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The relationship between zinc intake and growth in children aged 1-8 years: a systematic review and meta-analysis.

Running Title: Zinc and growth in children

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Abstract

Background/Objectives: It is estimated that zinc deficiency affects 17% of the world's population and because of periods of rapid growth, children are at an increased risk of deficiency which may lead to stunting. This paper presents a systematic review and meta-analysis of the randomised controlled trials that assess zinc intake and growth in children aged 1-8 years. This review is part of a larger systematic review by the European Micronutrient Recommendations Aligned (EURRECA) Network of Excellence that aims to harmonise the approach to setting micronutrient requirements for optimal health in European populations (www.eurreca.org).

Subject/Methods: Searches were performed of literature published up to and including December 2013 using MEDLINE, Embase, and the Cochrane Library databases. Included studies were RCTs in apparently healthy child populations aged from 1 to 8 years that supplied zinc supplements either as capsules or part of a fortified meal. Pooled meta-analyses were performed when appropriate.

Results: Nine studies met the inclusion criteria. We found no significant effect of zinc supplementation of between 2 weeks to 12 months duration on weight gain, HAZ, WAZ, LAZ, WHZ or WHZ scores in children aged 1-8 years.

Conclusion: Many of the children in the included studies were already stunted and may have been suffering multiple micronutrient deficiencies and therefore zinc supplementation alone may have only a limited effect on growth.

Keywords: Zinc; Child; Growth; Systematic review; EURRECA

INTRODUCTION

Suboptimal dietary zinc intake is increasingly recognised as an important public health issue. It is estimated that the risk of low dietary intake of absorbable zinc and consequent zinc deficiency affects 17% of the world's population.[1] Factors that contribute to zinc deficiency include consumption of high phytate-containing cereal and low protein intake, commonly found in the diets of non-industrialised populations, which impairs zinc absorption.[2,3] Zinc deficiency is particularly prevalent in South and Southeast Asia, Latin America and sub-Saharan Africa.[2,4,5] Frequent clinical infections such as diarrhoea, also common in non-industrialised regions, also affect zinc absorption.[6,7]

Children are particularly vulnerable to zinc deficiency due to an increased requirement during periods of rapid growth.[6] Zinc deficiency may impair growth and contribute to stunting in children.[3,8,9] One suggested mechanism is altered growth hormone metabolism.[10] It has been estimated that 171 million children (167 million in developing countries) are stunted and 20% of children under 5 years in low and middle income countries have a WAZ score (weight for age Z score) of less than -2.[5] While severe zinc deficiency is uncommon in European populations, marginal deficiency is likely to be much more prevalent.[11] Although the global prevalence of childhood stunting has decreased in the last decade (from 39·7% in 1990 to 26·7% in 2010), stunting remains a major public health problem.[12]

Several systematic reviews have explored the relationship between preventive zinc supplementation and growth in children, but have reported discordant findings.[13-16] A high degree of heterogeneity, however, was observed in many of the meta-analyses performed, due in part to inclusion of data from children with a wide age range in pooled analyses. Brown *et al*[13] pooled data from infants and pre-pubertal children; Ramakrishnan *et al*[15] and

Imdad *et al*[16] pooled data from infants and children under 5 years of age and Brown *et al*[14] included infants, children and adolescents in their meta-analyses. Such wide-ranging ages incorporate several periods where growth is particularly rapid (during infancy and puberty for example) and during which the child's nutrient needs correspond with these changes in growth rates. Growth during the first year of life is particularly rapid, with more than a doubling of birth weight and a 50% increase in body length.[17] The velocity of statural growth, which may reach as much as 30 cm/year in the first 2 months of life, decreases to a third of this rate by 10 months and continues to decline sharply until 2-3 years of age.[18] After 2 years of age rates of weight gain and statural growth show a slow, downward trend and reach a nadir just before the beginning of the pubertal growth spurt, sometime between ages 9 and 15.[19] In order to minimise the confounding influence of combining disparate age groups we conducted a systematic review and meta-analysis of all available randomized controlled trials (RCTs), meeting the EURRECA inclusion criteria, which investigated the relationship between zinc intake and growth (height, weight gain, growth z scores) in children aged 1 -8 years.

METHODS

Search strategy

This research was conducted within the framework of the European Micronutrient Recommendations Aligned (EURRECA) Network of Excellence, that aims to harmonise the approach to setting the micronutrient requirements for optimal health in European populations (www.eurreca.org). This review was part of a wider review process to identify studies assessing the effect of zinc intake on different outcomes (biomarkers of zinc status and health outcomes). The wider searches were performed in literature published up to and including February 2010 using MEDLINE, Embase, and Cochrane, using search terms for

['study designs in humans'] AND [zinc] AND [intake OR status]. An updated search was conducted in December 2013. Both indexing and text terms were used. The full Ovid MEDLINE search strategy can be found as Supplementary information available at EJCN's website. Reference lists of retrieved articles and published literature reviews were also checked for relevant studies. Authors were contacted to request missing data or clarify methods or results. The search process is illustrated in Figure 1.

Inclusion/exclusion criteria

Included studies were RCTs in apparently healthy child populations aged from 1 to 8 years that supplied supplemental zinc as an oral dose or as part of a fortified meal. If supplemental zinc was provided as a component of a fortified meal, studies were only included if zinc was the only constituent that was different between treatment groups. Only studies that reported sufficient data or had sufficient data obtainable from the authors to estimate $\hat{\beta}$and SE($\hat{\beta}$) for the assumed linear relation on the $\log_e$-$\log_e$ scale were included. Studies were excluded if they included infants aged <12 months or pubertal children aged ≥ 9 years, were conducted in animals, or were group randomized controlled trials (community trials), case studies, uncontrolled trials, commentaries, reviews, or duplicate publications from the same study. Group randomised controlled trials were excluded from all reviews conducted by the EURRECA consortium due to the increased risk of confounding factors, such as the outbreak of disease, food shortage or differing school hours specific to each localized group, influencing specific outcomes of interest. Studies were excluded if children were hospitalised, had severe protein-energy malnutrition or a chronic disease or if supplemental zinc was provided for less than 2 weeks. Only studies available in languages (English, Dutch, French, German, Hungarian, Italian, Norwegian, Polish, Spanish, Greek and Serbian) spoken by the EURRECA Network were included.

Selection of articles

Of 9653 identified articles in the wider 2010 and updated 2013 search on zinc intake, status and priority health outcomes in all populations, 5042 were excluded based upon screening of the title and abstract. Two independent reviewers screened 10% of the abstracts in duplicate and any discrepancies were discussed before screening the remaining references. Following subdivision into appropriate population groups the full texts of the 340 manuscripts were assessed to determine inclusion and exclusion by two independent reviewers and disagreements rectified through discussion. 292 studies were excluded because they did not meet the inclusion criteria. Of the remaining 48 studies, 29 studies were excluded because they had not investigated the relationship between zinc intake and childhood growth, but related either intake to status directly and were reported elsewhere[20] or to a health endpoint other than growth. Six papers identified as reporting zinc intake and growth data were omitted from the review because there was lack of sufficient data on growth to calculate effect size, such as reporting growth velocity with no baseline data, or not providing the standard deviation or means to calculate the SD. A further 4 studies were omitted from the meta-analysis because they included children older than 8 years or younger than 12 months, despite the reported mean falling into the eligible age range. For the purpose of this review, 9 RCTs met our inclusion criteria. As one paper,[21] assessed three zinc doses in separate groups of participants, eleven estimates of zinc intake and child growth were eligible for meta-analysis.

Data extraction

For each of the identified manuscripts, data were extracted into a standardized database. All data extracted from the papers were checked in duplicate. Extracted data included population

149 characteristics, dose of zinc in intervention and placebo supplements, duration of the study,
150 dietary intake of zinc, weight, height for age (HAZ), weight for age (WAZ), length for age
151 (LAZ), weight for height (WHZ) and weight for length (WLZ).
152
153 *Data synthesis*
154 If a change in weight or z-score was reported as well as the baseline data, the final value was
155 calculated. If dietary intake of zinc (in addition to the intervention) was not reported we used
156 a value of 5.65 mg/day, this was the mean dietary intake level of the RCTs (n=8) that did
157 report dietary zinc intake. In instances where a factorial design was used only data where zinc
158 was the only difference could be used. In the meta analyses, one study that included three
159 zinc-treated groups and one control group was treated as three independent estimates.[21] Four
160 studies reported growth data at more than one time point and the growth data at the final time
161 point was used for 2 of the studies,[22,23] for the other two studies the growth data from the 6
162 month and 3 month time point respectively was used as this was the closest measurement
163 after the supplementation period ceased.[24,25]
164
165 *Statistical analyses*
166 Pooled meta-analyses were performed combining the evidence from the nine RCTs identified
167 in the search. The transformations used to derive coherent single-study estimates from the
168 available summary statistics per study have been described elsewhere.[26] In short, we
169 estimated an intake-growth regression coefficient ($\hat{\beta}$) for each individual study, based on the
170 assumption of a linear relation on the $\log_e$-$\log_e$-scale (natural logarithm of intake versus
171 natural logarithm of status). Algebraically deriving an estimate from each study of the
172 regression coefficient ($\hat{\beta}$) and its standard error (SE($\hat{\beta}$)) enabled us to compare the results
173 from studies with heterogeneously reported associations and effects. We calculated the

overall pooled $\hat{\beta}$ and SE($\hat{\beta}$) using random effects meta-analysis, which estimates the between-study variance using the method of DerSimonian and Laird and used this estimate to modify the weights used to calculate the summary estimate. Residual heterogeneity between studies was evaluated using the I^2 statistic. Meta analyses were run for six measures of growth; weight, HAZ, LAZ, WAZ, WHZ and WLZ. The statistical transformations to obtain $\hat{\beta}$'s and SE($\hat{\beta}$)'s were performed using GenStat version 13-SP2 (VSN International Ltd., http://www.vsni.co.uk/) and the meta-analysis was performed using STATA version 11.0 (College Station, TX), with statistical significance defined as $P<0.05$.

Assessment of risk of bias in included studies

In order to assess the quality of the study and the risk of bias, indicators of internal validity were collected during data extraction. Based on the indicators, two independent reviewers assessed the overall risk of bias and each study was classified as low, moderate or high risk. The criteria for judging these indicators were adapted from the Cochrane Handbook.[27]

RESULTS

Eleven estimates of zinc intake and child growth in nine RCTs were eligible for meta-analysis (Table 1). All studies were RCTs published between 1983 and 2008 which reported zinc intake and a growth outcome. The eleven estimates included a total of 1316 participants with sample sizes ranging from 20 to 165. One study was conducted in Africa, five in Central and South America, two in North America, and one in the Indian Sub-continent. All of the studies in this meta-analysis had low initial mean HAZ scores, below or approaching <-2.0 with varying levels of stunting reported. Gibson *et al*[22] included only male children and the remaining studies provided combined data on both boys and girls. Zinc was provided as zinc sulphate,[21-25,28,29] zinc methionine[30] or amino acid chelate as a chewable supplement,[31]

dissolved in a flavoured solution[30.], fresh fruit juice[22,23] or as a syrup[21,24,25,28,29.] Only two studies reported that they attempted to administer the zinc under fasting condition[21,29]. The duration of the studies ranged from 2 to 12 months and the supplementation periods ranged from 14 days to 12 months. Supplement doses ranged from 3-20 mg Zn/d (median 10 mg) and the doses were provided daily in most studies.[21,22,24,25,28,29] Some studies, however, provided zinc supplements several times per week[23,30,31] resulting in daily dose equivalents ranging from 7.14 to 14.29 mg zinc/day.

Weight

Weight was assessed in three studies.[21,23,31] Whilst weight gain was observed to occur in all included studies in both zinc supplemented and placebo groups, no significant differences between the zinc supplemented and placebo groups at the end of the study were reported (Table 1). Consequently no significant pooled effect of zinc supplementation was found for weight change (pooled beta-coefficient of 0.01; 95% CI -0.01, 0.02; Fig 2). The studies in this meta-analysis were homogenous (I-squared 0.0%, p=0.852).

HAZ Score

None of the 7 studies that reported HAZ scores[22-24,28-31] found a significant difference between the zinc supplemented and placebo groups at the end of the study and a pooled analysis found no significant association between zinc supplementation and change in HAZ score (pooled beta-coefficient 0.04; 95% CI -0.13, 0.22; Fig 3). The studies in this meta-analysis were homogenous (I-squared 48.6%, p=0.070).

WAZ Score

Eight studies reported WAZ scores.[21-25,28,30,31] None of these studies reported a significant difference in WAZ score between the zinc supplemented and placebo groups at the end of the study. Rahman *et al*[25] reported WAZ score gains in both the zinc supplemented and placebo group but the difference between the two groups was not significantly different. Our pooled analysis revealed no statistically significant association between zinc supplementation and change in WAZ score in children aged between 1-8 years (pooled beta-coefficient 0.04; 95% CI: -0.04, 0.12; Fig 4). The studies in this meta-analysis were highly homogenous (I-squared 0.0%, p=0.586).

LAZ Score

Only two studies investigated the relationship between LAZ and zinc supplementation and neither found a significant difference between zinc supplemented and placebo groups at the end of the study, although both reported an increased LAZ in both zinc supplemented and placebo groups over the duration of the studies.[21,25] Our pooled analysis confirmed that zinc supplementation was not significantly associated with a change in LAZ score in children aged between 1-8 years (pooled beta-coefficient -0.001; 95% CI -0.11, 0.10; Fig not shown). The studies in this meta-analysis were homogenous (I-squared 0.0%, p=0.780).

WLZ Score

Two studies investigated the relationship between WLZ and zinc supplementation and neither found a significant difference in WLZ score between the zinc supplemented and placebo groups at the end of the study.[21,25] Wuehler *et al*[21] reported an improved WLZ score over time in both zinc supplemented and placebo groups, whilst Rahman *et al*[25] reported a decline in WLZ scores over time in both zinc supplemented and placebo groups. A pooled analysis confirmed that zinc supplementation was not significantly associated with a change in WLZ

score (pooled beta-coefficient 0.05; 95% CI: -0.04, 0.14; Fig not shown). The studies in this meta-analysis were homogenous (I-squared 0.0%, p=0.612).

WHZ Score

Four studies investigated WHZ score in children[22,28-30] but none found a significant difference in WHZ score between the zinc supplemented and placebo groups at the end of the study. A pooled analysis confirmed that zinc supplementation was not significantly associated with a change in WHZ score in this population (pooled beta-coefficient 0.02; 95% CI -0.11, 0.16; Fig 5). The studies in this meta-analysis were homogenous (I-squared 0.0%, p=0.705).

Risk of bias

The risk of bias was low for Rahman *et al*[25] and Wuehler *et al*[21] moderate for Walravens *et al*[28], Sempertegui *et al*[24] and Kikafunda *et al*[23] and high for the remaining four studies (Supplementary information is available at EJCN's website).[22,29-31] Papers were given a high risk of bias rating due to reasons such as insufficient information provided on sequence generation and/or allocation, study blinding, drop-outs and funding bodies.

DISCUSSION

This systematic review was undertaken to investigate the association between zinc intake and indices of growth in children aged between 1 and 8 years of age. Eleven estimates in nine RCTs, which enrolled a total of 1316 children, were included in seven meta-analyses. In pooled analyses, no statistically significant effects of zinc supplementation were found on weight, HAZ, WAZ, LAZ, WHZ and WLZ scores in children of this age group. A major strength of the current review is the meta-analysis of statistically homogenous studies.

Although previous meta-analyses found statistically significant effect sizes on various aspects of child growth, all have suffered from high heterogeneity.

Four systematic reviews have been published that have investigated the relationship between zinc supplementation and growth in children, but there is considerable variability in their review inclusion criteria making it difficult to provide firm conclusions about the nature of this relationship.[13-16] In contrast to our study, the two systematic reviews by Brown *et al*[13,14] reported statistically significant positive effects of zinc supplementation on linear growth and weight gain. A marginally statistically significant effect of zinc on change in WHZ was reported by Brown *et al*[14], but not in their earlier study.[13] Imdad *et al*[16] also reported a significant positive effect of zinc supplementation on linear growth. Statistically significant heterogeneity was found among the studies included in linear growth and weight gain meta-analyses in all three reviews, likely to be due in part to the inclusion of data from infants, children and/or adolescents. In addition, Brown *et al* included hospitalised, severely malnourished children in their 2002 meta-analyses[13], although excluded such children in their subsequent review.[14]

Our findings confirm those of Ramakrishnan *et al*[15] who found no significant effect of zinc supplementation on height or weight gain in 43 studies of children under 5 years of age. They did, however, report a small positive effect (effect size = 0.06; 95% CI: 0.006, 0.11) on change in WHZ. This review differs from ours in that more than half of their included studies were conducted in infants (initial age <12 months) and some studies included small-for-gestational age infants.

Our review has combined homogenous studies to provide an accurate estimate of the influence of zinc supplementation on measures of growth in children. We achieved high homogeneity in our meta-analyses by restricting the age group. We also excluded studies that have been included in previous reviews that involved anaemic or malnourished children, children who were low birth weight or small for gestational age and community trials.

Whilst all studies included in our meta-analyses were undertaken in individuals without chronic disease or severe protein-energy malnutrition, other factors such as infection and inflammation may also have gone unreported. For example, only one study screened and excluded participants with parasitic infection,[29] other studies treated pre-existing micronutrient deficiencies by supplementing the children with multivitamin and/or mineral supplements during the baseline[31] or pre-baseline[21] period. Other limitations include the absence of large well designed trials, lack of studies that attempt to administer zinc under fasting conditions to avoid the influence of dietary factors such as phytate on zinc bioavailability, and the lack of data provided on baseline nutritional status which make it difficult to identify the conditions under which these interventions may be beneficial. The non significant effect of supplemental zinc on childhood growth identified in this meta analysis, however, cannot be explained by an ineffective absorption of zinc from a supplement per se because the fractional absorption of zinc from supplements is comparable to that of a phytate free meal[32,33].

CONCLUSIONS

The methods employed to conduct this review were thorough and robust allowing only the most rigorous and well-designed studies to be included, while reducing the impact that

confounding factors may have. The resulting meta analyses suggested no statistically significant improvement of several indices of childhood growth following zinc supplementation in children aged 1-8 years of age. As most of the studies included in the review involved children who were stunted, it is likely that multiple micronutrient deficiencies exist which is why zinc alone did not significantly improve growth.

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349

350 **Conflict of interest statement**

351 The authors declare that there are no competing financial interests in relation to the work
352 described in this manuscript.

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REFERENCES

1 Brown KH, Wuehler SE, Peerson JM. The importance of zinc in human nutrition and estimation of the global prevalence of zinc deficiency. *Food Nutr Bull* 2001; **22:** 113-125.

2 Hotz C, Brown KH. International Zinc Nutrition Consultative Group (IZiNCG). Assessment of the risk of zinc deficiency in populations and options for its control. *Food Nutr Bull 2004*; **25**: S94-S203.

3 Prasad AS. Impact of the discovery of human zinc deficiency on health. *Journal of Am Coll Nutr* 2009: **28**: 257-265.

4 Caulfield L, Black R. Zinc Deficiency. In: Ezzati M, Lopez A, Rodgers A, Murray C (eds). *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors.*World Health Organization: Geneva, Switzerland, 2004, **1**, pp 257–280.

5 Black RE, Allen LH, Bhutta ZA, Caulfield LE, De Onis M, Ezzati M *et al*. Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 2008; **371**: 243-260.

6 Gibson RS. Zinc: the missing link in combating micronutrient malnutrition in developing countries. *Proc Nutr Soc* 2006; **65:** 51-60.

7 Walker CLF, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA *et al*. Childhood Pneumonia and Diarrhoea 1 Global burden of childhood pneumonia and diarrhoea. *Lancet* 2013*;* **381:** 1405-1416.

8 Prasad AS. Discovery of human zinc deficiency and studies in an experimental human model. *Am J Clin Nutr* 1991; **5:** 403-412.

9 Hess SY, Lonnerdal B, Hotz C, Rivera JA, Brown KH. Recent advances in knowledge of zinc nutrition and human health. *Food Nutr Bull* 2009; **30:** S5-S11.

10 Mozaffair-Khosravi H, Shakiba M, Eftekhari MH, Fatehi F. Effects of zinc supplementation on physical growth in 2-5 year old children. *Biol Trace Elem Res* 2009; **128:** 118-127.

11 Gibson RS, Hess SY, Hotz C, Brown KH. Indicators of zinc status at the population level: a review of the evidence. *Br J Nutr* 2008; **99:** S14-S23.

12 De Onis M, Blossner M, Borghi E. Prevalence and trends of stunting among pre-school children, 1990–2020. *Public Health Nutr* 2012; **15**: 142-148.

13 Brown KH, Peerson JM, Rivera, J, Allen LH. Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2002; **75**: 1062-1071.

14 Brown KH, Peerson JM, Baker SK, Hess SY. Preventive zinc supplementation among infants, preschoolers, and older prepubertal children. *Food Nutr Bull* 2009; **30:** S12-S40.

15 Ramakrishnan U, Nguyen P, Martorell R. Effects of micronutrients on growth of children under 5 y of age: meta-analyses of single and multiple nutrient interventions. *Am J Clin Nutr* 2009; **89:** 191-203.

16 Imdad A, Bhutta ZA. Effect of preventive zinc supplementation on linear growth in children under 5 years of age in developing countries: a meta-analysis of studies for input to the lives saved tool. *BMC Public Health* 2011; **11**: S22-S35.

17 Underwood LE. Special considerations in the design of trials involving children. *J Nutr* 1999; ***129***: 264S-269S.

18 Underwood LE, Van Wyk JJ. Normal and aberrant growth. In: Wilson J, Foster D (eds). *Williams Textbook of Endocrinology*, WB Saunders: Philadelphia, PA, USA, 1991, pp 1097–1137.

19 Stettler N, Bhatia J, Parish A, Stallings VA. Feeding healthy infants, children, and adolescents. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, (eds). *Nelson Textbook of Pediatrics,* 19th edn. Saunders Elsevier: Philadelphia, PA, USA, 2011, pp 160-169.

20 Moran VH, Stammers A-L, Medina MW, Patel S, Dykes F, Souverein OW *et al*. The Relationship between Zinc Intake and Serum/Plasma Zinc Concentration in Children: A Systematic Review and Dose-Response Meta-Analysis. *Nutrients* 2012; **4**: 841-858.

21 Wuehler SE, Sempertegui F, Brown KH. Dose-response trial of prophylactic zinc supplements, with or without copper, in young Ecuadorian children as risk of zinc deficiency. *Am J Clin Nutr* 2008; **87**: 723-733.

22 Gibson RS, Vanderkooy PDS, MacDonald AC, Goldman A, Ryan BA, Berry M. A growth-limiting, mild zinc-deficiency syndrome in some Southern Ontario boys with low height percentiles. *Am J Clin Nutr* 1989; **49**: 1266-1273.

23 Kikafunda JK, Walker AF, Allan EF, Tumwine JK. Effect of zinc supplementation on growth and body composition of Ugandan preschool children: a randomised, controlled, intervention trial. *Am J Clin Nutr* 1998; **68**: 1261-1266.

24 Sempertegui F, Estrella B, Correa E, Aguirre L, Saa B, Torres M *et al*. Effects of short-term zinc supplementation on cellular immunity, respiratory symptoms, and growth of malnourished Equadorian children. *Eur J Clin Nutr* 1996; **50**: 42-46.

25 Rahman MM, Tofail F, Wahed MA, Fuchs GJ, Baqui AH, Alvarez JO. Short-term supplementation with zinc and vitamin A has no significant effect on the growth of undernourished Bangladeshi children. *Am J Clin Nutr* 2002; **75**: 87-91

26 Souverein OW, Dullemeijer C, Van ‘T Veer P, Van De Voet H. Transformations of summary statistics as input in meta-analysis for linear dose-response models on a

logarithmic scale: A methodology developed within EURRECA. *BMC Med Res Methodol* 2012; **12**: 57 doi:10.1186/1471-2288-12-57.

27 Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews for Interventions*, Version 5.0.2 (updated September 2009). The Cochrane Collaboration: Chichester, UK, 2009.

28 Walravens PA, Krebs NF, Hambidge KM. 1983. Linear growth of low income preschool children receiving a zinc supplement. *Am J Clin Nutr* 1983; **38**: 195-201.

29 Silva APR, Vitolo MR, Zara LF, Castro CFS. Effects of zinc supplementation on 1- to 5-year old children. *J Pediatr* 2006; **82**: 227-231.

30 Rosado JL, Lopez P, Munoz E, Martinez H, Allen LH. Zinc supplementation reduced morbidity, but neither zinc nor iron supplementation affected growth or body composition of Mexican pre-schoolers. *Am J Clin Nutr* 1997; **65**: 13-19.

31 Cavan KR, Gibson RS, Grazioso CF, Isalgue AM, Ruz M, Solomons NW. Growth and body composition of periurban Guatemalan children in relation to zinc status: a longitudinal zinc intervention trial. *Am J Clin Nutr* 1993; **57**: 344-352.

32 Tran CD, Miller LV, Krebs NF, Lei S, Hambidge KM. Zinc absorption as a function of the dose of zinc sulfate in aqueous solution. *Am J Clin Nutr* 2004; **80**: 1570-1573.

33 Hambidge KM, Miller LV, Westcott JE, Sheng X, Krebs NF. Zinc bioavailability and homeostasis. *Am J Clin Nutr* 2010; **91**: 1478S-1483S.

448 Figure Legends

449

450 Figure 1. Study selection process

451

452 Figure 2. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on
453 weight gain in children aged 1-8 years old. Beta's represent the regression coefficients for the
454 linear association between log transformed zinc intake and weight growth.

455

456 Figure 3. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on
457 HAZ score in children aged 1-8 years old. Beta's represent the regression coefficients for the
458 linear association between log transformed zinc intake and HAZ score
459

460 Figure 4. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on
461 WAZ score in children aged 1-8 years old. Beta's represent the regression coefficients for the
462 linear association between log transformed zinc intake and WAZ score.

463

464 Figure 5. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on
465 WHZ score in children aged 1-8 years old. Beta's represent the regression coefficients for the
466 linear association between log transformed zinc intake and WHZ score.

467

Figure 1. Study selection process for systematic review.

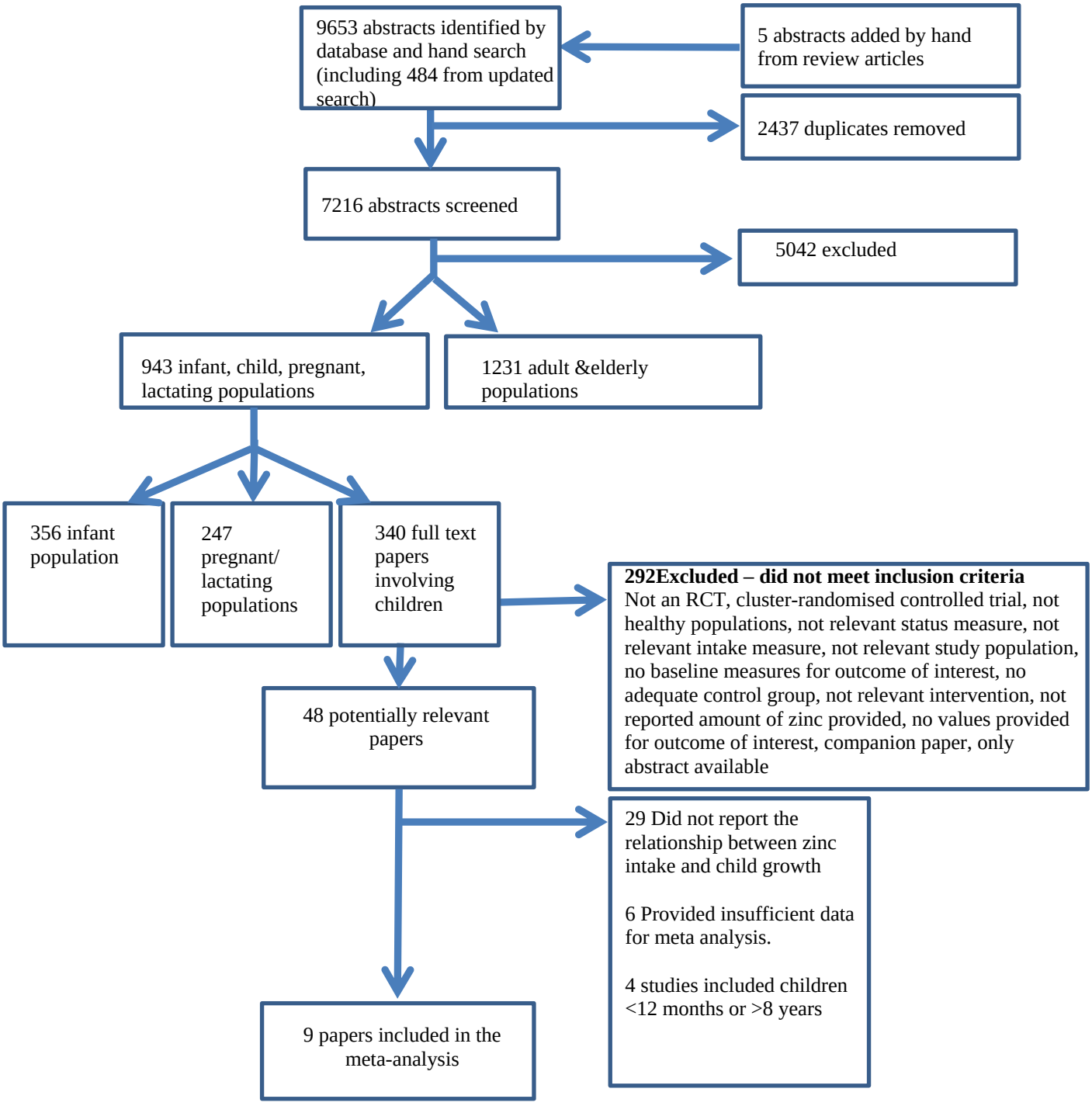

Figure 2. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on weight gain the children ages 1-8 years old. Beta's represent the regression coefficients for the linear association between loge transformed zinc intake and weight growth.

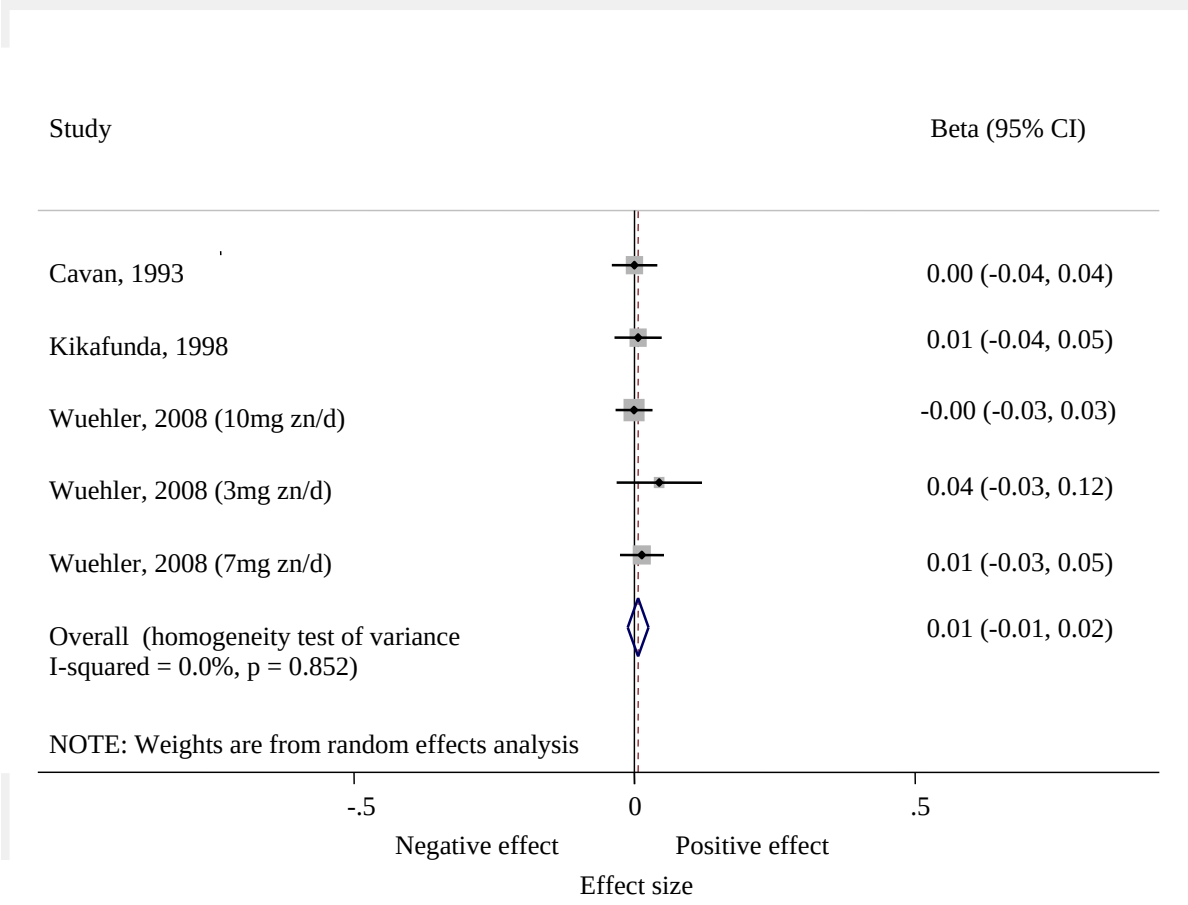

Figure 3. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on HAZ score in children ages 1-8 years old. Beta's represent the regression coefficients for the linear association between loge transformed zinc intake and HAZ score.

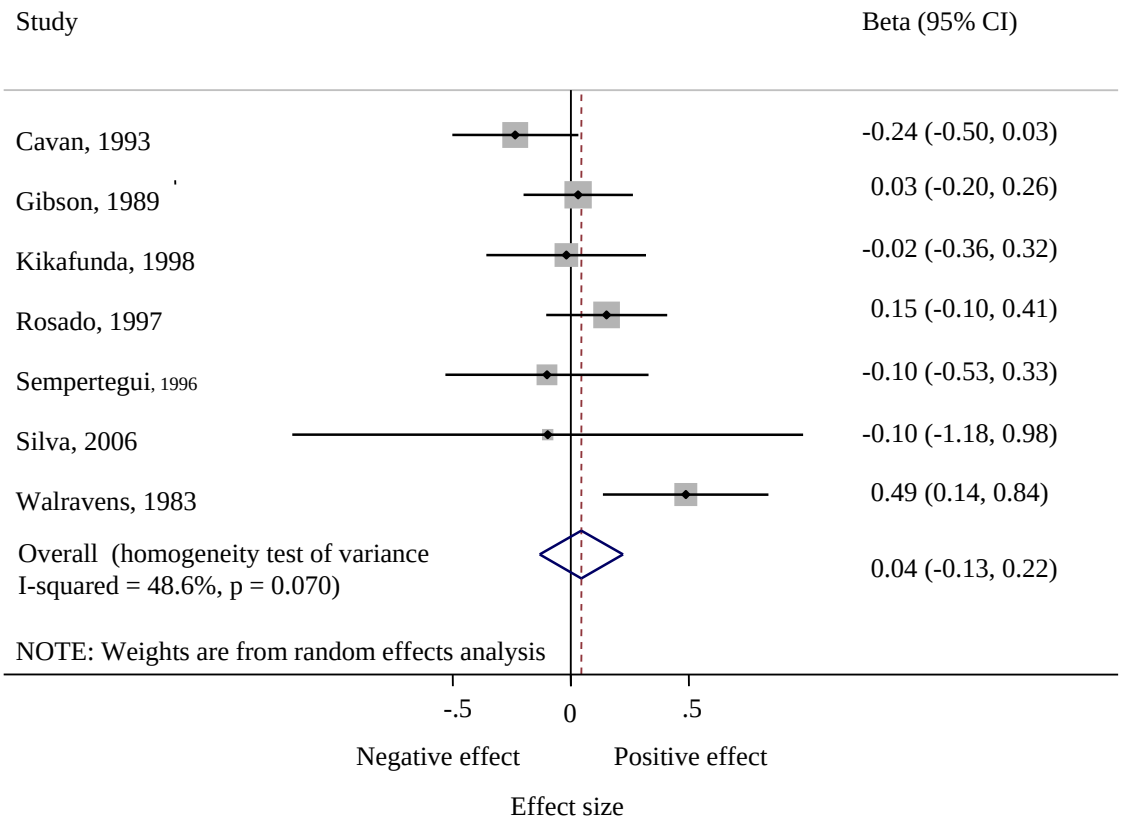

Figure 4. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on WAZ score in children ages 1-8 years old. Beta's represent the regression coefficients for the linear association between loge transformed zinc intake and WAZ score.

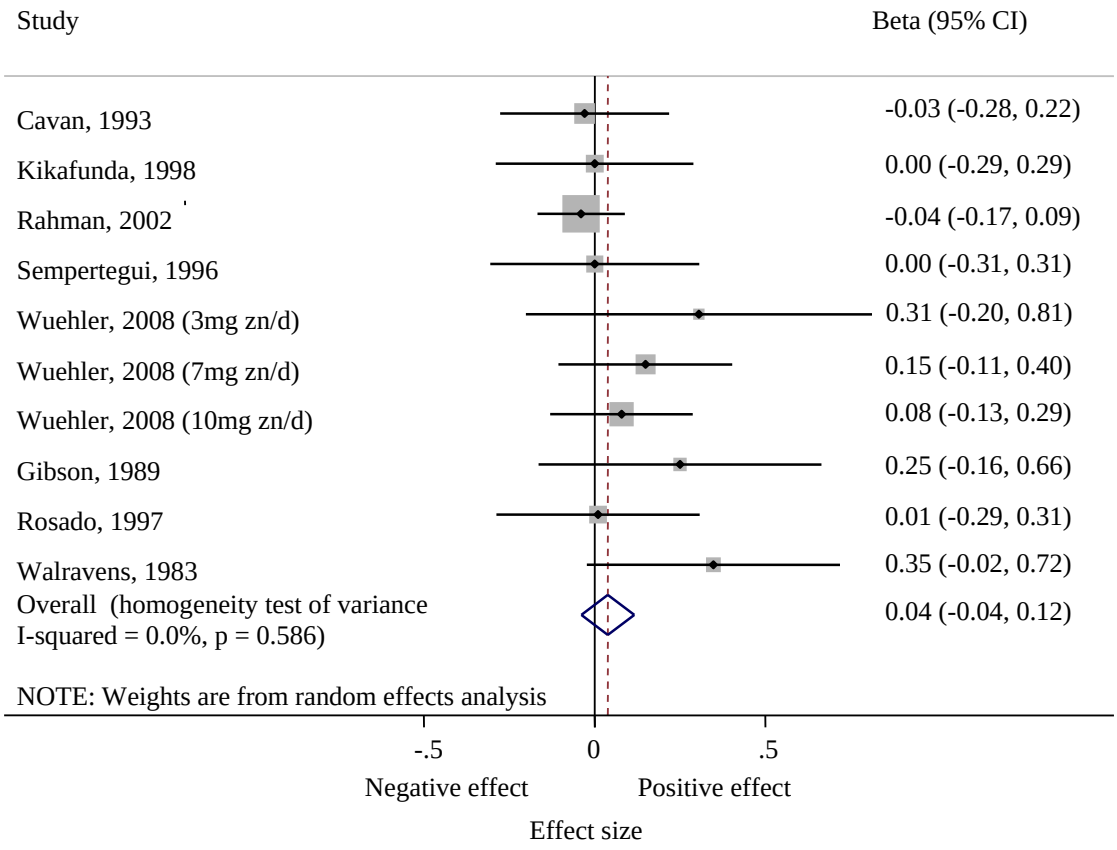

Figure 5. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on WHZ score in children ages 1-8 years old. Beta's represent the regression coefficients for the linear association between loge transformed zinc intake and WHZ score.

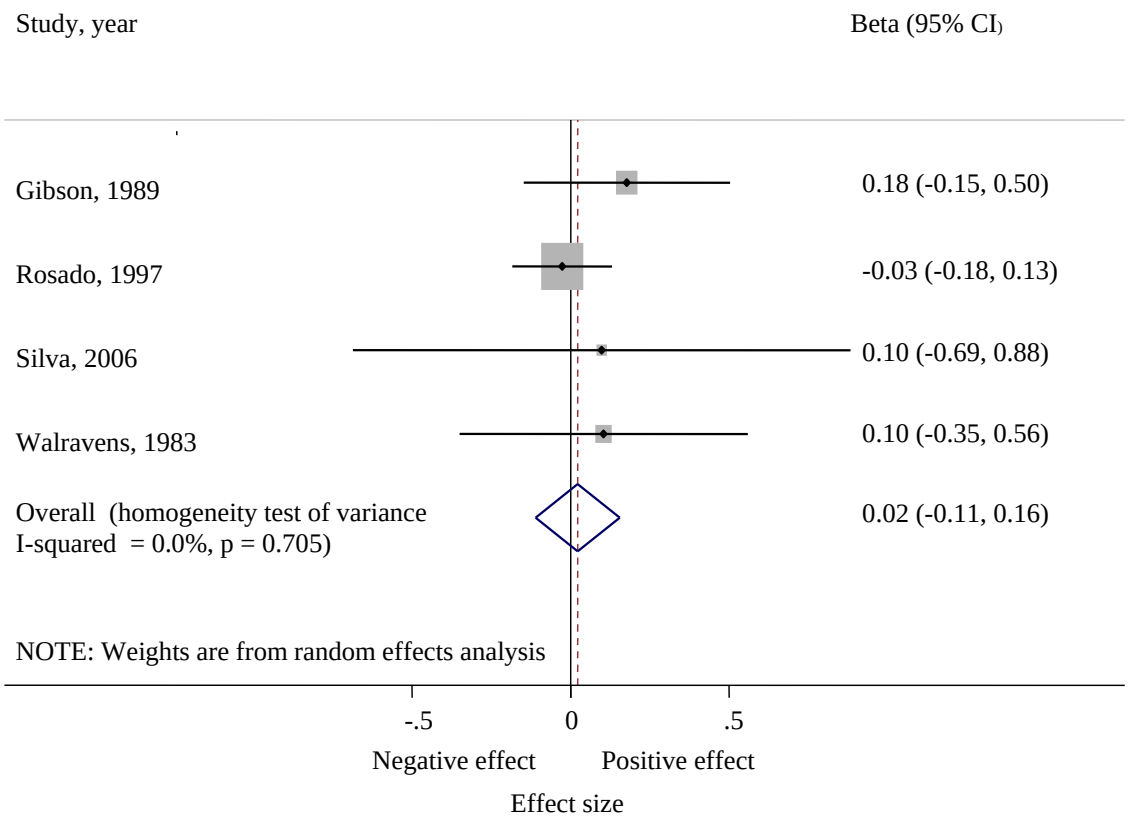

Table 1: Summary of included trials reporting the effect of dietary zinc intake on growth outcomes in children.

Study, year, country	**Sex, Age, Stunting**	**Treatment groups**	**Micronutrient type**	**Study Duration** **Measurement Time point** **Supplementation Duration**	**Growth outcome Mean (SD)**		**Significant results**
Cavan *et al* (1993), Guatemala	Males and females aged 81.5 ±7.0 months[2]. Initial mean HAZ -1.4.	Placebo (n80) 10 mg Zn/d school days only (n76) (all participants also received MN supplements)	Amino Acid Chelate	25 weeks 25 weeks 25 weeks	HAZ Height (cm) WAZ Weight (kg) WHZ	(P) -1.28[1]±0.98 (Z) -1.52[1]±0.73 (P) 115.7[1]±4.96 (Z) 115.2[1]±4.74 (P) -0.76[1]±0.85 (Z) -0.79[1]±0.75 (P) 21[1]±2.59 (Z) 21[1]±2.89 (P) 0.23[1]±0.70 (Z) -0.31[1]±0.89	None
Gibson *et al* (1989), Canada	Males aged 59-95 months. Initial mean HAZ -1.4.	Placebo (n30) 10 mg Zn/d (n30)	Zinc Sulphate	12 months 12 months 12 months	HAZ WAZ WHZ	(P) -1.26±0.44 (Z) -1.23±0.44 (P) -1.26±0.44 (Z) -1.23±0.44 (P) -1.07±0.66 (Z) -0.90±0.57	None
Kikafunda *et al* (1998), Uganda	Males and females aged 33-89 months. Initial mean HAZ -0.7	Placebo (n54) 10 mg Zn/d 5 days per week (n59)	Zinc Sulphate	8 months 8 months 2 x 3 months supplemented phases, separated by a 2 month non supplemented phase.	HAZ Height (cm) WAZ Weight (kg)	(P) -0.48±0.95 (Z) -0.50±0.92 (P) 107.95±5.4 (Z) 108.10±5.5 (P) -0.27±0.7 (Z) -0.27±0.88 (P) 17.95±2.1 (Z) 18.06±2.1	None
Rahman *et al* (2002), Bangladesh	Males and females aged 12-35 months. Initial mean LAZ -2.4	Placebo (n160) 20mg Zn/d for 14 days (n165)	Zinc Sulphate	6 months 3 months 14 days	WAZ LAZ WLZ	(P) -2.19±0.89 (Z) -2.25±0.89 (P) -2.31±1.18 (Z) -2.42±1.16 (P) -1.08±0.76 (Z) -1.04±0.74	None
Rosado *et al* (1997), Mexico	Males and females aged 18-36 months.	Placebo (n47) 20 mg Zn/d 5 days per week (n48)	Zinc Methionine	12 months 12 months	HAZ WAZ	(P) -1.67±0.89 (Z) -1.44±1.03 (P) -1.15±0.59	None

	Initial mean HAZ -1.7			12 months	WHZ	(Z) -1.14±0.88 (P) -0.11±0.59 (Z) -0.15±0.59	
Sempertegui *et al* (1996), Ecuador	Males and females aged 12-59 months. Initial mean HAZ -2.0	Placebo (n25) 10mg Zn/d (n23)	Zinc Sulphate	120 days 60 days 60 days	HAZ WAZ	(P) -1.7±0.8 (Z) -1.8±0.7 (P) -1.30±0.5 (Z) -1.30±0.6	None
Silva *et al* (2006), Brazil	Males and females aged 12-59 months. Initial mean HAZ -2.0	Placebo (n30) 10 mg/d Zn/d (n28) (all participants also received Fe fortified milk)	Zinc Sulphate	4 months 4 months 4 months	HAZ WHZ	(P) -1.6±1.6 (Z) -1.7±2.6 (P) 0.6±1.6 (Z) 0.7±1.5	None
Walravens *et al* (1983), USA	Males and females aged 24-72 months. Initial mean HAZ -2.0	Placebo (n20) 5 mg Zn/d (n20)	Zinc Sulphate	12 months 12 months 12 months	HAZ WAZ WHZ	(P) -2.22±0.6* (Z) -1.80±0.34* (P) -1.71±0.55 (Z) -1.41±0.48 (P) -0.45±0.58 (Z) -0.36±0.68	HAZ was sig ($p<0.05$) higher in the zn supplemented group with the male but not female subgroup analysis.
Wuehler *et al* (2008), Ecuador	Males and females aged 12-36 months. Initial mean LAZ -2.3	Placebo (n108) (S1) 3 mg Zn/d (n103) (S2) 7 mg Zn/d (n100) (S3) 10 mg Zn/d (n110)	Zinc Sulphate	6 months 6 months 6 months	WAZ Weight (kg) LAZ WLZ	(P) -1.26±0.8 (S1Z) -1.13±0.8 (S2Z) -1.14±0.7 (S3Z) -1.18±0.8 (P) 10.7±1.3 (S1Z) 10.9±1.3 (S2Z) 10.8±1.2 (S3Z) 10.7±1.4 (P) 10.7±1.3 (S1Z) 10.9±1.3 (S2Z) 10.8±1.2 (S3Z) 10.7±1.4 (P) -0.16±0.8 (S1Z) -0.01±0.9 (S2Z) -0.05±0.8 (S3Z) -0.13±1.0	None

[1] = Median

[2] = No age range reported

[*] = Significant result P=<0.05

MN = micronutrients

P = Placebo group

Z = Zinc group

S1 = Study 1

S2 = Study 2

S3 = Study 3