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- 1 The relationship between zinc intake and growth in children aged
- 2 1-8 years: a systematic review and meta-analysis.

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4 Running Title: Zinc and growth in children

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Abstract

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Background/Objectives: It is estimated that zinc deficiency affects 17% of the world's 26 population and because of periods of rapid growth, children are at an increased risk of 27 28 deficiency which may lead to stunting. This paper presents a systematic review and metaanalysis of the randomised controlled trials that assess zinc intake and growth in children 29 aged 1-8 years. This review is part of a larger systematic review by the European 30 Micronutrient Recommendations Aligned (EURRECA) Network of Excellence that aims to 31 harmonise the approach to setting micronutrient requirements for optimal health in European 32 33 populations (www.eurreca.org). Subject/Methods: Searches were performed of literature published up to and including 34 December 2013 using MEDLINE, Embase, and the Cochrane Library databases. Included 35 studies were RCTs in apparently healthy child populations aged from 1 to 8 years that 36 supplied zinc supplements either as capsules or part of a fortified meal. Pooled meta-analyses 37 were performed when appropriate. 38 Results: Nine studies met the inclusion criteria. We found no significant effect of zinc 39 supplementation of between 2 weeks to 12 months duration on weight gain, HAZ, WAZ, 40 LAZ, WHZ or WHZ scores in children aged 1-8 years. 41 Conclusion: Many of the children in the included studies were already stunted and may have 42 been suffering multiple micronutrient deficiencies and therefore zinc supplementation alone 43 44 may have only a limited effect on growth.

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

INTRODUCTION

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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. 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 nonindustrialised regions, also affect zinc absorption.^{6,7} Children are particularly vulnerable to zinc deficiency due to an increased requirement during periods of rapid growth. Einc 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,

73 Brown $et\ al^{13}$ pooled data from infants and pre-pubertal children; Ramakrishnan $et\ al^{15}$ and

due in part to inclusion of data from children with a wide age range in pooled analyses.

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.

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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 loge-loge scale were included. Studies were excluded if they included infants aged <12 months or pubertal children aged \ge 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.

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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 elsewhere²⁰ 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 metaanalysis.

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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

characteristics, dose of zinc in intervention and placebo supplements, duration of the study, dietary intake of zinc, weight, height for age (HAZ), weight for age (WAZ), length for age (LAZ), weight for height (WHZ) and weight for length (WLZ).

Data synthesis

If a change in weight or z-score was reported as well as the baseline data, the final value was calculated. If dietary intake of zinc (in addition to the intervention) was not reported we used a value of 5.65 mg/day, this was the mean dietary intake level of the RCTs (n=8) that did report dietary zinc intake. In instances where a factorial design was used only data where zinc was the only difference could be used. In the meta analyses, one study that included three zinc-treated groups and one control group was treated as three independent estimates.²¹ Four studies reported growth data at more than one time point and the growth data at the final time point was used for 2 of the studies,^{22,23} for the other two studies the growth data from the 6 month and 3 month time point respectively was used as this was the closest measurement after the supplementation period ceased.^{24,25}

Statistical analyses

Pooled meta-analyses were performed combining the evidence from the nine RCTs identified in the search. The transformations used to derive coherent single-study estimates from the available summary statistics per study have been described elsewhere. In short, we estimated an intake-growth regression coefficient $(\hat{\beta})$ for each individual study, based on the assumption of a linear relation on the \log_e - \log_e -scale (natural logarithm of intake versus natural logarithm of status). Algebraically deriving an estimate from each study of the regression coefficient $(\hat{\beta})$ and its standard error (SE $(\hat{\beta})$) enabled us to compare the results 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 I² 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 solution³⁰, 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).

222 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. 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. 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 248 meta-analysis were homogenous (I-squared 0.0%, p=0.612). 249 250 WHZ Score 251 Four studies investigated WHZ score in children^{22,28-30} but none found a significant difference 252 in WHZ score between the zinc supplemented and placebo groups at the end of the study. A 253 pooled analysis confirmed that zinc supplementation was not significantly associated with a 254 change in WHZ score in this population (pooled beta-coefficient 0.02; 95% CI -0.11, 0.16; 255 256 Fig 5). The studies in this meta-analysis were homogenous (I-squared 0.0%, p=0.705). 257 Risk of bias 258 The risk of bias was low for Rahman et al²⁵ and Wuehler et al²¹ moderate for Walravens et 259 al^{28} , Sempertegui et al^{24} and Kikafunda et al^{23} and high for the remaining four studies 260 (Supplementary information is available at EJCN's website). 22,29-31 Papers were given a high 261 risk of bias rating due to reasons such as insufficient information provided on sequence 262 generation and/or allocation, study blinding, drop-outs and funding bodies. 263 264 **DISCUSSION** 265 This systematic review was undertaken to investigate the association between zinc intake and 266 267 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 268 pooled analyses, no statistically significant effects of zinc supplementation were found on 269 weight, HAZ, WAZ, LAZ, WHZ and WLZ scores in children of this age group. A major 270

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-analyses¹³, 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-forgestational 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 baseline³¹ or pre-baseline²¹ 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}.

318 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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| 348 | growth regression coefficient $(\hat{\beta})$. |
| 349 | |
| 350 | Conflict of interest statement |
| | |
| 351 | The authors declare that there are no competing financial interests in relation to the work |
| 351 352 | The authors declare that there are no competing financial interests in relation to the work described in this manuscript. |
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| 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 | |
| 456 457 458 459 | Figure 3. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on HAZ score in children aged 1-8 years old. Beta's represent the regression coefficients for the linear association between log transformed zinc intake and HAZ score |
| 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. 9653 abstracts identified by 5 abstracts added by hand database and hand search from review articles (including 484 from updated search) 2437 duplicates removed 7216 abstracts screened 5042 excluded 943 infant, child, pregnant, 1231 adult &elderly lactating populations populations 356 infant 340 full text 247 population pregnant/ papers 292Excluded – did not meet inclusion criteria involving lactating Not an RCT, cluster-randomised controlled trial, not populations children healthy populations, not relevant status measure, not relevant intake measure, not relevant study population, no baseline measures for outcome of interest, no adequate control group, not relevant intervention, not 48 potentially relevant reported amount of zinc provided, no values provided papers for outcome of interest, companion paper, only abstract available 29 Did not report the relationship between zinc intake and child growth 6 Provided insufficient data for meta analysis. 4 studies included children <12 months or >8 years 9 papers included in the meta-analysis

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.

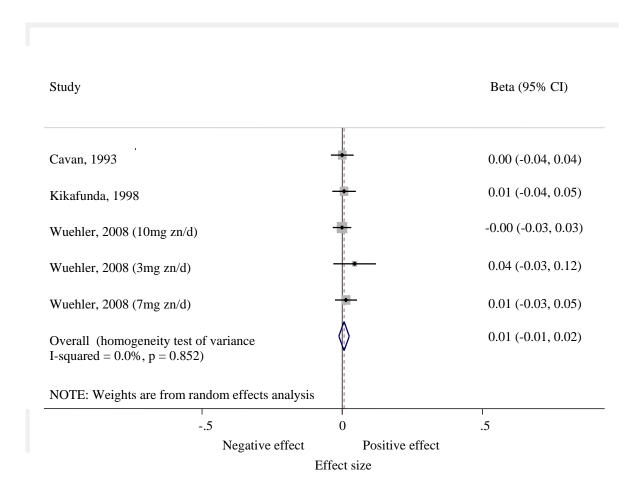


Figure 3. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on HAZ score in children ages 1-8 years old. Beta's represent the regression coefficients for the linear association between loge transformed zinc intake and HAZ score.

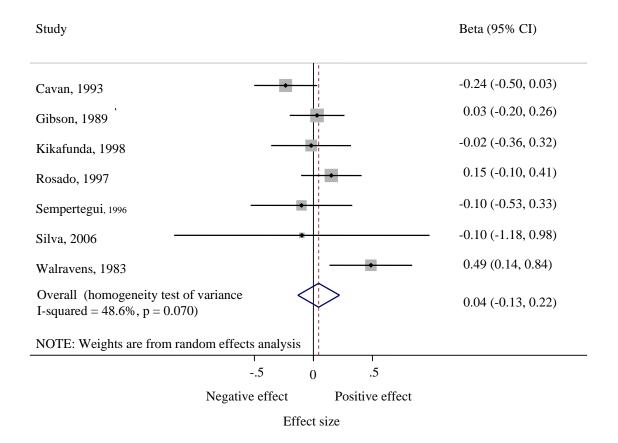


Figure 4. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on WAZ score in children ages 1-8 years old. Beta's represent the regression coefficients for the linear association between loge transformed zinc intake and WAZ score.

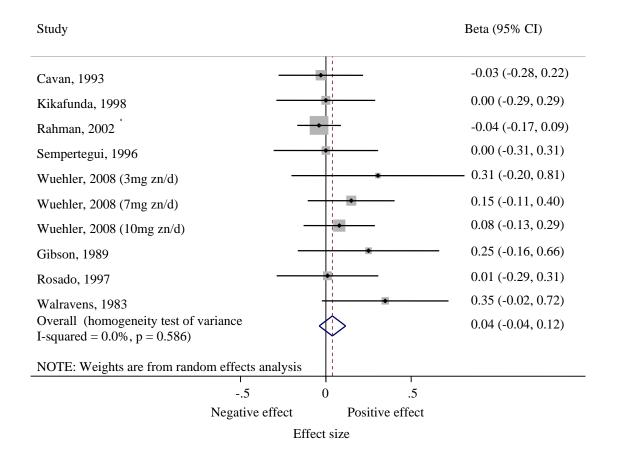


Figure 5. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on WHZ score in children ages 1-8 years old. Beta's represent the regression coefficients for the linear association between loge transformed zinc intake and WHZ score.

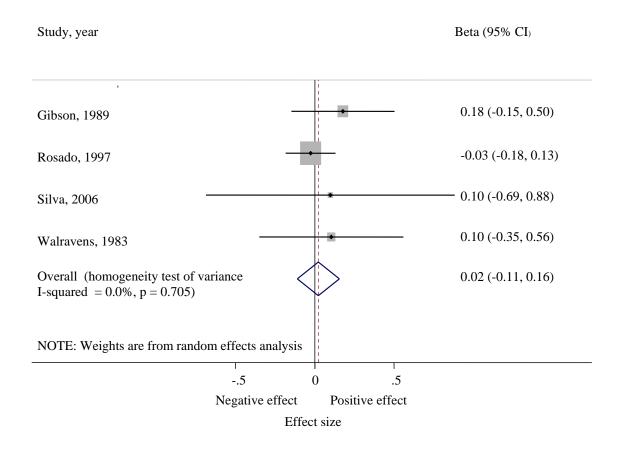


Table 1: Summary of included trials reporting the effect of dietary zinc intake on growth outcomes in children.

| Study, year, country | Sex, Age, Stunting | Treatment groups | Micronutrient type | Study Duration Measurement Time point Supplementation | Growth outcome Mean (SD) | | Significant results |
|--|--|---|-----------------------|---|-------------------------------------|---|---------------------|
| Cavan <i>et al</i> (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 | Duration 25 weeks 25 weeks 25 weeks | HAZ Height (cm) WAZ Weight (kg) WHZ | (P) $-1.28^{1}\pm0.98$ (Z) $-1.52^{1}\pm0.73$ (P) $115.7^{1}\pm4.96$ (Z) $115.2^{1}\pm4.74$ (P) $-0.76^{1}\pm0.85$ (Z) $-0.79^{1}\pm0.75$ (P) $21^{1}\pm2.59$ (Z) $21^{1}\pm2.89$ (P) $0.23^{1}\pm0.70$ (Z) $-0.31^{1}\pm0.89$ | 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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (1996), Ecuador | Males and females aged 12-59 months. | Placebo (n25) 10mg Zn/d (n23) | Zinc Sulphate | 120 days 60 days | HAZ WAZ | (P) -1.7±0.8 (Z) -1.8±0.7 (P) -1.30±0.5 | None |
| | Initial mean HAZ -2.0 | | | 60 days | | (Z) -1.30±0.6 | |
| Silva <i>et al</i> (2006), Brazil | Males and females aged 12-59 months. | Placebo (n30) 10 mg/d Zn/d (n28) | Zinc Sulphate | 4 months | HAZ | (P) -1.6±1.6 (Z) -1.7±2.6 | None |
| | Initial mean HAZ -2.0 | (all participants also received Fe fortified milk) | | 4 months | WHZ | (P) 0.6±1.6 (Z) 0.7±1.5 | |
| Walravens <i>et al</i> (1983), | Males and females aged 24-72 months. | Placebo (n20) 5 mg Zn/d (n20) | Zinc Sulphate | 12 months | HAZ | (P) -2.22±0.6* (Z) -1.80±0.34* | HAZ was sig (p<0.05) higher in the zn |
| ÙSA | Initial mean HAZ -2.0 | | | 12 months | WAZ | (P) -1.71±0.55 (Z) -1.41±0.48 | supplemented group with the male but not female |
| | | | | 12 months | WHZ | (P) -0.45±0.58 (Z) -0.36±0.68 | subgroup analysis. |
| Wuehler et al (2008), | Males and females aged 12-36 months. | Placebo (n108) (S1) 3 mg Zn/d (n103) | Zinc Sulphate | 6 months | WAZ | (P) -1.26±0.8 (S1Z) -1.13±0.8 | None |
| Ecuador | Initial mean LAZ -2.3 | (S2) 7 mg Zn/d (n100) (S3) 10 mg Zn/d (n110) | | 6 months | | (S2Z) -1.14±0.7 (S3Z) -1.18±0.8 | |
| | | | | 6 months | Weight (kg) | (P) 10.7±1.3 (S1Z) 10.9±1.3 (S2Z) 10.8±1.2 | |
| | | | | | LAZ | (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 | |
| | | | | | WLZ | (P) -0.16±0.8 (S1Z) -0.01±0.9 (S2Z) -0.05±0.8 (S3Z) -0.13±1.0 | |

 $^{^{1}}$ = 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