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Original Article

Levels of Zinc and Iron Serum in Children with Febrile Seizures: Systematic Review and Meta-Analysis

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ABSTRACT

Background: Febrile seizures are common in the paediatric population; the frequency of febrile seizures is significantly influenced by hereditary variables. Other variables, such as zinc and iron, may play an important role on the febrile seizures occurrence. This study aims to assess zinc and iron levels relation in febrile seizure children.

Methods: Data sources published from PubMed, Proquest, Portal Garuda, and Web of Science published in 2000-2021 are carefully examined for relevant research published in English and Indonesian. We gathered and reviewed the total 30,849 journals. Only observational studies on the relationship between serum zinc and iron levels as well as the frequency of febrile seizures in children aged six months old to five years old had included. Analysis was on zinc and iron variables (SI, TIBC, and ferritin), and febrile seizures. Sensitivity analysis was performed after all the data were combined with a random effect or fixed effect model.

Results: On 30 case-control studies with a total of 4,158 patients. From zinc examination, there were 15 studies with 922 patients with seizures with fever and 666 patients with fever without seizures. The results showed that patients with fever with seizures had lower zinc levels than patients with fever without seizures (SMD= -1.36 [-1.89, -0.84], $p<0.00001$). On examination, ferritin and serum iron levels were found to be low compared to patients with fever without seizures, (SMD= -0.79 [-1.15, -0.43], $p<0.00001$ and SMD= -0.60 [-1.04, -0.16], $p=0.007$). Studies of total iron binding capacity found a significant difference between patients with fever and seizure compared to the patients with fever but no seizure.

Conclusion: Serum zinc and iron levels were low in febrile seizure children. This meta-analysis discovered a relationship between low zinc and iron levels and seizure in febrile children.

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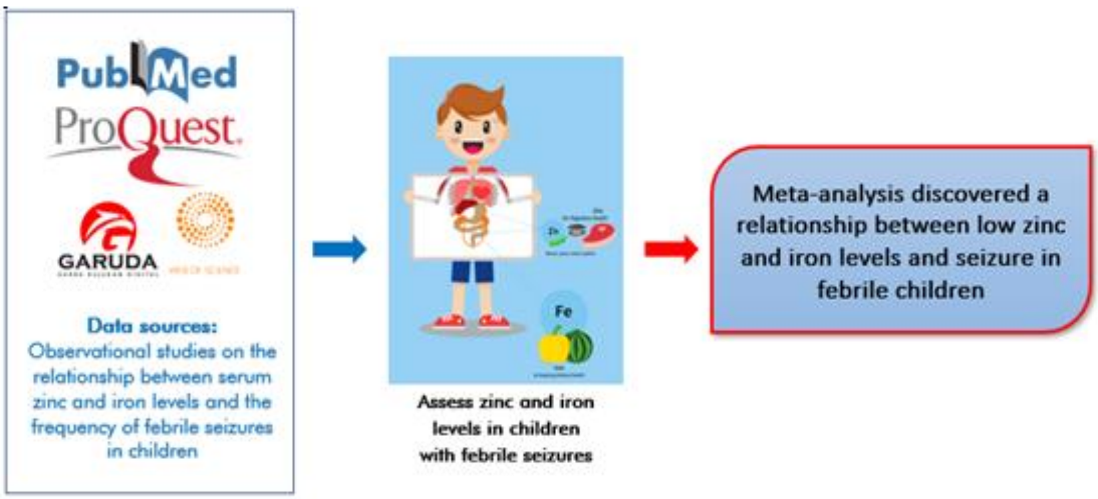
GRAPHICALABSTRACT



Introduction

Febrile seizures are cases that many found in the paediatric population. Research shows that patients with febrile seizure have an increased risk of developing mesial temporal sclerosis which may increase the likelihood of future focal epilepsy. Likewise, recent studies have shown that children, especially boys, with febrile seizures have an increased risk of attention-deficit/hyperactivity disorder [1].

In other studies, children with febrile seizures have a higher risk of atopic diseases such as allergic rhinitis and asthma. Similarly, the prevalence of hyperglycaemia stress which has been reported in children with febrile seizures.

On one national register study, 245 cases of sudden cardiac death were identified, of which 5.7% were treated with febrile seizures. The study demonstrated a significant two-fold increase in the frequency of febrile seizures before death in cases of sudden cardiac death at a young age compared to controls [1].

A febrile seizure is a seizure with a febrile condition without any Central Nervous System (CNS) infection or acute imbalance of electrolytes, without previous afebrile seizures in children above a month old [2].

The prevalence of febrile seizure in children is 3-5% [3, 4].

Cortical neurons in the CNS discharge abnormally and violently during seizures. Trace elements have influence in CNS in a number of ways. They participate in synaptogenesis, ion channels, membrane lipid peroxidation, and other processes. In the past, trace elements were assumed might be involved in the febrile seizures pathophysiology. There has been speculation that the necessary trace element zinc contributes to the seizures pathophysiology [5].

The action of various nervous system enzymes and neurotransmitters are influenced by iron as an essential micronutrient. Since iron is necessary for myelination, it is possible that having an iron will increase your risk of having seizures. Other effects of iron shortage include impaired sensory system performance, impaired motor function, and impaired cognitive development [6-8].

Numerous studies have been conducted to compare serum zinc levels in febrile seizures. When compared to fever patients without seizures, zinc levels in some investigations have been shown to be lower in febrile seizure cases. However, several investigations found no discernible difference [9-13]. Similar to iron, numerous researches have been carried out globally to determine the relationship between iron deficiency and febrile seizure, albeit the findings are debatable [14-16].

Previously, there has been a meta-analysis study conducted which showed a relationship between iron deficiency anaemia with the incidence of febrile seizures [17, 18]. While research by Heydarian *et al.* (2020) concluded there was a relationship between zinc deficiency and febrile seizures. We hypothesize that there is a relationship between zinc and iron levels with the incidence of febrile seizures in children.

This study aims to assess the relationship between zinc and iron level (SI, TIBC, and ferritin) with the incidence of febrile seizures in children. Assessment can be considered as an examination or administration of those substances for the prevention and treatment of febrile seizures. To evaluate the serum level of zinc and iron in febrile children with or without seizures, it was decided to conduct the current updated systematic review and meta-analysis.

Materials and Methods

Data search strategy

We conducted an electronic search from data sources, PubMed, Proquest, Portal Garuda, and Web of Science, and then analyzed the relevant studies in English and Indonesian, published from 2000-2021.

The search was performed in January 2022 until 31st March 2022. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to conduct this literature search [19].

The keywords search terms used Boolean Operator, as follows: ("zinc" OR "Zn" OR "zinc" OR "seng" AND "zat besi" OR "Fe" OR "iron" OR "Ferrous" AND "kejang demam" OR "kejang demam kompleks" OR "kejang demam sederhana" OR "febrile seizure" OR "febrile convulsion" OR"complex febrile seizure" OR "simple febrile seizure").

We calculated the effect size and confidence interval for each study, using the available data for Standardized Mean Difference (SMD); if it was not available then we conversed the data or asked the author. Heterogeneity was assessed by determining the chi-square with 50% limit, which determines the use of fixed or random effect models.

The variables of zinc and iron (SI, TIBC, and ferritin) with febrile seizures were analyzed, and the summary of the results was the overall effect size.

We eliminated journals with low factors or evidence, and then evaluated the sensitivity analysis.

For publication bias analysis, we used Funnel plot. The entire process of calculating data analysis and outcomes was carried out using the Revman Review Manager 5.4 software (Cochrane Collaboration, 2020).

Eligibility criteria

The study inclusion criteria were: (1) study design of observational study, (2) study population consists of 6 months old-5 years old children, (3) studies reported the association between serum zinc and iron levels and the incidence of febrile seizures, (4) English and Indonesian language publication, (5) study published in 2000-2021, (6) the data consisted of *Standardized Mean Difference* (SMD) and confidential interval (CI), (7) the following criteria of febrile seizure were seizure occurred in 6 months old-5 years old children with fever (the temperature was 38 °C or more) and without CNS infection.

If the following condition was met, the studies would be excluded:

(1) studies performed in an animal trial, they were only literature review, case reports, case series, letters to editors, randomized control trial, and conference abstracts, or only evaluating zinc and iron level indirectly by questionnaire, (2) incomplete full-text articles, (3) non-English and non-Indonesian studies, (4) duplicated studies, (5) study population was children with comorbid which could affect the study variables.

Data extraction and quality of assessment

We used Cochrane Library to collect the data from relevant studies. The data consist of:

(1) authors, (2) year of publication, (3) study location, (4) control size, (5) sample size, (6) study design, (7) age, (8) measurement indicator, (9) measurement method, (10) zinc and iron

level, and (11) type of zinc and iron. Two reviewers extracted and assessed all the studies. Both reviewers screened the eligibility of full-text articles, and if there is disagreement between reviewers will be resolved through group discussion.

Quality assessment

Newcastle-Ottawa Scale (NOS) was used to assess the quality of observational studies. Followed criteria were used to assess bias: selection, comparability, and exposure or outcome. Total scores≥ 6 for cross-sectional and ≥ 7 for cohort studies were employed to conclude high-quality studies [20].

Statistical analysis

Statistical analysis and outcome performed using Revman Review Manager 5.4 software. Presented data were using SMD with 95% of confidential interval. The chi-square test with a 50% confidence interval was used to assess study heterogeneity, and then calculated by fixed effect or random effect models. A random-effects model was used for the meta-analysis if the I2 value was higher than 50%. On the other hand, a fixed-effect model was applied. We analyzed zinc and iron variables, nutritional status, simple febrile seizure, and complex febrile seizure.

Analyzing publication bias was performed using a funnel plot. We added Egger's test to analyze potential publication bias quantitatively. Statistical significance in all analyses was P-value<0.05.

Results and Discussion

Overview of literature search

Total of 30,849 studies were identified using keyword search terms from the databases as mentioned before.

Following title and abstract screening, we excluded 30,789 irrelevant studies and reviewed 60 full-text studies based on eligibility criteria. Finally, this systematic review and meta-analysis included 30 studies in total.

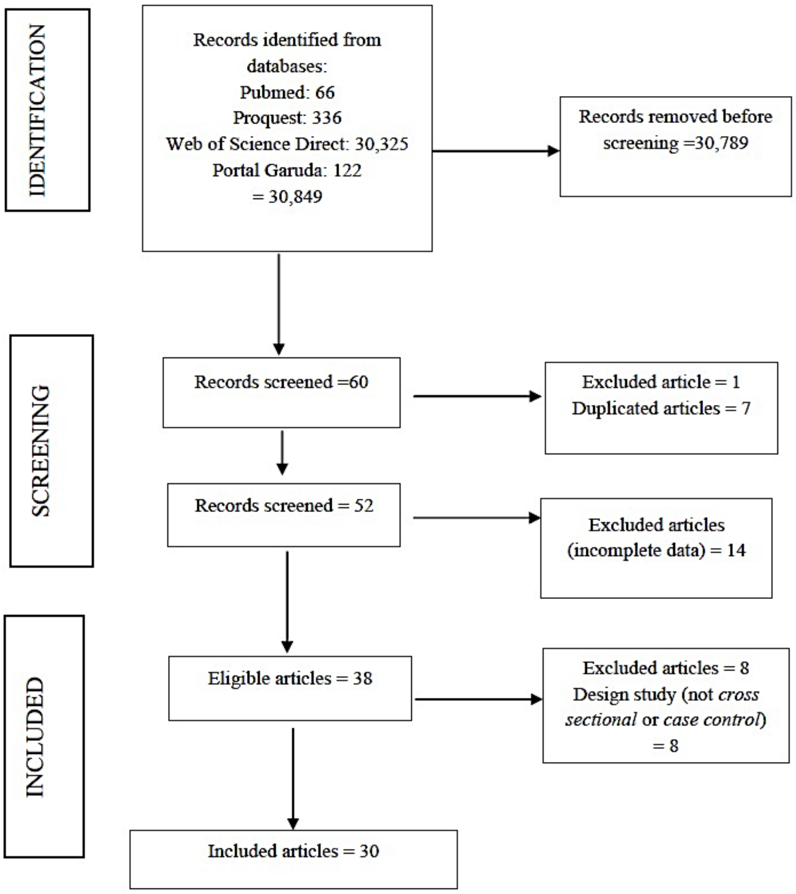


Figure 1: PRISMA flowchart selection

The overall flowchart selection is displayed in Figure 1.

Characteristics of the included studies

Total of 30 included studies consisted of one cross-sectional study and 29 case-control studies. The studies characteristics are presented in Table 1. The studies were performed in various countries such as Egypt, Turkey, India, Bangladesh, Indonesia, Pakistan, Iran, South Korea, Jordan, and Greece. The total number of participants was 4,158 patients.

Outcomes

Serum zinc level in children with febrile seizures

Zinc serum levels were reported in 15 studies. There were 922 patients with febrile seizures and 666 patients in the control group (fever without seizure). In 12 studies, children with febrile seizures had significantly lower zinc levels. Otherwise, in 3 studies, there was no significant difference. A meta-analysis of 15 studies revealed that children who had febrile seizures had markedly lower zinc levels than children who had a fever but did not have seizures (SMD= -1.36 [-1.89, -0.84], $p<0.00001$, I^2 =95%) (Figure 2).

Ferritin level in children with febrile seizures

Ferritin levels were reported in 15 studies. There were 1,313 patients with febrile seizures and 1,138 patients in the control group (fever without seizure). In 13 studies, ferritin levels in febrile seizure children were significantly lower. Otherwise, in the 2 studies, there was no significant difference. A meta-analysis of 15 studies revealed that ferritin serum levels were significantly lower in children who had febrile seizures than in children who had a fever but did not have a seizure (SMD = -0.79 [-1.15, -0.43], $p<0.00001$, I^2 =94%) (Figure 3).

Table 1: Main characteristics of included studies

No.	Name and year	Country	Age	Study Design	Sample (n)		Laboratory indicator	Measurement method
					Febrile Seizure	Control		
1	El Masry, 2018	Egypt	5 months old -6 years old	*Case-control*	40	40	Nitric oxide, malondialdehyde, superoxide dismutase, copper, zinc, and selenium	Colorimetric methods
2	Amiri, 2009	Turkey	FS: 2.6±1.7 years old Control: 2.3±1.9 years old	*Case-control*	30	30	Serum selenium, zinc, and copper	Atomic absorption Spectrometry
3	Ganesh, 2008	India	3 months-5 years old	*Case-control*	38	38	Zinc	Atomic absorption spectrometry using a Perkin Elmer Analyst-600 Model
4	Ganesh, 2011	India	3 months old - 5 years old	*Case-control*	23	22	Zinc	Atomic absorption Spectrometer
5	Mollah, 2008	Bangladesh	6-60 months old	*Case-control*	50	30	Zinc	Atomic absorbance Spectrophotometer
6	Turay, 2021	Turkey			98	64	Serum iron, ferritin, folate, vitamin B12, hemoglobin,	

							MCV, and RDW	
7	Hussain , 2018	Pakistan	6 months old -6 years old	*Case-control*	100	100	hemoglobin, MCHC, MCV, and serum ferritin	Sysmax KX-21 hematology counter and Access II Immunoassay Analyzer (Beckman Coulter)
8	Youseflchaijan, 2014	Iran	6 months old -6 years old	*Case-control*	191	191	Hemoglobin, hematocrit, RBC, reticulocyte, MCV, MCH, MCH, MCHC, leucocyte, platelet, FE, TIBC, and ferritin	
9	Jang, 2019	South Korea	6-60 months old	*Case-control*	63	65	RBC, hemoglobin, HCT, MCV, MCH, MCHC, RDW, reticulocyte, WBC, platelet, SI, TIBC, ferritin, and transferrin saturation	
10	Hammed, 2019	Egypt	6 months old - 5 years old	*Cross sectional*	50	50	RBC, HCT, MCV, MCH, MCHC, RDW, SI, ferritin, TIBC, and zinc	CBC: Celtac F analyzer. SI, ferritin and serum TIBC: Cobas C311 analyzer Zinc: colorimetrically Kits
11	Gencer, 2016	Turkey	3-60 months old	*Case control*	57	25	Hb, MCV, platelet, TIBC, ferritin	
12	Margaretha, 2010	Indonesia	6 months old -5 years old	*Cross sectional*	25 (simple febrile seizur)	25	Hemoglobin, HCT, WBC, platelet, and serum zinc	
13	Yuana, 2010	Indonesia	3 months old -5 years old	*Case control*	36	36	Zinc	Atomic absorption spectrophotometry
14	Khanis, 2010	Indonesia	3 months old - 5 years old	*Case control*	36	36	Hb, HCT, MCV, sTfR	ELISA
15	Papageogiou, 2014	Greece	6-60 months old	*Case control*	50	50	Hb, HCT, MCV, RDW, SI, TIBC, ferritin, and sTFR (soluble transferrin factor Receptors)	CBC: Abbott analyzer, Cell Dyn 3700 SI and TIBC: Olympus Medicon AU2700 analyzer
16	Kannachamk	India	6 months	*Case*	35	35	Copper,	quantitative

	andy, 2020		old - 5 years old	*control*			magnesium, and zinc	colorimetric method
17	Bidabadi, 2009	Iran	6 months old - 5 years old	*Case control*	200	200	RBC, HB, HCT, MCV, MCH, MCHC, SI, TIBC, and ferritin	IMx Ferritin assay in a microparticle enzyme immnoassay (MEIA)
18	Zareifar, 2012	Iran	6 months old - 5 years old	*Case control*	300	200	HB, MCV, and serum ferritin	Serum ferritin: ELISA
19	Potdar, 2017	India	6 months old - 5 years old	*Case control*	30	30	HB, RDW, SI, and serum ferritin	Automated hematology analyzer (CBC) and ELISA (ferritin)
20	Lee, 2012	Korea	>60 months old	*Case control*	248	40	Zinc, CRP	plasma mass spectrometry
21	Daoud, 2002	Jordan	3 months old - 6 years old	*Case control*	75	75	Hb, MCV, MCH, and plasma ferritin	Ferritin: IMx Ferritin assay in a microparticle enzyme immunoassay
22	Vaswani, 2010	India	6 months old -6 years old	*Case control*	50	50	HB, MCV, MCH, and Ferritin	
23	Sharawat, 2015	India	6 months old - 5 years old	*Case control*	63	63	HB, MCV, MCH, and serum ferritin	Ferritin: Chemiluminescence Immunoassay CBC: auto-analyzer (Coutler counter)
24	Tutuncuoglu, 2001	Turkey	8-16 months old	*Case control*	15	20	IL-1a, IL-1B, TNF-a of plasma levels and cerbrospinals fluid, PGE2, PGF2, PGD 2 of plasma and CSF levels, and zinc	Cytokine: ELISA Prostaglandin: solid-phase extraction method Zinc: inductively coupled plasma–atomic emission spectrometry
25	Kartal, 2021	Turkey	6 months old - 6 years old	*Case control*	47	35	SI, ferritin, HB, MCV, and RDW	CBC: automatic blood count device LH 750 SI and ferritinL Cobas C501 analyzer
26	Salma, 2015	Indonesia	3 months old -5 years old	*Case control*	40	40	HB, SI, TIBC, transferrin saturation, ferritin, and sTfR	

27	Subarro, 2019 (1)	India	6 months old - 5 years old	*Case control*	100	100	Hb, MCV, MCH, Ferritin, and RDW	Ferritin: chemiluminescent method
28	Subarro, 2019 (2)	India	6-60 months old	*Case control*	75	75	Hb, zinc, protein energy malnutrition, and underlying causes of illness	
29	Amoouian, 2013	Iran	6 months old -5 years old	*Case control*	160	160	Ferrous, TIBC, Zinc, calcium, and magnesium	Photometric method
30	Arul, 2020	India	>5 ye ar s ol d	*Case control*	40	40	Zinc, albumin, and CRP	Spectrophotometr y method

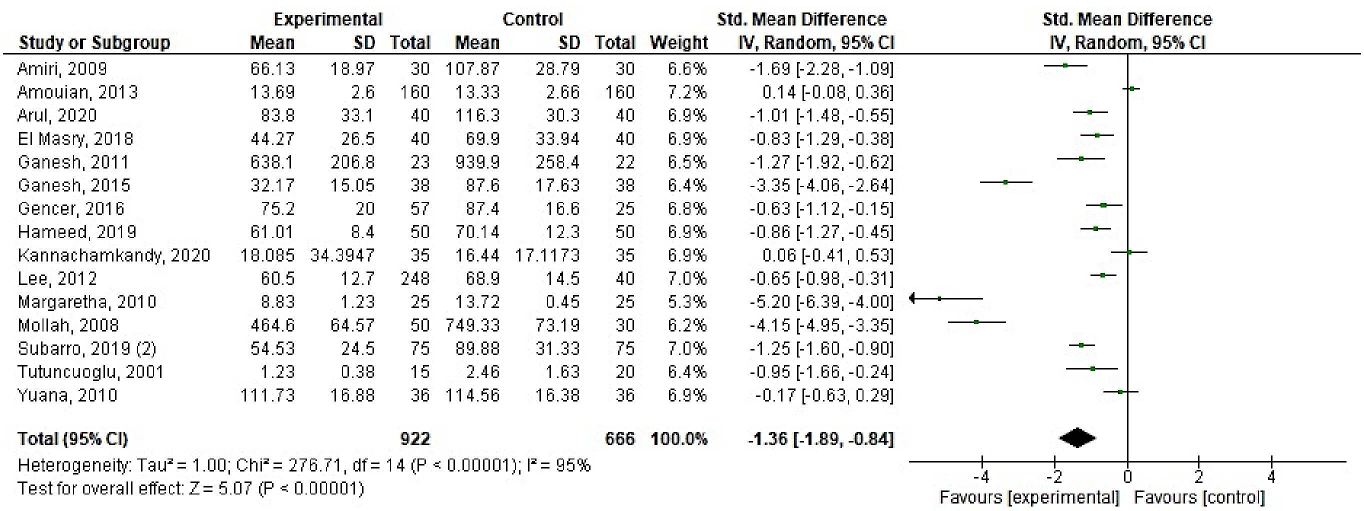


Figure 2: Forest plot of zinc serum level in children with febrile seizure

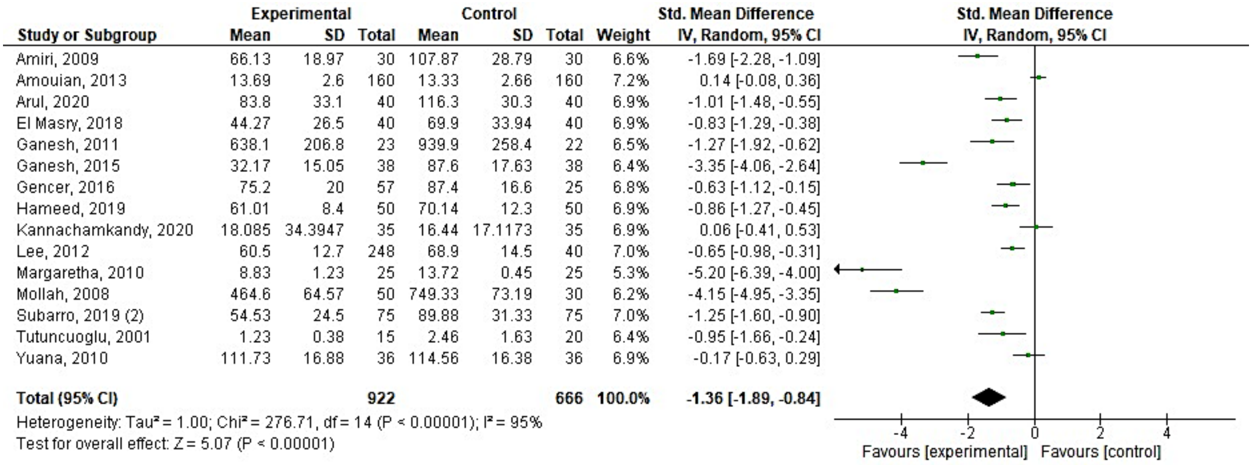


Figure 3: Forest plot of ferritin serum level in children with febrile seizure

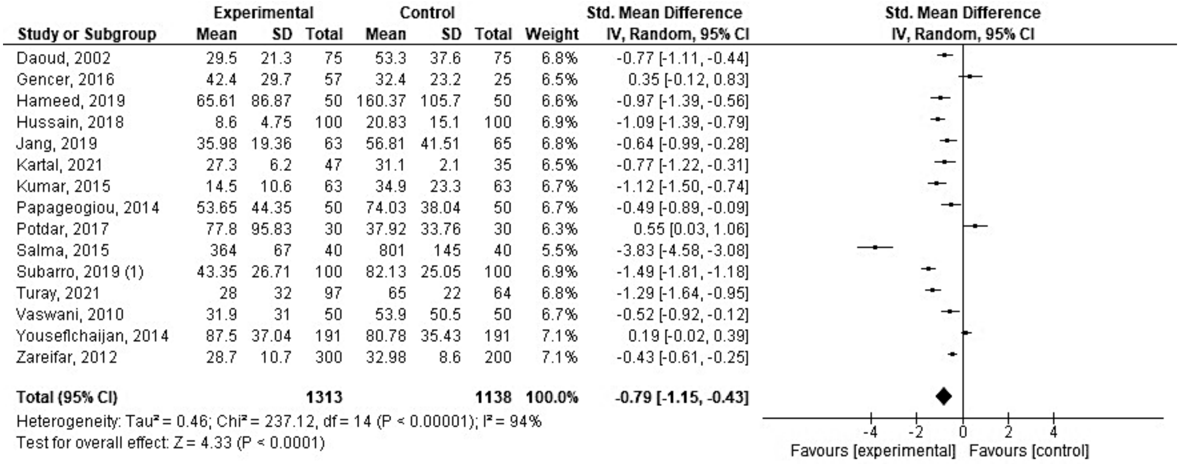


Figure 4: Forest plot of serum iron level in children with febrile seizure

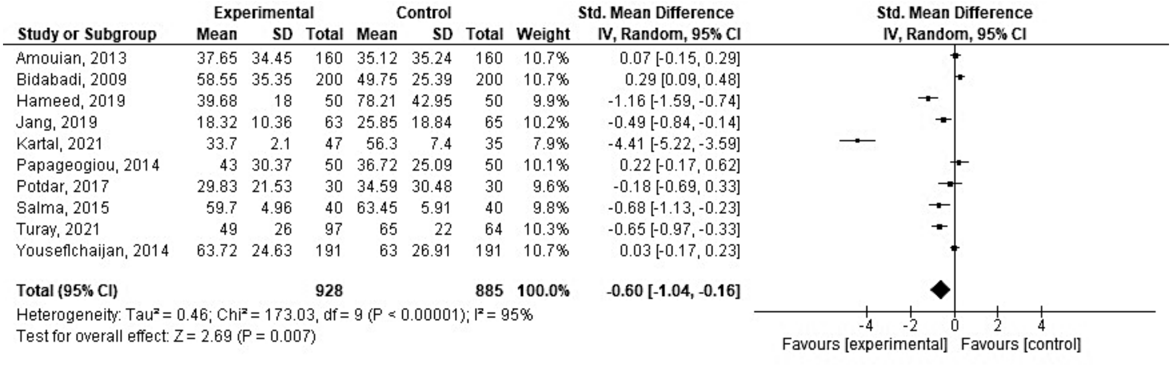


Figure 5: Forest plot of TIBC level in children with febrile seizure

Serum iron (SI) level in children with febrile seizures

Ten studies reported serum iron levels. There were 928 patients with febrile seizures and 885 patients in the control patients (fever without seizure). Six studies revealed serum iron levels were significantly lower in children with febrile seizures. Otherwise, in 4 studies, there was no significant difference. Analysis of 10 studies revealed that SI levels was significantly lower in children who had febrile seizures than in children with fever but no seizure (SMD= -0.60 [-1.04, -0.16], p=0.007, I^2 =95%) (Figure 4).

Total Iron Binding Capacity (TIBC) level in children with febrile seizures

Total Iron Binding Capacity levels were reported in 6 studies. There were 678 patients with febrile seizures and 646 patients without seizures in the control group.
Analysis of 6 studies revealed a significant difference between patients with fever and seizure compared to the patients with fever but no seizure (SMD= -0.67[-1.21, 0.13], p=0.01, I^2 =95%) (Figure 5).

Publication bias and quality assessment

The data were also analyzed for publication bias by funnel plot. The results were no outlier found to be affected significantly by p overall. A sensitivity analysis was performed. The results revealed no significant change in p overall when the exclusion was performed in some studies alternatively.
The present study evaluated 30 studies about the relationship between serum zinc and iron levels and the incidence of febrile seizures.Current investigation comprehensively evaluated clinical information comparing the serum zinc and iron levels in febrile children with or without seizures.
A meta-analysis found that in febrile seizures children, the serum zinc and iron levels were considerably lower than those of febrile cases without seizures. The pooled SMD did not significantly alter after subgroup or sensitivity analysis.
The variance between studies was significantly affected by sample size as a continuous variable in the meta-regression analysis. Based on a previous meta-analysis on zinc deficiency in children with febrile seizures, there is substantial relationship between low zinc levels and seizures in febrile children. The etiology of febrile seizures may be influenced by zinc deficiency, which is considered to be related to seizure occurrences [21].
One of the body's necessary trace elements, zinc is needed at particularly high concentrations in the human brain. It participates in a multiple biological processes, including cell differentiation and metabolism. In addition, it aids in the formation and regular operation of brain cells. Zinc is known as co-factor in the release and production of neurotransmitters [22].
A previous meta-analysis by Karimi *et al.* revealed that anemia due to iron deficiency was a predisposing factor for febrile seizures in children. Overall Odd Ratio (OR) on their study was 1.27 [23].
Another study mentioned the same as Karimi *et al.* [18]. Hypoxemia, altered neuronal and brain metabolism, altered gamma-butyric acid metabolism, decreased levels of this neurotransmitter, impaired myelination, and decreased levels of enzymes like aldehyde oxidase are all possible mechanisms by which an iron deficiency could cause seizures [24-27].
In meta-analysis, heterogeneity between trials was a frequent result. The meta-analysis of the current study revealed notable heterogeneity in the pooled SMD analysis. The current review's findings were solid. Sensitivity analysis revealed that the estimated pooled SMD was unaffected by any study. The main limitations of the current study are as follow: (i) Despite efforts to conduct a thorough search, there was possibility of overlooked paper. (ii) Significant heterogeneity was seen which may have affected the outcomes. (iii) Publication bias might have had an impact on the combined findings. (iv) The majority of the studies included were case-controlled. Case-control studies have inherent flaws like selection bias in the case and control groups and numerous other variables that could skew the overall findings.
Further studies are needed for defining more precisely the important variable in zinc or iron substance roles in various types of febrile seizure. In addition, interventional studies could be performed to assess the effect of iron and zinc on febrile seizure patients in the long term.

Conclusion

We found low levels of zinc and iron in children with febrile seizure. This meta-analysis discovered a significant association between low zinc and iron levels and febrile seizures in children.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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