or placebo, and for a period of 6 months
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

Moore 2011 (*Continued*)

Starting date	October 1, 2009
Contact information	Sophie Moore MRC Keneba MRC Laboratories Fajara, Banjul Gambia PO Box 273 Email: smoore@mrc.gm
Notes	800 mother-infant pairs

West 2011

Trial name or title	Antenatal Micronutrient Supplementation and Infant Survival (JiVitA-3)
Methods	Community-based randomised, double blind trial to to examine whether a daily antenatal and postnatal multiple micronutrient 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 will be recruited. Women not interviewed for consent within 12 consecutive weeks after being ascertained as pregnant by urine testing will be excluded
Interventions	Dietary Supplement: Multiple micronutrient 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).Mothers instructed to take 1 tablet per day, from the 1st trimester through 12 weeks post-partum. 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 mo 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
Starting date	January 2008
Contact information	Keith West, Jr, Johns Hopkins Bloomberg School of Public Health
Notes	

DATA AND ANALYSES

Comparison 1. Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm births	17		Risk Ratio (Fixed, 95% CI)	Subtotals only
1.1 All trials	17		Risk Ratio (Fixed, 95% CI)	0.99 [0.97, 1.02]
1.2 Trials with loss to follow up > 20% excluded	12		Risk Ratio (Fixed, 95% CI)	1.00 [0.97, 1.02]
2 Small-for-gestational age	15		Risk Ratio (Fixed, 95% CI)	Subtotals only
2.1 All trials	15		Risk Ratio (Fixed, 95% CI)	0.87 [0.83, 0.92]
2.2 Trials with loss to follow up > 20% excluded	8		Risk Ratio (Fixed, 95% CI)	0.87 [0.82, 0.93]
3 Small-for-gestational age: maternal BMI	15		Risk Ratio (Fixed, 95% CI)	Subtotals only
3.1 Maternal BMI < 20 kg/m 2	4		Risk Ratio (Fixed, 95% CI)	0.90 [0.83, 0.98]
3.2 Maternal BMI ≥ 20 kg/m 2	11		Risk Ratio (Fixed, 95% CI)	0.85 [0.80, 0.91]
4 Small for gestational age: maternal height	15		Risk Ratio (Fixed, 95% CI)	Subtotals only
4.1 Maternal height < 154.9 cm	8		Risk Ratio (Fixed, 95% CI)	0.91 [0.85, 0.98]
4.2 Maternal height ≥ 154.9 cm	7		Risk Ratio (Fixed, 95% CI)	0.82 [0.76, 0.89]
5 Small-for-gestational age: supplementation	15		Risk Ratio (Fixed, 95% CI)	Subtotals only
5.1 Supplementation started before 20 weeks	10		Risk Ratio (Fixed, 95% CI)	0.90 [0.84, 0.96]
5.2 Supplementation started after 20 weeks	5		Risk Ratio (Fixed, 95% CI)	0.83 [0.76, 0.91]
6 Low birthweight	15		Risk Ratio (Fixed, 95% CI)	Subtotals only
6.1 All trials	15		Risk Ratio (Fixed, 95% CI)	0.86 [0.80, 0.91]
6.2 Trials with loss to follow up > 20% excluded	10		Risk Ratio (Fixed, 95% CI)	0.86 [0.81, 0.93]
7 Low birthweight: maternal BMI	14		Risk Ratio (Random, 95% CI)	Subtotals only
7.1 BMI < 20 kg/m^2	4		Risk Ratio (Random, 95% CI)	0.78 [0.65, 0.93]
7.2 Maternal BMI ≥ 20 kg/m 2	10		Risk Ratio (Random, 95% CI)	0.88 [0.81, 0.96]
8 Low birthweight: maternal height	15		Risk Ratio (Random, 95% CI)	Subtotals only
8.1 Maternal height < 154.9 cm	8		Risk Ratio (Random, 95% CI)	0.86 [0.76, 0.98]
8.2 Maternal height ≥ 154.9 cm	7		Risk Ratio (Random, 95% CI)	0.86 [0.77, 0.95]

9 Low birthweight: supplementation	15	Risk Ratio (Fixed, 95% CI)	Subtotals only
9.1 Supplementation started before 20 weeks	10	Risk Ratio (Fixed, 95% CI)	0.88 [0.81, 0.95]
9.2 Supplementation started after 20 weeks	5	Risk Ratio (Fixed, 95% CI)	0.82 [0.75, 0.91]
10 Pre-eclampsia	4	Risk Ratio (Fixed, 95% CI)	0.47 [0.22, 1.03]
11 Miscarriage (loss before 28 weeks)	8	Risk Ratio (Fixed, 95% CI)	Subtotals only
11.1 All trials	8	Risk Ratio (Fixed, 95% CI)	0.90 [0.79, 1.02]
11.2 Trials with loss to follow up > 20% excluded	7	Risk Ratio (Fixed, 95% CI)	0.90 [0.78, 1.02]
12 Maternal mortality	3	Risk Ratio (Fixed, 95% CI)	Subtotals only
12.1 All trials	3	Risk Ratio (Fixed, 95% CI)	0.97 [0.63, 1.48]
12.2 Trial with loss to follow up > 20% excluded	2	Risk Ratio (Fixed, 95% CI)	1.05 [0.66, 1.64]
13 Perinatal mortality	12	Risk Ratio (Random, 95% CI)	Subtotals only
13.1 All trials	12	Risk Ratio (Random, 95% CI)	0.96 [0.84, 1.10]
13.2 Trials with loss to follow up > 20% excluded	8	Risk Ratio (Random, 95% CI)	0.96 [0.82, 1.14]
14 Stillbirths	13	Risk Ratio (Fixed, 95% CI)	Subtotals only
14.1 All trials	13	Risk Ratio (Fixed, 95% CI)	0.95 [0.85, 1.06]
14.2 Trials with loss to follow up > 20% excluded	9	Risk Ratio (Fixed, 95% CI)	0.97 [0.87, 1.09]
15 Neonatal mortality	10	Risk Ratio (Fixed, 95% CI)	1.01 [0.89, 1.16]
16 Maternal anaemia (third trimester Hb < 110 g/L)	8	Risk Ratio (Random, 95% CI)	Subtotals only
16.1 All trials	8	Risk Ratio (Random, 95% CI)	0.81 [0.66, 0.98]
16.2 Trials with loss to follow up > 20% excluded	5	Risk Ratio (Random, 95% CI)	0.74 [0.58, 0.96]
17 Placental abruption	1	Risk Ratio (Fixed, 95% CI)	Totals not selected
18 Very preterm birth (before 34 weeks of gestation)	1	Risk Ratio (Fixed, 95% CI)	Totals not selected
19 Side effects of supplements	1	Risk Ratio (Fixed, 95% CI)	Totals not selected
20 Congenital anomalies (including neural tube defects)	1	Risk Ratio (Fixed, 95% CI)	Totals not selected
21 Neurodevelopmental outcome: BSID scores	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
21.1 Mental development scores at 6 months of age	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.2 Mental development scores at 12 months of age	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.3 Psychomotor development scores ar 6 months of age	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.4 Psychomotor development scores at 12 months of age	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Multiple micronutrients versus iron folate only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm births	15		Risk Ratio (Fixed, 95% CI)	Subtotals only
1.1 All trials	15		Risk Ratio (Fixed, 95% CI)	0.99 [0.96, 1.02]
1.2 Trials with loss to follow up > 20% excluded	9		Risk Ratio (Fixed, 95% CI)	0.99 [0.96, 1.02]
2 Small-for-gestational age	14		Risk Ratio (Random, 95% CI)	Subtotals only
2.1 All trials	14		Risk Ratio (Random, 95% CI)	0.87 [0.81, 0.95]
2.2 Trials with loss to follow up > 20% excluded	7		Risk Ratio (Random, 95% CI)	0.88 [0.79, 0.98]
3 Small-for-gestational age: maternal BMI	14		Risk Ratio (Random, 95% CI)	Subtotals only
3.1 BMI < 20 kg/m^2	4		Risk Ratio (Random, 95% CI)	0.86 [0.69, 1.08]
3.2 BMI ≥ 20 kg/m^2	10		Risk Ratio (Random, 95% CI)	0.85 [0.79, 0.91]
4 Small-for-gestational age: maternal height	14		Risk Ratio (Fixed, 95% CI)	Subtotals only
4.1 Maternal height < 154.9 cm	8		Risk Ratio (Fixed, 95% CI)	0.97 [0.90, 1.04]
4.2 Maternal height ≥ 154.9 cm	6		Risk Ratio (Fixed, 95% CI)	0.82 [0.76, 0.89]
5 Small-for-gestational age: supplementation	14		Risk Ratio (Fixed, 95% CI)	Subtotals only
5.1 Supplementation started before 20 weeks	9		Risk Ratio (Fixed, 95% CI)	0.94 [0.88, 1.01]
5.2 Supplementation after 20 weeks	5		Risk Ratio (Fixed, 95% CI)	0.83 [0.76, 0.91]
6 Low birthweight	14		Risk Ratio (Fixed, 95% CI)	Subtotals only
6.1 All trials	14		Risk Ratio (Fixed, 95% CI)	0.89 [0.83, 0.94]
6.2 Trials with loss to follow up > 20% excluded	9		Risk Ratio (Fixed, 95% CI)	0.90 [0.84, 0.97]
7 Low birthweight: maternal BMI	14		Risk Ratio (Random, 95% CI)	Subtotals only
7.1 BMI < 20 kg/m^2	4		Risk Ratio (Random, 95% CI)	0.80 [0.62, 1.02]
7.2 BMI ≥ 20 kg/m^2	10		Risk Ratio (Random, 95% CI)	0.88 [0.81, 0.96]
8 Low birthweight: maternal height	14		Risk Ratio (Random, 95% CI)	Subtotals only
8.1 Maternal height < 154.9 cm	8		Risk Ratio (Random, 95% CI)	0.90 [0.77, 1.04]
8.2 Maternal height ≥ 154.9 cm	6		Risk Ratio (Random, 95% CI)	0.85 [0.76, 0.94]
9 Low birthweight: supplementation	14		Risk Ratio (Fixed, 95% CI)	Subtotals only
9.1 Supplementation before 20 weeks	9		Risk Ratio (Fixed, 95% CI)	0.93 [0.86, 1.02]
9.2 Supplementation after 20 weeks	5		Risk Ratio (Fixed, 95% CI)	0.82 [0.75, 0.91]
10 Pre-eclampsia	1		Risk Ratio (Fixed, 95% CI)	Totals not selected

11 Miscarriage (loss before 28 weeks)	8	Risk Ratio (Fixed, 95% CI)	Subtotals only
11.1 All trials	8	Risk Ratio (Fixed, 95% CI)	0.90 [0.79, 1.02]
11.2 Trial with loss to follow up > 20% excluded	7	Risk Ratio (Fixed, 95% CI)	0.90 [0.78, 1.02]
12 Maternal mortality	3	Risk Ratio (Fixed, 95% CI)	Subtotals only
12.1 All trials	3	Risk Ratio (Fixed, 95% CI)	0.97 [0.63, 1.48]
12.2 Trial with loss to follow up < 20% excluded	2	Risk Ratio (Fixed, 95% CI)	1.05 [0.66, 1.64]
13 Perinatal mortality	11	Risk Ratio (Random, 95% CI)	Subtotals only
13.1 All trials	11	Risk Ratio (Random, 95% CI)	0.99 [0.84, 1.16]
13.2 Trials with loss to follow up > 20% excluded	8	Risk Ratio (Random, 95% CI)	1.02 [0.83, 1.24]
14 Perinatal mortality: maternal BMI	11	Risk Ratio (Random, 95% CI)	Subtotals only
14.1 BMI < 20 kg/m²	3	Risk Ratio (Random, 95% CI)	1.19 [0.94, 1.50]
14.2 BMI ≥ 20 kg/m²	8	Risk Ratio (Random, 95% CI)	0.93 [0.78, 1.11]
15 Perinatal mortality: maternal height	11	Risk Ratio (Random, 95% CI)	Subtotals only
15.1 Maternal height < 154.9 cm	7	Risk Ratio (Random, 95% CI)	0.95 [0.77, 1.17]
15.2 Maternal height ≥ 154.9 cm	4	Risk Ratio (Random, 95% CI)	1.08 [0.79, 1.50]
16 Perinatal mortality: supplementation	11	Risk Ratio (Random, 95% CI)	Subtotals only
16.1 Supplementation before 20 weeks	8	Risk Ratio (Random, 95% CI)	1.09 [0.84, 1.42]
16.2 Supplementation after 20 weeks	3	Risk Ratio (Random, 95% CI)	0.88 [0.80, 0.97]
17 Stillbirths	13	Risk Ratio (Fixed, 95% CI)	Subtotals only
17.1 All trials	13	Risk Ratio (Fixed, 95% CI)	0.96 [0.86, 1.07]
17.2 Trials with loss to follow up > 20% excluded	9	Risk Ratio (Fixed, 95% CI)	0.99 [0.88, 1.10]
18 Neonatal mortality	9	Risk Ratio (Fixed, 95% CI)	1.01 [0.89, 1.15]
19 Maternal anaemia (third trimester Hb <110 g/L)	6	Risk Ratio (Fixed, 95% CI)	Subtotals only
19.1 All trials	6	Risk Ratio (Fixed, 95% CI)	0.96 [0.86, 1.07]
19.2 Trials with loss to follow up > 20% excluded	4	Risk Ratio (Fixed, 95% CI)	0.97 [0.85, 1.10]
20 Very preterm birth (before 34 weeks of gestation)	1	Risk Ratio (Fixed, 95% CI)	Totals not selected
21 Side effects	1	Risk Ratio (Fixed, 95% CI)	Totals not selected
22 Congenital anomalies	1	Risk Ratio (Fixed, 95% CI)	Totals not selected
23 Neurodevelopmental outcome: BSID scores	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
23.1 Mental development scores at 6 months of age: new subgroup	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.2 Mental development scores at 12 months of age	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

23.3 Psychomotor development scores ar 6 months of age	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.4 Psychomotor development scores at 12 months of age	1	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 1 Preterm births.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 1 Preterm births

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 All trials				
Rumiris 2006	-1.1086 (1.2234)		0.0 %	0.33 [0.03, 3.63]
Dieckmann 1943	-0.3147 (0.5266)		0.1 %	0.73 [0.26, 2.05]
Tofail 2008	-0.2876 (0.14904)		0.8 %	0.75 [0.56, 1.00]
Friis 2004	-0.2357 (0.1847)		0.5 %	0.79 [0.55, 1.13]
Osrin 2005	-0.1392 (0.1896)		0.5 %	0.87 [0.60, 1.26]
Bhutta 2009a	-0.13196 (0.2139)		0.4 %	0.88 [0.58, 1.33]
Christian 2003	-0.0726 (0.1039)		1.7 %	0.93 [0.76, 1.14]
Gupta 2007	-0.07257 (1.3983)		0.0 %	0.93 [0.06, 14.41]
SUMMIT 2008	-0.01005 (0.0157)		76.1 %	0.99 [0.96, 1.02]
Fawzi 2007	0.00995 (0.04761)		8.3 %	1.01 [0.92, 1.11]
Zagre 2007	0.019802 (0.05264)		6.8 %	1.02 [0.92, 1.13]
Roberfroid 2008	0.03922 (0.16678)		0.7 %	1.04 [0.75, 1.44]
Zeng 2008	0.0583 (0.1563)		0.8 %	1.06 [0.78, 1.44]
Sunawang 2009	0.07696 (0.0873)		2.5 %	1.08 [0.91, 1.28]
Brough 2010	0.0953 (0.5035)		0.1 %	1.10 [0.41, 2.95]
Ramakrishnan 2003	0.13102 (0.2866)		0.2 %	1.14 [0.65, 2.00]
Vadillo-Ortega 2011	0.1655 (0.1857)		0.5 %	1.18 [0.82, 1.70]
Subtotal (95% CI)			**100.0 %**	**0.99 [0.97, 1.02]**
Heterogeneity: Chi^2 = 10.19, df = 16 (P = 0.86); I^2 =0.0%				

0.5 0.7 1 1.5 2

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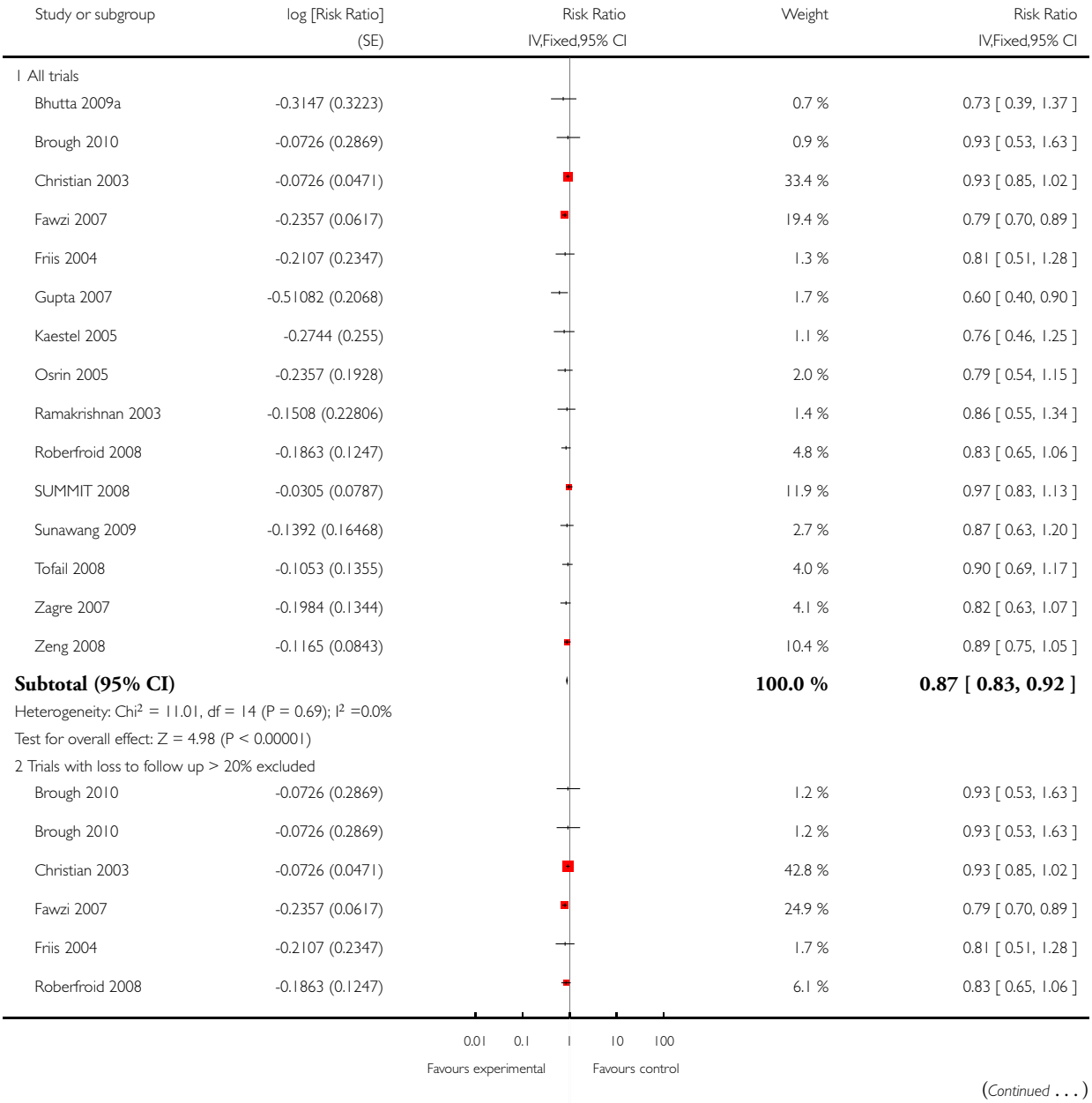
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Test for overall effect: Z = 0.60 (P = 0.55)				
2 Trials with loss to follow up > 20% excluded				
Rumiris 2006	-1.1086 (1.2234)		0.0 %	0.33 [0.03, 3.63]
Osrin 2005	-0.1392 (0.1896)		0.5 %	0.87 [0.60, 1.26]
Bhutta 2009a	-0.13196 (0.2139)		0.4 %	0.88 [0.58, 1.33]
Christian 2003	-0.0726 (0.1039)		1.8 %	0.93 [0.76, 1.14]
SUMMIT 2008	-0.01005 (0.0157)		77.4 %	0.99 [0.96, 1.02]
Fawzi 2007	0.00995 (0.04761)		8.4 %	1.01 [0.92, 1.11]
Zagre 2007	0.019802 (0.05264)		6.9 %	1.02 [0.92, 1.13]
Roberfroid 2008	0.03922 (0.16678)		0.7 %	1.04 [0.75, 1.44]
Zeng 2008	0.0583 (0.1563)		0.8 %	1.06 [0.78, 1.44]
Sunawang 2009	0.07696 (0.0873)		2.5 %	1.08 [0.91, 1.28]
Brough 2010	0.0953 (0.5035)		0.1 %	1.10 [0.41, 2.95]
Vadillo-Ortega 2011	0.1655 (0.1857)		0.6 %	1.18 [0.82, 1.70]
Subtotal (95% CI)			**100.0 %**	**1.00 [0.97, 1.02]**
Heterogeneity: Chi^2 = 4.51, df = 11 (P = 0.95); I^2 =0.0%				
Test for overall effect: Z = 0.34 (P = 0.74)				

Analysis 1.2. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 2 Small-for-gestational age.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 2 Small-for-gestational age



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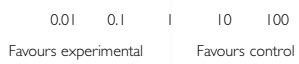
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Sunawang 2009	-0.1392 (0.16468)		3.5 %	0.87 [0.63, 1.20]
Zagre 2007	-0.1984 (0.1344)		5.3 %	0.82 [0.63, 1.07]
Zeng 2008	-0.1165 (0.0843)		13.4 %	0.89 [0.75, 1.05]
Subtotal (95% CI)			**100.0 %**	**0.87 [0.82, 0.93]**
Heterogeneity: Chi^2 = 5.05, df = 8 (P = 0.75); I^2 =0.0%				
Test for overall effect: Z = 4.46 (P < 0.00001)				



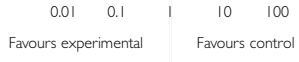
Analysis 1.3. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 3 Small-for-gestational age: maternal BMI.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 3 Small-for-gestational age: maternal BMI

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Maternal BMI < 20 kg/m^2				
Christian 2003	-0.0726 (0.0471)		81.1 %	0.93 [0.85, 1.02]
Gupta 2007	-0.51082 (0.2068)		4.2 %	0.60 [0.40, 0.90]
Osrin 2005	-0.2357 (0.1928)		4.8 %	0.79 [0.54, 1.15]
Tofail 2008	-0.1053 (0.1355)		9.8 %	0.90 [0.69, 1.17]
Subtotal (95% CI)			**100.0 %**	**0.90 [0.83, 0.98]**
Heterogeneity: Chi^2 = 4.78, df = 3 (P = 0.19); I^2 =37%				
Test for overall effect: Z = 2.41 (P = 0.016)				
2 Maternal BMI $\geq$ 20 kg/m^2				
Bhutta 2009a	-0.3147 (0.3223)		1.2 %	0.73 [0.39, 1.37]
Brough 2010	-0.0726 (0.2869)		1.5 %	0.93 [0.53, 1.63]
Fawzi 2007	-0.2357 (0.0617)		33.0 %	0.79 [0.70, 0.89]



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Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Friis 2004	-0.2107 (0.2347)		2.3 %	0.81 [0.51, 1.28]
Kaestel 2005	-0.2744 (0.255)		1.9 %	0.76 [0.46, 1.25]
Ramakrishnan 2003	-0.1508 (0.22806)		2.4 %	0.86 [0.55, 1.34]
Roberfroid 2008	-0.1863 (0.1247)		8.1 %	0.83 [0.65, 1.06]
SUMMIT 2008	-0.0305 (0.0787)		20.3 %	0.97 [0.83, 1.13]
Sunawang 2009	-0.1392 (0.16468)		4.6 %	0.87 [0.63, 1.20]
Zagre 2007	-0.1984 (0.1344)		7.0 %	0.82 [0.63, 1.07]
Zeng 2008	-0.1165 (0.0843)		17.7 %	0.89 [0.75, 1.05]
Subtotal (95% CI)			**100.0 %**	**0.85 [0.80, 0.91]**

Heterogeneity: Chi^2 = 5.19, df = 10 (P = 0.88); I^2 =0.0%

Test for overall effect: Z = 4.47 (P < 0.00001)

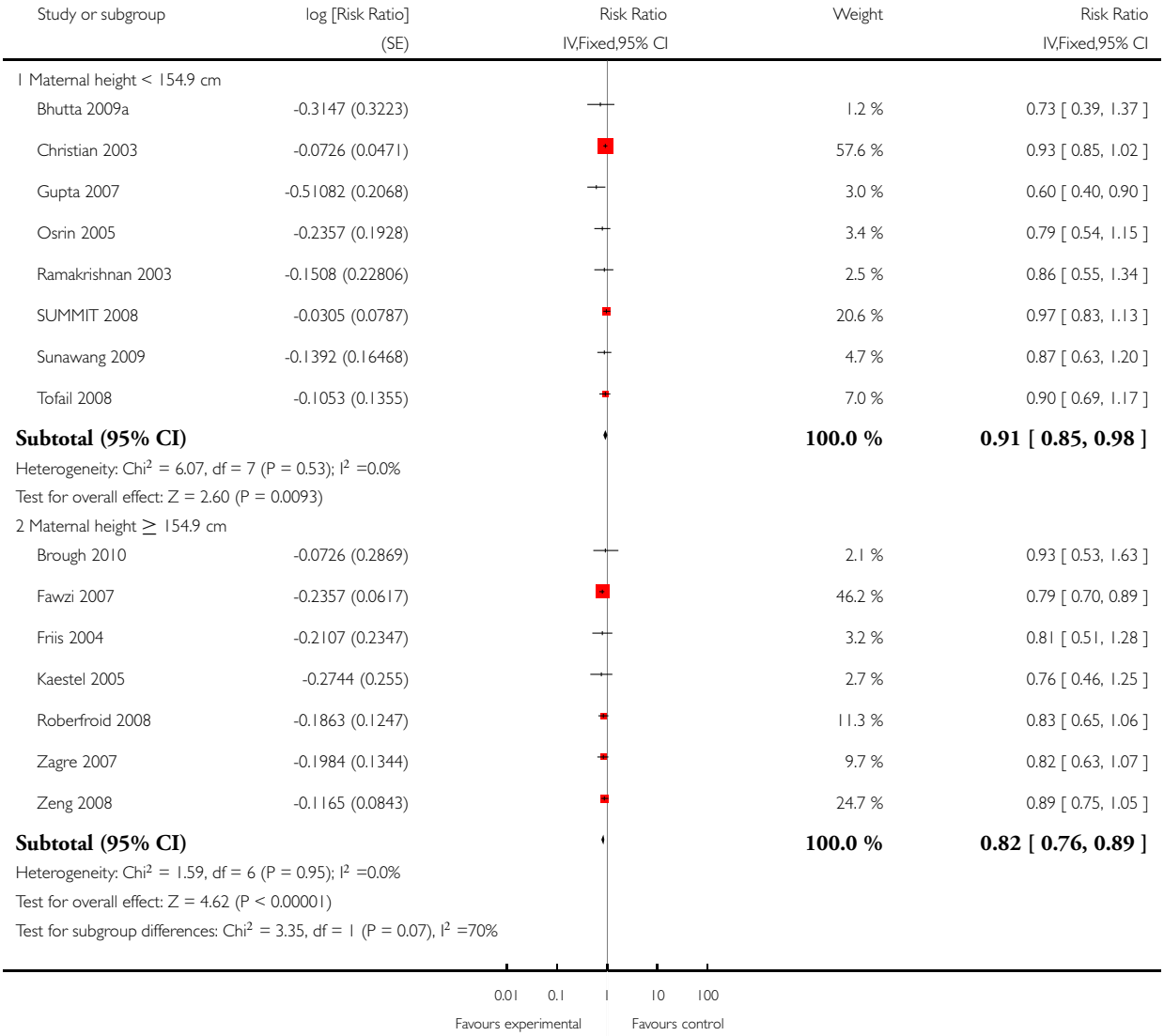
Test for subgroup differences: Chi^2 = 1.04, df = 1 (P = 0.31), I^2 =4%

Analysis 1.4. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 4 Small for gestational age: maternal height.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 4 Small for gestational age: maternal height



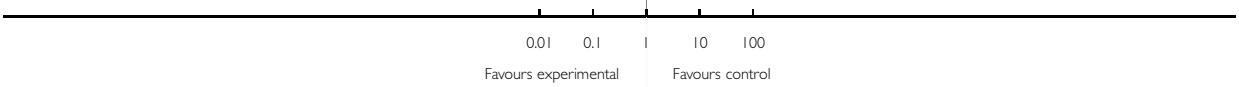
Analysis 1.5. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 5 Small-for-gestational age: supplementation.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 5 Small-for-gestational age: supplementation

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Supplementation started before 20 weeks				
Bhutta 2009a	-0.3147 (0.3223)		1.1 %	0.73 [0.39, 1.37]
Brough 2010	-0.0726 (0.2869)		1.4 %	0.93 [0.53, 1.63]
Christian 2003	-0.0726 (0.0471)		51.8 %	0.93 [0.85, 1.02]
Osrin 2005	-0.2357 (0.1928)		3.1 %	0.79 [0.54, 1.15]
Ramakrishnan 2003	-0.1508 (0.22806)		2.2 %	0.86 [0.55, 1.34]
Roberfroid 2008	-0.1863 (0.1247)		7.4 %	0.83 [0.65, 1.06]
Sunawang 2009	-0.1392 (0.16468)		4.2 %	0.87 [0.63, 1.20]
Tofail 2008	-0.1053 (0.1355)		6.3 %	0.90 [0.69, 1.17]
Zagre 2007	-0.1984 (0.1344)		6.4 %	0.82 [0.63, 1.07]
Zeng 2008	-0.1165 (0.0843)		16.2 %	0.89 [0.75, 1.05]
Subtotal (95% CI)			**100.0 %**	**0.90 [0.84, 0.96]**
Heterogeneity: Chi^2 = 2.35, df = 9 (P = 0.98); I^2 =0.0%				
Test for overall effect: Z = 3.26 (P = 0.0011)				
2 Supplementation started after 20 weeks				
Fawzi 2007	-0.2357 (0.0617)		54.6 %	0.79 [0.70, 0.89]
Friis 2004	-0.2107 (0.2347)		3.8 %	0.81 [0.51, 1.28]
Gupta 2007	-0.51082 (0.2068)		4.9 %	0.60 [0.40, 0.90]
Kaestel 2005	-0.2744 (0.255)		3.2 %	0.76 [0.46, 1.25]
SUMMIT 2008	-0.0305 (0.0787)		33.6 %	0.97 [0.83, 1.13]
Subtotal (95% CI)			**100.0 %**	**0.83 [0.76, 0.91]**
Heterogeneity: Chi^2 = 7.14, df = 4 (P = 0.13); I^2 =44%				
Test for overall effect: Z = 3.96 (P = 0.000075)				
Test for subgroup differences: Chi^2 = 1.52, df = 1 (P = 0.22), I^2 =34%				



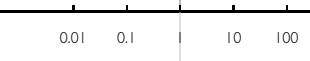
Analysis 1.6. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 6 Low birthweight.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 6 Low birthweight

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 All trials				
Bhutta 2009a	0.1838 (0.19606)		2.7 %	1.20 [0.82, 1.76]
Brough 2010	0.4886 (0.4613)		0.5 %	1.63 [0.66, 4.03]
Christian 2003	-0.1625 (0.0674)		22.6 %	0.85 [0.74, 0.97]
Fawzi 2007	-0.1863 (0.07255)		19.5 %	0.83 [0.72, 0.96]
Friis 2004	-0.3011 (0.2537)		1.6 %	0.74 [0.45, 1.22]
Gupta 2007	-0.9675 (0.3026)		1.1 %	0.38 [0.21, 0.69]
Kaestel 2005	-0.1278 (0.1954)		2.7 %	0.88 [0.60, 1.29]
Osrin 2005	-0.2876 (0.1138)		7.9 %	0.75 [0.60, 0.94]
Ramakrishnan 2003	-0.04082 (0.2571)		1.6 %	0.96 [0.58, 1.59]
Roberfroid 2008	-0.09431 (0.17166)		3.5 %	0.91 [0.65, 1.27]
SUMMIT 2008	-0.1508 (0.0819)		15.3 %	0.86 [0.73, 1.01]
Sunawang 2009	0.1988 (0.2027)		2.5 %	1.22 [0.82, 1.81]
Tofail 2008	-0.1508 (0.09778)		10.7 %	0.86 [0.71, 1.04]
Zagre 2007	-0.1392 (0.1487)		4.6 %	0.87 [0.65, 1.16]
Zeng 2008	-0.1054 (0.1797)		3.2 %	0.90 [0.63, 1.28]
Subtotal (95% CI)			**100.0 %**	**0.86 [0.80, 0.91]**
Heterogeneity: Chi² = 17.51, df = 14 (P = 0.23); I² =20%				
Test for overall effect: Z = 4.86 (P < 0.00001)				
2 Trials with loss to follow up > 20% excluded				
Bhutta 2009a	0.1838 (0.19606)		3.2 %	1.20 [0.82, 1.76]
Brough 2010	0.4886 (0.4613)		0.6 %	1.63 [0.66, 4.03]
Christian 2003	-0.1625 (0.0674)		27.5 %	0.85 [0.74, 0.97]
Fawzi 2007	-0.1863 (0.07255)		23.7 %	0.83 [0.72, 0.96]
Osrin 2005	-0.2876 (0.1138)		9.6 %	0.75 [0.60, 0.94]
Roberfroid 2008	-0.09431 (0.17166)		4.2 %	0.91 [0.65, 1.27]



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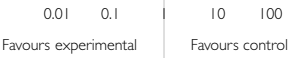
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
SUMMIT 2008	-0.1508 (0.0819)		18.6 %	0.86 [0.73, 1.01]
Sunawang 2009	0.1988 (0.2027)		3.0 %	1.22 [0.82, 1.81]
Zagre 2007	-0.1392 (0.1487)		5.6 %	0.87 [0.65, 1.16]
Zeng 2008	-0.1054 (0.1797)		3.9 %	0.90 [0.63, 1.28]
Subtotal (95% CI)			**100.0 %**	**0.86 [0.81, 0.93]**
Heterogeneity: Chi^2 = 9.68, df = 9 (P = 0.38); I^2 =7%				
Test for overall effect: Z = 4.12 (P = 0.000038)				



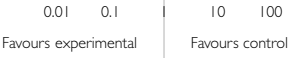
Analysis 1.7. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 7 Low birthweight: maternal BMI.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 7 Low birthweight: maternal BMI

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 BMI < 20 kg/m^2				
Gupta 2007	-0.9675 (0.3026)		7.5 %	0.38 [0.21, 0.69]
Osrin 2005	-0.2876 (0.1138)		26.5 %	0.75 [0.60, 0.94]
Christian 2003	-0.1625 (0.0674)		36.3 %	0.85 [0.74, 0.97]
Tofail 2008	-0.1508 (0.09778)		29.7 %	0.86 [0.71, 1.04]
Subtotal (95% CI)			**100.0 %**	**0.78 [0.65, 0.93]**
Heterogeneity: Tau^2 = 0.02; Chi^2 = 7.58, df = 3 (P = 0.06); I^2 =60%				
Test for overall effect: Z = 2.79 (P = 0.0053)				
2 Maternal BMI $\geq$ 20 kg/m^2				
Friis 2004	-0.3011 (0.2537)		2.8 %	0.74 [0.45, 1.22]
Fawzi 2007	-0.1863 (0.07255)		34.1 %	0.83 [0.72, 0.96]



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Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
SUMMIT 2008	-0.1508 (0.0819)		26.8 %	0.86 [0.73, 1.01]
Zagre 2007	-0.1392 (0.1487)		8.1 %	0.87 [0.65, 1.16]
Kaestel 2005	-0.1278 (0.1954)		4.7 %	0.88 [0.60, 1.29]
Zeng 2008	-0.1054 (0.1797)		5.6 %	0.90 [0.63, 1.28]
Roberfroid 2008	-0.09431 (0.17166)		6.1 %	0.91 [0.65, 1.27]
Ramakrishnan 2003	-0.04082 (0.2571)		2.7 %	0.96 [0.58, 1.59]
Bhutta 2009a	0.1838 (0.19606)		4.7 %	1.20 [0.82, 1.76]
Sunawang 2009	0.1988 (0.2027)		4.4 %	1.22 [0.82, 1.81]
Subtotal (95% CI)			**100.0 %**	**0.88 [0.81, 0.96]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.49$, df = 9 (P = 0.69); $I^2 = 0.0\%$

Test for overall effect: Z = 2.95 (P = 0.0031)

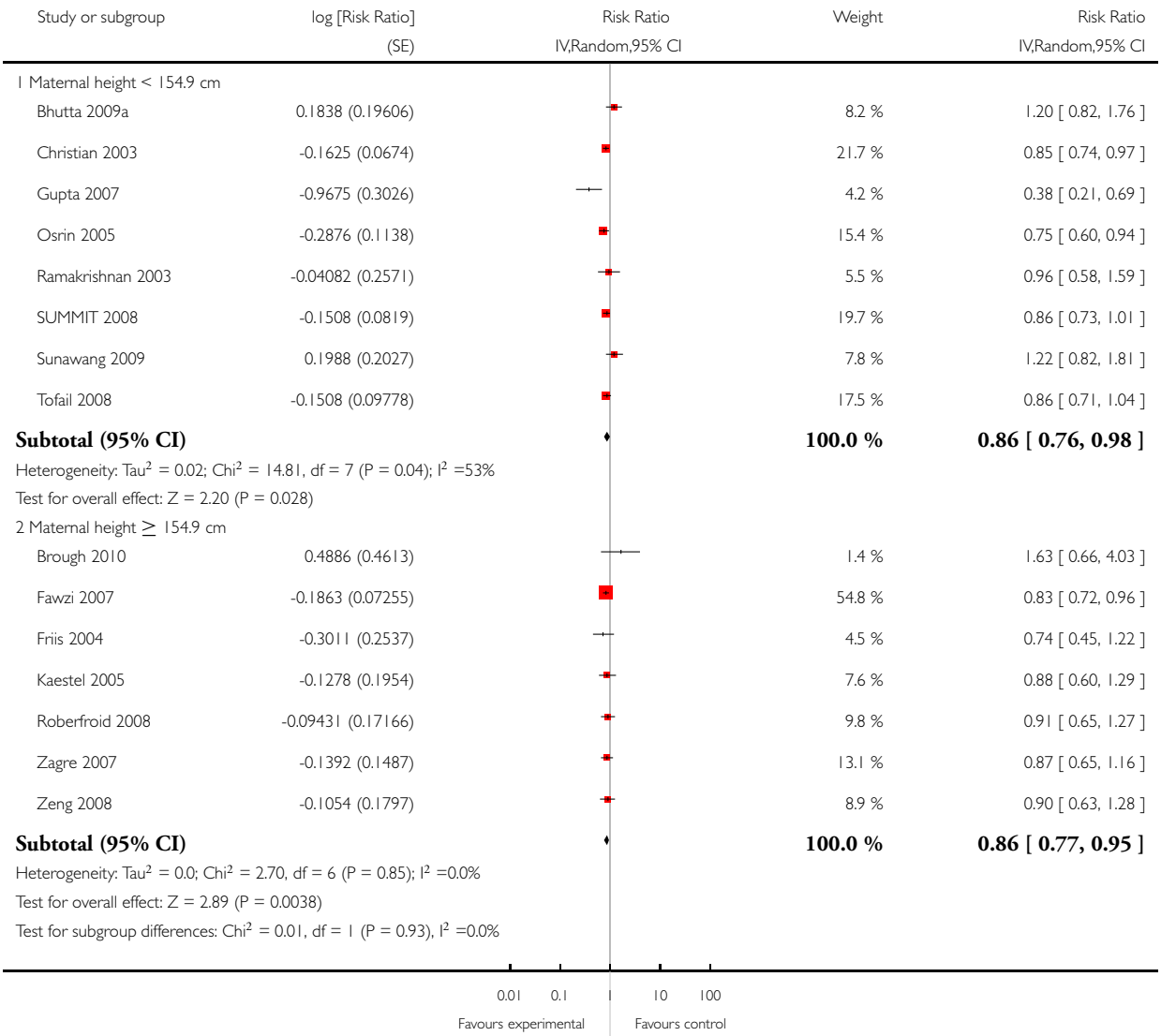
Test for subgroup differences: $Chi^2 = 1.62$, df = 1 (P = 0.20), $I^2 = 38\%$

Analysis 1.8. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 8 Low birthweight: maternal height.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 8 Low birthweight: maternal height

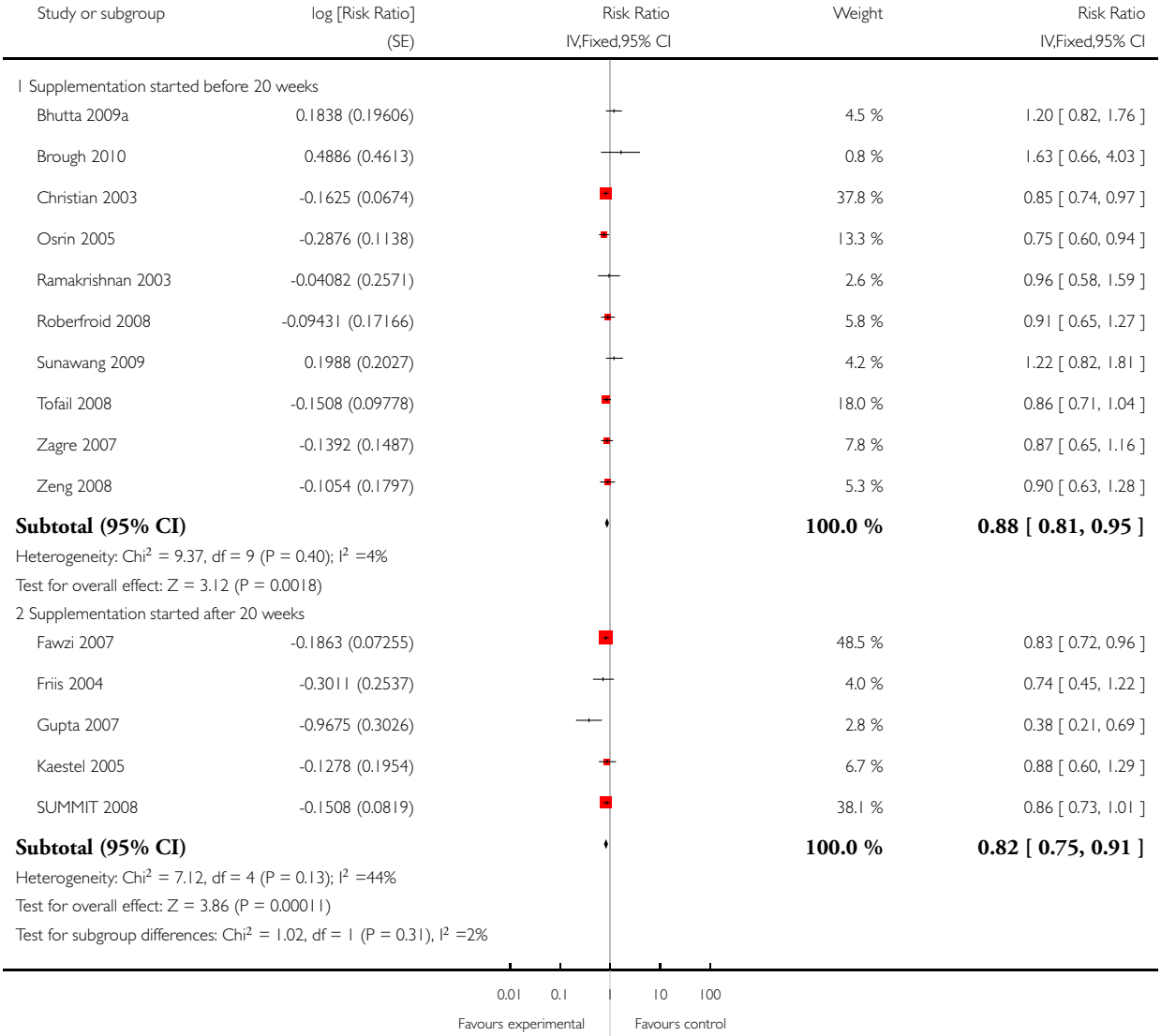


Analysis 1.9. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 9 Low birthweight: supplementation.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 9 Low birthweight: supplementation

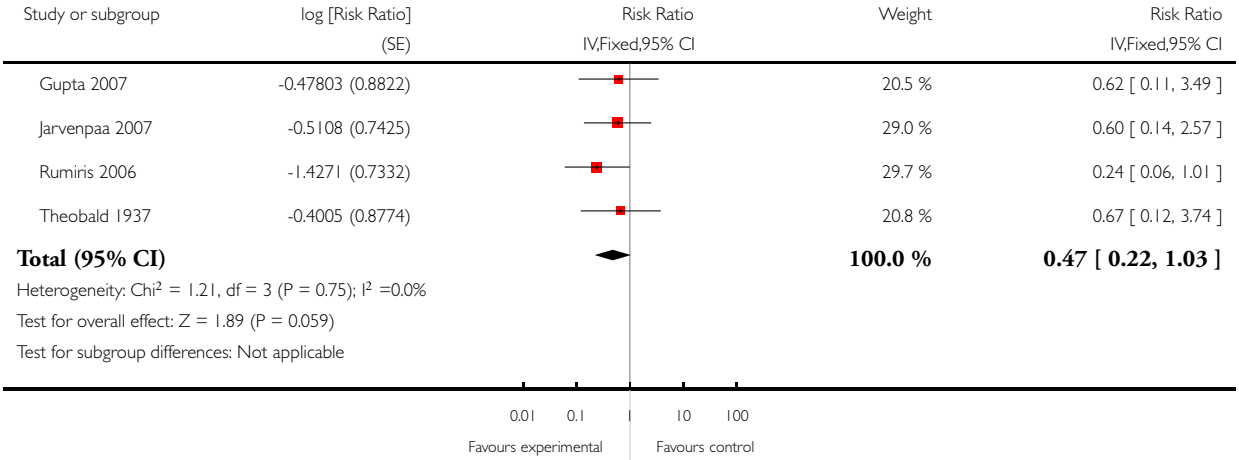


Analysis 1.10. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 10 Pre-eclampsia.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 10 Pre-eclampsia

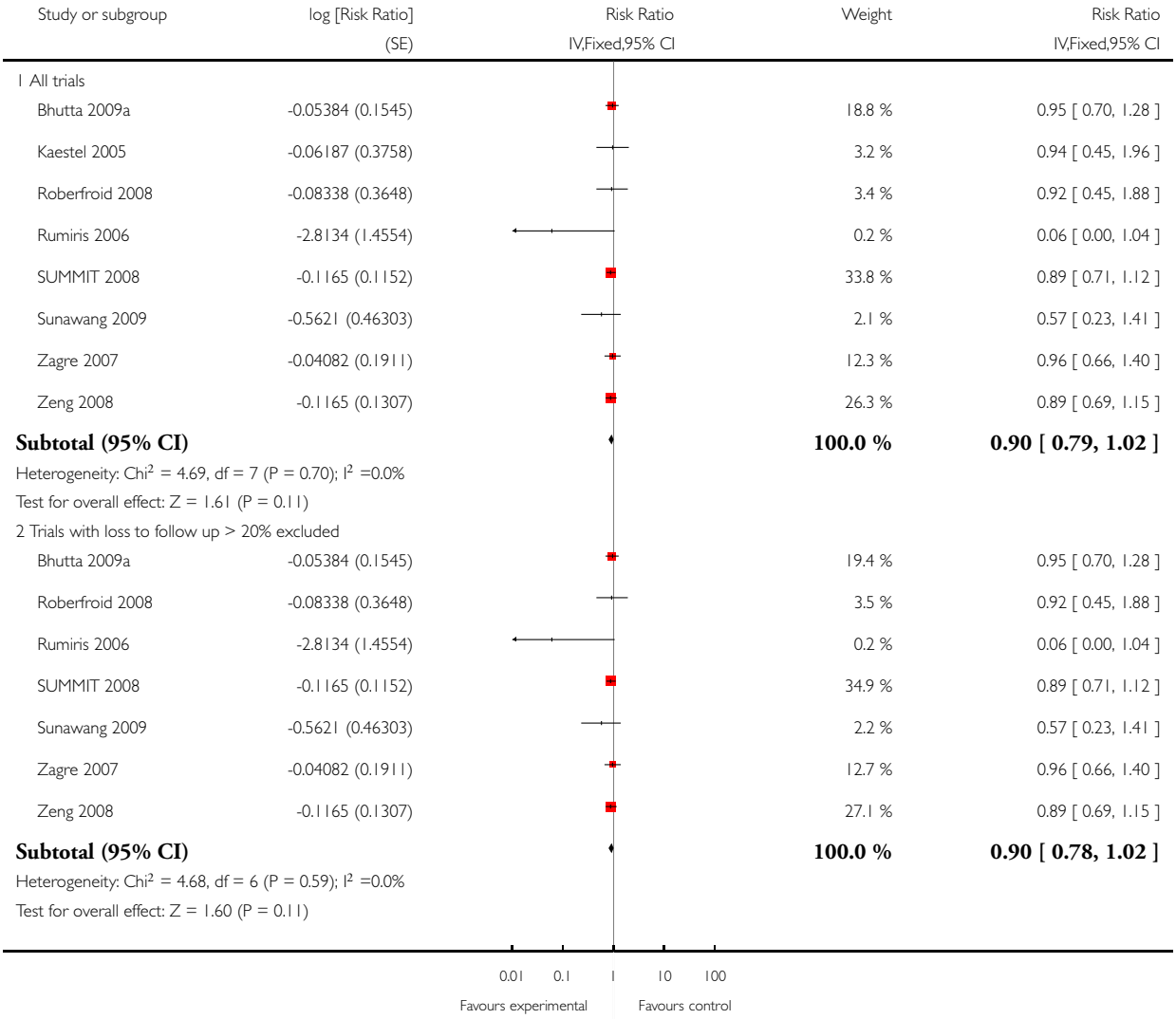


Analysis 1.11. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 11 Miscarriage (loss before 28 weeks).

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 11 Miscarriage (loss before 28 weeks)

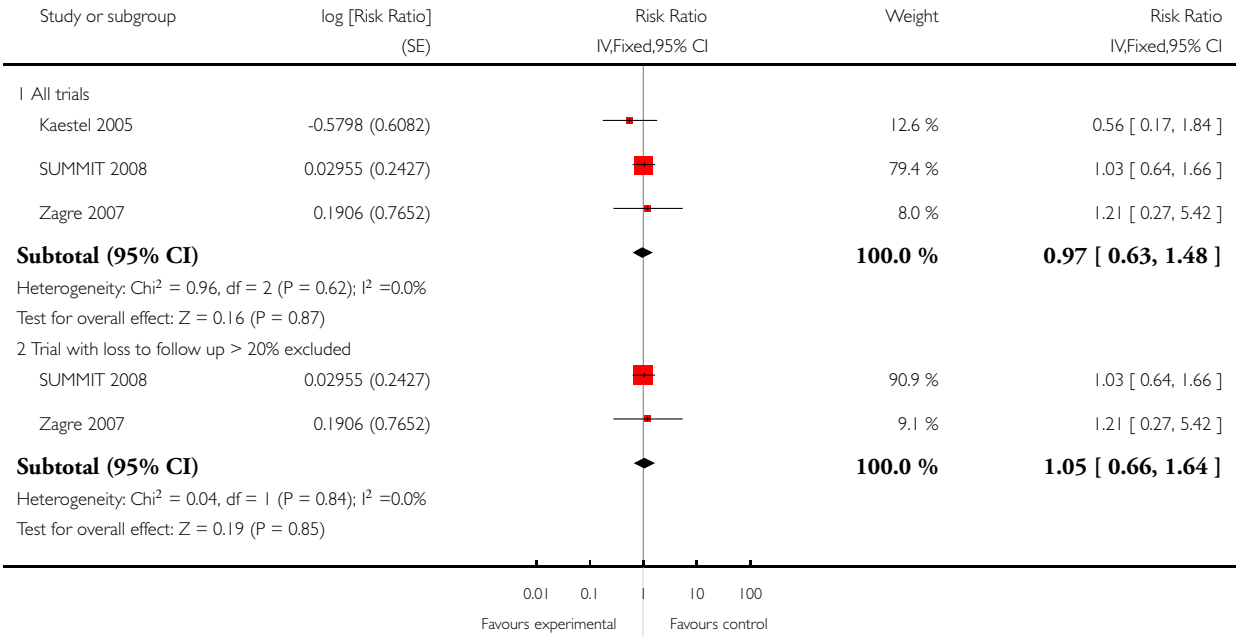


Analysis 1.12. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 12 Maternal mortality.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 12 Maternal mortality

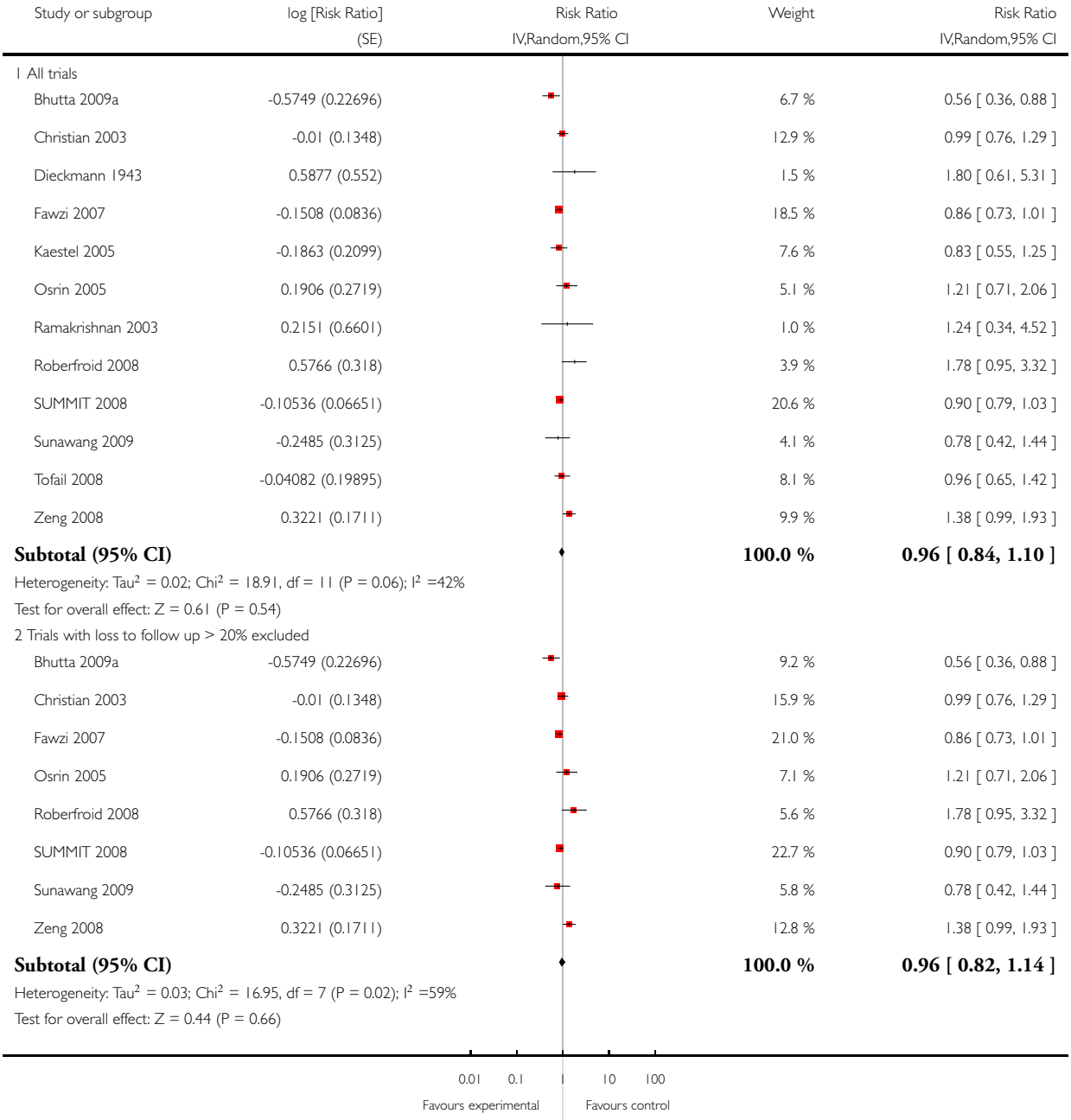


Analysis 1.13. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 13 Perinatal mortality.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 13 Perinatal mortality

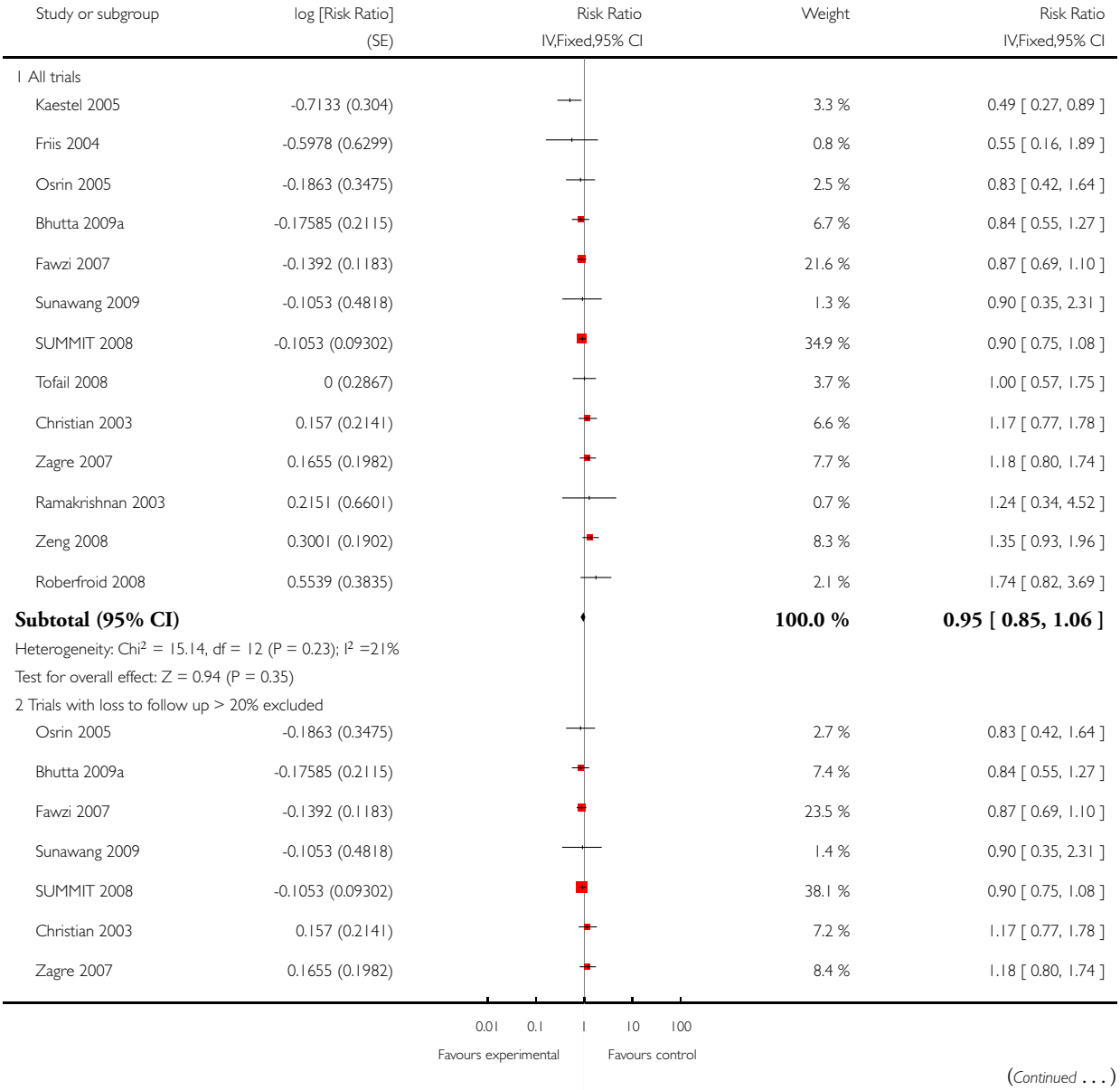


Analysis 1.14. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 14 Stillbirths.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 14 Stillbirths



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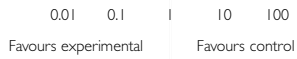
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Zeng 2008	0.3001 (0.1902)		9.1 %	1.35 [0.93, 1.96]
Roberfroid 2008	0.5539 (0.3835)		2.2 %	1.74 [0.82, 3.69]
Subtotal (95% CI)			**100.0 %**	**0.97 [0.87, 1.09]**
Heterogeneity: Chi² = 9.27, df = 8 (P = 0.32); I² =14%				
Test for overall effect: Z = 0.48 (P = 0.63)				



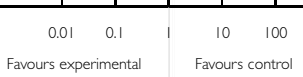
Analysis 1.15. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 15 Neonatal mortality.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 15 Neonatal mortality

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Bhutta 2009a	-0.0266 (0.2023)		11.1 %	0.97 [0.66, 1.45]
Christian 2003	0.4055 (0.2334)		8.3 %	1.50 [0.95, 2.37]
Kaestel 2005	0.2231 (0.3996)		2.8 %	1.25 [0.57, 2.74]
Osrin 2005	0.4253 (0.3829)		3.1 %	1.53 [0.72, 3.24]
Roberfroid 2008	0.7419 (0.5041)		1.8 %	2.10 [0.78, 5.64]
SUMMIT 2008	-0.1053 (0.08626)		60.9 %	0.90 [0.76, 1.07]
Sunawang 2009	-0.61618 (0.5067)		1.8 %	0.54 [0.20, 1.46]
Tofail 2008	0.2927 (0.2814)		5.7 %	1.34 [0.77, 2.33]
Vadillo-Ortega 2011	0.4055 (0.9079)		0.5 %	1.50 [0.25, 8.89]
Zeng 2008	0.1398 (0.3401)		3.9 %	1.15 [0.59, 2.24]
Total (95% CI)			**100.0 %**	**1.01 [0.89, 1.16]**
Heterogeneity: Chi² = 11.13, df = 9 (P = 0.27); I² =19%				
Test for overall effect: Z = 0.19 (P = 0.85)				
Test for subgroup differences: Not applicable				

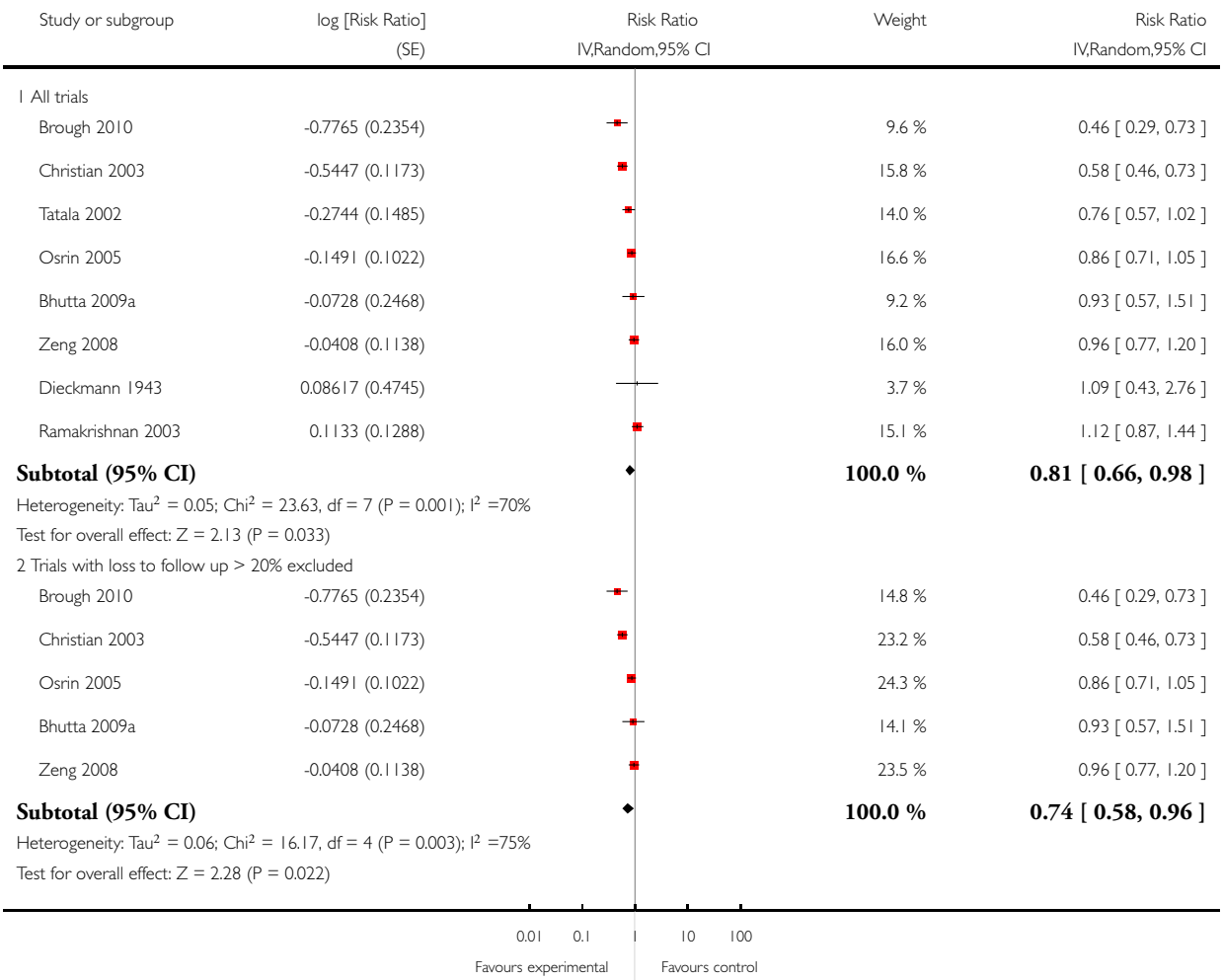


Analysis 1.16. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 16 Maternal anaemia (third trimester Hb < 110 g/L).

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 16 Maternal anaemia (third trimester Hb < 110 g/L)

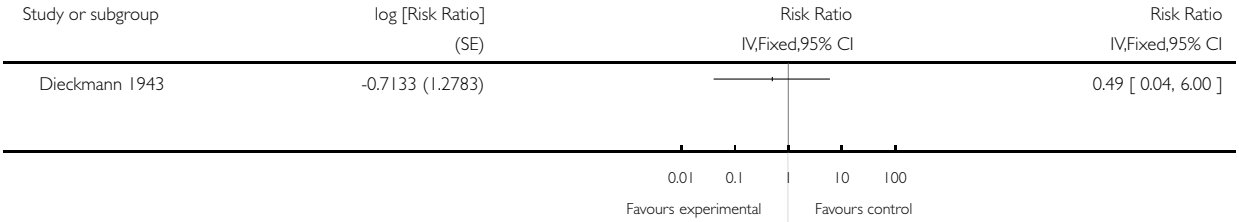


Analysis 1.17. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 17 Placental abruption.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 17 Placental abruption

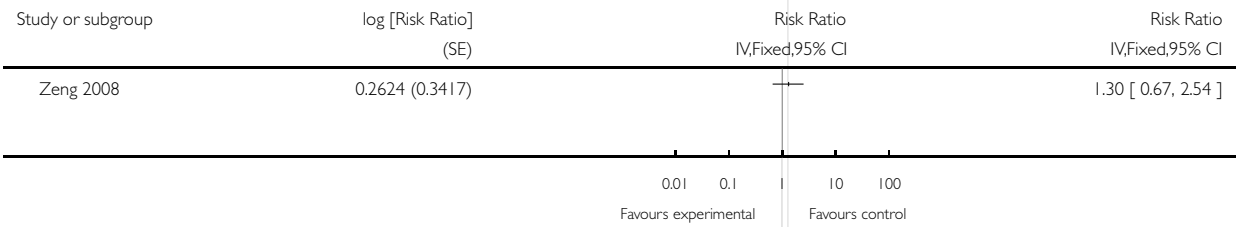


Analysis 1.18. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 18 Very preterm birth (before 34 weeks of gestation).

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 18 Very preterm birth (before 34 weeks of gestation)

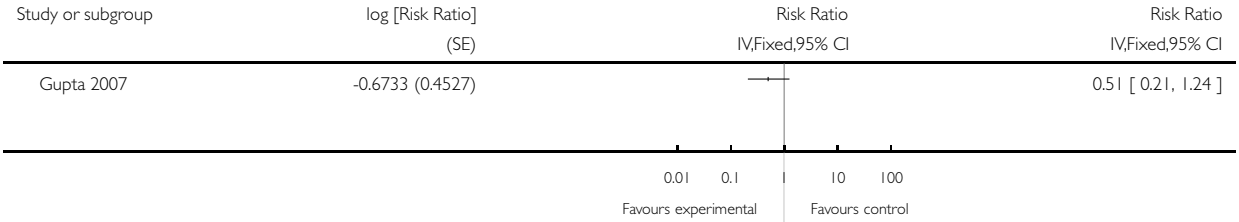


Analysis 1.19. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 19 Side effects of supplements.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 19 Side effects of supplements

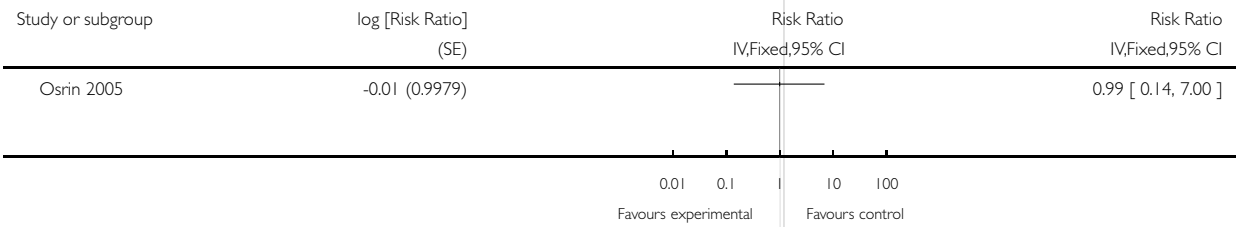


Analysis 1.20. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 20 Congenital anomalies (including neural tube defects).

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 20 Congenital anomalies (including neural tube defects)



Analysis 1.21. Comparison 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients), Outcome 21 Neurodevelopmental outcome: BSID scores.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 1 Multiple micronutrients versus controls (no supplements, placebo or two or less than two micronutrients)

Outcome: 21 Neurodevelopmental outcome: BSID scores

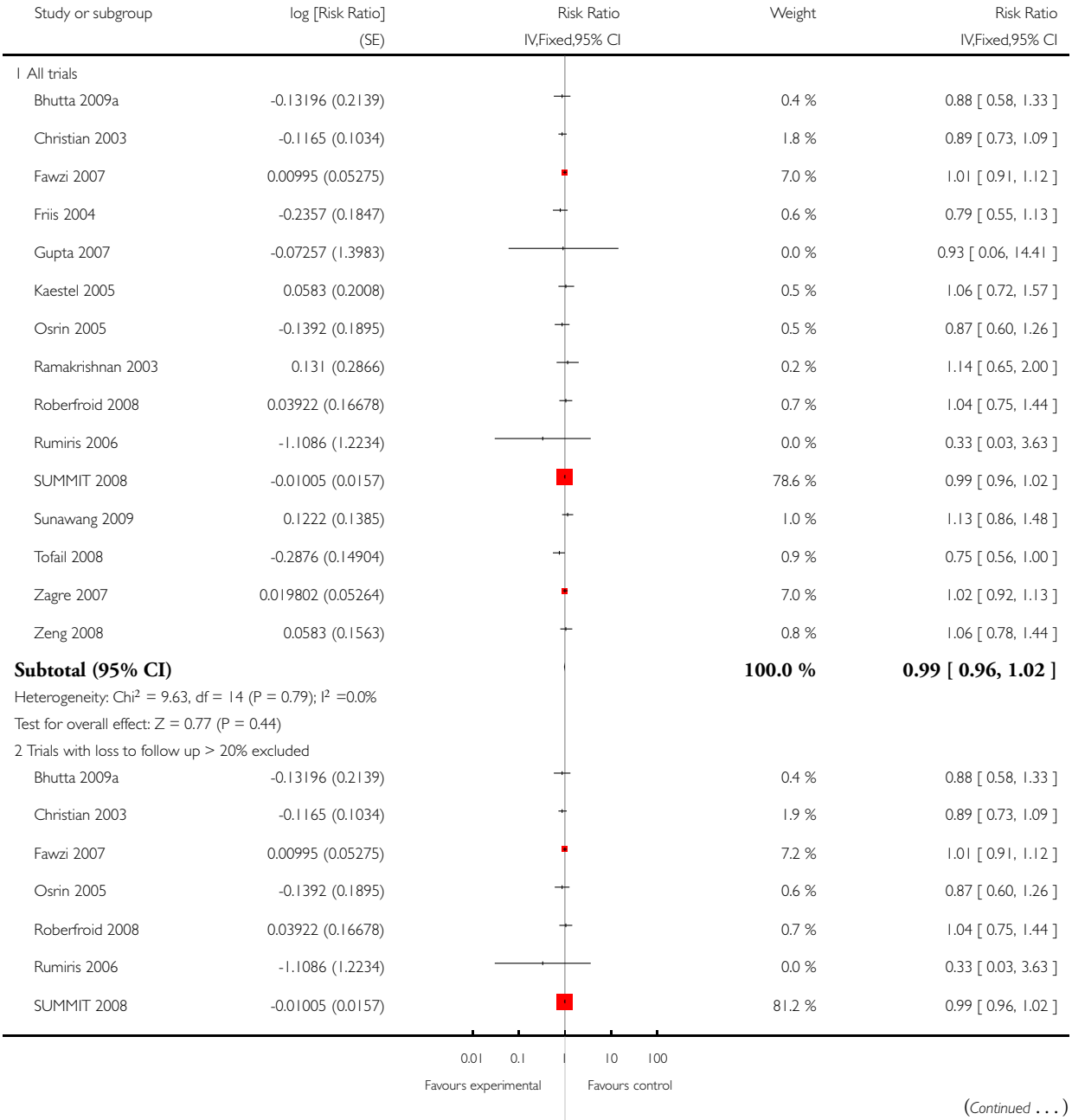
Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Mental development scores at 6 months of age						
Zeng 2008	364	67.6 (46.14)	406	67.62 (49.5)		-0.02 [-6.78, 6.74]
2 Mental development scores at 12 months of age						
Zeng 2008	351	103.65 (42.06)	393	102.44 (45.21)		1.21 [-5.06, 7.48]
3 Psychomotor development scores ar 6 months of age						
Zeng 2008	364	28.16 (25.6)	406	28.32 (27.45)		-0.16 [-3.91, 3.59]
4 Psychomotor development scores at 12 months of age						
Zeng 2008	351	45.64 (20.55)	393	45.3 (22.15)		0.34 [-2.73, 3.41]

Analysis 2.1. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 1 Preterm births.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 1 Preterm births



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Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Zagre 2007	0.019802 (0.05264)		7.2 %	1.02 [0.92, 1.13]
Zeng 2008	0.0583 (0.1563)		0.8 %	1.06 [0.78, 1.44]
Subtotal (95% CI)			**100.0 %**	**0.99 [0.96, 1.02]**
Heterogeneity: Chi^2 = 3.39, df = 8 (P = 0.91); I^2 =0.0%				
Test for overall effect: Z = 0.63 (P = 0.53)				

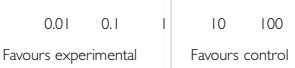
Analysis 2.2. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 2 Small-for-gestational age.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 2 Small-for-gestational age

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 All trials				
Bhutta 2009a	-0.3147 (0.3223)		1.5 %	0.73 [0.39, 1.37]
Christian 2003	0.0392 (0.0513)		18.0 %	1.04 [0.94, 1.15]
Fawzi 2007	-0.2357 (0.06171)		15.9 %	0.79 [0.70, 0.89]
Friis 2004	-0.2107 (0.2347)		2.6 %	0.81 [0.51, 1.28]
Gupta 2007	-0.5108 (0.2068)		3.3 %	0.60 [0.40, 0.90]
Kaestel 2005	-0.2744 (0.255)		2.3 %	0.76 [0.46, 1.25]
Osrin 2005	-0.2357 (0.1928)		3.7 %	0.79 [0.54, 1.15]
Ramakrishnan 2003	-0.1508 (0.22806)		2.8 %	0.86 [0.55, 1.34]
Roberfroid 2008	-0.1863 (0.1247)		7.4 %	0.83 [0.65, 1.06]
SUMMIT 2008	-0.0305 (0.0787)		12.8 %	0.97 [0.83, 1.13]



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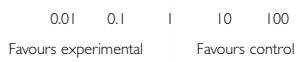
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Sunawang 2009	-0.1392 (0.16468)		4.8 %	0.87 [0.63, 1.20]
Tofail 2008	-0.1053 (0.1355)		6.5 %	0.90 [0.69, 1.17]
Zagre 2007	-0.1984 (0.1344)		6.6 %	0.82 [0.63, 1.07]
Zeng 2008	-0.1165 (0.0843)		12.0 %	0.89 [0.75, 1.05]
Subtotal (95% CI)			**100.0 %**	**0.87 [0.81, 0.95]**
Heterogeneity: Tau² = 0.01; Chi² = 19.67, df = 13 (P = 0.10); I² =34%				
Test for overall effect: Z = 3.35 (P = 0.00080)				
2 Trials with loss to follow up > 20% excluded				
Christian 2003	0.0392 (0.0513)		23.9 %	1.04 [0.94, 1.15]
Fawzi 2007	-0.2357 (0.06171)		21.9 %	0.79 [0.70, 0.89]
Friis 2004	-0.2107 (0.2347)		4.8 %	0.81 [0.51, 1.28]
Roberfroid 2008	-0.1863 (0.1247)		12.1 %	0.83 [0.65, 1.06]
Sunawang 2009	-0.1392 (0.16468)		8.4 %	0.87 [0.63, 1.20]
Zagre 2007	-0.1984 (0.1344)		11.0 %	0.82 [0.63, 1.07]
Zeng 2008	-0.1165 (0.0843)		17.9 %	0.89 [0.75, 1.05]
Subtotal (95% CI)			**100.0 %**	**0.88 [0.79, 0.98]**
Heterogeneity: Tau² = 0.01; Chi² = 13.53, df = 6 (P = 0.04); I² =56%				
Test for overall effect: Z = 2.30 (P = 0.022)				

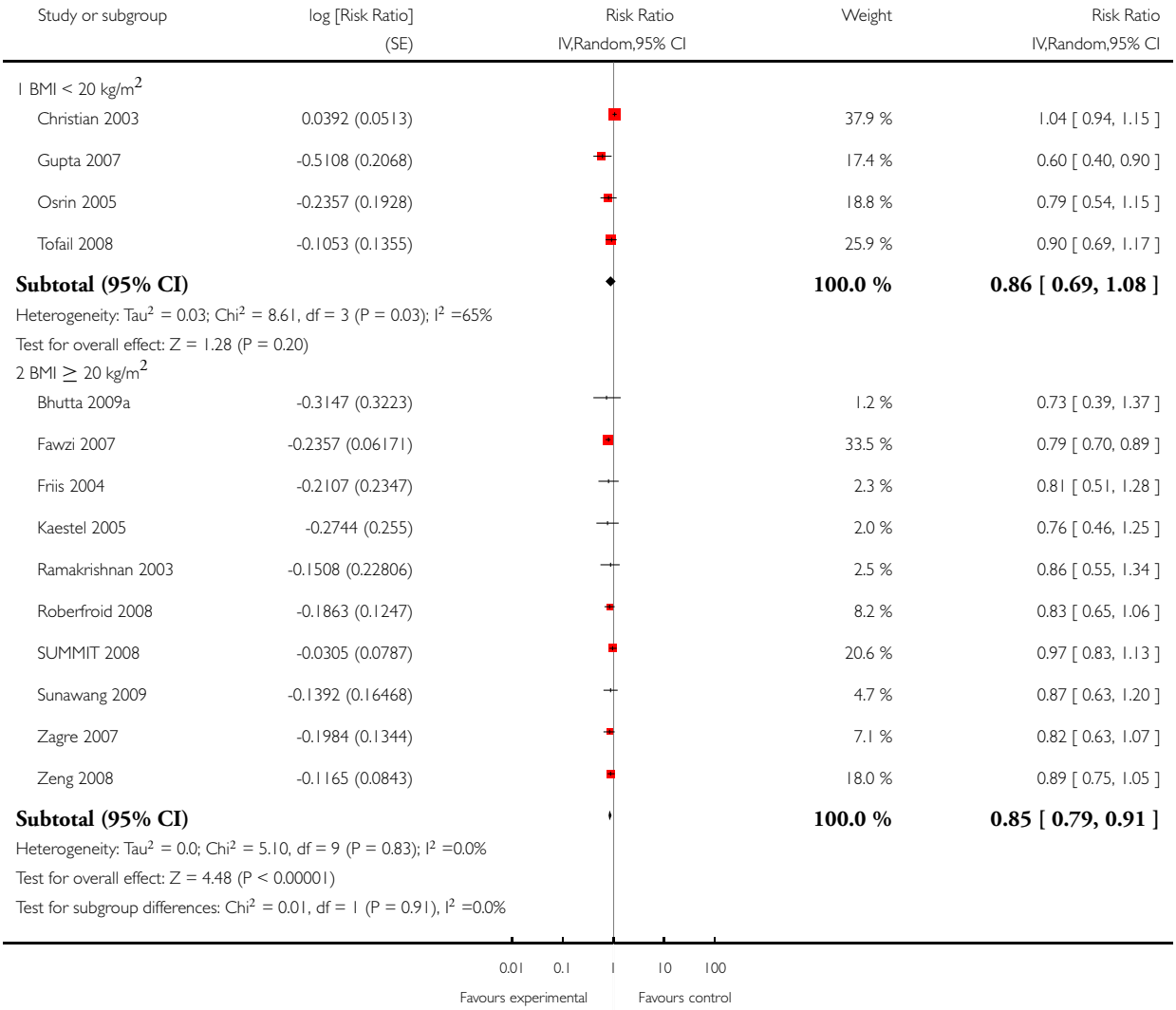


Analysis 2.3. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 3 Small-for-gestational age: maternal BMI.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 3 Small-for-gestational age: maternal BMI



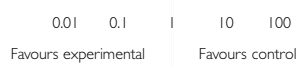
Analysis 2.4. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 4 Small-for-gestational age: maternal height.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 4 Small-for-gestational age: maternal height

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Maternal height < 154.9 cm				
Bhutta 2009a	-0.3147 (0.3223)		1.4 %	0.73 [0.39, 1.37]
Christian 2003	0.0392 (0.0513)		53.4 %	1.04 [0.94, 1.15]
Gupta 2007	-0.5108 (0.2068)		3.3 %	0.60 [0.40, 0.90]
Osrin 2005	-0.2357 (0.1928)		3.8 %	0.79 [0.54, 1.15]
Ramakrishnan 2003	-0.1508 (0.22806)		2.7 %	0.86 [0.55, 1.34]
SUMMIT 2008	-0.0305 (0.0787)		22.7 %	0.97 [0.83, 1.13]
Sunawang 2009	-0.1392 (0.16468)		5.2 %	0.87 [0.63, 1.20]
Tofail 2008	-0.1053 (0.1355)		7.7 %	0.90 [0.69, 1.17]
Subtotal (95% CI)			**100.0 %**	**0.97 [0.90, 1.04]**
Heterogeneity: Chi^2 = 10.15, df = 7 (P = 0.18); I^2 =31%				
Test for overall effect: Z = 0.94 (P = 0.35)				
2 Maternal height ≥ 154.9 cm				
Fawzi 2007	-0.2357 (0.06171)		47.2 %	0.79 [0.70, 0.89]
Friis 2004	-0.2107 (0.2347)		3.3 %	0.81 [0.51, 1.28]
Kaestel 2005	-0.2744 (0.255)		2.8 %	0.76 [0.46, 1.25]
Roberfroid 2008	-0.1863 (0.1247)		11.6 %	0.83 [0.65, 1.06]
Zagre 2007	-0.1984 (0.1344)		9.9 %	0.82 [0.63, 1.07]
Zeng 2008	-0.1165 (0.0843)		25.3 %	0.89 [0.75, 1.05]
Subtotal (95% CI)			**100.0 %**	**0.82 [0.76, 0.89]**
Heterogeneity: Chi^2 = 1.41, df = 5 (P = 0.92); I^2 =0.0%				
Test for overall effect: Z = 4.63 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 8.11, df = 1 (P = 0.00), I^2 =88%				

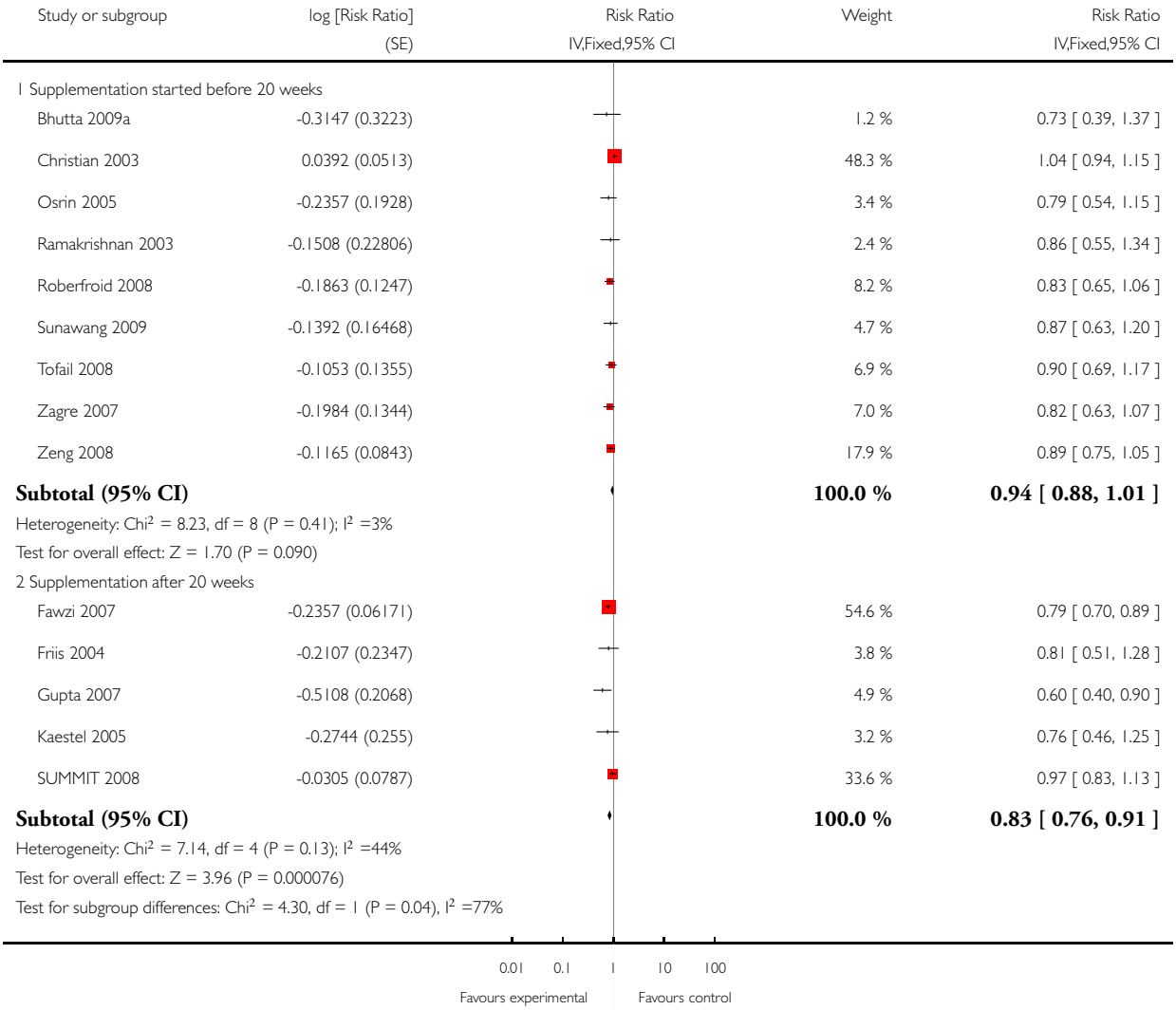


Analysis 2.5. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 5 Small-for-gestational age: supplementation.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 5 Small-for-gestational age: supplementation



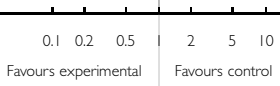
Analysis 2.6. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 6 Low birthweight.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 6 Low birthweight

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 All trials				
Bhutta 2009a	0.1838 (0.19606)		2.8 %	1.20 [0.82, 1.76]
Christian 2003	0.029 (0.0739)		19.6 %	1.03 [0.89, 1.19]
Fawzi 2007	-0.1863 (0.07253)		20.4 %	0.83 [0.72, 0.96]
Friis 2004	-0.3011 (0.2537)		1.7 %	0.74 [0.45, 1.22]
Gupta 2007	-0.9675 (0.3025)		1.2 %	0.38 [0.21, 0.69]
Kaestel 2005	-0.1278 (0.1954)		2.8 %	0.88 [0.60, 1.29]
Osrin 2005	-0.2876 (0.1138)		8.3 %	0.75 [0.60, 0.94]
Ramakrishnan 2003	-0.0408 (0.2571)		1.6 %	0.96 [0.58, 1.59]
Roberfroid 2008	-0.09431 (0.17166)		3.6 %	0.91 [0.65, 1.27]
SUMMIT 2008	-0.1508 (0.0819)		16.0 %	0.86 [0.73, 1.01]
Sunawang 2009	0.1988 (0.2027)		2.6 %	1.22 [0.82, 1.81]
Tofail 2008	-0.1508 (0.09778)		11.2 %	0.86 [0.71, 1.04]
Zagre 2007	-0.1392 (0.1487)		4.9 %	0.87 [0.65, 1.16]
Zeng 2008	-0.1054 (0.1797)		3.3 %	0.90 [0.63, 1.28]
Subtotal (95% CI)			**100.0 %**	**0.89 [0.83, 0.94]**
Heterogeneity: Chi^2 = 20.68, df = 13 (P = 0.08); I^2 =37%				
Test for overall effect: Z = 3.70 (P = 0.00022)				
2 Trials with loss to follow up > 20% excluded				
Bhutta 2009a	0.1838 (0.19606)		3.4 %	1.20 [0.82, 1.76]
Christian 2003	0.029 (0.0739)		24.1 %	1.03 [0.89, 1.19]
Fawzi 2007	-0.1863 (0.07253)		25.0 %	0.83 [0.72, 0.96]
Osrin 2005	-0.2876 (0.1138)		10.2 %	0.75 [0.60, 0.94]
Roberfroid 2008	-0.09431 (0.17166)		4.5 %	0.91 [0.65, 1.27]
SUMMIT 2008	-0.1508 (0.0819)		19.6 %	0.86 [0.73, 1.01]
Sunawang 2009	0.1988 (0.2027)		3.2 %	1.22 [0.82, 1.81]
Zagre 2007	-0.1392 (0.1487)		6.0 %	0.87 [0.65, 1.16]



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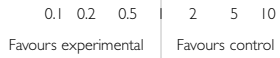
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Zeng 2008	-0.1054 (0.1797)		4.1 %	0.90 [0.63, 1.28]
Subtotal (95% CI)			**100.0 %**	**0.90 [0.84, 0.97]**
Heterogeneity: Chi^2 = 11.90, df = 8 (P = 0.16); I^2 =33%				
Test for overall effect: Z = 2.83 (P = 0.0047)				



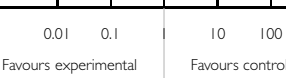
Analysis 2.7. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 7 Low birthweight: maternal BMI.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 7 Low birthweight: maternal BMI

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 BMI < 20 kg/m^2				
Christian 2003	0.029 (0.0739)		31.5 %	1.03 [0.89, 1.19]
Gupta 2007	-0.9675 (0.3025)		11.8 %	0.38 [0.21, 0.69]
Osrin 2005	-0.2876 (0.1138)		27.5 %	0.75 [0.60, 0.94]
Tofail 2008	-0.1508 (0.09778)		29.2 %	0.86 [0.71, 1.04]
Subtotal (95% CI)			**100.0 %**	**0.80 [0.62, 1.02]**
Heterogeneity: Tau^2 = 0.05; Chi^2 = 14.17, df = 3 (P = 0.003); I^2 =79%				
Test for overall effect: Z = 1.79 (P = 0.074)				
2 BMI $\geq$ 20 kg/m^2				
Bhutta 2009a	0.1838 (0.19606)		4.7 %	1.20 [0.82, 1.76]
Fawzi 2007	-0.1863 (0.07253)		34.2 %	0.83 [0.72, 0.96]
Friis 2004	-0.3011 (0.2537)		2.8 %	0.74 [0.45, 1.22]
Kaestel 2005	-0.1278 (0.1954)		4.7 %	0.88 [0.60, 1.29]
Ramakrishnan 2003	-0.0408 (0.2571)		2.7 %	0.96 [0.58, 1.59]



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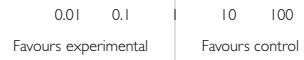
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Roberfroid 2008	-0.09431 (0.17166)		6.1 %	0.91 [0.65, 1.27]
SUMMIT 2008	-0.1508 (0.0819)		26.8 %	0.86 [0.73, 1.01]
Sunawang 2009	0.1988 (0.2027)		4.4 %	1.22 [0.82, 1.81]
Zagre 2007	-0.1392 (0.1487)		8.1 %	0.87 [0.65, 1.16]
Zeng 2008	-0.1054 (0.1797)		5.6 %	0.90 [0.63, 1.28]
Subtotal (95% CI)			**100.0 %**	**0.88 [0.81, 0.96]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.49$, df = 9 (P = 0.69); $I^2 = 0.0\%$

Test for overall effect: Z = 2.95 (P = 0.0031)

Test for subgroup differences: $Chi^2 = 0.59$, df = 1 (P = 0.44), $I^2 = 0.0\%$



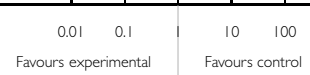
Analysis 2.8. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 8 Low birthweight: maternal height.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 8 Low birthweight: maternal height

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Maternal height < 154.9 cm				
Bhutta 2009a	0.1838 (0.19606)		9.3 %	1.20 [0.82, 1.76]
Christian 2003	0.029 (0.0739)		19.2 %	1.03 [0.89, 1.19]
Gupta 2007	-0.9675 (0.3025)		5.1 %	0.38 [0.21, 0.69]
Osrin 2005	-0.2876 (0.1138)		15.5 %	0.75 [0.60, 0.94]
Ramakrishnan 2003	-0.0408 (0.2571)		6.5 %	0.96 [0.58, 1.59]
SUMMIT 2008	-0.1508 (0.0819)		18.5 %	0.86 [0.73, 1.01]
Sunawang 2009	0.1988 (0.2027)		9.0 %	1.22 [0.82, 1.81]



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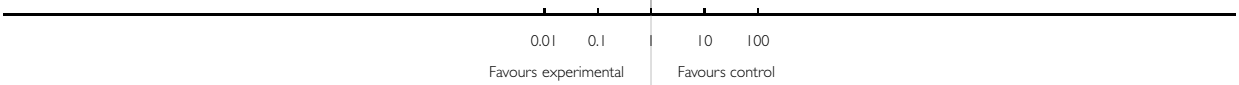
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Tofail 2008	-0.1508 (0.09778)		17.0 %	0.86 [0.71, 1.04]
Subtotal (95% CI)			**100.0 %**	**0.90 [0.77, 1.04]**
Heterogeneity: Tau^2 = 0.03; Chi^2 = 18.96, df = 7 (P = 0.01); I^2 =63%				
Test for overall effect: Z = 1.41 (P = 0.16)				
2 Maternal height ≥ 154.9 cm				
Fawzi 2007	-0.1863 (0.07253)		55.6 %	0.83 [0.72, 0.96]
Friis 2004	-0.3011 (0.2537)		4.5 %	0.74 [0.45, 1.22]
Kaestel 2005	-0.1278 (0.1954)		7.7 %	0.88 [0.60, 1.29]
Roberfroid 2008	-0.09431 (0.17166)		9.9 %	0.91 [0.65, 1.27]
Zagre 2007	-0.1392 (0.1487)		13.2 %	0.87 [0.65, 1.16]
Zeng 2008	-0.1054 (0.1797)		9.1 %	0.90 [0.63, 1.28]
Subtotal (95% CI)			**100.0 %**	**0.85 [0.76, 0.94]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.72, df = 5 (P = 0.98); I^2 =0.0%				
Test for overall effect: Z = 3.04 (P = 0.0024)				
Test for subgroup differences: Chi^2 = 0.34, df = 1 (P = 0.56), I^2 =0.0%				

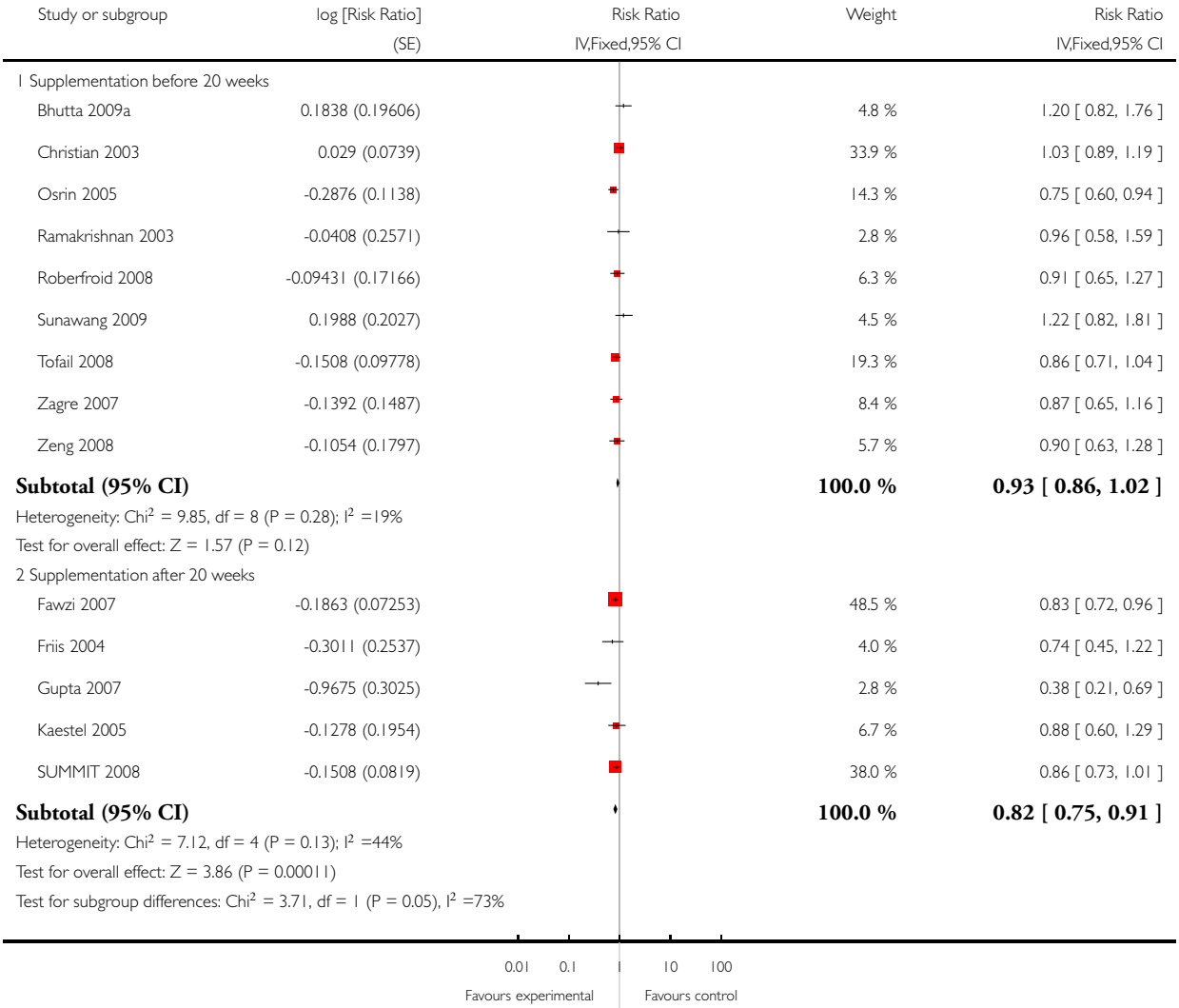


Analysis 2.9. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 9 Low birthweight: supplementation.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 9 Low birthweight: supplementation



Analysis 2.10. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 10 Pre-eclampsia.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 10 Pre-eclampsia

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Risk Ratio IV,Fixed,95% CI
Rumiris 2006	-1.4271 (0.7332)		0.24 [0.06, 1.01]

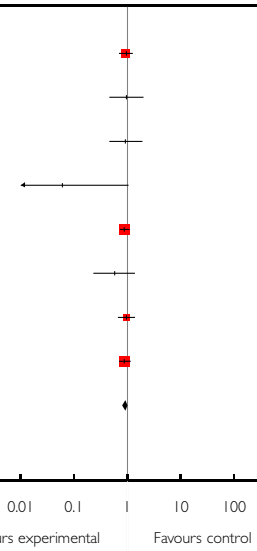
Analysis 2.11. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 11 Miscarriage (loss before 28 weeks).

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 11 Miscarriage (loss before 28 weeks)

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 All trials				
Bhutta 2009a	-0.05384 (0.1545)		18.8 %	0.95 [0.70, 1.28]
Kaestel 2005	-0.06187 (0.3758)		3.2 %	0.94 [0.45, 1.96]
Roberfroid 2008	-0.08338 (0.3648)		3.4 %	0.92 [0.45, 1.88]
Rumiris 2006	-2.8134 (1.4554)		0.2 %	0.06 [0.00, 1.04]
SUMMIT 2008	-0.1165 (0.1152)		33.8 %	0.89 [0.71, 1.12]
Sunawang 2009	-0.5621 (0.46303)		2.1 %	0.57 [0.23, 1.41]
Zagre 2007	-0.04082 (0.1911)		12.3 %	0.96 [0.66, 1.40]
Zeng 2008	-0.1165 (0.1307)		26.3 %	0.89 [0.69, 1.15]
Subtotal (95% CI)			**100.0 %**	**0.90 [0.79, 1.02]**
Heterogeneity: Chi^2 = 4.69, df = 7 (P = 0.70); I^2 =0.0%				



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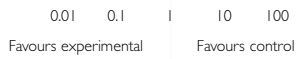
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Test for overall effect: Z = 1.61 (P = 0.11)				
2 Trial with loss to follow up > 20% excluded				
Bhutta 2009a	-0.05384 (0.1545)		19.4 %	0.95 [0.70, 1.28]
Roberfroid 2008	-0.08338 (0.3648)		3.5 %	0.92 [0.45, 1.88]
Rumiris 2006	-2.8134 (1.4554)		0.2 %	0.06 [0.00, 1.04]
SUMMIT 2008	-0.1165 (0.1152)		34.9 %	0.89 [0.71, 1.12]
Sunawang 2009	-0.5621 (0.46303)		2.2 %	0.57 [0.23, 1.41]
Zagre 2007	-0.04082 (0.1911)		12.7 %	0.96 [0.66, 1.40]
Zeng 2008	-0.1165 (0.1307)		27.1 %	0.89 [0.69, 1.15]
Subtotal (95% CI)			**100.0 %**	**0.90 [0.78, 1.02]**
Heterogeneity: Chi^2 = 4.68, df = 6 (P = 0.59); I^2 =0.0%				
Test for overall effect: Z = 1.60 (P = 0.11)				

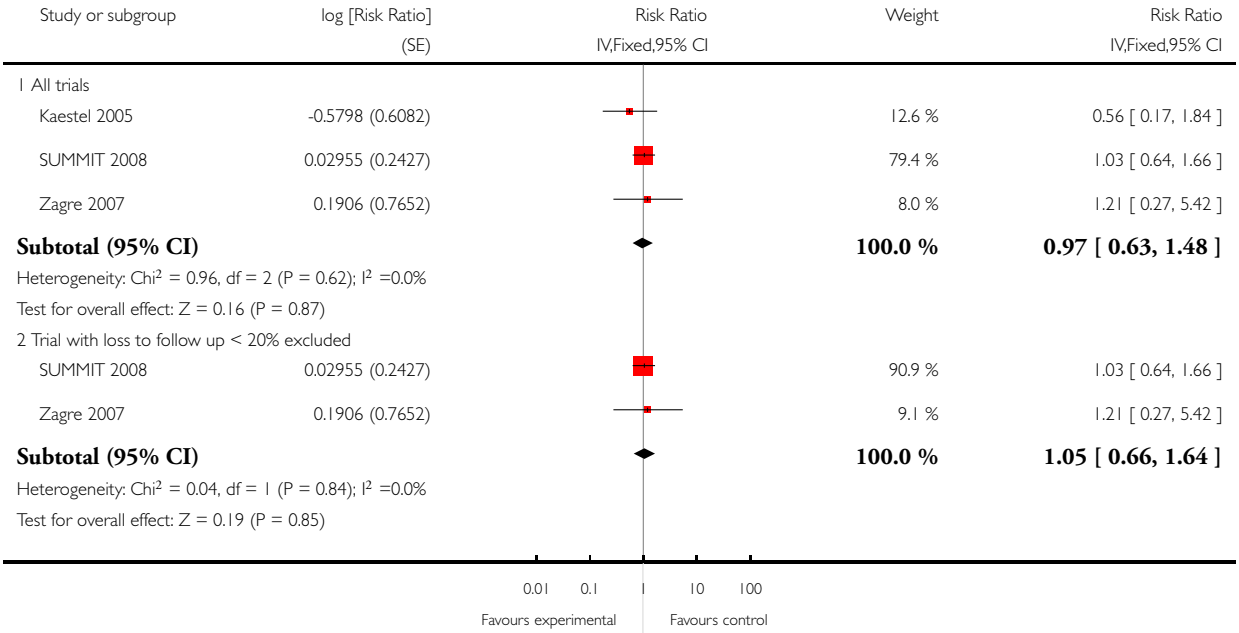


Analysis 2.12. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 12 Maternal mortality.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 12 Maternal mortality

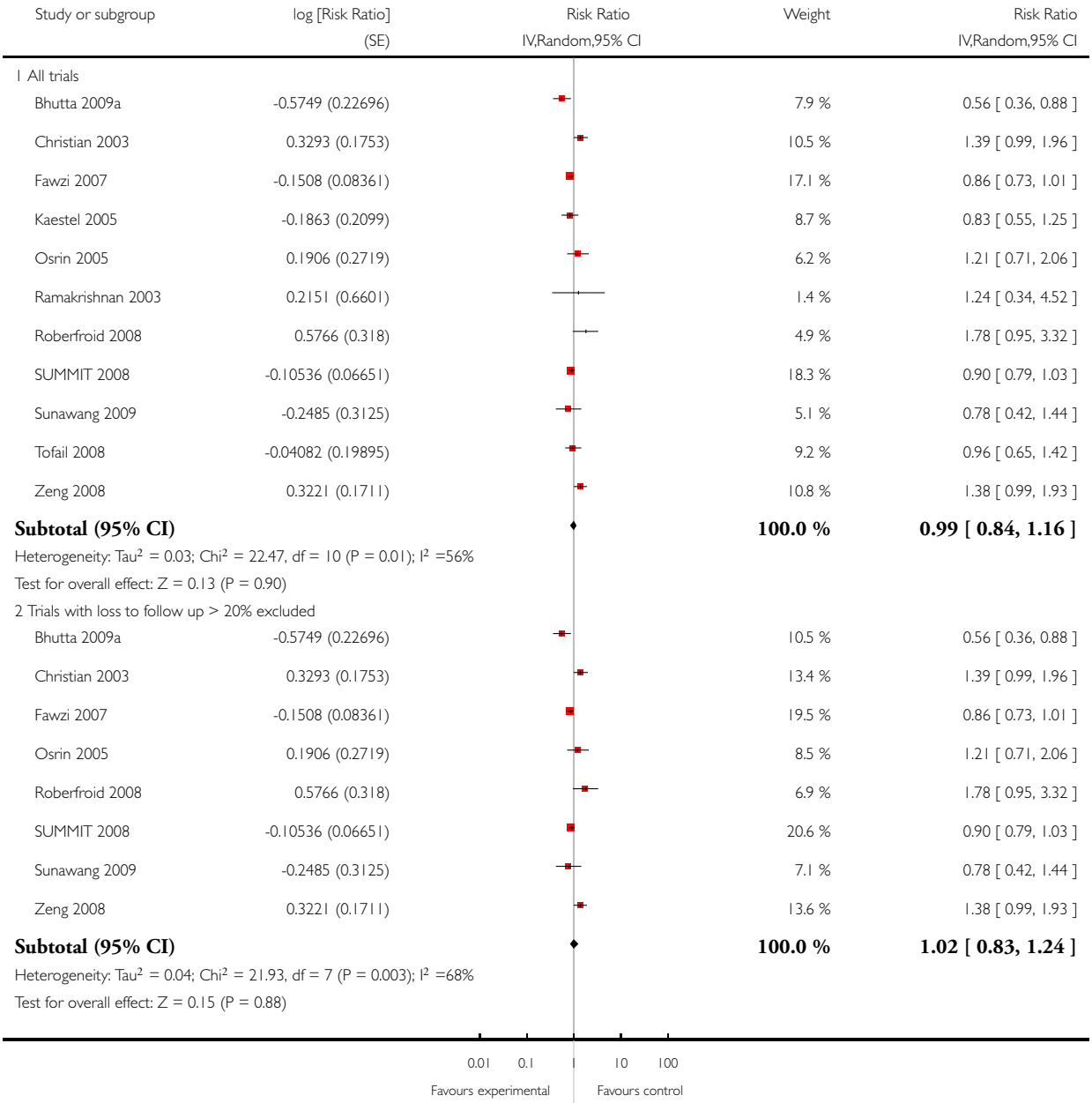


Analysis 2.13. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 13 Perinatal mortality.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 13 Perinatal mortality



Analysis 2.14. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 14 Perinatal mortality: maternal BMI.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 14 Perinatal mortality: maternal BMI

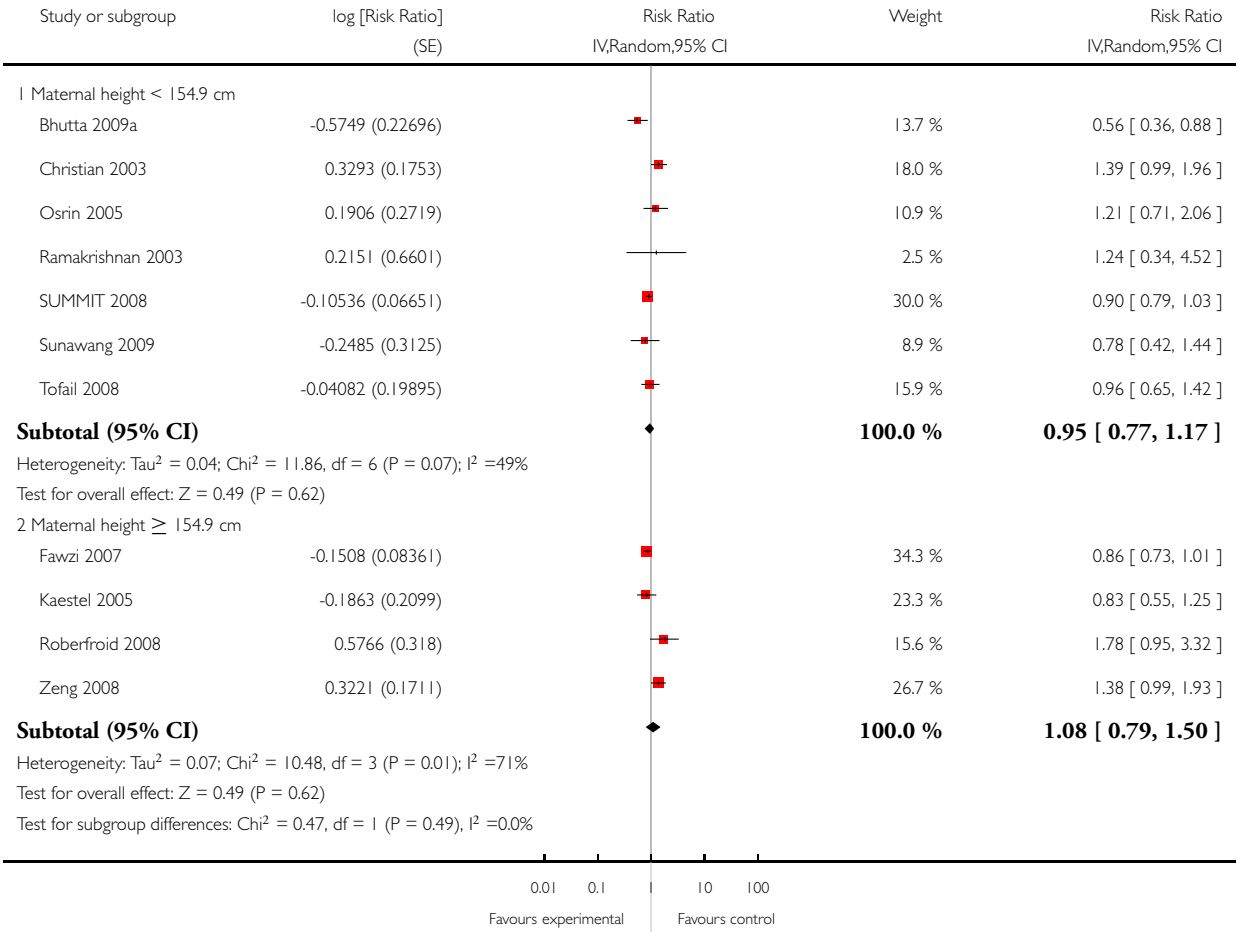
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 BMI < 20 kg/m^2				
Christian 2003	0.3293 (0.1753)		45.6 %	1.39 [0.99, 1.96]
Osrin 2005	0.1906 (0.2719)		19.0 %	1.21 [0.71, 2.06]
Tofail 2008	-0.04082 (0.19895)		35.4 %	0.96 [0.65, 1.42]
Subtotal (95% CI)			**100.0 %**	**1.19 [0.94, 1.50]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.95, df = 2 (P = 0.38); I^2 =0.0%				
Test for overall effect: Z = 1.45 (P = 0.15)				
2 BMI ≥ 20 kg/m^2				
Bhutta 2009a	-0.5749 (0.22696)		10.5 %	0.56 [0.36, 0.88]
Fawzi 2007	-0.1508 (0.08361)		23.4 %	0.86 [0.73, 1.01]
Kaestel 2005	-0.1863 (0.2099)		11.5 %	0.83 [0.55, 1.25]
Ramakrishnan 2003	0.2151 (0.6601)		1.8 %	1.24 [0.34, 4.52]
Roberfroid 2008	0.5766 (0.318)		6.5 %	1.78 [0.95, 3.32]
SUMMIT 2008	-0.10536 (0.06651)		25.2 %	0.90 [0.79, 1.03]
Sunawang 2009	-0.2485 (0.3125)		6.7 %	0.78 [0.42, 1.44]
Zeng 2008	0.3221 (0.1711)		14.5 %	1.38 [0.99, 1.93]
Subtotal (95% CI)			**100.0 %**	**0.93 [0.78, 1.11]**
Heterogeneity: Tau^2 = 0.03; Chi^2 = 15.99, df = 7 (P = 0.03); I^2 =56%				
Test for overall effect: Z = 0.79 (P = 0.43)				
Test for subgroup differences: Chi^2 = 2.66, df = 1 (P = 0.10), I^2 =62%				

Analysis 2.15. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 15 Perinatal mortality: maternal height.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 15 Perinatal mortality: maternal height

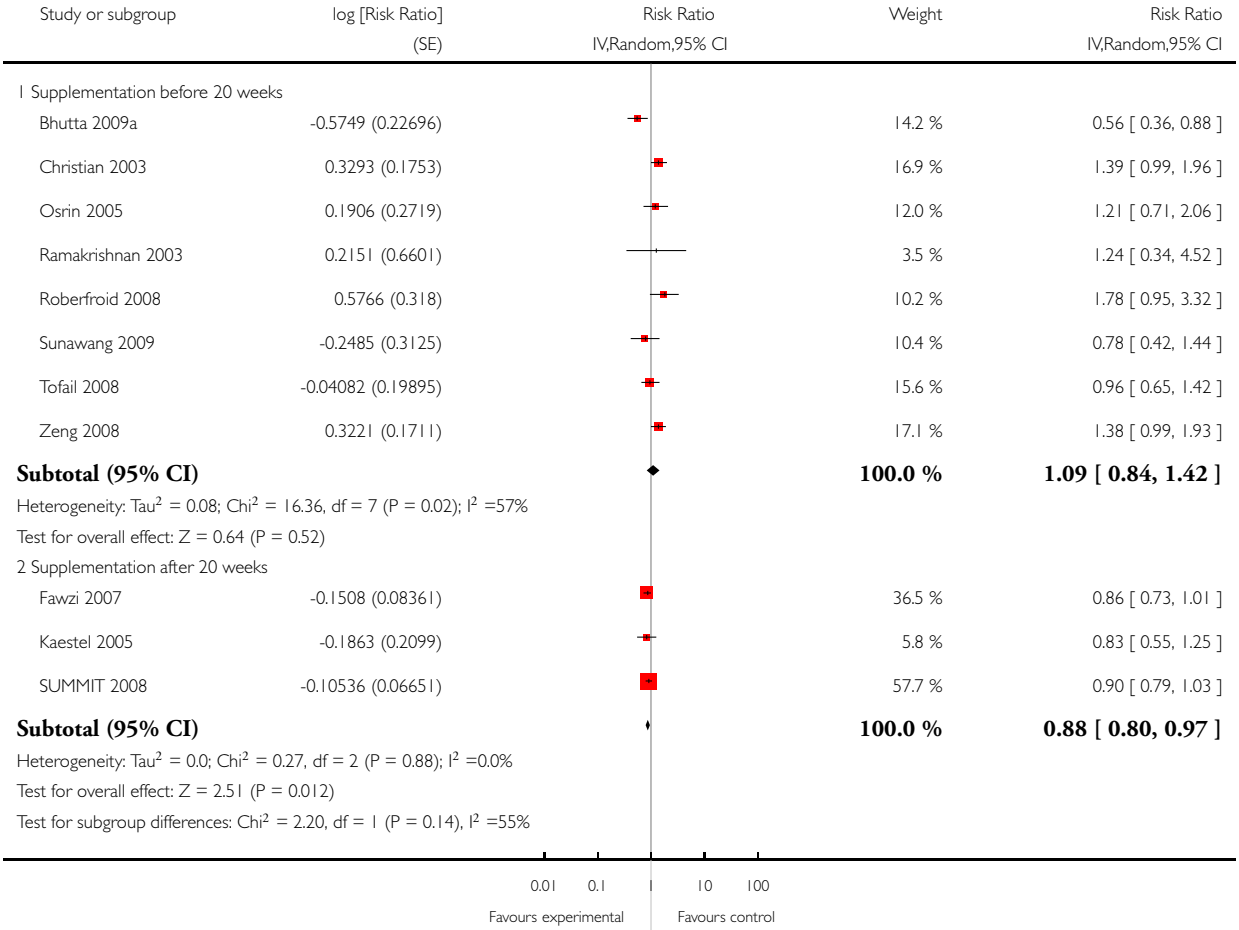


Analysis 2.16. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 16 Perinatal mortality: supplementation.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 16 Perinatal mortality: supplementation

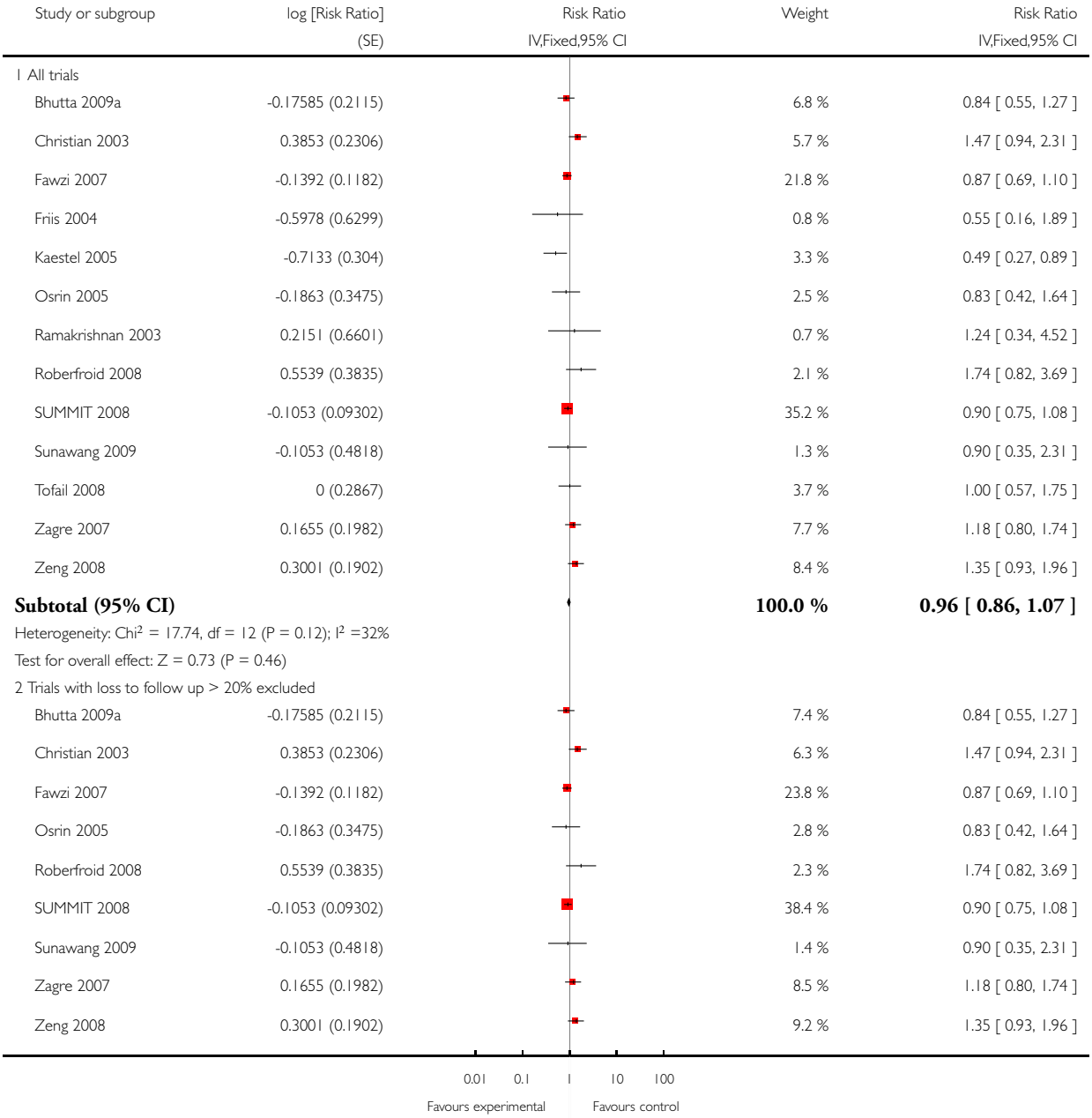


Analysis 2.17. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 17 Stillbirths.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 17 Stillbirths



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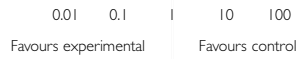
Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Subtotal (95% CI)			**100.0 %**	**0.99 [0.88, 1.10]**
Heterogeneity: Chi² = 11.69, df = 8 (P = 0.17); I² =32%				
Test for overall effect: Z = 0.26 (P = 0.79)				



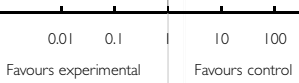
Analysis 2.18. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 18 Neonatal mortality.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 18 Neonatal mortality

Study or subgroup	log [Risk Ratio] (SE)	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Bhutta 2009a	-0.0266 (0.2023)		11.1 %	0.97 [0.66, 1.45]
Christian 2003	0.3988 (0.2324)		8.4 %	1.49 [0.94, 2.35]
Kaestel 2005	0.2231 (0.3996)		2.9 %	1.25 [0.57, 2.74]
Osrin 2005	0.4253 (0.3829)		3.1 %	1.53 [0.72, 3.24]
Roberfroid 2008	0.7419 (0.5041)		1.8 %	2.10 [0.78, 5.64]
SUMMIT 2008	-0.1053 (0.08626)		61.2 %	0.90 [0.76, 1.07]
Sunawang 2009	-0.61618 (0.5067)		1.8 %	0.54 [0.20, 1.46]
Tofail 2008	0.2927 (0.2814)		5.8 %	1.34 [0.77, 2.33]
Zeng 2008	0.1398 (0.3401)		3.9 %	1.15 [0.59, 2.24]
Total (95% CI)			**100.0 %**	**1.01 [0.89, 1.15]**
Heterogeneity: Chi² = 10.87, df = 8 (P = 0.21); I² =26%				
Test for overall effect: Z = 0.16 (P = 0.88)				
Test for subgroup differences: Not applicable				

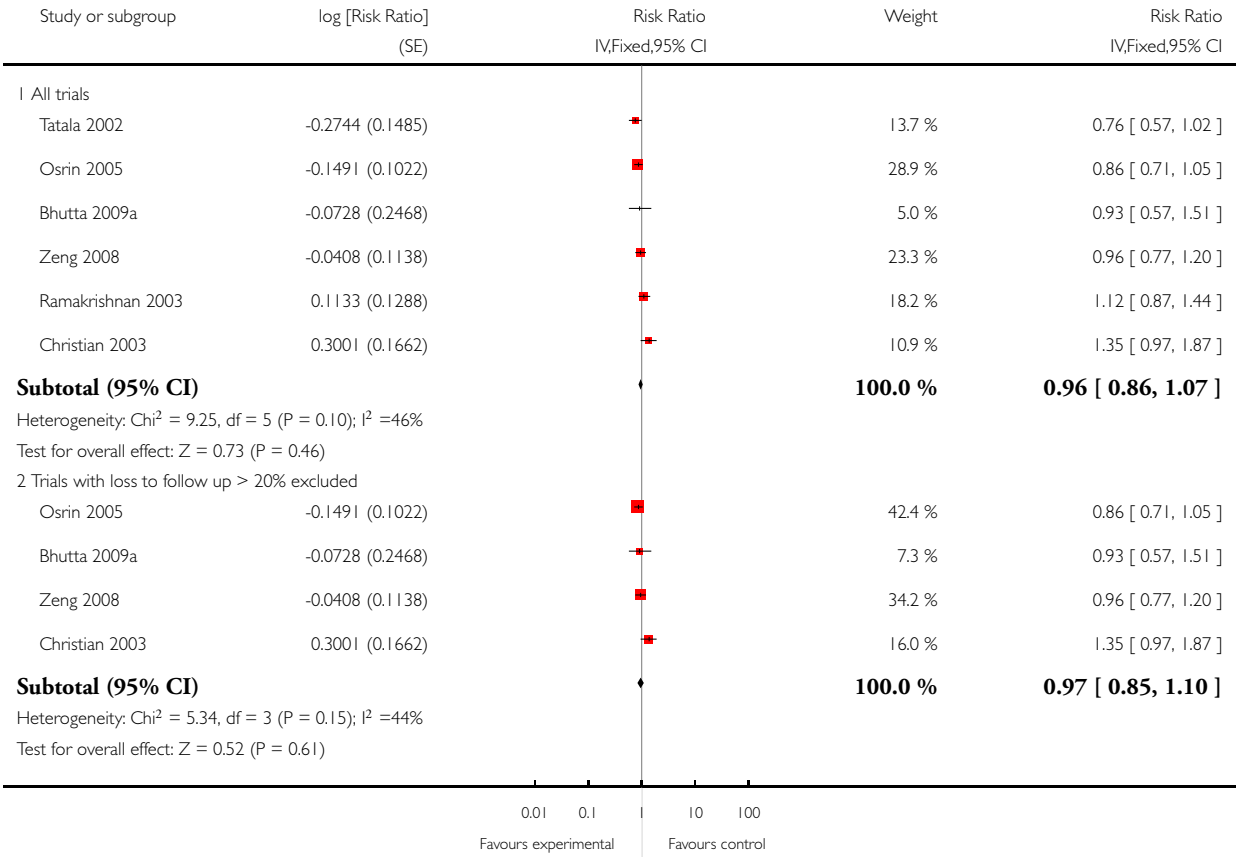


Analysis 2.19. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 19 Maternal anaemia (third trimester Hb <110 g/L).

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 19 Maternal anaemia (third trimester Hb <110 g/L)

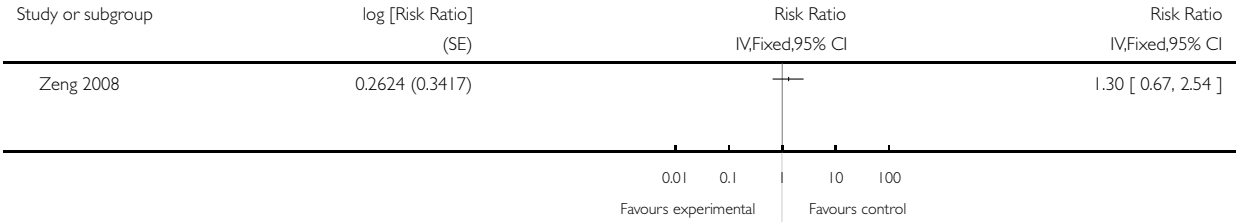


Analysis 2.20. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 20 Very preterm birth (before 34 weeks of gestation).

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 20 Very preterm birth (before 34 weeks of gestation)

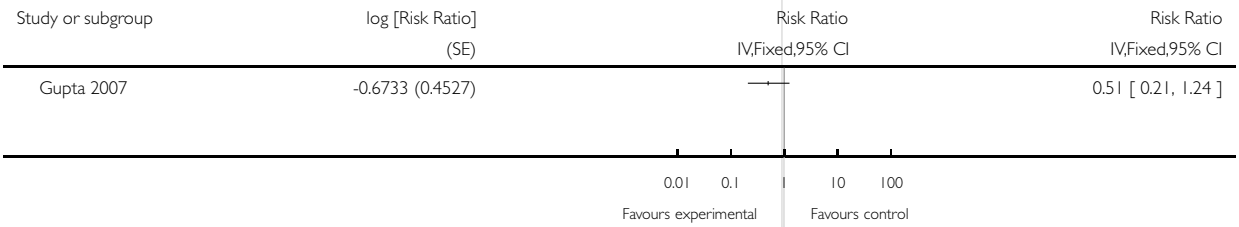


Analysis 2.21. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 21 Side effects.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 21 Side effects

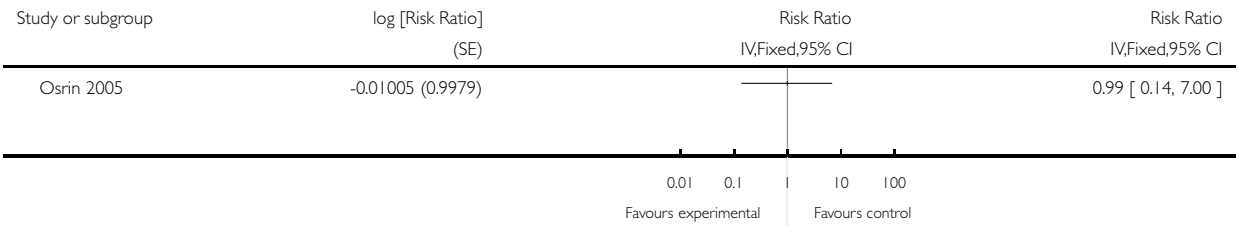


Analysis 2.22. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 22 Congenital anomalies.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 22 Congenital anomalies



Analysis 2.23. Comparison 2 Multiple micronutrients versus iron folate only, Outcome 23 Neurodevelopmental outcome: BSID scores.

Review: Multiple-micronutrient supplementation for women during pregnancy

Comparison: 2 Multiple micronutrients versus iron folate only

Outcome: 23 Neurodevelopmental outcome: BSID scores