Systematic Review and Meta-analysis of Zinc Supplementation and Stunting in Children under 5 years of age

Gihan Fouad Ahmad[1], Hanaa Sabry Ahmed[2]and Enas Sayed Abbas[3]

1. Head of National Nutrition Institute- Cairo - Egypt
2. Harvard Medical School Associate
3. Clinical Nutrition Department- National Nutrition Institute- Cairo - Egypt

Corresponding author: Enas Sayed Abbas - Email:enas.sayed09@yahoo.com Mobil +201222426248

ABSTRACT

The prevalence of zinc deficiency is 28 % of stunted Egyptian children. Therefore, this study was done to determine whether zinc supplementation strategy is feasible and effective for reducing growth retardation at national level. We conducted literature searches of electronic databases of the international standard randomized control trial number register that reported on the effect of zinc supplementation in infants or children below 5 years old. The findings were pooled using random effects meta-analysis; we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelinesduring all stages of implementation, analysis, and reporting of these meta-analyses after testing of homogeneity. The final fifty four randomized controlled trials included in the meta-analysis showed the zinc supplementation had a greater effect on height and Height for age z-score in children compared with infants (P-interaction = 0.002 and 0.06, respectively). Among children aged ≥2 years, zinc increased height (N = 7 trials; WMD = 1.37 cm, 95%CI: 0.50–2.25) and,height for age z-score (N = 6 trials; WMD = 0.12, 95%CI: 0.05–0.19). Zinc supplementation significantly increased height (N = 40 trials, WMD = 0.23 cm, 95%CI: 0.09–0.38; I2 = 66.9%) showed 28 of 40 studies (70%) had a positive effect of zinc supplementation among children aged < 5 years old on height in randomized controlled trials and, ten of them were statistically significant. Oral zinc supplementation among children aged from 2-5 years is recommended. However, further studies are needed.

Key Words: *Stunting, infants, zinc supplementation, height, children*.

BACKGROUND

Stunting is defined by a height-for-age *z*-score of more than 2 standard deviations below the World Health Organization (WHO) Child Growth Standards main **(WHO,1995),** 154.8 million (22.9%) children under 5 years of age suffered from child stunting worldwide in **2016 (WHO, 2020)**. The current worldwide prevalence of stunting among children under the age of5 years is of the order of 25% and its reduction by 40% global target for 2030 (**Cash and Patel, 2020).**

Stunting can occur in the first 1000 days of life and is related to many factors, such as socioeconomic status, dietary intake, infections, maternal nutritional status, infectious diseases, micronutrient deficiencies and the environment **(Black et al., 2008, Ikeda et al., 2013)**. Childstunting is a complex entity that may reflect several etiologies, particularly a poor, unbalanced diet and insufficient vitamin/micronutrient intake. It also involves social factors, including family's resources and configuration, as well as the broader political and economic conditions in which children live **(Stewart et al., 2013)**. Therefore, the current potential causes of stunting range from inadequate food to poor hygiene and repeated infections **(Schaible and Stefan, 2007)**.

It affects the function and structure of the brain, impeding mental development and possibly affecting human capital and social progress in the long term **(Hashad, 2014)**.

In 2016, 87 million stunted children lived in Asia, 59 million in Africa and 6 million in the Latin American and Caribbean regions **(WHO, 2020)**. Five sub regions have child-stunting rates that exceed 30%: western Africa (31.4%), middle Africa (32.5%), eastern Africa (36.7%), southern Asia (34.1%) and Oceania (38.3%; excluding Australia and New Zealand. Both Asia and Oceania have experienced slow or no progress in reducing child stunting. In Latin America and the Caribbean, stunting has declined twice as quickly as in Africa from 2000 to 2016 **(WHO, 2020)**. However, the reduction of child stunting has not been the same in all groups of the population, (from 1990 to 2013) in the Asia-Pacific, Latin

American and Caribbean regions **(WHO, 2018)**, that amounts to 2.1 million individuals, the largest number of stunted children in the Middle East and North Africa (MENA) region **(Hashad, 2014).**

Stunting can be reduced by many factors such as environmental, water sanitation and nutritional. The important one is nutritional, whereas applying several nutritional modifications like zinc supplementation **(Huynh et al., 2014)**.

Zinc is an essential mineral that is required for normal skeletal growth and bone homeostasis. Furthermore, zinc appears to be able to promote bone regeneration **(O'Connor et al., 2020)**.

Zinc affects GH metabolism, therefore its deficiency may result in reduced GH production and/or IGF-I. The interrelationship among zinc, growth and GH–IGF-I axis appears to be complex **(Nishi, 1996)**.

The mean intake of zinc was 75.7% of reference nutrient intake among children aged 3-5 years, and serum zinc levels positively correlated with their height and weight (Yu, 2007). There after zinc supplementation should be included in national strategies to reduce stunting in children younger than 5 years of age in developing countries **(Abdollahi etal., 2019)**.

Benefits of zinc supplementation for height, HAZ and weight might be more effective among children aged 2 years **(Liu etal., 2018)**. The smaller effect in infants could be due to maternal breastfeeding **(Brown etal., 2009)**, or better initial zinc body stores from in utero development, compared to later in life **(Underwood, 1999)**.

Globally, nearly 17% of the world's population is at risk of zinc deficiency due to inadequate dietary intake of major sources including lean meat, shellfish, and nuts, with Asia and Africa having the highest prevalence. Thus, zinc supplementation may be a crucial intervention to improve child growth and reduce underweight and stunting globally **(Liu et al., 2018)**.

Childhood stunting is a serious health problem in Egypt as well as zinc deficiency. Prevalence of stunting is 21% of Egyptian children under the age

of five years **(Hashad, 2014)**.Whereas prevalence of zinc deficiency is 28 % of stunted Egyptian children **(Saleh etal., 2020)**.

The aim of this pragmatic study is to determine whether zinc supplementation strategy is feasible and effective for reducing growth retardation at national level.

METHODS

After testing of homogeneity, we searched Pub Med, EMBASE, Cochrane Library, Web of Science, and trial registries for eligible trials. Inclusion selection and data extractions were performed independently and in duplicate. The Cochrane Risk of Bias tool evaluated study quality. Findings were pooled using random effects meta-analysis; we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines during all stages of implementation, analysis, and reporting of these meta-analyses after testing of homogeneity (**Liu et al., 2018).**

Search Strategy*:*

This study conducted literature searches of electronic databases including Pub Med, EMBASE Web of Science, The Cochrane Library, and the international standard randomized control trial number register. Examples of search terms included: (zinc or zinc supplement) and (stunting or height or birth weight) Infant or child and (randomized or clinical trial). Complete search terms and strategies for each database are supplementary "Table 1".

These electronic searches were supplemented by hand searching of citation lists and electronic searching of "related articles" on Pub Med for all final included publications; as well contacts with experts to identify any other recently published studies , grey literatures to avoid published bias. Authors were contacted to request missing data or to clarify methods or results.

Primary Exposure and Outcomes:

The exposure of interest was zinc supplementation in children (below 5 years). Whereas the recommended dietary allowance (RDA) for infants aged 0-6 month(s) is 2 mg, 3 mg for young children aged 7-36 months and 5mg perday for children aged 4-5 years **(Larson et al., 2008)**. Although, the

amount of zinc needed in young infants to keep a positive zinc balance in regions with a high prevalence of zinc deficiency is still unknown. The majority of published results of efficacy trials of zinc treatment have tested doses ranging from 10 mg (infants) to 20 mg (below 5 years children) of elemental zinc per day, a safe dosage in these children. Doses of up to 70 mg twice a week have been provided without any toxic effect or clinically significant copper deficiency **(Bates et al., 1993)**. For endpoints measured at birth, the growth outcomes of interest were birth weight and low birth weight (LBW, defined as birth weight < 2500 g).For outcomes measured in children, the growth outcomes of interest were height, weight, corresponding Z-scores including height-for-age (HAZ), weight-for-age (WAZ), and weight-for-height (WHZ), and risk of stunting (HAZ < -2) , measure association between exposure and outcomes by measure risk ratios and attribute risk **(Liu et al., 2018)**.

Study Selection:

Current study included some randomized controlled trials that reported on the effect of zinc supplementation in infants or children below 5 years old including low birth weight, stunted children, on birth or child growth outcomes, including an effect measure and information to compute its standard error.

The title and abstract of the studies identified in the computerized search were scanned in duplicate to exclude references that were obviously irrelevant. In orderto determine eligibility for inclusion of the remaining articles, their full texts were reviewed, and multiple reports of the same study were linked together.

Inclusion criteria:

Included studies were RCTs in child population aged below 5 years that provided supplemental zinc as an oral dose. Trials with simultaneous fortification or supplementation of additional micronutrients, or simultaneous co-interventions like health education and/or drugs (for example, deworming or antimalarials) wereincluded if the only difference between the intervention and comparison arms waszinc supplementation.

Exclusion criteria:

Search excluded studies if they included children aged more

than 5 years or if they were conducted in animals or with other intervention components, in which theeffect of zinc could not be separated between treatment groups due to other unequal interventions. Which the dose of zinc supplementation intake could not be quantitatively measured, or with duration of supplementation < 3 months.

Given our interest in the sustained effects on child growth, we excluded observational studies, cross-sectional ecological studies, commentaries, general reviews, or case reports; or trials conducted in populations with major chronic disease (e.g., sickle-cell disease, cystic fibrosis, HIV infection, and severe protein. Energy malnutrition or if were hospitalized. Group RCTs were excluded from all reviews conducted by the EURRECA consortium due to the increased risk of confounding factors. When duplicate publications from the same study were identified, we included the publication reporting the largest number of participants for each outcome of interest.

Data Extraction:

Data from included studies were independently extracted in duplicate by two investigators using a standardized electronic form (Microsoft Excel, SPSS), with any differences resolved by consensus. Information was extracted on the publication (first author, contact information, Publication year). Study details (name, location, year(s) of enrollment); population (age, socioeconomic status, number of participants in treatment and control arms), baseline nutritional status (e.g., proportion of low birth weight or stunting), zinc intervention (type, daily dose, and duration), duration of follow-up, and age at outcome assessment, dropout rate, and outcomes including effect measures and associated uncertainty. Missing information was obtained by direct author contact or, if necessary, estimated using a standard approach. Study quality was assessed using the Cochrane Collaboration risk-of-bias tool for randomized controlled trials, including potential for selection bias, performance bias, detection bias, attrition bias, and reporting bias through a six-question quality

control check list **(Higgins, 2011)**. We evaluated the risk of bias for each trial using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions **(Higgins, 2019)**. Plots of 'Riskof bias' assessments was created in Review Manager (RevMan) **(Gera et al., 2018)**. Risk ratio (AR) estimates with 95% confidence intervals (CI) were used for binary outcomes; for continuous outcomes, mean differences (MD) were used. In order to maximizethe data input for the pooled outcome measures, we utilized post-intervention values (means and standard deviations (SDs)) in preference to the changes from baseline **(Higgins, 2019)**. In factorial trials and in multi-arm designs yielding two or moreintervention groups (different zinc doses or salts used) and a single control group,the data in the intervention groups, including the variation in the interventioncharacteristic, was pooled and compared against the single control group to preventunit of analysis error. For cluster-randomized trials, we used the stated cluster- adjusted RR or means and 95% CI, irrespective of the method employed for adjustment. In case of missing data, we contacted trial authors for information wherever possible; and where this could not be done, or the authors did not respond,we imputed the missing values, where feasible. In case any assumptions were made for such imputations, they were recorded, and are detailed in Web Appendix.

RESULTS

Out of 1107 identified articles, 54 trials were eligible, totaling 21,185 unique participants including 20,412 infants < 2 years old (47 trials), and 773 children aged 2 years or older (7 trials) who took supplementation. One trial only was cluster- randomized, the rest were individually randomized. 15 trials had a factorial design. Those 54 trials were conducted on 5 different continents, including 7 studies in the US and Caribbean, 2 in Europe, 15 in Asia, 13 in South and Central America, 7 in Africa, and 10 in the Middle East. The mean age at randomization for infants is 8.7 months and for children, 43.4 months. The mean duration of intervention was 30.9 weeks in infants, and 38.9 weeks in children; with mean zinc doses of 7.6, and 8.5 mg/day,

respectively.

The follow-up period for majority of the 54 trials was the same length as the intervention, however eight trials only upon children, an extended follow-up after the intervention was carried out. For zinc formulation, 37 (69%) of the 54 trialsused sulfate zinc; 6 trials (11%), gluconate zinc; 4 (8%) acetate; 4(8%) unknown; the remaining 2 trials (4%) are citrate, lactate and methionine, respectively. According to Cochrane Collaboration risk-of-bias tool for randomized controlled trials, 36 (66.7%) of the 54 trials had a quality score of 5 or 6, classified as high quality, and 8 (14.8%) trials had a score 2 or below, classified as low quality. **(Table 1).** All trials used zinc supplementation while trials regarding zinc fortification were evaluated and excluded due to other unequal interventions between treatment groups that would prevent isolation of the effect of zinc.

1 All studies were randomized controlled trials. Most were also placebo-controlled, except for 1 open-label trial in infants, and 1 in children.

2 If not reported in the text, socioeconomic status was estimated based on study characteristics, determined by two reviewers independently and in duplicate. "–"stands for missing.

3 The Cochrane Collaboration's tool for assessing risk of bias was used to score studies as having a low (-6 to 2), medium (3–4), or high score (5– 6) using a 12-question form.

Study quality was assessed using the Cochrane Collaboration risk-of-bias tool for randomized controlled trials, including potential for selection bias, performance bias, detection bias, attrition bias, and reporting bias through a 6-question quality control checklist. Each question was answered as low (score=1), high (score=-1), or unclear (score=0) risk of bias; and values were summed (potential range: (-6 to +6). **(Table 2).**

Infant and Child Zinc Supplementation and Growth Outcomes

Amongst trials conducted, when we explored potential factors that might modify the effect of zinc supplementation, significant heterogeneity was not identified

by world region, duration of supplementation, daily dose of zinc supplementation, socio-economic status and zinc type **(Table 3).** However, zinc had a greater effect on height and HAZ for supplementation in children compared with infants (P-interaction = 0.002 and 0.06, respectively). Among children aged ≥2 years, zinc increased height (N = 7 trials; WMD = 1.37 cm, 95%CI: 0.50–2.25) andHAZ (N = 6 trials; WMD = 0.12, 95%CI: 0.05–0.19).

Table 4 showed that publication year also appeared significant in meta- regression, with stronger effects reported in trials published before year 2000 than thereafter (P= 0.08 for height, P = 0.002 for HAZ). In multivariable meta-regression including both child age and publication year in the models, child age was an independent predictor of heterogeneity for height (P-interaction < 0.05), whilepublication year was for HAZ (P-interaction < 0.05). Nine trials evaluated theeffect of zinc supplementation on stunting. No statistically significant effect was identified (RR= 1.01, 95%CI: 0.96–1.06; I2 = 0.0%).

Among trials conducted after birth, zinc supplementation significantly increasedheight (N = 40 trials, WMD = 0.23 cm, 95%CI: 0.09–0.38; I2 = 66.9%) as shown in**(Figure 2).** Twenty-eight of 40 studies (70%) had a positive effect size, and 10 were statistically significant.

While **(Figure 3)** declared that the effect on HAZ was not statisticallysignificant (N = 40 trials; WMD = 0.02; 95%CI: 0.01–0.06; I2 = 65.6%)**;** about half(22 of 40) reported a positive effect size, and only 4 were statistically significant.

In 29 trials, zinc supplementation did not significantly affect WHZ (WMD: 0.02, 95%CI: –0.03–0.06, I^2 = 56.1) **(Figure 4)**. Six trials appraised risk of underweight while seven trials, wasting. Upon merging these studies, significant effects were not recognized on risk of underweight (RR = 1.03, 95%CI: 0.97–1.09; I2 = 0.0%) or wasting (RR = 0.88, 95%CI: 0.74–1.05; I2 = 57.0%).

Influence of Study Quality

Throughout sensitivity analyses, we excluded six infant/child trials categorized as being of a low quality score (≤2).

Whereas the remaining trials, zinc supplementation significantly increased height (N = 34 trials, WMD = 0.19 cm, 95%CI: 0.05–0.34), HAZ (N = 37, WMD = 0.03, 95%CI: –0.01–0.06), or WHZ (N = 26, WMD = 0.02, 95%CI: –0.03, 0.06).

Evaluation of Publication Bias

Funnel plots visual inspection implied asymmetry consistent with potential publication bias and small-study effects for height, HAZ. Egger's test recognized statistical evidence for potential small-study effects for height ($p = 0.01$), HAZ ($p < 0.001$). On the other hand, findings for Begg's test were not statistically significant for any of these outcomes ($p \geq 0.12$ each). Upon exploring the potential publication bias influence using the trim-and-fill method, 6 hypothetically missing studies were evaluated for height and, 2 for HAZ. Besides these missing studies resulted in a theoretical corrected pooled estimate of 0.14 cm (95%CI: –0.03, 0.31) for height and 0.02 (95%CI: –0.02, 0.05) for HAZ.

DISCUSSION

This systematic review was undertaken to investigate the association between zinc intake and indices of growth for stunting in children aged below 5 years. A major strength of the current review is the meta-analysis of statistically homogeneous studies. Despite the fact that previous meta-analyses found statistically significant effect sizes on various aspects of child growth, all have had high heterogeneity.

In this systematic review and meta-analysis of randomized controlled trials, we realized that zinc supplementation in infants and children, improved specific growth outcomes including height. We also identified evidence for potentially stronger effects on height and HAZ by child age, with greater effects when supplements were given to children aged ≥2 years, rather than infants. This might explain why zinc supplementation may be more effective among children than infants may, because during the first year there was rapid growth leading to negative zinc balance, which leads afterwards to increasing supplementation benefits and, during the second year of life most infants have

been weaned or are weaning from breastfeeding, making diet a crucial source for zinc intake. In the current meta- analysis, most trials did not assess zinc status at enrollment, making it difficult to know if results would vary based on baseline zinc levels. A smaller effect during infancy could also relate to in-field challenges of reliably measuring growth, especially WHZ, during infancy compared with childhood **(Mwangome and Berkley, 2014)**.

Possible small-study effects were seen for height and HAZ, but not other outcomes. This could be due to publication bias or, alternatively, differences in effects of smaller studies from true heterogeneity in certain populations or study designs studying these outcomes.

Similar to our study, the two systematic reviews by **Brown et al., 2002, (2009)**, declared statistically significant positive effects of zinc supplementation on linear growth and weight gain. **Brown et al., (2002),** reported by **Brown et al., (2009)**, but not in their prior study a marginally statistically significant effect of zinc on change in WHZ. A second meta-analysis, published in 2011, included 36 trials and found a positive effect only on linear growth, measured by height or HAZ **(Imdad and Bhutta, 2011)**. Our findings confirm those of **Imdad and Bhutta, 2011**, who 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. As well, **Brown et al., 2002**, involved severely malnourished, hospitalized children in their 2002 meta-analyses; however, they ruled out such children in their subsequent review Brown et al., 2009. Other prior meta-analyses **(Brown et al., 2002 and, 2009, Mayo-Wilson et al., 2014)**, included trials of zinc supplementation throughout childhood. Up to age 12 years, and found that zinc supplementation 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 years, but not 6–<12 months **(Mayo-Wilson et al., 2014)**.

In contrast to our study, **Ramakrishnan et al., 2009**, 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 that ofours in that more than half of their included studies were conducted in infants (initial age below12 months) and some studies included small-for-gestational age infants. Previous meta-analyses of zinc supplementation in children aged <5 years, published in 2009, identified 43 trials with no significant effect on height or weight **(Ramakrishnan et al., 2009)**.

Current review includes combined homogeneous studies to provide a precise estimate of zinc supplementation influence on growth measures in children. We attained high homogeneity in our meta-analyses through restricting the age group. We also excluded studies that involved anemic or malnourished children, lowbirth weight or small-for-gestational age children, as well as community trials.

Present review also recognized potential evidence for small study effects, andevaluated its impact using trim and fill methods. Our findings cannot exclude the possibility of publication bias, and our results should be interpreted in this light. However, small-study effects (asymmetrical funnel plots) cannot be equated with publication bias since such a pattern could also result from other factors including true heterogeneity in effect sizes and differences in populations or methodology **(Higgins, 2011)**.

Potential limitations should be considered. As with all meta-analyses, our findings are based on available studies and their measurements. From another point of view, our comprehensive literature search of multiple databases together with citations of related articles made it unlikely that we missed any major studies and maximized statistical power. We did not formally assess whether long-term studies might have recruited a subset of subjects

who were acutely ill (e.g., diarrhea or pneumonia) at enrollment, which might have temporarily decreased initial zinc bioavailability. Although 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 instance, only one study screened and excluded participants with parasitic infection **(Silva et al., 2006)**. We did not review the potential side effects of zinc supplementation or biochemical indicators such as serum or plasma zinc concentration, which are relevant questions for future investigations. In addition, since most trials did not havedata on baseline plasma zinc concentrations, we were not able to study the influence of baseline zinc status on the effect of zinc supplementation.

Another limitation include the absence of large well-designed trials,lack of studies in Egypt as well as studies that attempt to give zinc under fasting conditions to avoid the influence of dietary factors like phytate on zinc bioavailability. The lack of data provided on baseline nutritional status thatmake it hard to identify the conditions under which these interventions may be useful.

Finally yet importantly, our systematic review and meta-analysis of randomized controlled trials reveals that zinc supplementation in children improves specific growth outcomes, with potentially stronger effects of supplementation in children after the age of 2 years.

CONCLUSION

The methods used to manage this review were precise and powerful, allowing only the most accurate and well-designed studies to be included, while reducing the impact that confounding factors may have. Our findings support a roleof zinc for child growth outcomes in infants and children under five years of age. The modest effect size we identified may not justify universal zinc supplementation. Although, larger effects may be observable among children with sub-optimal zinc status.

In conclusion, our review suggests that zinc supplementation has a positive effect on linear growth especially

when supplemented in a mean dose of 8.5mg/day for a mean duration of 38.9 weeks led to an increase gain in length by 1.37 cm among children aged ≥2 years.

Our results also highlight a need for further trials and studies to confirm the potential stronger benefit on child growth after age of two years, especially as most existing trials focused on the first 1000 days of life.

Our novel findings notify policy recommendations and program development for zinc supplementation to improve stunting among young children. Our policy is to administer zinc orally as a supplement for preschool children aged from 2-5 years with a dose " RDA" of 3mg and 5 mg daily for children aged 2-3years and 4-5 years respectively. Since, the body is not able to store excess zinc, so continuous dietary intake is further required.

Clinical relevance of results: Since the results suggest that zinc supplementation has a positive effect on linear growth so it can be concluded that oral zinc supplement for preschool children aged from 2-5 years is recommended. However, these recommendations should be taken with caution since the study indicates limitations in the current evidence.

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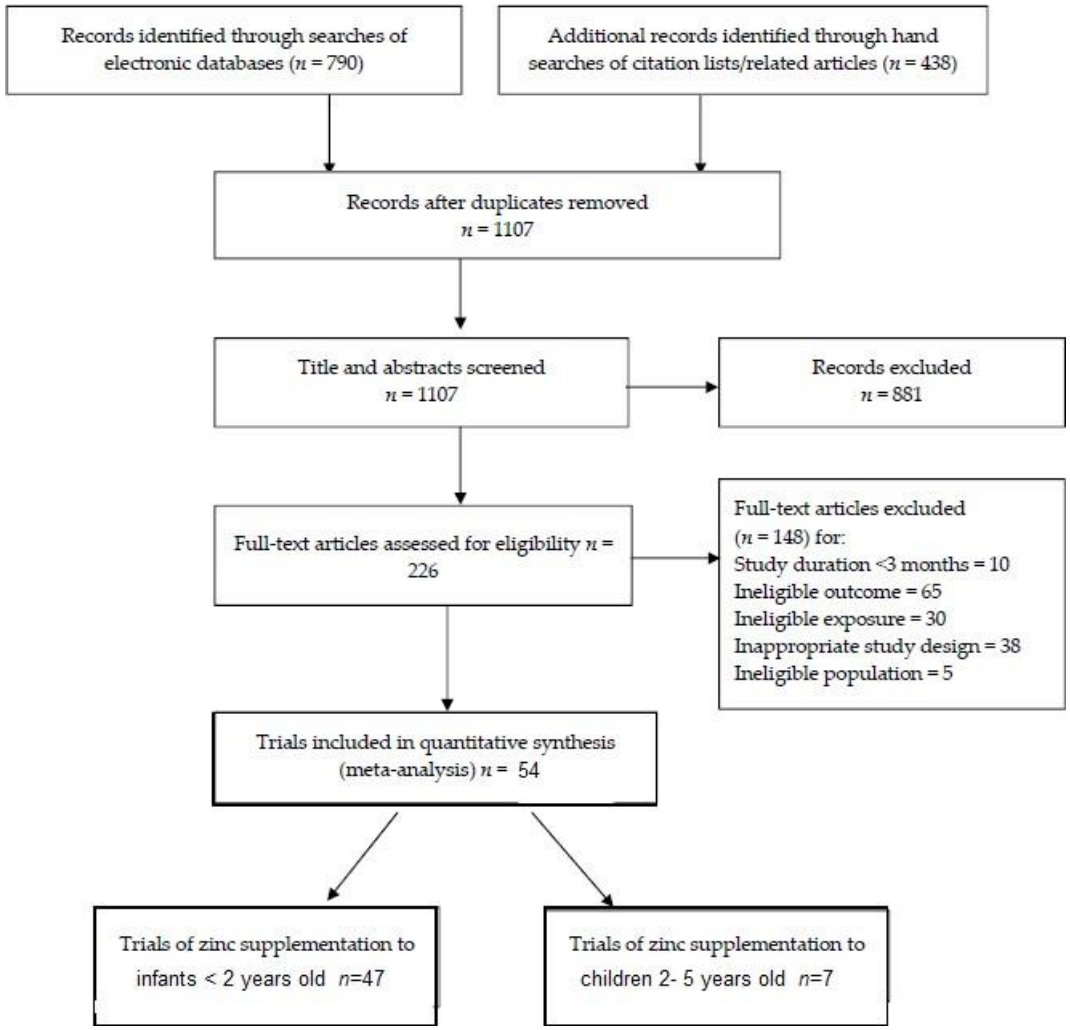

Figure 1. *PRISMA Flowchart of study selection and inclusion.*

Table 1. Summary of 54 randomized controlled trials included in the meta-analysisof the effect of zinc supplementation during infancy, or childhood on growthoutcomes.

	Infants (<2 Years)	Children (2–5 Years)
Trials [1], *n*	47	7
Total participants, *n*	20,412	773
Subject socioeconomic status [2]	Low, 37; Medium, 6; High, 3; -, 1	Low, 5; Medium, 1; High, 0; -, 1
Mean age (range)	8.7 (0–23.5) months	43.4 (28.7–55.8) months
Mean gestational age, weeks (range)		
Mean supplement duration, weeks (range)	30.9 (12.0–78.0)	38.9 (26.0–64.5)
Mean duration to last f/u, weeks (range)	34.7 (12.0–87.0)	43.8 (26.0–64.5)
Mean zinc dose, mg/day (range)	7.6 (2.0–20.0)	8.5 (0.37–20.0)
Zinc Formulation	Acetate, 5; Gluconate 6; Sulfate 30, unknown 6	Gluconate, 1; Methionine, 1; Sulfate, 5
Growth outcomes	Weight, Height, WAZ, WHZ, HAZ, stunting, wasting, underweight	Weight, Height, WAZ, WHZ, HAZ, stunting, wasting, underweight
Quality score [3], *n* trials	Low, 6; Medium, 10; High, 31	Low, 1; Medium, 0; High, 6

LBW = Low birth weight; WAZ = Weight-for-age; WHZ = Weight-for-Height; HAZ = Height-for-age; BW = Birthweight; - indicates information is unavailable.

Table 2: Characteristics of infant and child trials

First author	Year	Country	study score*
Walravens	1983	USA	4
Matsuda	1984	Japan	1
Walravens	1989	USA	5
alravens	1992	France	5
Shrivastava	1992	India	2
Bates	1993	Gambia	6
Castillo-Duran	1994	Chile	4
Dirren	1994	Ecuador	5
Castillo-Duran	1995	Chile	5
Ninh	1996	Vietnam	5
Rosado	1997	Mexico	5
Rivera	1997	Guatemala	5
Gardner	1997	Jamaica	5
Kikafunda	1998	Uganda	5
Hershkovitz	1999	Israel	5
Shankar	2000	Papua Guinea	6
Osendarp	2001	Bangladesh	5
Dijkhuizen	2001	Indonesia	6

Castillo-Duran	2001	Chile	4
Yang	2002	China	3
Muller	2003	Burkina Faso	6
Sur	2003	India	6
Penny	2004	Peru	6
Black	2004	Bangladesh	5
Alarcon	2004	Peru	5
Black	2004	India	4
Lind	2004	Indonesia	6
Gardner	2005	Jamaica	2
Brooks	2005	Bangladesh	5
Berger	2006	Vietnam	6
Heinig	2006	USA	6
Silva	2006	Brasil	4
Olney	2006	Tanzania	3
Wasantwisut	2006	Thailand	6
Brown	2007	Peru	4
Garenne	2007	Burkina Faso	2
Fahmida	2007	Indonesia Indonesia Thailand	6
Dijkhuizen	2008	Vietnam	4
Wuehler	2008	Ecuador	4
Bueno	2008	Spain	4

Fischer Walker	2009	Bangladesh	5
Mozaffari-Khosravi	2009	Iran	5
Taneja	2009	India	5
Taneja	2009	India	6
Mazariegos	2010	Guatemala	5
Aminisani	2011	Iran	6
Chen	2012	China	2
Radhakrishna	2013	India	5
Owusu-Agyei	2013	Ghana	1
Soofi	2013	Pakistan	6
Colombo	2014	Peru	6
Adriani	2014	Indonesia	6
Abdollahi	2014	Iran	-2
Locks	2016	Tanzania	6

Table 3. Main and subgroup analyses of zinc supplementation during infancy/childhood on height and HAZ.

	Height (cm)					HAZ				
	n	MD (95%CI)	I^2	τ^2	*P*-interaction [1]	*n*	MD (95%CI)	I^2	τ^2	*P*-interaction [1]
Overall	40	0.23 (0.09–0.38)	66.9%	0.10		40	0.02 (−0.01, 0.06)	66.1%	0.00	
Child age at intervention										
0–<2 years	33	0.10 (−0.02 0.22)	44.7%	0.03	0.002	34	0.01 (−0.03, 0.04)	64.6%	0.00	0.06
2–5 years	7	1.37 (0.50, 2.25)	82.0%	0.82		6	0.12 (0.05, 0.19)	0.0%	0.00	
World region										
Africa	5	0.07 (−0.35, 0.49)	58.4%	0.09	0.86	5	0.05 (−0.09, 0.19)	78.9%	0.02	0.63
Asia	17	0.26 (0.03, 0.48)	78.4%	0.13		15	−0.02 (−0.06, 0.02)	49.2%	0.00	
Western	6	0.53 (0.19–0.88)	0.0%	0.00		6	0.05 (−0.07, 0.18)	61.0%	0.10	
Americas	12	0.25 (−0.03, 0.53)	48.8%	0.09		14	0.06 (−0.03, 0.14)	49.6%	0.10	
Socioeconomic status										
Lower	31	0.18 (0.03, 0.32)	60.6%	0.07	0.43	32	0.03 (−0.02, 0.07)	69.1%	0.01	0.99
Medium	5	0.88 (0.18–1.59)	89.2%	0.46		4	0.03 (−0.03, 0.07)	0.0%	0.00	
Higher	3	0.14 (−0.81, 1.08)	0.0%	0.00		2	0.13 (−0.26, 0.53)	72.3%	0.06	
Unknown	1	0.10 (−1.58, 1.78)		0.00		2	0.13 (−0.26, 0.53)	72.3%	0.07	
Intervention Duration										
<26 weeks	11	0.11 (−0.10, 0.31)	36.6%	0.03	0.79	9	0.05 (−0.06, 0.16)	39.4%	0.01	0.78
≥26 weeks	29	0.27 (0.08, 0.48)	71.6%	0.15		31	0.02 (−0.02, 0.06)	69.8%	0.01	
Intervention dose										
<8.4mg/day	18	0.37 (0.05, 0.70)	74.5%	0.28	0.67	17	−0.01 (−0.05, 0.04)	67.2%	0.00	0.23
≥8.4 mg/day	22	0.19 (0.03, 0.35)	58.2%	0.05		23	0.05 (−0.00, 0.10)	53.4%	0.01	
Zinc formulation										
Acetate	3	0.68 (−0.06, 1.42) (−0.54, 0.34)	69.9%	0.28	0.86	4	−0.05 (−0.11, 0.11) .	0.0%	0.09	0.58
Gluconate	6	0.23 (−0.24, 0.70)	89.2%	0.22		5	−0.01 (−0.05, 0.02)	69.4%	0.00	
Methionine	1	0.59 (−1.12, 2.29)	NA	NA		1	0.19 (−0.10, 0.49)	.	0.00	
Sulfate	25	0.23 (0.06, 0.40)	46.0%	0.05		27	0.03 (−0.01, 0.08)	72.3%	0.06	
Unknown	4	−0.01 (−0.64, 0.61)	75.2%	0.27		3	−0.05 (−0.11, 0.01)	0.0%	0.00	

1 p value for heterogeneity between subgroups based on meta-regression analysis.

Table 4. Main and subgroup analyses of zinc supplementation regarding publication year and quality score of the study during infancy/childhood on heightand HAZ.

	Height (cm)					HAZ				
	n	MD (95%CI)	I^2	τ^2	*P*-interaction [1]	*n*	MD (95%CI)	I^2	τ^2	*P*-interaction [1]
Publication year										
Before 2000	13	0.58 (0.20, 0.95)	30.5%	0.12	0.08	11	0.18 (0.08, 2.29)	34.6%	0.00	0.002
2000 and after	27	0.15 (0.001, 0.30)	68.6%	0.08		29	−0.01 (−0.04, 0.03)	60.3%		
Quality score [2]										
≤2	6	0.80 (−0.33, 1.92)	83.4%	1.45	0.23	3	−0.07 (−0.33, 0.20)	44.6%	0.02	0.33
3~4	7	0.25 (0.03, 0.48)	60.6%	0.04		9	−0.02 (−0.07, 0.04)	27.7%	0.00 0.01	
≥5	27	0.18 (−0.01, 0.37)	60.8%	0.11		28	0.04 (0.00, 0.09)	72.7%	0.00	

1 p value for heterogeneity between subgroups based on meta-regression analysis;2 Cumulative score (out of -6 to +6) on Cochrane Risk of Biastool.

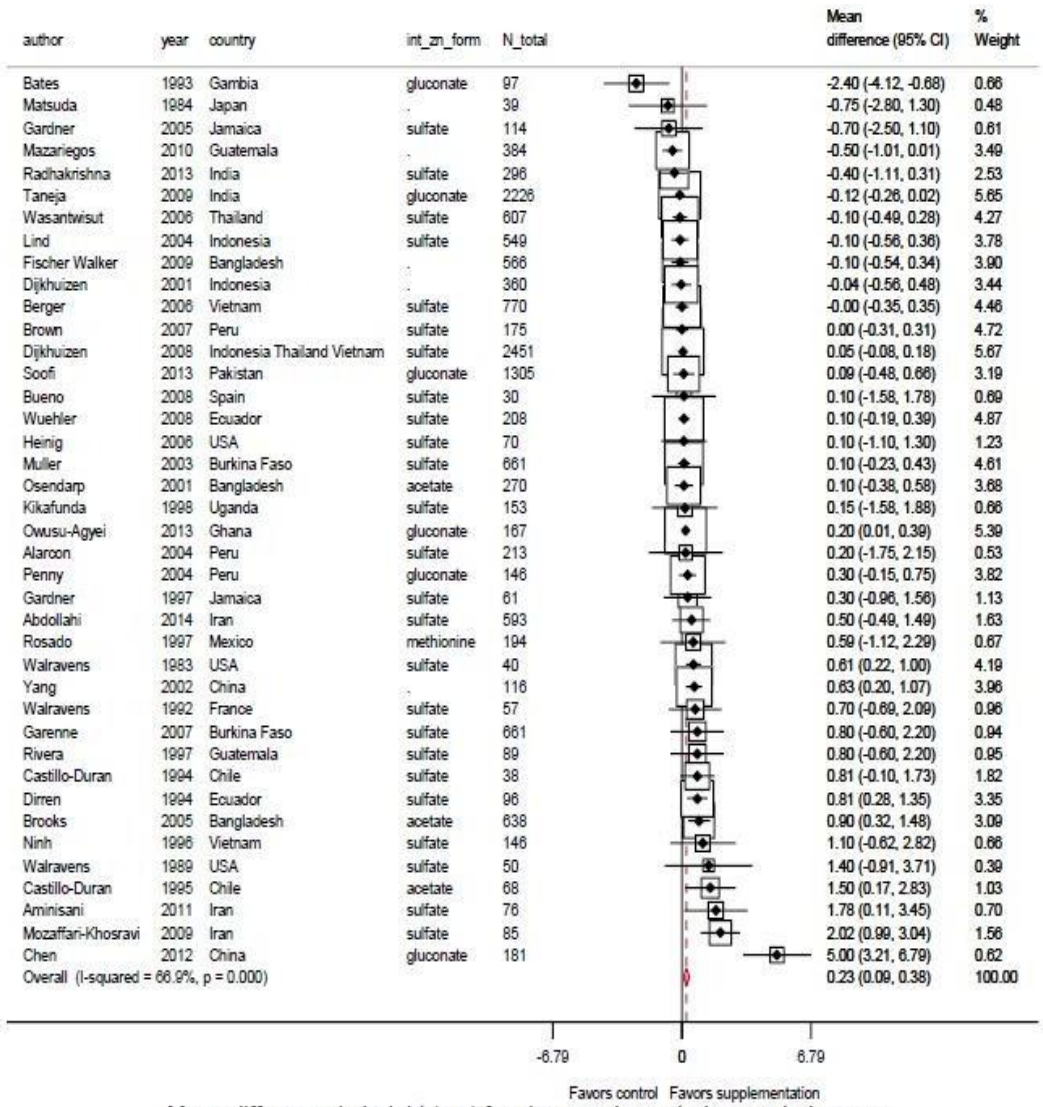

Figure 2. *Effect of zinc supplementation among children aged < 5 y old on heightin randomized controlled trials.*

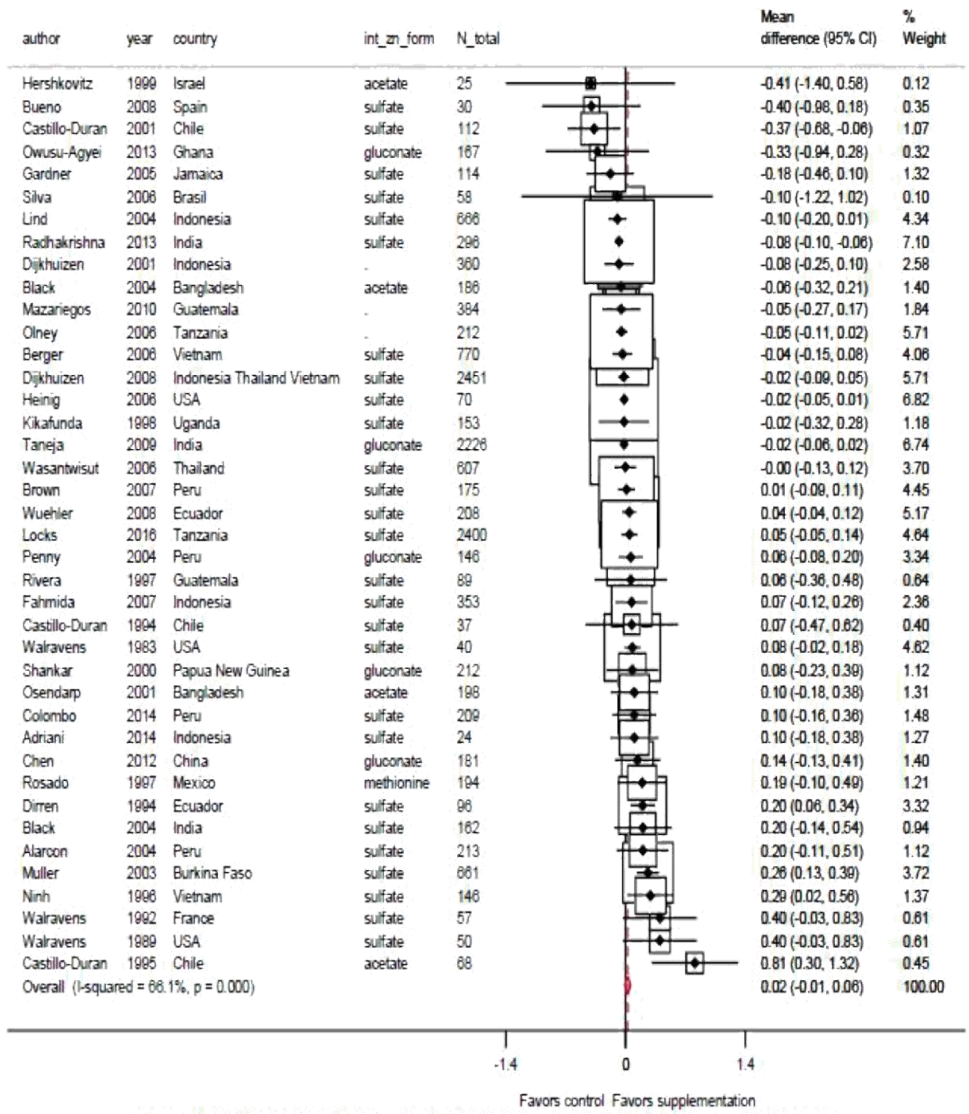

Figure 3. *Effect of zinc supplementation among children aged < 5 y old on HAZ in randomized controlled trials.*

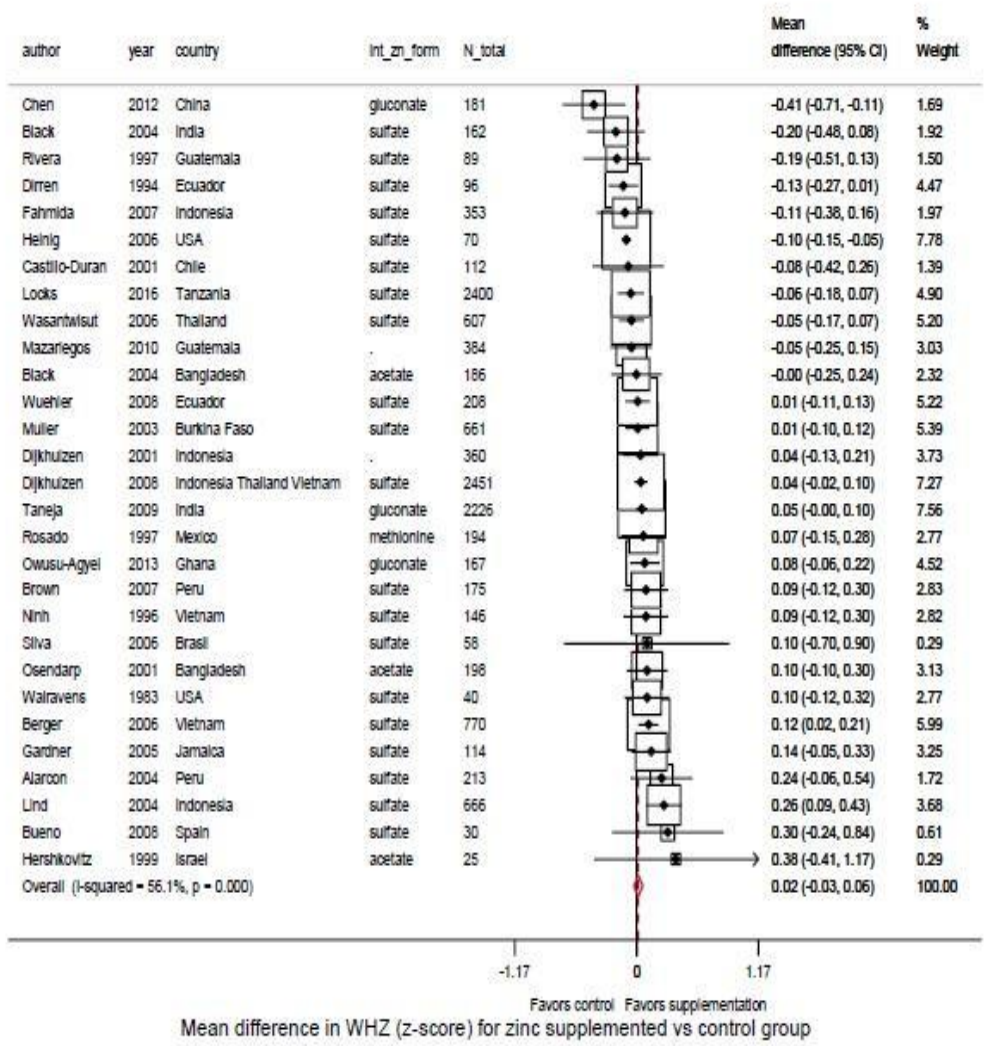

Figure 4. *Effect of zinc supplementation among children aged < 5 y old on WHZin randomized controlled trials.*

تحليل دراسي إحصائي للدراسات البحثية عن مكملات الزنك والتقزم في الأطفال عمرهم أقل من خمس سنوات

جيهان فؤاد احمد١، هناء صبري احمد٢ وايناس سيد عباس٣

١ عميد المعهد القومي للتغذية- القاهرة – مصر
٢ جامعة هارفرد
٣ قسم التغذية الاكلينيكية - المعهد القومي للتغذية -القاهرة – مصر

الملخص العربي

معدل التقزم في الأطفال المصريين يصل إلي ٢١% . تقزم الأطفال تعد مشكلة معقدة نتيجة أسباب متعددة خاصا الغذاء الناقص وغير متوازن و عدم تناول كميات كافية من الفيتامينات و المغذيات الدقيقة. إمكانية تقليل التقزم عن طريق العديد من التعديلات الغذائية مثل تناول المكملات المحتوية علي الزنك. حيث يعد عنصر الزنك من المعادن الهامة في نمو الطبيعي للعظام. هدف البحث هو معرفة قابلية وفاعلية تناول مكملات الزنك في تقليل معدل التقزم عن طريق البحث في المراجع الالكترونية البحثية عن الدراسات والمحاولات البحثية الإكلينيية الدولية في تأثير تناول مكملات الزنك في الرضع والأطفال أقل من خمس سنوات في العمر مع إتباع المعايير المطلوبة للتحليل الأحصائي للدراسات البحثية في الأنتقاء والتنفيذ والتحليل والتقرير للأبحاث. قد نتج عن ذلك اربع و خمسون دراسة نهائية. ووجد أن تناول مكملات الزنك لها تأثير كبير علي زيادة الطول بشكل واضح في الأطفال أكثر بالمقارنة بالرضع. أن معدل زيادة الطول في الأطفال أكثر من أو يساوي سنتين في العمر كان في سبع دراسات إكلينيكية١,٣٧ سم بينما في ست دراسات أخري كان ١٢ . ٠ سم . أن ٢٨ دراسة من ٤٠ (٧٠%) تظهر أن تناول مكملات الزنك له تأثير إيجابي علي زيادة الطول في الأطفال أقل من ٥ سنوات و لذلك نوصي بتناول مكملات الزنك لهولاء الأطفال من عمر ٢ - ٥ سنوات مع عمل دراسات أخري في هذا المجال .

الكلمات المفتاحية: *التقزم - الرضع – مكملات الزنك - الطول - الطفل*