

Allocation

Allocation concealment was considered adequate in 10 trials (China 2001; Indonesia 1999; Iran 2010; Nepal 2003; Peru 1999; Peru 2004; S Africa 1985; UK 1989; USA 1985; USA 1983). Allocation concealment was rated as unclear in 10 trials: Bangladesh 2000; Chile 2001; Denmark 1996; Ghana 2009; Pakistan 2005; UK 1991a; UK 1991b; USA 1985; USA 1995 (method not described or not clearly described); and in Indonesia 2001 there was third party randomisation but no details of how allocations were concealed.

Blinding

All trials stated that both investigators and mothers were blinded or that the trial was double-blinded.

Blinding of outcome assessors was not well described but was likely to have happened in most trials (at least for short-term outcomes) as the majority were placebo-controlled.

Incomplete outcome data

Losses to follow-up ranged from 1% in UK 1989 to 40% in Denmark 1996. Attrition bias was judged to be at high risk in only three trials.

Selective reporting

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

Other potential sources of bias

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

Effects of interventions

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

Primary outcomes:

There was a 14% reduction in preterm birth in zinc groups compared with no zinc groups (risk ratio (RR) 0.86, 95% confidence interval (CI) 0.76 to 0.97; 16 RCTs, 7637 women; Analysis 1.1). No significant differences between zinc and no zinc were seen for stillbirth or neonatal death: RR 1.57 95% CI 0.83 to 2.98; 4 RCTs

of 1364 women; low zinc or RR 0.93 95% CI 0.24 to 3.65; 3 RCTs of 683 women; normal zinc (Analysis 1.2).

There was no significant difference in birthweight between zinc and no-zinc groups (mean difference (MD) -9.48 g, 95% CI -34.28 to 15.33; 16 RCTs, 5780 babies; Analysis 1.3); small-for-gestational age (RR 1.02 95% CI 0.94 to 1.11; 8 RCTs, 4252 babies; or low birthweight (RR 0.93, 95% CI 0.78 to 1.12; 14 RCTs, 5643 babies; Analysis 1.5).

Secondary outcomes

Maternal outcomes

No significant difference was seen for pregnancy hypertension or pre-eclampsia (RR 0.83, 95% CI 0.64 to 1.08; seven RCTs, 2975 women; Analysis 1.7) or prelabour rupture of membranes (Analysis 1.8), antepartum haemorrhage (Analysis 1.6), post-term birth (Analysis 1.9), retention of placenta (Analysis 1.15), meconium in liquor (Analysis 1.12), instrumental vaginal birth (Analysis 1.14) and smell or taste dysfunction (Analysis 1.17; Analysis 1.18), but these outcomes were measured in only one or two trials. In one trial of women at risk for small-for-gestational age babies (UK 1991a), significantly fewer women in the zinc group than in the no-zinc group were induced (RR 0.27, 95% CI 0.10 to 0.73, 52 women; Analysis 1.10).

No significant differences were seen for postpartum haemorrhage (Analysis 1.16) or maternal infections (Analysis 1.11) (three trials each) or gestational age at birth (Analysis 1.25) (six trials) or caesarean section (Analysis 1.13; random effects) (six trials). The heterogeneity in the caesarean section seemed to be contributed to by the income settings of the countries, as trials in high-income settings tend to favour zinc supplement, while trials in low-income settings tend to favour the controls.

Birthweight and associated outcomes

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

Other neonatal outcomes

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

There were no significant differences between the zinc and no-zinc groups for the following outcomes : Apgar scores less than five at five minutes, neonatal hypoxia, jaundice, fever, infant umbilical infection, neonatal sepsis, respiratory distress syndrome, neonatal intraventricular haemorrhage, necrotising enterocolitis, and neonatal hospital stay. Each of these outcomes was only available from one or two RCTs.

In one RCT of 176 babies (Peru 2004), four measures of fetal heart rate (fetal heart rate, number of fetal movement bouts, fetal activity level, and fetal movement amplitude) showed no evidence of differences between the zinc and no-zinc groups, while fetal heart rate variability and number of fetal accelerations were significantly higher in the zinc groups.

In one RCT of 196 infants (Bangladesh 2000), the zinc group had significantly fewer episodes per infant of acute diarrhoea over six months (MD -0.4 episodes, 95% CI -0.79 to -0.01; Analysis 1.37), and significantly fewer episodes per infant of impetigo. No significant differences were seen for episodes of persistent diarrhoea, dysentery, cough, and acute lower respiratory infection) over the same period.

Results of infant weight-for-age (Z-score) showed no evidence of difference at six months for the zinc and no-zinc groups in two RCTs (304 infants), but by 13 months, the no-zinc group showed significantly higher scores (in one RCT of 168 infants, Bangladesh 2000). No evidence of difference was seen for weight-for-height at six months in one RCT of 136 infants (Indonesia 2001).

Infant/child development

Three RCTs (Bangladesh 2000; Peru 2004; USA 1995) measured child development outcomes. A subset of 168 infants from

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

Subgroup analyses

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

Reporting bias

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

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

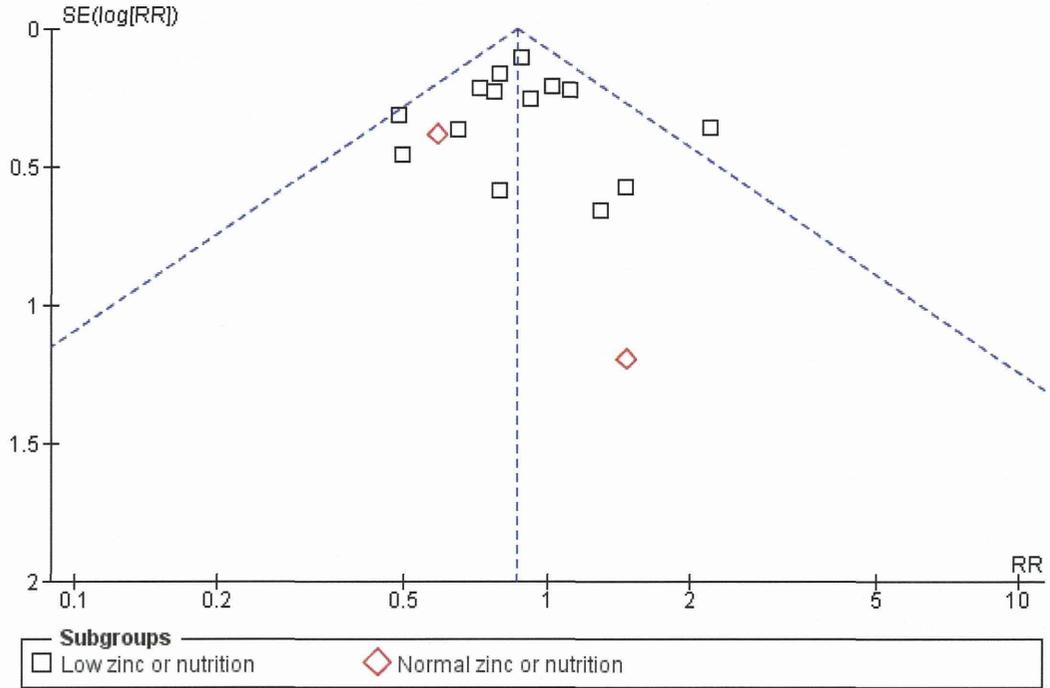


Figure 4. Funnel plot of comparison: I Zinc supplementation versus no zinc (with or without placebo), outcome: I.3 Birthweight.

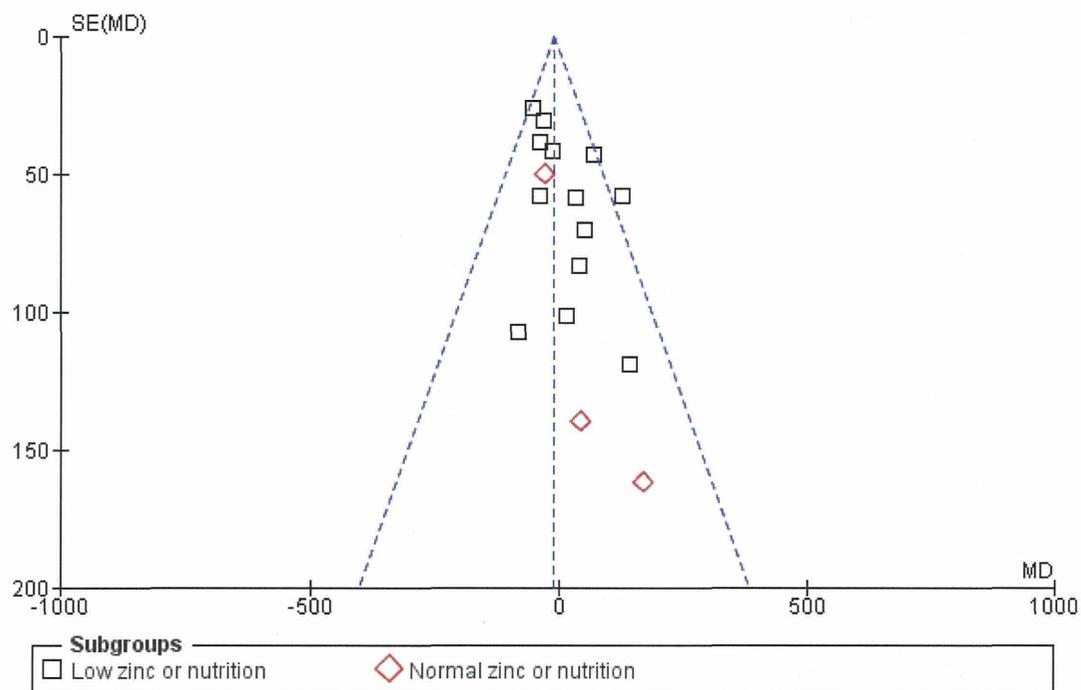
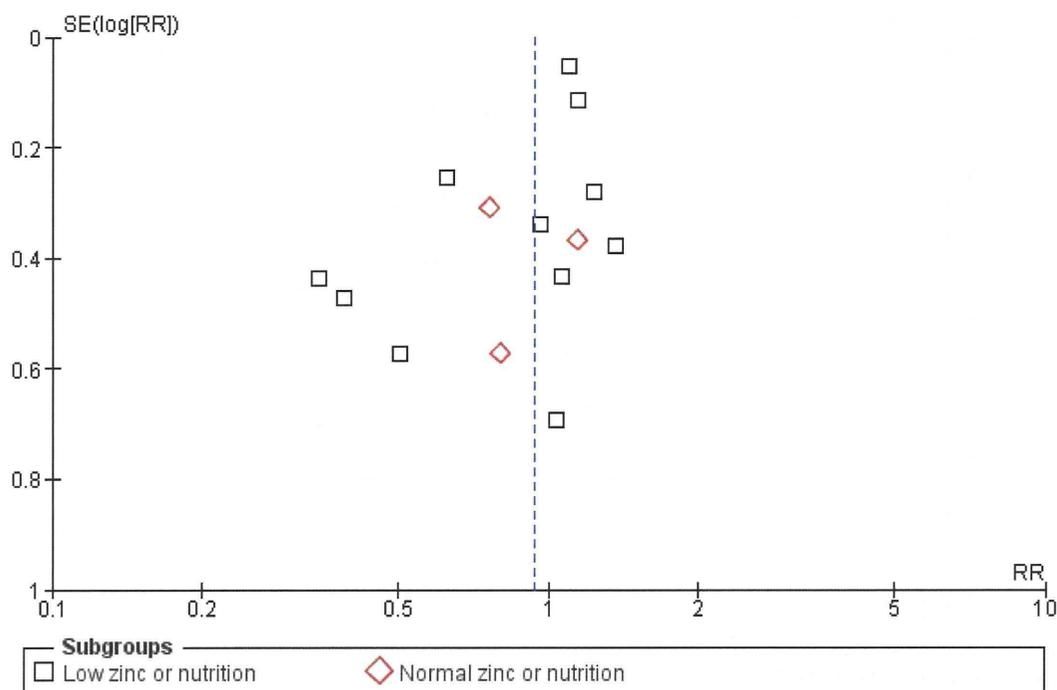


Figure 5. Funnel plot of comparison: I Zinc supplementation versus no zinc (with or without placebo), outcome: I.5 Low birthweight.



DISCUSSION

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

This review of 20 randomised controlled trials, including over 15,000 women and their babies, has not provided compelling evidence for routine zinc supplementation during pregnancy, although the finding of a reduction in preterm births warrants further investigation, as does the suggestion of reporting bias from the funnel plot on small-for-gestational age. Subgroup analysis of

the 17 studies involving women who are or are likely to be zinc deficient, such as populations from developing countries or from low socioeconomic groups from western countries, also did not make a case for zinc supplementation in those groups of women. This is consistent with a review of maternal zinc supplementation in developing countries (Osendarp 2003).

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

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

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

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

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

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

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

AUTHORS' CONCLUSIONS

Implications for practice

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

Implications for research

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

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REFERENCES

References to studies included in this review

Bangladesh 2000 *{published data only}*

Hamadani JD, Fuchs GJ, Osendarp SJM, Huda SN, Grantham-McGregor SM. Zinc supplementation during pregnancy and effects on mental development and behaviour of infants: a follow-up study. *Lancet* 2002;**360** (9329):290–4.

Osendarp S. *Zinc supplementation in Bangladeshi women and infants: effects on pregnancy outcome, infant growth, morbidity and immune response [thesis]*. Wageningen: Wageningen

University, 2001.

Osendarp SJM, Raaij JMA, Darmstadt GL, Baqui AH, Hautvast JG, Fuchs GJ. Zinc supplementation during pregnancy and effects on growth and morbidity in low birthweight infants: a randomised placebo controlled trial. *Lancet* 2001;**357**(9262):1080–5.

* Osendarp SJM, Van Raaij JMA, Arifeen SE, Wahed MA, Baqui AH, Fuchs GJ. A randomized, placebo-controlled trial of the effect of zinc supplementation during pregnancy outcome in Bangladeshi urban poor. *American Journal of Clinical Nutrition* 2000;**71**(1):114–9.

Chile 2001 {published data only}

Castillo-Duran C, Marin V, Alcazar LS, Iturralde H, Ruz MO. Controlled trial of zinc supplementation in Chilean pregnancy adolescents. *Nutrition Research* 2001;**21**:715–24.

China 2001 {published data only}

* Xie L, Chen X, Pan J. The effects of zinc supplementation to Chinese rural pregnant women and their pregnancy outcome. *Journal of Shanghai Second Medical University* 2001;**13**(2):119–24.

Yuan W, Geng G, Chen A, Wu J, Zhang Z, Gao E. Effects of zinc supplementation of rural pregnant women on the growth of offspring in early childhood. *Fudan University Journal of Medical Sciences* 2004;**31**(5):496–501.

Denmark 1996 {published data only}

Jonsson B, Hauge B, Larsen MF, Hald F. Zinc supplementation during pregnancy: a double blind randomised controlled trial. *Acta Obstetrica et Gynecologica Scandinavica* 1996;**75**:725–9.

Ghana 2009 {published data only}

Saaka M, Oosthuizen J, Beatty S. Effect of prenatal zinc supplementation on birthweight. *Journal of Health, Population & Nutrition* 2009;**27**(5):619–31.

Indonesia 1999 {published data only}

Hakimi M, Dibley MJ, Surjono A, Nurdianti D. Impact of vitamin A and zinc supplementation on puerperal sepsis: a randomized controlled trial in rural Indonesia. In: Nurdianti D editor(s). *Nutrition and reproductive health in central Java, Indonesia; an epidemiological approach [PhD thesis]*. Umea, Sweden: Umea University Medical Dissertations, 2001.

Indonesia 2001 {published data only}

* Dijkhuizen MA, Wieringa FT. *Vitamin A, iron and zinc deficiency in Indonesia: micronutrient interactions and effects of supplementation [thesis]*. Wageningen: Wageningen University, 2001.

Dijkhuizen MA, Wieringa FT, West CE, Muhilal. Zinc plus β -carotene supplementation of pregnant women is superior to β -carotene supplementation alone in improving vitamin A status in both mothers and infants. *American Journal of Clinical Nutrition* 2004;**80**:1299–307.

Wieringa FT, Dijkhuizen MA, Muhilal, Van der Meer JW. Maternal micronutrient supplementation with zinc and beta-carotene affects morbidity and immune function of infants during the first 6 months of life. *European Journal of Clinical Nutrition* 2010;**64**(10):1072–9.

Iran 2010 {published data only}

Danesh A, Janghorbani M, Mohammadi B. Effects of zinc supplementation during pregnancy on pregnancy outcome in women with history of preterm delivery: a double-blind randomized, placebo-controlled trial. *Journal of Maternal-Fetal and Neonatal Medicine* 2010;**23**(5):403–8.

Nepal 2003 {published data only}

Christian P, Jiang T, Khattry SK, LeClerq SC, Shrestha SR, West KP Jr. Antenatal supplementation with micronutrients and biochemical indicators of status and subclinical

infection in rural Nepal. *American Journal of Clinical Nutrition* 2006;**83**(4):788–94.

* Christian P, Khattry SK, Katz J, Pradhan EK, LeClerq SC, Ram Shrestha S, et al. Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: double blind randomised community trial. *BMJ* 2003;**326**:571–6.

Christian P, Shrestha J, LeClerq SC, Khattry SK, Jiang T, Wagner T, et al. Supplementation with micronutrients in addition to iron and folic acid does not further improve the hematologic status of pregnant women in Nepal. *Journal of Nutrition* 2003;**133**(11):3492–8.

Christian P, West KP, Khattry SK, LeClerq SC, Pradhan EK, Katz J, et al. Effects of maternal micronutrient supplementation on fetal loss and infant mortality: a cluster-randomized trial in Nepal. *American Journal of Clinical Nutrition* 2003;**78**:1194–202.

Pakistan 2005 {published data only}

Hafeez A, Mahmood G, Hassan M, Batool T, Hayat H, Mazhar F, et al. Serum zinc levels and effects of oral supplementation in pregnant women. *JCPSP - Journal of the College of Physicians and Surgeons Pakistan* 2005;**15**(10):612–5.

* Hafeez A, Mehmood G, Mazhar F. Oral zinc supplementation in pregnant women and its effect on birth weight: a randomised controlled trial. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2005;**90**:F170–F171.

Peru 1999 {published data only}

Caulfield LE, Donangelo CM, Chen P, Junco J, Meriardi M, Zavaleta N. Red blood cell metallothionein as an indicator of zinc status during pregnancy. *Nutrition* 2008;**24**(11-12):1081–7.

* Caulfield LE, Zavaleta N, Figueroa A. Adding zinc to prenatal iron and folate supplements improves maternal and neonatal zinc status in a Peruvian population. *American Journal of Clinical Nutrition* 1999;**69**(6):1257–63.

Caulfield LE, Zavaleta N, Figueroa A, Zulema L. Maternal zinc supplementation does not affect size at birth or pregnancy duration in Peru. *Journal of Nutrition* 1999;**129**(8):1563–8.

Iannotti LL, Zavaleta N, Leon Z, Huasquiche C, Shankar AH, Caulfield LE. Maternal zinc supplementation reduces diarrheal morbidity in Peruvian infants. *Journal of Pediatrics* 2010;**156**(6):960-4, 964.e1- 964.e2.

Iannotti LL, Zavaleta N, Leon Z, Shankar AH, Caulfield LE. Maternal zinc supplementation and growth in Peruvian infants. *American Journal of Clinical Nutrition* 2008;**88**(1):154–60.

Meriardi M, Caulfield LE, Zavaleta N, Figueroa A, DiPietro JA. Adding zinc to prenatal iron and folate tablets improves fetal neurobehavioral development. *American Journal of Obstetrics and Gynecology* 1999;**180**(2 Pt 1):483–90.

O'Brien KO, Zavaleta N, Caulfield LE, Wen J, Abrams SA. Prenatal iron supplements impair zinc absorption in pregnant Peruvian women. *Journal of Nutrition* 2000;**130**:2251–5.

O'Brien KO, Zavaleta N, Caulfield LE, Yang D-X, Abrams

- SA. Influence of prenatal iron and zinc supplements on supplemental iron absorption, red blood cell incorporation, and iron status in pregnant Peruvian women. *American Journal of Clinical Nutrition* 1999;**69**:509–15.
- Zavaleta N, Caulfield LE, Garcia T. Changes in iron status during pregnancy in Peruvian women receiving prenatal iron and folic acid supplements with or without zinc. *American Journal of Clinical Nutrition* 2000;**71**(4):956–61.
- Peru 2004 {published data only}**
- Caulfield LE, Putnick DL, Zavaleta N, Lazarte F, Albornoz C, Chen P, et al. Maternal gestational zinc supplementation does not influence multiple aspects of child development at 54 mo of age in Peru. *American Journal of Clinical Nutrition* 2010;**92**(1):130–6.
- Caulfield LE, Zavaleta N, Chen P, Lazarte F, Albornoz C, Putnick DL, et al. Maternal zinc supplementation during pregnancy affects autonomic function of Peruvian children assessed at 54 months of age. *Journal of Nutrition* 2011;**141**(2):327–32.
- Merialdi M, Caulfield LE, Zavaleta N, Figueroa A, Costigan KA, Dominici F, et al. Randomized controlled trial of prenatal zinc supplementation and fetal bone growth. *American Journal of Clinical Nutrition* 2004;**79**:826–30.
- * Merialdi M, Caulfield LE, Zavaleta N, Figueroa A, Dominici F, DiPietro JA. Randomized controlled trial of prenatal zinc supplementation and the development of fetal heart rate. *American Journal of Obstetrics and Gynecology* 2004;**190**:1106–12.
- S Africa 1985 {published data only}**
- Ross SM, Nel E, Naeye RL. Differing effects of low and high bulk maternal dietary supplements during pregnancy. *Early Human Development* 1985;**10**:295–302.
- UK 1989 {published data only}**
- James DK, Golding J, Mahomed K, McCabe R. A randomised double blind placebo controlled trial of zinc supplementation in pregnancy. Proceedings of 27th Autumn meeting of British Association of Perinatal Medicine; 1989; UK. 1989.
- Mahomed K, James DK, Golding J, McCabe R. Failure to taste zinc sulphate solution does not predict zinc deficiency in pregnancy. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1993;**48**:169–75.
- * Mahomed K, James DK, Golding J, McCabe R. Zinc supplementation during pregnancy: a double blind randomised controlled trial. *BMJ* 1989;**299**:826–30.
- UK 1991a {published data only}**
- Simmer K, Lort-Phillips L, James C, Thompson RPH. A double blind trial of zinc supplementation in pregnancy. *European Journal of Clinical Nutrition* 1991;**45**:139–44.
- UK 1991b {published data only}**
- Robertson JS, Heywood B, Atkinson SM. Zinc supplementation during pregnancy. *Journal of Public Health Medicine* 1991;**13**:227–9.
- USA 1983 {published data only}**
- * Hunt IF, Murphy NJ, Cleaver AE, Faraji B, Swendseid ME, Coulson AH, et al. Zinc supplementation during pregnancy: effects on selected blood constituents and on progress and outcome of pregnancy in low-income women of Mexican descent. *American Journal of Clinical Nutrition* 1984;**40**:508–21.
- Hunt IF, Murphy NJ, Cleaver AE, Faraji B, Swendseid ME, Coulson AM, et al. Zinc supplementation during pregnancy: zinc concentration of serum and hair from low-income women of Mexican descent. *American Journal of Clinical Nutrition* 1983;**37**:572–82.
- USA 1985 {published data only}**
- Hunt IF, Murphy NJ, Cleaver AE, Faraji B, Swendseid ME, Browdy BL, et al. Zinc supplementation during pregnancy in low income teenagers of Mexican descent: effects on selected blood constituents and on progress and outcome of pregnancy. *American Journal of Clinical Nutrition* 1985;**42**:815–28.
- USA 1989 {published data only}**
- Cherry FF, Sandstead HH, Rojas P, Johnson LK, Batson HK, Wang XB. Adolescent pregnancy: associations among body weight, zinc nutriture, and pregnancy outcome. *American Journal of Clinical Nutrition* 1989;**50**:945–54.
- USA 1995 {published data only}**
- Goldenberg R, Tamura T, Neggers Y, Copper R, Johnston K, DuBard M, et al. Maternal zinc supplementation increases birthweight and head circumference. *American Journal of Obstetrics and Gynecology* 1995;**172**(1 Pt 2):368.
- * Goldenberg RL, Tamura T, Neggers Y, Cooper RL, Johnston KE, DuBard MB, et al. The effect of zinc supplementation on pregnancy outcome. *JAMA* 1995;**274**:463–8.
- Hogg B, Tamura T, Johnston K, DuBard M, Goldenberg RL. Homocysteine levels in pregnancy induced hypertension (PIH), preeclampsia (PE) and intrauterine growth retardation (IUGR) [abstract]. *American Journal of Obstetrics and Gynecology* 2000;**182**(1 Pt 2):S90.
- Hogg BB, Tamura T, Johnston KE, DuBard MB, Goldenberg RL. Second-trimester plasma homocysteine levels and pregnancy-induced hypertension, preeclampsia, and intrauterine growth restriction. *American Journal of Obstetrics and Gynecology* 2000;**183**(4):805–9.
- Neggers YH, Goldenberg RL, Tamura T, Johnston KE, Copper RL, DuBard M. Plasma and erythrocyte zinc concentrations and their relationship to dietary zinc intake and zinc supplementation during pregnancy in low-income African-American women. *Journal of the American Dietetic Association* 1997;**97**:1269–74.
- Tamura T, Goldenberg RL, Ramey SL, Nelson KG, Chapman VR. Effect of zinc supplementation of pregnant women on the mental and psychomotor development of their children at 5 y of age. *American Journal of Clinical Nutrition* 2003;**77**(6):1512–6.
- Tamura T, Goldenberg RN, Johnston KE, DuBard MB. Effect of smoking on plasma ferritin concentrations in pregnant women. *Clinical Chemistry* 1995;**41**(8):1190–1.
- Tamura T, Olin KL, Goldenberg RL, Johnston KE, Dubard MB, Keen CL. Plasma extracellular superoxide dismutase activity in healthy pregnant women is not influenced by

zinc supplementation. *Biological Trace Element Research* 2001;**80**(2):107–13.

References to studies excluded from this review

An 2001 *{published data only}*

An H, Yin S, Xu Q. Effects of supplementing calcium, iron and zinc on the fetus development and growth during pregnancy [Chinese]. *Chung-Hua Yu Fang i Hsueh Tsa Chih [Chinese Journal of Preventive Medicine]* 2001;**35**(6):370–3.

Appelbaum 1979 *{published data only}*

Appelbaum PC, Ross SM, Dhupelia I, Naeye RL. The effect of diet supplementation and addition of zinc in vitro on the growth-supporting property of amniotic fluid in African women. *American Journal of Obstetrics and Gynecology* 1979;**135**:82–4.

Christian 2001 *{published data only}*

Christian P, Khattry SK, LeClerq SC, Shrestha SR, Kimbrough-Pradhan E, West KP Jr. Iron and zinc interactions among pregnant Nepali women. *Nutrition Research* 2001;**21**(1-2):141–8.

* Christian P, Khattry SK, Yamini S, Stallings R, LeClerq SC, Shrestha SR, et al. Zinc supplementation might potentiate the effect of vitamin A in restoring night vision in pregnant Nepalese women. *American Journal of Clinical Nutrition* 2001;**73**(6):1045–51.

Fawzi 2005 *{published data only}*

Fawzi WW, Villamor E, Msamanga GI, Antelman G, Aboud S, Urassa W, et al. Trial of zinc supplements in relation to pregnancy outcomes, hematologic indicators, and T cell counts among HIV-1-infected women in Tanzania. *American Journal of Clinical Nutrition* 2005;**81**(1):161–7.

France 2004 *{published data only}*

Hininger I, Favier M, Arnaud J, Faure H, Thoulon JM, Hariveau E, et al. Effects of a combined micronutrient supplementation on maternal biological status and newborn anthropometrics measurements: a randomized double-blind, placebo-controlled trial in apparently healthy pregnant women. *European Journal of Clinical Nutrition* 2004;**58**:52–9.

Hambidge 1983 *{published data only}*

Hambidge KM, Krebs NF, Jacobs MA, Favier A, Guyette L, Ikle DN. Zinc nutritional status during pregnancy: a longitudinal study. *American Journal of Clinical Nutrition* 1983;**37**:429–42.

India 1993 *{published data only}*

Garg HK, Singal KC, Arshad Z. Zinc taste test in pregnant women and its correlation with serum zinc level. *Indian Journal of Physiology and Pharmacology* 1993;**37**(4):318–22.

* Garg HK, Singal KC, Arshad Z. A study of the effect of oral zinc supplementation during pregnancy on pregnancy outcome. *Indian Journal of Physiology and Pharmacology* 1993;**37**(4):276–84.

Garg HK, Singal KC, Arshad Z. Effect of oral zinc supplementation on copper and haemoglobin levels in pregnant women. *Indian Journal of Physiology and Pharmacology* 1994;**38**:272–6.

Kynast 1986 *{published data only}*

Kynast G, Saling E. Effect of oral zinc application during pregnancy. *Gynecologic and Obstetric Investigation* 1986;**21**:117–23.

Mahmoudian 2005 *{published data only}*

Mahmoudian A, Khademloo MD. The effect of simultaneous administration of zinc sulfate and ferrous sulfate in the treatment of anemic pregnant women. *Journal of Research in Medical Sciences* 2005;**10**(4):205–9.

Makola 2003 *{published data only}*

Makola D, Ash DM, Tatala SR, Latham MC, Ndossi G, Mehanso H. A micronutrient-fortified beverage prevents iron deficiency, reduces anemia and improves the hemoglobin concentration of pregnant Tanzanian women. *Journal of Nutrition* 2003;**133**:1339–46.

Nishiyama 1999 *{published data only}*

Nishiyama S, Kiwaki K, Miyazaki Y, Hasuda T. Zinc and IGF-I concentrations in pregnant women with anemia before and after supplementation with iron and/or zinc. *Journal of the American College of Nutrition* 1999;**18**(3):261–7.

Nogueira 2003 *{published data only}*

Nogueira NDN, Macedo ADS, Parente JV, Cozzolino SMF. Nutritional profile of newborns of adolescent mothers supplemented with iron, in different concentrations, zinc and folic acid. *Revista de Nutricao* 2002;**15**:193–200.

* Nogueira Ndo N, Parente JV, Cozzolino SM. Changes in plasma zinc and folic acid concentrations in pregnant adolescents submitted to different supplementation regimens. *Cadernos de Saude Publica* 2003;**19**(1):155–60.

Van Vliet 2001 *{published data only}*

Van Vliet T, Boelsma E, De Vries AJ, Van den Berg H. Retinoic acid metabolites in plasma are higher after intake of liver paste compared with a vitamin A supplement in women. *Journal of Nutrition* 2001;**131**(12):3197–203.

Villamor 2006 *{published data only}*

Villamor E, Aboud S, Koulinska IN, Kupka R, Urassa W, Chaplin B, et al. Zinc supplementation to HIV-1-infected pregnant women: effects on maternal anthropometry, viral load, and early mother-to-child transmission. *European Journal of Clinical Nutrition* 2006;**60**(7):862–9.

Yalda 2010 *{published data only}*

Yalda MA, Ibrahiem AA. The effect of combined supplementation of iron and zinc versus iron alone on anemic pregnant patients in Dohuk. *Jordan Medical Journal* 2010;**44**(1):9–16.

References to ongoing studies

Zahiri 2010 *{published data only}*

Zahiri Z. Assessment the effect of zinc supplementation on adverse outcomes of pregnancy, a randomized controlled clinical trial. IRCT Iranian Registry of Clinical Trials (www.irct.ir) (accessed 6 December 2010).

Additional references

- Aggett 1991**
Aggett PJ. The assessment of zinc status: a personal view; workshop on assessment of zinc status. *Proceedings of the Nutrition Society* 1991;**50**:9–17.
- Apgar 1970**
Apgar J. Effect of zinc deficiency in maintenance of pregnancy in the rat. *Journal of Nutrition* 1970;**100**:470.
- Cherry 1981**
Cherry FF, Bennett EA, Bazzono GS, Johnson LK, Fosmire GJ, Batson HK. Plasma zinc in hypertension/toxaemia and other reproductive variables in adolescent pregnancy. *American Journal of Clinical Nutrition* 1981;**34**:194–201.
- Chesters 1982**
Chesters JK. Metabolism and Biochemistry of Zinc. In: Prasad AS editor(s). *Clinical biochemistry and nutritional aspects of trace elements*. New York: Alan R Liss, 1982.
- DiPietro 1996**
DiPietro JA, Hodgson DM, Costigan KA, Johnson TRB. Fetal neurobehavioral development. *Child Development* 1996;**67**:2553–7.
- Golub 1995**
Golub MS, Keen CL, Gershwin ME, Hendrickx AG. Developmental zinc deficiency and behaviour. *Journal of Nutrition* 1995;**125** Suppl:2263S–2271S.
- Haider 2006**
Haider BA, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD004905.pub2]
- Hepper 1995**
Hepper PG. The Behavior of the Fetus as an Indicator of Neural Functioning. In: Lecaneut J, Fifer W, Krasnegor N, Smotherman W editor(s). *Fetal development: a psychological perspective*. Hillsdale (NJ): Lawrence Erlbaum Associates, 1995:405–17.
- Higgins 2005**
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.4 [updated March 2005]. In: The Cochrane Library, Issue 2, 2005. Chichester, UK: John Wiley & Sons, Ltd.
- Higgins 2011**
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
- Jameson 1976**
Jameson S. Effect of zinc deficiency in human reproduction. *Acta Medica Scandinavica Supplement* 1976;**593**:3.
- Jameson 1993**
Jameson S. Zinc status in pregnancy: the effect of zinc therapy on perinatal mortality, prematurity and placental ablation. *Annals of the New York Academy of Science* 1993;**678**:178–92.
- Jones 1981**
Jones RB, Keeling PWN, Hilton PJ, Thompson RP. The relationship between leucocyte and muscle zinc in health and disease. *Clinical Sciences* 1981;**60**:237–9.
- Kiilholma 1984a**
Kiilholma P, Gronroos M, Erkkola P, Pakarinen P, Nanto V. The role of calcium, iron, copper and zinc in preterm delivery and premature rupture of membranes. *Gynecologic and Obstetric Investigation* 1984;**17**:194–201.
- Kiilholma 1984b**
Kiilholma P, Erkkola P, Pakarinen P, Gronroos M. Trace metals in post date pregnancy. *Gynecologic and Obstetric Investigation* 1984;**18**:45–6.
- Kirksey 1994**
Kirksey A, Wachs TD, Yunis F, Srinath U, Rahmanifar A, McCabe GP, et al. Relation of maternal zinc nutrition to pregnancy outcome and infant development in an Egyptian village. *American Journal of Clinical Nutrition* 1994;**60**:782–92.
- Kirksey 1991**
Kirksey A, Rahmanifar A, Wachs TD, McCabe GP, Bessily NS, Bishry Z, et al. Determinants of pregnancy outcome and newborn behaviour in a semirural Egyptian population. *American Journal of Clinical Nutrition* 1991;**54**:657–67.
- Koblinsky 1995**
Koblinsky MA. Beyond maternal mortality - magnitude, interrelationship, and consequences of women's health, pregnancy related complications and nutritional status on pregnancy outcomes. *International Journal of Gynecology & Obstetrics* 1995;**48**:S21–S32.
- Lassi 2010**
Lassi ZS, Haider BA, Bhutta ZA. Zinc supplementation for the prevention of pneumonia in children aged 2 months to 59 months. *Cochrane Database of Systematic Reviews* 2010, Issue 12. [DOI: 10.1002/14651858.CD005978.pub2]
- McKenzie 1975**
McKenzie JM, Fosmire CJ. Zinc deficiency during the latter third of pregnancy: effect on fetal rat brain, liver and placenta. *Journal of Nutrition* 1975;**105**:1466–73.
- Osendarp 2003**
Osendarp SJM, West CE, Black RE, on behalf of the Maternal Zinc Supplementation Study Group. The need for maternal zinc supplementation in developing countries: an unresolved issue. *Journal of Nutrition* 2003;**133**:817S–827S.
- Parr 1996**
Parr RM. Assessment of dietary intakes. *Trace elements in human nutrition and health*. Geneva: World Health Organization, 1996:265–88.
- Pena-Rosas 2006**
Pena-Rosas JP, Viteri FE. Effects of routine oral iron supplementation with or without folic acid for women during pregnancy. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [DOI: 10.1002/14651858.CD004736.pub2]

- Prema 1980**
Prema K, Ramalagshmi BA, Neelakumari S. Serum copper and zinc in pregnancy. *Indian Medical Research* 1980;**71**: 547–53.
- RevMan 2003**
The Cochrane Collaboration. Review Manager (RevMan). 4.2 for Windows. Oxford, England: The Cochrane Collaboration, 2003.
- RevMan 2011**
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.
- Sanstead 1991**
Sandstead HH. Zinc deficiency: a public health problem?. *American Journal of Diseases of Children* 1991;**145**:853–9.
- Sanstead 1996**
Sandstead HH, Smith JC. Deliberations and evaluations of approaches, endpoints and paradigms for determining zinc dietary recommendations. *Journal of Nutrition* 1996;**126**: 2410S–2418S.
- Shrimpton 2005**
Shrimpton R, Gross R, Darnton-Hill I, Young M. Zinc deficiency: what are the most appropriate interventions?. *BMJ* 2005;**330**:347–9.
- Simmer 1985**
Simmer K, Thompson RPH. Maternal zinc and intrauterine growth retardation. *Clinical Sciences* 1985;**68**:395–9.
- Valee 1993**
Valee BL, Flachuk KH. The biochemical basis of zinc physiology. *Physiology Review* 1993;**73**:79–118.
- Verburg 1974**
Verburg DI, Burd LJ, Hoxtill EO, Merrill LK. Acrodermatitis enteropathica and pregnancy. *Obstetrics & Gynecology* 1974;**593**:233.
- Villar 2003**
Villar J, Meriardi M, Gulmezoglu AM, Abalos E, Carroli G, Kulier R, et al. Nutritional interventions during pregnancy for the prevention or treatment of maternal morbidity and preterm delivery: an overview of randomized controlled trials. *Journal of Nutrition* 2003;**133**:1606S–1625S.
- WHO 1996**
World Health Organization Committee. Zinc. *Trace elements in human nutrition and health*. Geneva: WHO, 1996:72–104.

References to other published versions of this review

- Mahomed 1995**
Mahomed K. Routine zinc supplementation in pregnancy. [revised 28 April 1993]. In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) Pregnancy and Childbirth Module. In: The Cochrane Pregnancy and Childbirth Database [database on disk and CDROM] The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.
- Mahomed 1997**
Mahomed K. Zinc supplementation in pregnancy. *Cochrane Database of Systematic Reviews* 1997, Issue 3. [DOI: 10.1002/14651858.CD000230]
- Mahomed 2006**
Mahomed K. Zinc supplementation in pregnancy. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [DOI: 10.1002/14651858.CD000230.pub2]
- Mahomed 2007**
Mahomed K, Bhutta ZA, Middleton P. Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD000230.pub3]
* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bangladesh 2000

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

Risk of bias

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

Bangladesh 2000 (Continued)

trial, with only 168 of these infants being included in the 13-month analysis

Selective reporting (reporting bias)	Unclear risk	Some primary outcomes such as mode of birth not reported.
Other bias	Low risk	No apparent source of other bias.

Chile 2001

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

Risk of bias

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

Chile 2001 (Continued)

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

China 2001

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

Risk of bias

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

China 2001 (Continued)

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

Denmark 1996

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

Denmark 1996 (Continued)

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

Risk of bias

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

Ghana 2009

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

Risk of bias

Ghana 2009 (Continued)

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

Indonesia 1999

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

Risk of bias

Bias	Authors' judgement	Support for judgement
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Indonesia 1999 (Continued)

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

Indonesia 2001

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

Indonesia 2001 (Continued)

blue/floppy (neonatal hypoxia);
jaundice;
fever/not drinking;
umbilical infection;
6-month Z-scores;
6-month haemoglobin, plasma retinol, plasma zinc.

Notes Adherence: mean adherence was over 80%.

Risk of bias

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

Iran 2010

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

Outcomes	Maternal Caesarean section. Neonatal Small-for-gestational age; low birthweight; gestational age at birth; preterm birth; low birthweight.
Notes	
<i>Risk of bias</i>	
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)