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Review Article

Exploring the Effect of Vitamin B12 on Febrile Seizures in Children: A Systematic Review and Meta-analysis of Case-control Studies

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Abstract

Background: Vitamin B12 (VB12) is a water-soluble vitamin, deficiency of which causes an extensive heterogeneous spectrum of neurological symptoms including vision disturbances, paresthesia, tremor, and seizure. The aim of this investigation is to determine the effect of serum VB12 levels on pediatric patients with febrile seizure (FS).

Methods: In this meta-analysis, case-control studies that evaluated the effect of serum VB12 levels in pediatric patients with FS were included. Web of Science, PubMed, Scopus, and Google Scholar were searched until August 13, 2024. The PICO criteria for this meta-analysis were as follows: Population/Patients (P: pediatric patients with febrile seizures); Issue of interest (I: serum levels of VB12); Comparison (C: control); Outcome (O: occurrence of febrile seizure). Quality assessment was assessed according to the Newcastle-Ottawa Scale (NOS) tool for case-control studies. The outcome assessment scales, study groups, and serum VB12 levels were extracted.

Results: Of 435 initial articles, eventually 6 studies remained in the meta-analysis. Existing evidence indicated that serum VB12 concentrations were insignificantly lower in FS patients than controls (WMD= -1.09 pg/ml; 95% CI: -2.23, 0.04; P= 0.06), although a significant between-study heterogeneity was observed (I^2= 98.10%, P< 0.001).

Conclusion: The results of our study pointed out that there is low serum VB12 concentrations in FS patients compared with controls. Despite the fact, one of the best ways to prevent FS in children can be VB12 supplementation and proper diet therapy.

Introduction

Febrile seizure (FS) is the most prevalent seizure disturbance that is accompanied by fever (up to 38 centigrade) in children younger than 5 years old.[1,2] FS is defined via the International League Against Epilepsy (ILAE) as absence of prior afebrile seizure history and any trauma, intoxication, electrolyte or metabolic impairment, or infection of the central nervous system.[3] The prevalence rate of FS varies between countries, ranging from 2%–5% in the USA[4-7] to Europe and 8%–11% in East Asia.[8,9] Moreover, the combined prevalence of FS is 47.9% in Iran.[10] Approximately 65-70 percent of all FS cases appear as simple FS (15 minutes or less) without lateralizing features such as intellectual disability and hemiplegia.[1,11] The accurate etiopathogenesis of FS is yet unclear and considered to be multifactorial. Particularly certain genes may increase the risk of familial epilepsy syndromes that can lead to FS, immunologic repercussion, trace element disturbances (i.e. selenium, iron, and zinc) and vitamin deficiencies (i.e. pyridoxine, folic acid, vitamin B6 and B12).[12,13]

Various studies have investigated the effect of nutrients such as vitamins, zinc, iron, homocysteine, copper, magnesium, etc. on febrile seizure. Previously conducted meta-analysis has indicated that there are significant differences in zinc concentration between febrile seizure patients and the control group; while there is no significant difference in the concentration of copper, magnesium and selenium between these two groups.[13] Jang *et al.*[14] also showed in a study that serum iron deficiency was associated with an increased risk of febrile seizure, and therefore it is necessary to monitor the status of iron and even hemoglobin in children with this disease. Also, it has been determined that vitamin D level is lower in children with febrile seizure.[15]

Several studies have shown the preventive effects of

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serum vitamin B12 (VB12) in patients with FS.[2,11,16-18] VB12 is a water-soluble vitamin that cannot be synthesized by the human body.[19,20] VB12 deficiency is associated with inadequate dietary intake, which can lead to a wide range of heterogeneous neurological symptoms including lethargy, orthostatic hypotension, gastrointestinal motility disorder, stomatitis, tachycardia, visual disturbances, hyporeflexia, seizures, and tremors.[21] One of the causes of nerve attack is hyperhomocysteinemia[22] and VB12 is effective in its metabolism. VB12 is a cofactor in methylmalonyl coenzyme A (CoA) degradation and homocysteine (Hcy) remethylation.[23] On the other hand, VB12 together with folic acid plays a key role in the conversion of Hcy to methionine and with these mechanisms prevents hyperhomocysteinemia (Hhcy).[20,24] However, the exact mechanism of neurological symptoms in VB12 deficiency is not fully understood and further studies should be conducted in this field.

Since VB12 levels children plays a significant role on the occurrence of febrile seizure, the present meta-analysis was conducted to collect and review the results of studies conducted in this field, and evaluate the relationship between serum VB12 levels and FS occurrence and its association with severity of clinical symptoms.

Methods

This systematic review and meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[25]

The search strategy of literature

Three online databases (Web of Science, PubMed and Scopus) and Google Scholar were searched independently (by H.A and N.SH) until August 13, 2024. Moreover, the reference lists of published researches were reviewed by 2 independent authors (N.SH and H.A) for avoiding missing data. The search strategy of scientific databases is described in Supplementary Material.

Eligibility criteria

Studies were included in this systematic review if they met at least one of the following criteria: (1) Evaluated the serum level of VB12 in FS patients; (2) Determined the relationship of serum VB12 levels with clinical symptoms; and (3) observational studies. Studies were excluded in the case of: (1) Non English studies; (2) Case reports or case series; (3) Letters, review articles and commentaries; (4) experimental studies; and (5) Conference abstracts.

Study selection

The eligible articles for this systematic review were differentiated by four investigators (N.SH, E.A.B, S.KH, K.T.N) based on titles and abstracts of the articles and above mentioned eligibility criteria. After screening studies based on their title and abstract in the first step, 4 researchers (N.SH, E.A.B, S.KH and H.A) checked the initially included studies by performing a precise screening based on the full-text and excluded studies that didn't report appropriate quantitative data to be included in the systematic review.

Methodological quality assessment

Determining the quality of articles was done using the Newcastle-Ottawa Scale (NOS) critical appraisal tool by a researcher (H.A) and checked by another author (S.S). This tool is designed to assess the quality of observational studies encompassing case-control and cohort studies which has three domains containing selection (four questions), comparability (one question), and exposure (three questions) and its results range from 0 to 9.[26] Studies with a minimum score of 7 were considered as a good quality.

Data extraction

The acquired data was extracted independently by two researchers (N.SH, H.A) and checked by third researcher (S.S), afterwards, to insure accuracy and minimize bias. The publication year, country, outcome assessment scales, first author of the study and participants' characteristics (including age, number, health condition, serum levels of VB12) were extracted from the included studies. In case of missing data in the manuscript, corresponding author of the relevant article were contacted to solve the problem. The outcome assessment scales, study groups, summary of the results and conclusion of the systematic review were also extracted.

Data synthesis and statistical analysis

For statistical analysis, random-effects restricted maximum likelihood model was utilized to estimate the combined effect size. With using the I_2 index, between-study heterogeneity was evaluated. Indeed, I_2 index exceeding 50% was considered as a high heterogeneity.[27] To present the data, means ± standard deviation (S.D.) were used. In cases and controls which were reported variously were estimated via suitable statistical calculations. The effect size was reported as weighted mean difference (WMD) along with 95% confidence intervals (CIs). Subgroup meta-analysis was done to identify the sources of potential heterogeneity. For estimating the impact of each study on the pooled effect size of the meta-analysis, sensitivity analysis considering the Leave-one-out Method was performed. The funnel plot inspection with Begg's rank correlation and Egger's weighted regression tests were conducted to identify any publication bias.[28,29] In cases of publication bias, Duval & Tweedie "trim and fill" analysis was performed. STATA version 16 (Stata Corporation, College Station, TX, US) was used for all statistical analyses with considering a significant level of $p < 0.05$.

Results

Study selection

In the present meta-analysis, 435 articles were identified during our initial search; 69 of which were removed due

to duplication. After screening the remaining 366 articles, 349 articles were excluded from the study after reviewing the title and abstract, and 17 articles entered the next stage for full-text review. From these articles, eight articles were excluded due to being case report.[30-37] One study were excluded because they were based on animal models.[38] Also, in the study of Xiaoxue *et al.*[39], although febrile seizure was mentioned, the main investigated outcome was the severity of autism in children. For this reason, they were excluded from the study.One study were excluded due to they assessed the cerebrospinal fluid level of vitamin B12.[40] After excluding these studies, six case-control studies were examined in this meta-analysis. From these included studies, all cases measured the serum VB12 levels and investigated its relationship with febrile seizure.[11,16,17,41-43] Other labortory findings that were examined in addition to serum VB12 levels in these studies included white bood cell (WBC) count, platelet (PLT) count, nucleated red blood cell (NRBC) count, mean corpuscular hemoglobin (MCH), iron, hematocrit (Hct), immunoglobulin (IG), vitamin D, selenium, zinc, ferritin, magnesium, red cell distribution width (RDW), hemoglobin and homocysteine, mean corpuscular volume (MCV) and Serum Folic Acid. The PRISMA flowchart of the included articles is shown in Figure 1.

Study characteristics

The specifications of the included studies are summarized in Table 1. The total number of participants in these six studies was 772, placed in two groups: Case (n = 401) and control (n = 371). The control group in three included studies were healthy in terms of health status.[11,17,42,43] In one study, control group had a febrile illness without seizure[41] and in one study, control group had a fever without seizure.[17] The average age of the participants in the included studies was 27.10 months, and the participants included both males and females. The studies were conducted in the years 2015 to 2023. Four studies were conducted in Turkey,[11,16,17,42,43] one study was conducted in India.[42] Three studies separately reported data for people with simple and complex febrile seizures. In all included studies, febrile seizure in the case group was diagnosed using the recorded data in the hospital; and to determine the serum VB12 levels, one study used the data recorded from the hospital,[11] one study used the immunoenzymatic assay method,[16] and three studies used the immunoassay method.[18,41,42]

Result of quality assessment

As illustrated Table 2, the result of quality assessment was performed via NOS critical appraisal tool by a researcher (H.A) and checked by another author (S.S). Three studies have received the highest points They had representative cases and controls, adequate case definition, no history of disease in controls, community controls, secure record of exposure, adjustment for age and sex, same method of ascertainment for cases and controls, same rate of non-response for both groups, and pre-specified outcomes

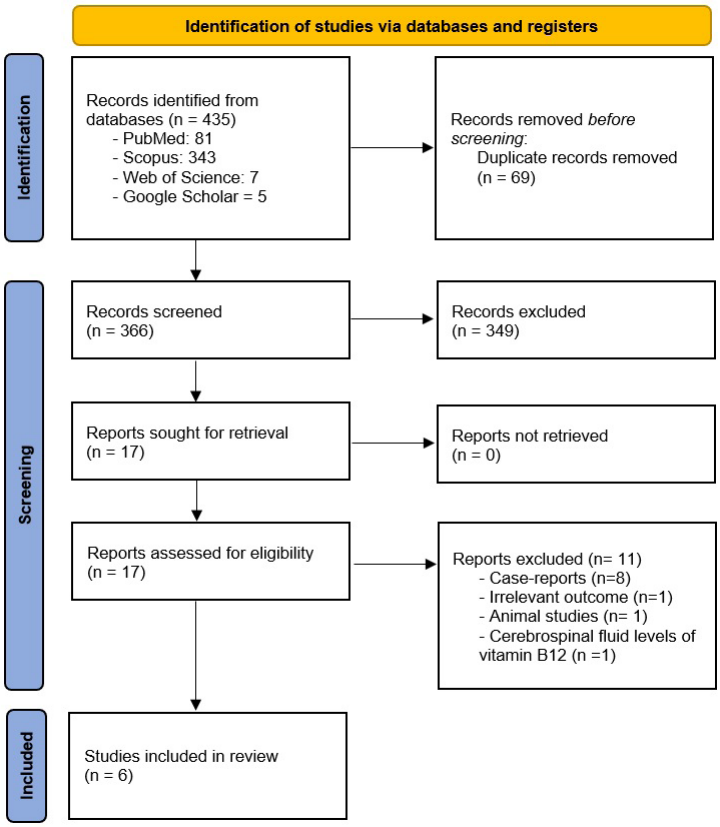

Figure 1. PRISMA flow diagram of included articles.

Table 1. The characteristics and main findings of the included studies.

Author, year	Design	Country	Sample size (case/ control)	Age, month (case/control)	Health condition (case/ control)	Outcome assessment scales	Serum vitamin B12 (pg/mL) (case/control)	p-value
Cigri *et al*. 2023	Case-control	Turkey	122 (61/61)	(35.36±13.91/ 35.54±13.87)	(FS/Fever without seizures)	PinAAcle 900 Z, SATURNO 300, CLIA, CBIA, AHA	(225±20.8/ 315±23.9)	<0.001
Aggarwal *et al*. 2021	Case-control	India	70 (35/35)	NR	(FS/Febrile illness without seizures)	CLIA, SYSMEX KX-CC	(222±86.7/ 305±80.7)	<0.001
Turay *et al.* 2021	Case-control	Turkey	161 (97/64)	(21±12/26±14)	(FS/Healthy)	FBS	(373±176/ 527± 259)	<0.001
Özkale *et al.* 2015	Case-control	Turkey	179 (104/75)	(24.24/24.12)	(FS/Healthy)	FBS, CLMI, CMS	(453.2±206.0/ 521.9± 246.6)	0.08
Yüce *et al.* 2023	Case-control	Turkey	104 (50/54)	(21.6±11.6/ 20.5±11.2)	(FS/Healthy)	HABA, EIA	(401±175/ 441± 288)	<0.05
Aydın *et al.* 2021	Case-control	Turkey	136 (54/82)	(30.31±14.64/ 32.32±19.70)	(FS/Healthy)	NR	(316±205/ 419±208)	<0.05

pg: picograms, mL: milliliter, FS: Febrile Seizure, PinAAcle 900 Z: Perkin Elmer Atomic Absorption method, SATURNO 300: homogeneous colorimetric enzyme technique, CLIA: chemiluminescence immunoassay, CBIA: Competitive binding immunoenzymatic assay, AHA: Automatic hematological analyzer, SYSMEX KX-CC: SYSMEX KX-cell counter, FBS: fasting blood sample, CLMI: chemoluminescent microparticle immunoassay, CMS: chromatography-mass spectrometry, HABA: Hitachi 7600-020 automatic biochemical analyzer, EIA: electrochemiluminescence immunoassay analyzer.

and analyses.[17,43,44] Additionally, Three publications have received the lowest points, demonstrating a moderate quality of the studies. They had potential for no adjustment for confounders, selection biases, some missing data, hospital controls, and no information on the characteristics or reasons of the missing data or the potential impact on the results.[11,42,43] Details of evaluating with NOS critical appraisal tool of the papers are shown in Table 2.

Findings from the meta-analysis

Serum VB12 concentrations in FS and control subjects

The results of this meta-analysis have indicated that serum VB12 concentrations were insignificantly lower in FS patients than controls (WMD= -1.09 pg/ml; 95% CI: -2.23, 0.04; P= 0.06) (Figure 2), although a significant between-study heterogeneity was observed (I^2= 98.10%, P< 0.001).

To find the potential source of heterogeneity, subgroup analysis was performed. Subgrouping indicated that age and quality score could be probable sources of heterogeneity (Figure 3). Also sub-group analyses of studies based on their quality assessment scores revealed that in studies with quality score higher than 7, serum VB12 concentrations were insignificantly lower in FS patients than controls (WMD= -0.61 pg/ml; 95% CI: -1.07, -0.15; P= 0.02) (Figure 4). The results of sub-group analyses based on sample size and country of origin have been summarized in Figure 5 and Figure 6, respectively.

The evidence of probable publication bias was observed (Egger's (P<0.05) and Begg's tests (P=0.09), however, publication bias analysis demonstrated that the shape of funnel plot was asymmetric (Figure 7). In accordance to that, trim and fill analysis was performed with 5 studies (WMD= -1.09 pg/mL; 95% CI: -2.23, 0.04; P>0.05).

Table 2. Quality assessment of the included articles based on NOS critical appraisal tool.

Study	Quality assesment items		
	Selection	Comparability	Exposure
Cigri et al.	****	**	***
Aggarwal et al.	**	*	**
Turay et al.	**	*	**
Özkale et al.	****	**	***
Yüce et al.	**	*	**
Aydin et al.	****	**	***

Discussion

In this current meta-analysis, utilizing case-control studies data, we evaluated the serum VB12 concentrations in both FS patients and controls. The limited accessible evidence suggested low levels of serum VB12 may be a risk factor for febrile seizure in children.[11,16,17,41-43] Remarkably, The results of our meta-analysis indicated that those in the FS groups had 1.09 pg/ml lower VB12 concentrations compared with those in the control groups.

VB12 is a water-soluble vitamin that cannot be synthesized in human body[20,21] and is taken from the diet. Animal foods are the only dietary sources of VB12.[45]

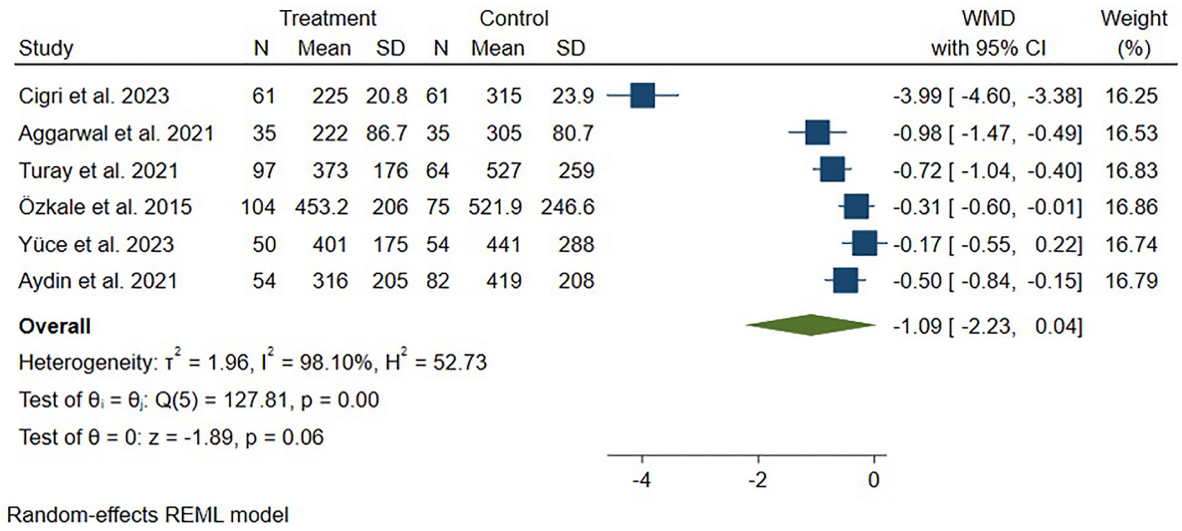

Figure 2. Weighted mean difference (WMD) with 95% confidence interval (CI) of the comparison of serum VB12 concentrations in FS patients and controls.

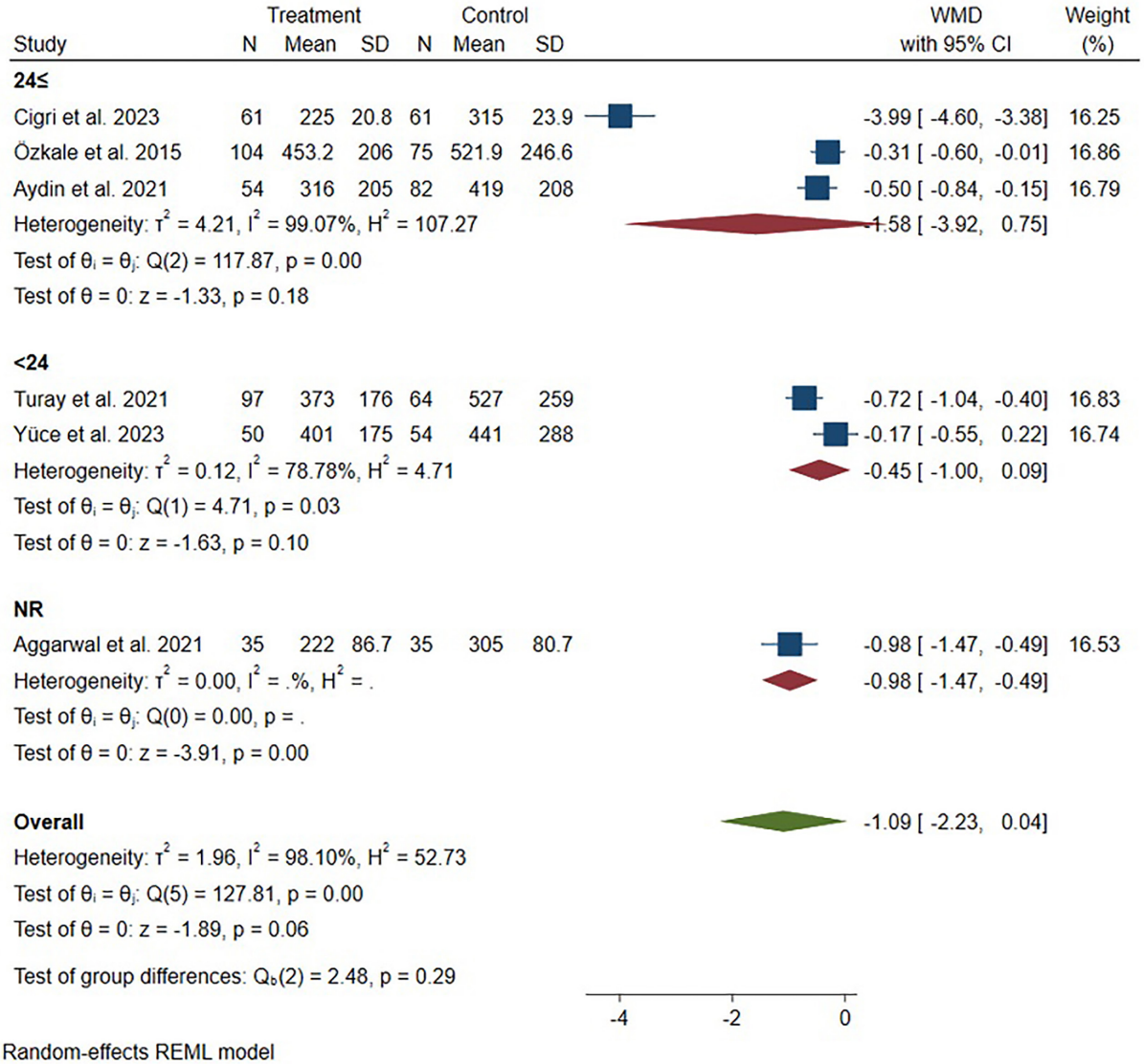

Figure 3. Weighted mean difference (WMD) with 95% confidence interval (CI) of the sub-group analyses on comparison of serum VB12 concentrations in FS patients and controls based on participants' age.

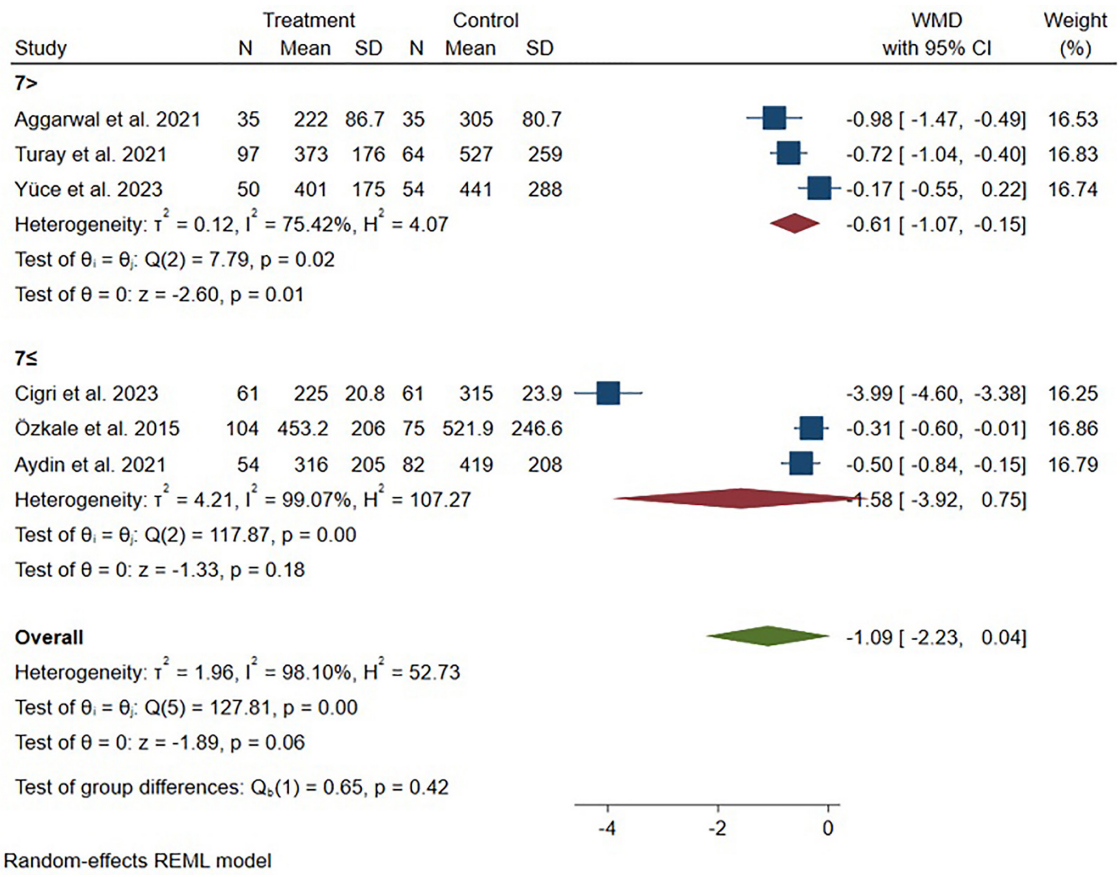

Figure 4. Weighted mean difference (WMD) with 95% confidence interval (CI) of the sub-group analyses on comparison of serum VB12 concentrations in FS patients and controls based on quality assessment scores.

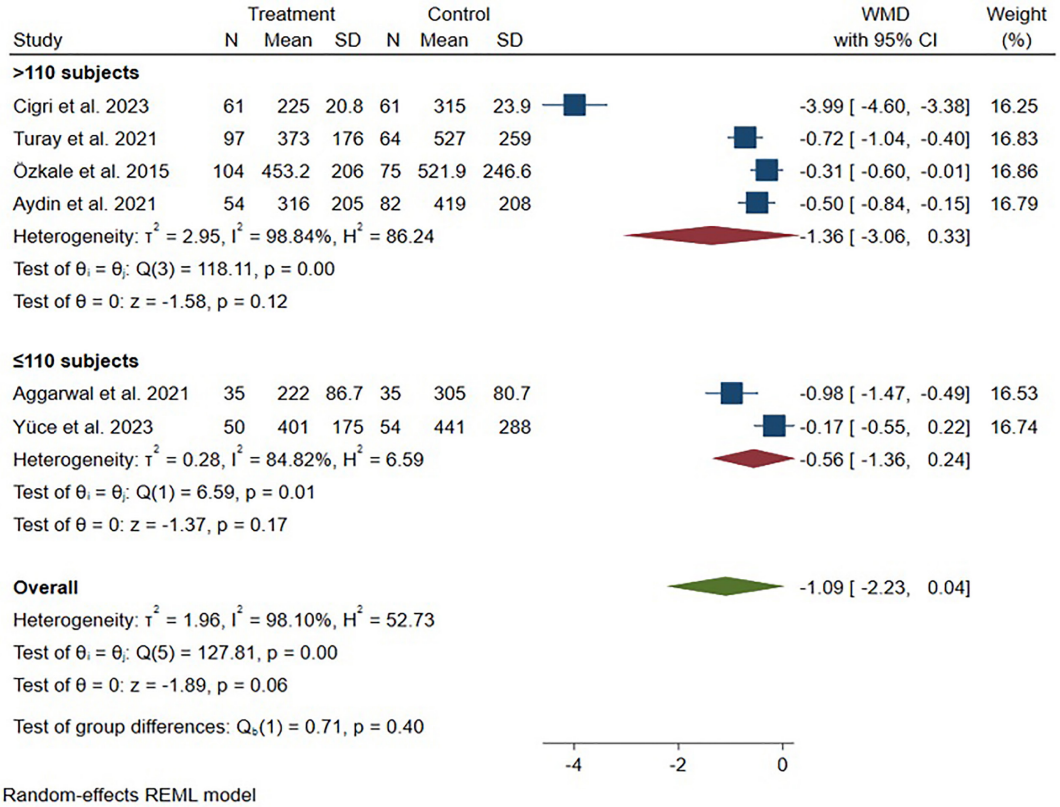

Figure 5. Weighted mean difference (WMD) with 95% confidence interval (CI) of the sub-group analyses on comparison of serum VB12 concentrations in FS patients and controls based on study sample size.

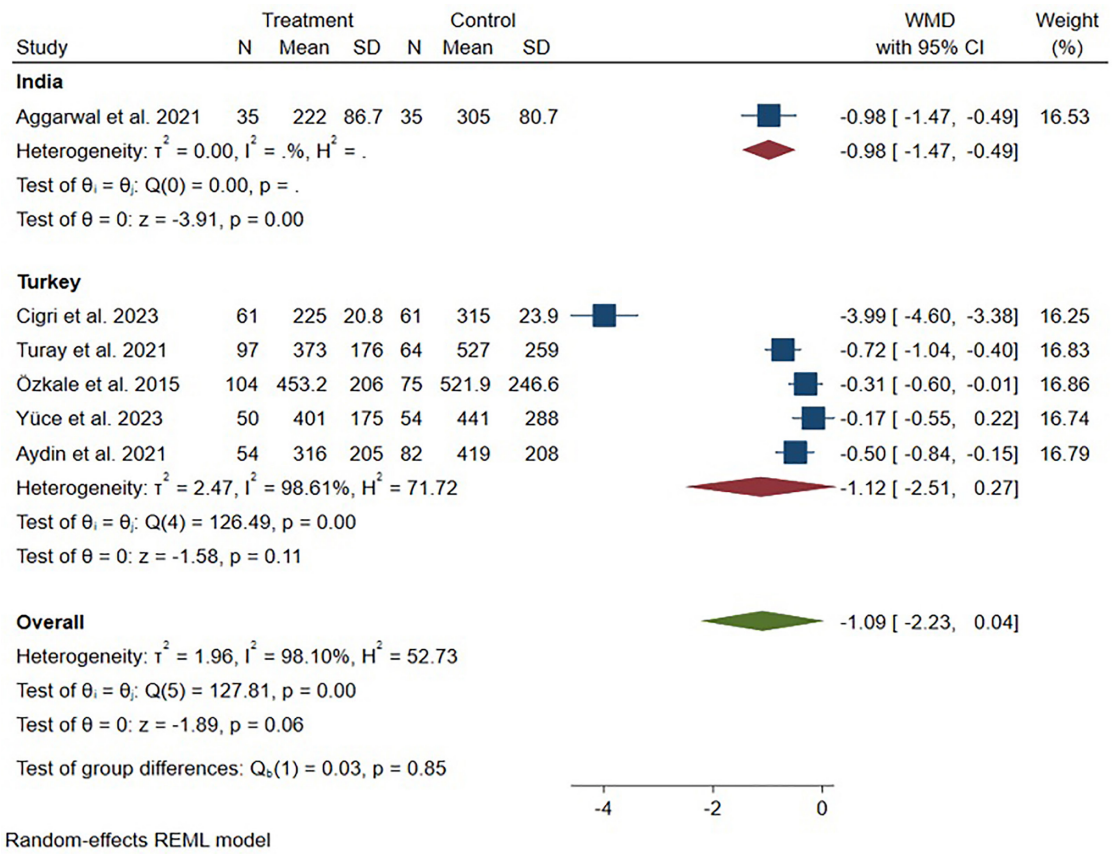

Figure 6. Weighted mean difference (WMD) with 95% confidence interval (CI) of the sub-group analyses on comparison of serum VB12 concentrations in FS patients and controls based on country of origin.

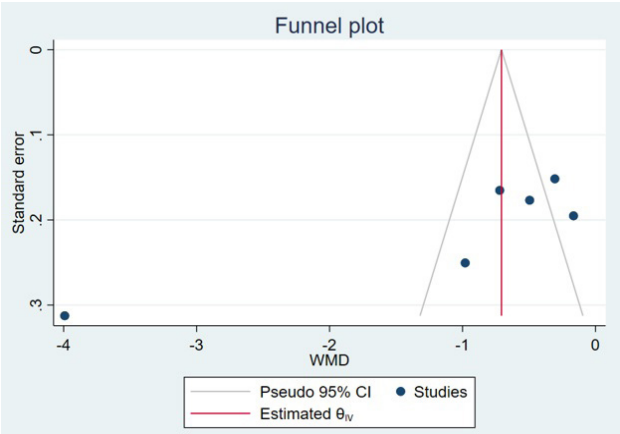

Figure 7. Funnel plot for publication bias.

VB12 deficiency may occurre in children due to the impairment in the transport and metabolism of VB12, its low dietary consumption, or abnormal absorption.[46] One of the possible mechanisms of low serum VB12 levels is associated with the conversion of methylmalonyl CoA to succinyl CoA which cannot occure in children with VB12 deficiency and causes fatty acids to be synthesized through the accumulation of methylmalonyl CoA. The adverse effect of this process is myelin synthesis disturbances in the central nervous system, which affects cognitive performance and neurodevelopment of children.[47] Low serum VB12 can decrease seizure threshold in children which may serve as a probable risk factor for FS.[18]

Low levels of serum VB12 appear to be a trigger for seizures, but its exact mechanism of action is unclear.[19] Several case-control studies have evaluated the association between VB12 deficiency and febrile seizures in pediatric patients. Çiğrı *et al.*[16] showed that the serum level of VB12 in FS patients was significantly lower in comparison to the children with only fever onset. It is noteworthy that in this study, in addition to the level of VB12, level of other minerals, such as zinc, vitamin D, selenium, etc., were examined, among which, the level of VB12 showed a significant difference between the study group and the control group. Yüce *et al.*[42] investigated the level of VB12 in febrile convulsions in a study and pointed out that the serum VB12 levels in children with febrile seizures was significantly lower than in the control group.

Ozkale *et al.*[17] showed that the serum level of VB12 was significantly lower in children with febrile seizures compared to the control group. Turay *et al.*[48] also investigated the relationship between the serum level of VB12, folate, and iron on febrile seizure and reported that the level of VB12 has significant effects on FS in children. The result of the study of Aggarwal *et al.*[2] was also consistent with the study of Turay *et al.*[48] All the studies reviewed in this systematic study state that the level of VB12 is probably effective on febrile seizure and its incidence, however for more certainty, more quality studies with a

Table 3. Subgroup analyses of comparison of serum VB12 concentrations in FS patients and controls.

Group	Effect size (number)	WMD (95% CI)	P-within	I^2(%)	P-heterogeneity
Total	6	-1.09 (-2.23, 0.04)	0.06	98.10	<0.001
Sample size (subjects)					
>110	4	-1.36 (-3.06, 0.33)	0.12	98.84	<0.001
≤110	2	-0.56 (-1.36, 0.24)	0.17	84.82	0.01
Quality score					
7≤	3	-1.58 (-3.92, 0.75)	0.18	99.07	<0.001
<7	3	-0.61 (-1.07, -0.15)	0.01	75.42	0.02
Country					
Turkey	5	-1.12 (-2.51, 0.27)	0.11	98.61	<0.001
India	1	-0.98 (-1.47, -0.49)	<0.001	-	-
Age (months)					
24≤	3	-1.58 (-3.92, 0.75)	0.18	99.07	<0.001
<24	2	-0.45 (-1.00, 0.09)	0.1	78.78	0.03
NR	1	-0.98 (-1.47, -0.49)	<0.001	-	-

WMD: weighted mean difference; NR: not reported

larger population and less bias are needed.[2,16-18,48]

The study analyzed the link between serum vitamin B12 (VB12) levels and febrile seizures (FS) in children through a meta-analysis of five case-control studies. Results showed that VB12 levels were lower in FS patients compared to controls, though the difference was not statistically significant. This suggests a possible trend but not a definitive link between VB12 deficiency and FS. The findings align with other research indicating nutritional deficiencies, such as zinc and iron, may play a role in FS. Future research should include larger, more diverse cohorts, longitudinal studies, and comprehensive nutritional assessments to better understand this relationship. Mechanistic studies and intervention trials could elucidate the biological pathways involved and potential benefits of VB12 supplementation in preventing FS.

This present study is the first meta-analysis which evaluates the link between VB12 and FS in children. This is an essential affair to acknowledge potential limitations in this study. The original restriction of this study were the limited number of well-designed case-control studies and only included 772 participants. Therefore, conducting more studies in this respect to achieve higher number of participants will improve the power of study. Furthermore, 5 studies out of overall included 6 studies in this meta-analysis have been conducted in Turkey, which may impact the generalizability of these findings regarding the impact of genetic or ethnic factors on the results, and further studies in other regions of the world are needed to have a better general understanding of this topic and establish a causal relationship. Additionally, the original strength of this meta-analysis includes comprehensive coverage of the published literature and study design guided by PRISMA.

Conclusion

Consequently, we found low serum levels of VB12 in FS patients in compared with control groups. To prevent FS in children, it seems that the best way in these patients is to properly evaluate children in terms of lack of nutrients, including VB12, zinc, folate, and iron, as well as supplement therapy with these substances and a suitable diet.

Ethics Issues

The ethics committee of the Tabriz University of Medical Science reviewed and approved the study protocol (Ethical Code: IR.TBZMED.VCR.REC.1402.179).

Acknowledgments

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Author Contributions

Navid Sherafati: Investigation, Methodology, Visualization, Validation, Writing - Original Draft. Hamid Abbasi: Conceptualization, Investigation, Methodology, Formal Analysis, Data curation, Supervision, Visualization, Validation, Writing - Original Draft. Sama Rahnemayan: Methodology, Visualization, Validation, Writing - Original Draft. Elahe Abdi Bastami: Methodology. Sepehr Khosravi: Methodology. Kiarash Tajernarenj: Investigation, Methodology. Sarvin Sanaie: Conceptualization, Supervision, Writing - Review & Editing.

Conflict of Interest

The authors declare no conflicts of interest.

Supplementary Data

Supplementary data are available at https://doi.org/10.34172/PS.024.40508.

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