SYSTEMATIC REVIEW

Zinc Supplementation for Prevention of Febrile Seizures Recurrences in Children: *A Systematic Review and Meta-Analysis*

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Background: Multiple studies have documented lower serum zinc levels in patients with febrile seizures in comparison to febrile patients without seizure. However, there is limited evidence comparing the effects of zinc supplementation with placebo on recurrence of febrile seizures in children. **Objectives:** To study the effects of zinc supplementation on recurrence rate of febrile seizures in children less than 60 months of age. **Design:** Systematic review and meta-analysis of randomized and quasi-randomized controlled trials. **Data Source and selection criteria:** We searched PubMed, EMBASE and CENTRAL databases for articles reporting randomized or quasi-randomized controlled trials comparing the effects of zinc supplementation with placebo on recurrence of febrile seizures in children aged less than 60 months. We performed a fixed effect meta-analysis to provide pooled odds ratio of febrile seizure recurrence. Quality of evidence was assessed using GRADE approach. **Participants:** Children aged less than 60 months. **Intervention:** Zinc supplementation **Outcome measures**: Odds of febrile seizure recurrence. **Results:** Four clinical trials with a total of 350 children were included in the review. There was no statistically significant difference between odds of febrile seizure recurrence during one year follow up, in children on zinc supplementation compared to those on placebo (OR 0.70; 95% CI 0.41 – 1.18, I^2 = 0%). **Conclusion:** Available evidence is very low quality and thus inadequate to make practice recommendations.

Keywords: *Epilepsy, Management, Outcome, Prevention, Recurrence.*

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Febrile seizures are the most common pediatric seizure disorder, primarily affecting children in the age group of 6 months to 5 years, with a global prevalence of 2-5% [1]. The pathophysiology of febrile seizures is not well understood and studies have identified various risk factors, including family history, genetic factors, metabolic changes and micronutrient deficiencies [2-5]. Putative role of zinc in the pathogenesis of febrile seizures has been hypothesized [6-8] with studies showing association of low zinc levels with higher neuronal excitability through its interactions with multiple ion channels and receptors [9-11]. A recent metanalysis found lower serum zinc levels in patients with febrile seizure compared to febrile cases without seizure [12]. However, there is limited available evidence about the role of zinc supplementation in prevention of febrile seizures recurrence, which this review attempts to identify, appraise and synthesize.

METHODS

This systematic review has been conducted in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13] The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database.

Search strategy and search eligibility: All authors independently searched the databases including PubMed, Embase, Cochrane Central Register of Controlled Trials, from inception to 28 September, 2020. Details of the electronic search strategy and the results are given as **Web Table I.** Cross references of all articles whose full text was screened, was also checked to find additional articles.

Inclusion criteria were original articles, in any language, having randomized or quasi-randomized controlled trial design; population included children less than 60 months of age; intervention studied was zinc supplementation; comparator being placebo; and outcome being febrile seizure recurrences during 1year follow-up.

Data extraction and quality assessment: Data were extracted by all authors independently using a pre-designed form. Any disagreements were resolved with consensus. The recorded details included lead author, year of publication, country, sample size, inclusion and exclusion criteria, gender distribution, mean age, type of zinc salt, dose of zinc, number of recurrences of febrile seizure in intervention and control group, and duration of follow-up.

Quality of each study was assessed using the criteria outlined in the Risk of bias tool in Cochrane handbook for

systematic reviews of interventions [14]. Quality of evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [15], and summary of findings table was generated on GRADEpro GDT software [16].

Statistical analysis: We performed a fixed effect meta-analysis to provide pooled odds ratio of febrile seizure recurrence. Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated for primary outcome. Heterogeneity was assessed using the I^2 statistics. Statistical analysis was performed using Review Manager version 5.4 [17]. .

RESULTS

Our search strategy yielded 132 articles and one additional article was included after manual search. Finally four articles with a total of 350 children were included in qualitative synthesis [18-21] (**Fig. 1**). **Table I** summarizes the characteristics of the included studies. Three of the included studies are from Iran [18-20], while one study was conducted in India [21]. One article was in Persian with English abstract [18]. Age of the children included varied across the studies. Studies by Fallah, et al. [19] and Kulkarni, et al. [21] included children with normal anthropometric measurements. Though zinc sulfate was used as intervention in all the four studies, the doses differed across the studies. All the studies had a follow-up of one year. While in the study by Ahmedabadi, et al. [18] and Fallah, et al. [19], follow up was conducted every three months, children enrolled in study by Kulkarni, et al. [21] were followed up on a monthly basis.

Three studies (18,20,21) had high risk of selection bias, performance bias and detection bias. **Web Fig. 1** summarizes risk of bias for each included study and **Web Fig. 2** depicts risk of bias graph as percentages across all studies. Publication bias was assessed with funnel plot (**Web Fig. 3**); however, this analysis was limited by small number of included studies. The pooled odds of recurrence of febrile seizure during one year follow up was less in intervention group, though it was not statistically

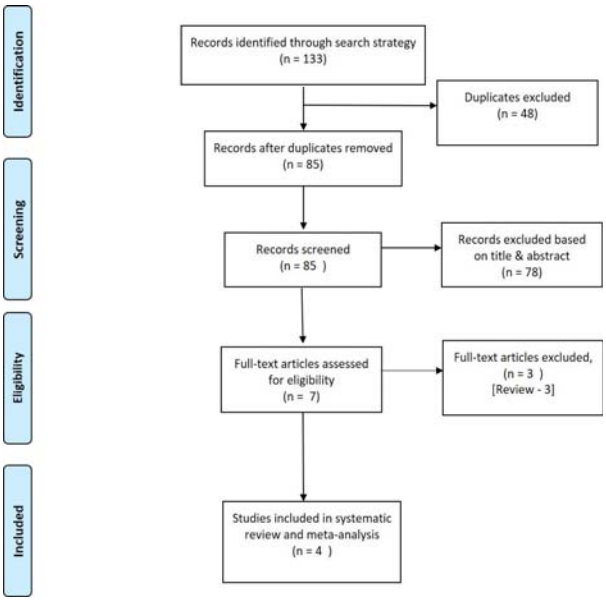

Fig.1 PRISMA flow diagram showing the study selection process.

significant (OR 0.70; 95% CI 0.41 – 1.18, I^2 = 0%). **Fig. 2** depicts the Forest plot for this outcome.

The quality of evidence pooled from included studies was assessed using GRADE approach and a summary of findings table (**Web Table II**) was generated on GRADEpro GDT software [16]. Due to inherent risk of bias of included studies along with inconsistent and imprecise results from these studies, the quality of evidence ranged from low to very low.

DISCUSSION

Available evidence from four randomized/quasi-randomized trials, including a total of 350 children, did not find any significant difference between recurrence rate of febrile seizure in children on zinc supplementation compared to children on placebo.

However, there were differences across the studies. While, Fallah, et al. [19] did not explain the reasons for their

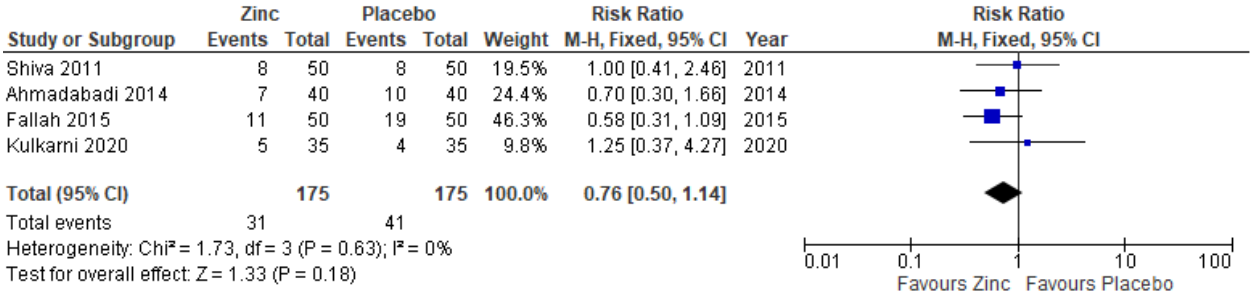

Fig. 2 Forest plot of effect of zinc supplementation on rate of febrile seizure recurrence in children less than 60 months of age.

Table I Characteristics of the Included Studies

Author; year; location	*Sample size (male: female)*	*Inclusion criteria*	*Exclusion criteria*	*Mean age*	*Serum zinc level before inter -vention (μg/dL)*	*Zinc salt; dose*	*Follow-up: duration; frequency*
Shiva; 2009; Iran	100 (60:40)	• Age 1-4 y		Intervention group: 2.1 (0.83) y Control group: 2.2 (1.04) y	Intervention group: 69.9 (10.8) Control group: 70.4 (8.77)	Zinc sulphate; 1mg/kg/d	1 y Not reported
Ahmeda-badi; 2011; Iran	80 (51:29)	• Age 1-5 y • Seizure duration < 15 min • Generalized tonic-clonic seizure • Only one seizure episode in 24 h • Normal neuro-logical develop-ment • No copper, calcium, iron supplementation • No special medication	• Copper, calcium, iron supplemen tation • Any special medication • Seizures associated with meningitis, abscess, Shigellosis • • •	Intervention group: 28.9 (16.19) mo Control group: 27.6 (13.5) mo		Zinc sulphate; 20 mg/d	1 y; Every three mo
Fallah; 2015; Iran	100 (59:41)	• Age: 18 to 60 mo • First simple febrile seizure • Weight and height above the third percentile (NHANES III) • Normal serum zinc level	• Received a zinc combination or supplementation within the past 2 mo • Central nervous system infections • History of previousfebrile or afebrile seizure, neuro developmental delay • Presence of any chronic systemic diseases • Iron deficiency, iron deficiency anemia	Intervention group: 2.37 (0.93) y Control group: 2.58 (1.07) y	Intervention group: 81.7 (13.3) Control group: 84.7 in (12.3)	Zinc Sulfate; 2 mg/kg/d (max 50 mg)	1 y; Every three mo
Kulkarni; 2020; India	70 (39:31)	• Age: 6-60 mo • Simple febrile seizures • Normal anthro-pometric measure-ments	• Taking zinc supplement • Apparent neuro-logical disturbance other than febrile seizure • Failure to thrive	Intervention group: 1.9 (1.01) y Control group: 1.8 (1.14) y	Intervention group: 65.4 (12.21) Control group: 67.3 (9.85)	Zinc Sulfate; 1mg/kg/d	1 year; Every mo

assumption of such a large difference, while calculating the sample size, the other three studies did not mention their strategy for calculation of sample size. Further, the study populations were not similar with respect to inclusion and exclusion criteria. Age groups of children enrolled in included studies had significant variation. Given the fact that febrile seizures are an age-dependent phenomenon with reported peak incidence between 12–18 months [22], such variations may have important ramifications in rate of febrile seizure recurrences across studies. Also, evolving evidence suggests that serum zinc level is lower in patients with febrile seizure [12]. In this light, variation in dose of zinc supplementation in intervention groups of the included studies can affect febrile seizure recurrences. Three of the included studies are on Iranian population, which may affect the generalizability of results for other population group.

Though we searched large and representative databases for this review, we recognize the limitation of not having searched other databases. Available evidence pertaining to zinc supplementation for prevention of febrile seizures is of low to very low quality and thus inappropriate to make a practice recommendation. Included trials were inadequately powered with high risk of bias. Further research, in the form of methodologically robust, multicentric randomized controlled trials, is needed.

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Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

Contributors: MK: conceptualized the review, literature search, data analysis and manuscript writing; SS: literature search, data analysis and manuscript writing; SK: literature search, data analysis and manuscript writing. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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REFERENCES

1. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics. Febrile seizures: Clinical Practice Guideline for the Long-Term Management of the Child with Simple Febrile Seizures. Pediatrics. 2008;121:1281-6.
2. Audenaert D, Van Broeckhoven C, De Jonghe P. Genes and loci involved in febrile seizures and related epilepsy syndromes. Hum Mutat. 2006;27:391-401.
3. Kang J-Q, Shen W, Macdonald RL. Why does fever trigger febrile seizures? GABAA receptor gamma2 subunit mutations associated with idiopathic generalized epilepsies have temperature-dependent trafficking deficiencies. J Neurosci. 2006;26:2590-7.
4. Dubé C, Vezzani A, Behrens M, et al. Interleukin-1â Contributes to the Generation of Experimental Febrile Seizures. Ann Neurol. 2005;57:152-5.
5. Reid AY, Galic MA, Teskey GC, Pittman QJ. Febrile seizures: current views and investigations. Can J Neurol Sci. 2009;36:679-86.
6. Reid CA, Hildebrand MS, Mullen SA, et al. Synaptic Zn2+ and febrile seizure susceptibility. Br J Pharmacol. 2017; 174:119-25.
7. Tütüncüoðlu S, Kütükçüler N, Kepe L, et al. Proinflammatory cytokines, prostaglandins and zinc in febrile convulsions. Pediatr Int. 2001;43:235-9.
8. Hildebrand MS, Phillips AM, Mullen SA, et al. Loss of synaptic Zn2+ transporter function increases risk of febrile seizures. Sci Rep. 2015;5:17816.
9. Marger L, Schubert CR, Bertrand D. Zinc: An underappreciated modulatory factor of brain function. Biochem Pharmacol. 2014;91:426-35.
10. Paoletti P, Vergnano AM, Barbour B, Casado M. Zinc at glutamatergic synapses. Neuroscience. 2009;158:126-36.
11. Khosravani H, Bladen C, Parker DB, et al. Effects of Cav3.2 channel mutations linked to idiopathic generalized epilepsy. Ann Neurol. 2005;57:745-9.
12. Heydarian F, Nakhaei AA, Majd HM, Bakhtiari E. Zinc deficiency and febrile seizure: A systematic review and meta-analysis. Turk J Pediatr. 2020;62:347-58.
13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ. 2009;339:b2700.
14. Assessing risk of bias in a randomized trial. Accessed September 29, 2020. Available from*: https://training.cochrane.org/handbook/current/chapter-08*
15. RevMan. Accessed September 29, 2020. Available from: *https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman*
16. GRADE handbook. Accessed September 29, 2020. Available from: *https://gdt.gradepro.org/app/handbook/handbook.html*
17. GRADEpro. Accessed September 29, 2020. Available from: *https://gradepro.org/*
18. Ahmadabadi F, Mirzarahimi M, Samadzadeh M, et al. The efficacy of zinc sulfate in prevention of febrile convulsion recurrences. J Isfahan Med Sch. 2014;31:1910-8.
19. Fallah R, Sabbaghzadegan S, Karbasi SA, Binesh F. Efficacy of zinc sulfate supplement on febrile seizure recurrence prevention in children with normal serum zinc level: A randomised clinical trial. Nutrition. 2015;31: 1358-61.
20. Shiva S, Barzegar M, Zokaie N, Shiva S. Dose supplemental zinc prevents recurrence of febrile seizures? Iran J Child Neurol. 2011;5:11-4.
21. Kulkarni S, Kulkarni M. Study of zinc supplementation in prevention of recurrence of febrile seizures in children at a tertiary care center. MedPulse Int J Pediatr. 2020;13:1-4.
22. Leung AK, Hon KL, Leung TN. Febrile seizures: an overview. Drugs Context. 2018;7:21253.

Web Table I Search Strategy

Database	*Search query*	*Results*
PubMed	(((((("febrile seizure"[Title/Abstract]) OR ("febrile seizures"[Title/Abstract])) OR ("febrile fits"[Title/Abstract])) OR ("Febrile Convulsions"[Title/Abstract])) OR ("febrile convulsion"[Title/Abstract])) AND ((Zinc[Title/Abstract]) OR ("zinc"[MeSH Terms]))	35
EMBASE	('zinc'/exp OR 'zinc') AND 'febrile convulsion'	92
CENTRAL	("zinc"): ti,ab,kw AND ("febrile seizure"): ti,ab,kw	5

Web Table II Summary of findings

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With Zinc		Risk with placebo	Risk difference with Zinc
Febrile Seizure Recurrence											
350 (4 RCTs)	very serious [a]	serious [b]	not serious	serious [c]	all plausible residual confounding would reduce the demonstrated effect	⨁◯◯◯ VERY LOW	41/175 (23.4 %)	31/175 (17.7 %)	**OR 0.70** (0.41 to 1.18)	234 per 1,000	**58 fewer per 1,000** (from 123 fewer to 31 more)

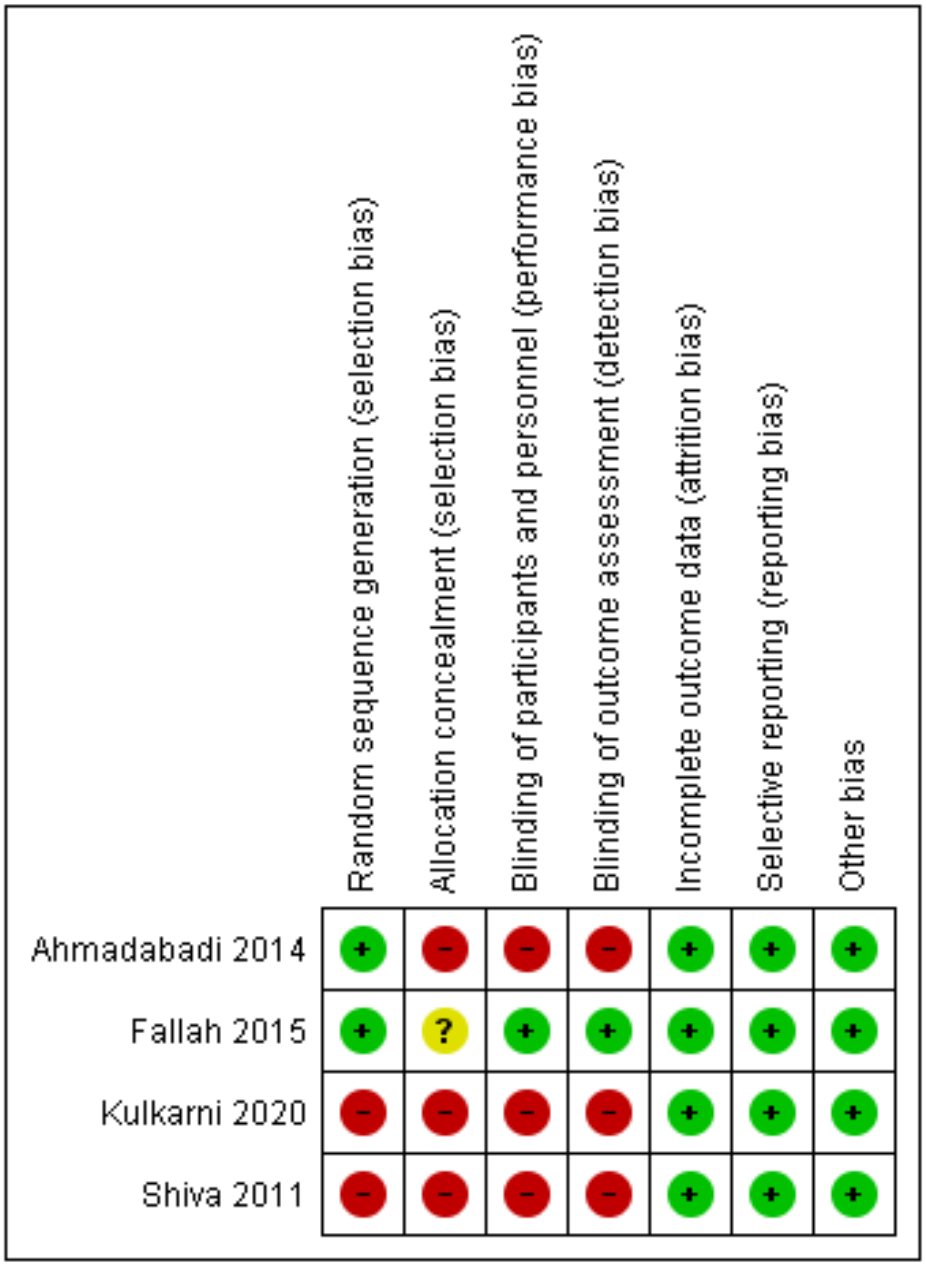
CI: Confidence interval; **OR:** Odds ratio

Explanations

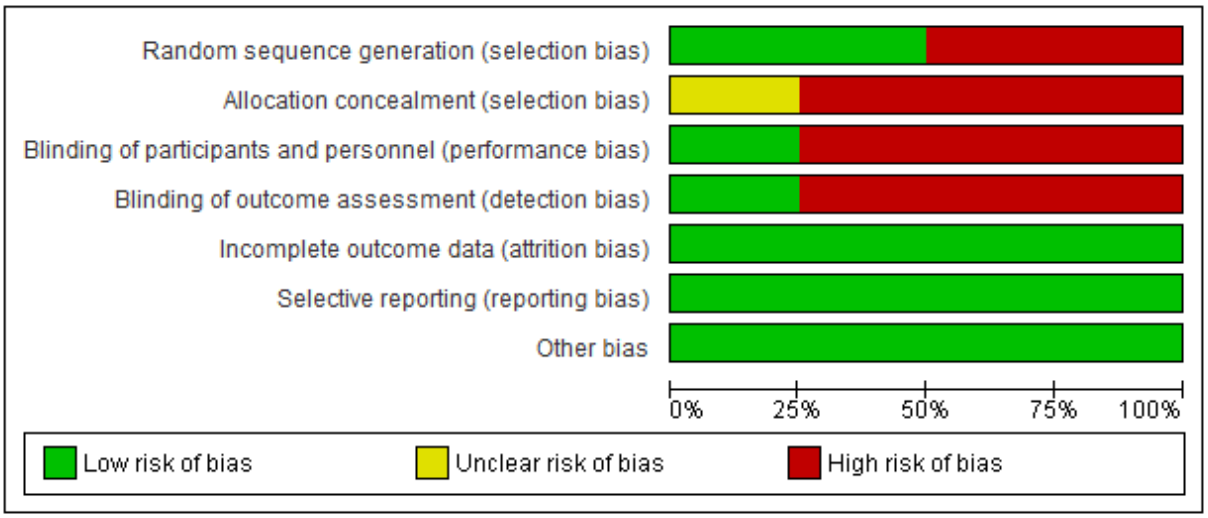
a. Shiva 2011, Ahmadabadi 2014 and Kulkarni 2020 had significant risk of bias

b. Odds of recurrence of febrile seizure in intervention group was more in study by Kulkarni 2020 unlike other 3 studies

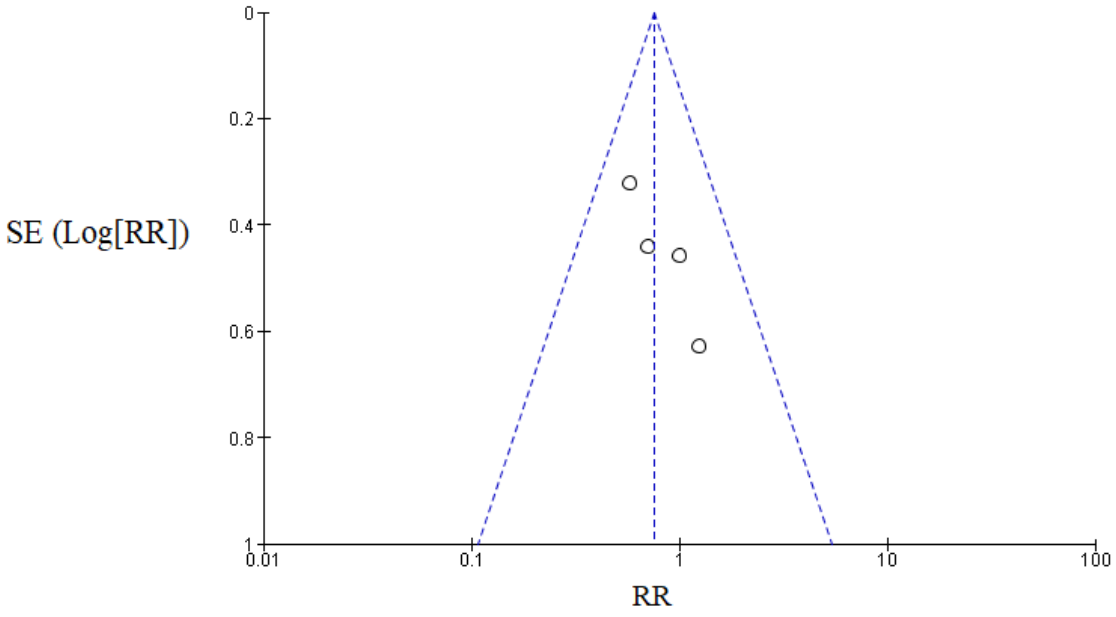
c. Pooled 95% CI for odds ratio is wide



Web Fig. 1 Risk of bias summary depicting authors' judgement regarding risk of bias for each included study.



Web Fig. 2 Risk of bias graph depicting authors' judgement regarding individual risk of bias item as percentages across all studies.



Web Fig. 3 Funnel plot depicting publication bias related to effect of zinc supplementation on rate of febrile seizure recurrence in children less than 60 months of age.