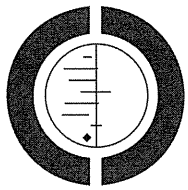
Zinc supplementation for improving pregnancy and infant outcome (Review)

Mori R, Ota E, Middleton P, Tobe-Gai R, Mahomed K, Bhutta ZA



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[Intervention Review]

Zinc supplementation for improving pregnancy and infant outcome

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ABSTRACT

Background

It has been suggested that low serum zinc levels may be associated with suboptimal outcomes of pregnancy such as prolonged labour, atonic postpartum haemorrhage, pregnancy-induced hypertension, preterm labour and post-term pregnancies, although many of these associations have not yet been established.

Objectives

To assess the effects of zinc supplementation in pregnancy on maternal, fetal, neonatal and infant outcomes.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 September 2011) and reference lists of retrieved studies.

Selection criteria

Randomized trials of zinc supplementation in pregnancy. We excluded quasi-randomised controlled trials.

Data collection and analysis

Three review authors applied the study selection criteria, assessed trial quality and extracted data. When necessary, we contacted study authors for additional information.

Main results

We included 20 randomised controlled trials (RCTs) reported in 51 papers involving over 15,000 women and their babies. Trials were generally at low risk of bias. Zinc supplementation resulted in a small but significant reduction in preterm birth (risk ratio (RR) 0.86, 95% confidence interval (CI) 0.76 to 0.97 in 16 RCTs; 16 trials of 7637 women). This was not accompanied by a similar reduction in numbers of babies with low birthweight (RR 0.93, 95% CI 0.78 to 1.12; 14 trials of 5643 women). No significant differences were seen between the zinc and no zinc groups for any of the other primary maternal or neonatal outcomes, except for induction of labour in a single trial. No differing patterns were evident in the subgroups of women with low versus normal zinc and nutrition levels or in women who complied with their treatment versus those who did not.

Authors' conclusions

The evidence for a 14% relative reduction in preterm birth for zinc compared with placebo was primarily represented by trials involving women of low income and this has some relevance in areas of high perinatal mortality. There was no convincing evidence that zinc supplementation during pregnancy results in other useful and important benefits. Since the preterm association could well reflect poor nutrition, studies to address ways of improving the overall nutritional status of populations in impoverished areas, rather than focusing on micronutrient and or zinc supplementation in isolation, should be an urgent priority.

PLAIN LANGUAGE SUMMARY

Zinc supplementation for improving pregnancy and infant outcome

Taking zinc during pregnancy helps to slightly reduce preterm births, but does not prevent other problems such as low birthweight babies.

Many women of childbearing age may have mild to moderate zinc deficiency. Low zinc concentrations may cause preterm birth or they may even prolong labour. It is also possible that zinc deficiency may affect infant growth as well. This review of 20 randomised controlled trials, involving over 15,000 women and their babies, found that although zinc supplementation has a small effect on reducing preterm births, it does not help to prevent low birthweight babies compared with not giving zinc supplements before 27 weeks' of pregnancy. No clear differences were seen for development of pregnancy hypertension or pre-eclampsia. The 14% relative reduction in preterm birth for zinc compared with placebo was primarily represented by trials of women with low incomes. In some trials all women were also given iron, folate or vitamins or combinations of these. UNICEF is already promoting antenatal use of multiple-micronutrient supplementation, including zinc, to all pregnant women in developing countries. Finding ways to improve women's overall nutritional status, particularly in low-income areas, will do more to improve the health of mothers and babies than supplementing pregnant women with zinc alone. In low-to-middle income countries, addressing anaemia and infections, such as malaria and hookworm, is also necessary.

BACKGROUND

The overall nutritional status of the mother during pregnancy is a significant contributor to both maternal and perinatal mortality and morbidity (Stoltzfus 1995). This is likely to be even more crucial in developing countries where anaemia and infections, such as malaria and hookworm, compound the issue even further.

Zinc is known to play an important role in many biological functions, including protein synthesis and nucleic acid metabolism (Vallee 1993). Although severe zinc deficiency is now considered rare, mild to moderate deficiency may be relatively common throughout the world (Sandstead 1991). In a review of literature published between 1970 and 1991, Parr 1996 noted that, on average, pregnant and lactating women worldwide consumed 9.6 mg zinc per day, well below the recommended 15 mg daily, during the last two trimesters of pregnancy (Sandstead 1996; WHO 1996). In animal studies, zinc deficiency during the early stages of pregnancy is associated with reduced fertility (Apgar 1970), fetal neurological malformations and growth retardation (McKenzie 1975), and deficiency in later stages of pregnancy negatively affects neuronal growth and may also be associated with impaired brain function and behavioural abnormalities (Golub 1995).

In humans, pregnant women with acrodermatitis enteropathica (an inherited defect in zinc absorption from the bowel) show association with increased risk of congenital malformations and pregnancy losses (Verburg 1974). Numerous reports have noted low serum zinc levels to be linked with abnormalities of labour such as prolonged labour and atonic postpartum haemorrhage (Prema 1980), pregnancy-induced hypertension (Jameson 1976; Jameson 1993), preterm labour (Jones 1981) and post-term pregnancies (Simmer 1985). Others (Cherry 1981; Chesters 1982) have failed to show any such association.

Some researchers have also reported an association between low zinc and small-for-gestational age babies, and poor perinatal outcome (Gillholma 1984a; Gillholma 1984b). Kirkley 1994 reported low maternal serum zinc levels during pregnancy to be associated with an increased risk of low birthweight and preterm birth. Low birthweight babies have higher rates of morbidity and mortality due to infectious disease and impaired immunity and, thus, it is possible that zinc deficiency may affect infant growth and wellbeing too.

Studies of the effects of zinc supplementation have differed in their findings. These inconsistencies in study findings could be due to lack of consensus on accurate assessment of zinc status (Aggett 1991) and to differences in the populations studied. Randomised controlled trials of zinc supplementation in pregnancy would help to address the association, if any, between zinc deficiency and pregnancy outcome and neonatal and infant health and wellbeing.

The fetal nervous system also develops progressively during pregnancy influencing motor and autonomic functions. Change in the pattern of fetal heart rate and movements monitored electronically have been related to fetal neurobehavioural development (DiPietro 1996) and atypical neurodevelopment has been shown in fetuses that exhibit other indicators of neurologic compromise (Hepper 1995). In a publication from Egypt, Kirkley 1991 also reported a positive association between maternal zinc status during the second trimester of pregnancy and newborn behaviour.

It is plausible that the effect of zinc supplementation would vary among different population groups depending on their nutritional status, with any effect likely to be more apparent in women from the developing world. Currently, UNICEF is already promoting antenatal use of multiple-micronutrient supplementation, including zinc, to all pregnant women in developing countries (Nepal 2003).

The aim of this review is to systematically review all randomised controlled trials of zinc supplementation in pregnancy and to evaluate the role of zinc as it relates to pregnancy, labour and birth as well as to maternal and infant health and wellbeing.

OBJECTIVES

1. To compare the effects on maternal, fetal, neonatal and infant outcomes in healthy pregnant women, supplemented with zinc, with those supplemented with either placebo or no zinc.

2. To assess the above outcomes in a subgroup analysis reviewing studies performed in women who are or are likely to be zinc deficient.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised trials of zinc supplementation versus no zinc supplementation or placebo administration during pregnancy, earlier than 27 weeks' gestation. Quasi-randomised controlled trials have been excluded. We intended to include studies presented only as abstracts, if they provided enough information or, if necessary, by contacting authors to analyse them against criteria; we did not find such studies.

Types of participants

Normal pregnant women with no systemic illness. Women may have had normal zinc levels or they may have been, or likely to have been, zinc deficient.

Types of interventions

Routine zinc supplementation versus no zinc supplementation, or placebo.

Types of outcome measures

We have included outcomes related to clinical complications of pregnancy on maternal, fetal, neonatal and infant outcomes. We have not included data related to biochemical outcomes or studies reporting only biochemical outcomes.

Primary outcomes

Maternal and pregnancy outcomes

Preterm labour or birth (less than 37 weeks), or both

Neonatal outcomes

Stillbirth or neonatal death
Birthweight
Small-for-gestational age (birthweight less than 10th centile for gestational age)
Low birthweight (less than 2.5 kg)

Secondary outcomes

Maternal and pregnancy outcomes

Antepartum haemorrhage
Pregnancy-induced hypertension
Prelabour rupture of membranes

Post-term pregnancy
Induction of labour
Any maternal infection
Meconium in liquor
Caesarean section
Instrumental vaginal birth
Retained placenta
Postpartum haemorrhage
Smell dysfunction
Taste dysfunction

Fetal neurodevelopmental assessment

Baseline fetal heart rate
Baseline variability
Number of accelerations
Number of fetal movements
Fetal activity level (minutes)
Movement amplitude

Neonatal outcomes

Gestational age at birth
High birthweight (more than 4.5 kg)
Apgar score of less than five at five minutes
Head circumference
Hypoxia
Neonatal sepsis
Neonatal jaundice
Respiratory distress syndrome
Neonatal intraventricular haemorrhage
Necrotising enterocolitis
Neonatal length of hospital stay
Congenital malformation (non-prespecified outcome)

Infant/child outcomes

Episodes of disease
Weight for age Z-score
Weight for height Z-score
Mid-upper arm circumference
Mental development index
Psychomotor development index
Other measures of infant or child development

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 (30 September 2011).

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 the references lists of retrieved studies and identified an unpublished study from a review article (Oestdarp 2003). We did not apply any language restrictions.

Data collection and analysis

For methods used to assess trials included in previous versions of this review, see Appendix 1.

The following methods were used to assess China 2001; Ghana 2009; Iran 2010.

Selection of studies

Review authors Rintaro Mori (RM), Erika Ota (EO), and Ruoyan Tobe-Gai (RT) independently assessed for inclusion all the potential studies we identify as a result of the search strategy. We resolved all the disagreements through discussion.

Data extraction and management

We designed a form to extract data. For eligible studies, RM, EO and RT extracted the data using the agreed form. We planned to resolve any discrepancies through discussion or, if required, we would have consulted PM. We entered data 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 provide further details.

Assessment of risk of bias in included studies

RM, EO and RT independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion. PM and RM independently re-assessed risk of bias using the updated format newly required for all the studies already included in the previous version due to changes in methods (Higgins 2011).

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

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

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

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

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

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

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

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

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

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

- low, high or unclear risk of bias.

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

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

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

(5) Selective reporting (checking for reporting bias)

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

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

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

We described for each included study any important concerns we have about other possible sources of bias.
We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

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

Measures of treatment effect

Dichotomous data

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

Continuous data

For continuous data, we used the mean difference if outcomes were measured in the same way between trials. We used the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We would have included cluster-randomised trials in the analyses along with individually-randomised trials. We would have adjusted their sample sizes or standard errors using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we used ICCs from other sources, we would have reported this and conducted sensitivity analyses to investigate the effect of variation in the ICC. If we had identified both cluster-randomised trials and individually-randomised trials, we planed to synthesise the relevant information. We would have 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 intervention and the choice of randomisation unit was considered to be unlikely.
We would have also acknowledged heterogeneity in the randomisation unit and performed a subgroup analysis to investigate the effects of the randomisation unit if necessary.
Cross-over trials were not considered in this review.

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, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they had been 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 30% 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

When there were 10 or more studies in a meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually, and used formal tests for funnel plot asymmetry. We performed exploratory analyses to investigate any asymmetry we detected.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2011). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary when an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful we did not combine trials.
When we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

When we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful, and when it was, used random-effects analysis to produce it.
We carried out the following subgroup analysis by incorporating zinc status as subgroups as part of the primary comparison.

1. Risk of populations (population with no or low risk of zinc deficiency versus population with assumed risk of zinc deficiency).
2. Study settings (studies conducted in high income settings versus low income settings).

The primary outcomes were used in the subgroup analysis.
We assessed differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we assessed differences between subgroups by interaction tests.

Sensitivity analysis

We carried out sensitivity analysis to explore the effects of adequate allocation concealment, but found that restricting to only trials with adequate allocation concealment made very little difference to the results for the primary outcomes.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
In this update we added three new randomised controlled trials (RCTs) to make a total of 20 included trials.
We included 20 RCTs involving over 15000 women and their babies. *See* table of Characteristics of included studies for details.

Participants and settings

Sixteen studies included women from low-income settings. One of the four studies in the higher-income or mixed-income settings only recruited women at risk of giving birth to small-for-gestational age babies (UK 1991a).

Baseline zinc concentrations and nutritional status

Women in most of the studies had, or were likely to have low zinc concentrations and low nutritional status. It is difficult to assess zinc status and most studies have assumed that pregnant women from low-income groups would be low in zinc as part of their overall poor nutritional status. Where studied, the improvement in serum zinc concentrations in the supplemented group supports this assumption (Bangladesh 2000; Peru 1999). The only studies likely to have included women with normal zinc concentrations were UK 1989; UK 1991a; UK 1991b.

Dosage of zinc supplementation

The dose of daily zinc supplementation ranged from 5 mg (China 2001) to 44 mg zinc per day (Denmark 1996). Some women in S Africa 1985 had doses of up to 90 mg zinc per day.

Duration of supplementation

Women were supplemented from before conception in Nepal 2003 with the shortest duration being from 26 completed weeks' gestation in some women in USA 1983; and USA 1985.

Types of interventions

Most trials (14/20) compared zinc with placebo (Bangladesh 2000; China 2001; Chile 2001; Denmark 1996; Ghana 2002; Iran 2010; Pakistan 2005; S Africa 1985; UK 1989; UK 1991a; USA 1983; USA 1985; USA 1989; USA 1995). In some trials (*see* Characteristics of included studies table); all women were also given iron, folate or vitamins or combinations of these. Three trials (Indonesia 1999; Indonesia 2001; Nepal 2003) had more than two arms, so these trials were analysed to compare women who received zinc with women who did not.
Nepal 2003 was a cluster-RCT - analyses adjusted for clustering were presented in study reports and so we did not need to perform additional calculations for these study results.

Adherence

Two studies (Chile 2001; Denmark 1996) excluded non-adhering women (85% and 60% compliance respectively) and the other 15 studies included or probably included non-adhering women in the analysis. Of the latter group, two studies (UK 1991a; USA 1983) presented at least some results separately for adhering women and non-adhering women. Adherence was generally reported to be over 70%, except for Pakistan 2005; UK 1989; UK 1991a, where it was 50% to nearly 70%.

Excluded studies

We excluded 15 studies. *See* table of Characteristics of excluded studies for details.

Risk of bias in included studies

Risk of bias for included studies is summarised in Figure 1 and Figure 2.

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

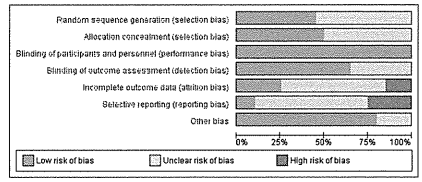
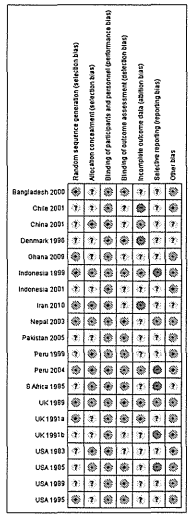


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Allocation concealment was considered adequate in 10 trials (China 2001; Indonesia 1999; Iran 2010; Nepal 2003; Peru 1999; Peru 2004; S Africa 1985; UK 1989; USA 1985; USA 1983). Allocation concealment was rated as unclear in 10 trials: Bangladesh 2000; Chile 2001; Denmark 1998; Ghana 2009; Pakistan 2005; UK 1991a; UK 1991b; USA 1985; USA 1995 (method not described or not clearly described); and in Indonesia 2001 there was third party randomisation but no details of how allocations were concealed.

Blinding

All trials stated that both investigators and mothers were blinded or that the trial was double-blinded.
Blinding of outcome assessors was not well described but was likely to have happened in most trials (at least for short-term outcomes) as the majority were placebo-controlled.

Incomplete outcome data

Losses to follow-up ranged from 1% in UK 1989 to 40% in Denmark 1998. Attrition bias was judged to be at high risk in only three trials.

Selective reporting

Selective reporting bias was mostly rated as unclear, with five RCTs judged to be at high risk due to expected outcomes not being reported, or reported incompletely.

Other potential sources of bias

Other sources of bias were not generally evident although several trials reported some baseline imbalances and several had restricted analyses.

Effects of interventions

We included 20 RCTs involving over 15,000 women and their babies.

Primary outcomes:

There was a 14% reduction in preterm birth in zinc groups compared with no zinc groups (risk ratio (RR) 0.86, 95% confidence interval (CI) 0.76 to 0.97; 16 RCTs, 7637 women; Analysis 1.1).
No significant differences between zinc and no zinc were seen for stillbirth or neonatal death: RR 1.57 95% CI 0.83 to 2.98; 4 RCTs of 1364 women; low zinc or RR 0.93 95% CI 0.24 to 3.65; 3 RCTs of 683 women; normal zinc (Analysis 1.2).
There was no significant difference in birthweight between zinc and no-zinc groups (mean difference (MD) -9.48 g, 95% CI -34.28 to 15.33; 16 RCTs, 5780 babies; Analysis 1.3); small-for-gestational age (RR 1.02 95% CI 0.94 to 1.11; 8 RCTs, 4252 babies; or low birthweight (RR 0.93, 95% CI 0.78 to 1.12; 14 RCTs, 5643 babies; Analysis 1.5).

Secondary outcomes

Maternal outcomes

No significant difference was seen for pregnancy hypertension or pre-eclampsia (RR 0.83, 95% CI 0.64 to 1.08; seven RCTs, 2975 women; Analysis 1.7) or prelabour rupture of membranes (Analysis 1.8), antepartum haemorrhage (Analysis 1.6), post-term birth (Analysis 1.9), retention of placenta (Analysis 1.15), meconium in liquor (Analysis 1.12), instrumental vaginal birth (Analysis 1.14) and smell or taste dysfunction (Analysis 1.17; Analysis 1.18), but these outcomes were measured in only one or two trials. In one trial of women at risk for small-for-gestational age babies (UK 1991a), significantly fewer women in the zinc group than in the no-zinc group were induced (RR 0.27, 95% CI 0.10 to 0.73, 52 women; Analysis 1.10).
No significant differences were seen for postpartum haemorrhage (Analysis 1.16) or maternal infections (Analysis 1.11) (three trials each) or gestational age at birth (Analysis 1.25) (six trials) or caesarean section (Analysis 1.13; random effects) (six trials). The heterogeneity in the caesarean section seemed to be contributed to by the income settings of the countries, as trials in high-income settings tend to favour zinc supplement, while trials in low-income settings tend to favour the controls.

Birthweight and associated outcomes

No differences between the zinc and no zinc groups were seen for high birthweight (Analysis 1.26) (five RCTs), head circumference (Analysis 1.28) (seven RCTs) or mid-upper arm circumference (Analysis 1.44) (three RCTs). A high level of heterogeneity was apparent in the results for head circumference (I^2 = 45%). A random-effects model did not change the conclusion of no significant difference between the zinc and no-zinc groups.

Other neonatal outcomes

No significant differences were seen for congenital malformations (six RCTs).

There were no significant differences between the zinc and no-zinc groups for the following outcomes : Apgar scores less than five at five minutes, neonatal hypoxia, jaundice, fever, infant umbilical infection, neonatal sepsis, respiratory distress syndrome, neonatal intraventricular haemorrhage, necrotising enterocolitis, and neonatal hospital stay. Each of these outcomes was only available from one or two RCTs.
In one RCT of 176 babies (Peru 2004), four measures of fetal heart rate (fetal heart rate, number of fetal movement bouts, fetal activity level, and fetal movement amplitude) showed no evidence of differences between the zinc and no-zinc groups, while fetal heart rate variability and number of fetal accelerations were significantly higher in the zinc groups.
In one RCT of 196 infants (Bangladesh 2000), the zinc group had significantly fewer episodes per infant of acute diarrhoea over six months (MD -0.4 episodes, 95% CI -0.79 to -0.01; Analysis 1.37), and significantly fewer episodes per infant of impetigo. No significant differences were seen for episodes of persistent diarrhoea, dysentery, cough, and acute lower respiratory infection) over the same period.
Results of infant weight-for-age (Z-score) showed no evidence of difference at six months for the zinc and no-zinc groups in two RCTs (304 infants), but by 13 months, the no-zinc group showed significantly higher scores (in one RCT of 168 infants, Bangladesh 2000). No evidence of difference was seen for weight-for-height at six months in one RCT of 136 infants (Indonesia 2001).

Infant/child development

Three RCTs (Bangladesh 2000; Peru 2004; USA 1995) measured child development outcomes. A subset of 168 infants from Bangladesh 2000 assessed at 13 months found that the zinc group had significantly worse mental development, psychomotor development index scores, emotional tone and co-operation than the no-zinc group, with infant approach, activity, and vocalisation showing no significant differences. The US RCT (USA 1995) followed up 355 infants at five years, finding no evidence of differences between zinc and no-zinc groups for differential abilities, visual or auditory sequential memory scores, Knox cube, gross motor scale and grooved pegboard scores. The trial in Peru (Peru 2004) reported intelligence quotient of infants at 54 months, which showed no evidence of difference.

Subgroup analyses

No differing patterns were clearly evident in the subgroups of women with low versus normal zinc concentrations and nutrition status (with the possible exception for small-for-gestational age where women with normal zinc concentrations may show more benefit for this outcome), or in women who adhered to their treatment versus those who did not (latter subgroup analysis not presented in the graphs), though the interaction test showed borderline P value (P = 0.06).

Reporting bias

There are three outcomes whose meta-analyses included more than 10 studies (Figure 3; Figure 4; Figure 5). Although there was no evidence of reporting bias in preterm birth and birthweight, the distribution of the results on low birthweight were skewed. This means there is a possibility of reporting bias and warrants careful interpretation of the results. The result on effectiveness by zinc could have been overestimated.

Figure 3. Funnel plot of comparison: 1 Zinc supplementation versus no zinc (with or without placebo), outcome: 1.1 Preterm birth.

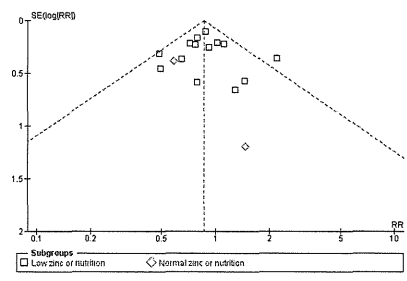


Figure 4. Funnel plot of comparison: 1 Zinc supplementation versus no zinc (with or without placebo), outcome: 1.3 Birthweight.

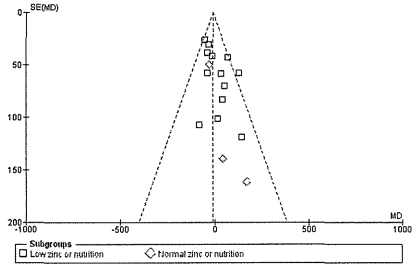
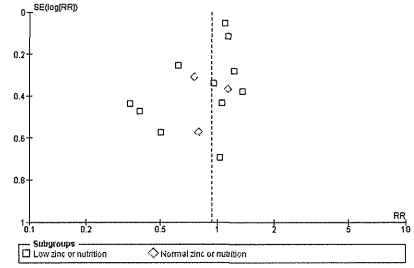


Figure 5. Funnel plot of comparison: 1 Zinc supplementation versus no zinc (with or without placebo), outcome: 1.5 Low birthweight.



DISCUSSION

Many studies have demonstrated some positive response on biochemical parameters such as serum zinc status of mother or baby, or both, with supplementation (Bangladesh 2000; Peru 1999) as have studies of iron supplementation in pregnancy (Pena-Rosas 2006). It is now crucial to focus on the impact of any intervention on outcomes that are of clinical significance and particularly those that may be related to maternal, fetal, neonatal and infant mortality and morbidity. This is relevant because of the limited resources, both financial and human, currently available worldwide but in particular to the developing countries where such morbidity and mortality is high.

This review of 20 randomised controlled trials, including over 15,000 women and their babies, has not provided compelling evidence for routine zinc supplementation during pregnancy, although the finding of a reduction in preterm births warrants further investigation, as does the suggestion of reporting bias from the funnel plot on small-for-gestational age. Subgroup analysis of the 17 studies involving women who are or are likely to be zinc deficient, such as populations from developing countries or from low socioeconomic groups from western countries, also did not make a case for zinc supplementation in those groups of women. This is consistent with a review of maternal zinc supplementation in developing countries (Osendarp 2003).

The small but significant reduction in preterm birth in the zinc group deserves further attention; is it possible that improving nutrition would cause an even greater reduction? The Cochrane review on micronutrient supplementation also shows a trend in the same direction (Haider 2006). Although dosage of zinc may play a role, no dose-response pattern was evident in this review (with the possible exception of pre-eclampsia). It is possible that zinc used in conjunction with iron may dilute the effect of supplementation. The intrauterine growth effect seen in UK 1991a, where women were selected on the basis of being at risk for giving birth to a small-for-gestational age baby, has not been replicated. In the Bangladesh 2000 study, where incidence of small-for-gestational age was 75% and low birthweight was 43%, supplementation with 30 mg zinc daily did not improve pregnancy outcomes. This is most likely due to the presence of other concurrent nutrient defi-

ciencies. The Peru (Peru 1999; Peru 2004); Bangladesh 2000 and USA 1995 studies attempted to assess the neurodevelopmental effect of zinc supplementation on infants. The inconsistencies in their results probably reflect the dependence of such outcomes on many variables.

Zinc is likely to be only one micronutrient in the overall picture of maternal nutrition prior to and during the course of pregnancy, although the Cochrane review on micronutrient supplementation concludes that there is "no added benefit of multiple-micronutrient supplements compared with iron folic acid supplementation" (Haider 2006). In order to make any significant impact on morbidity and mortality, we really need to address the underlying problem of poor nutrition, due to low socioeconomic status (Peru 1999). Villar and colleagues (Villar 2003) indicated that while zinc supplementation may be promising, they go on to say that "it is unlikely that any specific nutrient on its own ... will prevent .... preterm delivery or death during pregnancy".

Although improving birthweight particularly in women from low-income countries is desirable, data from Nepal 2003 imply a degree of caution. In the overall Nepal 2003 study, multiple-micronutrient supplementation (but not other combinations of micronutrients) compared with controls was associated with more babies with a birthweight greater than 3.3 kg; and this high birthweight was associated with an increased risk of symptoms of birth asphyxia (risk ratio 1.49, 95% confidence interval 1.04 to 2.13).

Despite uncertainty about the effects of maternal zinc supplementation, many pharmaceutical companies have added zinc to their multivitamin preparations.

Lack of any significant benefit from zinc supplementation of mothers suggests that we should now not waste valuable resources looking at zinc in isolation. In addition, infant micronutrient supplementation (including zinc) may be more effective than maternal supplementation (Lassi 2010; Shrimpton 2005).

Any future research aimed at improving outcomes related to maternal nutrition should address ways of modifying the overall nutritional status of pregnant women particularly in developing countries. This may not come from the scientific but from the political community where more resources need to be put into improving the overall socioeconomic status of impoverished populations and also to improve the status of the women in such populations. Future research should also address other interventions such as work reduction in populations of pregnant women at high risk of nutritional deficiency.

AUTHORS' CONCLUSIONS

Implications for practice

The 14% relative reduction in preterm birth for zinc compared with placebo was primarily in studies of women of low income and this has some relevance in areas of high perinatal mortality. Some trials showed inconsistent findings, but overall, there is not enough evidence to show that routine zinc supplementation in women results in other clinically relevant outcomes.

Implications for research

There appeared to be inconsistency between trials regarding some pregnancy outcomes. The reduction in preterm birth needs further assessment probably in association with protein-calorie nutrition. Future research aimed at improving outcomes related to maternal nutrition should address ways of modifying the overall nutritional status of pregnant women particularly in low-income regions, but avoid looking at zinc in isolation. Future research should also address other interventions such as work reduction in populations of pregnant women at high risk of nutritional deficiency.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bangladesh 2000

Methods	RCT.
Participants	559 pregnant women between 12 and 16 weeks' gestation, from Dhaka city slums. The 446 women who completed follow-up had a mean baseline serum zinc level of 15.3 [SD 4.3] µmol/L (similar to those lost to follow-up). Energy intakes were low at 4 months' gestation (median 6065 kJ/day)
Interventions	Zinc: 30 mg elemental zinc/day (n = 269 [214]). No zinc: placebo (n = 290 [232]).
Outcomes	**Maternal** Serum zinc concentrations at 7 months' gestation; haemoglobin concentrations at 7 months' gestation; blood pressure at 7 months' gestation; preterm birth and gestational age; stillbirth. **Neonatal** Birthweight.
Notes	Adherence: percentage of days during follow-up that a woman reported having consumed a supplement was 86% Final sample size of 410 infants was sufficient to detect a 110 g difference in birthweight

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated random letter assignment."
Allocation concealment (selection bias)	Unclear risk	"randomly assigned" - no details given regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both investigators and participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specifically mentioned but assessors were also likely to have been blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	113/559 (20.2%) women were lost to follow-up before birth: (55 (20.4%) in the zinc group and 58 (20.0%) in the placebo group) - most (60) due to migration out of the area By 13 months follow-up, 383 (68.5%) infants remained in the

Bangladesh 2000 *(Continued)*

		trial, with only 168 of these infants being included in the 13-month analysis
Selective reporting (reporting bias)	Unclear risk	Some primary outcomes such as mode of birth not reported.
Other bias	Low risk	No apparent source of other bias.

Chile 2001

Methods	RCT.
Participants	804 pregnant adolescents of low socio-economic status from Santiago, less than 19 years old and before 20 weeks' gestation. 220 randomly selected women showed a low zinc intake (7.4 SD 2.3 mg) at enrolment. Women showed adequate protein intakes but a relatively low mean energy intake
Interventions	Zinc: 20 mg zinc/day (n = 249). No zinc: placebo (n = 258). All women also received 40 mg iron per day.
Outcomes	**Maternal** Pre-eclampsia; plasma zinc; hair zinc; gestational age at birth; preterm birth; maternal oedema; maternal cholestasis. **Neonatal** Low birthweight; birthweight; spontaneous abortions.
Notes	Adherence: non-adherers were excluded from analysis; this included individuals who ingested less than 50% of zinc supplements in any month of the study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned" - no further details reported.
Allocation concealment (selection bias)	Unclear risk	"randomly assigned"; pharmacist kept codes - no further details reported

Chile 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind fashion."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up: 297/804 (37%) - failure to come to visits (137), taking less than 15 zinc capsules in any 1 month (115), spontaneous abortion (12), intervention began after 20 weeks' gestation (10), absence of pregnancy (7), change of address (6), apparent intolerance to zinc or placebo (6), twin pregnancy (4)
Selective reporting (reporting bias)	Unclear risk	Not all expected maternal primary outcomes reported, but most primary infant outcomes specified in this review were reported
Other bias	Low risk	No apparent risk of other bias.

China 2001

Methods	RCT.
Participants	146 pregnant women living in a rural area. They were thought to have mild to moderate zinc deficiency
Interventions	Daily supplementation of zinc. Group A 5 mg/day (n = 27); Group B 10 mg/day (n = 40); Group C 30 mg/day (n = 39); Group D 0 mg/day (n = 40)
Outcomes	**Maternal** Caesarean section. **Neonatal** Small-for-gestational age; neonatal sepsis; low birthweight; congenital malformations; stillbirth; preterm birth.
Notes	For the purposes of this review, Group A, B and C were combined as an intervention group and Group D served as a control group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description other than the allocation was made randomly.

China 2001 *(Continued)*

Allocation concealment (selection bias)	Low risk	All capsules were prepared by pharmacy and allocation was concealed for both investigators and women
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All capsules were prepared by pharmacy and both investigators and enrolled pregnant women were concealed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop out for maternal and neonatal clinical outcomes reported
Selective reporting (reporting bias)	Unclear risk	There is no information on protocol published prior to this trial and no information to make appropriate judgements on this
Other bias	Unclear risk	It was reported that obstetric and physical background data between the groups were not significantly different, though actual data were not reported

Denmark 1996

Methods	RCT.
Participants	Normal healthy middle-class population (at least 18 years old). First antenatal visit before 20 weeks with no intolerance to zinc or other medical problems. Dates were confirmed by scan. Women thought likely to be zinc deficient.
Interventions	Zinc: 2 tablets with 44 mg elemental zinc (n = 1000). No zinc: 2 placebo tablets indistinguishable from active tablets (n = 1000)
Outcomes	**Maternal** Prelabour rupture of membranes; preterm labour; pre-eclampsia; anteparrtum haemorrhage; caesarean section. **Neonatal** Low 5-minute Apgar score; large-for-gestational age; small-for-gestational age; birthweight (not able to be used in graphs since no SDs provided)
Notes	Adherence: non-adherers were excluded from the final analysis; reasons included side-effects from tablets, if a woman wished to stop or if a woman had not taken the tablets for 14 days in all. The authors noted that women did not differ in basic characteristics.

Denmark 1996 *(Continued)*

	There were however significantly more smokers in the non-adherers group and thus the numbers in the final analysis related to labour and birth have also excluded smokers

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation was performed in successive groups of 10 active and 10 placebos; no further details reported
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators and mothers were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported, but probably done as paper reports that the code was not broken until the end of the study
Incomplete outcome data (attrition bias) All outcomes	High risk	794/2000 (39.7%); 415 in zinc group and 379 in placebo group
Selective reporting (reporting bias)	Unclear risk	Not all expected maternal primary outcomes reported, but most primary infant outcomes specified in this review were reported
Other bias	Unclear risk	Analyses relating to labour and birth excluded smokers.

Ghana 2009

Methods	RCT.
Participants	400 pregnant women in Ghana earlier than 16 weeks of gestation N = 299 for intervention and n = 301 for control allocated. 27 out of 299 of the intervention group and 30 out of 301 of the control group were lost to follow-up and excluded from the analysis
Interventions	40 mg zinc plus 40 mg iron (n = 299) versus 40 mg iron only (n = 301)
Outcomes	Small-for gestational age; low birthweight; preterm birth; birthweight.
Notes	

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

Ghana 2009 *(Continued)*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	By computer-generated random number.
Allocation concealment (selection bias)	Unclear risk	Opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The capsules for both intervention and placebo were the same
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	27 out of 299 of the intervention group and 30 out of 301 of the control group were lost to follow-up and excluded from the analysis
Selective reporting (reporting bias)	Unclear risk	It was not clear if a protocol of this trial had been published prior to the study; no maternal outcomes reported
Other bias	Low risk	Baseline characteristics were compared, with no significant difference seen between groups

Indonesia 1999

Methods	RCT.
Participants	519 women from rural villages in Java, likely to have low zinc levels; supplementation from 17 weeks' gestation
Interventions	Zinc: zinc + iron + folate (58 women randomised) versus zinc + β-carotene + iron + folate (56 women randomised). No zinc: β-carotene + iron + folate (58 women randomised) versus iron + folate (57 women randomised) (i.e. 4 arms but treated as 2 arms for the purposes of this review - zinc versus no zinc)
Outcomes	**Maternal** Infection (feverishness and puerperal fever).
Notes	Adherence: mean adherence ranged from 71%-73% across the 4 arms of the study

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

Indonesia 1999 *(Continued)*

Random sequence generation (selection bias)	Low risk	Pseudo-random number generator in blocks of 12.
Allocation concealment (selection bias)	Low risk	Treatment allocation sequence was prepared and held at a remote site
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All investigators, field and laboratory staff and participants were blinded to the treatment code
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported but likely to have been done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	519 of the 1008 women had pregnancies ending between 1 April and 31 October 1997; data available for 503/519 (97%) of these women
Selective reporting (reporting bias)	High risk	Only 2 maternal outcomes and no infant outcomes specified in the review were reported in this trial
Other bias	Low risk	No apparent risk of other bias.

Indonesia 2001

Methods	RCT (factorial design).
Participants	229 pregnant women with a gestational age between 10 and 20 weeks from 13 adjacent villages in Bogor District, Indonesia. Women had mean plasma zinc concentrations of about 11 µmol/L
Interventions	Zinc (n = 92): zinc (n = 48) and zinc + β-carotene (n = 44). No zinc (n = 87): β-carotene (n = 45) and iron + folate alone (n = 42). All women received iron + folate.
Outcomes	**Maternal** Preterm birth; caesarean section; prolonged labour; retention of placenta; postpartum haemorrhage; infection; 6-month serum zinc. **Neonatal** Birthweight; low birthweight; congenital malformation; stillbirth/neonatal death;

Indonesia 2001 *(Continued)*

	blue/floppy (neonatal hypoxia); jaundice; fever/not drinking; umbilical infection; 6-month Z-scores; 6-month haemoglobin, plasma retinol, plasma zinc.
Notes	Adherence: mean adherence was over 80%.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported.
Allocation concealment (selection bias)	Unclear risk	Supplements were prepared by a third party (hospital pharmacy in the Netherlands), but no detail given of how the contents of the bottles were concealed from the investigators or the participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as being "double-blind"; probably done.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 50/229 (22%) women before giving birth; 136 newborns completed follow-up at 6 months
Selective reporting (reporting bias)	Unclear risk	Not all expected maternal primary outcomes reported, but most primary infant outcomes specified in the review were reported
Other bias	Low risk	No apparent risk of other bias.

Iran 2010

Methods	RCT.
Participants	110 healthy pregnant women with a previous preterm birth receiving prenatal care between 12 and 16 weeks' gestation
Interventions	50 mg/day Zn as Zn sulfate (n = 42) versus placebo (n = 42).

Iran 2010 (*Continued*)

Outcomes	**Maternal** Caesarean section. **Neonatal** Small-for-gestational age; low birthweight; gestational age at birth; preterm birth; low birthweight.	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Women were randomised according to a pre-existing list produced by a computer program
Allocation concealment (selection bias)	Low risk	Both woman and physician who assessed the outcome were not aware of treatment type that the woman was receiving. The masking of the active and placebo treatments was preserved by creating treatments that looked identical. The hospital pharmacist was informed of all randomization assignments and was responsible for labelling the study drug and maintaining a master list linking the women and their treatment assignments
Blinding of participants and personnel (performance bias) All outcomes	Low risk	As above.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 42 out of allocated 55 women in the intervention group and 42 out of 55 women in the control group were analysed (26% lost to follow-up in each group)
Selective reporting (reporting bias)	Unclear risk	Not enough information to make this judgement. No information on if the protocol had been published prior to the trial
Other bias	Unclear risk	No significant baseline differences except for higher haemoglobin concentrations in the zinc group (MD 0.5 g/dl)

Nepal 2003

Methods	Cluster RCT (also factorial design).
Participants	4926 pregnant women and 4130 liveborn infants in a rural community in Nepal = 426 sectors (communities of about 100-150 households) - only 2 of the 5 arms (total of 1659 infants) used in this review). Women who were currently pregnant, breastfeeding a baby less than 9 months old, menopausal, sterilised or widowed were excluded. Supplementation commenced before conception.
Interventions	Zinc: zinc + iron + folate (n = 858). No zinc: iron + folate (n = 801).
Outcomes	**Maternal** Preterm birth. **Neonatal** Stillbirth or neonatal death; birthweight; chest circumference; head circumference; length; low birthweight; small-for-gestational age.
Notes	Adherence: mean adherence was 88%. RRs adjusted for the cluster-design effects were presented for each of the 5 arms of the RCT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised sectors by "drawing numbered identical chips from a hat" (in blocks of 5 within each community)
Allocation concealment (selection bias)	Low risk	Supplements were of identical shape, size and colour and arrived in Nepal in opaque, sealed and labelled bottles coded 1-5. The code allocation was kept locked at the Johns Hopkins University, Baltimore
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators, field staff and statisticians were all blinded to the codes throughout the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators, field staff and statisticians were all blinded to the codes throughout the study

Nepal 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	155/827 (19%) of infants in the zinc group and 167/872 (19%) in the non-zinc group were lost to follow-up or excluded from analysis (infant died, mother refused, home was inaccessible, birthweight was measured more than 72 hours after birth or missing data)
Selective reporting (reporting bias)	Low risk	Most expected outcomes were reported with some exceptions such as mode of birth and postpartum haemorrhage
Other bias	Low risk	No apparent evidence of other sources of bias apart from a small imbalance between groups in maternal weight (which was adjusted for in the analyses)

Pakistan 2005

Methods	RCT.
Participants	242 women from 2 urban hospitals and 1 rural community; 10-16 weeks' gestation. Women with known systemic disease were excluded. Serum zinc at enrolment was mean 71.51 µg/dl (SD 21) in the zinc group and 74.09 (SD 23.2) in the placebo group
Interventions	Zinc: 20 mg elemental zinc (zinc sulphate powder capsule) (n = 121). No zinc: placebo (n = 121) (capsule); in addition, all women had routine supplements of folic acid and iron
Outcomes	**Maternal** Preterm birth. **Neonatal** Occipitofrontal circumference; low birthweight; abortion/intrauterine death; birthweight; length.
Notes	Adherence: about 65% of women had good adherence, which was similar in both groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"simple random sampling with preassigned code."

Pakistan 2005 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Women and health workers were blinded to content of medication
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported but likely to have been done.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 15% (actual figures not given, but paper notes that losses were non-differential)
Selective reporting (reporting bias)	Unclear risk	Only 1 of the maternal outcomes specified in the review were reported in the trial
Other bias	Low risk	No apparent risk of other bias.

Peru 1999

Methods	RCT.
Participants	1295 women with low zinc intakes from an urban shanty town in Lima, Peru; at 10 to 24 weeks' gestation
Interventions	Zinc: 15 mg zinc plus 60 mg iron plus 250 µg folate (n = 521). Non-zinc: 60 mg iron plus 250 µg folate (n = 495).
Outcomes	**Maternal** Duration of pregnancy; preterm birth (< 37 weeks); very preterm birth (< 33 weeks); post-term birth (> 42 completed weeks); serum and urinary zinc concentrations; haemoglobin; serum ferritin; fetal heart rate and movement measures. **Neonatal** Birthweight; low birthweight; high birthweight; cord vein zinc; cord vein haemoglobin; cord vein serum ferritin; crownheel length; head circumference; chest, calf and mid-upper arm circumference; biceps, subscapular and calf skinfold thicknesses.

Peru 1999 (*Continued*)

Notes	Adherence: mean of about 85% of capsules consumed, which was similar across the groups. Adjustments for baseline differences in maternal age and in-home electricity were made by multiple regression

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported.
Allocation concealment (selection bias)	Low risk	Coded blister packages were prepared by a local pharmaceutical company, and allocation was thus concealed by use of this third party
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators, other health personnel and women were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported but likely to have been done due to use of placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	21.5% (279/1295) women lost to follow-up by time of giving birth - 18 (1%) were found to live in another community and therefore not eligible to participate; 92 (7%) declined to participate; 71 (5%) moved out of the study area; 30 (2%) miscarried; 58 (4%) left the study for other reasons; 10 (1%) were subsequently found to have twin pregnancies or to have developed pregnancy complications
Selective reporting (reporting bias)	Unclear risk	Expected outcomes such as caesarean birth and perinatal death were not reported
Other bias	Low risk	No apparent risk of other bias.

Peru 2004

Methods	RCT.
Participants	242 low-income Peruvian women, with maternal dietary zinc intake approximately 8 mg/day; low-risk women with singleton pregnancy; supplementation commenced 10-16 weeks' gestation; exclusions made according to a protocol for fetal neurobehavioural assessment

Peru 2004 (*Continued*)

Interventions	Zinc: zinc + iron + folate (n = 109 [94]). No zinc: iron + folate (n = 113 [101]).
Outcomes	**Maternal** Preterm birth with complications; gestational age at birth. **Neonatal and infant** Fetal heart rate measures; birthweight; length; biparietal diameter; abdominal circumference; femur diaphysis length; infant feeding; infant growth; child development at 54 months; dietary and nutritional status at 54 months; mean arterial pressure at 54 months; BMI at 54 months; haemoglobin concentration at 54 months; plasma zinc concentration at 54 months; C-reactive protein concentration at 54 months; Home Observation for the Measurement of the Environment (HOME) Scale assessment at 54 months; heart rate measures at 54 months.
Notes	Adherence: mean adherence rate was 87% (86% in the zinc group and 88% in the no zinc group)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Women were randomly assigned in blocks of 2 using computer-generated lists from Johns Hopkins and sent to Peru
Allocation concealment (selection bias)	Low risk	The randomisation code was made by the pharmaceutical company and maintained in a sealed and secured envelope in Lima; supplements had the same appearance and taste
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both study personnel and participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not specifically stated, but we have assumed that outcome assessors were blinded and remained blinded for the longer-term analyses

Peru 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	222/242 (90.1%) women completed the protocol and 195 (80.6%) were included in the analysis of birth outcomes - 94 (78%) zinc and 101 (84%) no zinc. The 47 lost were made up of 20 change of address, declining to continue in the study, or travel and 27 exclusions for significant obstetric or medical complications At 54-month follow-up, there were 205 eligible children (includes children of 10 mothers excluded from the initial analysis), and evaluations were completed for 184 (90%) of these children (86 (87%) from the zinc group and 98 (92%) from the non-zinc group
Selective reporting (reporting bias)	High risk	A number of birth outcomes such as postpartum haemorrhage, stillbirth or neonatal death, low birthweight or Apgar scores were not reported; and preterm birth was only reported as preterm birth with complications which were treated as study exclusions
Other bias	Low risk	No apparent source of other bias although the study was designed to primarily assess neonatal and infant outcomes (see selective reporting above)

S Africa 1985

Methods	RCT.
Participants	Black women before 20 weeks' gestation at antenatal clinic near Durban, South Africa. Women specifically selected on the basis of being at high risk for low zinc status. Dietary recall histories showed women to be deficient in energy, protein, B vitamins, calcium and iron. Women in the zinc group in this study had a significantly lower mean weight than the women in the placebo group
Interventions	Zinc: zinc gluconate 30-90 mg daily (n = 32). No zinc: placebo (n = 33).
Outcomes	Gestational age at birth; birthweight.
Notes	Adherence: figures for adherence were not given, but the authors commented that it was high, due to free transportation to the clinic where the supplements or placebo were consumed under supervision. Groups given dietary supplements are not included in the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement

S Africa 1985 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported.
Allocation concealment (selection bias)	Low risk	Randomisation by numbered packets prepared at the pharmacy, code held by pharmacy until the end of the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding by use of placebo until end of study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported but likely to have been blinded due to use of placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 10% (exact figures not given) of women before giving birth, principally due to moving out of the area
Selective reporting (reporting bias)	High risk	Only 2 of the outcomes specified in this review were reported in the trial
Other bias	Unclear risk	No apparent risk of other bias.

UK 1989

Methods	RCT.
Participants	500 women at first antenatal visit below 20 weeks' gestation. Median zinc concentrations at enrolment were 1.192 µmol/10 x 10 cells in the zinc group and 1.147 in the placebo group
Interventions	Zinc: 20 mg elemental zinc (n = 246). No zinc: placebo (n = 248).
Outcomes	**Maternal** Preterm delivery (< 37 weeks); post-term delivery (> 42 weeks); prelabour rupture of membranes; pregnancy hypertension; any maternal infection - (pre or postdelivery); caesarean section; postpartum haemorrhage; congenital malformations. **Neonatal** Low birthweight (< 2500 g); birthweight > 3500 g; small-for-gestational age (< 10th centile); Apgar score at 1 minute < 6; Apgar score at 5 minutes < 8;

UK 1989 (*Continued*)

	stillbirth/neonatal death.
Notes	Adherence: adherence levels were not reported, but non-adherers were included in study results. At 28 to 32 weeks' gestation, just over half the women claimed to be taking the supplement every day, and nearly 2 thirds were doing so by the time of giving birth. Although results were not presented separately for adherers and non-adherers, the authors state that no significant differences between them were found, apart from a significantly lower risk of postpartum infection among the adherers

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation tables.
Allocation concealment (selection bias)	Low risk	Bottles prepared by drug company and labelled A/B.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Use of placebo; code not broken until the end of the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported but likely to have been done due to use of placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: 6/500 (1%) - 4 women moved and 2 miscarried
Selective reporting (reporting bias)	Low risk	Most of the outcomes specified in the review were reported.
Other bias	Low risk	No apparent risk of other bias.

UK 1991a

Methods	RCT.
Participants	56 women with pre-pregnancy weight less than 95% of ideal or previous small-for-gestational age infant or Asian or primigravida smoking > 5 cigarettes per day, from last 15-25 weeks of pregnancy. Iron/folate as per doctor's instructions.
Interventions	Zinc: 22.5 mg elemental zinc (n = 30). No zinc: placebo (n = 26).
Outcomes	Pregnancy hypertension; preterm delivery; post-term labour;

UK 1991a (*Continued*)

	induction of labour; caesarean section; small-for-gestational age; low birthweight; birthweight > 3500 g; congenital malformations; stillbirth/neonatal death.
Notes	Adherence was 43% in the zinc group and 67% in the placebo group - outcomes were presented separately for adherers and non-adherers

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table, no mention of how the numbers were generated but probably adequately done
Allocation concealment (selection bias)	Unclear risk	"coded placebo or non-placebo tablet or 22.5 mg effervescent zinc...was randomly prescribed."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind, "all clinical decisions were made by staff in the labour and delivery wards who were unaware of the trial details"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported, but probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/60 (7%); 2 women moved home, 1 termination of pregnancy, 1 miscarriage (all in the placebo group)
Selective reporting (reporting bias)	Unclear risk	Trial did not report all of the primary outcomes expected or specified for this review
Other bias	Low risk	No apparent source of other bias.

UK 1991b

Methods	RCT.
Participants	134 women less than 18 weeks' gestation.
Interventions	Zinc: 62 mg elemental zinc (n = 72). No zinc: spansules without zinc (n = 62). All women were also given iron and folate.

UK 1991b (*Continued*)

Outcomes	Low birthweight < 2500 g; birthweight > 3500 g; congenital malformations; stillbirth/neonatal death.
Notes	Adherence was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 18/152 (12%) due to GI effects, aborted or woman moved, leaving 72 in the zinc group and 62 in the control group
Selective reporting (reporting bias)	High risk	No maternal outcomes reported.
Other bias	Low risk	No apparent risk of other bias.

USA 1983

Methods	RCT.
Participants	213 Mexican women of Mexican descent, not adolescent (> 17 years age). Less than 27 weeks' gestation. No medical problems. Women specifically selected on the basis of being at high risk for low zinc status - at baseline, 81% of women had recalled dietary intakes providing < 2/3 RDA
Interventions	Zinc: 20 mg elemental zinc plus vitamins (n = 107). No zinc: placebo with vitamins (n = 106).
Outcomes	Pregnancy hypertension; low serum zinc before. birth (< 53.3 micrograms/dl); low hair zinc;

USA 1983 (*Continued*)

	smell dysfunction; taste dysfunction; preterm birth; low birthweight.
Notes	Adherence: defined as a woman who was in the study long enough to take supplements for more than 60 days and who returned to the pharmacy for 1 or more refills of 60 capsules. According to this definition, 82% overall (90% (81/90) in the control group and 75% (65/87) in the zinc group) were adherent in those 177 women who were not lost to follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not reported.
Allocation concealment (selection bias)	Low risk	"randomly assigned" - not definitively stated but likely to have been third party randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind"; "capsules were indistinguishable."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported but stated that "code was not broken until the study was completed"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	36/213 (16.9%) lost to follow-up (3 spontaneous abortions < 20 weeks, 2 sets of twins, 31 records that could not be located). The breakdown was 20/107 (18.7%) lost from the zinc group and 16/106 (15.1%) from the placebo group. Breakdown of reasons was not reported except for spontaneous abortions - 1 in the zinc group and 2 in the control group
Selective reporting (reporting bias)	Unclear risk	A number of primary maternal, pregnancy and neonatal outcomes were not reported (e.g. caesarean section, postpartum haemorrhage, perinatal death)
Other bias	Low risk	No apparent source of other bias.

USA 1985

Methods	RCT.
Participants	138 Hispanic teenagers in Los Angeles; mean dietary zinc intakes were about 50% of the RDA. Under 17 years, were not over 27 weeks' gestation according to LMP, and did not have diabetes, heart, renal or thyroid disease
Interventions	Zinc (20 mg) versus no zinc (placebo): all women were also given a supplement of 8000 IU vitamin A, 400 IU vitamin D, 30 IU vitamin E, 2 mg thiamin mononitrate, 2 mg riboflavin, 20 mg niacinamide, 5 mg pyridoxine HCl, 1 mg folic acid, 10 µg vitamin B12 (cyanocobalamin), 10 mg pantothenic acid, 60 mg vitamin C, 100 mg calcium (as carbonate), 20 mg iron (as ferrous fumarate), 50 mg magnesium (as oxide), 1 mg manganese (as sulphate) and 150 µg iodine (as potassium iodide). In addition, 108 mg iron/day was prescribed routinely at 20 weeks' gestation
Outcomes	Infant weight; placental weight; pregnancy-induced hypertension; meconium-stained amniotic fluid; birthweight > 2500 g; Apgar scores; preterm birth; fetal death; plasma zinc; haemoglobin; haematocrit; ferritin levels; folacin levels.
Notes	Adherence: defined as those in study long enough to take supplements for more than 60 days and who then returned to the pharmacy for 1 or more refills of 60 capsules = 93% of teenagers who returned for a final interview. No significant difference in adherence rates between the groups, so results were not presented separately for adherers and non-adherers

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned" - not further described.
Allocation concealment (selection bias)	Low risk	Third party (dispensed by clinic pharmacy).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Capsules were identical in composition and indistinguishable in taste and appearance, and the code was not broken until the end of the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported but likely to have been blinded due to the use of a placebo

USA 1985 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Birthweight data not available for 31/138 (22%); due to 2 spontaneous abortions and 29 records that could not be located
Selective reporting (reporting bias)	High risk	Data for outcomes such as perinatal death and preterm birth were collected but not fully reported (only that no significant differences were found)
Other bias	Low risk	No apparent source of other bias.

USA 1989

Methods	RCT.
Participants	652 low-income adolescents (average age 17.6 years; range 13.5 to 19.6); less than 25 weeks' gestation; women thought be at risk for zinc deficiency.
Interventions	Zinc: 30 mg zinc (n = 268). No zinc: placebo (n = 288).
Outcomes	**Maternal** Preterm birth; weight. **Neonatal** Birthweight; respiratory assistance.
Notes	Reported compliance was good - 87% consumed 6 or 7 tablets per week

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned."
Allocation concealment (selection bias)	Unclear risk	"randomly assigned."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind"; "identical-appearing tablets".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Neither the subjects nor the investigators were informed of tablet identity until after completion of the data collection."

USA 1989 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: 10.9% (71/652) at entry and 14.7% (96/652) (cumulative) at birth. Breakdown of losses by group was not reported, nor were reasons for losses
Selective reporting (reporting bias)	Unclear risk	A number of primary maternal, pregnancy and neonatal outcomes were not reported (e.g. caesarean, postpartum haemorrhage, perinatal death)
Other bias	Low risk	No apparent source of other bias.

USA 1995

Methods	RCT.
Participants	589 Afro American women. At 19 weeks' gestation. Plasma zinc level less than median gestation specific for the population. No medical problems.
Interventions	Zinc: 25 mg elemental zinc per day (n = 286). No zinc: placebo (n = 294). All women also received multivitamins.
Outcomes	Preterm birth; pregnancy hypertension; low birthweight; small-for-gestational age; stillbirth/neonatal death; neonatal sepsis; child mental and psychomotor development at 5 years.
Notes	Adherence: mean was 78% of days for both groups. Adherence was defined as the percentage of zinc tablets consumed compared with the number of days enrolled in the project prior to birth

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"both caregivers and subjects were blind regarding the content of the supplement."

USA 1995 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported but likely to have been done due to the use of a placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up: samples unavailable from 24.7% (143/580 women; 63/294 (21.4%) in the zinc group and 80/286 (28%) in the placebo group At 5 years of age, results were available for 355/580 children (61%)
Selective reporting (reporting bias)	Unclear risk	Not all outcomes specified in the review, or expected, were reported in the trial
Other bias	Low risk	No apparent source of other bias.

BMI: body mass index
dl: decilitre
g: gram
GI: gastrointestinal
IU: international units
kJ: kilojoule
L: litre
LMP: last menstrual period
mg: milligram
RCT: randomised controlled trial
RDA: recommended daily allowance
RR: risk ratio
SD: standard deviation
µg: micrograms
µmol: micromoles

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

Study	Reason for exclusion
An 2001	Not truly randomised - allocation was by order of hospital visits
Appelbaum 1979	Only outcome is zinc level in amniotic fluid.
Christian 2001	Women had night blindness: no prespecified outcomes reported
Fawzi 2005	Population was not women in a normal state of health (women with HIV)
France 2004	Compared micronutrients (including zinc) with placebo.

(Continued)

Hambidge 1983	No mention of randomisation, or method of allocating women to zinc or no-zinc groups
India 1993	Large discrepancies in numbers of participants and losses to follow-up
Kynast 1986	Not truly randomised - allocation was by a form of alternation
Mahmoudian 2005	Different population and not relevant outcomes.
Makola 2003	Some women with gestation greater than 26 weeks; micronutrients versus placebo
Nishiyama 1999	Not a randomised controlled trial - mothers chose 1 of 3 intervention groups
Nogueira 2003	No mention of randomisation; serum zinc levels only outcome.
Van Vliet 2001	Different intervention.
Villamor 2006	Different population.
Yalda 2010	Different population and not relevant outcomes.

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

Zahiri 2010

Trial name or title	Assessment of the effect of zinc supplementation on adverse outcomes of pregnancy
Methods	Randomised controlled trial.
Participants	Inclusion criteria: gestational age of 12-16 weeks based on reliable LMP or first trimester ultrasound, lack of history of high-risk pregnancy, lack of chronic underlying diseases (such as heart disease, HTN, DM). Exclusion criteria: lack of complete treatment or lack of follow-up
Interventions	Zinc 30 mg from 12th week of gestation every other day in the intervention group and no zinc is supplemented in the control group
Outcomes	Gestation, birthweight and other pregnancy and neonatal clinical outcomes
Starting date	March 2009.
Contact information	Dr Ziba Zahiri (drzibazahiri@gums.ac.ir).
Notes	

DM: diabetes mellitus
HTN: hypertension

LMP: last menstrual period

DATA AND ANALYSES

Comparison 1. Zinc supplementation versus no zinc (with or without placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Preterm birth	16	7637	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.76, 0.97]
1.1 Low zinc or nutrition	14	7099	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.77, 0.98]
1.2 Normal zinc or nutrition	2	538	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.31, 1.32]
2 Stillbirth or neonatal death	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Low zinc or nutrition: stillbirth or neonatal death	4	1364	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.83, 2.98]
2.2 Low zinc or nutrition: stillbirth or deaths in first 7 days	1	1555	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.71, 1.51]
2.3 Low zinc or nutrition: deaths from 0 to 28 days	1	1498	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.68, 1.71]
2.4 Normal zinc or nutrition: stillbirth or neonatal death	3	683	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.24, 3.65]
3 Birthweight	16	5780	Mean Difference (IV, Fixed, 95% CI)	-9.48 [-34.28, 15.33]
3.1 Low zinc or nutrition	13	5103	Mean Difference (IV, Fixed, 95% CI)	-9.87 [-35.70, 15.96]
3.2 Normal zinc or nutrition	3	677	Mean Difference (IV, Fixed, 95% CI)	-4.78 [-93.67, 84.11]
4 Small-for-gestational age	8	4252	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.94, 1.11]
4.1 Low zinc or nutrition	7	4200	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.12]
4.2 Normal zinc or nutrition	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.05, 1.10]
5 Low birthweight	14	5643	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.78, 1.12]
5.1 Low zinc or nutrition	11	4964	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.75, 1.14]
5.2 Normal zinc or nutrition	3	679	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.58, 1.36]
6 Antepartum haemorrhage	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Second trimester	1	1206	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.57, 4.45]
6.2 Third trimester	1	1206	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.39, 2.33]
7 Pregnancy hypertension or pre-eclampsia	7	2975	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.64, 1.08]
8 Prelabour rupture of membranes	2	1691	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.78, 1.11]
9 Post-term birth	3	1554	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.74, 1.60]
10 Induction of labour	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.10, 0.73]
11 Any maternal infection	3	1185	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.74, 1.53]
12 Meconium in liquor	2	1385	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.86, 1.56]
13 Caesarean section	6	2164	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.58, 1.53]
14 Instrumental vaginal birth	1	1206	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.79, 1.59]
15 Retention of placenta	1	179	Risk Ratio (M-H, Fixed, 95% CI)	6.62 [0.83, 52.71]
16 Postpartum haemorrhage	3	718	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.78, 2.26]
17 Smell dysfunction	1	170	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.55, 1.86]
18 Taste dysfunction	1	170	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.36, 1.50]
19 Fetal heart rate (beats/minute)	1	176	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-3.31, 0.91]

20 Fetal heart rate variability (beats/minute)	1	176	Mean Difference (IV, Fixed, 95% CI)	0.60 [0.04, 1.16]
21 Number of fetal accelerations	1	176	Mean Difference (IV, Fixed, 95% CI)	1.9 [0.91, 2.89]
22 Number of fetal movement bouts	1	176	Mean Difference (IV, Fixed, 95% CI)	1.70 [-2.53, 5.93]
23 Fetal activity level	1	176	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-2.66, 2.06]
24 Fetal movement amplitude	1	176	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.79, 1.19]
25 Gestational age at birth	7	2857	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.07, 0.22]
26 High birthweight	5	2857	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.84, 1.18]
27 Five-minute Apgar score less than 5	2	1692	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.26, 4.03]
28 Infant head circumference (cm)	7	3991	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.17, 0.11]
29 Blue or floppy (neonatal hypotia)	1	179	Risk Ratio (M-H, Fixed, 95% CI)	5.67 [0.70, 46.18]
30 Neonatal sepsis	2	736	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.03, 1.01]
31 Neonatal jaundice	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.20, 4.56]
32 Respiratory distress syndrome	2	1136	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.40, 1.14]
33 Neonatal intraventricular haemorrhage	1	580	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.14, 6.86]
34 Necrotising enterocolitis	1	580	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.18, 21.34]
35 Neonatal hospital stay	1	580	Mean Difference (IV, Fixed, 95% CI)	-1.1 [-2.39, 0.19]
36 Congenital malformation	6	1240	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.33, 1.34]
37 Diarrhoea (episodes/infant over 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
37.1 Acute diarrhoea	1	410	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.79, -0.01]
37.2 Persistent diarrhoea	1	410	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.13, 0.13]
38 Dysentery (episode/infant over 6 months)	1	410	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.12, 4.66]
39 Cough (episodes/infant over 6 months)	1	410	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.56, 0.16]
40 Acute lower respiratory infection (episodes/infant over 6 months)	1	410	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.34, 0.14]
41 Impetigo (episodes/infant over 6 months)	1	410	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.44, -0.16]
42 Infant weight-for-age (Z-score)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
42.1 Z-score at 6 months	2	304	Mean Difference (IV, Random, 95% CI)	0.20 [-0.19, 0.59]
42.2 Z-score at 12 months	1	168	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.70, -0.10]
43 Infant weight-for-height (Z-score)	1	136	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.33, 0.23]
44 Infant mid-upper arm circumference (mm)	3	1844	Mean Difference (IV, Fixed, 95% CI)	0.74 [-0.17, 1.65]
45 Infant mental development index	1	168	Mean Difference (IV, Fixed, 95% CI)	-3.30 [-6.51, -0.09]
46 Infant psychomotor development index	1	168	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-11.92, -2.08]
47 Infant approach	1	168	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.38, 0.58]
48 Infant emotional tone	1	168	Mean Difference (IV, Fixed, 95% CI)	-0.65 [-1.13, -0.17]
49 Infant activity	1	168	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.43, 0.23]
50 Infant co-operation	1	168	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.16, -0.04]
51 Infant vocalisation	1	168	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.54, 0.38]

52 Differential abilities score at 5 years	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
52.1 Non-verbal ability	1	355	Mean Difference (IV, Fixed, 95% CI)	-2.40 [-5.70, 0.90]
52.2 Verbal ability	1	355	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-2.56, 1.96]
52.3 General conceptual ability, IQ	1	355	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-3.74, 1.54]
53 Visual sequential memory score	1	355	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-2.24, 0.64]
54 Auditory sequential memory score	1	355	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.65, 1.85]
55 Knox cube score	1	355	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.19, 0.39]
56 Gross motor scale score	1	355	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-4.79, 0.79]
57 Grooved pegboard score	1	355	Mean Difference (IV, Fixed, 95% CI)	Subtotals only
57.1 Dominant hand	1	355	Mean Difference (IV, Fixed, 95% CI)	2.5 [-1.26, 6.26]
57.2 Non-dominant hand	1	355	Mean Difference (IV, Fixed, 95% CI)	1.20 [-2.71, 5.11]
58 Intelligence quotient of infants at 54 months	1	181	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-3.33, 2.53]

Analysis 1.1. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 1 Preterm birth.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 1 Preterm birth

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low zinc or nutrition					
Bangladesh 2000	341/194	341/216		6.5 %	1.11 [0.72, 1.72]
Chile 2001	14/249	30/258		6.0 %	0.48 [0.26, 0.89]
China 2001	101/116	7/40		2.1 %	0.49 [0.20, 1.21]
Denmark 1996	33/585	49/621		9.7 %	0.71 [0.47, 1.10]
Ghana 2009	40/272	39/271		7.9 %	1.02 [0.68, 1.54]
Indonesia 2001	5/92	6/87		1.3 %	0.79 [0.25, 2.49]
Iran 2010	9/42	14/42		2.8 %	0.64 [0.31, 1.32]
Nepal 2003	127/628	137/593		28.7 %	0.88 [0.71, 1.08]
Pakistan 2005	22/121	10/121		2.0 %	2.20 [1.09, 4.45]
Peru 1999	29/521	30/495		6.3 %	0.92 [0.56, 1.51]
Peru 2004	7/109	5/113		1.0 %	1.45 [0.47, 4.44]

0.1 0.2 0.5 1 2 5 10

Favours zinc Favours control

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Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
USA 1983	5/87	4/90		0.8 %	1.29 [0.36, 4.66]
USA 1989	30/268	68/288		13.3 %	0.79 [0.57, 1.09]
USA 1995	30/294	38/286		7.8 %	0.77 [0.49, 1.20]
Subtotal (95% CI)	**3578**	**3521**		**96.3 %**	**0.87 [0.77, 0.98]**
Total events: 415 (Zinc), 471 (Control)					
Heterogeneity: Chi² = 16.99, df = 13 (P = 0.20); I² =23%					
Test for overall effect: Z = 2.32 (P = 0.020)					
2 Normal zinc or nutrition					
UK 1989	10/243	17/243		3.5 %	0.59 [0.27, 1.26]
UK 1991a	2/30	1/22		0.2 %	1.47 [0.14, 15.17]
Subtotal (95% CI)	**273**	**265**		**3.7 %**	**0.64 [0.31, 1.32]**
Total events: 12 (Zinc), 18 (Control)					
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² =0.0%					
Test for overall effect: Z = 1.20 (P = 0.23)					
Total (95% CI)	**3851**	**3786**		**100.0 %**	**0.86 [0.76, 0.97]**
Total events: 427 (Zinc), 489 (Control)					
Heterogeneity: Chi² = 18.15, df = 15 (P = 0.25); I² =17%					
Test for overall effect: Z = 2.51 (P = 0.012)					
Test for subgroup differences: Chi² = 0.64, df = 1 (P = 0.42), I² =0.0%					

0.1 0.2 0.5 1 2 5 10

Favours zinc Favours control

Analysis 1.2. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 2 Stillbirth or neonatal death.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 2 Stillbirth or neonatal death

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Low zinc or nutrition: stillbirth or neonatal death				
Bangladesh 2000	12/214	7/232		1.86 [0.75, 4.63]
China 2001	0/116	0/40		0.0 [0.0, 0.0]
Indonesia 2001	5/93	1/89		4.78 [0.57, 40.15]
USA 1995	6/294	7/286		0.83 [0.28, 2.45]
Subtotal (95% CI)	**717**	**647**		**1.57 [0.83, 2.98]**
Total events: 23 (Zinc), 15 (Control)				
Heterogeneity: Chi² = 2.51, df = 2 (P = 0.29); I² =20%				
Test for overall effect: Z = 1.38 (P = 0.17)				
2 Low zinc or nutrition: stillbirth or deaths in first 7 days				
Nepal 2003	52/804	47/751		1.03 [0.71, 1.51]
Subtotal (95% CI)	**804**	**751**		**1.03 [0.71, 1.51]**
Total events: 52 (Zinc), 47 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.17 (P = 0.87)				
3 Low zinc or nutrition: deaths from 0 to 28 days				
Nepal 2003	37/775	32/723		1.08 [0.68, 1.71]
Subtotal (95% CI)	**775**	**723**		**1.08 [0.68, 1.71]**
Total events: 37 (Zinc), 32 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.32 (P = 0.75)				
4 Normal zinc or nutrition: stillbirth or neonatal death				
UK 1989	3/248	3/249		1.00 [0.20, 4.93]
UK 1991a	1/30	1/22		0.73 [0.05, 11.10]
UK 1991b	0/72	0/62		0.0 [0.0, 0.0]
Subtotal (95% CI)	**350**	**333**		**0.93 [0.24, 3.65]**
Total events: 4 (Zinc), 4 (Control)				
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² =0.0%				
Test for overall effect: Z = 0.11 (P = 0.92)				

0.01 0.1 1 10 100

Favours zinc Favours control

Analysis 1.3. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 3 Birthweight.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 3 Birthweight

Study or subgroup	Zinc N	Zinc Mean(SD)	Control N	Control Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Low zinc or nutrition							
Bangladesh 2000	194	2513 (390)	216	2554 (393)		10.7 %	-41.00 [-116.89, 34.89]
Chile 2001	249	3319 (460)	258	3250 (514)		8.5 %	69.00 [-15.84, 153.84]
Ghana 2009	272	3105 (490)	271	3120 (486)		9.1 %	-15.00 [-97.09, 67.09]
Indonesia 2001	84	3200 (500)	80	3150 (400)		3.2 %	50.00 [-88.26, 188.26]
Iran 2010	42	2961 (468)	42	2819 (609)		1.1 %	142.00 [-90.28, 374.28]
Nepal 2003	553	2598 (428)	522	2652 (429)		23.4 %	-54.00 [-105.25, -2.75]
Pakistan 2005	121	3023 (456)	121	3061 (444)		4.8 %	-38.00 [-151.40, 75.40]
Peru 1999	488	3267 (461)	469	3300 (498)		16.6 %	-33.00 [-93.86, 27.86]
Peru 2004	94	3351 (427)	101	3319 (389)		4.7 %	32.00 [-82.92, 146.92]
S Africa 1985	32	3088 (277)	33	3171 (483)		1.4 %	-83.00 [-293.28, 127.28]
USA 1983	86	3413 (574)	89	3373 (521)		2.3 %	40.00 [-122.58, 202.58]
USA 1985	55	3352 (430)	51	3338 (592)		1.6 %	14.00 [-184.27, 212.27]
USA 1995	294	3214 (609)	286	3088 (728)		4.7 %	126.00 [12.13, 239.87]
Subtotal (95% CI)	**2564**		**2539**			**92.2 %**	**-9.87 [-35.70, 15.96]**
Heterogeneity: Chi² = 16.84, df = 12 (P = 0.16); I² =29%							
Test for overall effect: Z = 0.75 (P = 0.45)							
2 Normal zinc or nutrition							
UK 1989	247	3291 (581)	244	3319 (531)		6.3 %	-28.00 [-126.43, 70.43]
UK 1991a	30	2990 (542)	22	2820 (600)		0.6 %	170.00 [-146.54, 486.54]
UK 1991b	72	3264 (722)	62	3220 (871)		0.8 %	44.00 [-229.53, 317.53]
Subtotal (95% CI)	**349**		**328**			**7.8 %**	**-4.78 [-93.67, 84.11]**
Heterogeneity: Chi² = 1.51, df = 2 (P = 0.47); I² =0.0%							
Test for overall effect: Z = 0.11 (P = 0.92)							
Total (95% CI)	**2913**		**2867**			**100.0 %**	**-9.48 [-34.28, 15.33]**
Heterogeneity: Chi² = 18.36, df = 15 (P = 0.24); I² =18%							
Test for overall effect: Z = 0.75 (P = 0.45)							
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² =0.0%							

-1000 -500 0 500 1000

Favours control Favours zinc

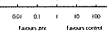
Analysis 1.4. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 4 Small-for-gestational age.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 4 Small-for-gestational age

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low zinc or nutrition					
Bangladesh 2000	145/194	161/216		27.3 %	1.00 [0.90, 1.12]
China 2001	7/116	6/40		1.6 %	0.40 [0.14, 1.13]
Denmark 1996	37/585	38/621		6.6 %	1.03 [0.67, 1.60]
Ghana 2009	14/272	18/271		3.2 %	0.77 [0.39, 1.53]
Iran 2010	0/42	1/42		0.3 %	0.33 [0.01, 7.96]
Nepal 2003	354/628	306/593		54.4 %	1.09 [0.98, 1.21]
USA 1995	16/294	18/286		3.3 %	0.86 [0.45, 1.66]
Subtotal (95% CI)	**2131**	**2069**		**98.8 %**	**1.03 [0.95, 1.12]**
Total events: 573 (Zinc), 548 (Control)					
Heterogeneity: Chi² = 6.07, df = 6 (P = 0.42); I² =1%					
Test for overall effect: Z = 0.78 (P = 0.44)					
2 Normal zinc or nutrition					
UK 1991a	2/30	6/22		1.2 %	0.24 [0.05, 1.10]
Subtotal (95% CI)	**30**	**22**		**1.2 %**	**0.24 [0.05, 1.10]**
Total events: 2 (Zinc), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.84 (P = 0.066)					
Total (95% CI)	**2161**	**2091**		**100.0 %**	**1.02 [0.94, 1.11]**
Total events: 575 (Zinc), 554 (Control)					
Heterogeneity: Chi² = 9.68, df = 7 (P = 0.21); I² =28%					
Test for overall effect: Z = 0.55 (P = 0.58)					
Test for subgroup differences: Chi² = 3.52, df = 1 (P = 0.06), I² =72%					



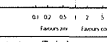
Analysis 1.5. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 5 Low birthweight.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 5 Low birthweight

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low zinc or nutrition					
Bangladesh 2000	89/194	87/216		19.2 %	1.14 [0.91, 1.42]
Chile 2001	6/249	16/258		3.3 %	0.39 [0.15, 0.98]
China 2001	9/116	9/40		3.8 %	0.34 [0.15, 0.81]
Ghana 2009	26/272	21/271		7.6 %	1.23 [0.71, 2.14]
Indonesia 2001	10/84	9/80		3.8 %	1.06 [0.45, 2.47]
Iran 2010	4/42	8/42		2.3 %	0.50 [0.16, 1.53]
Nepal 2003	332/588	287/556		25.0 %	1.09 [0.98, 1.22]
Pakistan 2005	15/121	11/121		4.8 %	1.36 [0.65, 2.85]
Peru 1999	17/488	17/469		5.8 %	0.96 [0.50, 1.86]
USA 1983	4/87	4/90		1.6 %	1.03 [0.27, 4.01]
USA 1995	23/294	26/286		8.8 %	0.62 [0.38, 1.02]
Subtotal (95% CI)	**2535**	**2429**		**86.1 %**	**0.93 [0.75, 1.14]**
Total events: 535 (Zinc), 505 (Control)					
Heterogeneity: Tau² = 0.04; Chi² = 19.39, df = 10 (P = 0.04); I² =48%					
Test for overall effect: Z = 0.71 (P = 0.48)					
2 Normal zinc or nutrition					
UK 1989	15/247	13/244		5.0 %	1.14 [0.55, 2.34]
UK 1991a	5/30	5/24		2.3 %	0.80 [0.26, 2.45]
UK 1991b	15/72	17/62		6.6 %	0.76 [0.41, 1.39]
Subtotal (95% CI)	**349**	**330**		**13.9 %**	**0.88 [0.58, 1.36]**
Total events: 35 (Zinc), 35 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.74, df = 2 (P = 0.69); I² =0.0%					
Test for overall effect: Z = 0.57 (P = 0.57)					
Total (95% CI)	**2884**	**2759**		**100.0 %**	**0.93 [0.78, 1.12]**
Total events: 570 (Zinc), 540 (Control)					
Heterogeneity: Tau² = 0.03; Chi² = 20.80, df = 13 (P = 0.08); I² =38%					
Test for overall effect: Z = 0.74 (P = 0.46)					
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.84), I² =0.0%					



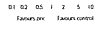
Analysis 1.6. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 6 Antepartum haemorrhage.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 6 Antepartum haemorrhage

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Second trimester					
Denmark 1996	9/585	6/621		100.0 %	1.59 [0.57, 4.45]
Subtotal (95% CI)	**585**	**621**		**100.0 %**	**1.59 [0.57, 4.45]**
Total events: 9 (Zinc), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.89 (P = 0.37)					
2 Third trimester					
Denmark 1996	9/585	10/621		100.0 %	0.96 [0.39, 2.33]
Subtotal (95% CI)	**585**	**621**		**100.0 %**	**0.96 [0.39, 2.33]**
Total events: 9 (Zinc), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.10 (P = 0.92)					



Analysis 1.7. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 7 Pregnancy hypertension or pre-eclampsia.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 7 Pregnancy hypertension or pre-eclampsia

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chile 2001	2/249	2/258		1.8 %	1.04 [0.15, 7.30]
Denmark 1996	20/585	22/621		20.1 %	0.97 [0.53, 1.75]
UK 1989	52/245	50/244		47.1 %	1.04 [0.73, 1.46]
UK 1991a	3/30	3/22		3.3 %	0.73 [0.16, 3.30]
USA 1983	2/87	14/90		12.9 %	0.15 [0.03, 0.63]
USA 1985	4/56	5/51		4.9 %	0.73 [0.21, 2.57]
USA 1995	6/231	10/206		9.9 %	0.54 [0.20, 1.45]
Total (95% CI)	**1483**	**1492**		**100.0 %**	**0.83 [0.64, 1.08]**
Total events: 89 (Zinc), 106 (Control)					
Heterogeneity: Chi² = 8.10, df = 6 (P = 0.23); I² =26%					
Test for overall effect: Z = 1.37 (P = 0.17)					
Test for subgroup differences: Not applicable					

Analysis 1.8. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 8 Prelabour rupture of membranes.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 8 Prelabour rupture of membranes

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Denmark 1996	127/585	145/621		70.5 %	0.93 [0.75, 1.15]
UK 1989	55/242	59/243		29.5 %	0.94 [0.68, 1.29]
Total (95% CI)	**827**	**864**		**100.0 %**	**0.93 [0.78, 1.11]**

Total events: 182 (Zinc), 204 (Control)
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.97); I^2 =0.0%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 9 Post-term birth.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 9 Post-term birth

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Peru 1999	22/521	17/495		1.23 [0.66, 2.29]
UK 1989	28/243	28/243		1.00 [0.61, 1.64]
UK 1991a	0/30	0/22		0.0 [0.0, 0.0]
Total (95% CI)	**794**	**760**		**1.09 [0.74, 1.60]**

Total events: 50 (Zinc), 45 (Control)
Heterogeneity: Chi^2 = 0.26, df = 1 (P = 0.61); I^2 =0.0%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 10 Induction of labour.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 10 Induction of labour

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
UK 1991a	4/30	11/22		100.0 %	0.27 [0.10, 0.73]
Total (95% CI)	**30**	**22**		**100.0 %**	**0.27 [0.10, 0.73]**

Total events: 4 (Zinc), 11 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 2.58 (P = 0.0098)
Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 11 Any maternal infection.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 11 Any maternal infection

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Indonesia 1999	13/249	19/270		36.6 %	0.74 [0.37, 1.47]
Indonesia 2001	1/92	0/87		1.0 %	2.84 [0.12, 68.76]
UK 1989	38/244	31/243		62.4 %	1.22 [0.79, 1.90]
Total (95% CI)	**585**	**600**		**100.0 %**	**1.06 [0.74, 1.53]**

Total events: 52 (Zinc), 50 (Control)
Heterogeneity: Chi^2 = 1.81, df = 2 (P = 0.41); I^2 =0.0%
Test for overall effect: Z = 0.22 (P = 0.75)
Test for subgroup differences: Not applicable

Analysis 1.12. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 12 Meconium in liquor.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 12 Meconium in liquor

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Denmark 1996	78/585	72/621		98.5 %	1.15 [0.85, 1.55]
Indonesia 2001	2/92	1/87		1.5 %	1.89 [0.17, 20.93]
Total (95% CI)	**677**	**708**		**100.0 %**	**1.16 [0.86, 1.56]**

Total events: 80 (Zinc), 73 (Control)
Heterogeneity: Chi^2 = 0.16, df = 1 (P = 0.68); I^2 =0.0%
Test for overall effect: Z = 0.98 (P = 0.33)
Test for subgroup differences: Not applicable

Analysis 1.13. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 13 Caesarean section.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 13 Caesarean section

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ohma 2001	39/116	8/40		18.3 %	1.68 [0.86, 3.29]
Denmark 1996	36/585	50/621		23.4 %	0.76 [0.51, 1.16]
Indonesia 2001	1/92	1/87		2.8 %	0.95 [0.06, 14.89]
Iran 2010	28/42	26/42		26.2 %	1.46 [1.13, 1.89]
UK 1989	24/244	32/243		21.7 %	0.75 [0.45, 1.23]
UK 1991a	2/30	7/22		7.8 %	0.21 [0.05, 0.91]
Total (95% CI)	**1109**	**1055**		**100.0 %**	**0.95 [0.58, 1.53]**

Total events: 140 (Zinc), 124 (Control)
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 19.46$, df = 5 (P = 0.002); $I^2 = 74\%$
Test for overall effect: Z = 0.22 (P = 0.82)
Test for subgroup differences: Not applicable

Analysis 1.14. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 14 Instrumental vaginal birth.

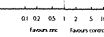
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 14 Instrumental vaginal birth

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Denmark 1996	58/585	55/621		100.0 %	1.12 [0.79, 1.59]
Total (95% CI)	**585**	**621**		**100.0 %**	**1.12 [0.79, 1.59]**

Total events: 58 (Zinc), 55 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 15 Retention of placenta.

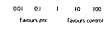
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 15 Retention of placenta

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Indonesia 2001	7/92	1/87		100.0 %	6.62 [0.83, 52.71]
Total (95% CI)	**92**	**87**		**100.0 %**	**6.62 [0.83, 52.71]**

Total events: 7 (Zinc), 1 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.79 (P = 0.074)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 16 Postpartum haemorrhage.

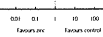
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 16 Postpartum haemorrhage

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Indonesia 2001	3/92	5/87		23.0 %	0.57 [0.14, 2.30]
UK 1989	26/244	16/243		71.8 %	1.62 [0.89, 2.94]
UK 1991a	1/30	1/22		5.2 %	0.73 [0.05, 11.10]
Total (95% CI)	**366**	**352**		**100.0 %**	**1.33 [0.78, 2.26]**

Total events: 30 (Zinc), 22 (Control)
Heterogeneity: $Chi^2 = 2.02$, df = 2 (P = 0.36); $I^2 = 1\%$
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable



Analysis 1.17. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 17 Smell dysfunction.

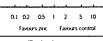
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 17 Smell dysfunction

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
USA 1983	16/82	17/88		100.0 %	1.01 [0.55, 1.86]
Total (95% CI)	**82**	**88**		**100.0 %**	**1.01 [0.55, 1.86]**

Total events: 16 (Zinc), 17 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable



Analysis 1.18. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 18 Taste dysfunction.

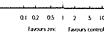
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 18 Taste dysfunction

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
USA 1983	11/82	16/88		100.0 %	0.74 [0.36, 1.50]
Total (95% CI)	**82**	**88**		**100.0 %**	**0.74 [0.36, 1.50]**

Total events: 11 (Zinc), 16 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.84 (P = 0.40)
Test for subgroup differences: Not applicable



Analysis 1.19. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 19 Fetal heart rate (beats/minute).

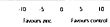
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 19 Fetal heart rate (beats/minute)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IVFixed95% CI	Weight	Mean Difference IVFixed95% CI
Peru 2004	85	142 (7)	91	143.2 (7.3)		100.0 %	-1.20 [-3.31, 0.91]
Total (95% CI)	**85**		**91**			**100.0 %**	**-1.20 [-3.31, 0.91]**

Heterogeneity: not applicable
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 20 Fetal heart rate variability (beats/minute).

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 20 Fetal heart rate variability (beats/minute)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IVFixed95% CI	Weight	Mean Difference IVFixed95% CI
Peru 2004	85	7.3 (2)	91	6.7 (1.8)		100.0 %	0.60 [0.04, 1.16]
Total (95% CI)	**85**		**91**			**100.0 %**	**0.60 [0.04, 1.16]**

Heterogeneity: not applicable
Test for overall effect: Z = 2.09 (P = 0.037)
Test for subgroup differences: Not applicable

Analysis 1.21. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 21 Number of fetal accelerations.

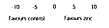
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 21 Number of fetal accelerations

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IVFixed95% CI	Weight	Mean Difference IVFixed95% CI
Peru 2004	85	5 (3.9)	91	3.1 (2.6)		100.0 %	1.90 [0.91, 2.89]
Total (95% CI)	**85**		**91**			**100.0 %**	**1.90 [0.91, 2.89]**

Heterogeneity: not applicable
Test for overall effect: Z = 3.78 (P = 0.00016)
Test for subgroup differences: Not applicable



Analysis 1.22. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 22 Number of fetal movement bouts.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 22 Number of fetal movement bouts

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IVFixed95% CI	Weight	Mean Difference IVFixed95% CI
Peru 2004	85	50.2 (14.4)	91	48.5 (14.2)		100.0 %	1.70 [-2.53, 5.93]
Total (95% CI)	**85**		**91**			**100.0 %**	**1.70 [-2.53, 5.93]**

Heterogeneity: not applicable
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable

Analysis 1.23. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 23 Fetal activity level.

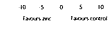
Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 23 Fetal activity level

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IVFixed95% CI	Weight	Mean Difference IVFixed95% CI
Peru 2004	85	12.9 (7.8)	91	13.2 (8.2)		100.0 %	-0.30 [-2.66, 2.06]
Total (95% CI)	**85**		**91**			**100.0 %**	**-0.30 [-2.66, 2.06]**

Heterogeneity: not applicable
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



Analysis 1.24. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 24 Fetal movement amplitude.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 24 Fetal movement amplitude

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IVFixed95% CI	Weight	Mean Difference IVFixed95% CI
Peru 2004	85	27.3 (3.1)	91	27.1 (3.6)		100.0 %	0.20 [-0.79, 1.19]
Total (95% CI)	**85**		**91**			**100.0 %**	**0.20 [-0.79, 1.19]**

Heterogeneity: not applicable
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable

Analysis 1.25. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 25 Gestational age at birth.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 25 Gestational age at birth

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IVFixed95% CI	Weight	Mean Difference IVFixed95% CI
Bangladesh 2000	194	38.8 (2.4)	216	38.9 (2.1)		11.2 %	-0.10 [-0.54, 0.34]
Chile 2001	249	38.6 (1.68)	258	38.4 (2.02)		20.7 %	0.20 [-0.12, 0.52]
Iran 2010	42	37.1 (2.4)	42	36.7 (2.4)		2.1 %	0.40 [-0.63, 1.43]
Peru 1999	521	39.4 (2.2)	495	39.5 (2)		32.4 %	-0.10 [-0.36, 0.16]
Peru 2004	94	39.8 (1.1)	101	39.7 (1)		24.7 %	0.10 [-0.20, 0.40]
S Africa 1985	32	39.4 (2.2)	33	38.9 (3.5)		1.1 %	0.50 [-0.92, 1.92]
USA 1995	294	38.8 (2.9)	286	38.3 (3.5)		7.9 %	0.50 [-0.02, 1.02]
Total (95% CI)	**1426**		**1431**			**100.0 %**	**0.08 [-0.07, 0.22]**

Heterogeneity: Chi² = 6.24, df = 6 (P = 0.40); I² = 4%
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable

Analysis 1.26. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 26 High birthweight.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 26 High birthweight

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Denmark 1996	73/585	71/621		33.9 %	1.09 [0.80, 1.48]
Peru 1999	19/488	28/469		14.1 %	0.65 [0.37, 1.15]
UK 1989	92/243	96/243		47.2 %	0.96 [0.77, 1.20]
UK 1991a	3/30	3/24		1.6 %	0.80 [0.18, 3.61]
UK 1991b	15/72	6/62		3.2 %	2.15 [0.89, 5.21]
Total (95% CI)	**1418**	**1419**		**100.0 %**	**1.00 [0.84, 1.18]**

Total events: 202 (Zinc), 204 (Control)
Heterogeneity: Chi² = 5.59, df = 4 (P = 0.23); I² =28%
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours zinc Favours control

Analysis 1.27. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 27 Five-minute Apgar score less than 5.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 27 Five-minute Apgar score less than 5

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Denmark 1996	1/585	1/621		24.4 %	1.06 [0.07, 16.93]
UK 1989	3/243	3/243		75.6 %	1.00 [0.20, 4.91]
Total (95% CI)	**828**	**864**		**100.0 %**	**1.02 [0.26, 4.03]**

Total events: 4 (Zinc), 4 (Control)
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.97); I² =0.0%
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours zinc Favours control

Analysis 1.28. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 28 Infant head circumference (cm).

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 28 Infant head circumference (cm)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bangladesh 2000	194	32.6 (1.4)	216	32.7 (1.5)		13.9 %	-0.10 [-0.38, 0.18]
Chile 2001	249	33.7 (1.2)	258	33.9 (1.5)		16.8 %	-0.20 [-0.44, 0.04]
Nepal 2003	590	32.6 (1.46)	557	32.7 (1.44)		22.4 %	-0.10 [-0.27, 0.07]
Pakistan 2005	121	34.96 (2.1)	121	34.99 (2)		5.8 %	-0.03 [-0.55, 0.49]
Peru 1999	475	34.2 (1.5)	443	34.3 (1.4)		20.7 %	-0.10 [-0.29, 0.09]
Peru 2004	91	34 (1.35)	96	33.8 (1.3)		9.3 %	0.20 [-0.18, 0.58]
USA 1995	294	34.2 (2)	286	33.8 (2.1)		11.2 %	0.40 [0.07, 0.73]
Total (95% CI)	**2014**		**1977**			**100.0 %**	**-0.03 [-0.17, 0.11]**

Heterogeneity: Tau² = 0.01; Chi² = 10.91, df = 6 (P = 0.09); I² =45%
Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Not applicable

-10 -5 0 5 10
Favours control Favours zinc

Analysis 1.29. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 29 Blue or floppy (neonatal hypoxia).

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 29 Blue or floppy (neonatal hypoxia)

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Indonesia 2001	6/92	1/87		100.0 %	5.67 [0.70, 46.18]
Total (95% CI)	**92**	**87**		**100.0 %**	**5.67 [0.70, 46.18]**

Total events: 6 (Zinc), 1 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 1.62 (P = 0.10)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours zinc Favours control

Analysis 1.30. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 30 Neonatal sepsis.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 30 Neonatal sepsis

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
China 2001	0/116	1/40		30.5 %	0.12 [0.00, 2.81]
USA 1995	1/294	5/286		69.5 %	0.19 [0.02, 1.66]
Total (95% CI)	**410**	**326**		**100.0 %**	**0.17 [0.03, 1.01]**

Total events: 1 (Zinc), 6 (Control)
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² =0.0%
Test for overall effect: Z = 1.95 (P = 0.052)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours zinc Favours control

Analysis 1.31. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 31 Neonatal jaundice.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 31 Neonatal jaundice

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Indonesia 2001	3/92	3/87		100.0 %	0.95 [0.20, 4.56]
Total (95% CI)	**92**	**87**		**100.0 %**	**0.95 [0.20, 4.56]**

Total events: 3 (Zinc), 3 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.07 (P = 0.94)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours zinc Favours control

Analysis 1.32. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 32 Respiratory distress syndrome.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 32 Respiratory distress syndrome

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
USA 1989	16/268	26/288		75.6 %	0.66 [0.36, 1.21]
USA 1995	6/294	8/286		24.4 %	0.73 [0.26, 2.08]
Total (95% CI)	**562**	**574**		**100.0 %**	**0.68 [0.40, 1.14]**

Total events: 22 (Zinc), 34 (Control)
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.87); I^2 =0.0%
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours zinc Favours control

Analysis 1.33. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 33 Neonatal intraventricular haemorrhage.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 33 Neonatal intraventricular haemorrhage

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
USA 1995	2/294	2/286		100.0 %	0.97 [0.14, 6.86]
Total (95% CI)	**294**	**286**		**100.0 %**	**0.97 [0.14, 6.86]**

Total events: 2 (Zinc), 2 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.03 (P = 0.98)
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10
Favours zinc Favours control

Analysis 1.34. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 34 Necrotising enterocolitis.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 34 Necrotising enterocolitis

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
USA 1995	2/294	1/286		100.0 %	1.95 [0.18, 21.34]
Total (95% CI)	**294**	**286**		**100.0 %**	**1.95 [0.18, 21.34]**

Total events: 2 (Zinc), 1 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours zinc Favours control

Analysis 1.35. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 35 Neonatal hospital stay.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 35 Neonatal hospital stay

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
USA 1995	294	3.6 (5)	286	4.7 (10)		100.0 %	-1.10 [-2.39, 0.19]
Total (95% CI)	**294**		**286**			**100.0 %**	**-1.10 [-2.39, 0.19]**

Heterogeneity: not applicable
Test for overall effect: Z = 1.67 (P = 0.095)
Test for subgroup differences: Not applicable

-10 -5 0 5 10
Favours zinc Favours control

Analysis 1.36. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 36 Congenital malformation.

Review: Zinc supplementation for improving pregnancy and infant outcome

Comparison: 1 Zinc supplementation versus no zinc (with or without placebo)

Outcome: 36 Congenital malformation

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
China 2001	1/116	0/40		1.05 [0.04, 25.30]
Indonesia 2001	2/92	2/87		0.95 [0.14, 6.57]
Peru 2004	4/109	6/113		0.69 [0.20, 2.38]
UK 1989	5/248	8/249		0.63 [0.21, 1.89]
UK 1991a	1/30	2/22		0.37 [0.04, 3.79]
UK 1991b	0/72	0/62		0.0 [0.0, 0.0]
Total (95% CI)	**667**	**573**		**0.67 [0.33, 1.34]**

Total events: 13 (Zinc), 18 (Control)
Heterogeneity: Chi^2 = 0.47, df = 4 (P = 0.98); I^2 =0.0%
Test for overall effect: Z = 1.14 (P = 0.25)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours zinc Favours control