Systematic Review

Zinc Supplementation for Promoting Growth in Children Under 5 Years of age in Low- and Middle-income Countries: A Systematic Review

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ABSTRACT

Objective: To study the effect of zinc supplementation on anthropometry and prevalence of malnutrition in children under 5 years of age.

Design: Systematic review of randomized controlled trials and cluster randomized trials.

Setting: Low- and middle-income countries (LMICs).

Participants: 63 trials with zinc supplementation, incorporating data on 27372 children. Trials conducted exclusively in specifically diseased participants and in children with severe acute malnutrition were excluded.

Intervention: Zinc supplementation, provided either as medicinal supplementation or through food fortification.

Outcome Measures: (*i*) Anthropometry: weight, height, weight-for-height, mid-arm circumference, head circumference; (*ii*) Prevalence of malnutrition.

Results: There was no evidence of effect on height-for-age Z score at the end of supplementation period (25 trials; 9165 participants; MD= 0.00 Z; 95% CI -0.07, 0.07; P=0.98; moderate quality evidence) with significant heterogeneity (I^2 = 57%; P<0.001) related to dose and duration of zinc between trials. There was little or no effect on change in height-for-age Z score (13 trials; 8852 participants; MD= 0.11 Z; 95% CI -0.00, 0.21; P=0.05), but the heterogeneity was considerable (I^2=94%; P<0.001). There was no evidence of effect on length (6303 participants; MD= 1.18 cm; 95% CI -0.63, 2.99 cm, P=0.20; moderate quality evidence; considerable heterogeneity, I^2=99%) but a little positive effect on change in length (19 trials; 10783 participants; MD= 0.43 cm; 95% CI 0.16, 0.70, P=0.002; moderate quality evidence; considerable heterogeneity, I^2=93%). There was no evidence of effect on weight-for-age Z score or change in weight-for-age Z score but a little positive effect on weight (19 trials; 8851 study participants; MD= 0.23 kg; 95% CI 0.03, 0.42; P=0.02; considerable heterogeneity, I^2=91%) and change in weight (kg) (23 trials; 10143 study participants; MD= 0.11 kg; 95% CI 0.05, 0.17, P<0.001, substantial heterogeneity, I^2=80%). There was no evidence of effect on weight-for-height Z score, and mid upper arm circumference at the end of supplementation period, but there was a little positive effect on change in MUAC from baseline (8 trials; 1724 participants; MD = 0.09 cm; 95% CI 0.01, 0.16; P=0.03; no heterogeneity, I^2=0%). Head circumference in zinc supplemented group was marginally higher compared to control (2966 study participants; MD= 0.39 cm; 95% CI 0.03, 0.75; P=0.03; substantial heterogeneity, I^2=67%). There was no evidence of benefit in stunting (10 trials; 11838 study participants; RR= 1.0; 95% CI 0.95, 1.06; P=0.89; Moderate Quality Evidence; no significant heterogeneity, I^2=11%), wasting (7 trials; 8988 study participants; RR= 0.94; 95% CI 0.82, 1.06; P=0.31; Moderate Quality Evidence; no significant heterogeneity, I^2=13%) or underweight (7 trials; 8677 study participants; RR= 1.08; 95% CI 0.96, 1.21; P=0.19; Moderate Quality Evidence; substantial heterogeneity, I^2=73%).

Conclusion: Available evidence suggests that zinc supplementation probably leads to little or no improvement in anthropometric indices and malnutrition (stunting, underweight and wasting) in children under five years of age in LMICs. Advocating zinc supplementation as a public health measure to improve growth, therefore appears unjustified in these settings with scarce resources.

Keywords: *Health interventions, Micronutrient supplementation, Protein energy malnutrition, Stunting, Wasting.*

Zinc-responsive deficits in body composition are widespread in low- and middle-income countries (LMICs), particularly in South East Asia and sub-Saharan Africa, mainly because of inadequate dietary zinc intakes [1], high consumption of cereal-based foods having inhibitors of zinc absorption, and fecal losses of zinc due to recurrent episodes of diarrhea. Zinc plays a critical role in the cellular growth and differentiation due to its direct impact on nucleic acid and protein synthesis [2] and hormonal mediators of growth [3], and its effects on appetite [4] and risk of infection [5]. Zinc deficiency is believed to be an important cause of childhood stunting, up to the extent that it is often considered as a marker of prevalence of zinc deficiency in the communities.

Multiple studies have been carried out to assess the effect of zinc supplementation on children's growth. The results of these studies are inconsistent, and the factors responsible for these varied outcomes are unknown. In the published systematic reviews on the topic [6,7], there is considerable variability in terms of participants, nature of interventions, choice of control groups, study setting, and other key variables. It is thus difficult to provide unambiguous evidence-based advice to policy makers in LMICs about the safety and benefits of investing in zinc supplementation programs to improve linear growth in under-five children. An updated systematic review, primarily focused on LMICs, may be helpful in crystalizing relevant policy. We conducted this systematic review to study the effect of zinc supplementation on growth (measured by anthropometry) and prevalence of malnutrition.

METHODS

We included randomized controlled trials with variations in design, including random allocation of individuals or clusters, multi-arm trials, factorial trials and cross-over trials for the first period of measurement only. Quasi-randomized controlled trials (individual or cluster allocation done on the basis of a pseudo-random sequence, for example, odd/even house number or date of birth, alternation) were also eligible for inclusion. We included trials conducted in children below 5 years of age from LMICs. Trials conducted exclusively in disease conditions and in children with severe acute malnutrition (SAM) were excluded

Type of Intervention: We included studies that provided zinc supplementation, either as medicinal supplementation or through food fortification. Trials with simultaneous fortification or supplementation of additional micronutrients, or simultaneous co-interventions like health education and/or drugs (for example, deworming or antimalarials) were included if the only difference between the intervention and comparison arms was zinc supplementation.

Outcomes: *Primary*: anthropometry: weight, height, weight-for-height (WFH), mid upper arm circumference (MUAC), head circumference; *Secondary*: prevalence of malnutrition.

Search Methods

We searched (June 2017) the following electronic databases: Medline, Web of Science, BIOSIS Previews, Greysource, Cochrane Controlled Trials Register, EMBASE and IBIDS. Reference lists of all included papers and relevant reviews were scanned to identify citations that have been missed in the primary search. We contacted authors of other relevant reviews in the field regarding additional studies of which they may be aware. We searched Science Citation Index and Social Sciences Citation Index for papers, which cite studies included in the review. Websites of organizations like Micronutrient Initiative and iZiNCG were also searched. The search results from the various databases and other sources were merged using reference management software (Endnote) to remove duplicate records. The title and abstract of the studies identified in the computerized search were scanned in duplicate to exclude references that were obviously irrelevant. In order to determine eligibility for inclusion of the remaining articles, their full texts were reviewed, and multiple reports of the same study were linked together. Two authors independently screened and assessed the eligibility of the studies, extracted relevant data and assessed the risk of bias for all included studies. Any dispute regarding these criteria was resolved among the investigators by mutual consultation. ***Web Appendix* 1** outlines the search strategy adopted for the electronic databases.

Data Management

We evaluated the risk of bias for each trial using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [8]. Plots of 'Risk of bias' assessments were created in Review Manager (RevMan) [9].

Risk ratio (RR) estimates with 95% confidence intervals (CI) were used for binary outcomes; for continuous outcomes mean differences (MD) were used. In order to maximize the data input for the pooled outcome measures, we utilized post-intervention values (means and standard deviations (SDs)) in preference to the changes from baseline [8]. In factorial trials and in multi-arm designs yielding two or more intervention groups (different zinc doses or salts used) and a single control group, the data in the intervention groups, including the variation in the intervention characteristic, was pooled and compared against the single control group to prevent unit-of-analysis error. For cluster-randomized trials, we used the stated cluster-adjusted RR or means and 95% CI, irrespective of the method employed for adjustment. In case of missing data, we contacted trial authors for information wherever possible; and where this could not be done, or the authors did not respond, we imputed the missing values, where feasible. In case any assumptions were made for such imputations, they were recorded, and are detailed in ***Web Appendix* 2**.

We assessed contextual heterogeneity on the basis of information collected on the context in which the intervention was implemented. We assessed for variability in the participants, interventions and outcomes studied to identify clinical heterogeneity, and for variability in study design to describe methodological diversity. Statistical heterogeneity was identified and measured as recommended [8]. A *P* value of 0.05 from the Chi^2 test was used to determine statistical significance with regard to heterogeneity.

We performed statistical analysis using the Revman software. Pooled estimates of the evaluated outcome measures were calculated by the generic inverse variance method. Pooled WMD and SMD were calculated as per standard recommendations. We expected variation in studies with respect to populations, interventions, comparators, outcomes and settings, and thus used the random-effects model. If it was not possible to synthesize the data from the included studies, we provided a narrative synthesis of the results. The data was finally synthesized as a 'Summary of findings' table. For each outcome, quality assessment of the results was also carried out using the GRADE approach [10], which specifies four levels of quality (high, moderate, low and very low) where the highest quality rating is for a body of evidence based on randomised trials. We planned to explore the following differences in effect for 'length', by subgroup analyses: (*i*) supplementation method (medicinal *versus* fortification); (*ii*) supplement compound; (*iii*) study population from South Asia; (*iv*) dose of zinc (mg); (*v*) duration of supplementation; (*vi*) compliance estimation (directly observed or replacement versus others); (*vii*) baseline zinc levels; and (*viii*) baseline prevalence of stunting. We chose length-for-age Z-score as the variable for subgroup analysis, as it is an age-independent parameter and more important from public health perspective. We could not do the subgroup analysis for the first parameter (supplementation method) as all studies had used medicinal supplementation.

RESULTS

The search output from various databases is detailed in ***Web Appendix* 1**, and the results are summarized in ***Fig.* 1**. We screened 3886 records, of which 237 were potentially eligible. Of these, 147 references were excluded and 91 publications (63 studies) were included in the final analyses [3,11-100]. These studies (5 cluster RCTs and 58 RCTs) incorporated data on 27372 children were included in the final analysis (***Web Table* I**). Twenty-eight (44%) of the included trials were conducted in Asia (17 from South Asia), 16 trials were conducted in Africa and 19 in Latin America. The details of study location, intervention and evaluated outcomes are summarized in ***Web Table* I**.

***Web Fig.* 1** and ***Web Fig.* 2** summarize the Risk of Bias for the included studies. The risk of bias for the 55 trials was low for random sequence generation. It was considered to be high for two trials and unclear for the remaining six studies. The risk of bias for allocation concealment was judged to be low in 39, unclear in 21 and high in 3 studies. Blinding of participants and research personnel was at unclear risk in 5, at high risk in 2 studies and low risk in 56 trials. The risk of blinding of outcome assessment was considered low for 34 trials, unclear for 27 and high for 2 trials. The risk of bias for attrition was judged to be high for 32 trials, unclear for 2 trials because of no information available, and low for remaining 29 trials. In the five cluster randomized trials, two studies were considered to be at unclear risk for incorrect analysis and one trial for baseline imbalance. Seven trials were judged to be having other potential causes of bias, including baseline imbalance of groups (3), formula milk use (2) and protocol deviations related to key intervention (2).

Effects of Interventions

Height/Length (***Web Appendix* 3A**): Twenty-nine trials reported data on height-for-age Z-score (HAZ) in the study participants. Quantitative synthesis from 25 trials (***Fig.* 2**) revealed no evidence of effect of zinc supplementation on HAZ (9165 participants; MD= 0.00; 95% CI -0.07, 0.07; *P*=0.98; Moderate Quality Evidence) in comparison to controls, with significant heterogeneity between trials (I^2=57%; *P*<0.001). In subset analysis to explore heterogeneity, the dose of zinc and duration of zinc supplementation were important predictors of heterogeneity. Supplement compound, location in South Asia, compliance estimation, baseline serum zinc levels, baseline prevalence of stunting and baseline HAZ did not predict heterogeneity. Thirteen trials studied the effect of zinc supplementation on change in HAZ. On quantitative synthesis in 8852 participants, the MD for change in HAZ was 0.11 (95% CI -0.00, 0.21; *P*=0.05; Moderate Quality Evidence; ***Fig.* 3**) with substantial heterogeneity between trials (I^2=94%; *P*<0.001). Twenty-one trials reported the effect of zinc supplementation on length/height at the end of supplementation period. On quantitative synthesis from 19 trials, there was no evidence of effect on length/height (6303 participants; MD= 1.18 cm; 95% CI -0.63, 2.99 cm, *P*=0.20; Moderate Quality Evidence; considerable heterogeneity, I^2=99%; ***Fig.* 4**) with zinc supplementation as compared to controls. Twenty-six trials reported the effect of zinc supplementation (*vs*. controls) on change in length/height (cm) from baseline to the end of supplementation period. In 25 of these trials with 10783 participants, the pooled change in length/height with zinc supplementation as compared to controls was 0.43 cm (95% CI 0.16, 0.70, *P*=0.002; considerable heterogeneity, I^2=93%; Moderate Quality Evidence; ***Fig.* 5**). Funnel plots of all height-related outcomes showed no evidence of publication bias (***Web Fig.* 3a** to **3d**).

Weight (***Web Appendix* 3B**): Twenty-five trials reported data on weight-for-age Z-score (WAZ) in the study participants. In 23 trials on 9033 participants (***Fig.* 6**), the mean difference in WAZ was 0.05 (95% CI -0.03, 0.13; *P*=0.19; Moderate Quality Evidence; substantial heterogeneity, I^2=75%) between zinc supplemented and control group. Thirteen trials studied the effect of zinc supplementation on change in WAZ from baseline. Quantitative synthesis from these trials (***Fig.* 7**) showed no evidence of effect on change in WAZ with zinc supplementation in comparison to controls

(8851 study participants; MD= 0.03; 95% CI -0.01, 0.08; *P*=0.17; Moderate Quality Evidence; substantial heterogeneity, I^2=66%). Weight at the end of the supplementation period was reported in 20 studies. Quantitative synthesis from 19 of these trials (***Fig.* 8**) showed positive effect of zinc supplementation on weight as compared to control population (8851 study participants; MD= 0.23 kg; 95% CI 0.03, 0.42; *P*=0.02; Moderate Quality Evidence). Twenty-three trials reported on change in weight (kg) from baseline to the end of supplementation period. Quantitative synthesis (***Fig.* 9**) revealed a positive effect (10143 participants; MD=0.11 kg; 95% CI 0.05, 0.17, *P<0.001*; Moderate Quality Evidence) of zinc supplementation in comparison to controls. There was significant heterogeneity between trials comparing weight parameters between the two groups, and funnel pots showed no evidence of publication bias (figures not shown).

Weight-for-height (***Web Appendix* 3C**): In 22 trials reporting data on weight-for-height Z-score (WHZ), there was no evidence of effect of zinc supplementation on WHZ in comparison to controls (19 trials; 8392 study participants; MD=0.03; 95% CI -0.02, 0.08; *P*=0.21; Moderate Quality Evidence; considerable heterogeneity, I^2=91% ***Fig.* 10**). In 12 trials evaluating the change in weight from height Z-scores, there was no evidence of effect on change in WHZ with zinc supplementation as against controls (8706 study participants; MD= 0.01; 95% CI -0.03, 0.04; *P*=0.74; Moderate Quality Evidence; substantial heterogeneity, I^2=80%; ***Fig.* 11**). There was no evidence of publication bias on examining the funnel plots (figures not shown).

MUAC (***Web Appendix* 3C**): In 7 trials evaluating MUAC, there was no effect of zinc supplementation (*vs*. controls) on MUAC (4236 participants; MD= 0.0 cm; 95% CI -0.08, 0.09; *P*=0.93; Moderate Quality Evidence) with no significant heterogeneity between trials (I^2 = 18%; *P*=0.29) (***Fig.* 12**). There was moderate quality evidence of little increase in the change in MUAC from baseline (8 trials; 1724 participants; MD = 0.09 cm; 95% CI 0.01, 0.16; *P*=0.03; no heterogeneity, I^2=0%) by zinc supplementation in comparison to controls (***Fig.* 13**).

Head circumference (***Web Appendix* 3D**): In quantitative synthesis from six trials (***Fig.* 14**) showed higher head circumference in zinc supplemented group as against control group (2966 participants; MD= 0.39 cm; 95% CI 0.03, 0.75; *P*=0.03; Moderate Quality Evidence; substantial heterogeneity, I^2=67%). However, change in head circumference was not different in the zinc supplemented and placebo groups (4 trials; 497 participants; MD = 0.26 cm; 95% CI -0.18, 0.71: *P*=0.24; Moderate Quality Evidence; substantial heterogeneity, I^2=79%) **(*Fig.* 15**).

Nutritional Status (***Web Appendix* 3D**): In trials reporting on stunting, underweight or wasting, funnel plots did not show any evidence of publication bias (figures not shown**)**. Quantitative synthesis from nine trials (***Fig.* 16**) showed no effect on stunting (11838 participants; RR= 1.0; 95% CI 0.95, 1.06; *P*=0.89; Moderate Quality Evidence; no significant heterogeneity, I^2=11%) with zinc supplementation in comparison to controls. In 7 trials reporting on the prevalence of underweight children, quantitative synthesis (***Fig.* 17**) showed no effect of zinc supplementation (*vs*. controls) on underweight (8988 participants; RR= 0.94; 95% CI 0.82, 1.06; *P*=0.31; Moderate Quality Evidence; substantial heterogeneity, I^2=73%). Quantitative synthesis (***Fig.* 18**) from seven trials showed no effect of zinc supplementation on wasting (8677 participants; RR= 1.08; 95% CI 0.96, 1.21; *P*=0.19; Moderate Quality Evidence) with no significant heterogeneity (I^2=13%, *P*=0.33).

DISCUSSION

In this systematic review of 63 trials incorporating data on 27372 children, there was no evidence of any difference in the final length/height for age or Z scores or change in length/height-for-age Z scores at the end of the supplementation period with zinc or placebo/no intervention, but studies assessing the change in length/height showed slight benefit with zinc supplementation. In addition, there was marginal increase in weight of children receiving zinc supplementation in comparison to placebo, but it did not affect weight-for-age or weight-for-height Z scores. There was a marginal positive effect on the change in MUAC from baseline. Zinc supplemented children also had a slightly higher head circumference at the end of supplementation period, but there was no evidence of effect on change in head circumference. Moreover, there was no evidence of a beneficial effect on prevalence of wasting, stunting or underweight at the end of supplementation period.

All included studies involved children under five years from LMICs. This is a population that is likely to have poor zinc nutriture and, therefore, benefit more from zinc supplementation. A large number of trials were available from varied geographical settings (28 from Asia, 16 from Africa, and 19 from Latin America), conducted in different age groups and in different population settings (ranging from tertiary level medical institutions to community studies in urban slums and rural communities). Control groups in most trials were comparable with intervention groups at baseline. Thus any observed effects, or lack thereof, in the intervention groups are more likely to be attributable to zinc supplementation. We, therefore, believe that the evidence from this review is largely applicable to real-life situations among under-five children in LMICs.

Most studies in this systematic review had a low risk of bias for key parameters, including sequence generation, allocation concealment and blinding. Also given the large number of studies available for most outcomes, the certainty of evidence is reasonable (moderate quality) for most of the important outcomes, and this review is likely to provide a good indication of the likely effect. The review was conducted by following the guidelines laid down in the Cochrane Handbook for Systematic Review [8], and this is likely to eliminate most sources of bias and identify the remaining. In some studies, anthropometric measurements were not available as the results were either depicted only in graphs or summary statistics, which is a potential source of bias. However, this is unlikely to affect the overall direction of results as narrative synthesis from these few studies was broadly in agreement with quantitative synthesis from this systematic review.

The earliest systematic review on this topic by Brown, *et al*. [6] included 33 studies, and reported a meaningful positive effects of zinc supplementation in height-for-age Z-score and weight-for-age Z-score without significant effect on weight-for-height indices. However, this review also included older children, besides being not restricted to LMICs. Ramakrishnan, *et al.* [7] reviewed 43 trials, and reported marginal benefits in terms of change in HAZ, WAZ and WHZ. Imdad, *et al*. [101] reported a significant positive effect of zinc supplementation on height gain in the developing countries, but studies providing other micronutrients in addition to zinc were also included. Mayo-Wilson, *et al*. [102], in a review of 50 studies (including children from all countries), showed no evidence of difference in height or stunting with little increase in weight and weight-to-height ratio. A very recent systematic review [103] evaluated effect of zinc supplementation provided during antenatal period or during childhood, and reported slightly increased height, weight and weight-for-age Z-score, but no effect on height-for-age Z-score, weight-for-height Z score, stunting, underweight or wasting, with supplementation provided after birth. In comparison to this review, our review focussed on LMICs where the problem of zinc deficiency is considered a major public health problem. In comparison to the review by Liu, *et al.* [103], the present review included more trials (63 *vs*. 54), probably because of a wide variety of database search and inclusion of trials with shorter (<3 mo) duration of supplementation. However, these results are broadly in conformity with our findings; marginal differences probably arise from variations in populations and analytical methods.

Evidence from this review suggests that zinc supplementation probably leads to little or no improvement in anthropometric indices and malnutrition (stunting, underweight and wasting) in children under five years of age from LMICs. Advocating zinc supplementation as a public health measure to improve growth, therefore appears unjustified in these settings with scarce resources. Using high stunting prevalence as an indicator of population-level zinc deficiency is also questionable. However, as most studies in this review examined the effects of medicinal supplementation with zinc, effect of fortification of foods with zinc on growth needs to be evaluated in pragmatic modes. Considering other potential benefits of zinc supplementation, comprehensive evaluation of cost effectiveness, including relative effects of medicinal and fortification routes, is also desirable.

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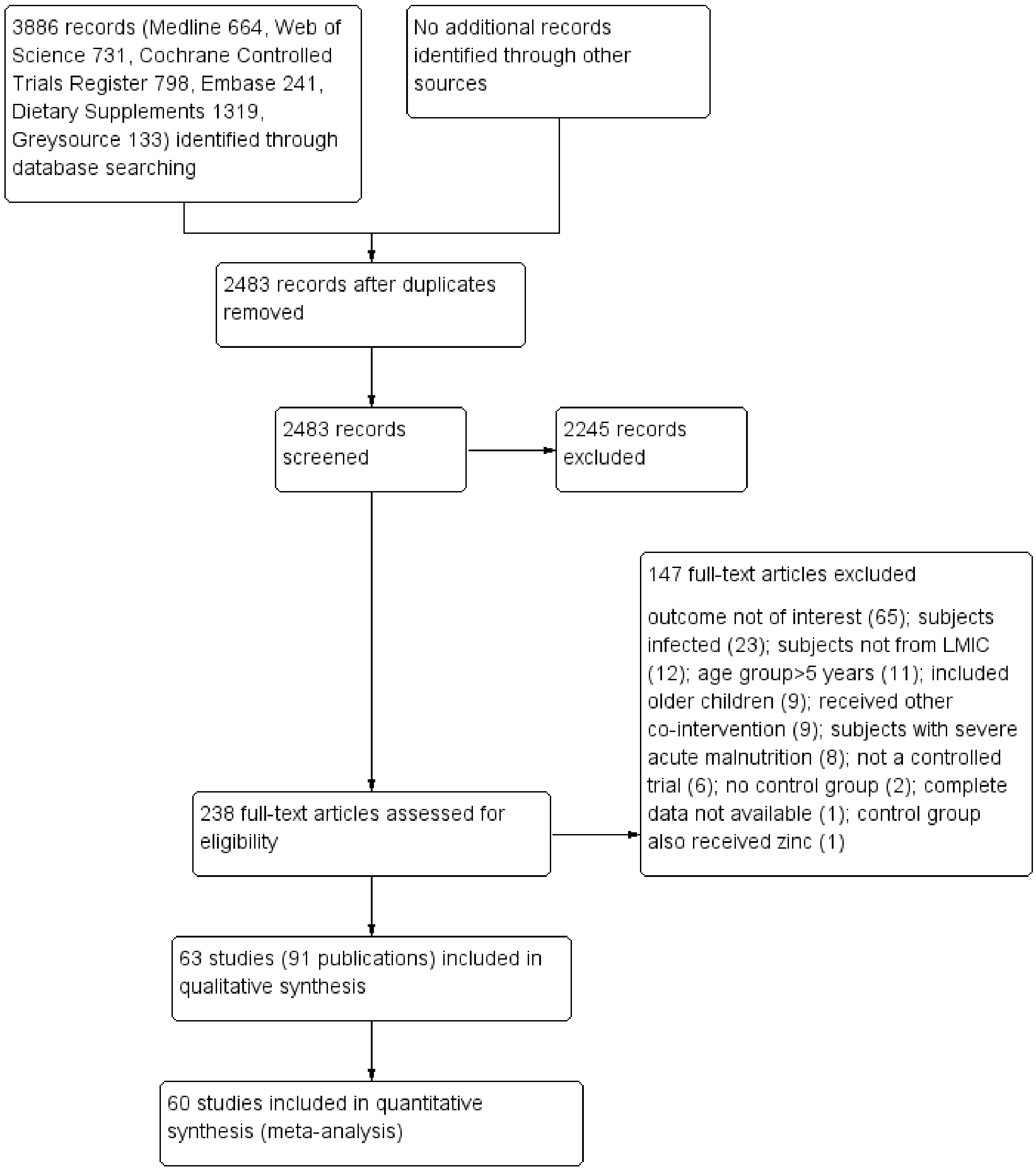

***Fig*. 1.** The PRISMA flow chart.

	Zinc			Control				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Adriani 2014	0.3	0.3	12	0.2	0.4	12	3.7%	0.10 [-0.18, 0.38]
Alarcon 2004	-0.69	1.12	109	-0.89	1.15	104	3.4%	0.20 [-0.11, 0.51]
Black 2004	-1.8	1.1	79	-2	1.1	71	2.8%	0.20 [-0.15, 0.55]
Castillo Duran 2001	-0.44	0.94	57	-0.07	0.75	55	3.2%	-0.37 [-0.68, -0.06]
Castillo-Duran 1995	-0.66	0.79	35	-1.47	1.28	33	1.5%	0.81 [0.30, 1.32]
Colombo 2014	-0.5	1	108	-0.6	0.9	101	4.2%	0.10 [-0.16, 0.36]
de Romana 2005	-2.5	0.64	22	-1.69	1.09	12	0.9%	-0.81 [-1.48, -0.14]
Dijkhuizen 2008	-1.334	0.851	1205	-1.315	0.864	1246	9.5%	-0.02 [-0.09, 0.05]
Dirren 1994	0.27	0.35	48	0.08	0.37	48	7.1%	0.19 [0.05, 0.33]
Fahmida 2007	-1.39	0.96	189	-1.47	0.94	192	5.7%	0.08 [-0.11, 0.27]
Gardner 2005	-1.26	0.71	55	-1.08	0.8	59	3.8%	-0.18 [-0.46, 0.10]
Hershkowitz 1999	-1.71	1.08	14	-1.3	1.38	11	0.5%	-0.41 [-1.40, 0.58]
Hess 2015	-1.44	1.06	1833	-1.44	1.05	602	8.6%	0.00 [-0.10, 0.10]
Lind 2004	-0.83	0.91	323	-0.74	0.89	327	7.3%	-0.09 [-0.23, 0.05]
Ninh 1996	-2.66	0.76	73	-2.95	0.9	73	4.0%	0.29 [0.02, 0.56]
Olney 2013	-0.38	0.26	100	-0.34	0.25	112	9.4%	-0.04 [-0.11, 0.03]
Osendarp 2002	-1.7	1	103	-1.7	1	109	4.0%	0.00 [-0.27, 0.27]
Owus-Ageyi 2013	0.86	1.33	100	1.19	2.48	100	1.3%	-0.33 [-0.88, 0.22]
Rahman 2002	-2.58	1.15	336	-2.27	1.18	317	6.1%	-0.31 [-0.49, -0.13]
Rivera 1998	-2.94	0.84	45	-3	1.16	44	2.1%	0.06 [-0.36, 0.48]
Sampaio 2013	-0.57	1.49	75	-0.38	1.78	68	1.4%	-0.19 [-0.73, 0.35]
Sempertegui 1996	-1.8	0.7	23	-1.7	0.8	25	2.1%	-0.10 [-0.52, 0.32]
Shankar 2000	-1.88	1.19	103	-1.96	1.07	109	3.4%	0.08 [-0.23, 0.39]
Silva 2006	-1.7	2.6	28	-1.6	1.6	30	0.4%	-0.10 [-1.22, 1.02]
Zlotkin 2003	-1.81	1.1	121	-1.86	1.1	109	3.7%	0.05 [-0.23, 0.33]
Total (95% CI)			**5196**			**3969**	**100.0%**	**-0.00 [-0.07, 0.07]**

Heterogeneity: Tau² = 0.01; Chi² = 55.40, df = 24 (P = 0.0003); I² = 57%

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

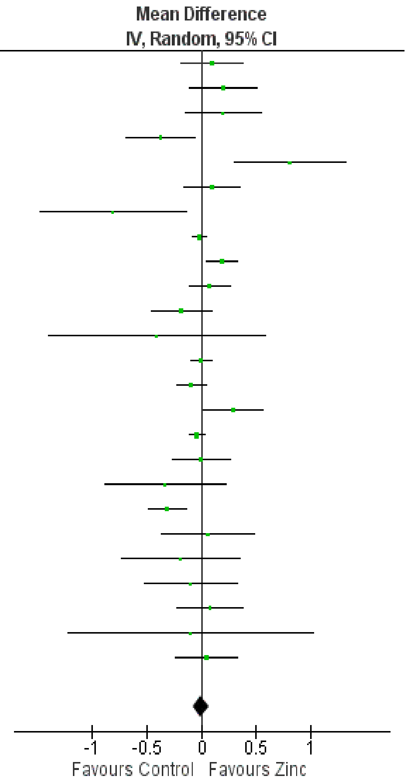

***Fig*. 2**. Forest plot of effect of zinc supplementation on height-for-age Z scores.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Alarcon 2004	0.32	0.7	109	0.17	0.63	104	7.0%	0.15 [-0.03, 0.33]
Becquey 2016	-0.4	0.89	391	-0.32	1.24	962	7.8%	-0.08 [-0.20, 0.04]
Brown 2007	-0.17	0.36	167	-0.16	0.37	92	8.1%	-0.01 [-0.10, 0.08]
Garenne 2007	0.06	0.8	332	-0.02	0.8	329	7.8%	0.08 [-0.04, 0.20]
Locks 2016	-0.86	1.22	1198	-0.9	1.22	1202	8.1%	0.04 [-0.06, 0.14]
Penny 2004	0.16	0.44	71	0.1	0.43	75	7.5%	0.06 [-0.08, 0.20]
Rahman 2002	0.0593	0.5	336	0.055	0.48	317	8.3%	0.00 [-0.07, 0.08]
Rivera 1998	-0.74	0.68	45	-0.89	0.74	44	5.2%	0.15 [-0.15, 0.45]
Rosado 1997	0.11	0.39	97	0.07	0.42	97	7.9%	0.04 [-0.07, 0.15]
Ruz 1997	-0.08	0.23	27	-0.16	0.23	26	7.8%	0.08 [-0.04, 0.20]
Taneja 2010	-0.14	0.44	1093	-0.12	0.43	1133	8.6%	-0.02 [-0.06, 0.02]
Umeta 2000	-0.02	0.42	92	-0.98	0.52	92	7.6%	0.96 [0.82, 1.10]
Wuhler 2008	0.1	0.31	313	0.11	0.32	108	8.4%	-0.01 [-0.08, 0.06]
Total (95% CI)			**4271**			**4581**	**100.0%**	**0.11 [-0.00, 0.21]**

Heterogeneity: Tau² = 0.03; Chi² = 195.08, df = 12 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.94 (P = 0.05)

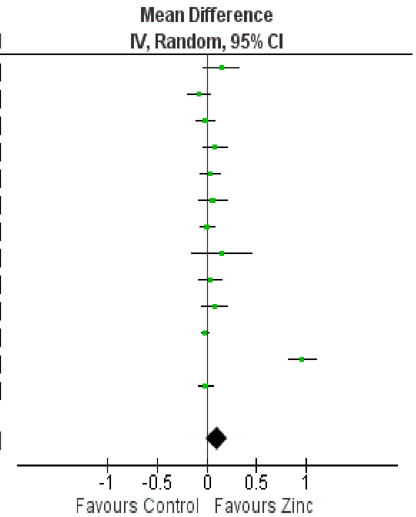

***Fig.* 3**. Forest plot of effect of zinc supplementation on change in height-for-age Z scores

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Abdollahi 2014	81.5	6.2	291	81	6.1	302	5.3%	0.50 [-0.49, 1.49]
Alarcon 2004	81.7	7.34	109	81.5	7.17	104	5.1%	0.20 [-1.75, 2.15]
Bates 1993	85.8	4.43	51	88.2	4.21	46	5.2%	-2.40 [-4.12, -0.68]
Brooks 2005	75.2	3.5	329	74.3	4	309	5.4%	0.90 [0.32, 1.48]
Castillo-Duran 1995	64.9	1.8	35	63.4	3.5	33	5.3%	1.50 [0.17, 2.83]
de Romana 2005	93.06	5.14	22	93.5	3.7	12	4.7%	-0.44 [-3.44, 2.56]
Dirren 1994	9.42	1.22	48	8.58	1.47	48	5.4%	0.84 [0.30, 1.38]
El-Farghali 2015	63.14	3.93	96	61.93	3.49	83	5.3%	1.21 [0.12, 2.30]
Fischer Walker 2010	70.85	2.69	276	70.94	2.64	290	5.4%	-0.09 [-0.53, 0.35]
Gardner 2005	83.6	4.4	55	84.3	5.4	59	5.1%	-0.70 [-2.50, 1.10]
Hess 2015	77.7	3	602	77.7	2.998	1833	5.4%	0.00 [-0.28, 0.28]
Islam 2010	50.3	2.8	50	47.4	3.2	50	5.3%	2.90 [1.72, 4.08]
Mathur 2015	57	2.5	50	56.2	2.7	50	5.3%	0.80 [-0.22, 1.82]
Ninh 1996	76.2	5.1	73	75.1	5.5	73	5.2%	1.10 [-0.62, 2.82]
Osendarp 2002	62.7	2.6	138	62.5	2.7	133	5.4%	0.20 [-0.43, 0.83]
Owus-Ageyi 2013	89.6	1.3	100	79.9	1.3	100	5.4%	9.70 [9.34, 10.06]
Radhakrishna 2013	77.4	2.82	154	77.5	3.53	147	5.4%	-0.10 [-0.82, 0.62]
Ram Kumar 2012	55.9	2.4	36	50.7	3.9	27	5.2%	5.20 [3.53, 6.87]
Rivera 1998	70	3	45	69.2	3.7	44	5.2%	0.80 [-0.60, 2.20]
Total (95% CI)			**2560**			**3743**	**100.0%**	**1.18 [-0.63, 2.99]**

Heterogeneity: Tau² = 15.75; Chi² = 2213.87, df = 18 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.28 (P = 0.20)

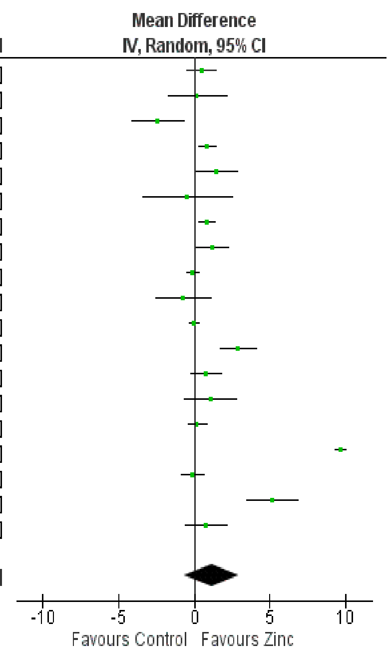

***Fig*. 4**. Forest plot of effect of zinc supplementation on height/length at the end of supplementation period.

Study or Subgroup	Experimental Mean [cm]	Experimental SD [cm]	Experimental Total	Control Mean [cm]	Control SD [cm]	Control Total	Weight	Mean Difference IV, Random, 95% CI [cm]
Abdollahi 2014	4	1.6	291	3.5	2	302	4.7%	0.50 [0.21, 0.79]
Alarcon 2004	5.03	1.8	109	4.53	1.58	104	4.3%	0.50 [0.05, 0.95]
Aminisani 2010	16.85	3.2	40	15.07	4.1	36	1.7%	1.78 [0.11, 3.45]
Bates 1993	10	2.07	51	10.5	1.97	46	3.4%	-0.50 [-1.30, 0.30]
Becquey 2016	9.6	2.97	391	9.8	4.03	962	4.5%	-0.20 [-0.59, 0.19]
Black 2004	18.7	3.2	79	18.6	2.6	71	3.1%	0.10 [-0.83, 1.03]
Brown 2007	6.95	1.05	167	7	1.1	92	4.7%	-0.05 [-0.33, 0.23]
Dijkhuizen 2008	7.55	1.65	1205	7.5	1.7	1246	4.9%	0.05 [-0.08, 0.18]
Garenne 2007	4.9	2.1	332	5	2.2	329	4.6%	-0.10 [-0.43, 0.23]
Hong 1992	16.3	1.07	32	14.99	1.19	33	4.1%	1.31 [0.76, 1.86]
Lira 1998	16.67	2.44	112	17.06	2.35	54	3.5%	-0.39 [-1.16, 0.38]
Mathur 2015	14.7	2.1	50	13.8	1.7	50	3.6%	0.90 [0.15, 1.65]
Meeks Gardner 1998	2.5	1.3	31	2.6	1.5	30	3.7%	-0.10 [-0.81, 0.61]
Mozaraffi-Khosravi 2009	10.46	2.06	40	8.31	2.68	45	2.9%	2.15 [1.14, 3.16]
Osendarp 2002	11.5	1.9	138	11.4	2.1	133	4.3%	0.10 [-0.38, 0.58]
Penny 2004	5.3	1.4	71	5	1.4	75	4.3%	0.30 [-0.15, 0.75]
Rahman 2002	4.2	1.42	336	4.29	1.4	317	4.8%	-0.09 [-0.31, 0.13]
Rivera 1998	6.1	2	45	5.7	2	44	3.4%	0.40 [-0.43, 1.23]
Rosado 1997	9.1	1.4	97	9.05	1.42	97	4.5%	0.05 [-0.35, 0.45]
Ruz 1997	8.46	1.16	27	7.97	0.91	26	4.1%	0.49 [-0.07, 1.05]
Sur 2003	23.7	3.39	50	21.4	3.39	50	2.3%	2.30 [0.97, 3.63]
Taneja 2010	3.43	1.58	1093	3.55	1.74	1133	4.9%	-0.12 [-0.26, 0.02]
Umeta 2000	6.8	0.97	92	3.97	1.35	92	4.6%	2.83 [2.49, 3.17]
Wuhler 2008	4.9	1.14	313	4.9	1.1	108	4.8%	0.00 [-0.24, 0.24]
Yang 2002	7.66	1.1	60	7.12	1.37	56	4.3%	0.54 [0.09, 0.99]
Total (95% CI)			**5252**			**5531**	**100.0%**	**0.43 [0.16, 0.70]**

Heterogeneity: Tau² = 0.39; Chi² = 337.08, df = 24 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.09 (P = 0.002)

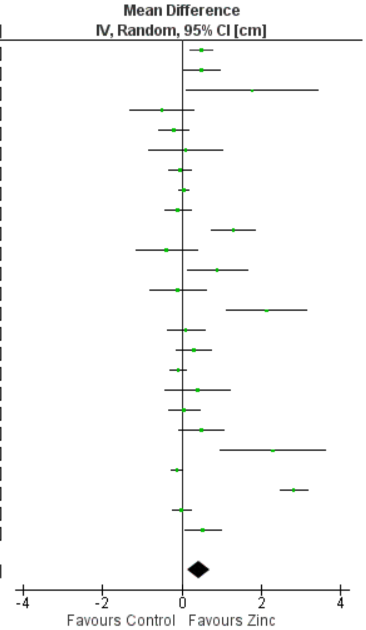

Fig. 5. Forest plot of effect of zinc supplementation on change in height/length.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Alarcon 2004	-0.25	1.09	109	-0.54	1	104	3.8%	0.29 [0.01, 0.57]
Castillo Duran 2001	-0.23	1.04	57	0.22	0.86	55	3.0%	-0.45 [-0.80, -0.10]
Castillo-Duran 1995	-0.24	0.64	35	-1.07	0.61	33	3.6%	0.83 [0.53, 1.13]
Colombo 2014	0.1	0.9	108	0.1	0.8	101	4.5%	0.00 [-0.23, 0.23]
de Romana 2005	-1.01	0.75	22	-0.62	0.8	12	1.6%	-0.39 [-0.94, 0.16]
Dijkhuizen 2008	-1.499	0.884	1205	-1.52	0.905	1246	6.8%	0.02 [-0.05, 0.09]
Dirren 1994	0.2	0.27	48	0.18	0.32	48	6.2%	0.02 [-0.10, 0.14]
Fahmida 2007	-1.71	0.89	189	-1.86	0.93	192	5.2%	0.15 [-0.03, 0.33]
Gardner 2005	-2.04	0.56	55	-2.03	0.58	59	4.8%	-0.01 [-0.22, 0.20]
Hershkowitz 1999	-1.82	0.68	14	-1.85	0.62	11	1.8%	0.03 [-0.48, 0.54]
Hess 2015	-1.23	0.99	1833	-1.22	0.94	602	6.6%	-0.01 [-0.10, 0.08]
Lind 2004	-1.57	1.05	323	-1.69	1.04	327	5.5%	0.12 [-0.04, 0.28]
Ninh 1996	-2.46	0.62	73	-2.76	0.53	73	5.1%	0.30 [0.11, 0.49]
Olney 2013	-0.25	0.48	100	-0.16	0.49	112	6.0%	-0.09 [-0.22, 0.04]
Osendarp 2002	-1.5	0.9	103	-1.5	1	109	4.1%	0.00 [-0.26, 0.26]
Owus-Ageyi 2013	0.34	0.37	100	0.54	0.41	100	6.3%	-0.20 [-0.31, -0.09]
Rahman 2002	-2.41	0.83	336	-2.34	0.88	317	6.0%	-0.07 [-0.20, 0.06]
Rivera 1998	-2.11	0.82	45	-2.07	0.9	44	2.9%	-0.04 [-0.40, 0.32]
Sampaio 2013	-0.1	1.54	75	0.08	1.88	68	1.5%	-0.18 [-0.75, 0.39]
Sempertegui 1996	-1.3	0.6	23	-1.3	0.5	25	3.4%	0.00 [-0.31, 0.31]
Shankar 2000	-0.69	0.82	103	-0.76	0.82	109	4.6%	0.07 [-0.15, 0.29]
Sur 2003	-1.45	0.95	50	-2.17	0.9	50	2.9%	0.72 [0.36, 1.08]
Zlotkin 2003	-1.89	0.94	121	-1.95	1.09	109	4.0%	0.06 [-0.20, 0.32]
Total (95% CI)			**5127**			**3906**	**100.0%**	**0.05 [-0.03, 0.13]**

Heterogeneity: Tau² = 0.02; Chi² = 89.06, df = 22 (P < 0.00001); I² = 75%
Test for overall effect: Z = 1.31 (P = 0.19)

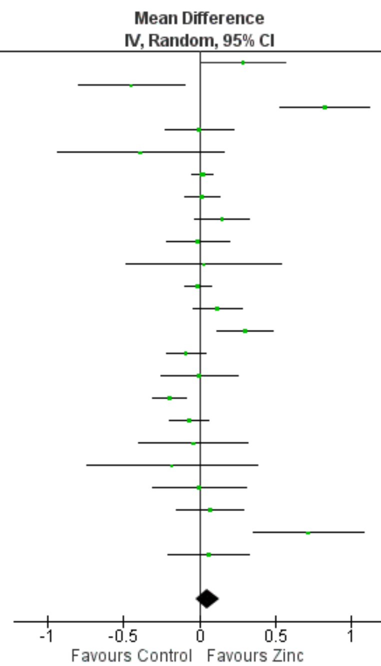

Fig. 6. Forest plot of effect of zinc supplementation on weight-for-age Z scores

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Alarcon 2004	-0.05	0.73	109	-0.21	0.74	104	4.1%	0.16 [-0.04, 0.36]
Becquey 2016	0.01	0.59	391	0.08	0.62	962	10.8%	-0.07 [-0.14, 0.00]
Brown 2007	-0.67	0.64	167	-0.69	0.51	92	6.2%	0.02 [-0.12, 0.16]
Garenne 2007	-0.002	0.6	332	-0.08	0.6	329	9.3%	0.08 [-0.01, 0.17]
Locks 2016	-0.48	0.99	1198	-0.51	0.98	1202	10.2%	0.03 [-0.05, 0.11]
Penny 2004	0.34	0.49	71	0.24	0.39	75	6.2%	0.10 [-0.04, 0.24]
Rahman 2002	-0.004	0.37	336	0.004	0.35	317	11.9%	-0.01 [-0.06, 0.05]
Rivera 1998	-0.87	0.55	45	-0.96	0.56	44	3.3%	0.09 [-0.14, 0.32]
Rosado 1997	0.21	0.39	97	0.27	0.38	97	8.2%	-0.06 [-0.17, 0.05]
Ruz 1997	-0.07	0.62	27	0.15	0.62	26	1.8%	-0.22 [-0.55, 0.11]
Taneja 2010	-0.04	0.51	1093	-0.06	0.59	1133	12.5%	0.02 [-0.03, 0.07]
Umeta 2000	0.02	0.59	91	-0.37	0.56	92	5.2%	0.39 [0.22, 0.56]
Wuhler 2008	0.05	0.4	313	0.04	0.33	108	10.4%	0.01 [-0.07, 0.09]
Total (95% CI)			**4270**			**4581**	**100.0%**	**0.03 [-0.01, 0.08]**

Heterogeneity: Tau² = 0.00; Chi² = 35.29, df = 12 (P = 0.0004); I² = 66%
Test for overall effect: Z = 1.39 (P = 0.17)

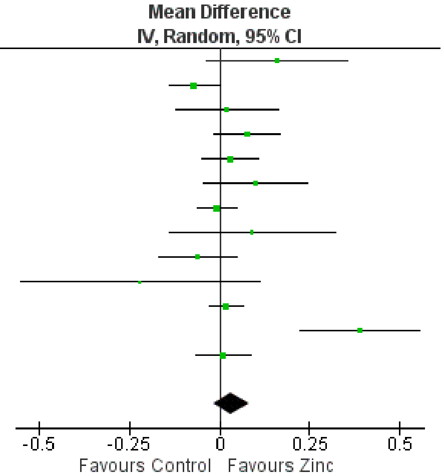

Fig. 7. Forest plot of effect of zinc supplementation on change in weight-for-age Z scores

Study or Subgroup	Zinc Mean [kg]	Zinc SD [kg]	Zinc Total	Control Mean [kg]	Control SD [kg]	Control Total	Weight	Mean Difference IV, Random, 95% CI [kg]
Abdollahi 2014	11.2	1.7	291	11	1.6	302	5.6%	0.20 [-0.07, 0.47]
Alarcon 2004	11.5	2	109	11.3	1.8	104	4.4%	0.20 [-0.31, 0.71]
Bates 1993	11.07	1.38	53	11.63	1.34	50	4.3%	-0.56 [-1.09, -0.03]
Brooks 2005	8.7	1.1	329	8.5	1.2	309	6.0%	0.20 [0.02, 0.38]
de Romana 2005	14.82	1.85	22	14.8	1.4	12	2.1%	0.02 [-1.09, 1.13]
Dirren 1994	2.3	0.46	48	2.28	0.5	48	5.9%	0.02 [-0.17, 0.21]
El-Farghali 2015	6.867	1.247	96	6.35	1.134	83	5.2%	0.52 [0.17, 0.87]
Fischer Walker 2010	8.08	1.02	276	8.09	1.05	290	6.0%	-0.01 [-0.18, 0.16]
Gardner 2005	10.03	1.02	55	10.02	1.19	59	4.9%	0.01 [-0.40, 0.42]
Hess 2015	9.3	1.08	1833	9.31	1	602	6.2%	-0.01 [-0.10, 0.08]
Islam 2010	2.779	0.638	50	2.474	0.442	50	5.8%	0.30 [0.09, 0.52]
Mathur 2015	4.295	0.789	50	4.172	0.902	50	5.3%	0.12 [-0.21, 0.46]
Ninh 1996	8.9	1.1	73	8.5	1.1	73	5.2%	0.40 [0.04, 0.76]
Osendarp 2002	6.33	0.94	138	6.23	1.01	133	5.8%	0.10 [-0.13, 0.33]
Owus-Ageyi 2013	10.3	1	100	10.4	1.1	100	5.5%	-0.10 [-0.39, 0.19]
Radhakrishna 2013	8.85	1.005	154	8.79	0.988	147	5.8%	0.06 [-0.17, 0.29]
Ram Kumar 2012	4.12	0.635	36	3.404	0.802	27	5.2%	0.72 [0.35, 1.08]
Rivera 1998	8.25	0.95	45	8.12	1.05	44	4.9%	0.13 [-0.29, 0.55]
Shrivastava 1993	3.742	0.488	26	2.035	0.383	26	5.8%	1.71 [1.47, 1.95]
Total (95% CI)			**3784**			**2509**	**100.0%**	**0.23 [0.03, 0.42]**

Heterogeneity: Tau² = 0.16; Chi² = 208.65, df = 18 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.26 (P = 0.02)

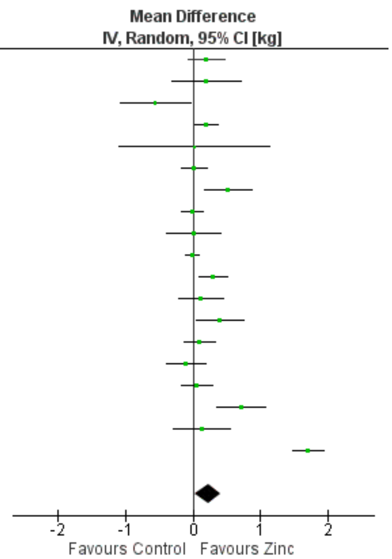

Fig. 8. Forest plot of effect of zinc supplementation on weight at the end of supplementation period.

Study or Subgroup	Experimental Mean [kg]	Experimental SD [kg]	Experimental Total	Control Mean [kg]	Control SD [kg]	Control Total	Weight	Mean Difference IV, Random, 95% CI [kg]
Alarcon 2004	1.06	0.76	109	0.88	0.72	104	4.2%	0.18 [-0.02, 0.38]
Aminisani 2010	4.295	0.741	40	3.896	0.865	36	2.1%	0.40 [0.03, 0.76]
Bates 1993	2.39	0.73	53	2.38	0.92	50	2.5%	0.01 [-0.31, 0.33]
Becquey 2016	2.1	0.83	391	2.1	0.93	962	6.3%	0.00 [-0.10, 0.10]
Black 2004	4.1	0.8	79	4.2	0.9	71	3.0%	-0.10 [-0.37, 0.17]
Brown 2007	1.32	0.54	167	1.33	0.46	92	5.8%	-0.01 [-0.13, 0.11]
Dijkhuizen 2008	1.34	0.53	1205	1.32	0.57	1246	7.2%	0.02 [-0.02, 0.06]
Garenne 2007	1	0.7	332	0.9	0.7	329	6.1%	0.10 [-0.01, 0.21]
Hong 1992	4.647	0.434	32	4.207	0.333	33	4.4%	0.44 [0.25, 0.63]
Lira 1998	4.28	0.96	112	4.036	1.064	54	2.4%	0.24 [-0.09, 0.58]
Mathur 2015	2.652	0.604	50	2.501	0.622	50	3.5%	0.15 [-0.09, 0.39]
Meeks Gardner 1998	0.5	0.8	31	0.3	0.6	30	2.2%	0.20 [-0.15, 0.55]
Mozaraffi-Khosravi 2009	2.64	0.98	40	2.05	0.84	45	1.9%	0.59 [0.20, 0.98]
Osendarp 2002	2.85	0.73	138	2.79	0.72	133	4.7%	0.06 [-0.11, 0.23]
Penny 2004	1.48	0.67	71	1.42	0.54	75	4.3%	0.06 [-0.14, 0.26]
Rahman 2002	0.77	0.49	336	0.81	0.45	317	6.8%	-0.04 [-0.11, 0.03]
Rivera 1998	1.03	0.54	45	0.97	0.5	44	3.9%	0.06 [-0.16, 0.28]
Rosado 1997	2.35	0.49	97	2.4	0.48	97	5.5%	-0.05 [-0.19, 0.09]
Sur 2003	6.084	1.18	50	5.28	1.18	50	1.5%	0.80 [0.34, 1.27]
Taneja 2010	0.67	0.47	1093	0.68	0.49	1133	7.3%	-0.01 [-0.05, 0.03]
Umeta 2000	1.45	0.47	92	0.99	0.36	92	5.8%	0.46 [0.34, 0.58]
Wuhler 2008	1.06	0.47	313	1	0.4	108	6.5%	0.06 [-0.03, 0.15]
Yang 2002	2.34	0.94	60	2.49	1.08	56	2.0%	-0.15 [-0.52, 0.22]
Total (95% CI)			**4936**			**5207**	**100.0%**	**0.11 [0.05, 0.17]**

Heterogeneity: Tau² = 0.01; Chi² = 108.37, df = 22 (P < 0.00001); I² = 80%
Test for overall effect: Z = 3.39 (P = 0.0007)

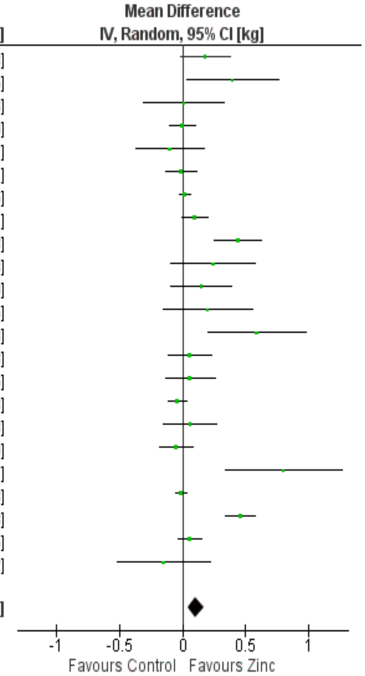

***Fig.* 9**. Forest plot of effect of zinc supplementation on change in weight.

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Alarcon 2004	0.29	1.13	109	0.05	1.09	104	2.6%	0.24 [-0.06, 0.54]
Black 2004	-1.1	0.9	79	-0.9	0.9	71	2.7%	-0.20 [-0.49, 0.09]
Castillo Duran 2001	0.18	0.88	57	0.26	0.95	55	2.0%	-0.08 [-0.42, 0.26]
de Romana 2005	0.65	0.85	22	0.56	0.66	12	0.9%	0.09 [-0.43, 0.61]
Dijkhuizen 2008	-0.655	0.891	1205	-0.695	0.8	1246	16.2%	0.04 [-0.03, 0.11]
Dirren 1994	0.08	0.39	48	0.24	0.35	48	7.7%	-0.16 [-0.31, -0.01]
Fahmida 2007	-0.88	0.97	189	-1	0.93	192	5.4%	0.12 [-0.07, 0.31]
Gardner 2005	-1.56	0.51	55	-1.7	0.53	59	5.4%	0.14 [-0.05, 0.33]
Hershkowitz 1999	-0.64	0.88	14	-1.02	1.09	11	0.4%	0.38 [-0.41, 1.17]
Hess 2015	-0.73	0.94	1833	-0.72	0.89	602	14.1%	-0.01 [-0.09, 0.07]
Lind 2004	-0.78	1.06	323	-1.04	1.19	327	6.2%	0.26 [0.09, 0.43]
Ninh 1996	-1.18	0.71	73	-1.27	0.6	73	4.5%	0.09 [-0.12, 0.30]
Osendarp 2002	-0.1	0.8	103	-0.1	0.9	109	4.1%	0.00 [-0.23, 0.23]
Owus-Ageyi 2013	-0.05	0.48	100	-0.13	0.45	100	9.2%	0.08 [-0.05, 0.21]
Rahman 2002	-1.32	0.74	336	-1.32	0.73	317	10.7%	0.00 [-0.11, 0.11]
Rivera 1998	-0.28	0.76	45	-0.09	0.8	44	2.2%	-0.19 [-0.51, 0.13]
Sampaio 2013	0.12	1.55	75	0.32	1.96	68	0.7%	-0.20 [-0.78, 0.38]
Silva 2006	0.7	1.5	28	0.6	1.6	30	0.4%	0.10 [-0.70, 0.90]
Zlotkin 2003	-0.88	0.71	121	-0.92	0.93	109	4.5%	0.04 [-0.18, 0.26]
Total (95% CI)			**4815**			**3577**	**100.0%**	**0.03 [-0.02, 0.08]**

Heterogeneity: Tau² = 0.00; Chi² = 25.36, df = 18 (P = 0.12); I² = 29%
Test for overall effect: Z = 1.25 (P = 0.21)

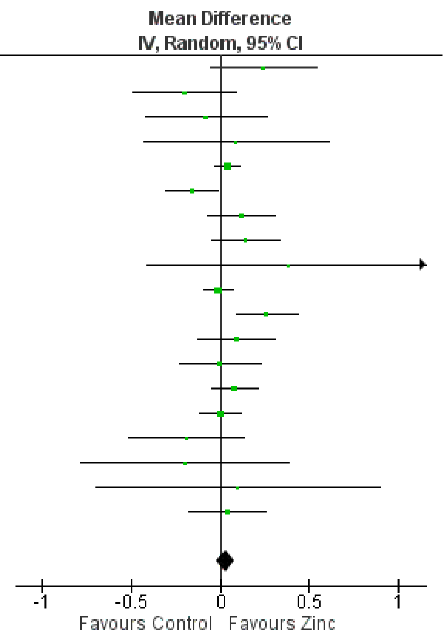

***Fig.* 10**. Forest plot of effect of zinc supplementation on weight-for-height Z scores at the end of supplementation period.

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Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Alarcon 2004	-0.27	0.83	109	-0.43	0.97	104	1.7%	0.16 [-0.08, 0.40]
Becquey 2016	0.27	0.75	391	0.3	0.84	962	12.1%	-0.03 [-0.12, 0.06]
Brown 2007	-0.54	0.76	167	-0.56	0.65	92	3.3%	0.02 [-0.16, 0.20]
Garenne 2007	-0.09	0.8	332	-0.1	0.7	329	7.7%	0.01 [-0.10, 0.12]
Locks 2016	-0.44	1.72	1198	-0.38	1.71	1202	5.4%	-0.06 [-0.20, 0.08]
Rahman 2002	-0.124	0.58	336	-0.11	0.55	317	13.5%	-0.01 [-0.10, 0.07]
Rivera 1998	-0.91	0.78	45	-0.84	0.88	44	0.8%	-0.07 [-0.42, 0.28]
Rosado 1997	0.22	0.49	97	0.33	0.41	97	6.3%	-0.11 [-0.24, 0.02]
Ruz 1997	-0.05	0.45	27	0.01	0.45	26	1.7%	-0.06 [-0.30, 0.18]
Taneja 2010	-0.02	0.64	1093	-0.07	0.67	1133	34.2%	0.05 [-0.00, 0.10]
Umeta 2000	-0.3	0.54	92	-0.27	0.5	92	4.5%	-0.03 [-0.18, 0.12]
Wuhler 2008	0.07	0.56	313	0.04	0.46	108	8.9%	0.03 [-0.08, 0.14]
Total (95% CI)			**4200**			**4506**	**100.0%**	**0.01 [-0.03, 0.04]**

Heterogeneity: Tau² = 0.00; Chi² = 9.85, df = 11 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)

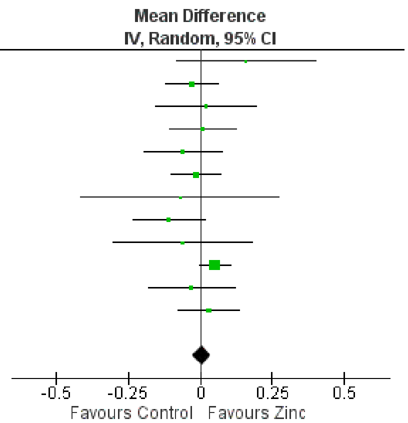


***Fig.* 11**. Forest plot of effect of zinc supplementation on change in weight-for-height Z scores.

Study or Subgroup	Zinc Mean [cm]	Zinc SD [cm]	Zinc Total	Control Mean [cm]	Control SD [cm]	Control Total	Weight	Mean Difference IV, Random, 95% CI [cm]
Bates 1993	14.3	1.09	53	14.5	0.91	49	4.7%	-0.20 [-0.59, 0.19]
El-Farghali 2015	13.71	1.84	96	13.07	1.71	86	2.7%	0.64 [0.12, 1.16]
Fischer Walker 2010	13.65	1	276	13.69	1.06	290	19.6%	-0.04 [-0.21, 0.13]
Hess 2015	13.8	1.029	1833	13.8	1	602	41.3%	0.00 [-0.09, 0.09]
Lind 2004	14.7	1.09	323	14.7	1.15	327	19.1%	0.00 [-0.17, 0.17]
Rivera 1998	14.2	1.1	45	14.1	1.1	44	3.4%	0.10 [-0.36, 0.56]
Shankar 2000	14.6	1	103	14.6	1	109	9.2%	0.00 [-0.27, 0.27]
Total (95% CI)			**2729**			**1507**	**100.0%**	**0.00 [-0.08, 0.09]**

Heterogeneity: Tau² = 0.00; Chi² = 7.33, df = 6 (P = 0.29); I² = 18%
Test for overall effect: Z = 0.08 (P = 0.93)

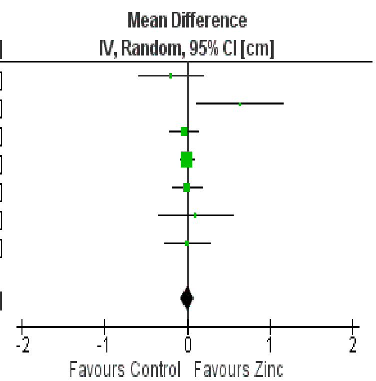


***Fig.* 12**. Forest plot of effect of zinc supplementation on mid upper arm circumference at the end of supplementation period.

Study or Subgroup	Zinc Mean	Zinc SD	Zinc Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Bates 1993	0.87	0.73	53	0.77	0.98	49	5.2%	0.10 [-0.24, 0.44]
Garenne 2007	-0.3	1	332	-0.4	1.1	329	23.3%	0.10 [-0.06, 0.26]
Mozaraffi-Khosravi 2009	1.5	0.53	40	1.33	0.49	45	12.6%	0.17 [-0.05, 0.39]
Osendarp 2002	2.5	1.1	138	2.6	1	133	9.6%	-0.10 [-0.35, 0.15]
Penny 2004	0.73	0.92	71	0.74	0.81	75	7.5%	-0.01 [-0.29, 0.27]
Rivera 1998	0.2	0.8	45	0	1	44	4.2%	0.20 [-0.18, 0.58]
Rosado 1997	0.8	0.38	94	0.7	0.54	92	33.1%	0.10 [-0.03, 0.23]
Umeta 2000	0.25	1.25	92	0.15	1.26	92	4.5%	0.10 [-0.26, 0.46]
Total (95% CI)			**865**			**859**	**100.0%**	**0.09 [0.01, 0.16]**

Heterogeneity: Tau² = 0.00; Chi² = 3.58, df = 7 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.17 (P = 0.03)

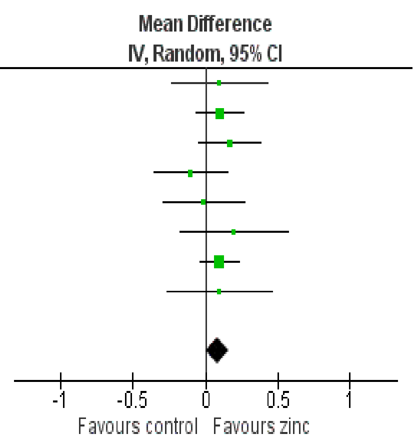


***Fig.* 13**. Forest plot of effect of zinc supplementation on change in mid upper arm circumference.

Study or Subgroup	Zinc Mean [cm]	Zinc SD [cm]	Zinc Total	Control Mean [cm]	Control SD [cm]	Control Total	Weight	Mean Difference IV, Random, 95% CI [cm]
El-Farghali 2015	41.16	2.17	96	40.35	2.16	83	15.1%	0.81 [0.17, 1.45]
Hess 2015	44.6	1.33	1833	44.6	1.4	602	27.9%	0.00 [-0.13, 0.13]
Islam 2010	34.4	1.1	50	34.1	1.5	50	18.0%	0.30 [-0.22, 0.82]
Mathur 2015	38.5	1.2	50	38.2	1.4	50	18.1%	0.30 [-0.21, 0.81]
Ram Kumar 2012	37.5	1.7	36	36.1	2.2	27	8.8%	1.40 [0.40, 2.40]
Rivera 1998	45	2.2	45	44.7	1.5	44	12.1%	0.30 [-0.48, 1.08]
Total (95% CI)			**2110**			**856**	**100.0%**	**0.39 [0.03, 0.75]**

Heterogeneity: Tau² = 0.11; Chi² = 15.01, df = 5 (P = 0.01); I² = 67%
Test for overall effect: Z = 2.15 (P = 0.03)

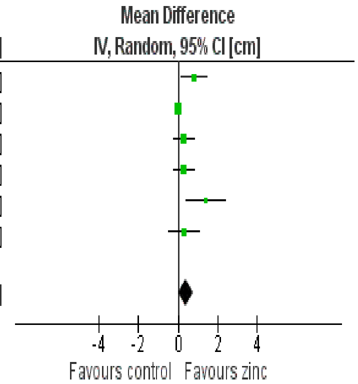


***Fig.* 14**. Forest plot of effect of zinc supplementation on head circumference at the end of supplementation period.

Study or Subgroup	Zinc Mean	Zinc SD	Zinc Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Aminisani 2010	8.68	1.39	40	7.43	1.51	36	19.6%	1.25 [0.60, 1.90]
Meeks Gardner 1998	0.7	0.6	31	0.6	0.6	30	29.5%	0.10 [-0.20, 0.40]
Osendarp 2002	5.1	1.1	138	5.2	1.1	133	30.5%	-0.10 [-0.36, 0.16]
Rivera 1998	2	2	45	1.9	0.8	44	20.3%	0.10 [-0.53, 0.73]
Total (95% CI)			**254**			**243**	**100.0%**	**0.26 [-0.18, 0.71]**

Heterogeneity: Tau² = 0.15; Chi² = 14.08, df = 3 (P = 0.003); I² = 79%
Test for overall effect: Z = 1.17 (P = 0.24)

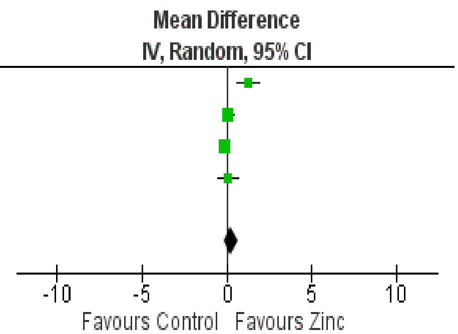


***Fig.* 15**. Forest plot of effect of zinc supplementation on change in head circumference.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Dijkhuizen 2008	258	1205	280	1246	12.0%	0.95 [0.82, 1.11]
Fahmida 2007	46	189	54	192	2.6%	0.87 [0.62, 1.21]
Hess 2015	427	1833	146	602	10.2%	0.96 [0.82, 1.13]
Locks 2016	349	1167	333	1161	16.0%	1.04 [0.92, 1.18]
Long 2007	24	364	23	343	1.0%	0.98 [0.57, 1.71]
Mozaraffi-Khosravi 2009	1	40	9	45	0.1%	0.13 [0.02, 0.94]
Radhakrishna 2013	95	154	91	147	8.8%	1.00 [0.83, 1.19]
Soofi 2013	310	622	320	617	20.3%	0.96 [0.86, 1.07]
Taneja 2009	516	959	477	952	29.1%	1.07 [0.99, 1.17]
Total (95% CI)		**6533**		**5305**	**100.0%**	**1.00 [0.95, 1.06]**
Total events	2026		1733			

Heterogeneity: Tau² = 0.00; Chi² = 8.95, df = 8 (P = 0.35); I² = 11%
Test for overall effect: Z = 0.13 (P = 0.89)

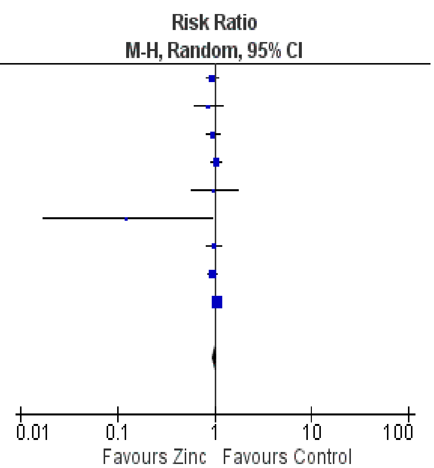


***Fig.* 16**. Forest plot of effect of zinc supplementation on stunting.

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Fahmida 2007	74	189	80	192	12.0%	0.94 [0.74, 1.20]
Hess 2015	304	1833	91	602	13.3%	1.10 [0.88, 1.36]
Locks 2016	207	1167	209	1161	15.2%	0.99 [0.83, 1.17]
Makonnen 2003	57	138	83	116	12.6%	0.58 [0.46, 0.73]
Radhakrishna 2013	59	154	56	147	10.2%	1.01 [0.75, 1.34]
Soofi 2013	267	691	271	687	17.3%	0.98 [0.86, 1.12]
Taneja 2009	498	959	486	952	19.4%	1.02 [0.93, 1.11]
Total (95% CI)		**5131**		**3857**	**100.0%**	**0.94 [0.82, 1.06]**
Total events	1466		1276			

Heterogeneity: Tau² = 0.02; Chi² = 22.27, df = 6 (P = 0.001); I² = 73%
Test for overall effect: Z = 1.02 (P = 0.31)

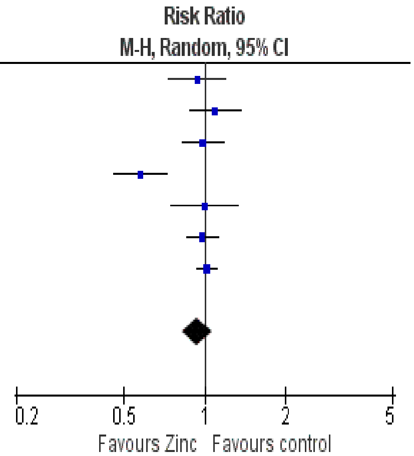


***Fig.* 17**. Forest plot of effect of zinc supplementation on underweight.

Study or Subgroup	Zinc Events	Zinc Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Fahmida 2007	19	189	26	192	3.9%	0.74 [0.43, 1.29]
Hess 2015	135	1833	35	602	8.9%	1.27 [0.88, 1.82]
Locks 2016	238	1167	215	1161	32.0%	1.10 [0.93, 1.30]
Mozaraffi-Khosravi 2009	3	40	2	45	0.4%	1.69 [0.30, 9.59]
Radhakrishna 2013	10	154	15	147	2.1%	0.64 [0.30, 1.37]
Soofi 2013	131	622	104	614	19.1%	1.24 [0.99, 1.57]
Taneja 2009	229	959	227	952	33.6%	1.00 [0.85, 1.18]
Total (95% CI)		**4964**		**3713**	**100.0%**	**1.08 [0.96, 1.21]**
Total events	765		624			

Heterogeneity: Tau² = 0.00; Chi² = 6.90, df = 6 (P = 0.33); I² = 13%
Test for overall effect: Z = 1.32 (P = 0.19)

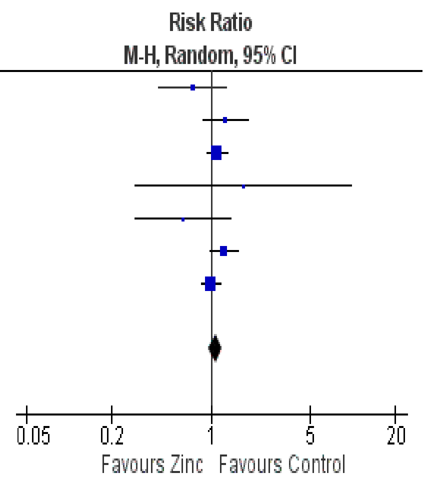
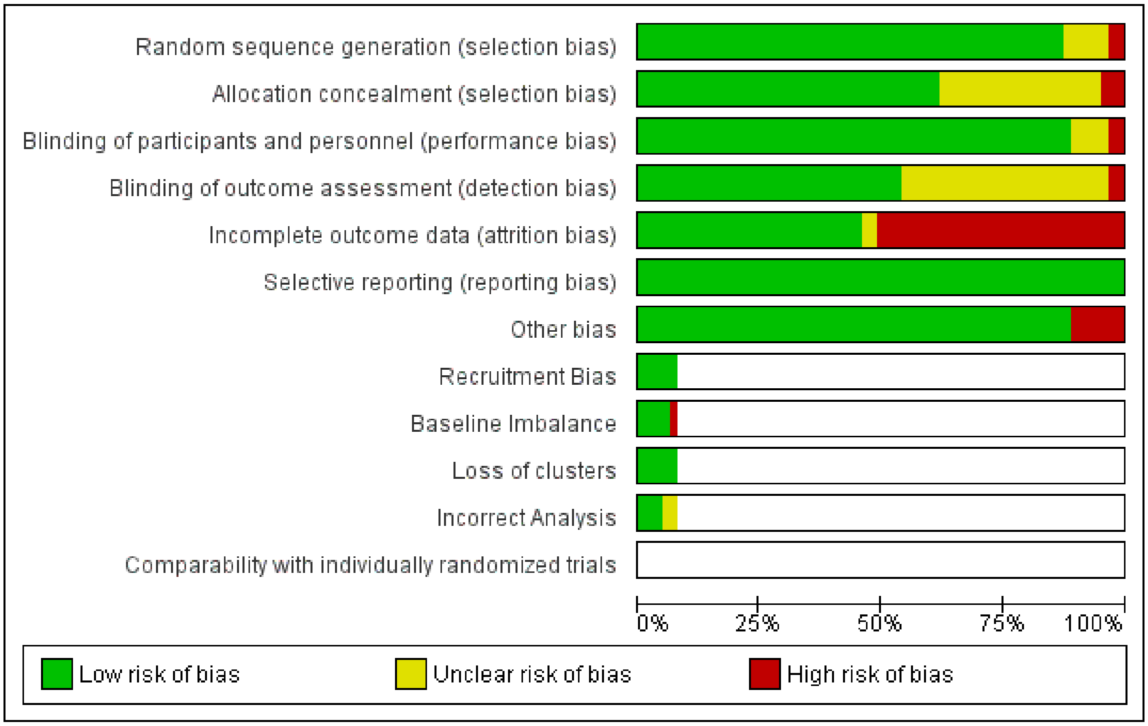
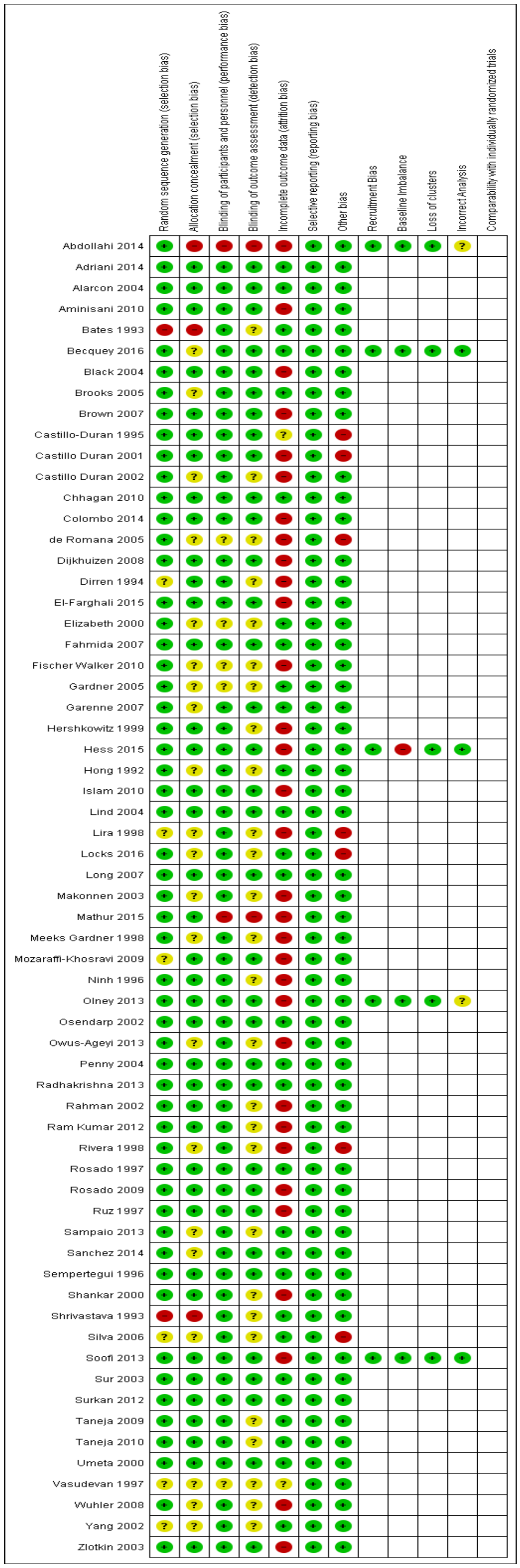


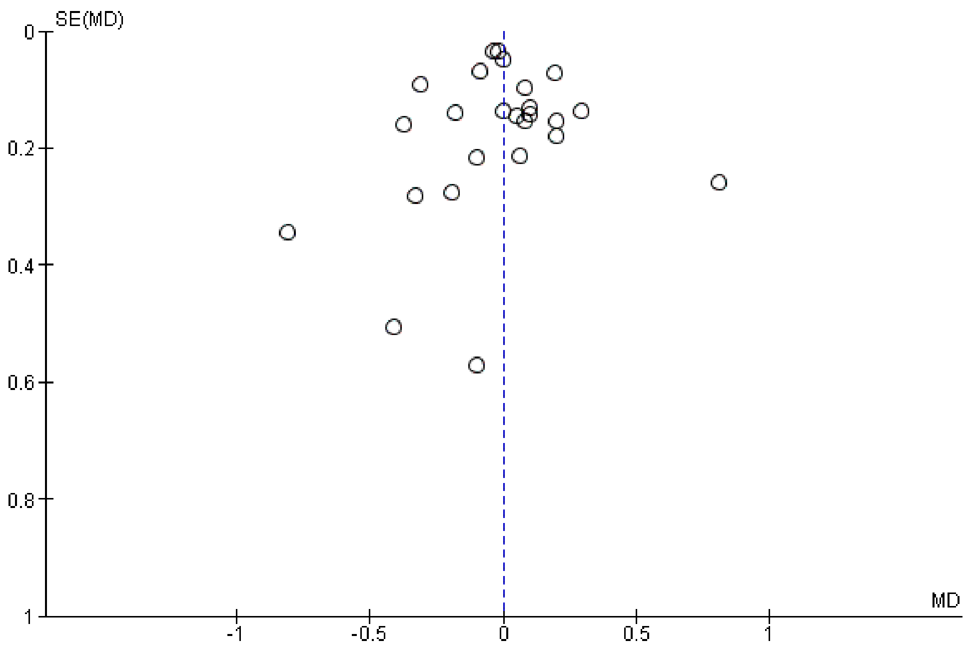
***Fig.* 18**. Forest plot of effect of zinc supplementation on wasting.



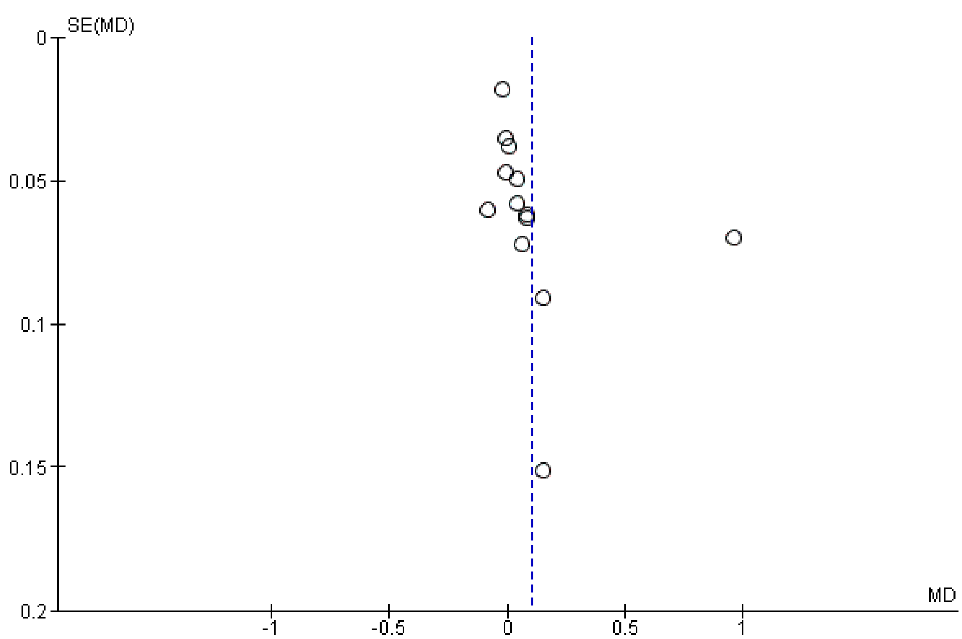
***Web Fig.* 1**. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



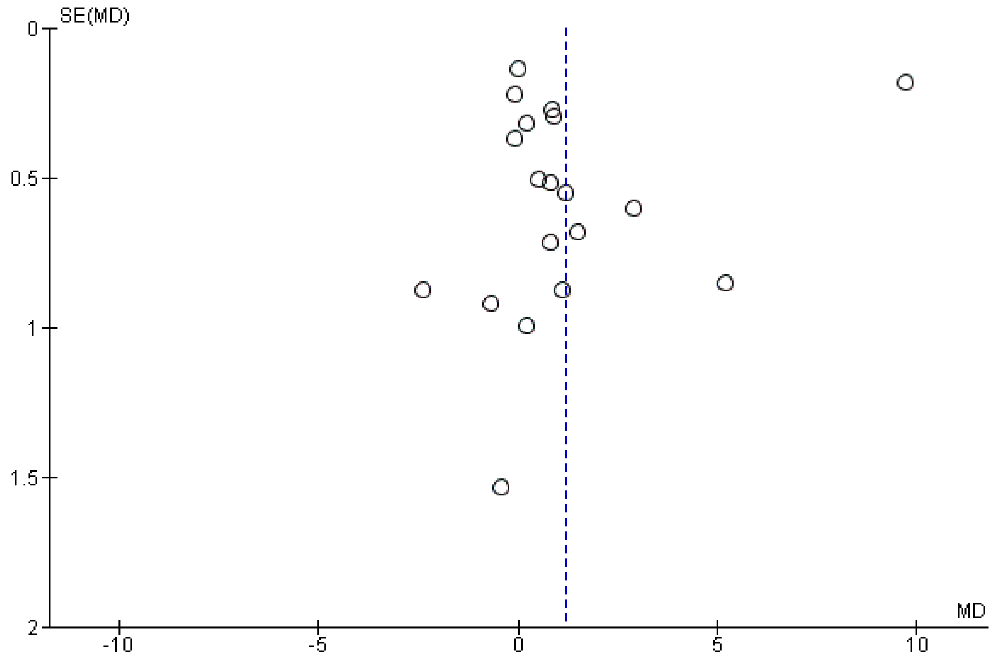
Web Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



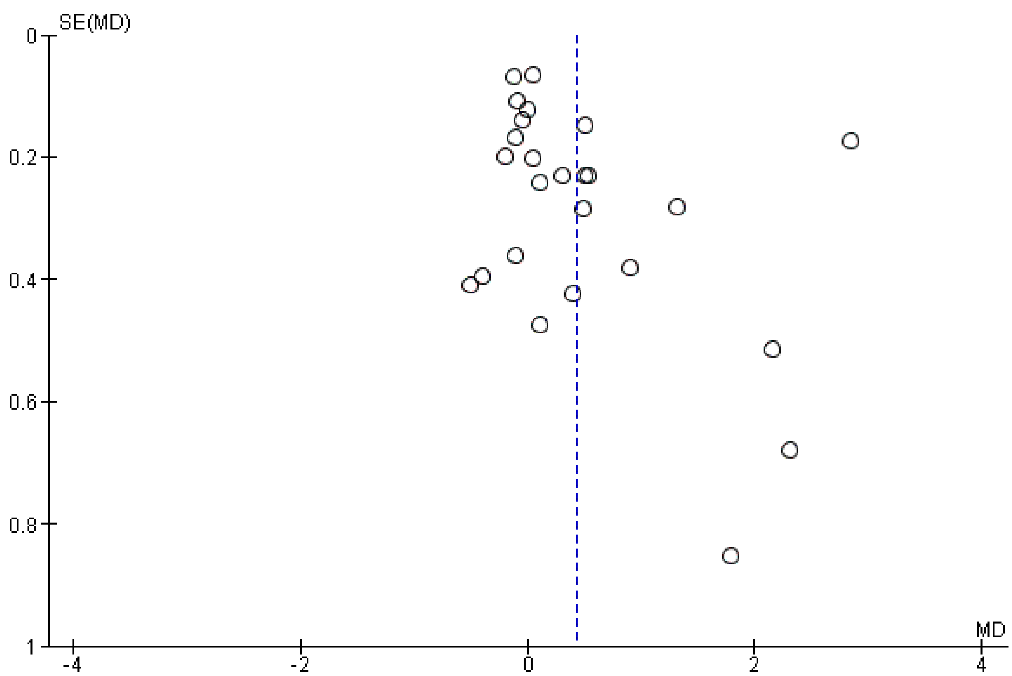
***Web Fig.* 3a**. Funnel plots depicting publication bias related to effect of zinc supplementation on length/height-for-age Z-score.



***Web Fig.* 3b**. Funnel plots depicting publication bias related to effect of zinc supplementation on change in length/height-for-age Z-score.



***Web Fig.* 3c**. Funnel plots depicting publication bias related to effect of zinc supplementation on endline length/height.



***Web Fig.* 3d**. Funnel plots depicting publication bias related to effect of zinc supplementation on change in endline length/height.

WEB APPENDIX 1 DETAILS OF DATABASE SEARCH

Database	*Date*	*Search Strategy*	*Number of references*
Medline	June 4, 2017	"Zinc"[Mesh] OR "Zinc Sulfate"[Mesh] OR "Zinc Compounds"[Mesh]) AND ("Clinical Trial" or "Controlled Clinical Trial" or "Randomized Controlled Trial" or "Pragmatic Clinical Trial"[MeSH Terms]) AND ((("Child, Preschool" or "Infant"[MeSH Terms])) OR (Child[Text Word] OR Children[Text Word] OR Infant[Text Word] OR Under-5 Children[Text Word])))	664
Web of Science (including Biosis Previews)	June 8, 2017	TOPIC: ("Zinc" OR "Zinc Supplement*") AND TOPIC: ("Child" OR "Children") AND TOPIC: ("Clinical Trial" or "Controlled Clinical Trial" or "Randomized Controlled Trial"); Timespan: All years; Search language=Auto	731
Cochrane Controlled Trials Register	June 8, 2017	"'zinc compound" in Title, Abstract, Keywords or zinc in Title, Abstract, Keywords and "Clinical Trial" or "Controlled Clinical Trial" or "Randomized Controlled Trial" in Publication Type and "Child" OR "Children" in Title, Abstract, Keywords	798
Embase	June 8, 2017	"Zinc OR "Zinc Sulfate" OR "Zinc Compounds" (all fields): 206513 limit 1 to (controlled clinical trial and preschool child <1 to 6 years>): 241	241
IBIDS	June 9, 2017	("zinc"[MeSH Terms] OR "zinc"[All Fields]) AND "Child"[All Fields] AND dietsuppl[sb]:	1319

WEB APPENDIX 2 ASSUMPTIONS AND CALCULATIONS FOR IMPUTATION/INTERPRETATION OF DATA FROM STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Locks 2016

SDs derived from SEM

Means and SDs of Zn and Zn+MV combined as intervention, that for placebo and MV combined as control

Sampaio 2013

Data given as median and IQR; mean assumed to be the same as median

IQR=1.35 SD

Mozaraffi-Khosravi 2009

Data for boys and girls given seperately. The means and SDs were combined for analysis

Fajolu 2008a

Means and *P* value for difference between means given

P given as 0.00, assumed to be 0.001 for SD calculation

Brown 2007

Data for medicinal zinc and fortified zinc group combined for comparison with control

Garenne 2007

SDs calculated from means and *P* value

Means for boys and girls given separately, which were combined for analyses

de Romana 2005

Data for 3 mg and 9 mg zinc group combined as intervention

Lind 2004

Data for Fe+ Zn and Zn groups combined as intervention group; and placebo and Fe groups as control

Sur 2003

Change in weight and length for intervention and control groups mentioned in text without SD with $P < 0.001$. *P* vale was assumed to be equal to 0.001 and SD estimated accordingly

Yang 2002

Means for Zn and ZnCaVa combined as intervention; control and CaVa as control

Khatun 2001a

Means for Zinc and Zinc plus vit A combined as intervention, vit A and control groups combined as control

Rosado 1997

SE converted to SD

Data for Fe+ Zn and Zn groups combined as intervention group; and placebo and Fe groups as control

Roy 1999a

Mean change in height given for the two groups with *P* <0.05. *P* assumed to be equal to 0.049 and SD estimated from that.

SD derived from 95% CI for weight

Lira 1998

Data from 1 mg and 5 mg zinc combined as intervention group

Vasudevan 1997

P mentioned as >0.1, assumed to be 0.11 and SDs calculated from that.

Ruz 1997

For change in length means and SDs of children with different baseline HAZ given, which were combined to estimate the ones for the entire intervention and control group

Change in HAZ, WAZ and WLZ given as figures with exact *P* values. The means were estimated from the figures and then the SDs calculated from the *P* value

Dirren 1994

Data given as means and SEM from which SDs were derived

Data given separately for boys and girls, which was combined

Hong 1992

Data for boys and girls given separately; combined for analysis.

WEB APPENDIX 3 SUMMARY OF FINDINGS TABLES

A. Effect of Zinc Supplementation on Length/Height

Patient or population: Children under 5 years
Settings: Low and Middle Income Countries
Intervention: Zinc Supplementation versus No supplementation

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Zinc versus No Zinc**				
Length/Height for Age Z score (LAZ/HAZ)		The mean LAZ/HAZ in the intervention groups was **0 higher** (0.07 lower to 0.07 higher)		9165 (25 studies)	⊕⊕⊕⊝ **moderate**[1]	Probably leads to little or no difference in endline HAZ score. Among five additional trials not included in meta-analysis, three reported no significant difference while 2 reported higher HAZ with Zinc supplementation.
Change in LAZ/HAZ		The mean change in LAZ/HAZ in the intervention groups was **0.11 higher** (-.0.0 to 0.21 higher)		8852 (13 studies)	⊕⊕⊕⊝ **moderate**[2]	Probably leads to little increase in change in HAZ score.
Length/Height (cm)		The mean length/height in the intervention groups was **1.18 cm higher** (0.63 lower to 2.99 higher)		6303 (19 studies)	⊕⊕⊕⊝ **moderate**[3]	Probably leads to little or no difference in endline lenghth or height. Two additional trials, not included in the meta-analysis reported no significant difference in endline length/height.
Change in Length (cm)		The mean change in length in the intervention groups was **0.43 cm higher** (0.16 to 0.7 higher)		10783 (25 studies)	⊕⊕⊕⊕ **high**	Results in little increase in change in length.

% Height for Age		The mean % height for age in the intervention groups was **1.9 % higher** (1.01 to 2.79 % higher)		57 (1 study)	⊕⊖⊖⊖ **very low**[4,5]	It is uncertain whether Zinc supplementation increases height for age % because the certainty of the evidence is very low
Change in % Height for Age		The mean change % height for age in the intervention groups was **2.24% higher** (1.56 to 2.92 % higher)		57 (1 study)	⊕⊖⊖⊖ **very low**[4,5]	It is uncertain whether Zinc supplementation increases height for age % change because the certainty of the evidence is very low
***The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).** **CI: Confidence interval;**						
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 Downgraded by 1 for serious risk of bias. 15 trials had high risk of bias for attrition, 5 for other bias and one for baseline incomparability between clusters.
2 Downgraded by 1 for serious risk of bias. 5 trials had unclear riak of bias for allocation concealment and blinding for outcome assessment, 5 were at high risk of bias for attrition
3 Downgraded by 1 for serious risk of bias. Several trials were at high risk: one for random sequence generation, two for allocation concealment, two for blinding, 12 for attrition, 3 for other bias and one for baseline comparability of clusters.
4 Downgraded by 2 for very serious indirectness. Only one trial with a small population from urban India the findings of which cannot be extrapolated to other countries and settings.
5 Downgraded by 1 for imprecision; small sample size with wide 95% CI around the effect estimate.

B. Effect of Zinc Supplementation on Weight

Patient or population: Children under 5 years
Settings: Low and Middle Income Countries
Intervention: Zinc Supplementation versus No supplementation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Zinc Supplementation versus No supplementation				
Weight for age Z score (WAZ)		The mean WAZ in the intervention groups was **0.05 Z higher** (0.03 lower to 0.13 higher)		9033 (23 studies)	⊕⊕⊕⊝ **moderate**[1]	Probably leads to little or no difference in endline WAZ score. Two additional trials also did not document any significant difference in WAZ in the Zinc supplemented group
Change in WAZ		The mean change in waz in the intervention groups was **0.03 higher** (0.01 lower to 0.08 higher)		8851 (13 studies)	⊕⊕⊕⊝ **moderate**[2]	Probably leads to little or no difference in change in WAZ score.
Weight (kg)		The mean weight in the intervention groups was **0.23 kg higher** (0.03 to 0.42 higher)		6293 (19 studies)	⊕⊕⊕⊝ **moderate**[3]	Probably leads to little increase in weight
Change in weight (kg)		The mean change in weight in the intervention groups was **0.11 kg higher** (0.05 to 0.17 higher)		10143 (23 studies)	⊕⊕⊕⊝ **moderate**[4]	Probably leads to little increase in change in weight
Rate of weight gain (g/kg/day)		The mean rate of weight gain in the intervention groups was **1.52 g/kg/day higher** (0.62 lower to 3.65 higher)		114 (2 studies)	⊕⊝⊝⊝ **very low**[5,6,7]	It is uncertain whether Zinc supplementation increases rate of weight gain because the certainty of the evidence is very low

% Weight for age		The mean % weight for age in the intervention groups was **3.9 higher** (1.72 to 6.08 higher)		57 (1 study)	⊕⊖⊖⊖ **very low**[7,8]	It is uncertain whether Zinc supplementation increases weight for age % because the certainty of the evidence is very low
Change % Weight for Age		The mean change % weight for age in the intervention groups was **3.2 higher** (1.27 to 5.13 higher)		57 (1 study)	⊕⊖⊖⊖ **very low**[7,8]	It is uncertain whether Zinc supplementation increases weight for age % change because the certainty of the evidence is very low
***The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval;**						
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] Downgraded by 1 for serious risk of bias. 14 trials had high risk of attrition bias, 4 had high risk of other bias and there was baseline imbalance in one cluster RCT

[2] Downgraded by 1 for serious risk of bias, 5 trials were at high risk of bias for attrition and 2 for other bias.

[3] Downgraded by 1 for serious risk of bias, 2 trials were at high risk for random sequence generation, 3 for allocation concealment, 2 for blinding, 12 for attrition, 2 for other bias and one for baseline comparability between clusters

[4] Downgraded by 1 for serious risk of bias, One trial was at high risk of bias for random sequence generation, one for allocation concealment, one for blinding, 11 for attrition and two for other bias

[5] Downgraded by 1 for serious risk of bias. Of the two included trials one was at high risk for random sequence generation and allocation concealment and the other had unclear risk of bias for random sequence generation, allocation concealment and blinding

[6] Downgraded by 1 for indirectness. Both trials from urban India with small datasets the conclusions of which cannot be extrapolated to other populations and settings

[7] Downgraded by 1 for imprecision. Small sample size with wide 95% CI around the effect estimate

[8] Downgraded by 2 for serious indirectness. Only one trial with a small population from urban India the findings of which cannot be extrapolated to other countries and settings.

C. Effect of Zinc Supplementation on Weight-for-Height and Mid Upper Arm Circumference

Patient or population: Children under 5 years
Settings: Low and Middle Income Countries
Intervention: Zinc Supplementation versus No supplementation

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Zinc Supplementation versus No supplementation**				
Weight for Height Z score (WHZ)		The mean WHZ in the intervention groups was **0.03 Z higher** (0.02 lower to 0.08 higher)		8392 (19 studies)	⊕⊕⊕⊝ **moderate**[1]	Probably leads to little or no difference in endline WHZ score. Three additional trials also did not document any significant difference in WHZ in the Zinc supplemented group
Change in WHZ		The mean change in WHZ in the intervention groups was **0.01 Z higher** (0.03 lower to 0.04 higher)		8706 (12 studies)	⊕⊕⊕⊝ **moderate**[2]	Probably leads to little or no difference in change in WHZ score.
% Weight for Height		The mean % weight for height in the intervention groups was **0.7% higher** (0.81 lower to 2.21 higher)		57 (1 study)	⊕⊝⊝⊝ **very low**[3,4]	It is uncertain whether Zinc supplementation increases weight for height % because the certainty of the evidence is very low
Change % Weight for Height		The mean change % weight for height in the intervention groups was **1.17% higher** (0.09 lower to 2.43 higher)		57 (1 study)	⊕⊝⊝⊝ **very low**[3,4]	It is uncertain whether Zinc supplementation increases weight for height % because the certainty of the evidence is very low
Mid Upper Arm Circumference		The mean MUAC in the intervention groups was **0 cm**		4236 (7 studies)	⊕⊕⊕⊝ **moderate**[5]	Probably leads to little or no difference in endline Mid Upper Arm Circumference.

(MUAC; cm)		**higher** (0.08 lower to 0.09 higher)				
Change in MUAC (cm)		The mean change in MUAC (cm) in the intervention groups was **0.09 cm higher** (0.01 to 0.16 higher)		1724 (8 studies)	⊕⊕⊕⊝ **moderate**[6]	Probably leads to little increase in Mid Upper Arm Circumference change.
***The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval;**						
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] Downgraded by 1 for serious risk of bias. 12 trials were at high risk of bias for attrition, 4 for other bias and one for baseline incomparability between clusters.
[2] Downgraded by 1 for serious risk of bias. 5 trials were at high risk of bias for attrition and 2 for other bias
[3] Downgraded by 2 for very serious indirectness. Only one trial with a small population from urban India, the findings of which cannot be extrapolated to other countries and settings.
[4] Downgraded by 1 for imprecision; small sample size with wide 95% CI around the effect estimate
[5] Downgraded by 1 for serious risk of bias. One trial was at high risk of bias for random sequence generation and allocation concealment, 5 for attrition and 2 for other bias.
[6] Downgraded by 1 for serious risk of bias. One trial was at high risk of bias for random sequence generation and allocation concealment, 2 for attrition and one for other bias.

D. Effect of Zinc Supplementation on Head Circumference, Stunting, Underweight and Wasting

Patient or population: Children under 5 years
Settings: Low and Middle Income Countries
Intervention: Zinc Supplementation versus No supplementation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Zinc Supplementation versus No supplementation				
Head Circumference (cm)		The mean head circumference in the intervention groups was **0.39 cm higher** (0.03 to 0.75 higher)		2966 (6 studies)	⊕⊕⊕⊝ **moderate**[1]	Probably leads to little increase in head circumference
Change in Head Circumference (cm)		The mean change in head circumference in the intervention groups was **0.26 cm higher** (0.18 lower to 0.71 higher)		497 (4 studies)	⊕⊕⊕⊝ **moderate**[2]	Probably leads to little or no difference in change in head circumference
Change in head circumference z score (Z)		The mean change in head circumference z score in the intervention groups was **0.12 higher** (0.11 to 0.13 higher)		569 (1 study)	⊕⊕⊝⊝ **low**[3]	May leads to little increase in change in head circumference
Stunting	**Study population**		**RR 1** (0.95 to 1.06)	11838 (9 studies)	⊕⊕⊕⊝ **moderate**[4]	Probably leads to little or no difference in stunting
	stunting327 per 1000	**327 per 1000** (310 to 346)				
	Moderate					
	281 per 1000	**281 per 1000** (267 to 298)				
Underweight	**Study population**		**RR 0.94** (0.82 to 1.06)	8988 (7 studies)	⊕⊕⊕⊝ **moderate**[5]	Probably leads to little or no difference in underweight
	331 per 1000	**311 per 1000** (271 to 351)				
	Moderate					
	395 per 1000	**371 per 1000** (324 to 419)				

Wasting	**Study population**		**RR 1.08** (0.96 to 1.21)	8677 (7 studies)	⊕⊕⊕⊖ **moderate**[5]	Probably leads to little or no difference in wasting
	168 per 1000	**182 per 1000** (161 to 203)				
	Moderate					
	135 per 1000	**146 per 1000** (130 to 163)				
***The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).** **CI: Confidence interval; RR: Risk ratio;**						
GRADE Working Group grades of evidence **High quality: Further research is very unlikely to change our confidence in the estimate of effect.** **Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.** **Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.** **Very low quality: We are very uncertain about the estimate.**						

[1] Downgraded by 1 for serious risk of bias. All included trials were at high risk of bias for attrition, one for blinding, one for attrition and one for baseline incomparability between clusters

[2] Downgraded by 1 for serious risk of bias. Three trials were at high risk of bias for attrition and one for other bias.

[3] Downgraded by 2 for very serious risk of bias. Only one trial from rural Nepal the findings of which cannot be extrapolated to other settings or populations.

[4] Downgraded by 1 for serious risk of bias. 4 trials were at high risk of bias for attrition, one for other bias and one for baseline incomparability between clusters.

[5] Downgraded by 1 for serious risk of bias. Three trials were at high risk of bias for attrition, one for other bias and one for baseline incomparability between clusters.

WEB TABLE I CHARACTERISTICS OF INCLUDED STUDIES

Study [Ref.]; Country	Zinc Salt	Intervention	Comparator	Initial age (mo)	Participants (n) (Test/Control)	Dose (mg or *mg/kg)	Duration (mo)	Baseline zinc level (mcg/dL)	Baseline HAZ	Baseline Stunting (%)	Outcomes
Hess, *et al.* [48]; Burkina Faso	Zinc sulfate	LNS+Zn	LNS+placebo	9	1833/602	5, 10	9	69.5	-1.21	21.9	Weight, Length, HC, MUAC, LAZ, WAZ, Stunting, Underweight, Wasting
Locks, *et al.* [57]; Tanzania	Zinc sulfate	Zn+MV Zinc	MV Placebo	1.5 -19	1198/1202	5-10	18	Not mentioned	-0.28	Not mentioned	Change in HAZ, WAZ, WHZ, Stunting, wasting, underweight
Mathur, *et al.* [62]; India	Zinc gluconate	Zn+MV	Multivitamins	0	50/50	2*	3	Not mentioned	Not mentioned	Not mentioned	Weight, Length, HC
Becquey, *et al.* [16]; Burkina Faso	Zinc sulfate	Zinc	No intervention	6-27	391/962	7	11	67	-1.22	28.6	Change in Weight, Length, WAZ, HAZ, WLZ,Wasting, underweight and stunting
El Farghali, *et al.* [38]; Egypt	Zinc sulfate	Zinc	Placebo	0	108/92	10	6	111.35	Not mentioned	Not mentioned	Weight, Length, MUAC, HC
Sanchez *et al.* [84]; Colombia	Zinc sulfate,	Zinc	Placebo	24-60	205/96	7	4	Not mentioned	Not mentioned	5	Weight, Height, BMI
Colombo, *et al.* [30]; Peru	Zinc sulfate	Zn + Iron + Copper	Iron+ copper	6	129/122	10	12	93.17	-0.55	Not mentioned	WAZ, LAZ
Adriani, *et al.* [12]; Indonesia	Zinc sulfate (Zn + vitamin A)	Zinc+Vitamin A	vitamin A+placebo	48-60	12/12	0.9	6	35	-2	100	HAZ
Abdollahi, *et al.* [11]; Iran	Zinc sulfate	Zinc	Placebo	6-24	291/302	5	3	Not mentioned	Not mentioned	Not mentioned	Weight, Height
Soofi, *et al.* [90]; Pakistan	Zinc gluconate	Zinc + micronutrient powder	Micronutrient powder	6	830/784	10	12	84	Not mentioned	Not mentioned	Wasting, stunting, underweight, length
Sampaio, *et al.* [83];	Zinc gluconate	Sprinkles with Zinc	Sprinkles without zinc	6-48	75/68	5	3	Not mentioned	-0.41	Not mentioned	WAZ, LAZ, WHZ

Brazil											
Radhakrishna, *et al.* [72]; India	Zinc sulfate	Zn+riboflavin	Riboflavin	4	154/147	5	14	Not mentioned	Not mentioned	Not mentioned	Wasting, stunting, underweight, length, weight, WAZ, HAZ, WHZ
Owusu-Ageyi, *et al.* [69]; Ghana	Zinc gluconate	Zinc+Vitamin A	vitamin A+placebo	6-24	100/100	10	6	69	-1	32	Weight, Height, WAZ, HAZ, WHZ
Olney, *et al.* [65]; Zanzibar	Zinc sulfate	Zn+Iron Zinc	Iron Placebo	1-35	247	10	12	Not mentioned	Not mentioned	30	HAZ
Surkan, *et al.* [93]; Nepal	Zinc sulfate	Zinc+iron+ folic acid Zinc	Iron+folicacid Placebo	4-17	288/281	5	12	Not mentioned	Not mentioned	22	Change in HC z score
Ram Kumar, [74]; *et al.*India	Zinc sulfate	Zinc	Placebo	0	36/27	10	2	Not mentioned	Not mentioned	Not mentioned	Weight, Length, HC
Aminisani, *et al.* [14]; Iran	Zinc sulfate	Zinc	Placebo	0-1	40/36	5	6	Not mentioned	Not mentioned	Not mentioned	Change in weight, height and HC
Taneja, *et al.* [95]; India	Zinc gluconate	Zinc	Placebo	6-30	1093/1133	10-20	4	80.4	-1.79	Not mentioned	Change in weight, height, WAZ, LAZ, WHZ
Islam, *et al.* [52]; Bangladesh	Zinc sulfate	Zinc+MV	MV	0-1	50/50	3	1.5	62.1	Not mentioned	Not mentioned	Weight, Length, HC
Chhagan, *et al.* [27]; South Africa	Zinc gluconate	Zinc+Vitamin A	Vitamin A	6	123/124	10	18	Not mentioned	-0.64	18.60	LAZ
Fischer Walker, *et al.* [41]; Bangladesh	Zinc acetate	Zinc+iron Zinc + riboflavin	Iron Riboflavin	6	276/290	20	6	55.1	-1.2	Not mentioned	Weight, Height, MUAC
Taneja, *et al.* [94]; India	Zinc sulfate	Zinc	Placebo	0-1	1026/1026	5-10	12	64	Not mentioned	Not mentioned	Weight, Length, Wasting, Stunting, Underweight
Rosado, *et al.* [80]; Mexico	Zinc Methionine	Zinc+Vitamin A Zinc	Vitamin A Placebo	5-24	395/391	20	12	Not mentioned	-0.97	19	HAZ
Mozaraffi-Khosravi, *et al.* [64]; Iran	Zinc sulfate	Zinc	Placebo	24-60	40/45	5	6	Not mentioned	-1.65	20	Weight, Height, MUAC, Wasting, Stunting
Wuehler, *et*	Zinc sulfate	Zinc	Placebo	10-30	313/108	3-10	6	70.8	-2.3	60	Change in weight, length,

al. [98]; Ecuador											WAZ, WLZ, HAZ
Dijkhuizen, *et al.* [33]; SE Asia	Zinc sulfate	Zinc+Iron Zinc	Iron Placebo	4-6	1246/1205	10	6	113.5	-0.83	7.30	WAZ, HAZ, WLZ, Stunting, Change in weight and length
Brown, *et al.* [23] Peru	Zinc sulfate#	Zinc+MV	MV	5-7	168/94	3	6	77.6	-1.19	Not mentioned	Change in weight, length, WAZ, WLZ, HAZ
Long, *et al.* [58]; Mexico	Zinc Methionine	Zinc+Vitamin A	Vitamin A+placebo	6-15	364/343	20	12	Not mentioned	Not mentioned	10	Stunting
Garenne, *et al.* [43]; Burkina Faso	Zinc sulfate	Zinc	Placebo	6-30	342/344	12.5	6	99.1	-1.59	Not mentioned	Change in Weight Height MUAC
Fahmida, *et al.* [40];Indonesia	Zinc sulfate	Zinc	Placebo	3-6	192/199	10	6	129.6	-1.01	15.50	Wasting, stunting, underweight, WAZ, HAZ, WLZ
Silva, *et al.* [88]; Brazil	Zinc sulfate	Zinc	Placebo	12-59	28/30	10	4	56.5	-1.9	Not mentioned	WHZ, HAZ
de Romana, *et al.* [31]; Peru	Zinc sulfate#	Zinc+iron	Iron	36-48	22/12	10	2.5	75	-2.67	100	Weight. Height, HAZ, WAZ, WHZ
Gardner, *et al.* [42]; Jamaica	Zinc sulfate	Zinc Zinc + stimulation	No intervention Stimulation	9-30	55/59	10	6	Not mentioned	-1.42	Not mentioned	Weight. Height, HAZ, WAZ, WHZ
Brooks, *et al.* [20]; Bangladesh	Zinc acetate	Zinc	Placebo	2-12	329/309	5	10	Not mentioned	Not mentioned	Not mentioned	Weight, Height
Penny, *et al.* [70]; Peru	Zinc gluconate	Zinc	Placebo	6-36	71/75	10	6	70.3	-1.56	32	Change in length, weight, LAZ, WAZ and MUAC
Lind, *et al.* [53]; Indonesia	Zinc sulfate	Zinc+Iron Zinc	Iron Placebo	6	323/327	10	6	Not mentioned	-0.34	3.50	WAZ, WHZ, HAZ, MUAC
Black, *et al.* [18]; India	Zinc sulfate	Zn + Micronutrient + Riboflavin	Micronutrient +Riboflavin	1	79/71	5	9	Not mentioned	Not mentioned	Not mentioned	Change in weight, length; HAZ, WHZ
Alarcon, *et al.* [13]; Peru	Zinc sulfate	Zn + Iron + vitamin A	Iron+Vitamin A+placebo	6-35	109/104	7	4.5	Not mentioned	-1.04	Not mentioned	Weight, height, WAZ, HAZ, WHZ, change in Weight, height, WAZ, HAZ, WHZ
Zlotkin, *et al.* [100]; Ghana	Zinc gluconate	Zn + Iron + vitamin C	Iron+Vitamin C	6-18	124/115	10	2	120.3	-1.76	Not mentioned	WAZ, HAZ, WHZ

Sur, *et al.* [91]; India	Zinc sulfate	Zn+vitamin B-complex	Vitamin B-complex	7 d	50/50	5	12	Not mentioned	Not mentioned	Not mentioned	Change in weight, length; WAZ
Makonnen, *et al.* [60]; South Africa	Zinc sulfate	Zinc	Placebo	6-60	138/116	10	3	Not mentioned	Not mentioned	Not mentioned	Underweight
Yang, *et al.* [99]; China	Zinc sulfate	Zinc Zn+calcium+ vitamin A	No intervention Calcium+vitamin A	36-60	60/56	3.5	12	Not mentioned	Not mentioned	Not mentioned	Change in weight, length
Rahman, *et al.* [73]; Bangladesh	Zinc sulfate	Zin+Vitamin A Zinc	Vitamin A Placebo	12-35	336/317	20	0.5	Not mentioned	-2.41	Not mentioned	Change in weight, length, WAZ, WLZ, HAZ
Osendarp, *et al.* [68]; Bangladesh	Zinc acetate	Zinc	Placebo	1	138/133	5	5	99.9	-1.1	Not mentioned	Weight, Length, WAZ, HAZ, WLZ, Change in weight, length, HC, MUAC
Castillo Duran, *et al.* [26]; Chile	Zinc sulfate	Zinc	Placebo	17-19	21/21	5	12	Not mentioned	Not mentioned	Not mentioned	Weight, Length
Castillo Duran, *et al.* [25]; Chile	Zinc sulfate	Zinc	Placebo	0.6	57/55	5	12	Not mentioned	Not mentioned	Not mentioned	WAZ, HAZ, WLZ
Umeta, *et al.* [96]; Ethiopia	Zinc sulfate	Zinc	Placebo	6-12	92/92	10	6	Not mentioned	-1.72	50	Change in weight, length, WAZ, WLZ, HAZ
Shankar, *et al.* [86]; Papua New Guinea	Zinc gluconate	Zinc	Placebo	6-60	103/109	10	10.5	70	-1.9	Not mentioned	WAZ, HAZ, MUAC
Elizabeth, *et al.* [39]; India	Not mentioned	Zinc + MV	MV	1-60	29/28	2*	3	49.8	Not mentioned	93	% weight for height, weight for age, height for age; change in % weight for height, weight for age, height for age
Rosado, *et al.* [79]; Mexico	Zinc Methionine	Zinc+Iron Zinc	Iron Placebo	18-36	97/97	20	12	Not mentioned	-1.6	36.5	Change in weight, height, WAZ, HAZ, WHZ
Hershkovitz, *et al.* [46]; Israel	Zinc acetate	Zinc	Placebo	3-9	14/11	2*	3	Not mentioned	-1.6	15	WAZ, LAZ, HAZ

Rivera, *et al.* [76]; Guatemala	Zinc sulfate	Zinc	Placebo	6-9	45/44	10	7	Not mentioned	-2.15	Not mentioned	Weight, height, MUAC, WAZ, LAZ, HAZ; Change in Weight, height, MUAC, WAZ, LAZ, HAZ
Meeks Gardner, *et al.* [63]; Jamaica	Zinc sulfate	Zinc	Placebo	6-24	31/30	5	3	Not mentioned	-2.85	100	Change in weight, length, HC
Lira, *et al.* [55]; Brazil	Zinc sulfate	Zinc	Placebo	0	112/54	1, 5	6	Not mentioned	Not mentioned	Not mentioned	Change in weight, length
Vasudevan, *et al.* [97]; India	Zinc sulfate	Zinc	Placebo	8-24	31/31	20	3	98.4	Not mentioned	Not mentioned	Rate of weight gain
Ruz, *et al.* [82]; Chile	Zinc sulfate	Zinc	Placebo	27-50	27/26	10	14	144	-0.52	Not mentioned	Change in length, WAZ, HAZ, WLZ
Sempertegui, *et al.* [15]; Ecuador	Zinc sulfate	Zinc	Placebo	12-59	25/25	10	2	86.5	-2	94	WAZ, HAZ
Ninh, *et al.* [3]; Vietnam	Zinc sulfate	Zinc	Placebo	4-36	/73/73	10	5	Not mentioned	-2.9	100	Weight, Height, WAZ, HAZ, WHZ
Castillo Duran, *et al.* [24]; Chile	Zinc acetate	Zinc	Placebo	0	35/33	3	6	104.2	-1.3	Not mentioned	Length, WAZ, HAZ, WHZ, HC
Dirren, *et al.* [37];	Zinc sulfate	Zinc	Placebo	12-50	48/48	10	15	73.5	-2.87	Not mentioned	Change in weight, height, WAZ, HAZ, WHZ
Shrivastava, *et al.*[87]; India	Zinc sulfate	Zinc+MV	MV	8-24	26/26	22.5	3	89.3	Not mentioned	Not mentioned	Weight, Rate of weight gain
Bates, *et al.* [15]; Gambia	Zinc gluconate	Zinc	Placebo	7-28	56/56	20	15	128.7	Not mentioned	Not mentioned	Weight, Length, MUAC; Change in Weight, Length, MUAC
Hong, *et al.* [51]; China	Zinc sulfate	Zinc+Vitamin B	Vitamin B	0	32/33	1.1-2.2*	6	111	Not mentioned	Not mentioned	Change in weight, length

#Used fortification as a strategy for zinc supplementation

Zn: Zinc; MV: Multivitamin; HC: head circumference; WAZ: weight-for-age Z-score; HAZ: height-for-age Z-score; LAZ: length-for-age Z-score; WHZ: weight-for-height Z-score; WLZ: weight-for-length Z-score MUAC: mid upper arm circumference.