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Zinc supplementation for improving pregnancy and infant outcome (Review)

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[Intervention Review]

Zinc supplementation for improving pregnancy and infant outcome

Erika Ota[1], Rintaro Mori[1], Philippa Middleton[2], Ruoyan Tobe-Gai[3], Kassam Mahomed[4], Celine Miyazaki[5], Zulfiqar A Bhutta[6]

[1]Department of Health Policy, National Center for Child Health and Development, Tokyo, Japan. [2]Women's and Children's Research Institute, The University of Adelaide, Adelaide, Australia. [3]School of Public Health, Shandong University, Jinan, China. [4]Ipswich Hospital, Ipswich, Australia. [5]Department of Health Policy, National Research Institute for Child Health and Development, Setagaya, Japan. [6]Center for Global Child Health, Hospital for Sick Children, Toronto, Canada

Contact address: Rintaro Mori, Department of Health Policy, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo, 157-8535, Japan. rintaromori@gmail.com.

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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 (31 October 2014) and reference lists of retrieved studies.

Selection criteria

Randomised 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. The quality of the evidence was assessed using GRADE.

Main results

We included 21 randomised controlled trials (RCTs) reported in 54 papers involving over 17,000 women and their babies. One trial did not contribute data. Trials were generally at low risk of bias. Zinc supplementation resulted in a small 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 clear 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. The GRADE quality of the evidence was moderate for preterm birth, small-for-gestational age, and low birthweight, and low for stillbirth or neonatal death and birthweight.

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 21 randomised controlled trials, involving over 17,000 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. One trial did not contribute data. The overall risk of bias was unclear in half of the studies. 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.

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

Zinc supplementation versus no zinc (with or without placebo) for improving pregnancy and infant outcome

Population: Normal pregnant women with no systemic illness
Settings: Bangladesh, Chile, China, Denmark, Egypt, Ghana, Indonesia, Iran, Nepal, Pakistan, Peru, South Africa, UK, USA
Intervention: Zinc supplementation versus no zinc (with or without placebo)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Zinc supplementation versus no zinc (with or without placebo)				
Preterm birth	Study population		RR 0.86 (0.76 to 0.97)	7637 (16 studies)	⊕⊕⊕◯ **moderate**[1]	
	129 per 1000	111 per 1000 (98 to 125)				
	Moderate					
	100 per 1000	86 per 1000 (76 to 97)				
Stillbirth or neonatal death	Study population		RR 1.12 (0.86 to 1.46)	5100 (8 studies)	⊕⊕◯◯ **low**[1,2]	
	40 per 1000	45 per 1000 (34 to 58)				
	Moderate					
	25 per 1000	28 per 1000 (22 to 37)				

Birthweight		The mean birthweight in the intervention groups was 0.9**lower** (22.2 lower to 24.0 higher)		6757 (17 studies)	⊕⊕◯◯ **low**[1,2]
Small-for-gestational age	**Study population**		**RR 1.02** (0.94 to 1.11)	4252 (8 studies)	⊕⊕⊕◯ **moderate**[1]
	265 per 1000	**270 per 1000** (249 to 294)			
	Moderate				
	108 per 1000	**110 per 1000** (102 to 120)			
Low birthweight	**Study population**		**RR 0.93** (0.78 to 1.12)	5643 (14 studies)	⊕⊕⊕◯ **moderate**[1]
	196 per 1000	**182 per 1000** (153 to 219)			
	Moderate				
	119 per 1000	**111 per 1000** (93 to 133)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

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

[1] Most studies contributing data had design limitations.

[2] Wide confidence interval crossing the line of no effect.

BACKGROUND

Description of the condition

The overall nutritional status of the mother during pregnancy is a significant contributor to both maternal and perinatal mortality and morbidity (Koblinsky 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.

Description of the intervention

Zinc is known to play an important role in many biological functions, including protein synthesis and nucleic acid metabolism (Valee 1993). Although severe zinc deficiency is now considered rare, mild to moderate deficiency may be relatively common throughout the world (Sanstead 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 (Sanstead 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).

How the intervention might work

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 (Kiilholma 1984a; Kiilholma 1984b). Kirksey 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 well being too.

Why it is important to do this review

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 well being.

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 neuro behavioural 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, Kirskey 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 well being.

OBJECTIVES

1. To compare the effects on maternal, fetal, neonatal and infant outcomes in healthy pregnant women receiving zinc supplementation, no zinc supplementation, or placebo.

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

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

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 October 2014).
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (OVID);
3. weekly searches of Embase (OVID);
4. 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, Embase and CINAHL, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

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

Searching other resources

We searched the references lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

For methods used in the previous version of this review, see Mori 2012.

For this update, the following methods, which are based on a standard template used by the Cochrane Pregnancy and Childbirth Group, were used to assess the eight new reports that were identified as a result of the updated search.

Selection of studies

Two review authors Erika Ota (EO), and Celine Miyazaki (CM) independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreements through discussion.

Data extraction and management

We designed a form to extract data. For eligible studies, EO and CM extracted the data using the agreed form. We planned to resolve any discrepancies through discussion or, if required, we would have consulted Rintaro Mori (RM). We entered data into Review Manager software (RevMan 2014) 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

EO and CM 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.

For this update the quality of the evidence was assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following primary outcomes for the main comparisons.

1. Preterm labour or birth (less than 37 weeks), or both.
2. Stillbirth or neonatal death.
3. Birthweight.
4. Small-for-gestational age (birthweight less than 10th centile for gestational age).
5. Low birthweight (less than 2.5 kg).

The GRADEprofiler (GRADE 2014) was used to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

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. If necessary, we planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We planned to include 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. Had we used

ICCs from other sources, we would have reported this and conducted sensitivity analyses to investigate the effect of variation in the ICC. We included one cluster-randomised trial (Nepal 2003) - analyses adjusted for clustering were presented in study reports and so we did not need to perform the above additional calculations for these study results

We synthesised the relevant information from Nepal 2003 and the individually-randomised trials. We considered it reasonable to combine the results from both as 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.

If necessary, we would have acknowledged heterogeneity in the randomisation unit and performed a subgroup analysis to investigate the effects of the randomisation unit.

Cross-over trials were not considered eligible for 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 Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either the Tau^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 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary 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.

Where we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

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

Results of the search

In this update, we found an additional seven reports. We added two reports for one new randomised controlled trial (Egypt 2014) to make a total of 21 included trials. We excluded one new trial

(Naher 2012) and added two new reports each for the included studies Indonesia 1999 (Prawirohartono 2011; Prawirohartono 2013), and Ghana 2009 (Saaka 2009; Saaka 2012).

Included studies

We included 21 RCTs involving over 17,000 women and their babies. *See* table of Characteristics of included studies for details.

Participants and settings

Eighteen studies included women from low- and middle-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 (15/21) compared zinc with placebo (Bangladesh 2000; China 2001; Chile 2001; Denmark 1996; Egypt 2014; Ghana 2009; Iran 2010; Pakistan 2005; S Africa 1985; UK 1989; UK 1991a; USA 1983; USA 1985; USA 1989; USA 1995). Two trials (Peru 1999; Peru 2004) compared zinc with non-zinc supplement (iron plus folate). In some trials (*see* Characteristics of included studies table), all women were also given iron, folate or vitamins or combinations of these. Four trials (Egypt 2014; 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 to treatment

Two studies (Chile 2001; Denmark 1996) excluded women who did not comply with their treatment (85% and 60% compliance respectively) and the other 19 studies included or probably included women in the analysis who did not comply. Of the latter group, two studies (UK 1991a; USA 1983) presented at least some results separately for those women who complied and those who did not comply. 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 16 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.

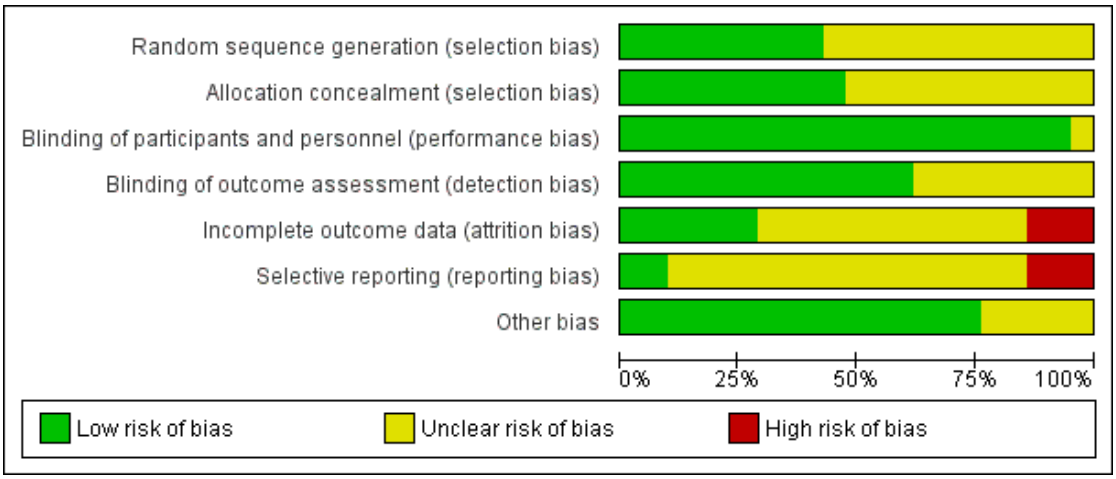


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

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 11 trials: Bangladesh 2000; Chile 2001; Denmark 1996; Egypt 2014; Ghana 2009; Indonesia 2001; Pakistan 2005; UK 1991a; UK 1991b; USA 1989; 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 1996. Attrition bias was judged to be at high risk in only three trials (Chile 2001; Denmark 1996; Iran 2010).

Selective reporting

Selective reporting bias was mostly rated as unclear, with three 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

See: **Summary of findings for the main comparison** Zinc supplementation versus no zinc (with or without placebo) for improving pregnancy and infant outcome

We included 21 RCTs involving over 17,000 women and their babies. Egypt 2014 did not report any of our primary or secondary outcomes, thus we were unable to include any data from this trial in the analyses.

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; *moderate quality evidence*, 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; four RCTs of 1364 women; low zinc or RR 0.93 95% CI 0.24 to 3.65; three RCTs of 683 women; normal zinc; *low quality evidence,* (Analysis 1.2).
There was no significant difference in birthweight between zinc and no-zinc groups (mean difference (MD) 0.90; 95% CI -22.23 to 24.02; 17 RCTs, 6757 babies; *low quality evidence*, Analysis 1.3); small-for-gestational age (RR 1.02 95% CI 0.94 to 1.11; eight RCTs, 4252 babies Analysis 1.4; *moderate quality evidence*) or low birthweight (RR 0.93, 95% CI 0.78 to 1.12; 14 RCTs, 5643 babies; *moderate quality evidence*, 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 dysfunction 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) (seven trials) or caesarean section (Analysis 1.13; random-effects) (six trials). The heterogeneity in 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 (Analysis 1.36) (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 410 infants (Bangladesh 2000), the zinc group (196 infants) had significantly fewer episodes per infant of acute diarrhoea over six months (MD -0.40 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) (Analysis 1.42). No evidence of difference was seen for weight-for-height at six months in one RCT of 136 infants (Indonesia 2001) (Analysis 1.43).

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.

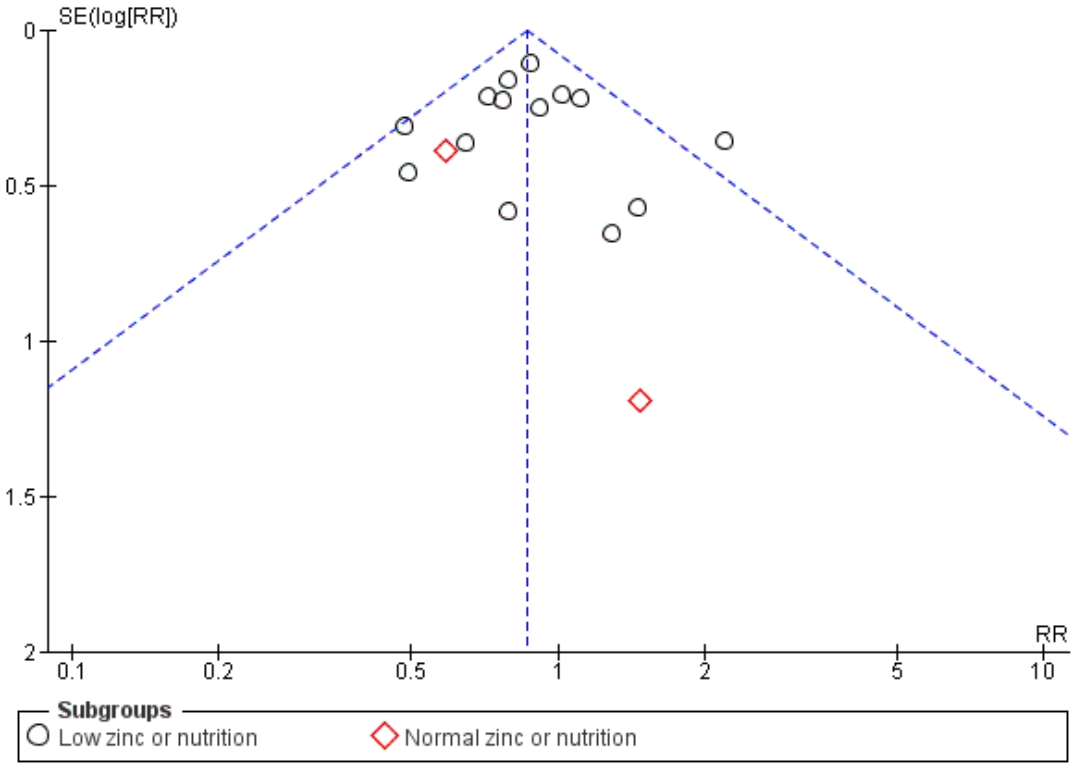


Figure 4. Funnel plot of comparison: 1 Zinc supplementation versus no zinc (with or without placebo), outcome: 1.3 Birthweight.

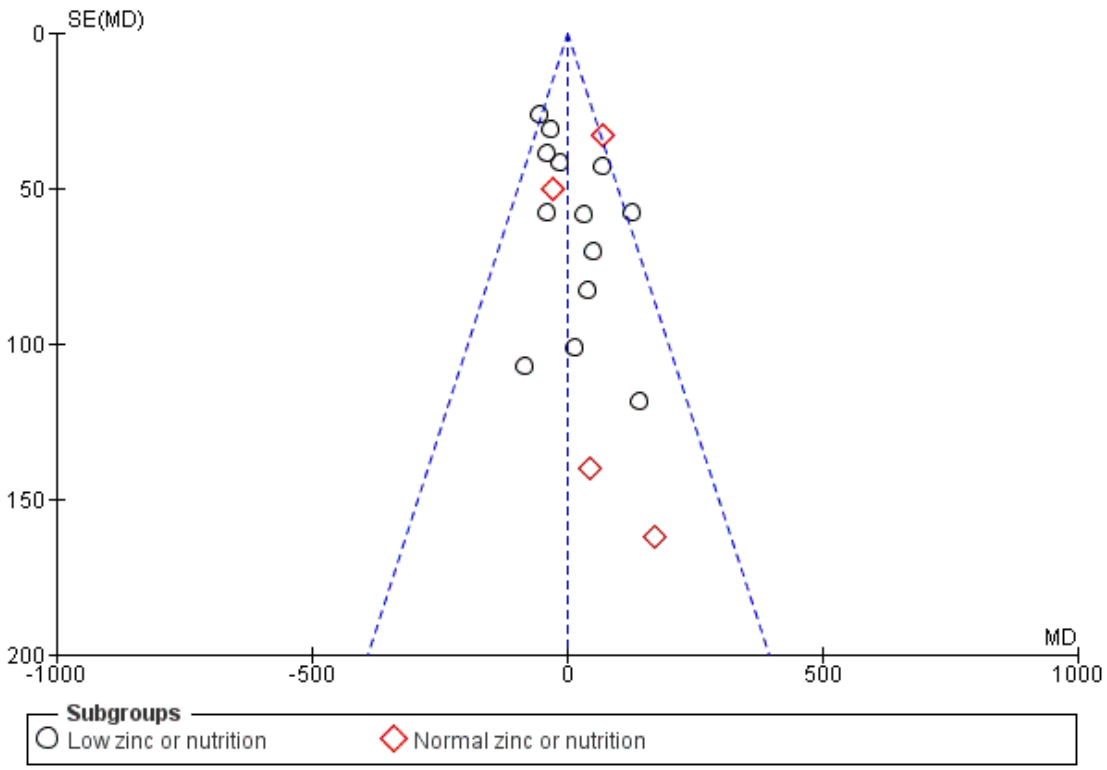
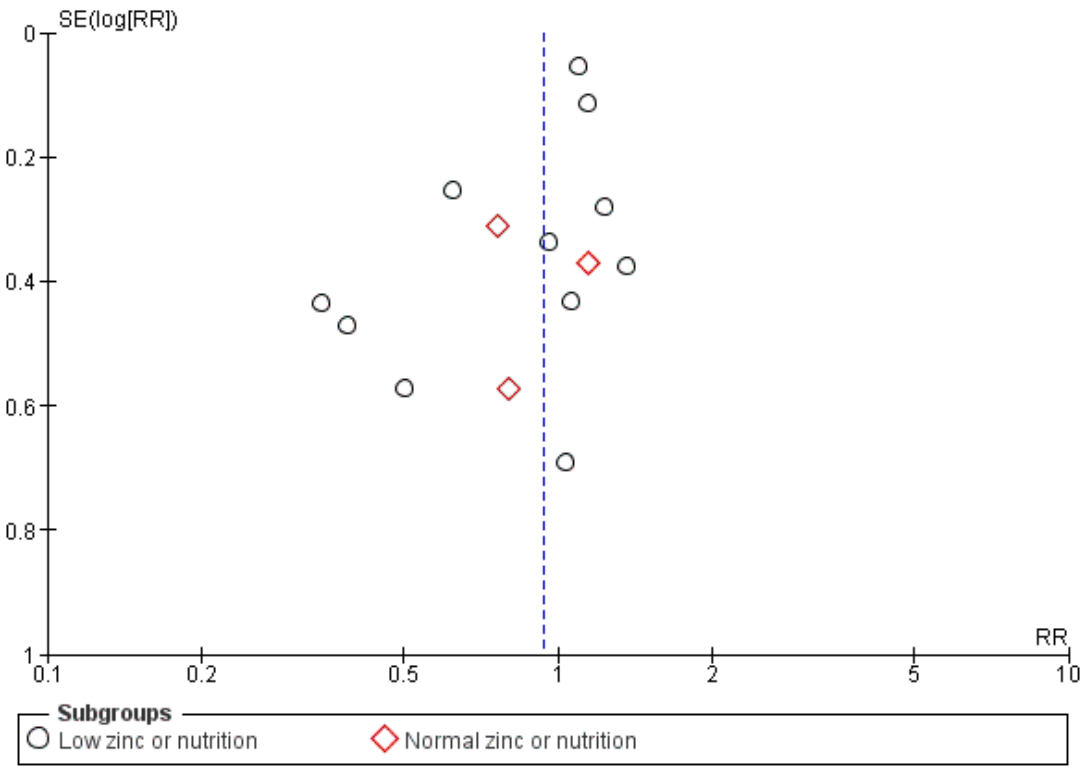


Figure 5. Funnel plot of comparison: 1 Zinc supplementation versus no zinc (with or without placebo), outcome: 1.5 Low birthweight.



DISCUSSION

Summary of main results

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 21 randomised controlled trials, including over 17,000 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).

Overall completeness and applicability of evidence

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 did not show any significance in reduction of preterm birth (Haider 2012). 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 the 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 deficiencies. Peru 1999, 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.

Quality of the evidence

The overall risk of bias was unclear in the half of the studies. We assessed the quality of the evidence using GRADE comparing the effects of zinc supplementation versus placebo/no intervention during pregnancy (Summary of findings for the main comparison). The GRADE quality of the evidence was moderate for preterm birth, small-for-gestational age, and low birthweight, downgraded by one level due to the fact that most studies had design limitations. Stillbirth or neonatal death, and birthweight were considered to be low quality of evidence, downgraded by two levels because of the design limitations and wide 95% CIs crossing the line of no effect.

Potential biases in the review process

We followed the Cochrane Pregnancy and Childbirth Group search strategies and review process to reduce potential biases.

Agreements and disagreements with other studies or reviews

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 a reduction for low birthweight and small-for-gestational age with multiple-micronutrient supplements compared with iron folic acid supplementation, but there is no added benefit for preterm birth (Haider 2012). 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	A double-blind, randomised, placebo-controlled trial.
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). A total of 559 pregnant women from selected areas of Dhaka city slums were identified between 12 and 16 weeks of gestation through an established pregnancy identification system between March and June 1996. Women were included if they remain at or near their residences in Dhaka for the delivery without established medical risk for reduced or excessive birth-weight (e.g. hypertension, renal disease, or diabetes). 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 was given twice the recommended daily intake during the last 2 trimesters of pregnancy. The zinc tablets contained (31.0 mg Zn/tablet; range: 28.6-32.6) and placebo tablets contained (0.0 mg Zn/tablet; range: 0.0-0.1) were was verified and confirmed by 2 independent laboratories. The placebo was a cellulose tablet indistinguishable from the zinc supplement in both appearance and taste. Health workers provided a 1-week supply of zinc or placebo tablets (ACME Ltd, Dhaka) to the houses of the women weekly and instructed the women to consume 1 tablet daily between meals and not together with other vitamin or mineral supplements. Compliance was assessed by counting the remaining tablets in each strip at the next visit. Unannounced compliance checks between regular visits were performed monthly in subsamples of 10% of the study participant Zinc: 30 mg elemental zinc/day (n = 269 [214]). Placebo: n = 290 [232]).
Outcomes	**Maternal outcomes** 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 outcomes** Birthweight; low birthweight, < 2500 g, < 2000 g, < 1500 g; gestational age (weeks); prematurity,< 37 weeks, < 32 weeks; small-for-gestational age; length (cm), head circumference (cm), chest circumference (cm), and mid-upper arm circumference (mm)

Bangladesh 2000 (*Continued*)

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 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	A double-blind, randomised, placebo-controlled trial.
Participants	804 pregnant adolescents were recruited from 5 Primary Care Centres in southern urban slums in Santiago, Chile. They were selected from their prenatal clinic visits before 20 weeks of gestation and aged < 19 years at the estimated time of delivery. The pregnant adolescents identified with chronic diseases, drug abuse, mental retardation, illiteracy or those with pregnancies due to incest or rape were not considered. Subgroup of 220 randomly selected pregnant adolescents at their 28-30 weeks of gestation with a low zinc intake (7.4 SD 2.3 mg) at the initial admission were evaluated for dietary nutrient

Chile 2001 (*Continued*)

	intake. Women showed adequate protein intakes but a relatively low mean energy intake
Interventions	Zinc-supplemented group (S) received 20 mg of Zn capsules daily (sulphate), or the placebo group (P) received an equivalent capsule of a placebo containing lactose. The group codes changed twice during the study and were kept by the pharmacist who prepared the capsules until the end of computational analysis for double-blinding procedure. The individuals who ingested less than 50% of the capsules in any month of the study were excluded. All subjects received 40 mg iron (sulphate) supplements daily. Compliance with zinc intake was evaluated by counting the remaining capsules during the monthly visits Zinc: 20 mg zinc/day (n = 249). Placebo: (n = 258). All women also received 40 mg iron per day.
Outcomes	**Maternal outcomes** Pre-eclampsia; plasma zinc; hair zinc; gestational age at birth; preterm birth; maternal oedema; maternal cholestasis. red blood cell membrane alkaline phosphatases; plasma alkaline phosphatases. **Neonatal outcomes** Low birthweight; birthweight; spontaneous abortions; length at birth; head circumference.
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
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind fashion."

Chile 2001 (*Continued*)

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	A double-blind, randomised, placebo-controlled trial. A 4-arm trial
Participants	146 pregnant women, less than 12 weeks' gestation, who were living in southwest Shanghai, Maqiao countryside and was attending the prenatal clinic at Maqiao Primary Health Care Center were selected for the study. The people living in this area were uneducated with nutritional knowledge, and took cereal-based diet with a little even no milk or milk products; therefore, they were supposed to have mild to moderate zinc deficiency according to Chinese recommended dietary allowance. The zinc content of drinking water in this area was considered negligible and no women received folic acid, iron supplementation and any commercial nutrition products during this trial study
Interventions	For the zinc treatment groups, zinc lactate in capsule were given daily. Group A (GpA, 5 mg/day of zinc (n = 27)); Group B (GpB 10 mg/day of zinc (n = 40)); Group C (GpC, 30 mg/day of zinc (n = 39)). Group D was given placebo where the capsule was of maize starch. (GpD, 0 mg/day of zinc (n = 40)). All capsules were prepared by Laboratory, Second Military Medical University with indistinguishable appearance. Women were instructed to take a single capsule per day 1 hour before or 3 hours after the evening meal. The content of the capsules and the code of the capsule bottles were not known by the investigator or the pregnant women. Only 156 women were followed up under antenatal care
Outcomes	**Maternal outcomes** Caesarean section; weight gains; gestational age; intrauterine growth restriction;

China 2001 (*Continued*)

	duration of labour; oxygen demand; forceps. **Neonatal outcomes** Small-for-gestational age; neonatal sepsis; low birthweight; congenital malformations; stillbirth; preterm birth. Apgar score; chest, neck, head circumference; crown-heel length; ponderal index.
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.
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 outs 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	A double-blinded, randomised placebo-controlled trial.
Participants	Normal healthy middle-class women were (at least 18 years old) less than 20 weeks pregnant confirmed by scan for their first visit and booked for delivery at Kolding hospital and Horsens hospital, Denmark. Any known intolerance towards zinc, diabetes mellitus, thyrotoxicosis or earlier rhesus immunization were excluded from the trials. The women thought likely to be zinc deficient by the previous study project 'Pregnancy, environment and way of life' in Denmark
Interventions	Women received 2 tablets of Zinclet@ (44 mg elemental zinc in total) or 2 placebo tablets containing inert substances. They were indistinguishable in appearance and taste. The tablets were prepared by the Gunnar Kjems Aps company. Women were advised to take 2 tablets daily after breakfast and to avoid taking tablets possibly containing iron together with those of the study, as iron reduces zinc uptake. Women were excluded later, if there were any side-effects caused by the tablets, if they wanted to stop or if she had not taken the tablets for 14 days in all Zinc: 2 tablets with 44 mg elemental zinc (n = 1000). No zinc: 2 placebo tablets indistinguishable from active tablets (n = 1000)
Outcomes	**Maternal outcomes** Prelabour rupture of membranes; preterm labour; pre-eclampsia; antepartum haemorrhage; caesarean section. **Neonatal outcomes** 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. 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.

Denmark 1996 (*Continued*)

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.

Egypt 2014

Methods	A double-blind, randomised, placebo-controlled trial. A 3-arm parallel group trial
Participants	1055 healthy pregnant women from low- and middle-income pregnant populations attending 2 antenatal care centres were screened for low level of zinc serum. Of these women, 675 were with low zinc serum level and were eligible for the trial in Alexandria, Egypt. The age range between 20 and 45 years, with gestational age below 16 weeks with normal course of pregnancy were included for the trial. Women identified through interviews to be on any other form of zinc supplements at any dosage, or risk of having reduced or excessive birthweight of infants (e.g. diabetes, hypertension, renal and heart disease) were excluded. Zinc supplements were provided from 16 weeks until delivery and a subgroup of 100 women were monitored for their dietary intake. Of the 675 women, 597 of women completed the study
Interventions	The control group (group 1) received placebo, the zinc group (group 2) received a daily supplement of 30 mg of zinc sulphate, and the zinc plus multivitamins group (group 3) received 30 mg zinc sulphate with added multivitamins. Placebo: (n = 199/223 (89%)). Zinc supplement (30 mg daily): (n = 198/225 (88%)). Zinc plus multivitamins (30 mg daily): (n = 200/227 (88%)).
Outcomes	**Maternal outcomes** Zinc serum level; haemoglobin level. **Subsample of women (n = 100)** Intake of macronutrients; intake of micronutrients; zinc absorption with dietary food enhancers;

Egypt 2014 (*Continued*)

	zinc absorption with dietary food inhibitors.
Notes	The mean maternal dietary intake of zinc was 7 mg/day in the 3 groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized trial." "participants were randomly assigned to one of the three parallel groups in a 1:1:1 ratio." Insufficient information on how the random sequence was generated to make a judgement
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blinded" without further information, so insufficient information to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"a structured interview was administered to mothers to collect the following data." Insufficient information on whether the interviewer was blinded to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No description of the women who dropped out from study, although drop out rates is in balance (intervention 88% versus placebo 89%)
Selective reporting (reporting bias)	Unclear risk	Protocol was not available so insufficient information to make a judgement
Other bias	Unclear risk	The report appears to be free of other sources of bias.

Ghana 2009

Methods	A double-blind, RCT.
Participants	400 pregnant women in Ghana earlier than 16 weeks of gestation who presented themselves for antenatal care and have been screened for their gestational age in the Wa Regional Hospital of the Upper West Region in Ghana. Women who were receiving zinc supplements at any dosage level or were severely anaemic (that is, Hb less than 7.0 g/dL) were excluded. The iron-zinc and iron-only supplements were pre-coded and supplied by Nutricaps pharmaceutical company in the United States of America. The supple-

Ghana 2009 (*Continued*)

	ments (in the form of capsules) were of the same shape, colour and taste and packaging. The women were advised to take the supplements at least 2 hours before or after meals, and at night, just before going to bed. Compliance was monitored by interviewing all participants after having being enrolled for 4 weeks using structured questionnaire to check the frequency and dosage of supplement intake. A subsample of 213 women at recruitment were assessed for serum ferritin but only 173 were repeated at 34-36 weeks' 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	Women received a combined supplement of 40 mg zinc as zinc gluconate and 40 mg iron as ferrous sulphate and women in the control group received 40 mg elemental iron as ferrous sulphate without zinc content. Both groups received malaria chemoprophylaxis in the form of sulphadoxine pyrimethamine, and 400 μg folic acid. The supplements were taken every other day from enrolment until delivery. Intervention group: 40 mg zinc plus 40 mg iron (n = 299). Control group: 40 mg iron only (n = 301).
Outcomes	Intrauterine growth restriction/small-for-gestational age; low birthweight; preterm birth; birthweight; haemoglobin concentration; serum ferritin concentration; plasma zinc concentration.
Notes	

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

Ghana 2009 (*Continued*)

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	A double-blinded, randomised placebo-controlled trial. A factorial design 4-arm (Zibuvita study) trial and then included a follow-up study of the infant (the Zinak and Pronak study)
Participants	5736 women who live in Purworejo district of central Java were identified as pregnant from the Indonesian Ministry of Health surveillance. Of these pregnant women, 2173 women at a gestational age of less than (120 days) 17 weeks were eligible for the trial study. After losses to follow-up, only 2098 delivery and 1956 neonates were analysed in the Zinak and Pronak study. The follow-up of the children were from birth up to 2 years of age
Interventions	Women were randomly allocated to 3 treatment groups and placebo group. The treatment groups were given micronutrient capsules from the date of inclusion in the study until delivery. The capsule contained either 2400 RE of vitamin A (as retinyl palmitate) or 20 mg of ZnSO4, or the same dose of both vitamin A and ZnSO4, or placebo. All capsules also contained 2 mg of DL-a-tocopherol as an antioxidant and 350 mg of soya bean oil, 20 mg of beeswax and 8 mg of lecithin as capsule filler. The supplements were manufactured by Tishcon Corp. (Westbury, NY, USA) and they were packaged in plastic strips in identical, opaque pink capsules that was sufficient supplements for 2 weeks or 1 month. Fieldworkers distributed capsules and monitored compliance at the home of the women by counting the unused capsule. Vitamin A (2400RE): n = 484/527 (91.8%). Zinc (20 mg): n = 477/531 (89.8%). Vitamin A (2400RE) + zinc (20 mg): n = 495/543 (91.2%). Placebo: n = 500/523 (95.6%).
Outcomes	**Maternal outcome** Pregnancy weight. **Neonatal outcomes** Birthweight; low birthweight; stillbirth/neonatal death; blue/floppy (neonatal hypoxia); fever/not drinking; umbilical infection; 6-month Z-scores; 6-month haemoglobin, plasma retinol, plasma zinc; birth size (weight and length); small-for-gestational age.

Indonesia 1999 (*Continued*)

Notes	Adherence: mean adherence ranged from 71% to 73% across the 4 arms of the study

Risk of bias

Bias	Authors' judgement	Support for judgement
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)	Unclear risk	The protocol was not available and there was not enough information to make this judgement
Other bias	Low risk	No apparent risk of other bias.

Indonesia 2001

Methods	A double-blinded, RCT. A follow-up study of the infants with a factorial design. A 4-arm trial
Participants	230 pregnant women were recruited before 20 weeks of gestational age from 13 adjacent villages in Bogor District, Indonesia. Of 230 women, 179 women remain until delivery and only and only 170 women were enrolled for follow up of infant and mother until 6 months postpartum study. Each woman was supplemented daily during pregnancy until delivery. Exclusion criteria at enrolment were twin pregnancy and congenital abnormalities. Women had mean plasma zinc concentrations of about 11 µmol/L
Interventions	All women received iron and folic acid (30 mg iron as ferrous fumarate/d and 0.4 mg pteroylglutamic acid/d). In addition, 1 group of women received ß-carotene (4.5 mg as water-soluble granulate/d; ß-carotene group), 1 group received zinc (30 mg zinc as sulphate/day; zinc group), 1 group received ß-carotene plus zinc (4.5 mg ß-carotene and 30 mg zinc/d; ß-carotene + zinc group), and 1 group received only iron and folic acid

Indonesia 2001 (*Continued*)

	(control group). Capsules were prepared by the pharmacy of the Gelderse Vallei Hospital (Ede, Netherlands) and given a letter code and the micronutrients were indistinguishable from each other. Compliance, expressed as a proportion of the intended supplements consumed during pregnancy, did not differ among the groups with a mean compliance of > 80% in all groups, and 90% of the women taking > 50% of the intended dose. Iron + folate acid: (n = 41). Iron + folate acid + β-carotene: (n = 43). Iron + folate acid + zinc: (n = 44). Iron + folate acid + β-carotene + zinc (n = 42).
Outcomes	**Maternal outcomes** Preterm birth; caesarean section; prolonged labour; retention of placenta; postpartum haemorrhage; infection; 6-month serum zinc. **Neonatal outcomes** Birthweight; low birthweight; congenital malformation; stillbirth/neonatal death; 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

Indonesia 2001 (*Continued*)

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	A double-blind, randomised, placebo-controlled trial.
Participants	110 healthy pregnant women with a previous preterm delivery who were receiving prenatal care from obstetrics and gynaecology outpatient clinics of Isfahan University of Medical Sciences were recruited for the trial. The healthy pregnant women were 18-35 years, at 12-16 weeks' gestational age at delivery, height > 150 cm, weight > 45 kg, non-smoker, no complicated pregnancy, but with history of preterm delivery, carrying a singleton fetus, living in Isfahan and willingness to continue current medications for the duration of the study
Interventions	The treatment group received (50 mg/day Zn as Zn sulphate) produced by a local pharmaceutical company, Alhavi Pharmaceutical Laboratory, Tehran, Iran, from the day of reporting (12-16th weeks of gestation) until delivery, and the control group received placebo. Both groups administered capsules orally before meals once a day. The capsules were distributed monthly during prenatal visit. Compliance with study treatment was established by asking the women about missed doses and by counting unused sachets. The doses used are safe during pregnancy. Intervention: 50 mg/day Zn as Zn sulphate (n = 42). Placebo: (n = 42).
Outcomes	**Maternal outcomes** Caesarean section; pre-eclampsia; intrauterine growth restriction. **Neonatal outcomes** Small-for-gestational age; 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 randomisation 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	A double-blind, cluster-randomised, controlled trial (also factorial design). It was an 1-5 treatment arms intervention
Participants	4926 pregnant women and 4130 liveborn infants in a rural plains district of Sarlahi, community in Nepal, which had 426 sectors (communities of about 100-150 households) - only 2 of the 5 arms (total of 1659 infants) used in this review. This is the same area of Nepal in which we previously recorded evidence of vitamin A, iron, and zinc deficiency among pregnant women. Women who were currently pregnant, breastfeeding a baby less than 9 months old, menopausal, sterilised or widowed were excluded. Supplementation commenced before conception
Interventions	The sectors were randomly assigned to 1 of 5 treatment arms. The control group was vitamin A (1000 µg retinol equivalents). FA group, vitamin A + folic acid (400 µg). FAFe group, vitamin A + folic acid + iron (60 mg). FAFeZn group, vitamin A + folic acid + iron + zinc (30 mg). MN group, vitamin A + folic acid + iron+ zinc + other micronutrients (10 µg vitamin D, 10 mg vitamin E, 1.6 mg thiamine, 1.8 mg riboflavin, 20 mg niacin, 2.2 mg vitamin B-6, 2.6 µg vitamin B-12, 100 mg vitamin C, 65 µg vitamin K, 2. 0 mg Cu, 100 mg Mg). The supplements were provided from UNICEF, identical in shape, size, and colour, arrived in Nepal in opaque, sealed, and labelled bottles coded 1-5. The code allocation was kept locked at the Johns Hopkins University, Baltimore. The investigators, field staff, and participants were blinded to the codes throughout the study. Zinc: zinc + iron + folate (n = 858).No zinc: iron + folate (n = 801)
Outcomes	**Maternal outcome** Preterm birth. **Neonatal outcomes** 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

Nepal 2003 (*Continued*)

		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
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	A double-blind, RCT.
Participants	By simple random sampling, 250 women from 2 urban hospitals and 1 rural community in Pakistan at 10-16 weeks' gestation were recruited. 242 women completed the study. The mean (SD) age of the women was 25.7 (4.8) years (range 16-4). 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	The supplement was a 20 mg of zinc sulphate powder capsule filled with glucose and a similar capsule as placebo. The supplement were given to the women from the time of booking to the end of their gestational week. In addition, routine supplements of folic acid and iron given. The dietary zinc intake was taken into account by a food diary and various food items were assigned a score. Women were followed up at monthly intervals by trained staff. Compliance was ensured by health visitors and pills were counted out every month before new supply were issued as to double check the consumption of the medicine. Zinc: 20 mg elemental zinc (zinc sulphate powder capsule) (n = 121). Placebo: (n = 121) (capsule); in addition, all women had routine supplements of folic acid and iron

Pakistan 2005 (*Continued*)

Outcomes	**Maternal outcome** Preterm birth. **Neonatal outcomes** 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."
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	The protocol is not available. Not enough information to make this judgement
Other bias	Low risk	No apparent risk of other bias.

Peru 1999

Methods	A double-blind, RCT.
Participants	1295 women with a low-risk pregnancy (uncomplicated and eligible for vaginal delivery) , at the Hospital Materno Infantil in Lima, Peru and low zinc intake who were carrying a singleton fetus, and had lived in coastal Peru for $\geq$ 6 months before pregnancy were recruited for the study. These women indicated with low zinc intake living in this region and at 10 to 24 weeks' gestation. The study protocol was approved by the institutional review boards of the Instituto de Investigación Nutricional (IIN) and The Johns Hopkins School of Hygiene and Public Health

Interventions	1 group received a daily supplements containing 60 mg Fe (ferrous sulphate) and 250 µg folate with 15 mg of Zn (zinc sulphate) and the other received the same Fe supplement but without an additional 15 mg Zn (zinc sulphate). Women were asked to take 1 pill daily midmorning with a vitamin C-containing drink or water according to the Peruvian guideline. Supplementation began at gestation week 10-24 and continued until 4 weeks postpartum. The supplements were produced by a local pharmaceutical company (Instituto Quimioterápico, SA, Lima, Peru) in coded blister packages. To verify the formulation of the supplements and the integrity of the coding scheme, samples of each supplement type were analysed by the IIN laboratory 2 times during the study. 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 outcomes** 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 outcomes** Birthweight; low birthweight; high birthweight; cord vein zinc; cord vein haemoglobin; cord vein serum ferritin; crown-heel length; head circumference; chest, calf and mid-upper arm circumference; biceps, subcapsular and calf skinfold thicknesses.
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

Peru 1999 (*Continued*)

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	No information on if the protocol had been published prior to the trial
Other bias	Low risk	No apparent risk of other bias.

Peru 2004

Methods	A double-blind, RCT.
Participants	242 (low-income) Peruvian pregnant women at 10 to 16 weeks' gestation receiving prenatal care at the Hospital Materno Infantil San Jose in Lima, Peru were recruited. The maternal dietary zinc intake is approximately 8 mg/d,12 an intake much lower than recommended intakes at that time of 15 mg/d (US Recommended Dietary Allowance) in this region. Women who were with singleton pregnancy, and had lived in coastal Peru for at least 6 months before becoming pregnant were included in the study. Exclusions was made according to a protocol for fetal neurobehavioural assessment
Interventions	Women were randomly assigned to receive a daily supplement containing 60 mg iron (ferrous sulphate) and 250 mg folic acid, with 25 mg zinc (zinc sulphate) or the same supplement but without 25 mg zinc (zinc sulphate). The supplements were manufactured in Lima, had the same appearance and taste, and both study personnel and study subjects were masked to treatment assignment. The supplements were distributed in blister packs at monthly intervals, beginning at entry into the study at 10 to 16 weeks' gestation and continuing until 1 month postpartum. Adherence with supplementation was checked biweekly by health workers who visited the women in their homes and observed the number of tablets remaining in each blister pack. The level of adherence was calculated as the percentage of tablets taken over the number of days in the study. They used a standard questionnaire with specific questions regarding potential benefits or side effects of supplement consumption. Zinc: zinc + iron + folate (n = 109 [94]). No zinc: iron + folate (n = 113 [101])

Peru 2004 (*Continued*)

Outcomes	**Maternal outcomes** Preterm birth with complications; gestational age at birth. **Neonatal and infant outcomes** 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
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

Peru 2004 (*Continued*)

		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	A double-blind, randomised, placebo-controlled. It was a 4-arm trial
Participants	127 black women before 20th week of pregnancy for antenatal medical care with expectation of spontaneous vaginal delivery and a willingness to attend the clinic at Kwa-Mashu Polyclinc near Durban, South Africa, daily until delivery to eat dietary supplements under supervision were selected for the study. Free transportation was provided daily to the clinic. At entry, each woman had a detailed medical and socioeconomic history, physical examination, assessment of the week of pregnancy by date of LMP and ultrasonic measurements. Serum levels of proteins, cholesterol, triglyceride, carotene, vitamin A, vitamin C, phosphorus, alkaline phosphatase, calcium and magnesium were also measured. An experienced dietitian calculated dietary intake before starting the supplements from a 24-hour, quantitative, dietary recall history. The recorded diets were deficient in energy, protein, the B vitamins, calcium and iron among these women. Women in the zinc group in this study had a significantly lower mean weight than the women in the placebo group
Interventions	Women were randomly assigned to 1 of 4 groups. Before supplementation the women in 3 of the 4 groups had similar body weights. Primigravidas were equally distributed by chance among the 4 groups. Group 1 received placebo pills and group 2, 30-90 mg zinc gluconate daily. Groups 3 and 4 were given food supplements from the 20th week of pregnancy to delivery, Monday through Friday. These supplements were designed to correct dietary deficiencies detected in the dietary recall histories, particularly deficiencies in energy and protein. Group 3 women received a high bulk supplement, a mixture of beans and maize in a 1.2 : 1 ratio as mush with added vitamins. Group 4 women received a low bulk supplement, a porridge containing 100 g dry skimmed milk, maize flour, vitamins and minerals. It differed from the group 3 supplement in its 36 g of animal protein and in its higher levels of several vitamins and calcium.

S Africa 1985 (*Continued*)

	Group 1: placebo (n = 33). Group 2: zinc: zinc gluconate 30-90 mg daily (n = 32). Group 3: high food supplement (n = 31). Group 4: low food supplement (n = 31).
Outcomes	**Maternal outcomes** Levels of constituents of serum samples: Albumin, cholesterol, triacylglycerol, carotene, vitamin A, vitamin C, phosphorus, alkaline phosphatase, calcium, magnesium **Neonatal 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**
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)	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 apparent risk of other bias.

UK 1989

Methods	A double-blind, randomised, placebo-controlled trial.
Participants	500 women who were less than 20 weeks pregnant at the first visit booking for delivery at Southmead Hospital, Bristol were recruited for study. An ultrasound scan was done in 95% of cases. At the end of the visit potential volunteers were seen by the research midwife, who explained the study fully. Median zinc concentrations at enrolment were 1.192 µmol/10 x 10 cells in the zinc group and 1.147 in the placebo group. 494 women remained to complete the study
Interventions	Women were randomly allocated to receive a capsule containing 20 mg elemental zinc (66 mg zinc sulphate) oral capsule containing inert substances (sucrose, maize starch, purified talc, kaolin, gelatin) but which was indistinguishable in appearance and taste from the one containing zinc. The capsules were prepared by Smith Kline and French Ltd. The mothers were advised to take 1 capsule daily after breakfast. Serum haemoglobin and ferritin concentrations were measured in all women at the first visit. Iron and folate supplementation was advised only if the haemoglobin concentration was less than 100 g/l or the serum ferritin concentration was less than 10 µg/l. Supplementation capsule supply were provided enough to last until the next visit. The research midwives visited the women at the 28-32 weeks and again on the day of delivery. During the study and after delivery clinical details were recorded by the research midwife by interview as well as from the case records. Compliance was assessed by the regularity with which the study capsules were taken. Those who took the supplement daily or on most days were grouped as compliers, and the rest were regarded as non-compliers. Zinc: 20 mg elemental zinc (n = 246). No zinc: placebo (n = 248)
Outcomes	**Maternal outcomes** 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 outcomes** 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; 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 two-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

UK 1989 (*Continued*)

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	A double-blind, randomised, placebo-controlled trial. It was a 2-arm trial
Participants	56 pregnant women between 15-25 weeks of pregnancy were selected at St Thomas' Hospital, London, UK. To fulfil the criteria for eligibility, women with low maternal pre-pregnancy weight (less than 95% ideal body weight) were selected. For this study, Asian women and primigravidae who smoked more than 5 cigarettes per day with previous small-for-gestational-age baby were set as criteria. For the zinc supplement group, women with previous small-for-gestational-age baby, Asian, with low pre-pregnancy weight and primigravidae who smoked were included. The placebo group were women with low pre-pregnancy weight, previous small-for-gestational-age baby, Asian, primigravidae who smoked. Social class was allocated from the classification of the Office of Population Censuses and Surveys (1980); classes 4-7 were grouped as lower socio-economic
Interventions	A coded placebo and non-placebo tablet were prepared by Thames Laboratories Ltd, UK. The effervescent Zn table were 22.5 mg. Zinc: 22.5 mg elemental zinc (n = 30). Placebo: (n = 26).

UK 1991a (*Continued*)

Outcomes	**Maternal outcomes** Pregnancy hypertension; preterm delivery; post-term labour; induction of labour; caesarean section; **Neonatal outcomes** 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	A double-blind, RCT.
Participants	152 women resident in Scunthorpe Health District who booked for care before the 18th week of gestation, and who were booked for delivery at either Scunthorpe Maternity Home or at Scunthorpe General Hospital, were recruited for the study. 134 women completed the trial
Interventions	Women were randomly assigned to 2 groups, X and Y. The the supplements were prepared by Smith Kline and French. The spansules contained 150 mg of FeSO4 and 0-5 mg of folic acid for Group X. For Group Y, 62 mg of zinc sulphide was added to the 150 mg of FeSO4 and 0-5 mg of folic acid . Participants were asked to take 1 spansule per day. Haematological tests were undertaken on entering the study and at the 28th week of gestation. Group X: iron + folic acid (n = 62). Group Y: iron + folic and zinc: (n = 72).
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	A double-blind, RCT.
Participants	213 Hispanic women of Mexican descent 17 years of age or older who were not over 27 weeks of gestational age. They were without diabetes or heart, renal or thyroid disease were selected for study. 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. All participants were agreed to take the test vitamin and mineral supplement as prescribed, return to the clinic for 2 interviews with the research nutritionist, allow 3 blood and 2 hair samples to be taken, and permit the nutritionist to obtain information from their clinic, delivery, and infant records
Interventions	Women were randomly assigned into 2 groups. The treatment group received a daily vitamin and mineral supplement as a single capsule providing about 20 mg of zinc as zinc acetate. The control group received a similar supplement without zinc. The capsules were indistinguishable in appearance. The capsule bottles were labelled A or B (Balancel Forte, Meyer Laboratories, Ft Lauderdale, FL). Meyer Laboratory provided the supervisor of the clinic pharmacy with the information necessary to identify the capsules containing zinc. The women were instructed to take the capsule with their evening meal to reduce the possible transitory effect on zinc concentrations in serum samples which were collected in the morning. All supplements were formulated to provide 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 HCI, 1 mg folic acid, 10 µg vitamin B12 (cyanocobalamin), 10 mg D-calcium pantothenate, 60 mg vitamin C, 100 mg calcium (as carbon ate), 20 mg iron (as ferrous fumarate), 50 mg of magnesium (as oxide), 1 mg of manganese (as sulphate), and 150 µg iodine (as potassium iodide) per day. Zinc: 20 mg elemental zinc plus vitamins (n = 107). Placebo with vitamins: (n = 106).
Outcomes	Pregnancy hypertension; low serum zinc before. birth (< 53.3 µg/dL; low hair zinc; 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.

USA 1983 (*Continued*)

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	A double-blind, RCT.
Participants	138 Hispanic teenagers who were under 17 years of age and were not over 27 weeks' gestation and who were attending prenatal clinic at Los Angeles were recruited for the study. The mean dietary zinc intakes among these women were about 50% of the RDA. according to LMP. These teenager did not have diabetes, heart, renal or thyroid disease. All participants were agreed to take the test vitamin and mineral supplement as prescribed, return to the clinic for 2 interviews with the research nutritionist, allow 3 blood and 2 hair samples to be taken, and permit the nutritionist to obtaining the study provided by the staff from their clinic, delivery, and infant records
Interventions	The teenagers were randomly assigned to control group and treatment group. For treatment group, they received daily vitamin and mineral supplement in a single capsule providing (20 mg) of zinc. The control group received a capsule that did not contain zinc. The supplements composed 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). The capsules between the 2 groups were identical in taste and appearance by (Pharmavite Pharmaceuticals Coporation, Pacoima, CA). The teenagers were instructed to take the capsule with their evening meal rather than at breakfast. In addition, 108 mg

USA 1985 (*Continued*)

	iron/day was prescribed routinely at 20 weeks' gestation. Zinc with vitamin and mineral group: (n = 70). Vitamin and mineral group: (n = 68).
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
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	A double-blind, randomised, placebo-controlled trial. It was a 2-arm trial for women in the groups of low weight, normal weight and high weight
Participants	The pregnant adolescent woman who were at risk for zinc deficiency and enrolled in the prenatal clinic of Charity Hospsital of New Orleans, a large urban state-supported hospital serving area women without access to private maternity care, were considered for the trial. At the first clinic visit, the pregnant adolescent woman attended the a nutrition lecture presented by nurse and data of their characteristics and background information were collected. In the second visit, 652 low-income pregnant adolescent women who were at less than 25 weeks' gestation (average age 17.6 years; range 13.5 to 19.6) were recruited for the trial. Women were grouped by their weight percentile, and treatment group. Total of 556 completed the study
Interventions	Women were randomly assigned to receiving tablets of 30 mg Zn as gluconate the Z group or the placebo (P) group containing cellulose. A sample of blood was taken for chemical analysis and the previous 24-hour dietary assessments were repeated 8-10 weeks after enrolment. The course of the pregnancy was documented by the physician at each prenatal visit. Compliance with the treatment regimen was assessed bu a tablet count at each clinic visit and questioning after delivery when details of labour and delivery events were collected. Zinc (30 mg): (n = 268). Placebo: (n = 288).
Outcomes	**Maternal outcomes** Preterm birth; weight. **Neonatal outcomes** 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	A double-blind, randomised, placebo-controlled trial.
Participants	5058 medically indigent African-American women receiving prenatal care in 4 Jefferson County (Alabama) Health Department clinics considered for selection. The pregnant women who were both nulliparous and multiparous ranged between 13 and 44 years of age were included for the selection criteria. Of these women, 589 at 14-23 weeks' gestation were selected for the randomisation trial based on a plasma zinc level below the estimated median for gestational age for the population at the time of enrolment in prenatal care. Only 580 women's data completed for analysis due to 9 women had insufficient outcome data
Interventions	Women were randomly assign to both the zinc supplement and placebo groups. Both group received a daily prenatal multivitamin/mineral tablet not containing zinc but containing folic acid, iron, and other minerals. The tablets were produced by Mission Pharmacal, San Antonio, Texas. Zinc supplement and placebo were prepared in a capsules by Rempak, Carteret, New Jersy and only the zinc supplement contained 25 mg of zinc (zinc sulphate). Women were asked to take 1 of each supplement daily, but the time was not specified. The zinc content of the tablets was verified independently in our laboratory. Prior to this study, pregnant women in this care system received only folic acid and iron supplementation. For each woman, compliance was defined as the percentage of zinc tablets consumed compared with the number of days enrolled in the project prior to delivery. Zinc: 25 mg elemental zinc per day (n = 286). Placebo (n = 294)
Outcomes	Preterm birth; pregnancy hypertension; low birthweight; small-for-gestational age; stillbirth/neonatal death; neonatal sepsis; child mental and psychomotor development at 5 years.

USA 1995 (*Continued*)

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."
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 enough information to make this judgement. No information on if the protocol had been published prior to 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	313 healthy pregnant women at their fifth month of gestation enrolled in the hospital for prenatal care in Beijin, China, were given fortified biscuits containing (vitamin D), (vitamin D + calcium), (vitamin D + calcium + iron), (vitamin D + calcium + iron + zinc). Only 1 woman selected from the same hospital (no fortified biscuits given) as control comparison. The study indicated quasi-randomised study, which there was no randomised sequence generation performed and allocation was by the order of hospital visits
Appelbaum 1979	The effect of diet supplementation throughout pregnancy on third-trimester amniotic fluid growth-supporting activity was studied in 100 African women; 32 were given zinc supplementation, 22 each animal and vegetable supplements, respectively, and 24 served as control subjects. Zinc level was measured among the groups and the inhibitory of zinc was conducted in vitro testing of the amniotic fluid collected. The study design did not indicate randomised controlled trial and the outcome was the zinc level of amniotic fluid only
Christian 2001	A placebo-controlled trial in Nepal was conducted on 202 women who reported to be night blind during pregnancy. They were randomly assigned in a double-blind manner, stratified on vitamin A, ß-carotene, or placebo receipt, to receive 25 mg Zn or placebo daily for 3 weeks. The participant selection was on women who had night blindness and there was no prespecified outcomes reported related to pregnancy except for vision restoration of pregnant women
Fawzi 2005	Pregnant women who were HIV-infected, who resided in Dar es Salaam, Tanzania, at the time of the baseline interview, and who intended to stay in the city until delivery and for were considered. 400 HIV-infected pregnant women were between 12 and 27 weeks of gestation were randomly assigned to daily oral supplementation with either 25 mg Zn or placebo between recruitment and 6 weeks after delivery. The population selected for the trial were not in healthy state of condition
France 2004	Healthy pregnant women (n = 100) receiving prenatal care between 12 and 16 weeks of gestation in the Obstetric Departments of Grenoble and Lyon Hospitals in France participated in a double-blind, randomised, placebo-controlled trial. The intervention was micronutrients supplement or placebo. The micronutrients contained vitamin C (60 mg), ß-carotene (4.8 mg), vitamin E (10 mg), thiamin (1.4 mg), riboflavin (1.6 mg), niacin (15 mg), pantothenic acid (6 mg), folic acid (200 mg), cobalamin (1 mg), Zn (15 mg as citrate), Mg (87. 5 mg as glycerophosphate), Ca (100 mg as carbonate). Zinc was not given separately as the main intervention
Hambidge 1983	A longitudinal study (monthly intervals) in 46 pregnant middle-income women. 10 of the women received a daily supplement of 15 mg Zn and the rest of the women did not receive any zinc supplement. The design was an observational study with no mention of randomisation or allocation to zinc or no-zinc groups
India 1993	90 pregnant women were randomly assigned to control (A) and 120 pregnant women were randomly assigned to zinc treated (B) groups. Group B women were administered a single daily dose of 45 mg zinc as a 200 mg zinc sulphate tablet (Zinfate, Yash Pharma) from the day of reporting till delivery. The control group women were not provided with zinc supplementation. The total number of subjects finally selected in group A served as control was 62, and that in Gp. B, was 106. The study design was a quasi-randomised study and with large discrepancies in numbers of participants at baseline and follow-up

(*Continued*)

Kynast 1986	A randomly selected study group of 179 pregnant women and a control group of 345 pregnant women were given zinc aspartate. This study investigates the prophylactic effectiveness of zinc replacement in reducing the overall complication rate for both mother and fetus and in particular for large-for-date and small-for-date infants. The study design was a quasi-randomised study and allocation was done by alternation
Mahmoudian 2005	A total of 118 anaemic women were recruited in this randomised controlled trial. Both groups received 100 mg elemental iron daily. The intervention group received an additional dose of 15 mg zinc every day for a period of 12 weeks while the control group received placebo. The participants were all anaemic women and outcomes were haemoglobin concentration only
Makola 2003	This study was a randomised, placebo-controlled double-blind effectiveness trial of a micronutrient-fortified dietary supplement conducted in pregnant women in Tanzania. Pregnant women who believed that they were between 12 and 34 weeks pregnant were invited to participate in the study. The intervention was micronutrient supplement (orange-flavoured micronutrient-fortified powdered beverage mix containing 11 micronutrients, including zinc) in comparison to placebo. Women with gestation greater than 26 weeks were included in the study and zinc was not provided separately as an supplemented intervention
Naher 2012	A total of 200 pregnant women, age ranging between 18-40 years and gestational age ranging from 37-42 weeks were selected for a cross-sectional study in Bangladesh. Among them, 100 were advised to take 61.8 mg zinc daily and the others did not. The study design was an observational study and not a randomised controlled trial
Nishiyama 1999	38 Japanese women at the second trimester of pregnancy had haemoglobin concentrations below 11.0 g/dL and 32 of 38 had normocytic erythrocytes. These women were divided into 3 groups, and they were compared for their haematological status and serum IGF-I levels before and after iron (Group A) or Zn (Group B) or iron plus Zn (Group C) supplementation. The the women were anaemic and the study design was a clinical controlled trial where women could chose 1 of 3 intervention groups
Nogueira 2003	74 low-income pregnant adolescents in Brazil ranging from 13-18 years of age received supplementation of (folic acid + iron), (folic acid + zinc sulphate + iron) or only (iron). The pregnant adolescents were divided into 5 groups. The study method was based on longitudinal design and zinc plasma concentration was measured as to support the folic acid metabolism
Van Vliet 2001	The study was an open, randomised study, using a cross-over approach for 2 sources of vitamin A (i.e. liver paste and retinyl palmitate containing oil) and a parallel approach for 3 dose levels of vitamin A (i.e. 3.0, 7.5, and 15 mg vitamin A) for women between 19-47 years of age. Pregnant women were excluded in the study. The intervention did not use zinc supplements or any zinc constituent supplements
Villamor 2006	Pregnant women with HIV and the HIV status of their babies was assessed at birth and at 6 weeks postpartum at Dar es Salaam Tanzania. Women 12-27 weeks of gestation were randomly assigned to receive a daily oral dose of 25 mg zinc or placebo from the day of the first prenatal visit until 6 weeks postdelivery. All the participants were infected with HIV
Yalda 2010	Single-blind randomised clinical control trial conducted in Kurdistan region, Iraq. 100 anaemic pregnant women were selected to receive, first group (A), supplemented daily with 120 mg iron and second group (B) received 120 mg iron + 22.5 mg zinc. The pregnant women were all diagnosed with anaemia and the outcome were to assess the improvement of anaemic condition

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	5100	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.86, 1.46]
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	17	6757	Mean Difference (IV, Fixed, 95% CI)	0.90 [-22.23, 24.02]
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	4	1654	Mean Difference (IV, Fixed, 95% CI)	44.46 [-7.49, 96.41]
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	2837	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 hypoxia)	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 (episodes/infant over 6 months)	1	410	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.12, 0.00]
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 13 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		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]

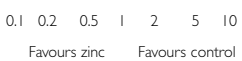
Analysis 1.1. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 1 Preterm birth.

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	34/194	34/216		6.5 %	1.11 [0.72, 1.72]
Chile 2001	14/249	30/258		6.0 %	0.48 [0.26, 0.89]
China 2001	10/116	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]
USA 1983	5/87	4/90		0.8 %	1.29 [0.36, 4.66]
USA 1989	50/268	68/288		13.3 %	0.79 [0.57, 1.09]
USA 1995	30/294	38/286		7.8 %	0.77 [0.49, 1.20]



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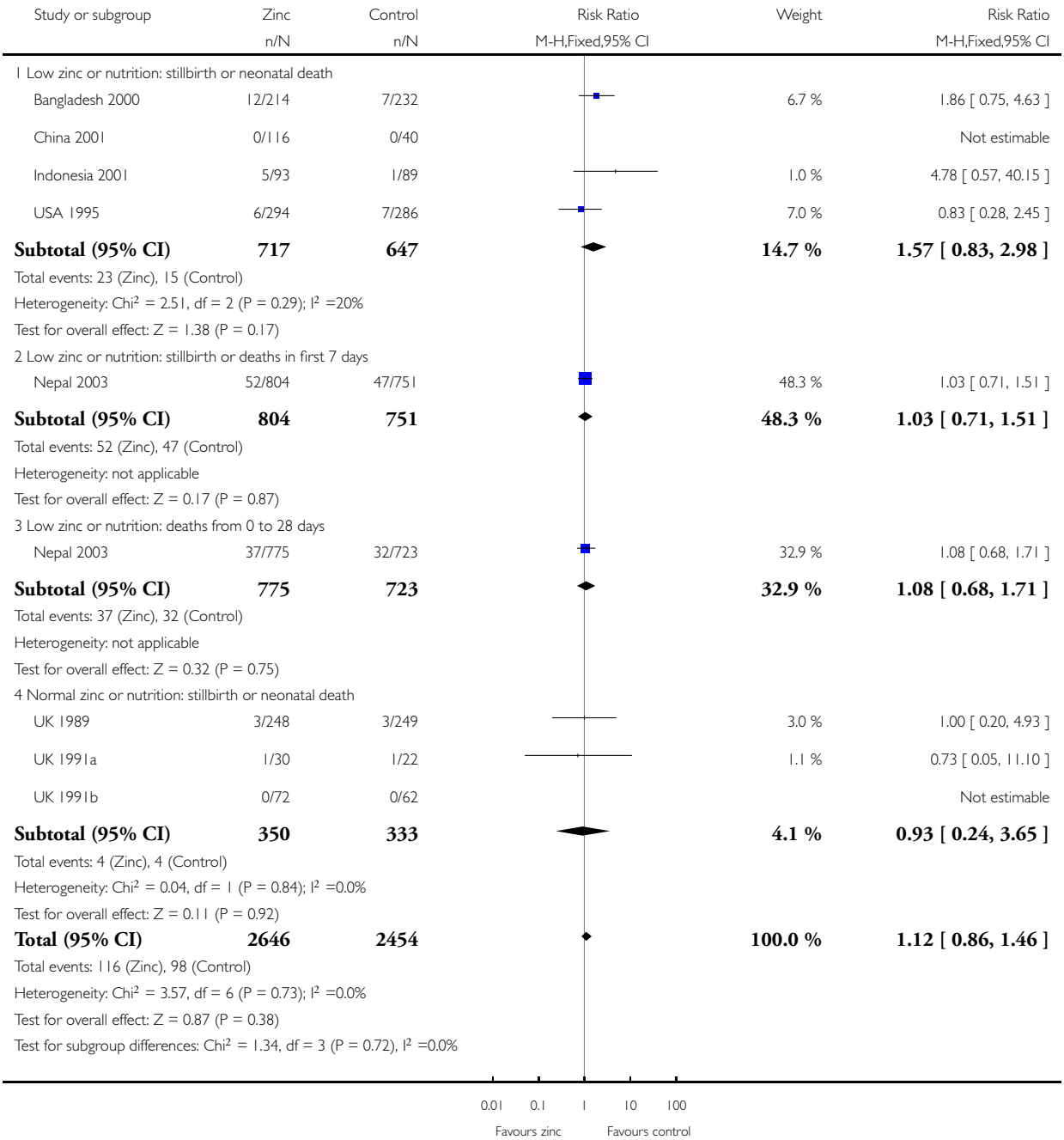
Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**3578**	**3521**		**96.3 %**	**0.87 [0.77, 0.98]**
Total events: 415 (Zinc), 471 (Control)					
Heterogeneity: Chi^2 = 16.99, df = 13 (P = 0.20); I^2 =23%					
Test for overall effect: 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: Chi^2 = 0.53, df = 1 (P = 0.47); I^2 =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: Chi^2 = 18.15, df = 15 (P = 0.25); I^2 =17%					
Test for overall effect: Z = 2.51 (P = 0.012)					
Test for subgroup differences: Chi^2 = 0.64, df = 1 (P = 0.42), I^2 =0.0%					

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



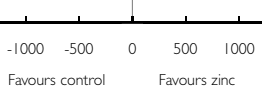
Analysis 1.3. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 3 Birthweight.

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	Mean(SD)	Control N	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)		9.3 %	-41.00 [-116.89, 34.89]
Chile 2001	249	3319 (460)	258	3250 (514)		7.4 %	69.00 [-15.84, 153.84]
Ghana 2009	272	3105 (490)	271	3120 (486)		7.9 %	-15.00 [-97.09, 67.09]
Indonesia 2001	84	3200 (500)	80	3150 (400)		2.8 %	50.00 [-88.26, 188.26]
Iran 2010	42	2961 (468)	42	2819 (609)		1.0 %	142.00 [-90.28, 374.28]
Nepal 2003	553	2598 (428)	522	2652 (429)		20.4 %	-54.00 [-105.25, -2.75]
Pakistan 2005	121	3023 (456)	121	3061 (444)		4.2 %	-38.00 [-151.40, 75.40]
Peru 1999	488	3267 (461)	469	3300 (498)		14.4 %	-33.00 [-93.86, 27.86]
Peru 2004	94	3351 (427)	101	3319 (389)		4.1 %	32.00 [-82.92, 146.92]
S Africa 1985	32	3088 (377)	33	3171 (483)		1.2 %	-83.00 [-293.28, 127.28]
USA 1983	86	3413 (574)	89	3373 (521)		2.0 %	40.00 [-122.58, 202.58]
USA 1985	55	3352 (430)	51	3338 (592)		1.4 %	14.00 [-184.27, 212.27]
USA 1995	294	3214 (669)	286	3088 (728)		4.1 %	126.00 [12.13, 239.87]
Subtotal (95% CI)	**2564**		**2539**			**80.2 %**	**-9.87 [-35.70, 15.96]**
Heterogeneity: Chi^2 = 16.84, df = 12 (P = 0.16); I^2 =29%							
Test for overall effect: Z = 0.75 (P = 0.45)							
2 Normal zinc or nutrition							
Indonesia 1999	477	3160 (520)	500	3090 (500)		13.1 %	70.00 [5.98, 134.02]
UK 1989	247	3291 (581)	244	3319 (531)		5.5 %	-28.00 [-126.43, 70.43]
UK 1991a	30	2990 (540)	22	2820 (600)		0.5 %	170.00 [-146.54, 486.54]
UK 1991b	72	3264 (722)	62	3220 (871)		0.7 %	44.00 [-229.53, 317.53]
Subtotal (95% CI)	**826**		**828**			**19.8 %**	**44.46 [-7.49, 96.41]**



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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
Heterogeneity: Chi² = 3.30, df = 3 (P = 0.35); I² =9%							
Test for overall effect: Z = 1.68 (P = 0.093)							
Total (95% CI)	**3390**		**3367**			**100.0 %**	**0.90 [-22.23, 24.02]**
Heterogeneity: Chi² = 23.51, df = 16 (P = 0.10); I² =32%							
Test for overall effect: Z = 0.08 (P = 0.94)							
Test for subgroup differences: Chi² = 3.37, df = 1 (P = 0.07), I² =70%							

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		56.4 %	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)					

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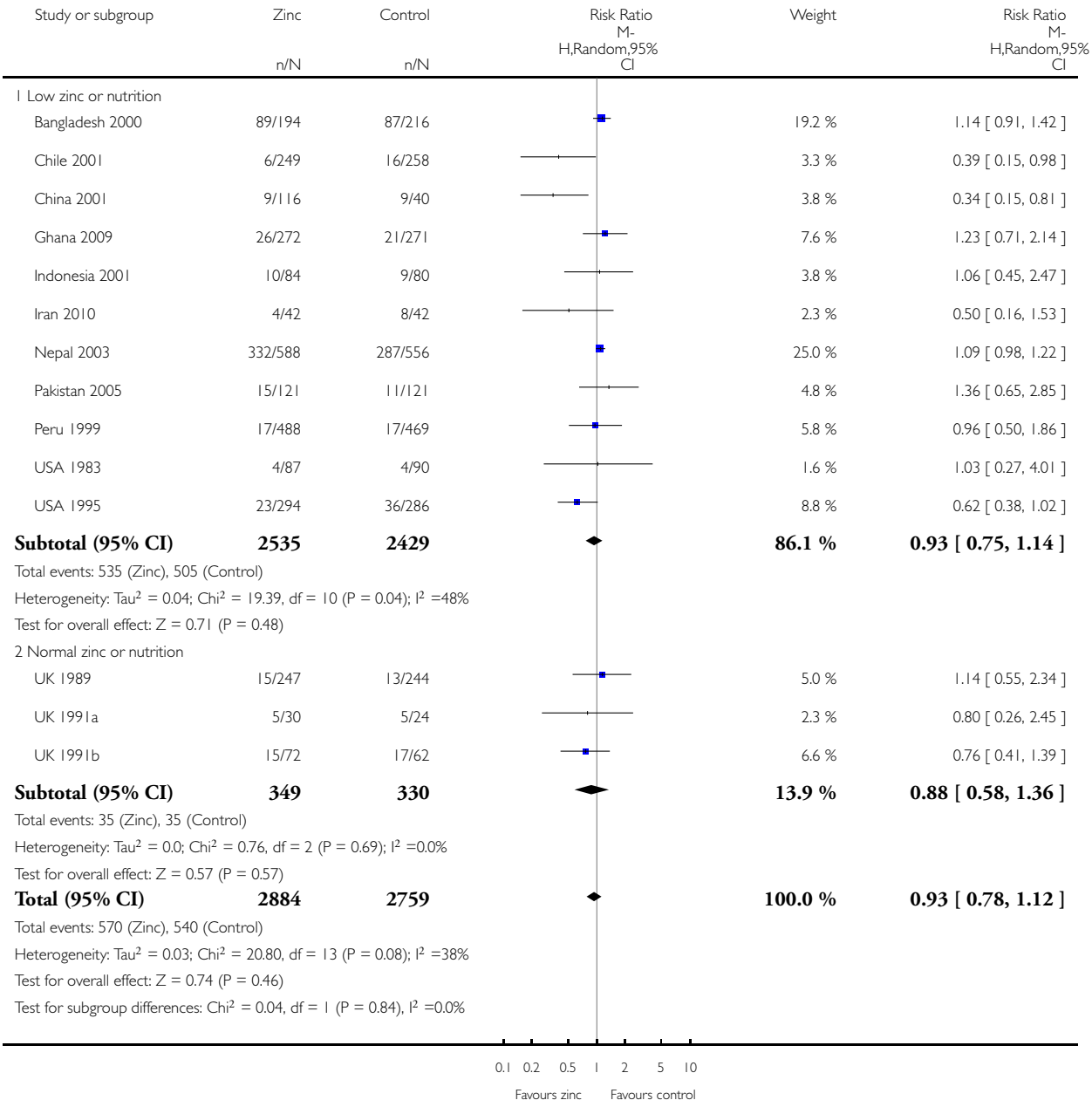
Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 Normal zinc or nutrition					
UK 1991a	2/30	6/22		1.2 %	0.24 [0.05, 1.10]
Subtotal (95% CI)	**30**	**22**		**1.2 %**	**0.24 [0.05, 1.10]**
Total events: 2 (Zinc), 6 (Control)					
Heterogeneity: not 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: Chi^2 = 9.68, df = 7 (P = 0.21); I^2 =28%					
Test for overall effect: Z = 0.55 (P = 0.58)					
Test for subgroup differences: Chi^2 = 3.52, df = 1 (P = 0.06), I^2 =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

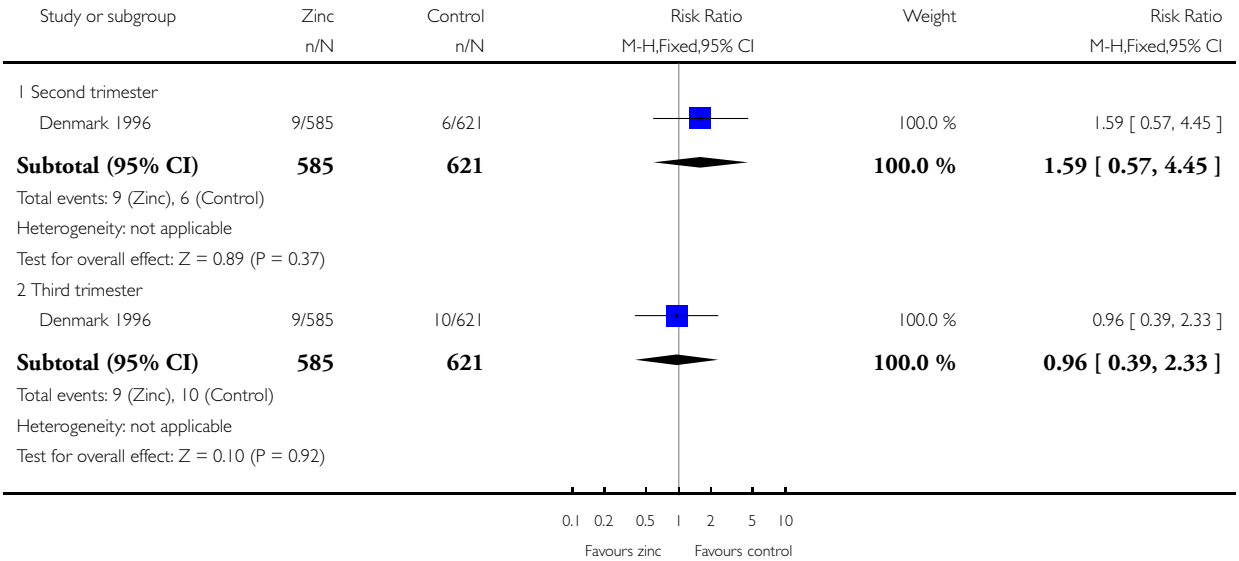


Analysis 1.6. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 6 Antepartum haemorrhage.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 6 Antepartum haemorrhage



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

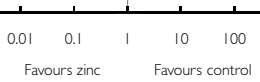
Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chile 2001	2/249	2/258		1.8 %	1.04 [0.15, 7.30]
Denmark 1996	20/585	22/621		20.1 %	0.97 [0.53, 1.75]
UK 1989	52/245	50/244		47.1 %	1.04 [0.73, 1.46]
UK 1991a	3/30	3/22		3.3 %	0.73 [0.16, 3.30]
USA 1983	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: Chi^2 = 8.10, df = 6 (P = 0.23); I^2 =26%

Test for overall effect: Z = 1.37 (P = 0.17)

Test for subgroup differences: Not applicable



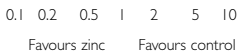
Analysis 1.8. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 8 Prelabour rupture of membranes.

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					



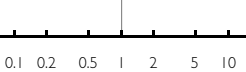
Analysis 1.9. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 9 Post-term birth.

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	Weight	Risk Ratio M-H,Fixed,95% CI
Peru 1999	22/521	17/495		38.4 %	1.23 [0.66, 2.29]
UK 1989	28/243	28/243		61.6 %	1.00 [0.61, 1.64]
UK 1991a	0/30	0/22			Not estimable
Total (95% CI)	**794**	**760**		**100.0 %**	**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					



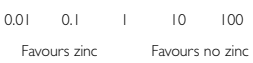
Analysis 1.10. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 10 Induction of labour.

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

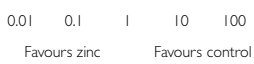
Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Indonesia 1999	13/249	19/270		36.6 %	0.74 [0.37, 1.47]
Indonesia 2001	1/92	0/87		1.0 %	2.84 [0.12, 68.76]
UK 1989	38/244	31/243		62.4 %	1.22 [0.79, 1.90]
Total (95% CI)	**585**	**600**		**100.0 %**	**1.06 [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 = 0.32 (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, 20.49]
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

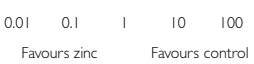
Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
China 2001	39/116	8/40		18.3 %	1.68 [0.86, 3.29]
Denmark 1996	36/585	50/621		23.4 %	0.76 [0.51, 1.16]
Indonesia 2001	1/92	1/87		2.8 %	0.95 [0.06, 14.89]
Iran 2010	38/42	26/42		26.2 %	1.46 [1.13, 1.89]
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



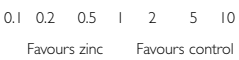
Analysis 1.14. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 14 Instrumental vaginal birth.

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					



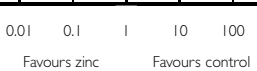
Analysis 1.15. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 15 Retention of placenta.

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					



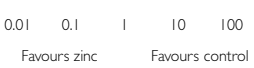
Analysis 1.16. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 16 Postpartum haemorrhage.

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					



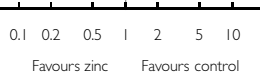
Analysis 1.17. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 17 Smell dysfunction.

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					

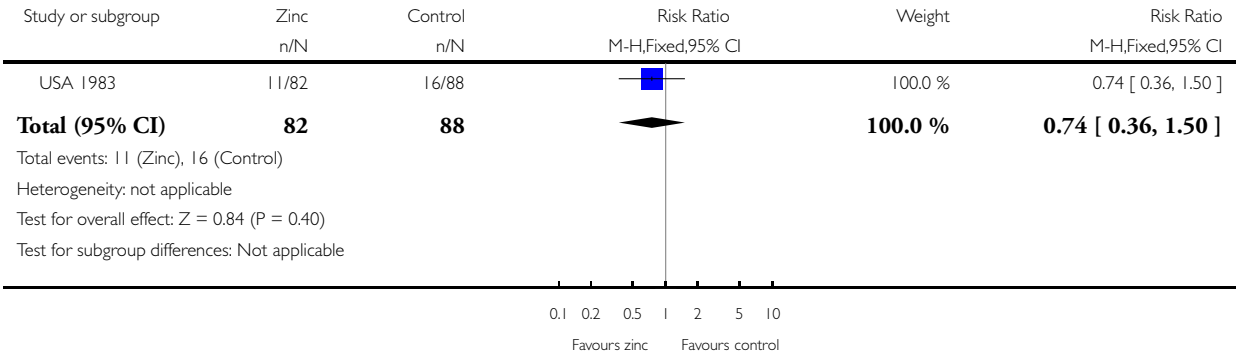


Analysis 1.18. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 18 Taste dysfunction.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 18 Taste dysfunction



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)

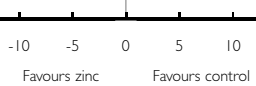
Outcome: 19 Fetal heart rate (beats/minute)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% 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 IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% 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)

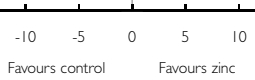
Outcome: 21 Number of fetal accelerations

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% 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)

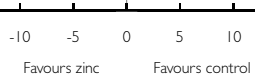
Outcome: 22 Number of fetal movement bouts

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% 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)

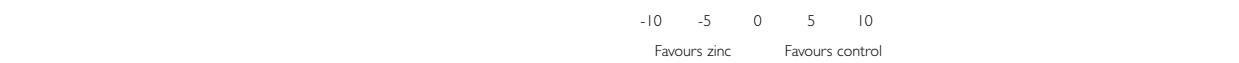
Outcome: 23 Fetal activity level

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% 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)

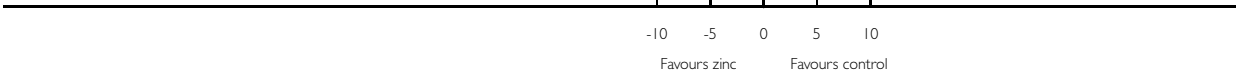
Outcome: 24 Fetal movement amplitude

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% 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		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% 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: Chi^2 = 6.24, df = 6 (P = 0.40); I^2 =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: Chi^2 = 5.59, df = 4 (P = 0.23); I^2 =28%

Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Not applicable

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: $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 0.02 (P = 0.98)

Test for subgroup differences: Not applicable

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: $Tau^2 = 0.01$; $Chi^2 = 10.91$, df = 6 (P = 0.09); $I^2 = 45\%$

Test for overall effect: Z = 0.42 (P = 0.67)

Test for subgroup differences: Not applicable

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					

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

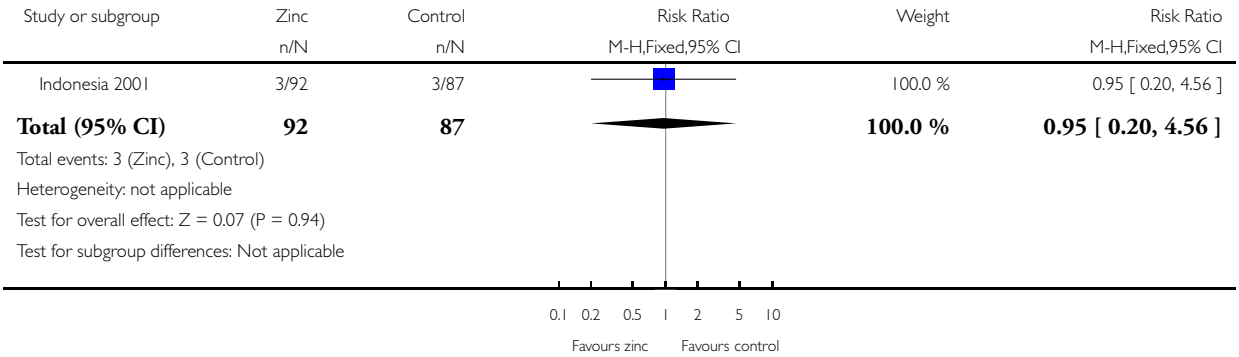
Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
China 2001	0/116	1/40		30.5 %	0.12 [0.00, 2.81]
USA 1995	1/294	5/286		69.5 %	0.19 [0.02, 1.66]
Total (95% CI)	**410**	**326**		**100.0 %**	**0.17 [0.03, 1.01]**
Total events: 1 (Zinc), 6 (Control)					
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 1.95 (P = 0.052)					
Test for subgroup differences: Not applicable					

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

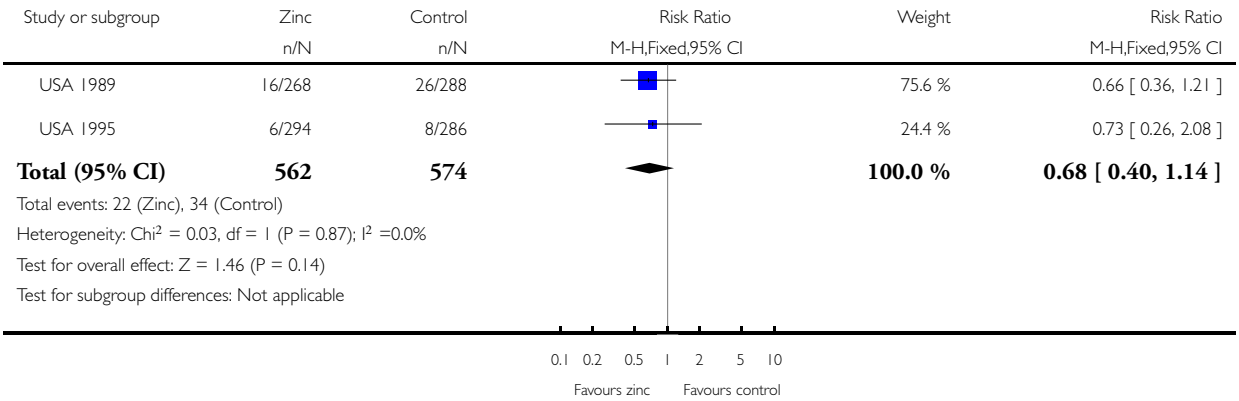


Analysis 1.32. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 32 Respiratory distress syndrome.

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



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					

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					

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)

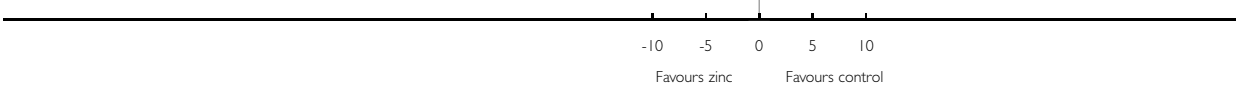
Outcome: 35 Neonatal hospital stay

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



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

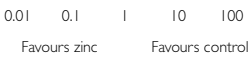
Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
China 2001	1/116	0/40		3.9 %	1.05 [0.04, 25.30]
Indonesia 2001	2/92	2/87		10.8 %	0.95 [0.14, 6.57]
Peru 2004	4/109	6/113		31.0 %	0.69 [0.20, 2.38]
UK 1989	5/248	8/249		42.1 %	0.63 [0.21, 1.89]
UK 1991a	1/30	2/22		12.2 %	0.37 [0.04, 3.79]
UK 1991b	0/72	0/62			Not estimable
Total (95% CI)	**667**	**573**		**100.0 %**	**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



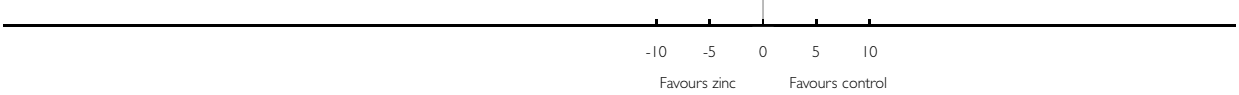
Analysis 1.37. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 37 Diarrhoea (episodes/infant over 6 months).

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 37 Diarrhoea (episodes/infant over 6 months)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Acute diarrhoea							
Bangladesh 2000	196	1.5 (1.9)	214	1.9 (2.1)		100.0 %	-0.40 [-0.79, -0.01]
Subtotal (95% CI)	**196**		**214**			**100.0 %**	**-0.40 [-0.79, -0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.02 (P = 0.043)							
2 Persistent diarrhoea							
Bangladesh 2000	196	0.3 (0.7)	214	0.3 (0.6)		100.0 %	0.0 [-0.13, 0.13]
Subtotal (95% CI)	**196**		**214**			**100.0 %**	**0.0 [-0.13, 0.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
Test for subgroup differences: Chi^2 = 3.70, df = 1 (P = 0.05), I^2 =73%							



Analysis 1.38. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 38 Dysentery (episodes/infant over 6 months).

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 38 Dysentery (episodes/infant over 6 months)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	196	0.04 (0.2)	214	0.1 (0.4)		100.0 %	-0.06 [-0.12, 0.00]
Total (95% CI)	**196**		**214**			**100.0 %**	**-0.06 [-0.12, 0.00]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.94 (P = 0.052)

Test for subgroup differences: Not applicable

Analysis 1.39. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 39 Cough (episodes/infant over 6 months).

Review: Zinc supplementation for improving pregnancy and infant outcome

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

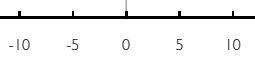
Outcome: 39 Cough (episodes/infant over 6 months)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	196	3.9 (1.9)	214	4.1 (1.8)		100.0 %	-0.20 [-0.56, 0.16]
Total (95% CI)	**196**		**214**			**100.0 %**	**-0.20 [-0.56, 0.16]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.09 (P = 0.27)

Test for subgroup differences: Not applicable



Analysis 1.40. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 40 Acute lower respiratory infection (episodes/infant over 6 months).

Review: Zinc supplementation for improving pregnancy and infant outcome

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

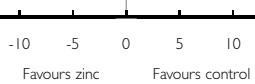
Outcome: 40 Acute lower respiratory infection (episodes/infant over 6 months)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	196	0.7 (1.2)	214	0.8 (1.3)		100.0 %	-0.10 [-0.34, 0.14]
Total (95% CI)	**196**		**214**			**100.0 %**	**-0.10 [-0.34, 0.14]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.81 (P = 0.42)

Test for subgroup differences: Not applicable



Analysis 1.41. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 41 Impetigo (episodes/infant over 6 months).

Review: Zinc supplementation for improving pregnancy and infant outcome

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

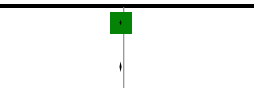
Outcome: 41 Impetigo (episodes/infant over 6 months)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	196	0.1 (0.6)	214	0.4 (0.8)		100.0 %	-0.30 [-0.44, -0.16]
Total (95% CI)	**196**		**214**			**100.0 %**	**-0.30 [-0.44, -0.16]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.32 (P = 0.000016)

Test for subgroup differences: Not applicable



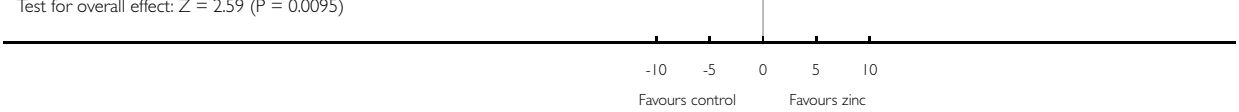
Analysis 1.42. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 42 Infant weight-for-age (Z-score).

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 42 Infant weight-for-age (Z-score)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Z-score at 6 months							
Bangladesh 2000	83	1.5 (0.9)	85	1.1 (0.9)		50.4 %	0.40 [0.13, 0.67]
Indonesia 2001	66	-0.17 (0.82)	70	-0.17 (0.85)		49.6 %	0.0 [-0.28, 0.28]
Subtotal (95% CI)	**149**		**155**			**100.0 %**	**0.20 [-0.19, 0.59]**
Heterogeneity: Tau^2 = 0.06; Chi^2 = 4.02, df = 1 (P = 0.04); I^2 =75%							
Test for overall effect: Z = 1.01 (P = 0.31)							
2 Z-score at 13 months							
Bangladesh 2000	83	-2.7 (1)	85	-2.3 (1)		100.0 %	-0.40 [-0.70, -0.10]
Subtotal (95% CI)	**83**		**85**			**100.0 %**	**-0.40 [-0.70, -0.10]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.59 (P = 0.0095)							



Analysis 1.43. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 43 Infant weight-for-height (Z-score).

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 43 Infant weight-for-height (Z-score)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Indonesia 2001	66	0.46 (0.89)	70	0.51 (0.77)		100.0 %	-0.05 [-0.33, 0.23]
Total (95% CI)	**66**		**70**			**100.0 %**	**-0.05 [-0.33, 0.23]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.35 (P = 0.73)

Test for subgroup differences: Not applicable

Analysis 1.44. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 44 Infant mid-upper arm circumference (mm).

Review: Zinc supplementation for improving pregnancy and infant outcome

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

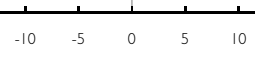
Outcome: 44 Infant mid-upper arm circumference (mm)

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	194	92 (8)	216	91 (8)		34.3 %	1.00 [-0.55, 2.55]
Peru 1999	445	103 (10)	409	103 (10)		45.8 %	0.0 [-1.34, 1.34]
USA 1995	294	112 (12)	286	110 (13)		19.9 %	2.00 [-0.04, 4.04]
Total (95% CI)	**933**		**911**			**100.0 %**	**0.74 [-0.17, 1.65]**

Heterogeneity: Chi^2 = 2.74, df = 2 (P = 0.25); I^2 =27%

Test for overall effect: Z = 1.60 (P = 0.11)

Test for subgroup differences: Not applicable



Analysis 1.45. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 45 Infant mental development index.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 45 Infant mental development index

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	83	99.34 (11.2)	85	102.64 (10)		100.0 %	-3.30 [-6.51, -0.09]
Total (95% CI)	**83**		**85**			**100.0 %**	**-3.30 [-6.51, -0.09]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.01 (P = 0.044)

Test for subgroup differences: Not applicable

Analysis 1.46. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 46 Infant psychomotor development index.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 46 Infant psychomotor development index

Study or subgroup	Zinc		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Bangladesh 2000	83	88.7 (17.4)	85	95.7 (15)		100.0 %	-7.00 [-11.92, -2.08]
Total (95% CI)	**83**		**85**			**100.0 %**	**-7.00 [-11.92, -2.08]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.79 (P = 0.0053)

Test for subgroup differences: Not applicable

Analysis 1.47. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 47 Infant approach.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

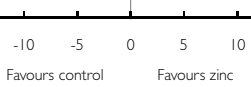
Outcome: 47 Infant approach

Study or subgroup	Zinc		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Bangladesh 2000	83	6.63 (1.76)	85	6.53 (1.4)		100.0 %	0.10 [-0.38, 0.58]
Total (95% CI)	**83**		**85**			**100.0 %**	**0.10 [-0.38, 0.58]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable



Analysis 1.48. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 48 Infant emotional tone.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 48 Infant emotional tone

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	83	5.25 (1)	85	5.9 (2)		100.0 %	-0.65 [-1.13, -0.17]
Total (95% CI)	**83**		**85**			**100.0 %**	**-0.65 [-1.13, -0.17]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.67 (P = 0.0075)

Test for subgroup differences: Not applicable

Analysis 1.49. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 49 Infant activity.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 49 Infant activity

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Bangladesh 2000	83	5.1 (1.2)	85	5.2 (1)		100.0 %	-0.10 [-0.43, 0.23]
Total (95% CI)	**83**		**85**			**100.0 %**	**-0.10 [-0.43, 0.23]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.59 (P = 0.56)

Test for subgroup differences: Not applicable

Analysis 1.50. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 50 Infant co-operation.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

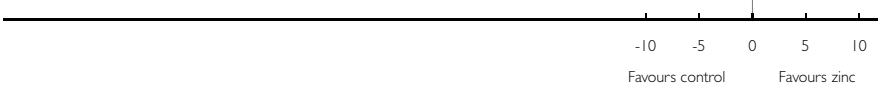
Outcome: 50 Infant co-operation

Study or subgroup	Zinc		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Bangladesh 2000	83	5.2 (1.8)	85	5.8 (1.9)		100.0 %	-0.60 [-1.16, -0.04]
Total (95% CI)	**83**		**85**			**100.0 %**	**-0.60 [-1.16, -0.04]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.10 (P = 0.036)

Test for subgroup differences: Not applicable



Analysis 1.51. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 51 Infant vocalisation.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 51 Infant vocalisation

Study or subgroup	Zinc		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Bangladesh 2000	83	4.9 (1.3)	85	4.98 (1.7)		100.0 %	-0.08 [-0.54, 0.38]
Total (95% CI)	**83**		**85**			**100.0 %**	**-0.08 [-0.54, 0.38]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.34 (P = 0.73)

Test for subgroup differences: Not applicable

Analysis 1.52. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 52 Differential abilities score at 5 years.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 52 Differential abilities score at 5 years

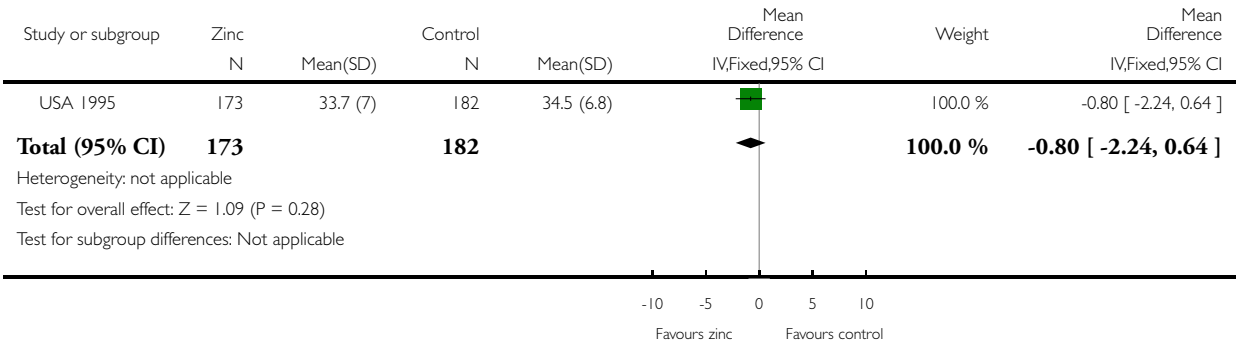
Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Non-verbal ability							
USA 1995	173	86.2 (16.5)	182	88.6 (15.1)		100.0 %	-2.40 [-5.70, 0.90]
Subtotal (95% CI)	**173**		**182**			**100.0 %**	**-2.40 [-5.70, 0.90]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.43 (P = 0.15)							
2 Verbal ability							
USA 1995	173	80 (11)	182	80.3 (10.7)		100.0 %	-0.30 [-2.56, 1.96]
Subtotal (95% CI)	**173**		**182**			**100.0 %**	**-0.30 [-2.56, 1.96]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.26 (P = 0.79)							
3 General conceptual ability, IQ							
USA 1995	173	81.5 (13.8)	182	82.6 (11.4)		100.0 %	-1.10 [-3.74, 1.54]
Subtotal (95% CI)	**173**		**182**			**100.0 %**	**-1.10 [-3.74, 1.54]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.82 (P = 0.41)							
Test for subgroup differences: Chi^2 = 1.07, df = 2 (P = 0.59), I^2 =0.0%							

Analysis 1.53. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 53 Visual sequential memory score.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 53 Visual sequential memory score

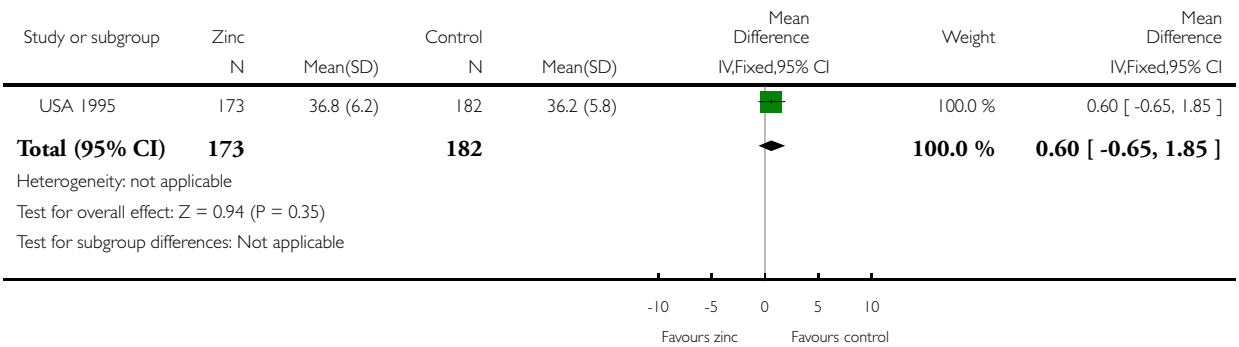


Analysis 1.54. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 54 Auditory sequential memory score.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 54 Auditory sequential memory score



Analysis 1.55. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 55 Knox cube score.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 55 Knox cube score

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	173	5 (1.5)	182	4.9 (1.3)		100.0 %	0.10 [-0.19, 0.39]
Total (95% CI)	**173**		**182**			**100.0 %**	**0.10 [-0.19, 0.39]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.67 (P = 0.50)

Test for subgroup differences: Not applicable

Analysis 1.56. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 56 Gross motor scale score.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

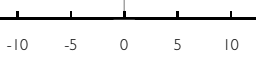
Outcome: 56 Gross motor scale score

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	173	331 (16)	182	333 (10)		100.0 %	-2.00 [-4.79, 0.79]
Total (95% CI)	**173**		**182**			**100.0 %**	**-2.00 [-4.79, 0.79]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.40 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 1.57. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 57 Grooved pegboard score.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 57 Grooved pegboard score

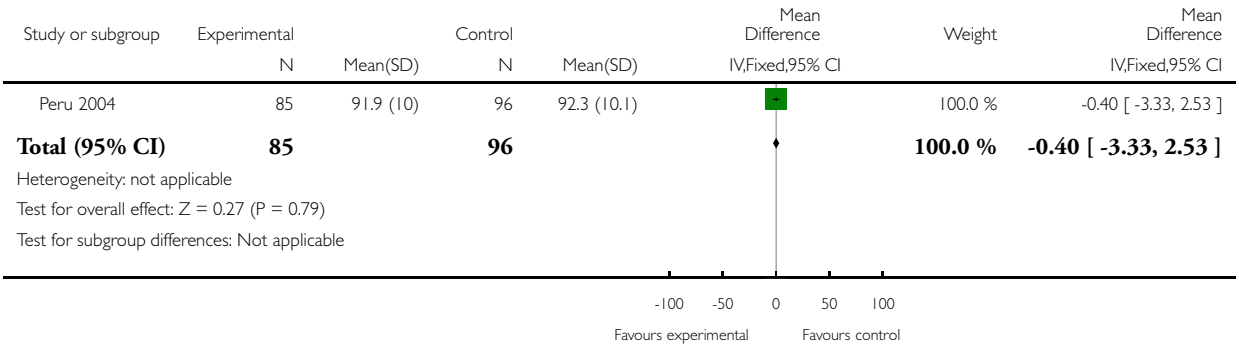
Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Dominant hand							
USA 1995	173	98 (14.8)	182	95.5 (21)		100.0 %	2.50 [-1.26, 6.26]
Subtotal (95% CI)	**173**		**182**			**100.0 %**	**2.50 [-1.26, 6.26]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.30 (P = 0.19)							
2 Non-dominant hand							
USA 1995	173	94.8 (16.8)	182	93.6 (20.7)		100.0 %	1.20 [-2.71, 5.11]
Subtotal (95% CI)	**173**		**182**			**100.0 %**	**1.20 [-2.71, 5.11]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.60 (P = 0.55)							
Test for subgroup differences: Chi^2 = 0.22, df = 1 (P = 0.64), I^2 =0.0%							

Analysis 1.58. Comparison 1 Zinc supplementation versus no zinc (with or without placebo), Outcome 58 Intelligence quotient of infants at 54 months.

Review: Zinc supplementation for improving pregnancy and infant outcome

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

Outcome: 58 Intelligence quotient of infants at 54 months



WHAT'S NEW

Last assessed as up-to-date: 31 October 2014.

Date	Event	Description
15 September 2015	Amended	Added additional information to Characteristics of included studies and Characteristics of excluded studies tables.

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 3, 1997

Date	Event	Description
31 October 2014	New search has been performed	Search updated. Seven new reports identified from the updated search: two reports of one new trial included (Egypt 2014); one new trial excluded (Naher 2012) and four new reports of existing trials added. Methods

(*Continued*)

		have been updated. A 'Summary of findings' table incorporated
31 October 2014	New citation required but conclusions have not changed	The inclusion of one new trial (Egypt 2014) did not change the conclusions.
9 November 2011	New search has been performed	Search updated. Three new trials included (China 2001; Ghana 2009; Iran 2010) and four new trials excluded (Mahmoudian 2005; Van Vliet 2001; Villamor 2006; Yalda 2010).
9 November 2011	New citation required but conclusions have not changed	New authors helped to update this review.
1 July 2011	Amended	Search updated. Thirteen trial reports added to Studies awaiting classification
6 November 2008	Amended	Converted to new review format.
20 December 2006	New search has been performed	Search updated. Nine new studies have been added to the original seven included studies, plus one previously excluded study (USA 1985) has now been included, making a total of 17 studies included in the 2006 update. A total of 11 studies have been excluded in this update and two studies have been placed in Studies awaiting classification. The Background and Methods sections have been expanded in this update, and additional outcomes have been added. The title has been changed from 'Zinc supplementation in pregnancy' to 'Zinc supplementation for improving pregnancy and infant outcome'. The conclusions regarding the effect of zinc supplementation on reducing preterm birth have been slightly strengthened

CONTRIBUTIONS OF AUTHORS

E Ota (EO) and C Miyazaki (CM) prepared the first version of this update. R Mori (RM) revised the draft. All the authors (RM, EO, R Tobe-Gai, P Middleton, CM, Z Bhutta and K Mahomed) read and approved the drafts of the updates. R Mori is the guarantor of the review.

DECLARATIONS OF INTEREST

Kassam Mahomed was principal investigator in a trial included in this review and was not involved in its assessment or data extraction.

SOURCES OF SUPPORT

Internal sources

- Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.
- National Center for Child Health and Development, Japan.

External sources

- Ministry of Health, Labour and Welfare, Japan.

Health Labour Sciences Research Grant (No.13800128)

- The Evidence and Programme Guidance, Department of Nutrition for Health and Development, World Health Organization, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have updated our methods to reflect the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Outcomes have been separated into 'Primary' and 'Secondary' outcomes.

We have added 'congenital malformation' to our secondary outcomes.

GIven the number of trials identified and the standard methods for the Cochrane Pregnancy and Childbirthbirth Group, quasi-randomised controlled trials have been excluded.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; *Infant, Low Birth Weight; Pregnancy Outcome; Premature Birth [*prevention & control]; Randomized Controlled Trials as Topic; Zinc [*administration & dosage]

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy