Title: The Effect of Zinc Supplementation on Growth-Related Factors in Infants with Failure to Thrive: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Running Title: Zinc Supplementation and Failure to Thrive

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To appear in: **Journal of Pediatrics Review**

Received date: 2023/11/01

Revised date: 2024/01/8

Accepted date: 2024/02/02

Please cite this article as:

Shahraki Jazinaki M, Rashidmayvan M, Safarian M, Norouzy A. The Effect of Zinc Supplementation on Growth-Related Factors in Infants with Failure to Thrive: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of Pediatrics Review. Forthcoming 2024.

Abstract

Background: Failure to Thrive (FTT) is known as one of the common developmental disorders in infants. Although the improvement effect of zinc supplementation in these patients was reported in some past studies, the results were conflicting.

Objective: This study aimed to investigate the effect of zinc supplementation on factors related to growth in infants with FTT by conducting a meta-analysis.

Methods: Medline, Web of Science, and Scopus databases were comprehensively searched to find RCTs investigating the effect of zinc on growth-related factors in infants with FTT. Eligible studies were extracted after screening their relevant information. The pooled effect size was estimated as a weighted mean difference with a 95% confidence interval using the random effect model method.

Results: Out of 85 reviewed papers, 4 studies were eligible to enter this review. The present meta-analysis revealed that zinc supplementation in infants with FTT led to a significant increase in weight (WMD, -0.25 Kg; 95% CI, (0.02 to 0.49), weight-for-age Z-score (WMD, 0.16; 95% CI, (0.03 to 0.28), and height-for-age Z-score (WMD, 0.15; 95% CI, (0.001 to 0.30), compared to control groups. In contrast, zinc supplementation had no significant effect on height and IGF-1 serum level.

Conclusion: The findings of the current meta-analysis indicated the effectiveness of zinc supplementation in improving the developmental status of infants with FTT. However, due to the small number of included trials, it was impossible to draw definitive conclusions, and conducting RCTs with a larger sample size and higher sensitivity is needed.

Keywords: Zinc, Infants, Failure to Thrive, Growth, Systematic review, Meta-analysis

1. Introduction

In the early years of life, growth is considered a parameter indicating the suitable condition of the infant (1). If the high energy requirements in infants are not met well, it leads to lower-than-expected weight growth based on specific growth charts for gender and age, it is a common definition for Failure to thrive (FTT). If a child weighs less than the fifth percentile for his age and gender on the growth chart, that is considered FTT according to more scientific definitions. Alternatively, the child's weight growth percentile line recedes as much as the two lines or more (2). Previous studies have reported the relationship between failure to thrive (FTT) and Developmental delay, long-term deficits in height, weight, and academic performance (1, 3, 4). Furthermore, FTT can increase the risk of overweight and obesity in later decades of life (5). Often, children with FTT are treated on an outpatient basis by referring them to interdisciplinary clinics and based on recommendations from the American Academy of Pediatrics Committee on Nutrition (1, 6-8). Chronic diseases and anemias, lack of access to food, dysfunction of the digestive system, digestive symptoms, and lack of appetite are among the most critical causes of FTT (9). Management of FTT includes providing energy and macronutrients, correcting nutrient deficiencies, financial support, family counseling, and ongoing nutritional assessments and long-term monitoring (9).

Zinc is an essential trace element in the structure of some proteins and molecules in the body (10). Zinc plays a role in cell division, cell differentiation, membrane integrity, enzyme, and antioxidant system function (11). Also, zinc is vital for synthesizing nucleic acid, and proteins. Furthermore, its necessary for maintaining lean body mass (12). In addition, zinc deficiency in children is known as a growth-limiting factor (13). In a number of past studies, a significant effect of zinc supplementation on the height and weight growth of children has been reported,

while there is no consensus about it yet (11, 14). We intend to conduct this meta-analysis to investigate the effect of zinc supplementation on growth related factors in infants with FTT.

2. Methods

This systematic review was based on Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) (15). The protocol for conducting this meta-analysis is registered in the Prospero database with the code: **CRD42023477547**

2.1. Search strategy

Medline, Scopus, and ISI databases were comprehensively searched until June 2023 to find eligible trials based on the inclusion criteria. This search did not include any language or time restrictions. The applied search strategy consisted of the following mesh and non-mesh terms:

("Zinc" OR "Zinc supplementation" OR "Zinc sulfate" OR "Zinc gluconate") AND ("Ftt" OR "Failure to thrive" OR "catch-up growth" OR "growth-retarded") AND ("intervention" OR "randomized" OR "placebo" OR "clinical trials" OR "trial" OR "randomized controlled trial" OR "RCT" OR "cross-over" OR "parallel").

All the reference lists of eligible studies were assessed, and Google Scholar was manually searched to avoid missing relevant articles.

2.2. Eligibility criteria

The studies obtained from the initial search were screened to find RCTs that investigating the effect of zinc supplementation on growth-related factors in children with FTT. Disagreements were discussed until a consensus was reached. Two researchers (M.Sh.J and M.Rm) performed

the screening independently via Endnote software, using the titles and abstracts of papers. Inclusion and exclusion criteria were design based on PICOs framework (Participant: FTT patients, Intervention: zinc supplement, Comparison: control group, Outcome: growth related outcomes, Study: randomized controlled trials) (16).

The inclusion criteria for meta-analysis include:

a) human intervention studies, b) with RCT design, c) intervention with zinc supplementation in the FTT population

d) reporting the changes in growth-related outcomes during the intervention (mean changes and standard deviation)

2.2.1. Exclusion criteria

Exclusion criteria include animal studies, combined treatment, no control group, observational studies, review articles, and letters to the editor.

2.3. Data extraction

Two authors (M.Sh.J and M.Rm) extracted the related data from relevant articles obtained from screening independently. The desired information of this review, including the name of the first author, the year of publication, country, the characteristics of each of the study groups (number of people, mean age and weight), type, and dose and duration of zinc supplementation, and mean changes, and the standard deviation (SD) of outcomes for both the intervention and control groups. were extracted from the studies entered by two authors. Disagreements were discussed until a consensus was reached.

2.4. ***Quality assessment***

Assessment of risk of bias in the included studies was performed by using the Cochran quality assessment tool (ROB 1) by two researchers (M.Sh.J and M.Rm), independently (17). This tool assessed the risk of bias for each study in the following 7 subclasses: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The risk of bias in each subclass was classified as high, unclear, and low.

The general risk of bias was considered high if the number of items with a high risk of bias in each study was ≥3; if it was 2, it was considered moderate; and if it was ≤1, it was considered low general bias. Disagreements were resolved in consultation with the third author (A.N).

2.5. Data synthesis and statistical analysis

The pooled effect size was estimated using weighted mean differences (WMD) and the SD of measures from both intervention and control groups for different variables and by implementing the random effect model based on DerSimonian and Laird method (18). In the case of not reporting mean changes and SD changes, mean change was calculated by subtracting variable values at the beginning of the intervention from the end. Also, Change SD was estimated using the following formula (19): Change SD = square root $[(SDbaseline)^2 + (SDfinal)^2 - (2 \times R \times SDbaseline \times SDfinal)]$

Reported Standard error (SE), medians and interquartile ranges and 95% CIs were converted to SDs using the method of Hozo et al (20). The Cochran Q test evaluated the studies' Heterogeneity and reported by I-square (I^2) statistic (21). $I^2 > 40\%$ or p-value < 0.05 was interpreted as significant heterogeneity. In order to investigate the effect of the quality and

characteristics of each study on the overall size effect, a sensitivity analysis was performed (22). In all the analyses performed using STATA software, version 17 (Stata Corp, College Station, TX) and p-values < 0.05 were considered statistical significance.

3. Results

3.1.Study selection

As a result of the comprehensive search, 94 studies were found in the databases. After removing 28 duplicate studies, 57 were screened based on their titles and abstracts. Next, the full text of 10 articles was read, 3 studies were excluded due to lack of RCT and 2 studies were excluded due to not reporting the desired data. Finally, 4 studies (5 effect sizes) with 222 participants were included in this systematic review (Figure 1) (23-26).

3.2.Study characteristics

Eligible studies were published from 1989 (23), to 2017(26). The countries where the studies were conducted were USA (23), Vietnam (24), Israel (25), and South Korea (26). The sample size of the included arms varied from 25 (23), to 66 individuals (26). The mean age of the participants was from 6.07 (25), to 17.55 months (24). The control group of all included studies except Cho et al. (26), received a placebo. The duration of zinc supplementation in the eligible studies was between 12 (25), and 24 weeks (23, 26) and the dose of elemental zinc received almost varied from 5 (26), to 10 mg day (24). The characteristics of the included studies are summarized in Table 1.

Risk of bias included studies were performed using the Cochrane Collaboration risk of bias tool. The general risk of bias was low for 3 studies (23-25) and moderate for one (26). Details of the risk of bias assessment are shown in Table 2 & Figure 2.

3.3. Meta‐analysis

3.3.1. Effect of zinc supplementation on weight

Pooling of 4 effect sizes showed that zinc supplementation led to a significant increase in weight compared to the control groups (WMD, -0.25 Kg; 95% CI, (0.02 to 0.49); p = 0.03; 197 participants). While significant heterogeneity was not detected among the included studies (I^2 = 0.0%, p = 0.50).

3.3.2. Effect of zinc supplementation on height

The combination of 4 effect sizes demonstrated that zinc supplementation did not cause a significant change in height compared to the control groups (WMD, 0.85 cm; 95% CI, (-0.42 to 2.13); p = 0.18; 197 participants). Also, no significant heterogeneity was observed among the included studies (I^2 = 0.0%, p = 0.90).

3.3.3. Effect of zinc supplementation on weight-for-age Z-score

Meta-analyzing 5 effect sizes showed that zinc supplementation led to a significant increase in weight-for-age z-score compared to control groups (WMD, 0.16; 95% CI, (0.03 to 0.28); p = 0.01; 222 participants). While there was no significant heterogeneity among the included studies (I^2 = 45.3%, p = 0.12).

3.3.4. The effect of zinc supplementation on height-for-age Z-score

The combination of 5 effect sizes showed a significant increasing effect of zinc supplementation compared to control groups on height-for-age Z-score (WMD, 0.15; 95% CI, (0.001 to 0.30); p = 0.04; 222 participants). While significant heterogeneity was observed among the included studies (I^2 = 4.6%, p = 0.38).

3.3.5. Effect of zinc supplementation on IGF-1 serum levels

The combination of 2 effect sizes revealed the non-significance of zinc supplementation on IGF-1 serum levels compared to the control groups (WMD, -7.01; 95% CI, (-38.36 to 24.33); p = 0.66; 105 participants). While high heterogeneity among included studies was mentioned (I^2 = 81.6%, p = 0.02).

3.4.Sensitivity analysis and publication bias

Sensitivity analysis of significant difference in overall effect size of zinc supplementation effect on weight after omitting Walravens et al. (WMD, 0.24 Kg; 95CI%: -0.10, 0.60) (23), and Ninh et al. (WMD, 0.16 Kg; 95CI%: -0.11, 0.43) (24), was reported. Also pooled effect size for weight for age z score after excluding Walravens et al. (WMD, 0.12; 95CI%: -0.10, 0.36) (23), Ninh et al. WMD, 0.12; 95CI%: -0.00, 0.24) (24), and Cho et al. B (WMD, 0.14; 95CI%: -0.03, 0.31) (26), changed significantly. Furthermore, the overall effect size for height for age z score significantly changed after excluding Walravens et al. (WMD, 0.10; 95CI%: - 0.13, 0.35) (23), Ninh et al. (WMD, 0.09; 95CI%: -0.06, 0.25) (24), and Hershkovitz et al. (WMD, 0.15; 95CI%: -0.02, 0.33) (25), was observed. While the significance of the overall effect of zinc supplementation on height was not dependent on the presence of any of the pooled effect sizes.

Because the effect sizes included in this meta-analysis were less than 10, publication bias was not evaluated according to the Cochrane Handbook (27). Because 10 effect sizes or more are needed to draw accurate and interpretable conclusions from publication bias.

4. **Discussion**

According to the results of our meta-analysis, zinc supplementation significantly increased weight, weight-for-age z-score (WAZ) and height-for-age Z-score (HAZ) compared to control groups in FTT infants. Although, we detected no significant effect of zinc supplementation on height. Additionally, the combination of 2 effect sizes revealed the non-significance of zinc supplementation on IGF-1 serum levels in FTT infants.

4.1.Effect of zinc supplementation on weight, height and growth

Prior report has demonstrated that zinc supplementation improves growth parameters in infants. The Weight for age z-score (WAZ) and Weight for Length z-score (WLZ) of an infant whose daily zinc intake is 10 mg are 4% greater than those of an infant whose daily zinc intake is 5 mg (28). On the other hand, neither healthy infants in The Gambia nor healthy infants in the United States responded to supplementation with increased growth (29, 30). A review of 25 studies on the effects of zinc supplements on the growth of children in developing countries found small but significant effects on growth, with effects sizes of +0.22 for height gains and +0.26 for weight gains (31). This meta-analysis was updated by Brown et al. and used 33 RCTs. It showed a very significant overall effect size of 0.350 (95% CI: 0.189–0.511) for height, 0.309 (95% CI: 0.178–0.439) for weight, and ≈0 for WLZ increments (32). Thus, the effects of zinc supplementation on children's development have been extensively studied in developing countries, but less is known

in industrialized nations (32). Therefore, the potential benefits of increased zinc intake for children in industrialized countries remain undetermined.

Previous meta-analyses estimated the dose-response relation between Zn intake and some growth parameters (WAZ and WLZ) in the infant population. These data can supplement evidence for supporting Zn reference values; however, it is important to note that extrapolation of results to other populations, especially developing populations, should be treated with caution (28). Other growth parameters in meta-analyses had no effect (28). Zinc supplementation improved specific growth outcomes, including height, weight, and WAZ in infants and children but not in pregnant women, according to another systematic review and meta-analysis of randomized controlled trials. Furthermore, evidence was found suggesting that the effects on height and HAZ may be more pronounced in children aged two years and older, as opposed to infants (33). Other growth outcomes, like the risk of stunting, underweight, or wasting, were not found to be significantly influenced by zinc supplementation (33).

In agreement with our results, zinc supplementation may be more beneficial for height, HAZ, and weight in children younger than 2 years of age. Infants may have a lower risk of zinc deficiency because their mothers are providing them with zinc through breastfeeding or because their zinc stores are already relatively full at birth (34). According to the last meta-analysis, most trials did not check the zinc status of participants before they started, so it was hard to tell if the results would be different depending on the zinc levels at the start. Possible explanations for the smaller effect size during infancy include the fact that measuring growth, especially WHZ, is more difficult in the field during infancy than it is during childhood (35).

According to Vakili's research, zinc supplementation has a greater impact on BMI and WAZ in women than in men. While zinc supplementation had a greater effect on HAZ in males than placebo, this effect was not statistically significant in females. This supports the finding that zinc improves growth velocity in short-statured boys (36), but not in females (37). Zinc has been shown to improve growth in relatively healthy children (8, 10, 11), but some studies in developing countries have found no effect of zinc on growth, likely due to other growth-limiting factors (29, 38, 39). Previous meta-analyses (32, 40, 41) that implemented trials of zinc supplementation throughout childhood found that it was associated with a small but significant increase in height and weight; in sub analysis, these benefits persisted in groups aged 1-5 and 5-13 but not 6-12 months (41).

4.2. Effect of zinc supplementation on IGF-1 serum levels

The previous study showed that providing humans with zinc supplements can make their IGF-1 levels rise significantly. Furthermore, more substantial improvements were noted under the conditions of an 8-week intervention period and a daily zinc intake of 10 mg (42). In contrast to the findings that zinc supplementation for >8 weeks significantly increased IGF-1. This could be because zinc-deficient patients need to take supplements for longer than 8 weeks to restore zinc deposits, which could be related to the baseline serum zinc concentrations of the subjects who were given zinc. The levels of IGF-1 are raised by zinc supplementation in both zinc-deficient and healthy individuals (43). However, earlier research has suggested that zinc supplementation is more helpful for patients with zinc deficiency and abnormal serum zinc levels. In a study on zinc supplementation and IGF1 levels in children with FTT, Park et al. found no significant

changes in serum IGF-1 levels after the study ended, likely because the study group had normal zinc and IGF-1 levels before the zinc intervention (44).

Due to its involvement in cell growth, immunity, tissue repair, protein and DNA synthesis, thyroid gland and optimal bone functioning, and more, zinc is often referred to as "the metal of life" (45, 46). Similar to proteins, phosphorus, magnesium, sodium, and potassium, zinc inhibits linear growth when present in deficiency (47). Infants who are small for their gestational age have lower levels of zinc in their placental proteins, iron stores, and hemoglobin compared to infants who are large for their gestational ages. This suggests that zinc is needed as early as fetal-placental development. Therefore, according to the study of Akram et al. zinc supplementation during pregnancy may reduce the risk of preterm birth and have a beneficial effect on the pregnancy's outcome and the birthweight of the infant (48). Interestingly, in murine models of zinc deficiency, increasing caloric intake or external administration do not reverse the growth retardation, despite increasing IGF-1 levels (49). Consuming an excessive amount of zinc every day any reasonable benefits, but zinc is an important part of raising IGF-1 levels. According to some studies, zinc supplementation does not affect IGF-1 levels. According to a Barffour et al. study, zinc supplementation (7 mg tablets or micronutrient powder consisting of 10 mg zinc + 6 mg iron +13 other micronutrients) to 419 Laotian children did not elevate IGF-1 levels. The recommended daily allowance (RDA) for zinc in humans is 14–30 mg, but values between 2.8 and 40 mg/day can reportedly yield physiological zinc homeostasis, with excess zinc being primarily eliminated through the gastrointestinal tract (50).

4.3. Limitation

To the best of our knowledge, this is the first systematic review and meta-analysis investigating the effect of zinc supplementation on growth-related factors in infants with FTT. Despite its novelty, this meta-analysis had several limitations, including the limited number of included studies, insufficient sample size, and non-uniformity of the type of zinc supplement received.

5. Conclusion

The current meta-analysis revealed that zinc supplementation significantly increased the weight and Z-score of

weight for age and height for age in infants with FTT. Furthermore, our review indicated that zinc supplementation did not lead to a significant change in the other growth parameters including height and IGF-1. Due to the limited number of included studies and the non-ideal quality of some of them, it is not possible to draw definitive conclusions and generalize the findings of this issue, so it is recommended that RCTs with larger sample sizes and higher sensitivity investigate this intervention on the growth-related parameters in the infants with FTT.

Acknowledgements

We are grateful to all the staff and employees of Mashhad University of Medical Sciences for their support of this study.

Authors' contributions

M.Sh.J and M.S was involved in the conception and design. M.Sh.J and M.Rm developed the search strategy, extracted the data, and assessed the risk of bias. M.S, M.Rm, and M.Sh.J drafted the manuscript. M.Sh.J conducted the analyses and interpreted the results. M.Sh.J, and A.N revised the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

All the authors declare that in all stages of designing and conducting this meta-analysis, there was no commercial or financial relationship affecting the results.

Data availability

Data will be made available on request.

Funding

No financial grant was received for this research.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Figure 1. Flowchart of study selection for inclusion trials in the systematic review.

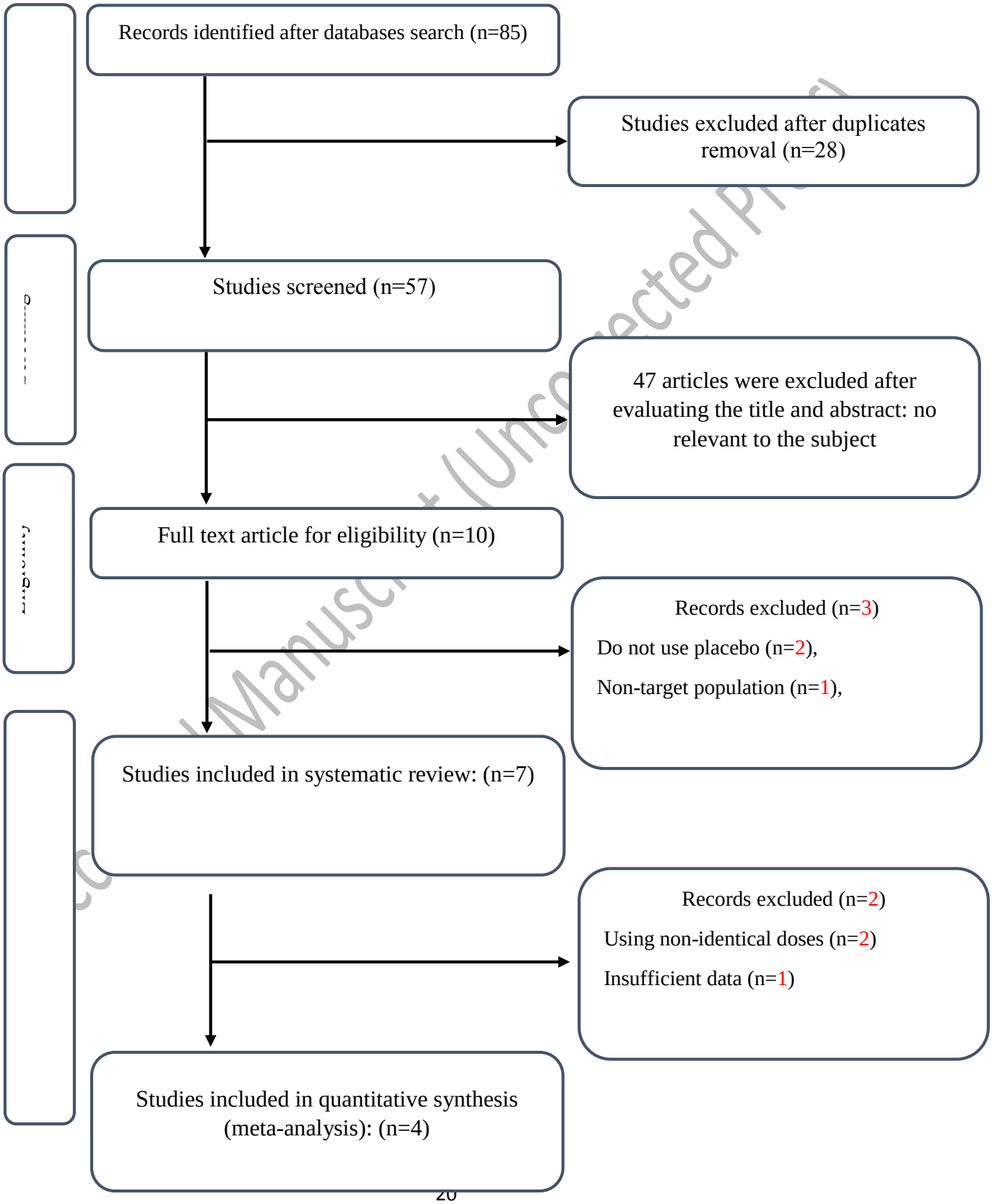


Figure 2. Risk of bias assessment plot

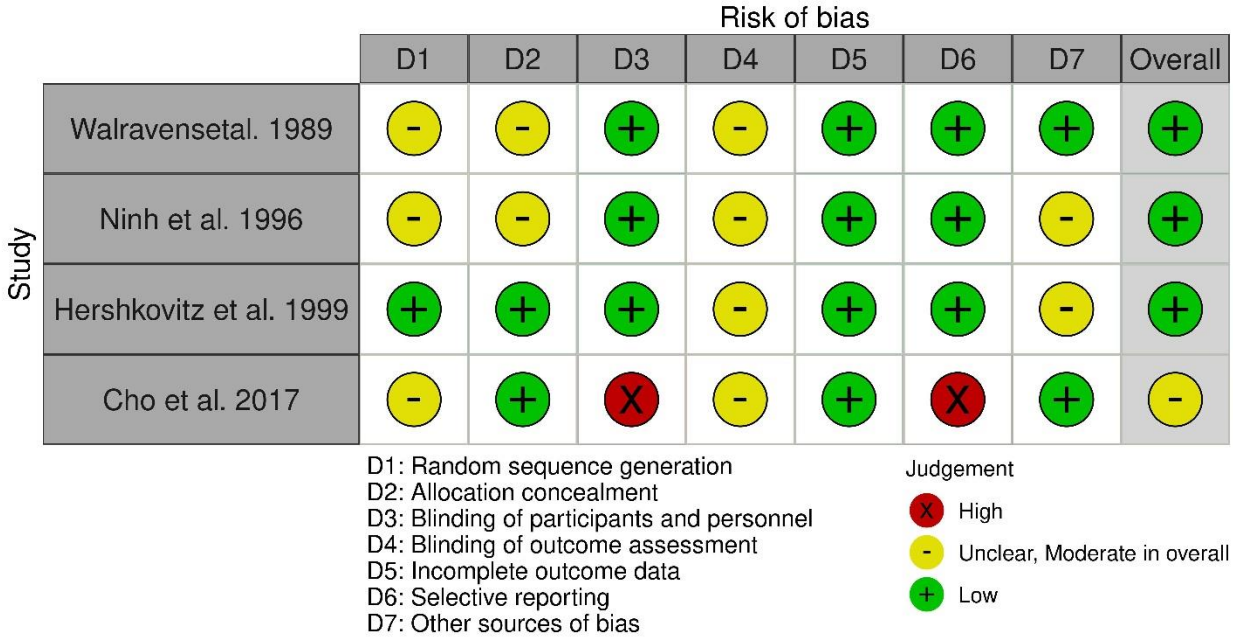
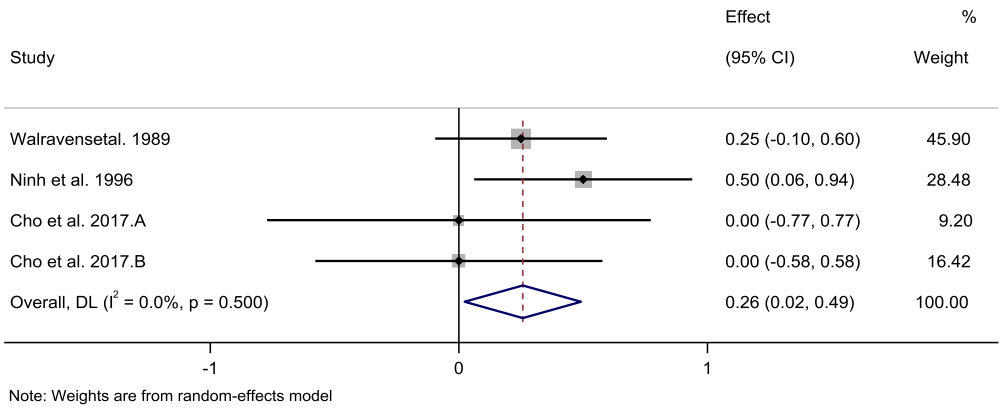
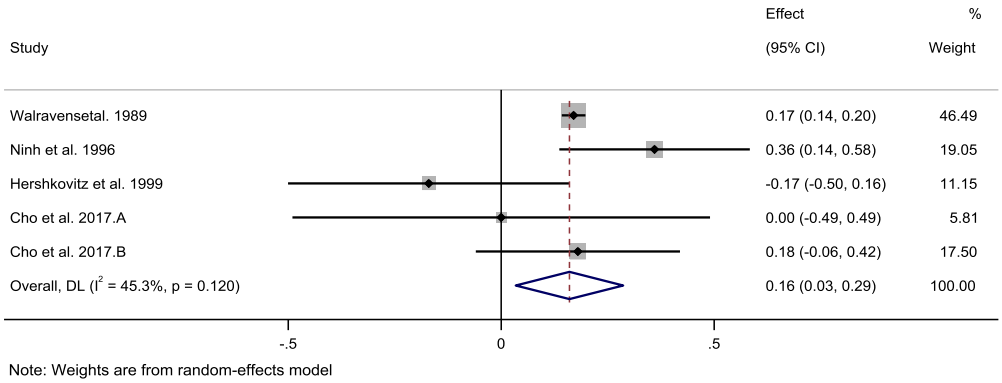


Figure 3. Forest plot detailing weighted mean difference and 95% confidence intervals (CIs) for the effect of zinc supplementation on A) Weight (kg); B) Weight-for-age Z score; C) Height (cm); Height-for-age Z score; and D) Serum IGF-1 (mg/dL).

3A.



3B.



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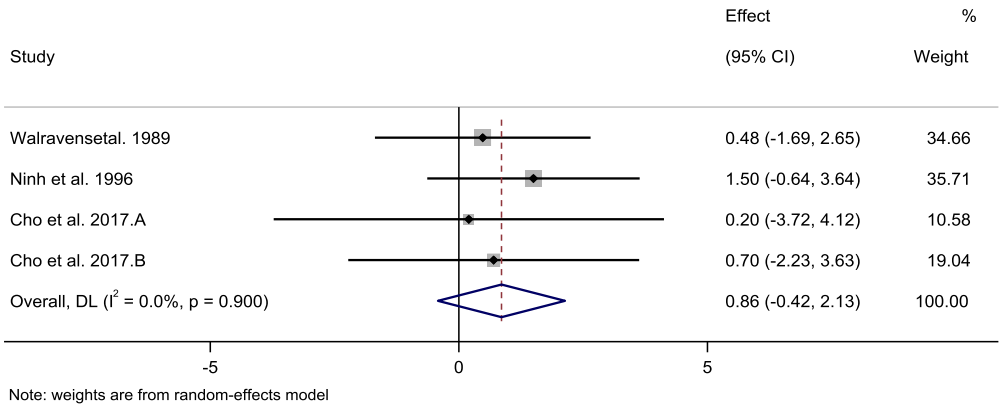

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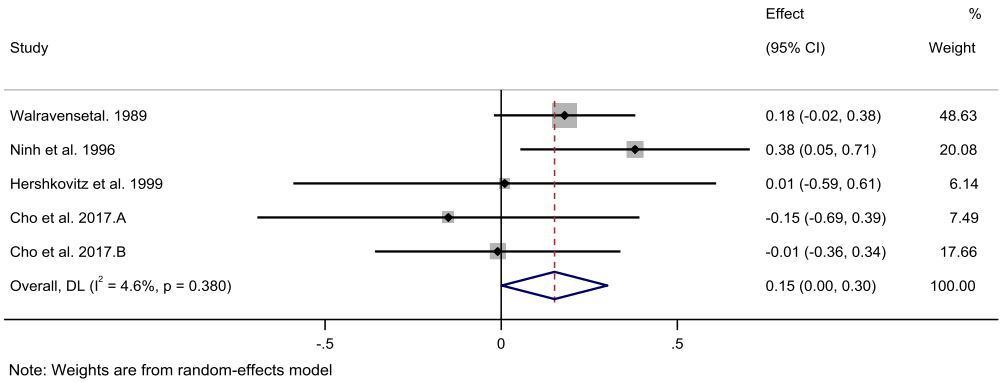

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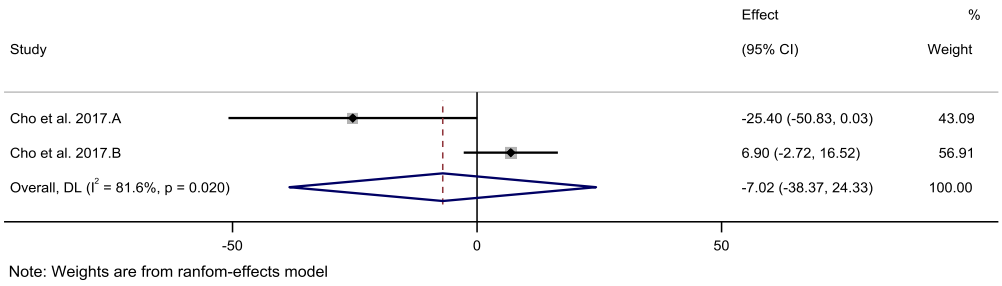

Note: Weights are from ranfom-effects model

Table 1. Characteristic of included studies in meta-analysis

studies	Country	Study Design	Participant	Sample Size	Sample size		Trial Duration (Week)	Means Age (Month)		Means WAZ		Intervention		MAIN outcomes
					IG	CG		IG	CG	IG	CG	Zinc supplement dose (mg/d)	Control group	WAZ, HAZ, Weight (kg) Height (cm)
Walravenset al. 1989	USA	parallel, R, PC, DB	Infants With a Nutritional Pattern of Failure to Thrive aged 8 to 27 months	50	25	25	24	NR	NR	-2.02 ± 0.08	-2.05 ± 0.08	5.7 mg/day elemental zinc	Placebo	Weight (kg) Height (cm) WAZ HAZ WHZ IGF-I concentration
Ninh et al. 1996	Vietnam	parallel, R, PC, DB	Growth-retarded children aged 4-36 months	42	24	18	20	17.5±6.6	17.6±6.8	-2.64 ± 0.60	-2.58 ± 0.57	10 mg/day elemental zinc	Placebo	Weight (kg), Height (cm), WAZ, HAZ, Serum IGF-1 level
Hershkovitz et al. 1999	Israel	parallel, R, PC, DB	3- to 9-month-old infants with nonorganic failure to thrive (NOFTT)	25	14	11	12	6.35±1.32	5.80±1.81	-1.81±0.32	-2.01±0.56	2 mg/kg/day elemental zinc	Placebo	WAZ, HAZ, WHZ
Cho et al. 2017.A	South Korea	parallel, R, C	NOFTT infants born preterm	39	21	18	24	11.8±7.2	9.6 ± 8.4	-2.14 ± 1.13	-2.33 ± 1.35	Oral zinc sulfate 22 mg (5 mg elemental zinc)	Non-supplemented	Weight (kg) Height (cm) WAZ HAZ Serum IGF-1 level
Cho et al. 2017.B	South Korea	parallel, R, C	NOFTT infants born term	66	49	17	24	13.9 ± 6.3	10.9 ± 6.1	-1.86 ± 0.85	-1.87 ± 0.55	Oral zinc sulfate 22 mg (5 mg elemental zinc)	Non-supplemented	WAZ, HAZ, Weight (kg) Height (cm)

Abbreviations: IG, intervention group; CG, control group; DB, double-blinded; SB, single-blinded; PC, placebo-controlled; CO, controlled; RA, randomized; NR, not reported; F, Female; M, Male; FTT, Failure to Thrive; NOFTT, Non-organic failure to thrive; NR, not reported.

Table 2. Risk of bias assessment

Study	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	General risk of bias
Walravensetal. 1989	U	U	L	L	L	U	L	L
Ninh et al. 1996	U	U	L	U	L	U	L	L
Hershkovitz et al. 1999	L	L	L	U	L	U	L	L
Cho et al. 2017	U	L	H	L	H	U	L	M

Abbreviation: L; low risk of bias; H, high risk of bias; U, unclear risk of bias.

General Low risk < 2 high risk

General moderate risk = high risk

General high risk > 2 high risk