Zinc supplementation for mental and motor development in children (Review)

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TABLE OF CONTENTS

[Intervention Review]

Zinc supplementation for mental and motor development in children

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ABSTRACT

Background

Zinc deficiency is a significant public health problem in low- and middle-income countries. Zinc is essential for the formation and migration of neurons along with the formation of neuronal synapses. Its deficiency could interfere with the formation of neural pathways and with neurotransmission, thus affecting behavior (for example, attention, activity, engagement, temperament) and development (for example, gross and fine motor skills, social skills). Zinc supplementation provided to infants and children is a possible strategy to improve the mental and motor development of infants and children at high risk of zinc deficiency.

Objectives

To assess the effects of zinc supplementation compared to placebo on measures of psychomotor development or cognitive function in children.

Search methods

We searched MEDLINE, PsycINFO, CINAHL and Latin American Database (LILACS) on 1 December 2011. We searched EMBASE and CENTRAL 2011 Issue 12 on 19 January 2012. We searched Dissertation Abstracts International and the metaRegister of Controlled Trials on 30 November 2011.

Selection criteria

Randomized or quasi-randomized placebo-controlled trials involving synthetic zinc supplementation provided to infants or children (less than five years of age) were eligible.

Data collection and analysis

Two review authors screened search results, selected studies, assessed the studies for their risk of bias and extracted data.

Main results

We included 13 trials in this review.

Eight studies reported data on the Bayley Scales of Infant Development (BSID) in 2134 participants. We combined the data in a meta-analysis to assess the effect on development as measured by the Mental Development Index (MDI) and Psychomotor Development

Index (PDI). There was no significant effect of zinc supplementation: the mean difference between the zinc supplementation and placebo groups on the MDI was -0.50 (95% confidence interval (CI) -2.06 to 1.06; P = 0.53; I^2 = 70%) and the mean difference between the groups for the PDI was 1.54 (95% CI -2.26 to 5.34; P = 0.43; I^2 = 93%). Most studies had low or unclear risk of bias but there was significant heterogeneity, which was not adequately explained by our subgroup analyses. The overall quality of evidence was considered 'moderate'.

Two trials provided data on motor milestone attainment. There was no significant difference in the time to attainment of milestones between the placebo group and the zinc supplementation group in either of the studies.

No study provided data on cognition score or intelligence quotient (IQ) or on adverse effects of zinc supplementation.

Authors' conclusions

There is no convincing evidence that zinc supplementation to infants or children results in improved motor or mental development.

PLAIN LANGUAGE SUMMARY

Zinc supplementation for mental and motor development in children

Zinc deficiency is a significant public health problem in low- and middle-income countries. Zinc is essential for the formation and migration of neurons, along with the formation of neuronal interconnections called synapses. Its deficiency could interfere with the formation of neural pathways and neurotransmission, thus affecting behavior and development. Zinc supplementation provided to infants and children is a possible strategy to improve the mental and motor development of infants and children at high risk of zinc deficiency.

The review authors searched the medical literature for studies that evaluated mental and motor development in infants and children randomly assigned to receive either zinc supplements or a 'placebo' (fake) supplement. We found 13 relevant studies.

Eight studies measured development using the Mental Development Index and the Psychomotor Development Index of the Bayley Scales of Infant Development. We found no difference between the results for those who had taken zinc supplements and those who had taken a placebo. Two studies measured children's attainment of motor milestones. Again, no difference as found whether zinc supplements were taken or not. No study measured possible side effects of zinc supplementation such as vomiting, diarrhea or anemia.

Overall, the results of the studies provided no convincing evidence that zinc supplements had any beneficial effect on mental and motor development in infants and children.

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

Zinc compared to placebo for mental and motor development in children

Patient or population: infants and children
Settings: populations at risk of zinc deficiency
Intervention: zinc
Comparison: 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				
	Placebo	Zinc				
Mental Development Index BSID II. Scale from: 0 to 100 Follow-up: median 6 months	The mean MDI ranged across control groups from **86.4 to 113 points**	The mean MDI in the intervention groups was **0.50 lower** (2.06 lower to 1.06 higher)		2134 (8 studies)	⊕⊕⊕◯ **moderate**[1]	
Psychomotor Development Index BSID II. Scale from: 0 to 100 Follow-up: median 6 months	The mean PDI ranged across control groups from **87.6 to 104.5 points**	The mean PDI in the intervention groups was **1.54 higher** (2.26 lower to 5.34 higher)		2134 (8 studies)	⊕⊕⊕◯ **moderate**[1]	
Cognition scores	Data not available					
Intelligence quotient	Data not available					
Adverse effects	Data not available					

*The basis for the **assumed risk** (for example, 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).
BSID: Bayley Scales of Infant Development; CI: confidence interval; MDI: Mental Development Index; PDI: Psychomotor Development Index

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] Heterogeneity was marked in the included trials with I^2 statistic being 67% to 92% and not explicable by the differences in study design, participants, form of intervention (included in subgroup analyses).

BACKGROUND

Description of the condition

Zinc is notable among individual nutrients that have been designated as 'problem' nutrients, adequate intake of which is difficult from complementary foods without fortification (Hambidge 2007). Unlike many other nutrients, there is no functional reserve or body store of available zinc, except possibly among infants, who may be able to draw on hepatic zinc accumulated during gestation. Fetal accumulation of zinc is a function of maternal zinc status, and therefore, newborn zinc deficiency (assessed as low serum zinc concentration) is likely among women with inadequate dietary zinc intakes during pregnancy (Caulfield 1999). This deficiency is likely to be transitory for all but the most vulnerable (preterm or low-birthweight infants) because the zinc content of colostrum is high and some zinc becomes available to the infant as part of the haematological changes accompanying the transition to extrauterine life (WHO 1996). However, beginning at around six months of age breast milk intake no longer provides sufficient zinc to meet requirements (Krebs 2000), making zinc-rich complementary foods necessary (Brown 1998). If zinc-rich sources are not available on a routine basis, zinc deficiency develops over time and persists until changes in the diet are made.

Severe or clinical zinc deficiency was defined as a condition characterized by short stature, hypogonadism, impaired immune function, skin disorders, cognitive dysfunction and anorexia (Prasad 1991). Although severe zinc deficiency is considered rare, mild-to-moderate zinc deficiency is likely to be prevalent throughout the world today, mostly due to a sub-optimal dietary intake (Sandstead 1991). The estimated global prevalence of zinc deficiency is 31%, and ranges from 4% to 73%. Lack of consensus on indicators of zinc deficiency has hampered efforts to document prevalence of zinc deficiency. The wide range of estimates of zinc deficiency quoted suggests that diagnostic standards or reference ranges or environmental factors are quite varied. The prevalence of zinc deficiency is high throughout southern and central Africa (37% to 62%), North Africa and the eastern Mediterranean region (25% to 52%), as well as South and South-east Asia (34% to 73%) (Ezzati 2004). Zinc deficiency is now regarded as a major public health problem with multiple health consequences (Temple 2004), involving the epidermal, gastrointestinal, central nervous, immune, skeletal and reproductive systems (Hambidge 1982).

In view of what is now known about the biology of zinc, it is likely that zinc-dependent metabolic functions are impaired in all tissues. Despite substantial evidence from animal experiments showing that zinc deprivation during periods of rapid development impairs behavior and brain development in animals (Halas 1977; Golub 1995), few studies have investigated zinc deficiency effects on behavior or brain function of children. In Egyptian infants, a relationship was found between mothers' consumption of foods high in available zinc and attention measured by the Brazelton Neonatal Development Assessment Scales administered shortly after birth (Kirksey 1991), and with motor development measured by the Bayley Scales of Infant Development (BSID) (Kirksey 1994). In older children, a direct association was found between an index of zinc status (measured by hair zinc concentration in the hair) and reading performance on a standardized test (Thatcher 1984). Zinc intakes of Egyptian children (aged seven to 10 years) were found to correlate with social behavior of girls and activity level of boys, but not with cognitive function (Wachs 1995). Zinc deficiency may be particularly relevant to early development because it plays fundamental roles in cell division and maturation, and in the growth and function of many organ systems, including the neurological system (Pfeiffer 1982; Sandstead 2000; Black 2003; Black 2003a). In addition, there is suggestive evidence from animal models (Halas 1977) and psychiatric patients (Katz 1987) that zinc deficiency may affect emotionality and response to stress, thus altering the child's ability to elicit or use nurturant interactions from carers (functional isolationism). Functional isolation may operate together with neural processing changes related to zinc deficiency to interfere with optimal development.

Description of the intervention

Zinc supplementation is commonly provided as oral zinc salts. The various zinc supplementation trials have provided zinc as zinc sulfate, zinc acetate, zinc gluconate, zinc amino acid chelates and zinc oxide. The supplementation periods have ranged from 2 weeks to 15 months. The periodic zinc supplementation doses ranged from 1 to 70 mg per dose. These doses have been provided daily, several times per week, or once per week, resulting in a daily dose equivalents ranging from 0.9 to 21.4 mg of zinc/day (Brown 2009).

How the intervention might work

Zinc is required for the activity of over 200 enzymes involved in most major metabolic pathways, and thus is necessary for a wide range of biochemical, immunological, and clinical functions (Gibson 2008). Zinc is able to constitute strong, but readily exchangeable and flexible, complexes with organic molecules, thereby enabling it to modify the three-dimensional structure of nucleic acids, specific proteins, and cellular membranes and influence the catalytic properties of many enzyme systems and intracellular signalling. Zinc has a fundamental role in gene expression, cell development and replication (Hambidge 2000).The exact mechanisms of action in the central nervous system are not clear but it appears that zinc is essential for neurogenesis, neuronal migration and synaptogenesis and its deficiency could interfere with neurotransmission and subsequent neuropsychological behavior. Zinc appears to induce the release of the neurotransmitter aminobutyric acid (GABA) and thus influence neuronal excitability and modulate synaptic transmission (Frederickson 1989; Smart 1990; Frederickson 2000). GABA may also have a trophic

role in neuronal cell growth and differentiation (Xie 1991). Zinc is concentrated in specific neuronal structures, notably in the nerve terminals of the hippocampus (mossy fibre system), cortex and pineal body (Xie 1991). Because zinc binds with proteins and is considered to be essential for nucleic acid and protein synthesis (Frederickson 2000), zinc deficiency may interfere with these processes and compromise subsequent development.

Why it is important to do this review

Since the early reports of human zinc deficiency, and particularly during the past 10 to 15 years, a considerable number of well-designed clinical trials have been completed to examine the relationships between zinc supplementation and human health (Brown 2001). Oral zinc supplementation trials among zinc-deficient infants have demonstrated beneficial effects of zinc on growth (Brown 2002), diarrhea and pneumonia morbidity (Bhutta 1999; Black 2001; Yakoob 2011) and mortality (Sazawal 2001). One trial of zinc supplementation during pregnancy examined fetal heart rate and activity. Pregnant women who received 15 mg of daily zinc, along with iron and folate supplementation, had fetuses with an increased fetal heart rate and more vigorous fetal activity compared to fetuses of non supplemented women (Merialdi 1999). Both measures are indices of fetal well-being that may be related to subsequent development (DiPietro 1996). Although initial findings provide some convincing evidence linking zinc deficiency to compromises in activity and motor development, it is important to measure the effect of oral zinc supplementation on mental and motor development in children. It is important to evaluate the effect of zinc administration on mental and motor development in children, including those in older age groups, to provide clarity about realistic expectations from zinc supplementation efforts. We therefore conducted a systematic review to determine the effect of zinc supplementation on mental and motor development in children.

OBJECTIVES

To assess the effects of zinc supplementation on measures of psychomotor development or cognitive function in children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials in which the assessment of psychomotor development or cognitive function was undertaken by assessors blind to treatment allocation.
We included studies in which other micronutrients and drugs were simultaneously administered if the only difference between the study and the control groups was zinc supplementation.

Types of participants

Children up to five years of age (at supplementation).
We excluded hospitalized or sick children or children with neurological disorders, lead exposure, developmental delay or mental retardation.

Types of interventions

- Oral zinc supplementation provided as synthetic zinc supplement (sulphate/acetate/gluconate/others) (irrespective of dose of zinc) compared to placebo.
- Oral zinc supplementation provided as a food fortificant (in formula milk) compared to unsupplemented formula or unmodified animal milk.

Studies involving administration of a diet containing zinc-rich foods were excluded.

Types of outcome measures

All outcomes were intended for use in a 'Summary of findings' table.

Primary outcomes

1. Standardized scores of development in children (for example, Bayley Scales of Infant Development (BSID) (Bayley 1993), Griffiths Mental Developmental Scales (Griffiths 1996), Alberta Infant Motor Scale (AIMS) (Piper 1992))
2. Cognition scores (Detroit Tests of Learning Aptitude (Hammill 2005), Cognition-Psychomotor Assessment System-Revised (CPAS-R) (Penland 1994), etc.)
3. Intelligence quotient (IQ) (for example, Roid 2003)

Secondary outcomes

1. Adverse effects (vomiting, diarrhea, anemia)

Search methods for identification of studies

Electronic searches

We searched the following databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL), 2011 (Issue 12), searched 19 January 2012

- MEDLINE, all available years searched 1 December 2011
- EMBASE, from 1900 to 2011, searched 19 January 2012
- Latin American Database (LILACS), all available years searched 1 December 2011
- PsycINFO, all available years searched 1 December 2011
- CINAHL, all available years searched 1 December 2011
- Dissertation Abstracts International all available years searched 30 November 30 2011

Searching other resources

The references of identified trials and of important review articles were scrutinized for possible trials missed by electronic searches. In addition, forward citation searches on trials from the primary search were performed within the Science Citation Index. Donor agencies, 'experts' and authors of recent zinc supplementation trials were contacted to identify any additional or ongoing trials.

Data collection and analysis

Selection of studies

Two review authors (SG and HS) independently scanned titles and abstracts of the trials identified in the computerised search to exclude studies that were obviously irrelevant. Both review authors read the full texts of the remaining studies and identified trials that fulfilled the inclusion criteria. Differences of opinion about suitability for inclusion were resolved by discussion.

Data extraction and management

See Appendix 1 for details of the types of data we extracted from the trial reports and entered into pre-designed forms.
Data were entered into Review Manager (RevMan) software (RevMan 2011) by one review author (SG) and then checked by the second review author (HS).

Assessment of risk of bias in included studies

Two review authors (SG and HS) independently assessed the risk of bias in each included study using the Cochrane Collaboration's 'Risk of bias' tool (Higgins 2008). Any disagreement was resolved through consultation with a third adjudicator. We assessed the degree to which:

- the allocation sequence was adequately generated ('sequence generation');
- the allocation was adequately concealed ('allocation concealment');
- participant and personnel knowledge of the allocated interventions was adequately prevented during the study ('participant/personnel blinding');
- outcome assessor knowledge of the allocated interventions was adequately prevented during the study ('outcome assessment blinding');
- incomplete outcome data were adequately addressed;
- reports of the study were free of suggestion of selective outcome reporting;
- the study was apparently free of other problems that could put it at high risk of bias (for example, conflict of interest, premature trial termination).

Each domain was allocated one of three possible categories for each of the included studies: low risk of bias, high risk of bias, and unclear risk of bias.

Measures of treatment effect

Binary data

Risk ratio (RR) estimations with 95% confidence intervals (CI) were used for binary outcomes.

Continuous data

Data on continuous outcomes were analysed using MDs, or standardised mean differences (SMDs) if continuous outcomes were measured with similar, but not identical, instruments across studies. All analyses included all participants in the treatment groups to which they were allocated, whenever possible.

Analysis of overall cognitive performance

How we planned to analyse overall cognitive performance can be found in Appendix 2.

Analysis of cognitive domains or broad cognitive abilities

- For children aged two to five years, we evaluated motor skills and development, attention span, hand-eye co-ordination and performance (shape recognition, block construction and block patterns).
- For children aged up to two years, we evaluated four developmental abilities that are traditionally taken into account in developmental scales such as the BSID, Griffiths Mental Developmental Scale or AIMS. These abilities are fine motor skills, gross motor skills, language development and social development.
- Additional information on analysis of cognitive domains or broad cognitive abilities can also be found in Appendix 2

Unit of analysis issues

No cluster-randomized trials were included in the meta-analysis. The approach we will take to the management of such trials when we update the review can be found in Appendix 2.

In studies with two or more zinc intervention groups (different dosage or administration regimens) and a single control group, the data from multiple zinc arms was pooled and this pooled group was compared with the control group.

Dealing with missing data

The following principles were used for derivations if actual variables were not stated.

1. In a group, the lower of the two stated sample sizes at the beginning or end of a trial was assumed to be the sample size.
2. Wherever feasible, SD was back-calculated from the stated standard errors, t or P values.
3. Wherever not stated, the mean age of participants was taken as the average of the stated range.

Assessment of heterogeneity

Heterogeneity among the trials was measured by the visual inspection of forest plots and by assessment of χ^2 statistic derived from Cochrane Q test, Tau^2 statistic (among study variance) and the I^2 statistic. If heterogeneity was substantial, reasons for it were sought as explained in subgroup analyses (Higgins 2002; Higgins 2003).

Assessment of reporting biases

We planned to assess the risk of publication bias using funnel plots (while recognising that there can be other causes of asymmetry in funnel plots). The funnel plots were symmetrical, indicating that publication bias does not seem to be a problem for this review. For identifying selective outcome reporting, outcomes listed in the methods section of the study were compared with those whose results were reported. Difference between protocol (if available) and study methods, and absence of reporting of outcomes generally documented by other included studies, were also considered as possible indicators of selective outcome reporting.

Data synthesis

The majority of the included trials used a developmental scale to evaluate the effect of zinc supplementation on mental and motor development in children. BSID was the most commonly used developmental scale.

In the case of factorial trials comparing zinc, other micronutrient, zinc plus other micronutrient and placebo; two data sets were formed. The first data set involved comparison of the zinc group with the placebo group, and the second data set involved comparison of the zinc plus other micronutrient group with the other micronutrient group. As the data sets were independent, they were included in the meta-analysis by combining the zinc and zinc plus other micronutrient group as the experimental group; and placebo and other micronutrient group as the placebo group. The new mean and SD thus calculated were used in the meta-analysis.

In case of repeat assessments made during the course of trial, the assessment period nearest to the one provided by other trials was used for analysis, so as to ensure homogeneity in the intervention groups.

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses were done to explore heterogeneity:

1. age at time of supplementation: neonatal (one month or less) or post-neonatal (more than one month);
2. duration: six months or less or more than six months;
3. type of zinc salt used (acetate/sulphate/gluconate/others);
4. low birthweight neonates;
5. developmental status of country (very high and high or medium and low) in which the trial was conducted (based on the UNDP Human Development Index figures; Human Development Index 2011).

Sensitivity analysis

Sensitivity analyses were performed to consider the impact of:

1. allocation concealment (low risk versus high or unclear risk);
2. attrition (< 10% versus ≥ 10%).

RESULTS

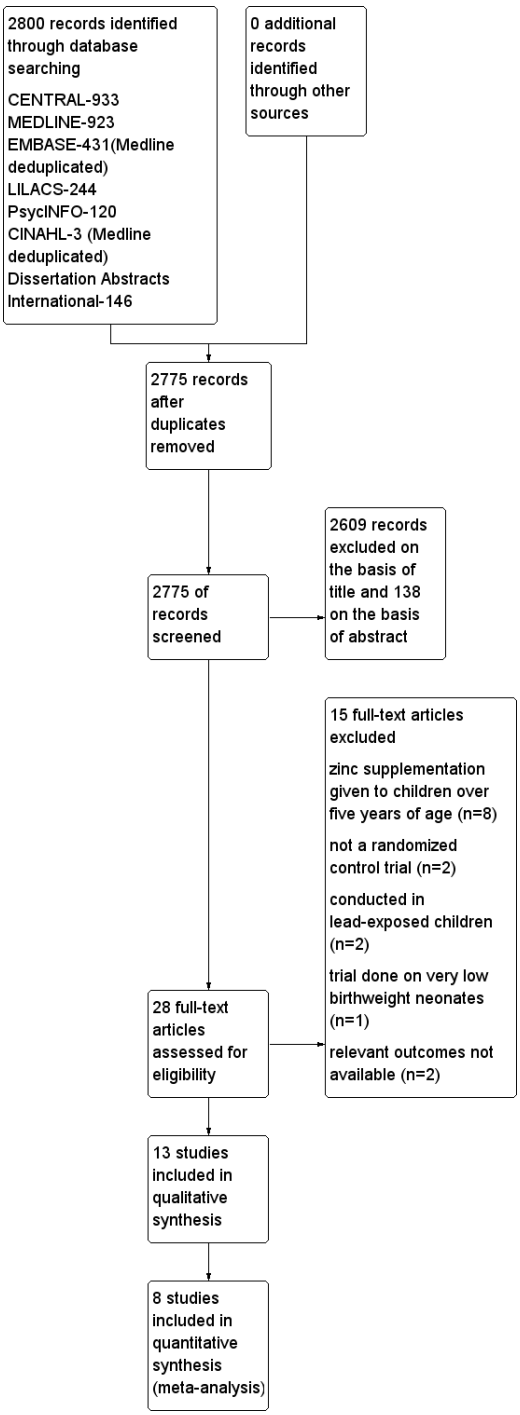
Description of studies

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

Results of the search

After applying the search strategy, 2800 records were retreived. After excluding 25 duplicates, 2609 were excluded on the basis of title and 138 on the basis of the abstract. The full text was obtained for 28 potentially eligible trials. We found 15 of these articles to be ineligible on reading the full text. We therefore included 13 trials in this systematic review. See Figure 1.

Figure 1. Study flow diagram



Included studies

Location

The studies were conducted in low-, middle- and high-income countries. There were seven studies from Asia (Sazawal 1996; Hamadani 2001; Black Baqui 2004; Black Sazawal 2004; Lind 2004; Taneja 2005; Katz 2010), four from North America (Bentley 1997; Gardner 2005; Heinig 2006; Jiminez 2007), two from South America (Ashworth 1998; Castillo-Duran 2001) and none from Africa.

Study designs

All 13 included studies were randomized trials. Only one trial was cluster-randomized (Katz 2010).

Sample sizes

Taneja 2005 included 650 participants and was the largest study included in the meta-analyses. Katz 2010 involved 2457 participants but was not included in the meta-analyses. Sample sizes of other studies included in the meta-analyses were between 85 and 340 participants.

Participants

Most of the studies were conducted in neonates (Ashworth 1998; Castillo-Duran 2001; Hamadani 2001; Jiminez 2007), infants (Bentley 1997; Black Baqui 2004; Black Sazawal 2004; Lind 2004; Heinig 2006) and toddlers (Sazawal 1996; Gardner 2005; Taneja 2005; Katz 2010). Though the majority of studies involved apparently normal children, Ashworth 1998, Black Sazawal 2004 and Jiminez 2007 included low birthweight infants. Gardner 2005 included children with weight-for-age z scores < 1.5 SDs of the National Center for Health Statistics (NCHS) references and weight-for-age < 2 SDs in the previous three months.

Intervention

Zinc supplementation was given as zinc sulphate in nine trials. Two studies used zinc acetate and the remaining two studies used zinc gluconate. Supplementation was provided for more than six months in six studies (Bentley 1997; Castillo-Duran 2001; Black Sazawal 2004; Heinig 2006; Jiminez 2007; Katz 2010) and for less than six months in seven studies (Sazawal 1996; Ashworth 1998; Hamadani 2001; Black Baqui 2004; Lind 2004; Gardner 2005; Taneja 2005).

Outcomes

In younger children, developmental aspects studied were mainly assessed via the BSID (eight studies) (Ashworth 1998; Castillo-Duran 2001; Hamadani 2001; Black Baqui 2004; Black Sazawal 2004; Lind 2004; Taneja 2005; Jiminez 2007). Other studies used motor milestones (Bentley 1997; Katz 2010), Griffiths Mental Developmental Scale (Gardner 2005), AIMS (Heinig 2006), CARS (Children's Activity Rating Scale) (Sazawal 1996) and infant activity sampling (Bentley 1997).

Five studies not included in meta-analyses reported effects of zinc supplementation on behavior, activity, attention and gross motor development (Sazawal 1996; Bentley 1997; Gardner 2005; Heinig 2006; Katz 2010). Since the majority of studies used BSID to report effects on mental and motor development, the eight studies reporting data in this format were included in meta-analysis (Ashworth 1998; Castillo-Duran 2001; Hamadani 2001; Black Baqui 2004; Black Sazawal 2004; Lind 2004; Taneja 2005; Jiminez 2007).

Excluded studies

The reasons for excluding 15 articles were as follows: zinc supplementation given to children over five years of age (eight trials), not a randomized trial (two trials), conducted in lead-exposed children (two trials), trial done on very low birthweight neonates (one trial) and relevant outcomes not available (two trials). See Characteristics of excluded studies table.

Risk of bias in included studies

The reasons for the risk of bias judgements in individual included studies are detailed in the Characteristics of included studies table and the judgements are summarized in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

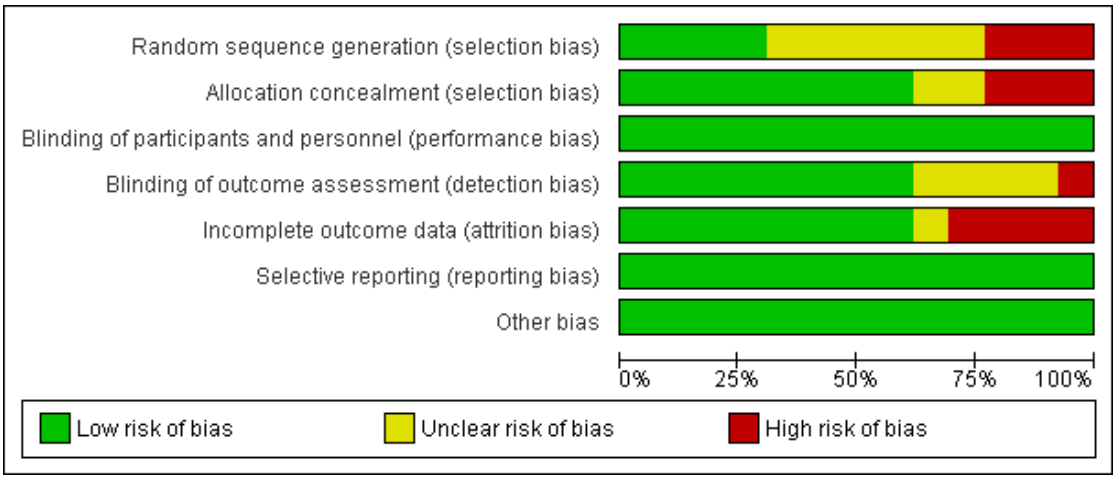
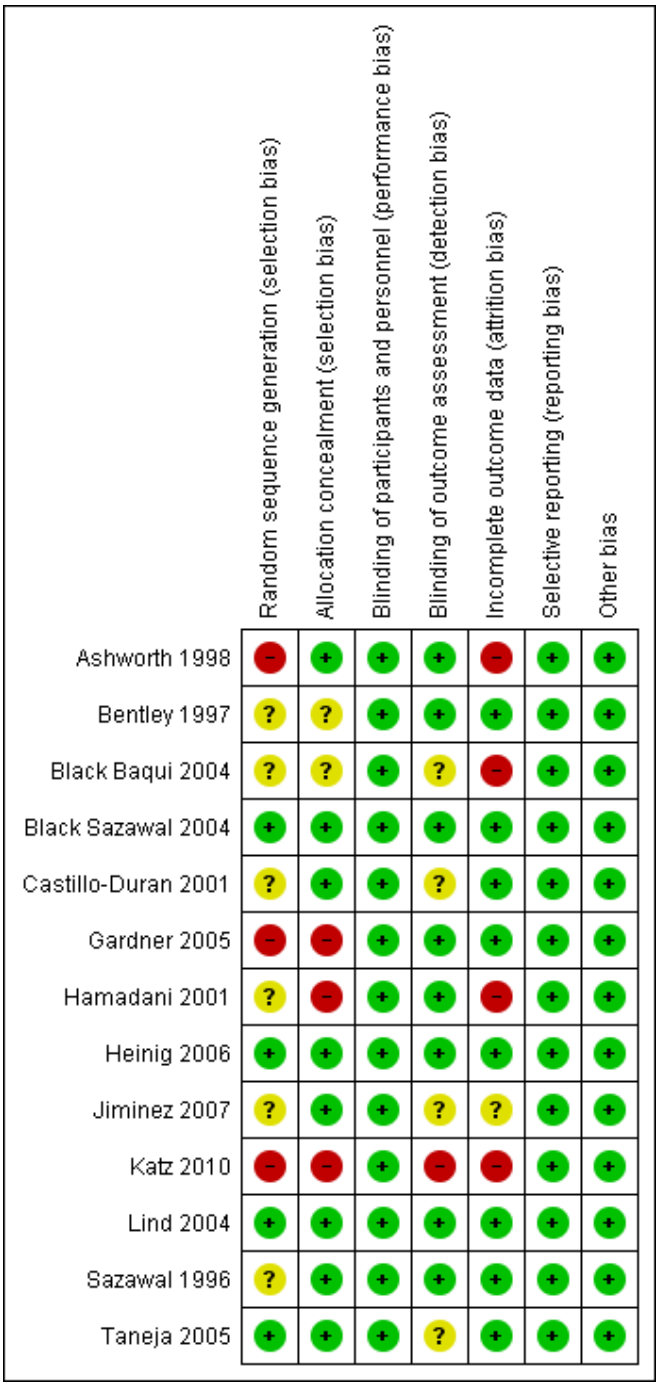


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Sequence generation

Of 13 trials included in the review, the risk of bias for sequence generation was judged to be low in four (Black Sazawal 2004; Heinig 2006; Lind 2004; Taneja 2005) and unclear in six trials (Sazawal 1996; Bentley 1997; Castillo-Duran 2001; Hamadani 2001; Black Baqui 2004; Jiminez 2007). It was at high risk of bias in three trials (Ashworth 1998; Gardner 2005; Katz 2010). Of the eight studies included in the meta-analysis, the risk of bias for sequence generation was judged as low in three trials, unclear in four and high in one.

Allocation concealment

The allocation concealment was assessed to be at low risk of bias in eight trials (Sazawal 1996; Ashworth 1998; Castillo-Duran 2001; Black Sazawal 2004; Lind 2004; Taneja 2005; Heinig 2006; Jiminez 2007) and at unclear risk in two trials (Bentley 1997; Black Baqui 2004). Three trials were judged to have a high risk of bias for allocation concealment (Hamadani 2001; Gardner 2005; Katz 2010). Of the eight studies included in the meta-analyses, the risk of bias for allocation concealment was judged low in six trials, unclear in one and high in one.

Blinding

Participants and personnel

All studies were at low risk of bias for this aspect, having adequate blinding of participants and personnel.

Outcome assessment

The risk of bias for blinding of outcome assessment was judged low in eight trials (Sazawal 1996; Bentley 1997; Ashworth 1998; Hamadani 2001; Black Sazawal 2004; Lind 2004; Gardner 2005; Heinig 2006), unclear in four (Castillo-Duran 2001; Black Baqui 2004; Taneja 2005; Jiminez 2007) and high in one (Katz 2010). Of the eight studies included in meta-analyses, the risk of bias for blinding of outcome assessment was judged low for four trials and unclear for four trials.

Incomplete outcome data

Of the 13 trials included in the review, the risk of bias for incomplete outcome data was judged low in eight (Sazawal 1996; Bentley 1997; Castillo-Duran 2001; Black Sazawal 2004; Lind 2004; Gardner 2005; Taneja 2005; Heinig 2006) and unclear in one trial (Jiminez 2007). Four trials were judged to have a high risk of bias for incomplete outcome data (Ashworth 1998; Hamadani 2001; Black Baqui 2004; Katz 2010). Of the eight studies included in the meta-analyses, the risk of bias for incomplete outcome data was judged low in four, unclear in one and high in three trials.

Selective reporting

All the included studies were free of selective reporting.

Other potential sources of bias

Studies were generally free of other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Zinc compared to placebo for mental and motor development in children

Primary outcomes

1. Standardised scores of development in children

The majority of the included studies used the BSID to assess the effect of zinc supplementation on mental and motor development of infants and children (Ashworth 1998; Castillo-Duran 2001; Hamadani 2001; Black Baqui 2004; Black Sazawal 2004; Lind 2004; Taneja 2005; Jiminez 2007). Other studies used Griffiths Mental Developmental Scale (Gardner 2005), AIMS (Heinig 2006) and time of attainment of motor milestones (Katz 2010). Some studies used infant activity sampling (Bentley 1997) and CARS (Sazawal 1996).

We anticipated that studies would use different developmental scales for evaluating the effect of zinc supplementation on mental and motor development in children. Hence, during the protocol stage, we had planned to combine the data derived from studies using BSID (usually reported as MDI and PDI) into a single composite measure in order to then combine this with studies using other developmental scales, notably the Griffiths Mental Developmental Scale, providing one composite measure of development. However, eight studies had reported data using BSID and only one study reported data in Griffiths Mental Developmental Scale. This presented an excellent opportunity to report effects on both MDI and PDI separately (given the absolute number and marked preponderance of studies using BSID), so as to delineate the exact developmental domains affected by zinc supplementation further. Hence we decided to include the eight studies reporting data using

BSID in the meta-analysis and to use MD so as to provide the exact benefit of zinc supplementation in terms of BSID units. The study using the Griffiths Mental Developmental Scale (Gardner 2005) has been reported in detail in the text and the Characteristics of included studies table.

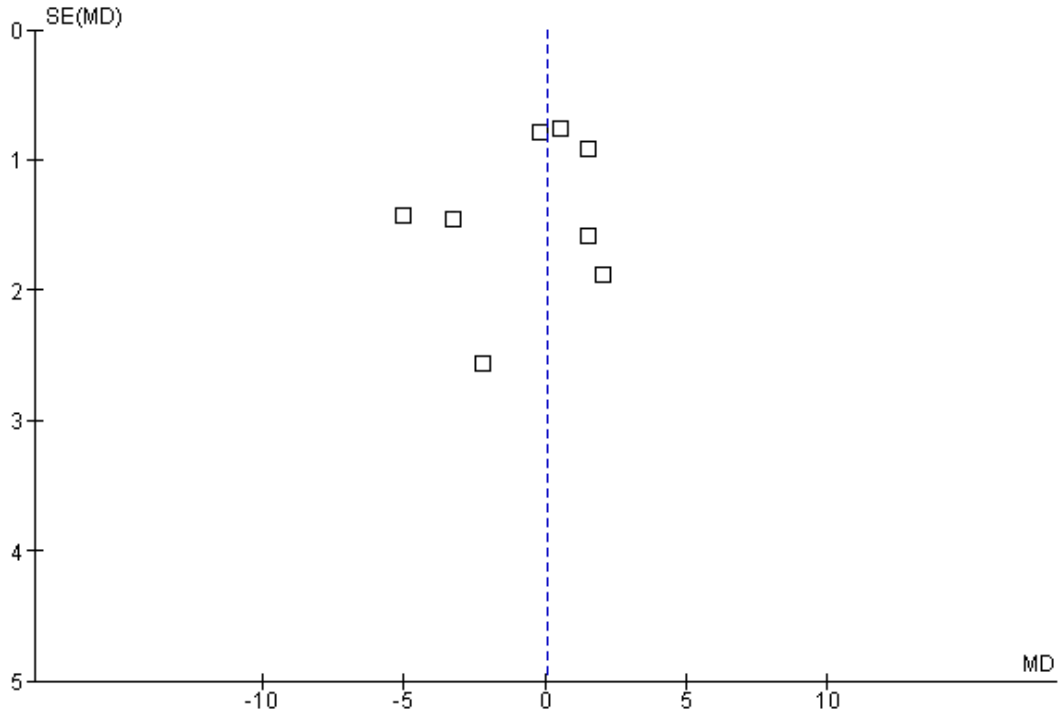
Outcome 1.1 Mental Development Index (MDI)

Relevant data for evaluating the effect of zinc supplementation on MDI were available from eight studies (Ashworth 1998; Castillo-Duran 2001; Hamadani 2001; Black Baqui 2004; Lind 2004; Taneja 2005; Heinig 2006; Jiminez 2007). Black Baqui 2004 and Lind 2004 involved two comparisons: 1) between the zinc supplementation group and the placebo group, and 2) between zinc plus micronutrient group and micronutrient group. These interventions are in mutually exclusive treatment and control groups (differing only with respect to zinc supplementation); and thus are independent. To facilitate data entry (which requires entering a single MD and SD for these four groups in each trial), means and SDs of MDI from zinc and zinc plus micronutrient group were combined and compared with the combined means and SDs of placebo and micronutrient group.

Outcome 1.1.1 MDI - main analysis

There was no significant evidence of a beneficial effect of zinc supplementation in infancy and childhood on MDI measured by BSID II. The MD was -0.50 (95% CI -2.06 to 1.06; P = 0.53; I^2 = 70%) (Ashworth 1998; Castillo-Duran 2001; Hamadani 2001; Black Baqui 2004; Lind 2004; Taneja 2005; Heinig 2006; Jiminez 2007) (Analysis 1.1). The funnel plot for the eight data sets included in the main analysis was symmetrical suggesting the absence of publication bias (Figure 4).

Figure 4. Funnel plot of comparison zinc versus placebo. Outcome 1.1 - Mental Development Index



Subgroup analyses for MDI

Outcome 1.1.2 MDI with initiation of zinc supplementation in neonatal period

Four studies provided relevant data for this subgroup analysis (

Ashworth 1998; Castillo-Duran 2001; Hamadani 2001; Jiminez 2007). There was no significant evidence of a beneficial effect of zinc supplementation initiated in the neonatal period on MDI measured by BSID II (MD -2.3; 95% CI -5.3 to 0.7; P = 0.13; I^2 = 67%).

Outcome 1.1.3 MDI with initiation of zinc supplementation in post-neonatal period

Four studies provided data for this subgroup analysis (Black Baqui 2004; Black Sazawal 2004; Lind 2004; Taneja 2005). There was no significant evidence of a beneficial effect of zinc supplementation initiated in the post-neonatal period on MDI measured by BSID II (MD 0.6; 95% CI -0.28 to 1.48; P = 0.18; I^2 = 0%).

Outcome 1.1.4 MDI with duration of zinc supplementation of six months of less

Five studies provided data for this subgroup analysis (Ashworth 1998; Hamadani 2001; Black Baqui 2004; Lind 2004; Taneja 2005). There was no significant evidence of a beneficial effect of zinc supplementation for duration of six months or less in infancy and childhood on MDI measured by BSID II (MD 0.00; 95% CI -1.70 to 1.71; P = 1.00; I^2 = 18%.

Outcome 1.1.5 MDI with duration of zinc supplementation more than six months

Three studies provided relevant data for this subgroup analysis (Castillo-Duran 2001; Black Sazawal 2004; Jiminez 2007). There was no significant evidence of a beneficial effect of zinc supplementation for more than six months' duration in infancy and childhood on MDI measured by BSID II (MD -1.15; 95% CI -4.74 to 2.44; P = 0.53; I^2 = 83%).

Outcome 1.1.6 MDI with zinc supplementation as sulphate salt

Five studies provided data for this subgroup analysis (Ashworth 1998; Castillo-Duran 2001; Black Sazawal 2004; Lind 2004; Jiminez 2007). There was no significant evidence of a beneficial effect of zinc supplementation as sulphate salt in infancy and childhood on MDI measured by BSID II (MD -0.84; 95% CI -2.89 to 1.22; P = 0.42; I^2 = 72%).

Outcome 1.1.7 MDI with zinc supplementation as acetate salt

Two studies provided data for this subgroup analysis (Hamadani 2001; Black Baqui 2004). There was no significant evidence of a beneficial effect of zinc supplementation as acetate salt in infancy and childhood on MDI measured by BSID II (MD -0.94; 95% CI -5.64 to 3.76; P = 0.70; I^2 = 80%).

Outcome 1.1.8 MDI with zinc supplementation as other salts

Only one study provided relevant data (Taneja 2005) for this subgroup analysis. There was no significant evidence of a beneficial effect of zinc supplementation as other salt in infancy and childhood on MDI measured by BSID II (MD 1.50; 95% CI -0.28 to 3.28; P = 0.10).

Outcome 1.1.9 MDI in low birthweight babies

Three studies provided relevant data (Ashworth 1998; Black Sazawal 2004; Jiminez 2007) for this subgroup analysis. There was no significant evidence of a beneficial effect of zinc supplementation in low birthweight babies on MDI measured by BSID II (MD -2.35; 95% CI -5.82 to 1.12; P = 0.18; I^2 = 77%).

Outcome 1.1.10 MDI in low and medium Human Development Index (HDI) countries

Five studies provided data for this subgroup analysis (Hamadani 2001; Black Baqui 2004; Black Sazawal 2004; Lind 2004; Taneja 2005). There was no significant evidence of a beneficial effect of zinc supplementation in infancy and childhood in developing countries on MDI measured by BSID II (MD 0.15; 95% CI -1.18 to 1.48; P = 0.83; I^2 = 55%).

Outcome 1.1.11 MDI in high and very high HDI countries

Three studies provided relevant data for this subgroup analysis (Ashworth 1998; Castillo-Duran 2001; Jiminez 2007). There was no significant evidence of a beneficial effect of zinc supplementation in infancy and childhood in developed countries on MDI measured by BSID II (MD -1.82; 95% CI -6.37 to 2.72; P = 0.43; I^2 = 77%).

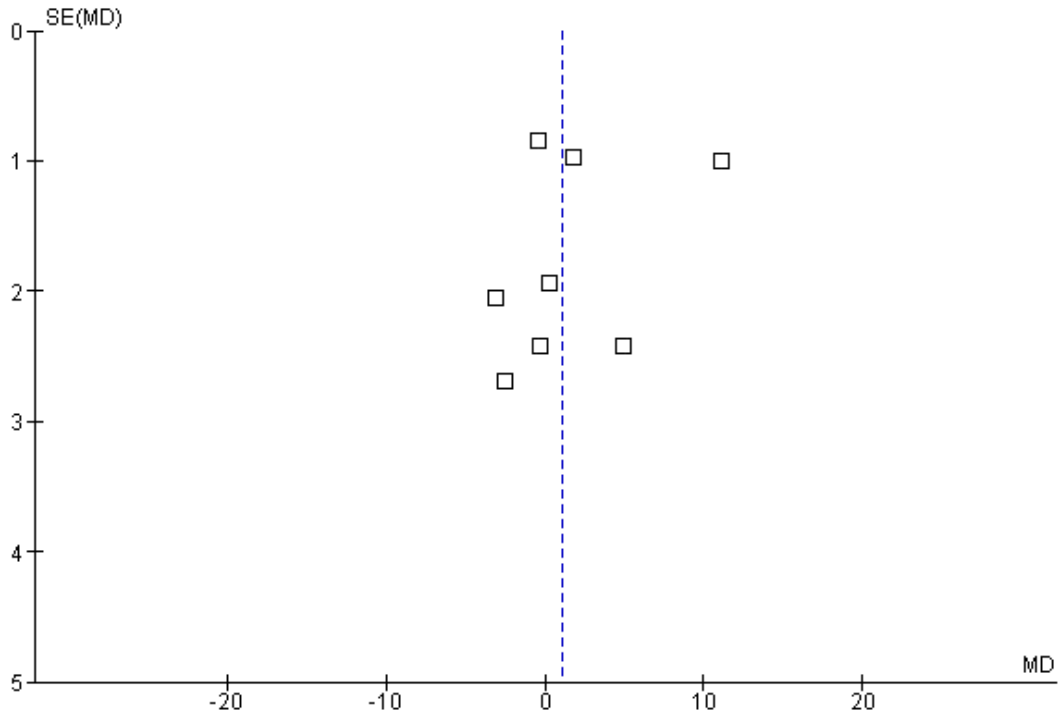
Outcome 1.2 Psychomotor Development Index (PDI)

Relevant data for evaluating the effect of zinc supplementation on PDI were available from eight studies (Ashworth 1998; Castillo-Duran 2001; Hamadani 2001; Black Baqui 2004; Lind 2004; Taneja 2005; Heinig 2006; Jiminez 2007). Black Baqui 2004 and Lind 2004 involved two comparisons: 1) between the zinc supplementation group and the placebo group, and 2) between zinc plus micronutrient group and micronutrient group. These interventions are in mutually exclusive treatment and control groups (differing only with respect to zinc supplementation); and thus are independent. So as to facilitate data entry (which requires entering a single MD and SD for these four groups in each trial), mean and SD of PDI from zinc and zinc plus micronutrient group were combined and compared with the combined mean and SD of placebo and micronutrient group.

Outcome 1.2.1 PDI - main analysis

There was no significant evidence of a beneficial effect of zinc supplementation in infancy and childhood on PDI measured by BSID II (MD 1.54; 95% CI -2.26 to 5.34; P = 0.43; I^2 = 93%) (Ashworth 1998; Castillo-Duran 2001; Hamadani 2001; Black Baqui 2004; Lind 2004; Taneja 2005; Heinig 2006; Jiminez 2007) (Analysis 1.2). The funnel plot for the eight data sets included in the main analysis was symmetrical suggesting the absence of publication bias (Figure 5).

Figure 5. Funnel plot of comparison zinc versus placebo. Outcome 1.2 - Psychomotor Development Index



Subgroup analysis for PDI

Outcome 1.2.2 PDI with initiation of zinc supplementation in neonatal period

Four studies provided relevant data (Ashworth 1998; Castillo-Duran 2001; Hamadani 2001; Jiminez 2007). There was no significant evidence of a beneficial effect of zinc supplementation initiated in the neonatal period on PDI measured by BSID II (MD 1.38; 95% CI -7.10 to 9.86; P = 0.75; I^2 = 95%).

Outcome 1.2.3 PDI with initiation of zinc supplementation in post-neonatal period

Four studies provided data for the concerned outcome (Black Baqui 2004; Lind 2004; Black Sazawal 2004; Taneja 2005). There was no significant evidence of a beneficial effect of zinc supplementation initiated in the post-neonatal period on PDI measured by BSID II (MD 1.01; 95% CI -0.84 to 2.86; P = 0.28; I^2 = 50%).

Outcome 1.2.4 PDI with duration of zinc supplementation less than or equal to six months

Five studies provided data for this subgroup (Ashworth 1998; Hamadani 2001; Black Baqui 2004; Lind 2004; Taneja 2005). There was no significant evidence of a beneficial effect of zinc supplementation for six months' duration or less in infancy and childhood on PDI measured by BSID II (MD 0.64; 95% CI -1.22 to 2.50; P = 0.50; I^2 = 47%).

Outcome 1.2.5 PDI with duration of zinc supplementation more than six months

Three studies provided relevant data (Castillo-Duran 2001; Black Sazawal 2004; Jiminez 2007). There was no significant evidence of a beneficial effect of zinc supplementation for more than six months' duration in infancy and childhood on PDI measured by BSID II (MD 2.82; 95% CI -6.64 to 12.28; P = 0.56; I^2 = 96%).

Outcome 1.2.6 PDI with zinc supplementation as sulphate salt

Five studies provided data for this outcome (Ashworth 1998; Castillo-Duran 2001; Black Sazawal 2004; Lind 2004; Jiminez 2007). There was no significant evidence of a beneficial effect of zinc supplementation as sulphate salt in infancy and childhood on PDI measured by BSID II (MD 1.21; 95% CI -4.07 to 6.49; P = 0.65; I^2 = 72%).

Outcome 1.2.7 PDI with zinc supplementation as acetate salt

Two studies provided data for this subgroup (Hamadani 2001; Black Baqui 2004). There was no significant evidence of a beneficial effect of zinc supplementation as acetate salt in infancy and childhood on PDI measured by BSID II (MD 1.21; 95% CI -6.07 to 8.49; P = 0.74; I^2 = 76%).

Outcome 1.2.8 PDI with zinc supplementation as other salts

Only one study provided relevant data (Taneja 2005). There was no significant evidence of a beneficial effect of zinc supplementation as other salt in infancy and childhood on PDI measured by BSID II (MD 1.70; 95% CI -0.20 to 3.60; P = 0.08).

Outcome 1.2.9 PDI in low birthweight babies

Three studies provided relevant data (Ashworth 1998; Black Sazawal 2004; Jiminez 2007). There was no significant evidence of a beneficial effect of zinc supplementation in low birthweight babies on PDI measured by BSID II (MD 3.77; 95% CI -4.67 to 12.21; P = 0.38; I^2 = 95%).

Outcome 1.2.10 PDI in low HDI countries

Five studies provided data for this subgroup (Hamadani 2001; Black Baqui 2004; Black Sazawal 2004; Lind 2004; Taneja 2005). There was no significant evidence of a beneficial effect of zinc supplementation in infancy and childhood in developing countries on PDI measured by BSID II (MD 0.68; 95% CI -1.09 to 2.46; P = 0.45; I^2 = 46%).

Outcome 1.2.11 PDI in high HDI countries

Three studies provided relevant data (Ashworth 1998; Castillo-Duran 2001; Jiminez 2007). There was no significant evidence of a beneficial effect of zinc supplementation in infancy and childhood in developed countries on PDI measured by BSID II (MD 2.64; 95% CI -7.36 to 12.64; P = 0.6; I^2 = 96%).

1.3 Other developmental scores

In one randomized double-blind intervention trial comparing zinc supplementation (5 mg/day for six months) with placebo in normal birth weight breastfed infants aged four to 10 months, the differences between groups in gross motor development based on AIMS scores at each age were not significant (Heinig 2006).

In one randomized controlled trial with four groups: psychosocial stimulation alone, zinc supplementation alone, both interventions and control (routine care only), 114 children aged nine to 30 months and below 1.5 z scores of the National Center for Health Statistics weight-for-age references were evaluated with Griffiths Mental Developmental Scale (Gardner 2005). Zinc benefited the developmental quotient only in children who received stimulation, and benefits from zinc to hand and eye coordination were greater in stimulated children. Zinc supplementation alone improved hand and eye coordination, and stimulation alone benefited the developmental quotient, hearing and speech, and performance.

2. Cognition scores

No included study used cognition scores as a tool to assess the effect of zinc supplementation on mental and motor development in children.

3. Intelligence quotient (IQ)

No included study used IQ as a tool to assess the effect of zinc supplementation on mental and motor development in children.

4. Motor milestone attainment

In one randomized, double-blind, placebo-controlled study, 85 Guatemalan infants recruited at six to nine months of age were studied (Bentley 1997). No differences in motor development

were observed between the placebo group and treatment group after seven months of supplementation (sitting, crawling, standing and walking).

One community-based, cluster-randomized, placebo-controlled trial of daily zinc with or without iron plus folic acid supplementation examined motor milestone attainment among 3264 children age one to 36 months. Treatment groups included placebo, zinc, iron plus folic acid and zinc plus iron plus folic acid. A total of 2457 children had not walked at the time of entry into the trial and 1775 were followed up for 36 months. Mean age (± SD) at first walking unassisted did not differ among groups and was 444 ± 81 days in the placebo group, 444 ± 81 days in the zinc group, 464 ± 85 days in the iron plus folic acid group and 446 ± 87 days in the iron plus folic acid plus zinc group (Katz 2010).

Sensitivity analysis

Sensitivity analyses were performed to consider the impact of allocation concealment (adequate versus inadequate or unclear) and attrition (< 10% versus ≥ 10%). Sensitivity analyses show that the overall result and conclusions were not affected by inclusion of trials with less than adequate allocation concealment and significant attrition (Table 1).

Secondary outcomes

No study provided data on adverse effects of zinc supplementation (vomiting, diarrhea, anemia).

DISCUSSION

Summary of main results

The results from our analysis of these studies show that there is no statistically significant evidence of a beneficial effect of zinc supplementation on the mental and motor development of children. There was no significant evidence of a beneficial effect of zinc supplementation in infancy and childhood on Mental Development Index (MDI) measured by the Bayley Scales of Infant Development (BSID). The mean difference (MD) was -0.50 (95% CI -2.06 to 1.06; P = 0.53; I^2 = 70%). There was no statistically significant evidence of a beneficial effect of zinc supplementation in infancy and childhood on Psychomotor Development Index (PDI) measured by BSID II. The MD was 1.54 (95% CI -2.26 to 5.34; P = 0.43; I^2 = 93%). The effect is not significant irrespective of the time of initiation of supplementation, duration of supplementation, dose of zinc used and the type of zinc salt used. In a separate analysis of low birthweight babies, in whom a greater benefit was anticipated, the effect remained non-significant. In the two trials studying the effect of zinc supplementation on motor milestone attainment among children aged one to 36 months (Bentley 1997; Katz 2010), no beneficial effect of zinc supplementation was documented. None of the analyses showed evidence of publication bias.

Overall completeness and applicability of evidence

The studies included both infants and children from developed as well as developing countries. Supplementation was started during the neonatal period in some trials and in the post-neonatal period in others. The studies also included low birthweight babies. Zinc supplementation was provided for variable durations using zinc as sulphate, acetate and other salts. Each subgroup included at least three representative trials. However, the outcomes were mostly MDI and PDI measured by BSID II. No study reported the effect of zinc supplementation on IQ and studies reporting the effect on various domains of cognition as listed in Measures of treatment effect were few in number and were not amenable to a meta-analysis. Majority of the studies did not attempt to determine the prevalence of zinc deficiency in the population before supplementation.

Quality of the evidence

The quality of evidence was judged using GRADEpro software (GRADEpro 2008), which was developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group to provide a common, transparent and sensible approach to grading the quality of evidence and strength of recommendations for guideline development.

For the trials included in the meta-analysis, risk of bias for sequence generation and allocation concealment was high only in one included trial. All studies included in the meta-analysis had adequate blinding of participants and personnel and risk of bias for blinding of outcome assessment was low for four and unclear for four trials. Risk of bias for incomplete outcome data was low in four, unclear in one and high in three trials. The trials were generally free of selective reporting and other biases. Overall, therefore, any potential limitations were regarded as unlikely to lower confidence in the estimate of effect and thus it was considered appropriate not to downgrade evidence in the GRADE assessment of study limitations for "risk of bias". There was no significant imprecision or indirectness of evidence and there was no evidence of a publication bias (Figure 4; Figure 5). However, the included trials had significant inconsistency with I^2 values for the cumulative MD for two primary outcomes being 67% (MDI) and 92% (PDI) and this heterogeneity was not adequately explained by the subgroup analyses. Therefore, in view of this serious inconsistency for MDI and PDI, the quality of evidence was downgraded by one level and the overall quality of the evidence considered 'moderate' for both MDI and PDI.

Potential biases in the review process

Since the review attempted to combine all studies examining mental or motor development irrespective of age, instrument used, setting or the specific aspect of development evaluated, several limitations merit consideration.

First, the tests used to assess improvement (for example, BSID) may not be sufficiently sensitive measures of development, particularly in younger participants. Infant development scales that yield a mental score (for example, the MDI in the BSID) are often used as tests of intelligence under the assumption that the psychological constructs that these scales assess are the same as or similar to the constructs assessed by intelligence tests that yield an IQ score (for example, Stanford-Binet, Wechsler Intelligence Scale for Children) (Pollitt 1999). This assumption has been seriously weakened by the consistency of findings from different studies showing that the mental development scores, particularly those obtained before 18 months of age, have little if any power to predict later IQ (McCall 1983; Colombo 1993). The difference between the moderate stability scores of the pre-school battery of cognitive tests and the high stability of the Stanford-Binet scale suggests that there is much room for improvement in the development of pre-school tests for the evaluation of early childhood development programmes. It is recommended not to use infant scales that allegedly tap mental development constructs during the first 18 months of life in the evaluation of whether early child development programmes foster cognition and educational competence. If such scales are used for evaluation of programmes, they should be used beginning at about 24 months of life (Pollitt 1999).

Second, like iron, zinc supplementation could benefit specific components of mental development with no demonstrable evidence on the total score. We cannot address this issue from the available data. Zinc deficiency may affect children's emotionality and response to stress, rather than cognitive performance per se. Thus, a zinc-deficient child may be particularly responsive to the social context and to environmental stress. In our review, one of the studies (Gardner 2005) documented the beneficial effect of zinc supplementation on developmental quotient only in children who received concominant psychosocial stimulation, and benefits from zinc to hand and eye coordination were greater in stimulated children. Zinc supplementation alone improved hand and eye coordination, and psychosocial stimulation alone benefited the developmental quotient, hearing and speech, and performance. Zinc deficiency may affect cognitive performance through alterations in attention, and other aspects of neuropsychological functioning, such as planning or inhibition. Thus, it may be possible for zinc-deficient children to demonstrate normal cognitive functioning, but still be impaired by deficits in neuropsychological functioning that undermine academic performance. Another possibility is that zinc deficiency leads to reduced levels of activity, which then inhibits the development of cognitive development. Zinc deficiency may cause irreversible structural brain changes, particularly in younger children. Lack of benefit in developmental scores could reflect irreversible effects of zinc deficiency on rapidly developing brain.

Third, most of the research linking zinc to child development has not addressed the possibility of interactions with other micronutrient deficiencies. Animal products, a primary source of zinc, are also important sources of iron and vitamin B-12, which suggests that children who are zinc deficient are also likely to be deficient in iron and vitamin B-12. All three micronutrients have been associated with deficits in cognitive functioning, which highlights the need for studies that address comorbidity and the interrelationships among micronutrients.

Fourth, most of the included trials did not control for differences in socioeconomic status and the extent of stimulation provided to the children. This is important, because lower cognition scores in zinc-deficient children have often been attributed to other confounding environmental factors such as poverty, lack of stimulation and undernutrition. Because the trials included were randomised and controlled, most of these factors would have been controlled for.

Fifth, in the absence of actual data on the variability of the change in outcome scores in all studies, the analyses were based on comparison of post-intervention scores.

Finally, while we think we have identified all relevant trials on this topic, the adaptation of our MEDLINE search strategy to other databases may not have been optimal. We will consult the Cochrane Group's Trials Search Co-ordinator to revise them when we update the review.

Agreements and disagreements with other studies or reviews

The findings of this systematic review are in agreement with Diling 2011 who assessed the efficacy of zinc supplementation for improving psychomotor and mental developmental outcomes in infants younger than three years of age. There was no significant difference between the two groups in the PDI (SMD 0.15; 95% CI 0.12 to 0.42) and MDI (weighted mean difference (WMD) -0.08; 95% CI -1.55 to 1.40). Similar results were also obtained by Brown 2009, who did a meta-analysis of studies that reported on children's developmental outcomes in relation to zinc supplementation. The overall estimated effect size for MDI was 0.021 (95% CI -0.133 to 0.175; P = 0.76; random-effects model). As with MDI, there was no significant overall impact of zinc supplementation on PDI. The estimated effect size was 0.025 (95% CI -0.149 to 0.198; P = 0.75).

AUTHORS' CONCLUSIONS

Implications for practice

There is no convincing evidence that providing zinc supplementation to infants and children below five years of age has a significant

benefit on mental or motor development in either developed or developing countries.

Implications for research

There is a need to perform more studies of zinc supplementation in infants and children. The studies should have cognitive outcomes in children two to five years of age and should assess IQ for children more than five years of age. Irrespective of the time point and period of zinc supplementation, the studies should have long-term follow-up to ascertain whether gains from zinc supplementation on mental and motor development are sustainable or not. Since children who are zinc deficient are also likely to be deficient in iron and vitamin B-12 (other micronutrients associated with deficits in cognitive functioning); there is a need for studies that address comorbidity and the interrelationships among micronutrients. More studies are required for populations such as low birthweight or stunted children who are at high risk of zinc deficiency and thus are likely to benefit from this intervention.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ashworth 1998

Methods	Part-randomized, double-blind trial
Participants	Number randomized: 205 Inclusion criteria: singleton LBW term infants weighing 1500 g to 2499 g born to families of low income (equivalent to < USD 280 per month) Exclusion criteria: congenital anomalies, abnormal neurological signs or signs of asphyxia
Interventions	Intervention group (number treated 71; number analyzed 46): zinc 5 mg as sulphate daily except Sundays, for 8 weeks from birth Intervention group (number treated 68; number analyzed 48): zinc 1 mg as sulphate daily except Sundays, for 8 weeks from birth Control group (number treated 66; number analyzed 44): equivalent dose of sorbitol and flavour
Outcomes	Developmental evaluation - BSID II at 6 and 12 months Behavior (at 12 months, 5 scales) • responsiveness to the tester in the first 10 min of the test • emotional tone • activity level • co-operation with the test procedure • amount of vocalization
Notes	A mistake in the manufacture of the zinc solution resulted in the initial cohort being given 1 mg instead of 5 mg. When this was discovered, the design was modified and the enrolment period was extended to include a second cohort of infants who would all receive zinc 5 mg. Inclusion and exclusion criteria remained the same and all field workers and participating families were unaware of the change and remained blind to treatment allocation. Thus, during a 13-month period from January 1993, 66 LBW term infants were randomly allocated to receive the placebo and 68 received zinc 1 mg. During February to August 1994, 71 LBW term infants received zinc 5 mg For data and analysis we compared the infants who received zinc 5 mg/day with placebo as zinc 1 mg/day supplementation is well below the RDA and does not qualify as supplementation Sample size calculation not given Study funded by The Wellcome Trust, UK (grant no. 036605 Z 92). Dr Lira was supported by CAPES (Fundac¸a ˜o Coordenac¸a ˜o de Aperfeic¸oamento de Pessoal de Ni ´ vel Superior), Brazil

Risk of bias

Bias	Authors' judgement	Support for judgement

Ashworth 1998 (*Continued*)

Random sequence generation (selection bias)	High risk	"Since infants were randomly allocated to placebo and 1 mg zinc treatments". "The 5 mg zinc group, however was not randomly allocated" Also see 'notes' above
Allocation concealment (selection bias)	Low risk	"All field workers and participating families were unaware of the change and remained blind to treatment allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All field workers and participating families were unaware of the change and remained blind to treatment allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Two paediatricians shared the testing at 6-months, and one of them undertook all the 12-month tests. Both were blind to treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was 20.5% at 6 months and 32.7% at 12 months; reasons for attrition and distribution in the groups were provided
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No evidence of other bias

Bentley 1997

Methods	Randomized, double-blind trial
Participants	Number randomized: 108 Inclusion criteria: children aged 6 to 9 months Exclusion criteria: none
Interventions	Intervention group (number treated unknown; number analyzed 43): zinc 10 mg as sulphate daily for 7 months Control group (number treated unknown; number analyzed 42): equivalent dose of placebo
Outcomes	Infant activity assessed by time sampling-observation method over a 12 hour, in-home data collection period; at enrolment, and after 3 and 7 months of supplementation Gross motor milestones achieved
Notes	Sample size calculation given This research was funded by the University of California, Davis Institute of Nutrition of Central America and Panama institutional linkage project, which is supported by the University Development Linkage Program of the United States Agency for International Development (cooperative agreement DAN-5063-A-00-1115-00). Additional funding

Bentley 1997 (*Continued*)

	was obtained from the Thrasher Research Fund (principal investigator: ME Bentley)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Each child was randomized at enrolment to receive a ...."
Allocation concealment (selection bias)	Unclear risk	No relevant quote found in text.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The supplements were indistinguishable, and neither the families nor the study staff were aware of the treatment group to which the infants belonged."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Data collectors were unaware of the household randomization."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 21%; reasons for attrition and distribution in the groups are provided
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported.
Other bias	Low risk	No evidence of other bias.

Black Baqui 2004

Methods	Randomized double-blind trial
Participants	Number randomized: 346 Inclusion criteria: children aged 6 months Exclusion criteria: received infant formula, severely malnourished (mid-upper arm circumference 110 mm), severely anemic (hemoglobin <90 g/L), and obvious neurologic disorders, physical disabilities or chronic illnesses
Interventions	Intervention group 1 (multiple micronutrient group) (number treated 65; number analysed 35): 2 times the RDA of thiamine, niacin, folic acid, pantothenic acid, iodine, copper, manganese, selenium, and vitamins C, D, E, B-6 and B-12 in addition to elemental iron 20 mg, elemental zinc 20 mg and riboflavin 1 mg weekly from 6 to 12 months Intervention group 2 (iron group (Fe)) (number treated 72; number analyzed 49): elemental iron 20 mg in the form of ferrous sulphate and riboflavin 1 mg weekly from 6 to 12 months Intervention group 3 (zinc group (Zn)) (number treated 70; number analyzed 49): elemental zinc 20 mg in the form of zinc acetate and riboflavin 1 mg weekly from 6 to 12 months Intervention group 4 (iron plus zinc group (FeZn)) (number treated 74; number analyzed

Black Baqui 2004 (*Continued*)

	43): both iron and zinc Control group (number treated 65; number analyzed 45): riboflavin 1 mg weekly from 6 to 12 months
Outcomes	Developmental evaluation - BSID II at 6 and 12 months Behaviour (at 6 and 12 months, 3 scales) • orientation-engagement • emotional regulation • motor quality
Notes	For data and analysis 2 data sets were used In Black Baqui (1) 2004 Zn group was compared with the control group In Black Baqui (2) 2004 FeZn was compared to Fe (as the difference between these 2 groups was only zinc supplementation) Sample size calculation given Funded by the US Agency for International Development and Nutricia Foundation through the International Centre for Diarrhoeal Disease Research (ICDDR), B: International Centre for Health and Population Research, Dhaka, Bangladesh

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"In this double-blind trial, the infants were randomly assigned to 1 of 5 treatment conditions"
Allocation concealment (selection bias)	Unclear risk	"In this double-blind trial, the infants were randomly assigned to 1 of 5 treatment conditions"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The mixtures were similar in taste and appearance"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"In this double-blind trial, the infants were randomly assigned to 1 of 5 treatment conditions"
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was 37%; distribution in the groups provided
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No evidence of other bias

Black Sazawal 2004

Methods	Randomized, double-blind trial
Participants	Number randomized: 200 Inclusion criteria: gestational age >36 weeks; birth weight below 10th percentile for gestational age Exclusion criteria: congenital problems, disabilities or severe illnesses
Interventions	Intervention group (number treated 100; number analyzed 85): 1) a micronutrient mix including riboflavin 0.5 mg/day, calcium 180 mg/day, phosphorus 90 mg/day, folate 60 mol/day and iron 10 mg/day with zinc sulphate 5 mg; 2) riboflavin with zinc sulphate 5 mg from 30 days through to 9 months of age Control group (number treated 100; number analyzed 77): 1) the same micronutrient mix without zinc; and 2) riboflavin from 30 days through to 9 months of age
Outcomes	Developmental evaluation - BSID II at 6 and 10 months Carer perception of infant temperament - measured by a modified version of the fussy-difficult factor of the Infant Characteristics Questionnaire. The 4-item questionnaire used a 4-point Likert scale to ask carers how much their infant cried and how easy or difficult it was to calm their infant, to put their infant to sleep and to provide daily care
Notes	Sample size calculation given Support was provided by the National Institute of Child Health and Human Development (R01 HD374430), The Gerber Foundation, The Thrasher Foundation, Child Health at Johns Hopkins University and the Lanata-Piazzon Partnership

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization charts were designed to select 200 infants (100 each from groups 1 and 2) for the developmental sub study"
Allocation concealment (selection bias)	Low risk	"The randomization procedure was designed to ensure that no members of the field or evaluation teams were aware of group assignment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The micronutrient preparations were identical in taste, consistency, appearance, and acceptability" "The randomization procedure was designed to ensure that no members of the field or evaluation teams were aware of group assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The examiners were not aware of the infants' supplementation status..."

Black Sazawal 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	7% at 6 months, 19% at 10 months. Distribution in the groups not provided. "Infants who were retained in the sample did not differ from those who were lost to follow-up on birth weight, ponderal index, gestational age, maternal education, or paternal education"
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No evidence of other bias

Castillo-Duran 2001

Methods	Randomized, double-blind trial
Participants	Number randomized: 150 Inclusion criteria: term (≥ 37 weeks) singleton, birth weight > 2300 g (appropriate for gestational age), literate mothers with no history of drug abuse Exclusion criteria: evidence of toxoplasmosis, rubella, herpes, cytomegalovirus or Chagas disease, fetal alcohol syndrome or congenital malformations that affect growth
Interventions	Intervention group (number treated 75; number analyzed 57): zinc 5 mg/day as sulphate started before 20 days of age for 1 year Control group (number treated 75; number analyzed 52): equivalent dose of lactose
Outcomes	Developmental evaluation - BSID II at 6 and 10 months
Notes	All infants received iron (sulfate) drops, 1 to 2 mg/kg/day, after 5 months of age Sample size calculation given Supported in part by the Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT), grant 1950248

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Infants were randomly assigned to..."
Allocation concealment (selection bias)	Low risk	"Codes were kept secret..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"5 mg zinc per day as sulfate in a single dose or to a placebo group receiving an equivalent dose of lactose in a double-blind fashion..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No relevant quote found in text

Castillo-Duran 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 25.3%; distribution in the groups provided
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No evidence of other bias

Gardner 2005

Methods	Randomized trial
Participants	Number randomized: 126 Inclusion criteria: children aged 9 to 30 months, present weight-for-age z scores below 1. 5 SDs of the NCHS references and weight-for-age below 2 SDs in the previous 3 months Exclusion criteria: twins, children with physical or mental impairments that could affect development
Interventions	Intervention group 1 (zinc group (Zn)) (number treated 35; number analyzed 30): elemental zinc 10 mg as sulphate daily for 6 months Intervention group 2 (psychosocial stimulation group (Psy)) (number treated 23; number analyzed 21): weekly psychosocial stimulation for 6 months Intervention group 3 (zinc plus psychosocial stimulation group (ZnPsy)) (number treated 26; number analyzed 25): zinc plus psychosocial stimulation Control group (number treated 42; number analyzed 38): equivalent dose of placebo syrup
Outcomes	Developmental evaluation - 4 sub-scales of the Griffiths Mental Developmental Scale at baseline and after 6 months • locomotor (large muscle activities such as walking or jumping) • hand and eye coordination • hearing and speech • performance (shape recognition, block construction and block patterns)
Notes	All children received a proprietary brand of micronutrients containing iron and vitamins 0.5 mL daily "...zinc supplementation trial was funded by the Nestle Foundation. The Grace, Kennedy Foundation (Jamaica); Dr Jeffrey Meeks; and the Matalon and Melhado families provided further financial assistance. The zinc supplement and the vitamin preparation were donated by Federated Pharmaceuticals Limited"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"It was not considered feasible to have both the stimulated and the nonstimulated groups of children at the same clinic; therefore, the 18 clinics were randomly assigned to stimulation or control. Within each clinic, the children were stratified into 2

		age groups (9-18 and 19-30 mo) and were then randomly assigned to receive the zinc supplement or the placebo. To detect a difference of 0.5 SD in developmental levels at P0.05 with 80% power, 64 children were required in each arm of the study (supplemented and placebo). Ninety-nine children were identified and enrolled over a period of 5mo. For logistic reasons, we could not extend the stimulation program. To achieve sufficient power to detect an effect of zinc, we continued enrolling children for a further 2 mo to the zinc trial only. A further 27 children were enrolled from all the clinics in this time period"
Allocation concealment (selection bias)	High risk	No relevant quote found in text
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...parents or guardians, who were unaware of the children's assignment to zinc or placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All tests were carried out by a single tester, who was unaware of the children's group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 11.7%; distribution in the groups provided
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No evidence of other bias

Hamadani 2001

Methods	Randomized, double-blind trial
Participants	Number randomized: 301 Inclusion criteria: infants less than 4 weeks of age Exclusion criteria: none
Interventions	Intervention group (number treated unknown; number analyzed 97): elemental Zn 5 mg as zinc acetate in a syrup daily for 5 months Control group (number treated unknown; number analyzed 101): equivalent dose of cellulose substance given in an identical syrup
Outcomes	Developmental evaluation - BSID II at 7 and 13 months of age Behavior rating - scales developed by Wolke Wolke 1990 • infants' activity • emotional tone • approach or responsiveness to the examiner in the first 10 min • co-operation with the test procedure • vocalization

Hamadani 2001 (*Continued*)

Notes	Sample size calculation not reported. Supported by UNICEF and ICDDR,B. ICDDR,B is also supported by aid agencies of the governments of Australia, Bangladesh, Belgium, Canada, Denmark, France, Japan, The Netherlands, Norway, Sweden, Switzerland, the UK, and the US; international organisations including the United Nations, the Capital Development Fund, the United Nation's Development Program, the United Nations Children's Fund, and the World Health Organization; and private foundations including the Ford Foundations and the Sasakawa Foundation. One author was partly funded by the Department for International Development, UK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"...were randomly assigned to a treatment or placebo group."
Allocation concealment (selection bias)	High risk	No relevant quote found in text.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...placebo was a cellulose substance given in an identical syrup."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Two testers who were unaware of the children's group assignment carried out the tests at 7 mo of age."
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was 29.6%; distribution in the groups provided.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported.
Other bias	Low risk	No evidence of other bias

Heinig 2006

Methods	Randomized, double-blind trial
Participants	Number randomized: 85 Inclusion criteria: 1) healthy term infant weighing 2500 g at birth; 2) healthy non-smoking mother 19 years of age, with no chronic medical condition that could interfere with lactation; 3) mother planned to fully breastfeed for 10 months (that is, would not give formula on a daily basis) and not to introduce complementary foods before 4 months; and 4) mother planned to remain in the study area throughout the study period Exclusion criteria: none

Heinig 2006 (*Continued*)

Interventions	Intervention group (number treated 41; number analyzed 33): elemental zinc 5 mg as sulphate daily between 4 to 10 months of age Control group (number treated 44; number analyzed 37): equivalent dose of placebo
Outcomes	Developmental evaluation - AIMS at 4 and 10 months of age
Notes	Sample size calculated for weight and length gain "Supported by grant no 94-37200-2536 from the US Department of Agriculture"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"...random assignment to groups was done by using the Moses-Oakford algorithm, as described by Meinert and Tonascia"
Allocation concealment (selection bias)	Low risk	"...where an assistant, who was not in contact with the study participants, labelled the bottles with 1 of 4 colors (2 colors were assigned to each group to reduce the chance that a group assignment would accidentally be revealed)"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Each mother-infant pair was assigned to a color group so that neither the primary investigator nor the mothers would know whether their infants received the zinc supplement"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Each mother-infant pair was assigned to a color group so that neither the primary investigator nor the mothers would know whether their infants received the zinc supplement"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 17.6%; distribution in the groups provided
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No evidence of other bias

Jiminez 2007

Methods	Randomized, double-blind trial
Participants	Number randomized: 212 Inclusion criteria: LBW babies Exclusion criteria: children with serious illnesses, mother receiving zinc supplementation during pregnancy and children with congenital malformations

Interventions	Intervention group (number treated unknown; number analyzed 87): zinc 10 mg as sulphate daily for first 6 months of life Control group (number treated unknown; number analyzed 76): equivalent saline solution
Outcomes	Developmental evaluation - BSID II at 6 months of age
Notes	The trial was available in Spanish. Google translation was used for data extraction "...support received from the Foundation of Sick Children."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"La aleatorización del estudio se hizo por bloques que se generaron en computadora." [The study was randomized blocks that were generated by computer]
Allocation concealment (selection bias)	Low risk	"El esquema de aleatorización lo llevó a cabo la dirección de farmacia del dispensario que elabora la fórmula..." [The randomization scheme was carried out by the staff of the clinic pharmacy who had made the formula]
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...antes del comienzo del estudio el investigador envió las copias de la aleatorización al personal designado paracontrolar y administrar el medicamento; los investigadores no tuvieron acceso a las mismas" [before the start of the study, the researcher sent copies of the randomization protocol, designated personnel and administration of the medication; the researchers did not have access to the details]
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No relevant quote found in text
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition was 23.1%; distribution in the groups provided
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No evidence of other bias

Katz 2010

Methods	Cluster-randomized, placebo-controlled trial
Participants	Number randomized: 2457 (children unable to walk at the time of enrolment) Inclusion criteria: children 1 to 35 months of age in October 2001 were eligible for enrolment. Infants born from this time until January 2006 were also eligible for the trial when they reached the age of one month. All children were discharged from the trial at age 36 months Exclusion criteria: none
Interventions	Intervention group: 1) elemental iron 12.5 mg as ferrous sulphate plus folic acid 50 mg, and elemental zinc 10 mg as zinc sulphate; 2) elemental iron 12.5 mg as ferrous sulphate plus folic acid 50 mg; 3) elemental zinc 10 mg as zinc sulphate. Infants were given one-half this dose Control group: equivalent dose of placebo Total (intervention and control group): 1775 followed to 36 months
Outcomes	Developmental evaluation - Motor Milestone attainment (14 motor milestones assessed weekly via an interview with the child's carer)
Notes	The analysis was intent to treat. Because children first enrolling in the study could be 1 to 35 months of age, the analysis was confined to those who had not yet started walking unassisted Sample size calculation not provided Supported by the NIH, Bethesda, MD (HD 38753), the Bill and Melinda Gates Foundation, Seattle, Washington (810-2054), and a Cooperative Agreement between Johns Hopkins University and the Office of Health and Nutrition, US Agency for International Development, Washington, DC (HRN-A-00-97-00015-00)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Children received 1 of 4 daily supplements, depending on sector of residence."
Allocation concealment (selection bias)	High risk	No relevant quote found in text.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A treatment code was imprinted on the package, but all tablets looked identical and study staff were unaware of the intervention."
Blinding of outcome assessment (detection bias) All outcomes	High risk	No relevant quote found in text.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was 27.8%; distribution in the groups not provided

Selective reporting (reporting bias)	Low risk	All expected outcomes were reported.
Other bias	Low risk	No evidence of other bias

Lind 2004

Methods	Randomized, double-blind trial
Participants	Number randomized: 680 Inclusion criteria: healthy singleton infants less than 6 months of age Exclusion criteria: children with metabolic or neurological disorders; disability affecting development, feeding, or activity; or severe or protracted illness, infants with hemoglobin 90 g/L
Interventions	Intervention group 1 (iron group (Fe)) (number treated 170; number analyzed 163): iron 10 mg as ferrous sulphate daily for 6 months Intervention group 2 (zinc group (Zn)) (number treated 170; number analyzed 167): zinc 10 mg as zinc sulphate daily for 6 months Intervention group 3 (iron and zinc (FeZn)) (number treated 170; number analyzed 160): iron 10 mg as ferrous sulphate and zinc 10 mg as zinc sulphate, daily for 6 months Control group (number treated 170; number analyzed 165): equivalent dose of placebo in a sweet-tasting syrup
Outcomes	Developmental evaluation - BSID II at 6 and 12 months
Notes	A maximum of 50 infants were assessed for eligibility per month. 131 eligible infants were not randomised because of this ceiling For data and analysis 2 data sets were used In Lind 2004 (1) Zn group was compared with the control group In Lind 2004 (2) FeZn was compared to Fe (as the difference between these 2 groups was only zinc supplementation)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was planned and generated by an independent statistician and was performed in blocks of 20. Participants were assigned to treatment groups by the recruitment field staff in strict accordance with the randomization list"
Allocation concealment (selection bias)	Low risk	"Researchers and field staff were blinded to the information on group assignment, because this information was kept in safes at the administrative offices of Gadjah Mada and Umeå universities until after the intent-to-treat analysis"

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The pharmaceutical company marked the 4 different supplements with letter codes to which the researchers and participants were blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...this information was kept in safes at the administrative offices of Gadjah Mada and Umeå universities until after the intent-to-treat analysis"
Incomplete outcome data (attrition bias) All outcomes	Low risk	3.7% attrition. No difference between participants and drop-outs
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No evidence of other bias

Sazawal 1996

Methods	Quasi-randomized control trial
Participants	Number randomized: 93 Inclusion criteria: children 6 to 35 months old with diarrhea presenting to the dispensary with reported passage of at least 4 unformed stools in the previous 24 hours, a diarrhoeal duration of less than 7 days and permanent residence in the trial area Exclusion criteria: children with malnutrition sufficiently severe to require hospitalization
Interventions	Intervention group (number treated 48; number analyzed 48): zinc 10 mg as zinc gluconate, daily for 1 to 6 months Control group (number treated 45; number analyzed 45): equivalent dose of placebo Both groups received vitamins A 800 U, B1 0.6 mg, B2 0.5 mg, B6 0.5 mg, D3 100 IU and E 3 mg and niacinamide 10 mg daily
Outcomes	CARS - percentage of time spent in each of 5 activity levels and 2 groups representing high and low movement and overall rating by 2 activity scores
Notes	Sample size calculation not provided "This work was supported by a grant from the World Health Organization Diarrheal Disease Control Program and the Thrasher Research Fund"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomization schedules with permuted blocks of fixed length appropriate for double-blind studies were used..." "Randomization was stratified by nutritional and breastfeeding status,..." "Two separate randomization

Sazawal 1996 (*Continued*)

		schedules were made by the World Health Organization for children to be followed..." "From the children enrolled in the main study, all children enrolled after September 1, 1993, 12 to 23 months of age and having received supplementation for at least 1 month were considered for selection"
Allocation concealment (selection bias)	Low risk	"A sealed envelope contained the assigned group for each enrolled child"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The bottles labelled with identification number and name were given to the mother and kept at the child's home" "A separate team of field assistants dedicated to dispensing the assigned preparation visited the family every day except Sundays and holidays and fed the preparation to the child" "At the time of the selection, the group allocations were double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Observers were unaware of group allocations"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition owing to nature of participant selection
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	No evidence of other bias

Taneja 2005

Methods	Randomized control trial
Participants	Number randomized: 2482 (650) Inclusion criteria: children 12 to 18 months of age Exclusion criteria: children planning to move within the next 4 months, hospitalization on the enrolment day, received a massive dose of vitamin A within 2 months
Interventions	Intervention group (number treated 327; number analyzed 283): 10 mg zinc as zinc gluconate for infants and 20 mg zinc as zinc gluconate for older children, daily for 4 months Control group (number treated 323; number analyzed 288): equivalent dose of placebo
Outcomes	Developmental evaluation - BSID II after 4 months of supplementation

Taneja 2005 (*Continued*)

Notes	2482 children were randomized for the main supplementation trial. Developmental testing was done in 650 children who were between 12 to 18 months of age at the time of enrolment Sample size calculation provided "Supported by the European Union (Contract no. IC18-CT96-0045), Norwegian Council of Universities' Committee for Development Research and Education (PRO 53/96), Department of Child and Adolescent Health and Development (CAH), World Health Organization"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"...were individually randomized by using a simple randomization scheme in blocks of 8."
Allocation concealment (selection bias)	Low risk	"The randomization scheme was generated by a statistician at the Statens Serum Institute, who was not otherwise involved with this study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Zinc or placebo syrups, similar in appearance and taste, were prepared and packaged in unbreakable bottles by GK Pharma Aps, Koge, Denmark; they also labelled bottles with unique child identification numbers according to the randomization scheme."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No relevant quote found in text.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 12.2%; distribution in the groups provided.
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported.
Other bias	Low risk	No evidence of other bias

AIMS: Alberta Infant Motor Scale; BSID: Bayley Scales of Infant Development; CARS: Children's Activity Rating Score; LBW: low birthweight; NCHS: National Center for Health Statistics; NIH: National Institutes of Health; RDA recommended daily allowance; SD: standard deviation

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

Study	Reason for exclusion
Cavan 1993	Zinc supplementation given to children more than 5 years of age
Christian 2011	Not a randomised control trial
DiGirolamo 2010	Zinc supplementation given to children more than 5 years of age
Friel 1993	Trial done on very low birthweight neonates
Gibson 1989	Zinc supplementation given to children more than 5 years of age
Kordas 2005	Trial done on lead-exposed children
Kordas 2009	Relevant outcomes not reported
Olney 2006	Excluded as outcome for zinc only group not known
Penland 1999	Zinc supplementation given to children more than 5 years of age
Pongcharoen 2011	Not a randomised control trial
Rico 2006	Trial done on lead-exposed children
Sandstead 1998	Zinc supplementation given to children more than 5 years of age
Sawada 2010	Zinc supplementation given to children more than 5 years of age
Tupe 2009	Zinc supplementation given to children more than 5 years of age
Uckardes 2009	Zinc supplementation given to children more than 5 years of age

DATA AND ANALYSES

Comparison 1. Zinc versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mental Development Index	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Primary analysis	8	2134	Mean Difference (IV, Random, 95% CI)	-0.50 [-2.06, 1.06]
1.2 Neonatal zinc supplementation	4	560	Mean Difference (IV, Random, 95% CI)	-2.30 [-5.30, 0.70]
1.3 Post-neonatal zinc supplementation	4	1574	Mean Difference (IV, Random, 95% CI)	0.60 [-0.28, 1.48]
1.4 Zinc supplementation for 6 months or less	5	1700	Mean Difference (IV, Random, 95% CI)	0.00 [-1.70, 1.71]
1.5 Zinc supplementation for more than 6 months	3	434	Mean Difference (IV, Random, 95% CI)	-1.15 [-4.74, 2.44]
1.6 Zinc sulphate supplementation	5	1179	Mean Difference (IV, Random, 95% CI)	-0.84 [-2.89, 1.22]
1.7 Zinc acetate supplementation	2	384	Mean Difference (IV, Random, 95% CI)	-0.94 [-5.64, 3.76]
1.8 Zinc supplementation with other salts	1	571	Mean Difference (IV, Random, 95% CI)	1.5 [-0.28, 3.28]
1.9 Zinc supplementation in low birthweight babies	3	415	Mean Difference (IV, Random, 95% CI)	-2.35 [-5.82, 1.12]
1.10 Zinc supplementation in low HDI countries	5	1772	Mean Difference (IV, Random, 95% CI)	0.15 [-1.18, 1.48]
1.11 Zinc supplementation in high HDI countries	3	362	Mean Difference (IV, Random, 95% CI)	-1.82 [-6.37, 2.72]
2 Psychomotor Development Index	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Primary analysis	8	2134	Mean Difference (IV, Random, 95% CI)	1.54 [-2.26, 5.34]
2.2 Neonatal zinc supplementation	4	560	Mean Difference (IV, Random, 95% CI)	1.38 [-7.10, 9.86]
2.3 Post-neonatal zinc supplementation	4	1574	Mean Difference (IV, Random, 95% CI)	1.01 [-0.84, 2.86]
2.4 Zinc supplementation for 6 months or less	5	1700	Mean Difference (IV, Random, 95% CI)	0.64 [-1.22, 2.50]
2.5 Zinc supplementation for more than 6 months	3	434	Mean Difference (IV, Random, 95% CI)	2.82 [-6.64, 12.28]
2.6 Zinc sulphate supplementation	5	1179	Mean Difference (IV, Random, 95% CI)	1.56 [-4.41, 7.53]
2.7 Zinc acetate supplementation	2	384	Mean Difference (IV, Random, 95% CI)	1.21 [-6.07, 8.49]
2.8 Zinc supplementation with other salts	1	571	Mean Difference (IV, Random, 95% CI)	1.70 [-0.20, 3.60]
2.9 Zinc supplementation in low birthweight babies	3	415	Mean Difference (IV, Random, 95% CI)	3.77 [-4.67, 12.21]

2.10 Zinc supplementation in low HDI countries	5	1772	Mean Difference (IV, Random, 95% CI)	0.68 [-1.09, 2.46]
2.11 Zinc supplementation in high HDI countries	3	362	Mean Difference (IV, Random, 95% CI)	2.64 [-7.36, 12.64]

Analysis 1.1. Comparison 1 Zinc versus placebo, Outcome 1 Mental Development Index.

Review: Zinc supplementation for mental and motor development in children

Comparison: 1 Zinc versus placebo

Outcome: 1 Mental Development Index

Study or subgroup	Zinc N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Primary analysis							
Ashworth 1998	46	106.9 (12.1)	44	109.1 (12.2)		6.5 %	-2.20 [-7.22, 2.82]
Black Baqui 2004	92	105.03 (9.93)	94	103.53 (11.55)		11.1 %	1.50 [-1.59, 4.59]
Black Sazawal 2004	85	86.2 (4.9)	77	86.4 (5.1)		16.5 %	-0.20 [-1.74, 1.34]
Castillo-Duran 2001	57	90.9 (10.5)	52	88.9 (9.1)		9.4 %	2.00 [-1.68, 5.68]
Hamadani 2001	97	103.1 (11)	101	106.4 (9.3)		11.9 %	-3.30 [-6.14, -0.46]
Jiminez 2007	87	108 (9.2)	76	113 (8.9)		12.1 %	-5.00 [-7.78, -2.22]
Lind 2004	327	100.5107 (9.5464)	328	99.99 (9.8878)		16.7 %	0.52 [-0.97, 2.01]
Taneja 2005	283	92.8 (10.9)	288	91.3 (10.8)		15.7 %	1.50 [-0.28, 3.28]
Subtotal (95% CI)	**1074**		**1060**			**100.0 %**	**-0.50 [-2.06, 1.06]**
Heterogeneity: $Tau^2 = 3.21$; $Chi^2 = 23.51$, df = 7 (P = 0.001); I^2 =70%							
Test for overall effect: Z = 0.63 (P = 0.53)							
2 Neonatal zinc supplementation							
Ashworth 1998	46	106.9 (12.1)	44	109.1 (12.2)		18.5 %	-2.20 [-7.22, 2.82]
Castillo-Duran 2001	57	90.9 (10.5)	52	88.9 (9.1)		24.3 %	2.00 [-1.68, 5.68]
Hamadani 2001	97	103.1 (11)	101	106.4 (9.3)		28.5 %	-3.30 [-6.14, -0.46]
Jiminez 2007	87	108 (9.2)	76	113 (8.9)		28.8 %	-5.00 [-7.78, -2.22]
Subtotal (95% CI)	**287**		**273**			**100.0 %**	**-2.30 [-5.30, 0.70]**
Heterogeneity: $Tau^2 = 6.11$; $Chi^2 = 9.10$, df = 3 (P = 0.03); I^2 =67%							
Test for overall effect: Z = 1.50 (P = 0.13)							
3 Post-neonatal zinc supplementation							
Black Baqui 2004	92	105.03 (9.93)	94	103.53 (11.55)		8.1 %	1.50 [-1.59, 4.59]
Black Sazawal 2004	85	86.2 (4.9)	77	86.4 (5.1)		32.5 %	-0.20 [-1.74, 1.34]

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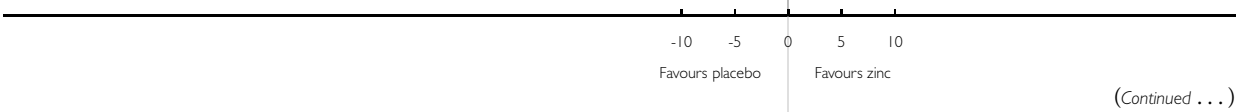
Study or subgroup	Zinc N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Lind 2004	327	100.5107 (9.5464)	328	99.99 (9.8878)		35.0 %	0.52 [-0.97, 2.01]
Taneja 2005	283	92.8 (10.9)	288	91.3 (10.8)		24.4 %	1.50 [-0.28, 3.28]
Subtotal (95% CI)	**787**		**787**			**100.0 %**	**0.60 [-0.28, 1.48]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.35$, df = 3 (P = 0.50); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.34 (P = 0.18)							
4 Zinc supplementation for 6 months or less							
Ashworth 1998	46	106.9 (12.1)	44	109.1 (12.2)		8.8 %	-2.20 [-7.22, 2.82]
Black Baqui 2004	92	105.03 (9.93)	94	103.53 (11.55)		16.8 %	1.50 [-1.59, 4.59]
Hamadani 2001	97	103.1 (11)	101	106.4 (9.3)		18.4 %	-3.30 [-6.14, -0.46]
Lind 2004	327	100.5107 (9.5464)	328	99.99 (9.8878)		29.3 %	0.52 [-0.97, 2.01]
Taneja 2005	283	92.8 (10.9)	288	91.3 (10.8)		26.7 %	1.50 [-0.28, 3.28]
Subtotal (95% CI)	**845**		**855**			**100.0 %**	**0.00 [-1.70, 1.71]**
Heterogeneity: $Tau^2 = 2.00$; $Chi^2 = 9.51$, df = 4 (P = 0.05); $I^2 = 58\%$							
Test for overall effect: Z = 0.00 (P = 1.0)							
5 Zinc supplementation for more than 6 months							
Black Sazawal 2004	85	86.2 (4.9)	77	86.4 (5.1)		38.3 %	-0.20 [-1.74, 1.34]
Castillo-Duran 2001	57	90.9 (10.5)	52	88.9 (9.1)		28.7 %	2.00 [-1.68, 5.68]
Jiminez 2007	87	108 (9.2)	76	113 (8.9)		33.0 %	-5.00 [-7.78, -2.22]
Subtotal (95% CI)	**229**		**205**			**100.0 %**	**-1.15 [-4.74, 2.44]**
Heterogeneity: $Tau^2 = 8.14$; $Chi^2 = 11.51$, df = 2 (P = 0.003); $I^2 = 83\%$							
Test for overall effect: Z = 0.63 (P = 0.53)							
6 Zinc sulphate supplementation							
Ashworth 1998	46	106.9 (12.1)	44	109.1 (12.2)		10.9 %	-2.20 [-7.22, 2.82]
Black Sazawal 2004	85	86.2 (4.9)	77	86.4 (5.1)		26.6 %	-0.20 [-1.74, 1.34]
Castillo-Duran 2001	57	90.9 (10.5)	52	88.9 (9.1)		15.6 %	2.00 [-1.68, 5.68]
Jiminez 2007	87	108 (9.2)	76	113 (8.9)		19.9 %	-5.00 [-7.78, -2.22]
Lind 2004	327	100.5107 (9.5464)	328	99.99 (9.8878)		26.9 %	0.52 [-0.97, 2.01]
Subtotal (95% CI)	**602**		**577**			**100.0 %**	**-0.84 [-2.89, 1.22]**
Heterogeneity: $Tau^2 = 3.52$; $Chi^2 = 14.15$, df = 4 (P = 0.01); $I^2 = 72\%$							
Test for overall effect: Z = 0.80 (P = 0.42)							
7 Zinc acetate supplementation							
Black Baqui 2004	92	105.03 (9.93)	94	103.53 (11.55)		49.2 %	1.50 [-1.59, 4.59]
Hamadani 2001	97	103.1 (11)	101	106.4 (9.3)		50.8 %	-3.30 [-6.14, -0.46]
Subtotal (95% CI)	**189**		**195**			**100.0 %**	**-0.94 [-5.64, 3.76]**
Heterogeneity: $Tau^2 = 9.22$; $Chi^2 = 5.01$, df = 1 (P = 0.03); $I^2 = 80\%$							
Test for overall effect: Z = 0.39 (P = 0.70)							
8 Zinc supplementation with other salts							



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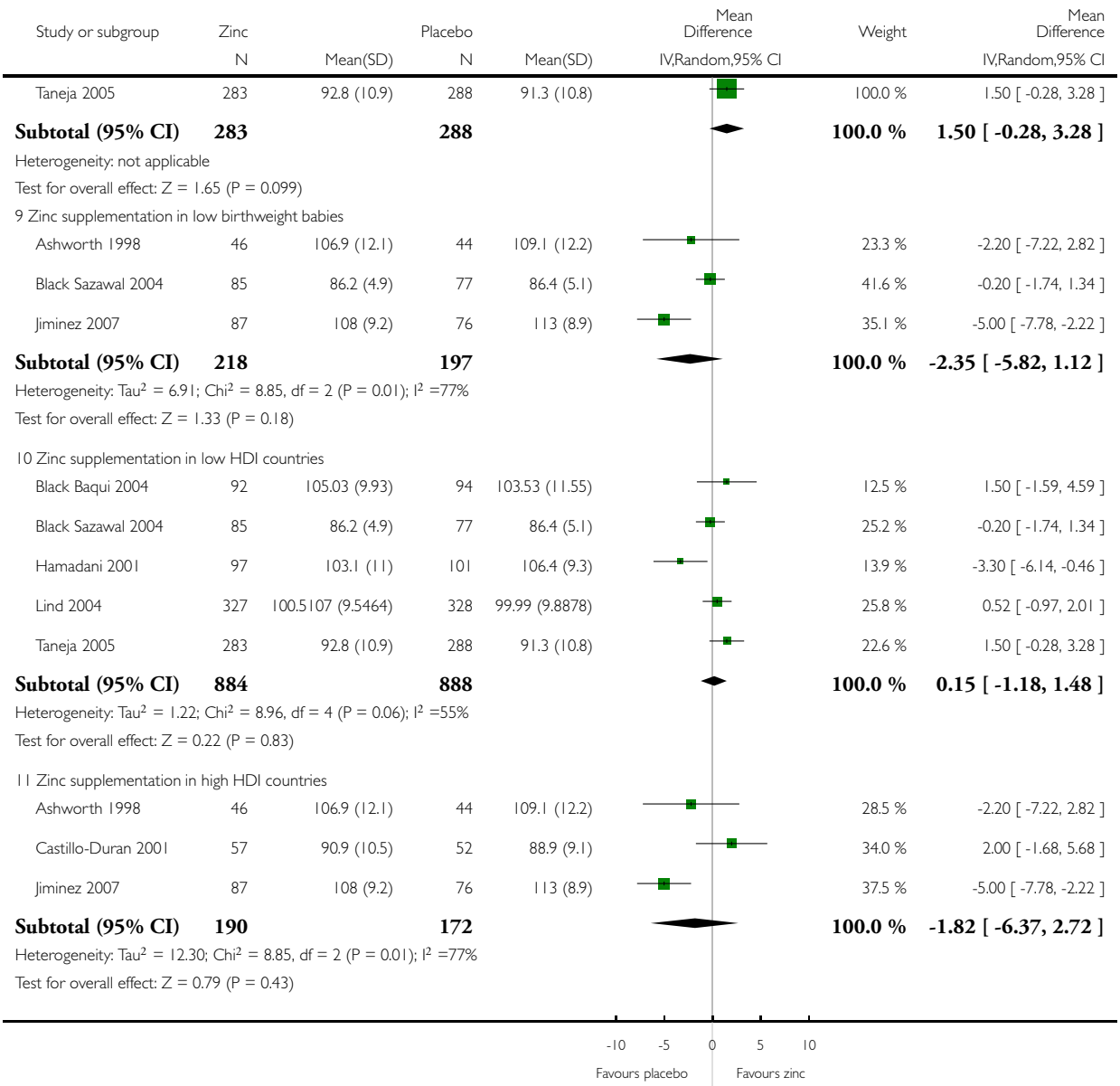
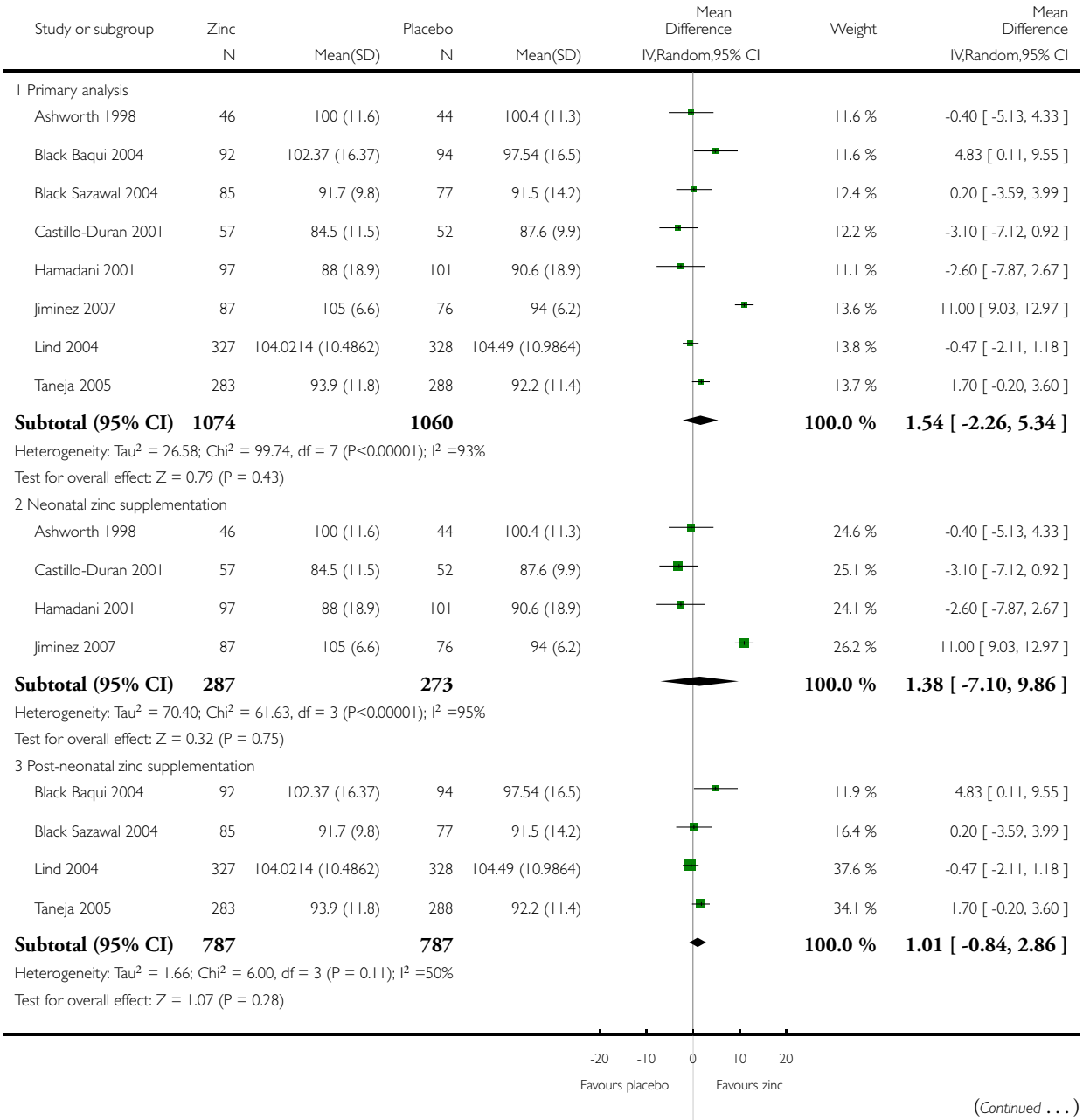


Analysis 1.2. Comparison 1 Zinc versus placebo, Outcome 2 Psychomotor Development Index.

Review: Zinc supplementation for mental and motor development in children

Comparison: 1 Zinc versus placebo

Outcome: 2 Psychomotor Development Index



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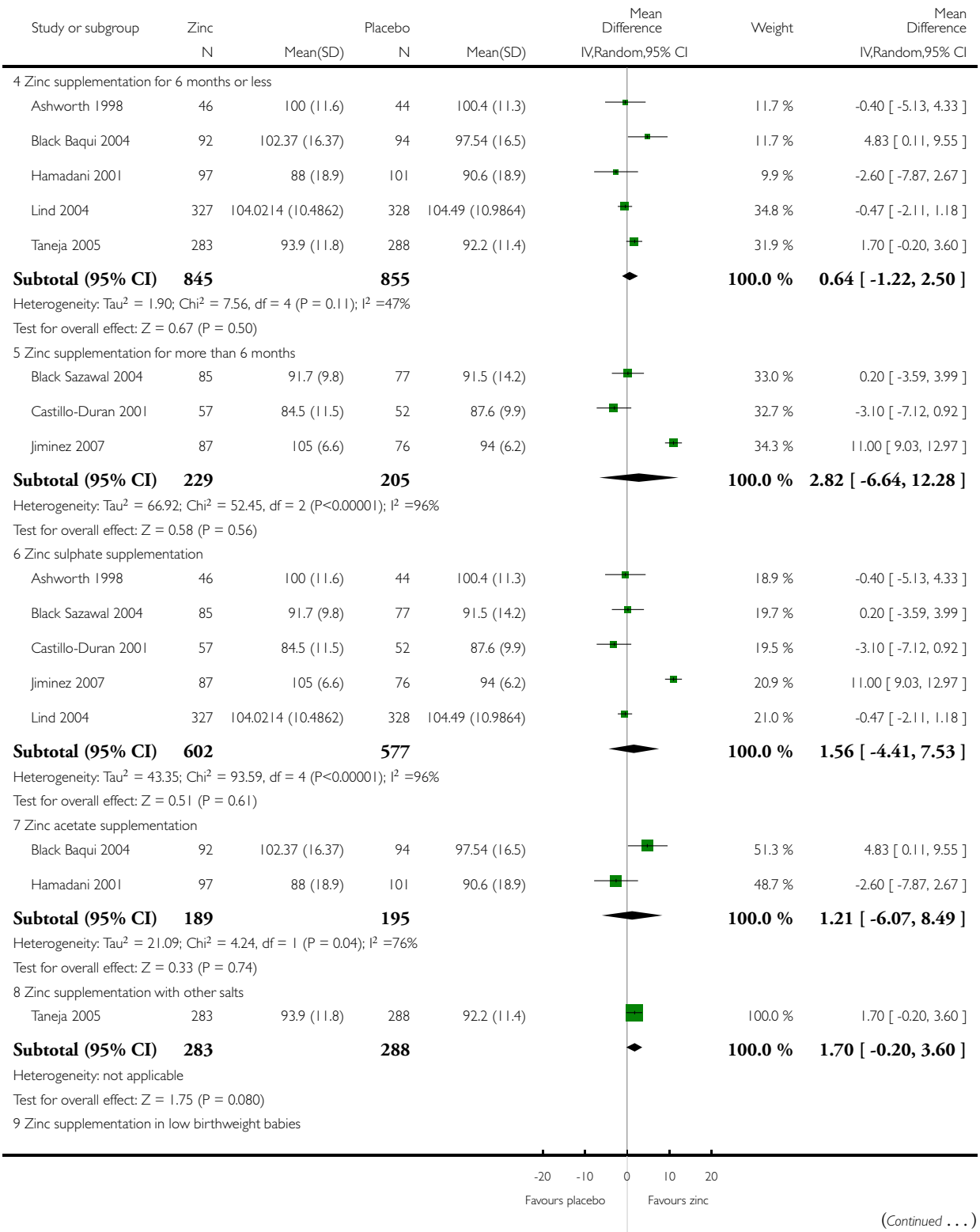

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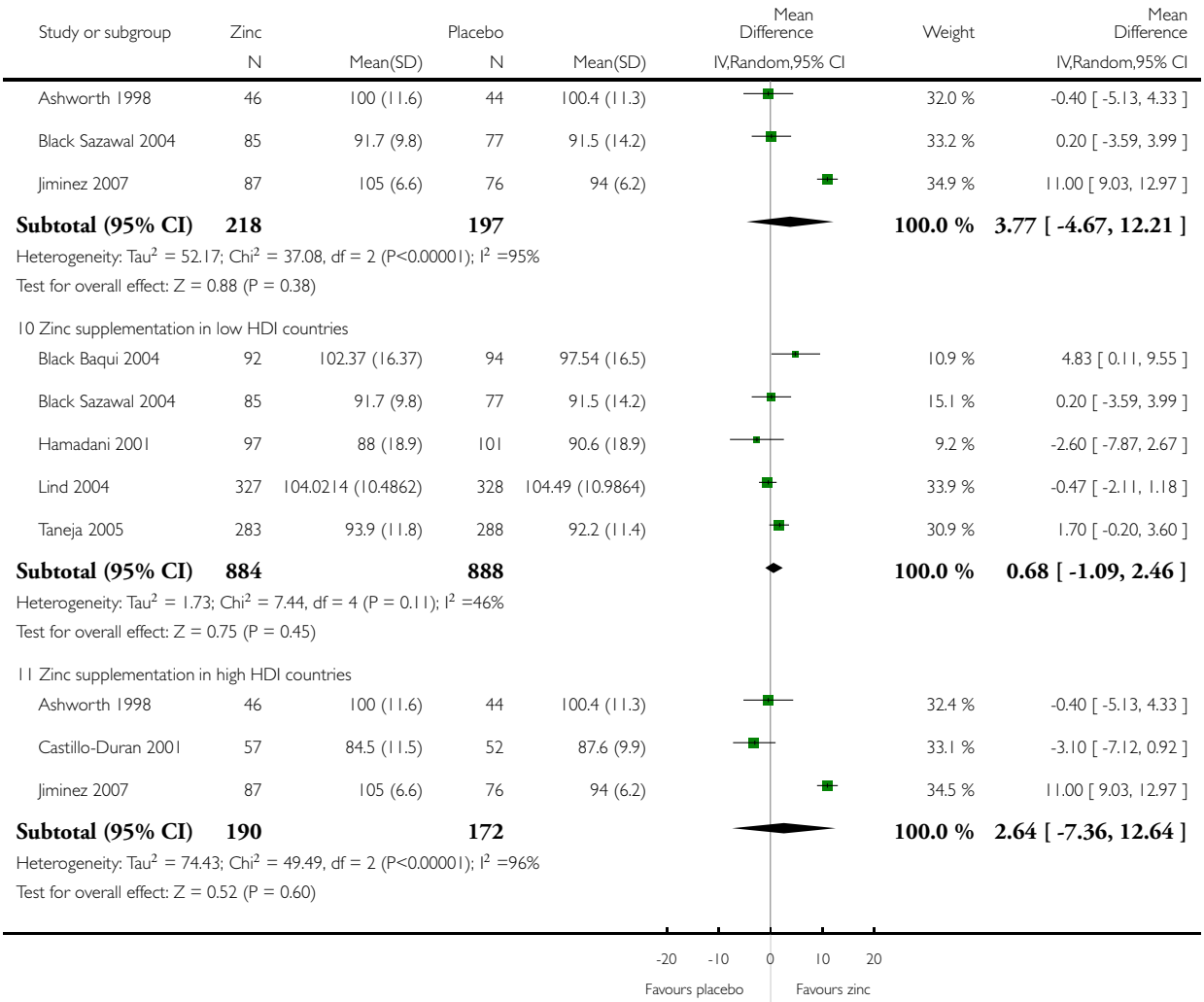

ADDITIONAL TABLES

Table 1. Sensitivity analyses

Variable	MDI RR (95% CI)	PDI RR (95% CI)
Attrition		
Less than 10%	0.17 (-0.9 to 1.24)	-0.36 (-1.87 to 1.15)
More than 10%	-1.09 (-3.25 to 1.07)	2.08 (-2.96 to 7.13)

Table 1. Sensitivity analyses (*Continued*)

Allocation concealment	-0.35 (-2.09 to 1.40)	1.63 (-2.86 to 6.12)
Adequate	-0.94 (-5.64 to 3.76)	1.21 (-6.07 to 8.49)
Inadequate		

CI: confidence interval; MDI: Mental Development Index; PDI: Psychomotor Development Index; RR: risk ratio

APPENDICES

Appendix 1. Data extraction topics

Study procedures including:

- recruitment;
- dosage;
- duration;
- setting;
- randomization method (including list generation);
- method of allocation concealment;
- blinding participants;
- blinding of investigators;
- blinding of outcome assessors.

Participant characteristics including:

- inclusion/exclusion criteria;
- number (total/per group);
- age distribution;
- gender;
- weight;
- developmental status of country (high, medium and low) in which the trial was conducted (based on the United Nations Development Programme (UNDP) Human Development Index figures; Human Development Index 2011);
- socioeconomic status.

Follow-up data including:

- duration of follow-up;
- loss to follow-up;
- reasons for loss to follow-up.

Details of analysis:

- methods of analysis (intention-to-treat/ per-protocol analysis);
- developmental (mental, psychomotor, behaviour), cognition and intelligence scores at baseline with standard deviation (SD);
- developmental (mental, psychomotor, behaviour), cognition and intelligence scores post intervention with SD;

- mean difference (MD) in post-intervention developmental (mental, psychomotor, behaviour), cognition and intelligence scores with SD;
- time point at which developmental milestones (social smile, sitting, standing, walking etc.) were achieved;
- adverse effects (incidence rates of vomiting, diarrhea and anemia).

Appendix 2. Additional methods

Analysis of overall cognitive performance

We planned to use the intelligence quotient (IQ) as the measure for overall cognitive performance. For studies that do not report IQ scores we planned to use data of cognitive tests that are representative for IQ:

1. when a test was available of which the outcome has a highly predictive value for IQ (such as the Raven's Progressive Matrices (Raven 2000));
2. when there were multiple tests used that measured multiple cognitive domains which can be combined into one score which has a highly predictive value for IQ.

Analysis of cognitive domains or broad cognitive abilities

For each study we planned to evaluate the cognitive tests that are used and define which cognitive ability they assess. The domains are defined as follows:

For children aged five to 18 years, the cognitive domains were chosen from Carroll's broad cognitive abilities (Carroll 1993). These abilities actually very often overlap with abilities also described in neuro-psychological models, viz:

1. fluid intelligence (or reasoning; described as planning and part of executive functions in neuro-developmental models);
2. crystallised intelligence (or verbal domain such as vocabulary and fluency);
3. visuo-spatial abilities that do not include memory components;
4. working memory, which includes verbal, visual and other perceptual inputs;
5. long-term memory, which also includes verbal, visual and other perceptual inputs; also described as learning ability and can cover recognition or retrieval of the information;
6. speed of processing (in Carroll's model there are two clusters, "cognitive processing speed" and "decision speed". We choose to group them together for pragmatic reasons, in order to avoid too many cognitive abilities for the meta-analysis, and because of the similarity (they are not reported as two separate abilities in neuro-developmental models);
7. academic skills. There are also two clusters here in the Carroll's model (mathematical and reading-spelling skills) but we grouped them here for practical reasons and because they are expected to be highly correlated in children from a general population;
8. sustained attention (ability which is not covered by Carroll's model because it corresponds to lower cognitive levels but is frequently found on neuro-psychological scales (more automatic processes)).

Unit of analysis issues

For extraction of data from cluster randomised trials, authors were to be contacted for intra-cluster correlation (ICC) estimates. With the help of ICC estimates, design effect was to be calculated and the variance inflated accordingly, for use in the review. If ICC estimates were not available, then these trials were to be analysed using imputed ICC estimates from similar trials and a sensitivity analysis conducted for the purpose. We did not anticipate cross-overs.

Appendix 3. Search strategies

MEDLINE

1 Zinc/
2 zinc.tw.
3 1 or 2
4 adolescent/ or child/ or child, preschool/ or infant/
5 (child$ or boy$ or girl$ or schoolchild$ or baby or babies or infant$ or toddler$ or preschool$ or pre-school$ or adolscen$ or teen$).tw.
6 4 or 5
7 randomized controlled trial.pt.
8 controlled clinical trial.pt.
9 randomized.ab.
10 placebo.ab.

11 drug therapy.fs.
12 randomly.ab.
13 trial.ab.
14 groups.ab.
15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 humans.sh.
17 15 and 16
18 6 and 3 and 17

EMBASE

zinc.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]		
		limit 1 to (human and exclude medline journals and embase and yr="1900 - 2011" and (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>))

CENTRAL

"MeSH descriptor:[Zinc], explode all trees, with qualifier(s) Administration & dosage; Adverse effects; Deficiency; Pharmacology; Therapeutic use and Toxicity in Trials"

LILACS

"zinc" in title

PsycINFO

TI zinc OR AB zinc OR KW zinc	**Limiters** - Published Date from: 19000101-20111130; Publication Type: All Journals, Dissertation Abstract; Age Groups: Childhood (birth-12 yrs), Neonatal (birth-1 mo), Infancy (2-23 mo), Preschool Age (2-5 yrs), School Age (6-12 yrs), Adolescence (13-17 yrs); Population Group: Human **Search modes** - Boolean/Phrase

Dissertation Abstracts International

ab(zinc) OR ti((zinc or zinc)) or su((zinc or zinc))

CINAHL

TI zinc OR AB zinc OR MW zinc	**Limiters** - Published Date from: 19000101-20111130; Exclude MEDLINE records; Human; Randomized Controlled Trials; Age Groups: Fetus, Conception to Birth, Infant, Newborn: birth-1 month, Infant: 1-23 months, Child, Preschool: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years **Expanders** - Apply related words; Also search within the full text of the articles **Search modes** - Boolean/Phrase

HISTORY

Protocol first published: Issue 3, 2009

Review first published: Issue 12, 2012

CONTRIBUTIONS OF AUTHORS

SG and HPS wrote the protocol. Both authors extracted data independently. Both authors analyzed data and drafted the final paper.

DECLARATIONS OF INTEREST

Siddhartha Gogia - received a consultancy fee from EHCRC/Cochrane Infectious Diseases Group, International Health Group, Liverpool School of Tropical Medicine, Liverpool, UK through The Institute of Child Care Research, Queen's University, Belfast, Northern Ireland to support loss of earnings while working on this Cochrane review.

Harshpal S Sachdev - is an editor in the Cochrane Developmental, Psychosocial and Learning Problems Group.

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Internal sources

- Sitaram Bhartia Institute of Science and Research, India.
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External sources

- Effective Health Care Research Consortium, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We anticipated that studies would use different developmental scales for evaluating the effect of zinc supplementation on mental and motor development in children. Hence, during the protocol stage, we had planned to combine the data derived from studies using BSID (usually reported as MDI and PDI) into a single composite measure for ease of combination with studies using developmental scales providing a single composite measure of development (for example, Griffiths Mental Developmental Scale). However, after applying the search strategy, eight studies had reported data using BSID and only one study reported data in Griffiths Mental Developmental Scale. It presented an excellent opportunity to report effects on both MDI and PDI separately (given the absolute number and marked preponderance of studies using BSID), so as to delineate the exact developmental domains affected by zinc supplementation further. Hence we decided to include the eight studies reporting data using BSID in the meta-analysis and to use MDI and PDI, so as to provide the exact benefit of zinc supplementation in terms of BSID units. The study using the Griffiths Mental Developmental Scale (Gardner 2005) has been reported in detail in the text and the Characteristics of included studies table.