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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.**

3

4 **Running Title: Zinc and growth in children**

5

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22

23

24

25 Abstract

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

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

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

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

45

46

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

48

49 INTRODUCTION

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

58

59 Children are particularly vulnerable to zinc deficiency due to an increased requirement during
60 periods of rapid growth.⁶ Zinc deficiency may impair growth and contribute to stunting in
61 children.^{3,8,9} One suggested mechanism is altered growth hormone metabolism.¹⁰ It has been
62 estimated that 171 million children (167 million in developing countries) are stunted and 20%
63 of children under 5 years in low and middle income countries have a WAZ score (weight for
64 age Z score) of less than -2.⁵ While severe zinc deficiency is uncommon in European
65 populations, marginal deficiency is likely to be much more prevalent.¹¹ Although the global
66 prevalence of childhood stunting has decreased in the last decade (from 39.7% in 1990 to
67 26.7% in 2010), stunting remains a major public health problem.¹²

68

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

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

89

90 **METHODS**

91 *Search strategy*

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

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

105

106 *Inclusion/exclusion criteria*

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

124

125 *Selection of articles*

126 Of 9653 identified articles in the wider 2010 and updated 2013 search on zinc intake, status
127 and priority health outcomes in all populations, 5042 were excluded based upon screening of
128 the title and abstract. Two independent reviewers screened 10% of the abstracts in duplicate
129 and any discrepancies were discussed before screening the remaining references. Following
130 subdivision into appropriate population groups the full texts of the 340 manuscripts were
131 assessed to determine inclusion and exclusion by two independent reviewers and
132 disagreements rectified through discussion. 292 studies were excluded because they did not
133 meet the inclusion criteria. Of the remaining 48 studies, 29 studies were excluded because
134 they had not investigated the relationship between zinc intake and childhood growth, but
135 related either intake to status directly and were reported elsewhere²⁰ or to a health endpoint
136 other than growth. Six papers identified as reporting zinc intake and growth data were
137 omitted from the review because there was lack of sufficient data on growth to calculate
138 effect size, such as reporting growth velocity with no baseline data, or not providing the
139 standard deviation or means to calculate the SD. A further 4 studies were omitted from the
140 meta-analysis because they included children older than 8 years or younger than 12 months,
141 despite the reported mean falling into the eligible age range. For the purpose of this review, 9
142 RCTs met our inclusion criteria. As one paper,²¹ assessed three zinc doses in separate groups
143 of participants, eleven estimates of zinc intake and child growth were eligible for meta-
144 analysis.

145

146 *Data extraction*

147 For each of the identified manuscripts, data were extracted into a standardized database. All
148 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

174 overall pooled $\hat{\beta}$ and $SE(\hat{\beta})$ using random effects meta-analysis, which estimates the
175 between-study variance using the method of DerSimonian and Laird and used this estimate to
176 modify the weights used to calculate the summary estimate. Residual heterogeneity between
177 studies was evaluated using the I^2 statistic. Meta analyses were run for six measures of
178 growth; weight, HAZ, LAZ, WAZ, WHZ and WLZ. The statistical transformations to obtain
179 $\hat{\beta}$'s and $SE(\hat{\beta})$'s were performed using GenStat version 13-SP2 (VSN International Ltd.,
180 <http://www.vsn.co.uk/>) and the meta-analysis was performed using STATA version 11.0
181 (College Station, TX), with statistical significance defined as $P < 0.05$.

182

183 *Assessment of risk of bias in included studies*

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

188

189 **RESULTS**

190 Eleven estimates of zinc intake and child growth in nine RCTs were eligible for meta-
191 analysis (Table 1). All studies were RCTs published between 1983 and 2008 which reported
192 zinc intake and a growth outcome. The eleven estimates included a total of 1316 participants
193 with sample sizes ranging from 20 to 165. One study was conducted in Africa, five in Central
194 and South America, two in North America, and one in the Indian Sub-continent. All of the
195 studies in this meta-analysis had low initial mean HAZ scores, below or approaching < -2.0
196 with varying levels of stunting reported. Gibson *et al*²² included only male children and the
197 remaining studies provided combined data on both boys and girls. Zinc was provided as zinc
198 sulphate,^{21-25,28,29} zinc methionine³⁰ or amino acid chelate as a chewable supplement,³¹

199 dissolved in a flavoured solution³⁰, fresh fruit juice^{22,23} or as a syrup^{21,24,25,28,29}. Only two
200 studies reported that they attempted to administer the zinc under fasting condition^{21,29}. The
201 duration of the studies ranged from 2 to 12 months and the supplementation periods ranged
202 from 14 days to 12 months. Supplement doses ranged from 3-20 mg Zn/d (median 10 mg)
203 and the doses were provided daily in most studies.^{21,22,24,25,28,29} Some studies, however,
204 provided zinc supplements several times per week^{23,30,31} resulting in daily dose equivalents
205 ranging from 7.14 to 14.29 mg zinc/day.

206

207 *Weight*

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

214

215 *HAZ Score*

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

221

222 *WAZ Score*

223 Eight studies reported WAZ scores.^{21-25,28,30,31} None of these studies reported a significant
224 difference in WAZ score between the zinc supplemented and placebo groups at the end of the
225 study. Rahman *et al*²⁵ reported WAZ score gains in both the zinc supplemented and placebo
226 group but the difference between the two groups was not significantly different. Our pooled
227 analysis revealed no statistically significant association between zinc supplementation and
228 change in WAZ score in children aged between 1-8 years (pooled beta-coefficient 0.04; 95%
229 CI: -0.04, 0.12; Fig 4). The studies in this meta-analysis were highly homogenous (I-squared
230 0.0%, p=0.586).

231

232 *LAZ Score*

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

240

241 *WLZ Score*

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

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

250

251 *WHZ Score*

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

257

258 *Risk of bias*

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

264

265 **DISCUSSION**

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

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

274

275 Four systematic reviews have been published that have investigated the relationship between
276 zinc supplementation and growth in children, but there is considerable variability in their
277 review inclusion criteria making it difficult to provide firm conclusions about the nature of
278 this relationship.¹³⁻¹⁶ In contrast to our study, the two systematic reviews by Brown *et al*^{13,14}
279 reported statistically significant positive effects of zinc supplementation on linear growth and
280 weight gain. A marginally statistically significant effect of zinc on change in WHZ was
281 reported by Brown *et al*¹⁴, but not in their earlier study.¹³ Imdad *et al*¹⁶ also reported a
282 significant positive effect of zinc supplementation on linear growth. Statistically significant
283 heterogeneity was found among the studies included in linear growth and weight gain meta-
284 analyses in all three reviews, likely to be due in part to the inclusion of data from infants,
285 children and/or adolescents. In addition, Brown *et al* included hospitalised, severely
286 malnourished children in their 2002 meta-analyses¹³, although excluded such children in their
287 subsequent review.¹⁴

288

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

295

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

301

302 Whilst all studies included in our meta-analyses were undertaken in individuals without
303 chronic disease or severe protein-energy malnutrition, other factors such as infection and
304 inflammation may also have gone unreported. For example, only one study screened and
305 excluded participants with parasitic infection,²⁹ other studies treated pre-existing
306 micronutrient deficiencies by supplementing the children with multivitamin and/or mineral
307 supplements during the baseline³¹ or pre-baseline²¹ period. Other limitations include the
308 absence of large well designed trials, lack of studies that attempt to administer zinc under
309 fasting conditions to avoid the influence of dietary factors such as phytate on zinc
310 bioavailability, and the lack of data provided on baseline nutritional status which make it
311 difficult to identify the conditions under which these interventions may be beneficial. The
312 non significant effect of supplemental zinc on childhood growth identified in this meta
313 analysis, however, cannot be explained by an ineffective absorption of zinc from a
314 supplement per se because the fractional absorption of zinc from supplements is comparable
315 to that of a phytate free meal^{32,33}.

316

317

318 **CONCLUSIONS**

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

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

326

327

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329

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336

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344

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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.

353

354

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- 447

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.

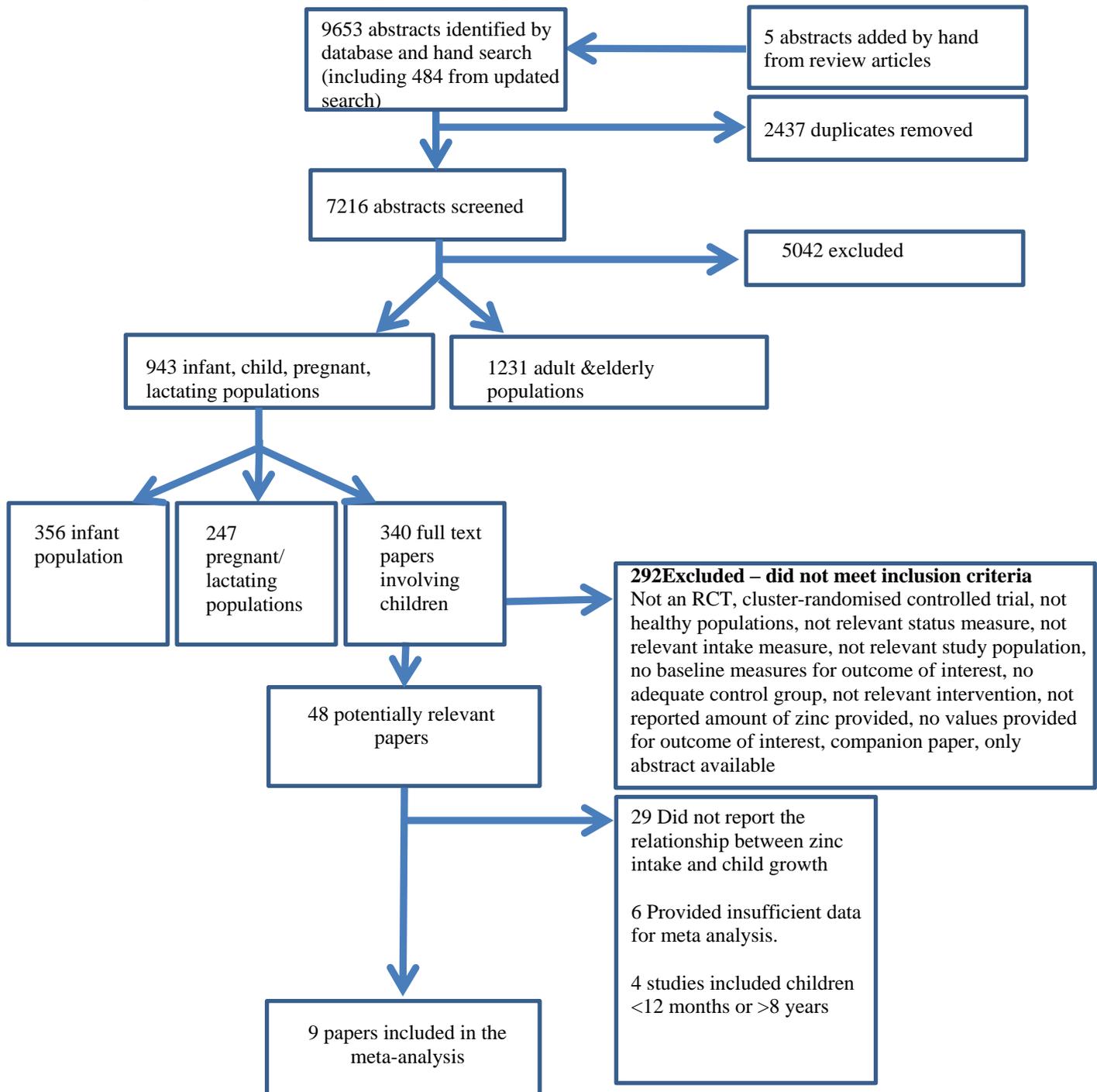


Figure 2. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on weight gain the children ages 1-8 years old. Beta's represent the regression coefficients for the linear association between loge transformed zinc intake and weight growth.

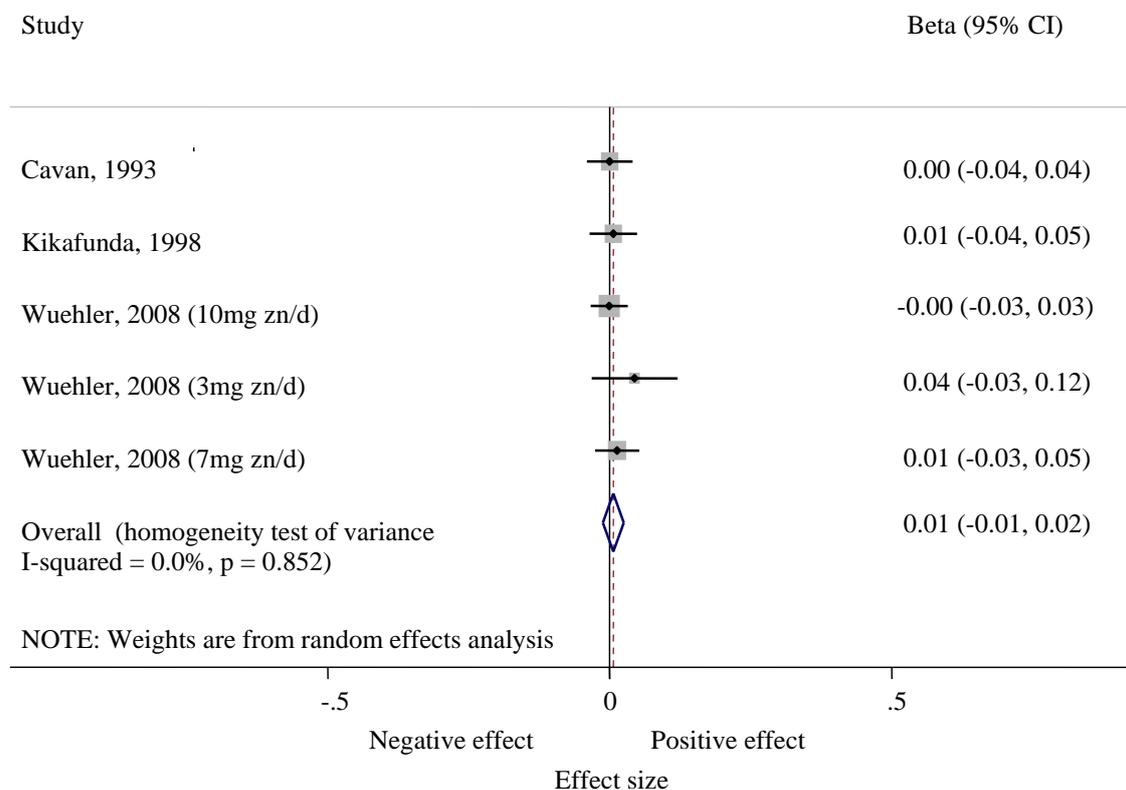


Figure 3. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on HAZ score in children ages 1-8 years old. Beta's represent the regression coefficients for the linear association between loge transformed zinc intake and HAZ score.

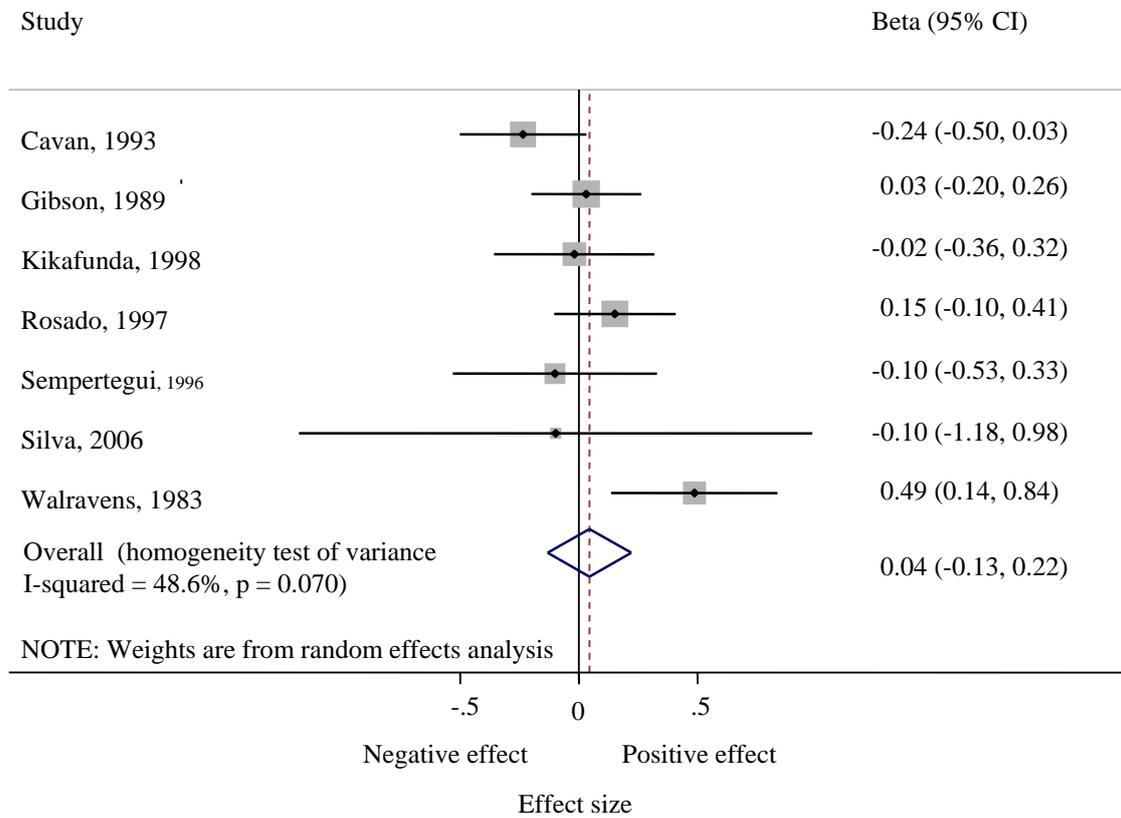


Figure 4. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on WAZ score in children ages 1-8 years old. Beta's represent the regression coefficients for the linear association between loge transformed zinc intake and WAZ score.

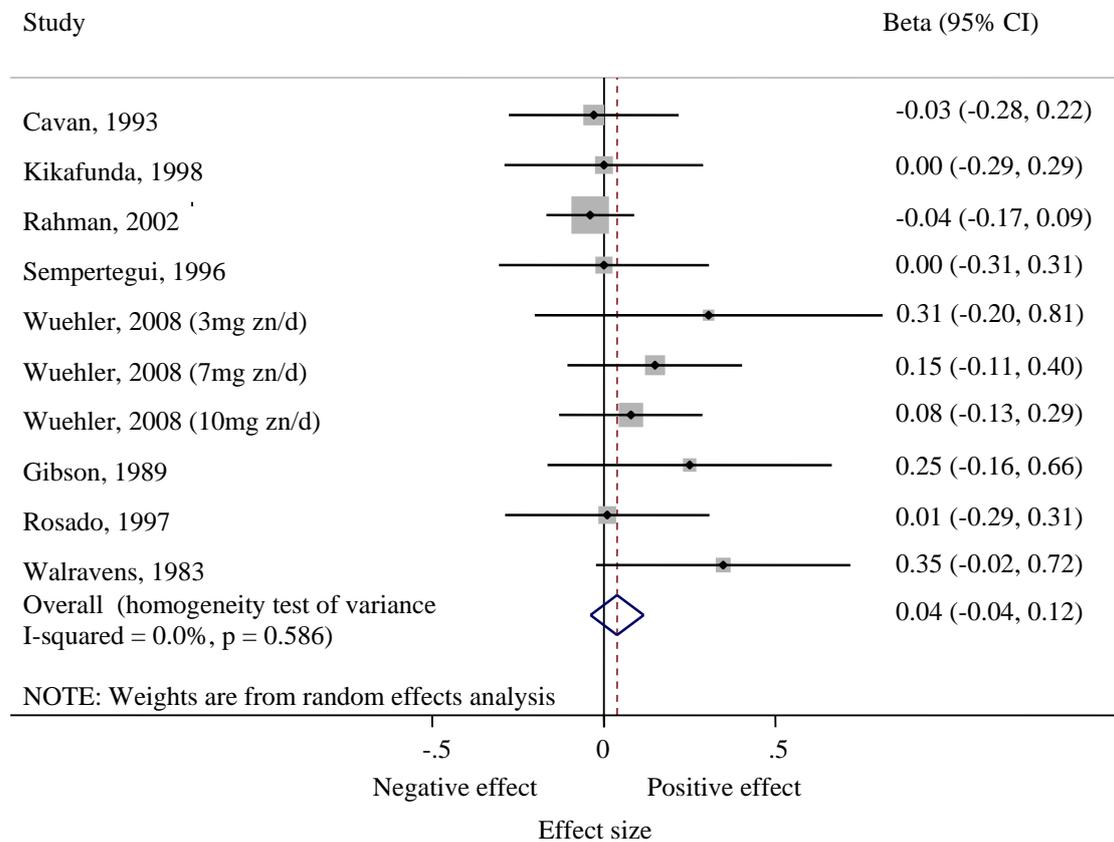


Figure 5. Random effects meta-analyses of RCTs evaluating the effect of dietary zinc on WHZ score in children ages 1-8 years old. Beta's represent the regression coefficients for the linear association between loge transformed zinc intake and WHZ score.

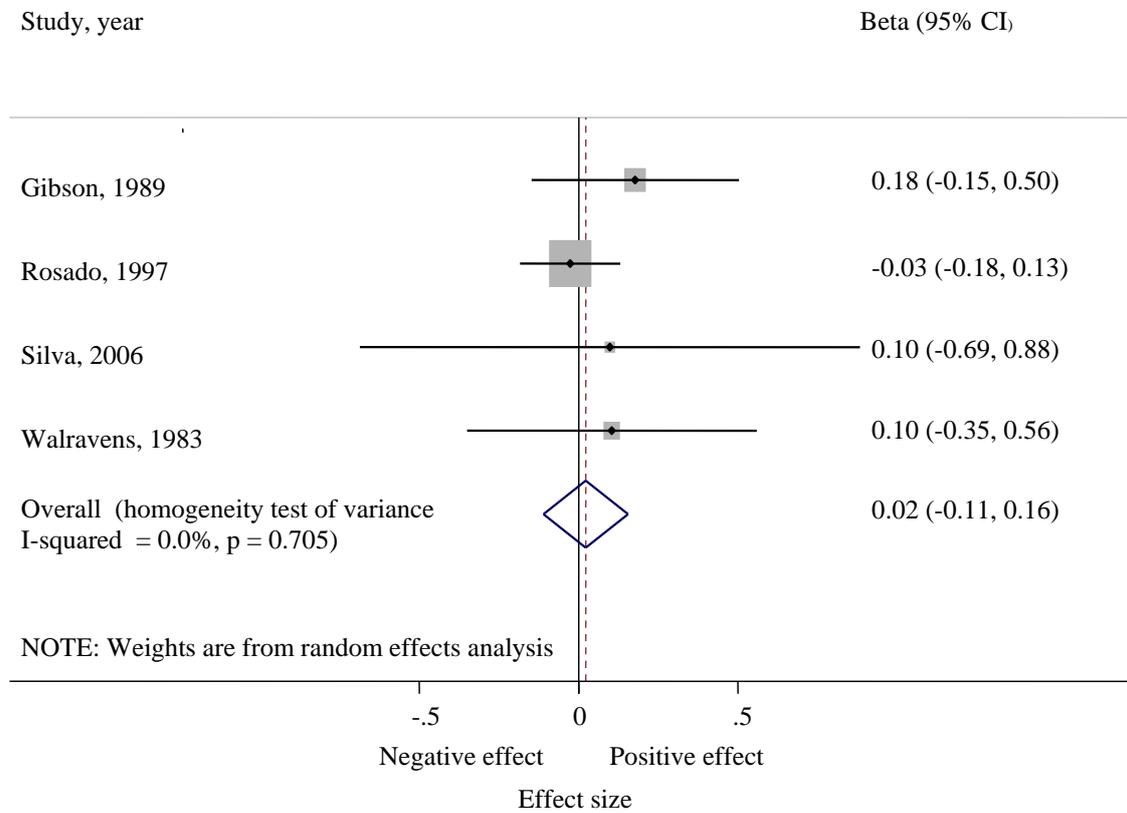


Table 1: Summary of included trials reporting the effect of dietary zinc intake on growth outcomes in children.

Study, year, country	Sex, Age, Stunting	Treatment groups	Micronutrient type	Study Duration	Growth outcome Mean (SD)		Significant results
					Measurement Time point	Supplementation Duration	
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	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 <i>et al</i> (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. 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 <i>et al</i> (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 <i>et al</i> (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 <i>et al</i> (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