

# Zinc deficiency and febrile seizure: a systematic review and meta-analysis

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## ABSTRACT

**Background and objectives.** Zinc has been reported to be low in children with febrile seizure compared to febrile cases without seizures, but results are inconsistent. A meta-analysis was performed to systematically evaluate the serum level of zinc in febrile children aged between 6-72 months with or without seizures.

**Material and methods.** A systematic search of databases was performed from January 2000 to January 2019. Studies comparing the serum level of zinc in febrile children with or without seizure were selected.

**Results.** The major outcome was serum level of zinc. Random effect model was used to calculate pooled standardized mean differences (SMD) with 95% confidence intervals (CIs). A total of 31 articles were included. Meta-analysis suggested that the serum level of zinc is lower in patients with febrile seizure versus febrile cases without seizure (SMD: -1.2, 95%CI= (-1.47, -0.93). In subgroup and sensitivity analysis no significant change was observed in pooled SMD. In meta-regression analysis sample size as a continuous variable had a significant influence on between-study variance ( $p=0.02$ ). According to cumulative analysis the difference of serum level of zinc in febrile children with or without seizure decreased with time.

**Conclusion.** This meta-result indicated a significant association of zinc deficiency with seizure in febrile children. It is suspected that decreased level of zinc may be involved in seizure occurrences and it may play a role in the pathogenesis of febrile seizure.

**Key words:** febrile seizure, children, zinc levels.

Seizure is one of the most common life-threatening events in childhood.<sup>1</sup> Febrile seizure (FS) has been defined as seizure in correlation with a febrile disease without the infection of the central nervous system (CNS) or acute imbalance of electrolytes in absence of previous afebrile seizures in children aged more than 1 month. The prevalence of FS is 3-5% worldwide.<sup>2,3</sup> FS could be simple or complex which is differed in frequency and duration.<sup>4</sup> Seizure is a result of abnormal and extreme discharge of cortical neurons in the CNS. Neuronal synapses are

responsible for the composition of excitatory or inhibitory signals in the post-synaptic space as well as chipping in the basal making of neuronal networks in the brain.<sup>5</sup> Trace elements have several influences in the CNS. They are involved in Ion channels, synaptogenesis, membrane lipid peroxidation, etc. Over the past years, it was considered that trace elements may play a role in the pathogenesis of febrile seizure. It has been suggested that zinc as an essential trace element plays a role in the pathogenesis of seizures.<sup>6</sup> There are many studies comparing the serum level of zinc in febrile seizure. In some studies levels of zinc in febrile seizure have been reported to be lower when compared with febrile cases without seizures<sup>7-9</sup> but in some studies no significant difference was reported.<sup>10-12</sup>

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To the best of our knowledge there is only one systematic review and one meta-analysis evaluating the serum or CSF level of zinc in patients with FS.<sup>2,13</sup> They reviewed published papers until 2013 and had different inclusion criteria compared with the present study. In one systematic review<sup>2</sup> the control group included were febrile cases, afebrile seizure and healthy children. On the other hand, there are more than 15 published papers comparing the serum level of zinc in febrile children with or without seizures between the years 2013 and 2018 with different results.<sup>7,8,14-22</sup> Therefore, the present updated review was carried out to systematically evaluate relevant papers comparing the serum level of zinc in febrile patients with or without seizures until January 2019.

## Material and Methods

### *Research strategy and study selection*

Published papers were searched by 2 independent researchers (EB and FH) in relevant databases including Pubmed, Scopus, Cochrane library and web of science from January 1th, 2000 up to January 31th, 2019. Also e-publications ahead of print were searched in Pubmed. Disagreement between the two independent researchers was verified by the third researcher (AA). The reference lists of all verified studies were also checked to detect additional relevant articles. Searched key words were ["febrile seizure" OR "febrile convulsion"] AND ["level" OR "concentration" OR "profile"] AND ["zinc"] AND ["serum" OR "plasma"] and ["deficiency"]. The present systematic review was conducted according to the standard protocol for meta-analyses of observational studies. Inclusion criteria were original case-control, nested case-control and cross-sectional papers studying febrile children aged 6-72 month with or without seizures without any neurological disorders. Full-text of English articles and English abstract of non-English articles were included. Exclusion criteria were animal or laboratory studies, review

studies, randomized clinical trials (RCT), non-controlled studies, healthy controls or control groups with epilepsy, afebrile seizure or any neurological complications or having received any pharmacological treatment. Articles which did not provide necessary data including patient's age, number of patients in each group and mean±SD of zinc level were excluded.

The following information was extracted from each article included: first author, year of publication, country of study, number of subjects in case and control groups, mean±SD of zinc level in both groups, significant difference between groups and method of zinc measurement. Studies were scored according to NOS (Newcastle-Ottawa Quality Assessment Scale Case-Control Studies).<sup>23</sup> Articles with at least 5 stars were considered as good quality and included in the meta-analysis. The present research was reviewed and approved by Mashhad University of Medical Sciences review board (code: 970646, ethic code: IR.MUMS.MEDICAL.REC.1398). Because the present study was a systematic review and did not relate to patients directly, it was not necessary to provide informed consent form.

### *Quantitative data synthesis and data analysis*

The data were extracted and meta-analysis was used to pool them. Results were expressed as standardized mean differences (SMD) with 95% confidence intervals (95%CI). If a study only reported the median, range and/or inter-quartile range (IQR); mean and standard deviation (SD) were estimated, as described by Wan et al.<sup>24</sup> Heterogeneity was checked using I<sup>2</sup> statistics. Heterogeneity was considered significant if I<sup>2</sup> was more than 50%. In significant heterogeneity, data were analyzed using random effect modelling.<sup>25</sup> Sensitivity analysis was applied to the evaluation of the results constancy. In order to discover the probable sources of heterogeneity, subgroup analysis, based on study sample size, method of zinc measurement and match of demographic characteristics was performed. Meta-regression was also performed to further explore which variables contribute to

substantial heterogeneity. Cumulative analysis was also performed to detect the time-based changes in the magnitude of research findings.

Publication bias was also verified by visually check of Begg's funnel plot symmetry and Egger's regression test.<sup>26</sup> There is significant publication bias if  $P < 0.05$ . The data were analyzed using comprehensive Meta-analysis software version 2.2.064 (Biostat, Englewood, NJ, USA).

## Results

### Search and study selection

The primary literature search retrieved 558 articles. Some articles were removed because they were not original studies; some were excluded because of duplication. Some articles were excluded, because they were books, book section, review paper or animal studies. Some studies were excluded because they had no control group or they had a control group with different inclusion criteria. Finally, 31 articles were included in the present review.<sup>7-12,14-22, 27-42</sup> All were case-control or cross sectional. The diagram of the study selection process is presented in Figure 1. Details of studies included are presented in Table I.

### Serum level of zinc

Serum level of zinc was reported in 31 studies. Totally 3642 febrile children with or without seizures were included as FS and febrile group without seizure. In the FS group there were 1803 patients and in the febrile group without seizure there were 1839 patients. A significant lower serum level of zinc in febrile seizure versus febrile children without seizure was reported in 27 studies.<sup>7-9,14-22,28-42</sup> In 4 studies no significant difference between groups was reported.<sup>10-12,27</sup> Totally 31 studies were included in the meta-analysis.<sup>7-12,14-22,27-42</sup> Meta-analysis using random effect modelling, suggested that patients with FS had a significantly lower serum level of zinc in comparison with febrile patients without seizure (SMD: -1.2, 95% CI:

(-1.47, -0.93),  $P$  value  $< 0.001$ ,  $I^2$ : 92.62%). Forest plot is shown in Figure 2.

### Heterogeneity analysis

To assess the probable sources of heterogeneity in the results, subgroup, meta-regression and sensitivity analysis were carry out. In the subgroup analysis, the SMD of serum levels of zinc did not differ substantially according to sample size, method of zinc measurement or matching of demographic characteristics (Table II). Higher serum levels of zinc were observed in the febrile seizure patients compared with febrile cases without seizure across all subgroups. To additionally explore the potential sources of heterogeneity within the results; meta-regression analysis was performed by considering all the potential factors including sample size, method of zinc measurement and matching of demographic characteristics. According to the meta-regression analysis, sample size ( $p = 0.02$ ) was found to be a significant contributing factor for

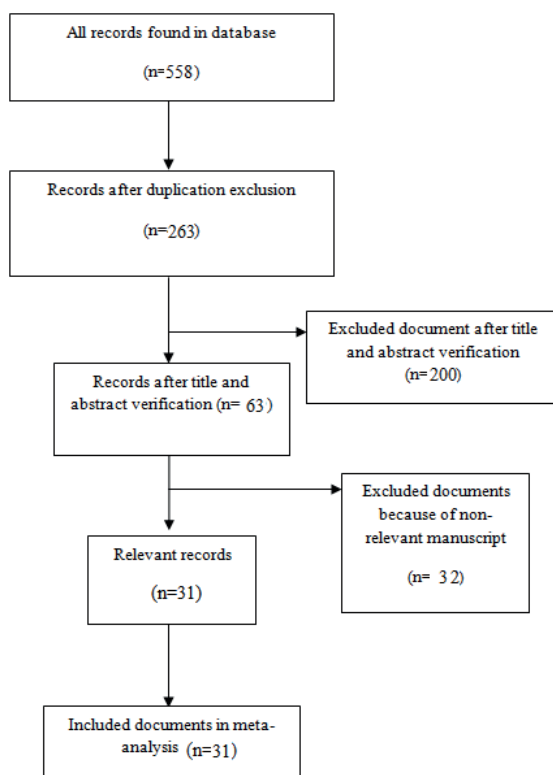


Fig. 1. Diagram of study selection.

**Table I.** Characteristics of eligible studies included in pooled SMD analysis.

Author	Country	Age group (month)	Sample size (FS)	Sample size (febrile)	Serum level of zinc(FS) (µg/dl)	Serum level of zinc (control) (µg/dl)	Significant difference	Matched	Method of measurement	Study design
El-masry (2018)	Egypt	6-60	40	40	44.27 ± 26.5 (µg/dl)	69.9 ± 33.94 (µg/dl)	yes	yes	Other methods	Case-control
Hubaira (2018)	India	6-60	100	100	61.53 ± 15.87 (µg/dl)	71.90 ± 18.5 (µg/dl)	yes	yes	Colorimetric test kits	Case-control
Sampathkumar (2018)	India	6-72	100	200	59.17 ± 10.39 (µg/dl)	73.12 ± 15.15 (µg/dl)	yes	Not declared	Calorimetric method	Cross sectional
Maheshwari (2018)	Pakistan	6-36	60	60	62.82 ± 14.66 (µg/dl)	79.03 ± 24.17 (µg/dl)	yes	yes	Randox Elisa kit	Cross sectional
Pravin Soni (2017)	India	6-60	120	120	62.5 ± 3.43 (µg/dl)	72.14 ± 7.39 (µg/dl)	yes	Not declared	Colorimetric Test kits	Case-control
Nemichandra (2017)	India	6-60	82	82	8.93 ± 2.01 (µmol/l)	12.74 ± 3.47 (µmol/l)	yes	yes	Calorimetric method	Case-control
Khajeh (2016)	Iran	6-60	30	30	56.86 ± 52.78 (µg/dl)	96.14 ± 53.46 (µg/dl)	yes	yes	Spectrophotometry	Case-control
Shokrzadeh(2016)	Iran	6-72	92	93	0.43 ± 0.38 (mg/l)	0.66 ± 0.37 (mg/l)	yes	Not declared	Spectrophotometry	Case-control
Bonu (2016)	India	6-60	44	40	76.8 ± 24.4 (mg/l)	90.1 ± 14.6 (mg/l)	yes	yes	Spectrophotometry	Case-control
Namakin (2016)	Iran	6-60	48	48	80.5 ± 21.7 (mg/l)	117.2 ± 35.5 (mg/l)	yes	yes	Spectrophotometry	Case-control
Gatto (2015)	India	6-60	100	100	61.53 ± 15.87 (µg/dl)	71.90 ± 18.50 (µg/dl)	yes	Not declared	Colorimetric test kits	Case-control
Pannerselvam (2015)	India	6-60	50	50	68.4 ± 25 (µg/dl)	94.1 ± 36.8 (µg/dl)	yes	Not declared	Calorimetric method	Cross sectional
Sreenivasa (2015)	India	6-60	50	50	61.53 ± 16.87 (µg/dl)	50.49 ± 15.17 (µg/dl)	yes	Not declared	Colorimetric method	Cross sectional
Salah (2014)	Egypt	6-72	20	20	52.8 ± 24.4 (µg/dl)	56.1 ± 23.5 (µg/dl)	no	yes	Spectrophotometry	Cross sectional
S. Joshi (2014)	India	6-60	50	50	155.09 ± 17.57 (µg/dl)	132.04 ± 14.7 (µg/dl)	no	yes	Spectrophotometry	Case-control

mg: milligram, µg: microgram, dl: deciliter, l: liter, SMD: standardized mean difference.

Table I. Continue.

Author	Country	Age group (month)	Sample size (FS)	Sample size (febrile)	Serum level of zinc(FS) (µg/dl)	Serum level of zinc (control) (µg/dl)	Significant difference	Matched	Method of measurement	Study design
Mohammad Aly (2014)	Egypt	6-36	40	40	53±29 (µg/dl)	95 ± 11 (µg/dl)	yes	yes	Colorimetric method	Case-control
Taherya (2013)	Iran	6-60	40	40	70 (µg/dl)	90 (µg/dl)	yes	Not declared	Spectrophotometry	Case-control
Salehiomran (2013)	Iran	6-72	50	50	0.704 ± 0.179 (mg/l)	0.585 ± 0.166 (mg/l)	yes	yes	Spectrophotometry	Case-control
Amouian (2013)	Iran	6-60	160	160	13.33 ± 2.66 (µg/dl)	13.69 ± 2.60 (µg/dl)	no	yes	Photometric method	Case-control
Iyshwarya (2013)	India	6-60	20	20	67.25 ± 4.97 (µg/dl)	50.49 ± 5.17 (µg/dl)	yes	Not declared	Spectrophotometry	Case-control
Kafadar (2012)	Turkey	6-72	45	23	107.12 ± 21.66 (µg/dl)	110.49 ± 35.03 (µg/dl)	no	Not declared	Spectrophotometry	Cross sectional
Okposio (2012)	Nigerian	6-60	90	90	90.3 ± 33.0 (µg/dl)	58.7 ± 25.4 (µg/dl)	yes	yes	Spectrophotometry	Case-control
Modarresi (2011)	Iran	9-60	30	30	130.54 ± 25.89 (µg/dl)	93.39 ± 73.88 (µg/dl)	yes	Not declared	Spectrophotometry	Cross sectional
Margaretha (2010)	indonesia	6-60	25	25	13.72 ± 0.45 (µmol/l)	8.83 ± 1.23 (µmol/l)	yes	Not declared	Not declared	Cross sectional
Heydarian (2010)	Iran	6-60	30	30	758.33 ± 80.29 (µg/L)	663.7 ± 107.6 (µg/L)	yes	Not declared	Spectrophotometry	Case-control
Amiri (2010)	Iran	6-60	30	30	107.87 ± 28.79 (µg/dl)	66.13 ± 18.97 (µg/dl)	yes	Not declared	Spectrophotometry	Case-control
Radhakrishnan Palliana (2010)	India	6-60	75	50	90.38 ± 6.88 (µg/dl)	81.84 ± 13.23 (µg/dl)	yes	Not declared	Spectrophotometry	Case-control
Ehsanipour (2009)	Iran	6-60	34	40	90.1 ± 14.6 (mg/l)	76.8 ± 24.4 (mg/l)	yes	yes	Spectrophotometry	Case-control
Talebian (2009)	Iran	6-72	60	60	116.280 ± 50.1 (mg/dl)	146 ± 56.6 (mg/dl)	yes	Not declared	Centerior kit	Case-control
Mullah (2008)	Bangladesh	5-60	50	30	749.33 ± 73.19 (µg/l)	464 ± 64.57 (µg/l)	yes	yes	Spectrophotometry	Cross sectional

mg: milligram, µg: microgram, dl: deciliter, l: liter, SMD: standardized mean difference.

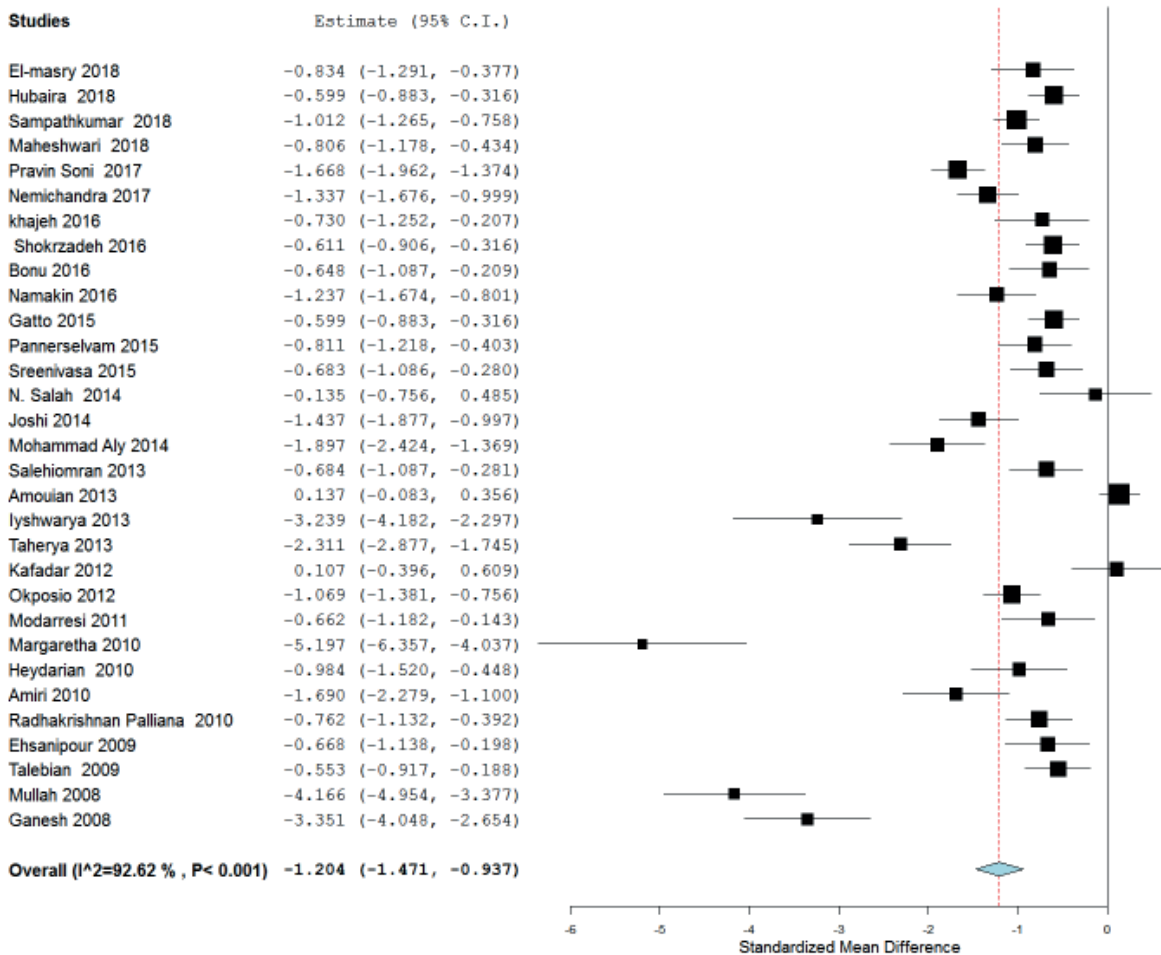


Fig. 2. The serum level of zinc in febrile children with or without seizure in pooled SMD.

Table II. Subgroup analysis of articles included according to sample size, method of zinc measurement and matched demographic characteristics.

Sub groups	No. of studies	Difference between FS and febrile group without seizure		Test of heterogeneity		
		SMD (95% CI)	p value	Model	I <sup>2</sup> (%)	P value
Sample size						
Less than 100	16	-1.66(-2.21,-1.1)	<0.001	R	93.67	<0.001
100 or more	15	-0.82 (-1.08, -0.57)	<0.001	R	89.53	<0.001
Method of zinc measurement						
Spectrophotometry	18	-1.29(-1.67,-0.9)	<0.001	R	91.58	<0.001
Other methods	13	-1.08(-1.46, -0.7)	<0.001	R	93.08	<0.001
Demographic characteristics matching						
Matched	16	-1.17(-1.57, -0.76)	<0.001	R	93.75	<0.001
Not declared	15	-1.23(-1.59, -0.87)	<0.001	R	91.38	<0.001

FS: febrile seizure, SMD: standardized mean difference, CI: confidence interval, R: random.

between study variance for SMD analysis but not method of zinc measurement ( $p= 0.82$ ) and matching of demographic characteristics ( $p= 0.58$ ).

In the sensitivity analysis the effect of each study on the overall pooled SMD was assessed. According to sensitivity analysis no significant change in the direction of pooled SMD was observed, indicating the stability and robustness of the results. Forest plot is shown in Figure 3.

### Cumulative analysis

In cumulative analysis studies were added according to date of publication and the results were summarized as each new study was added.

According to cumulative analysis the difference of serum level of zinc in febrile children with or without seizures decreased over time. Forest plot is shown in Figure 4.

### Publication bias

Begg’s funnel plot and Egger’s regression test are usually used to determine publication bias of the included studies. Egger’s test revealed significant asymmetry ( $p$  value=0.0006). Funnel plot is shown in Figure 5.

### Discussion

Presently, clinical evidence support the relationship between zinc deficiency and

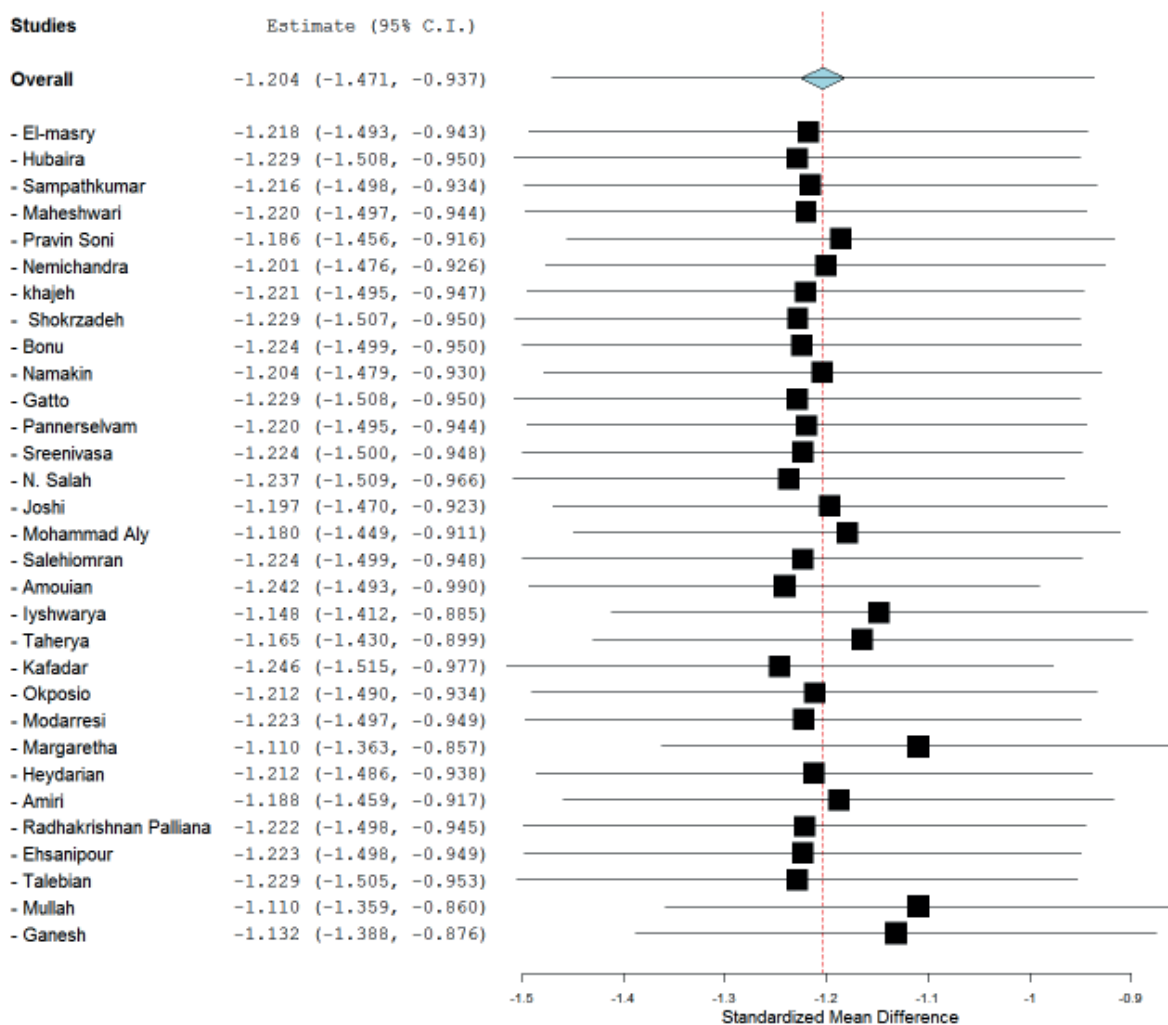


Fig. 3. Sensitivity analysis of included studies.

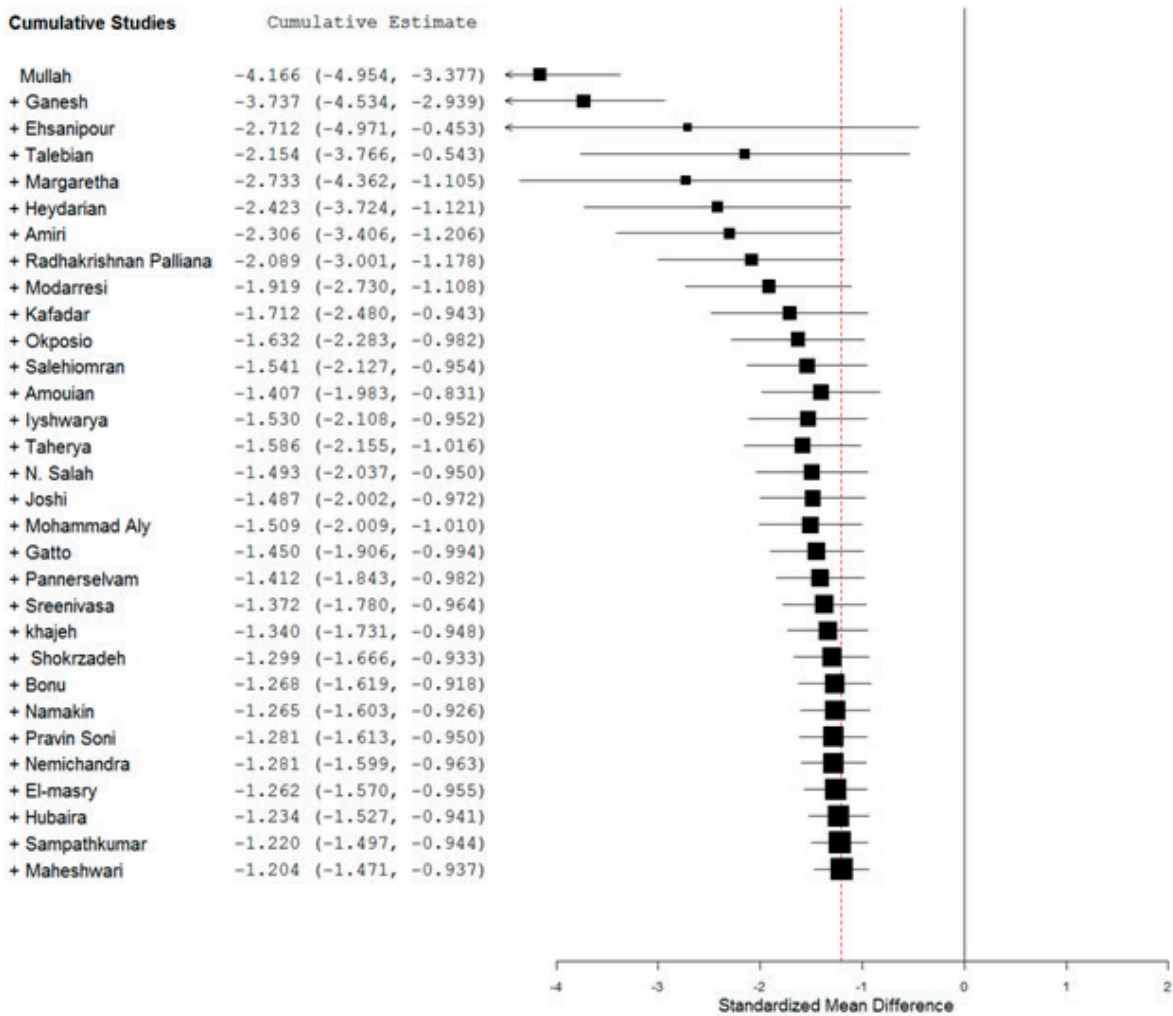


Fig. 4. Cumulative analysis of included studies.

seizure occurrence in febrile children. Therefore clinical data comparing the serum level of zinc in febrile children with or without seizures were systematically reviewed in the present study. According to a meta-analysis the serum level of zinc was significantly lower in FS children compared with febrile cases without seizure. In subgroup and sensitivity analysis no significant change was observed in pooled SMD. Sample size as continuous variable had a significant influence on between-study variance in the meta-regression analysis.

Daily intake of zinc is necessary because there is no storage system for zinc. Sources of zinc include whole grains, cheese, meat, shellfish and legumes.<sup>43</sup> Many people in developing

countries suffer from zinc deficiency, including approximately 79% in south Asia.<sup>44</sup>

Zinc is one of the essential trace elements in the body, an especially high level is required in the human brain. It is involved in many biological activities, metabolism and differentiation of cells. It is also effective in normal functioning and development of brain cells.<sup>45</sup> Zinc has also been recognized as a cofactor in the synthesis and secretion of neurotransmitters.<sup>46</sup> Pyridoxal phosphate (PP) is an essential cofactor for the biosynthesis of neurotransmitters in brain neurons. Hippocampus with nearly 30 µg/g dry weight has the most amount of zinc in brain tissues. Zinc is essential for the synthesis of PP.<sup>47</sup> Imbalance of zinc leads to



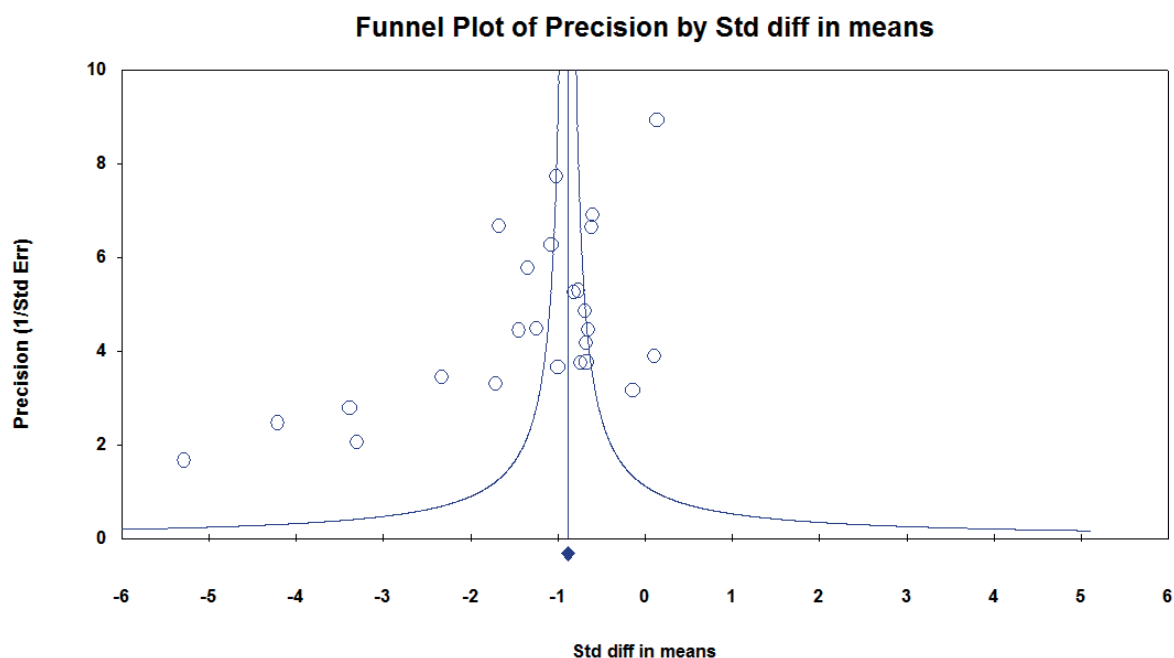


Fig. 5. The funnel plot of publication bias in pooled SMD analysis.

neurodegenerative disorders, oxidative stress, etc. Also the function of some proteins involved in seizures is affected by zinc imbalance. Some excitatory mechanisms can be suppressed by zinc. Zinc is a regulator of a rate-limiting enzyme, glutamic acid decarboxylase in the synthesis of gamma aminobutyric acid (GABA). Decrease of zinc leads to N-Methyl-D-Aspartate (NMDA) receptors activation, GABA inhibition and changes in calcium channel function. These changes could lead to seizure occurrence.<sup>48-50</sup> GABA brain level is reduced due to low serum level of zinc and as a result, threshold of seizure occurrence is reduced. Serum level of zinc can be affected by fever and acute phase response during infectious diseases. It is suggested that cytokines such as interleukin 6, interferon, tumor necrosis factor and interleukin 1 can reduce serum levels of zinc during infections.<sup>51</sup> So in cases with borderline serum level of zinc, infections may trigger hypozincemia.

As reviewed in the present study, the relationship between zinc and seizures was studied. To date, only one systematic review and one meta-analysis evaluating the serum or CSF levels of zinc in febrile seizures has

been published, but the inclusion criteria were different.<sup>2,13</sup> Additionally, more than 15 papers have been published between 2013 and 2018 with different results. Therefore, we felt a new systematic review and meta-analysis was necessary.

Between studies heterogeneity was a common finding in the meta-analyses. In the present study, the meta-analysis showed significant heterogeneity in the pooled SMD analysis. Sensitivity analysis, subgroup analysis and meta-regression were used to discover the possible causes of between-study heterogeneity as well as heterogeneity decrement. The results of the present review were robust. According to sensitivity analysis any single study did not affect the estimated pooled SMD. Meta-regression confirmed that the sample size of the study had a significant effect on the pooled SMD and could be considered as a confounder but not the method of zinc measurement and group matching. Cumulative analysis showed a decreasing trend in the difference of serum levels of zinc in febrile children with or without seizures during the time. Despite dietary intake and supplementation reducing

micronutrient and nutrient deficiencies, remain a common problem in developing countries. Therefore, preventative zinc supplementation may outweigh any potentially adverse effects in areas where risk of zinc deficiency is high.

This meta-result indicated a significant association of zinc deficiency with seizures in febrile children. It is suspected that decreased level of zinc may be involved in seizure occurrence and it may play a role in the pathogenesis of febrile seizure.

The major limitations of the present study were:

A) In spite of an attempt for a comprehensive search, it may be the case that some articles were missed. B) Despite subgroup analysis, significant heterogeneity was seen and could have influenced the results. C) Potential confounders were not verified in almost all of the studies so we were unable to analyze them. D) Publication bias may have affected the pooled results. E) Most included studies were case-controlled. It is well known that case-controlled studies have unavoidable limitations such as selection bias in case and control groups and many other confounders which may affect the pooled results.

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