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Clinical trials of vitamin-mineral supplementations in people with epilepsy: a systematic review

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Not applicable.

Contributions

Name	Contribution
Ali A. Asadi-Pooya	Designed and conceptualized the study; acquisition of data; analyzed the data; drafted and revised the manuscript
Leila Simani	Acquisition of data; revised the manuscript

None of the authors listed on the manuscript are employed by a government agency. All are academicians.

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Abstract

Objective: The purpose of the current study was to systematically review the literature on the clinical trials of vitamin-mineral supplementations in people with epilepsy (PWE) to treat their seizures.

Methods: MEDLINE and Scopus from inception to August 25, 2020 were searched for related published manuscripts. The search keywords included "vitamin or folate or folic acid or biotin or thiamine or carnitine or zinc or manganese or selenium or omega-3 fatty acid or linoleic acid or micronutrient or trace element or supplementation" AND "epilepsy or seizure".

Results: We could identify 26 related articles. Seventeen studies provided class 2 of evidence and the rest provided class 3 of evidence. Eight studies investigated polyunsaturated fats, seven groups studied folic acid, four studies explored the effects of vitamin D, two investigated vitamin E, and three others studied multivitamin cocktails. There was one study on zinc and one on selenium. There is some evidence on the efficacy of polyunsaturated fats in treating seizures in PWE. The evidence on the efficacy of multivitamin cocktails in adults is promising.

Conclusion: High quality data on the efficacy of nutritional (vitamins-minerals) supplementations in treating seizures in PWE is scarce; however, designing future clinical trials of polyunsaturated fatty acid supplementation for drug-resistant seizures in adults with focal epilepsy and in children, and also multivitamin supplementations in adults with focal epilepsy seems reasonable and promising. Such clinical trials should be well-designed, randomized, and placebo controlled, with enough sample size and adequate follow-up of 12 months or more.

Key words: Epilepsy; Mineral; Seizure; Vitamin

1. Introduction

Epilepsy is a common chronic neurological disorder. Prevalence of epilepsy is 7 cases per 1,000 people and its incidence is 47 cases per 100,000 people per year worldwide [1,2]. Antiseizure medications (ASMs) are the first-line treatment for people with epilepsy (PWE), and many patients attain complete freedom from seizures when prescribed an appropriate ASM. However, about one-third of PWE suffer from drug-resistant seizures despite use of appropriate ASMs [3]. Drug-resistant epilepsy is associated with increased risk of morbidity and mortality, serious psychosocial consequences, and reduced quality of life [4-6]. Based on the current evidence pharmacoresistance in epilepsy seems to be a multifactorial phenomenon [6]. On the other hand, ASMs may have significant drug-nutrients interactions [7]. Many ASMs have been associated with nutritional deficiencies (e.g., vitamin D, folate, vitamin B12, biotin, thiamine, carnitine, etc.) in PWE [7]. Some nutritional deficiencies (e.g., thiamine deficiency, vitamin B12 deficiency, etc.) have been associated with causing seizures [8,9]; therefore, one might hypothetically expect a better seizure control if these nutrients are supplemented to the users of these drugs. On the other side of the coin, some evidence from animal studies suggest that nutritional supplements (e.g., polyunsaturated fatty acids) may modulate voltage-gated ion channels and neuronal excitation and provide membrane stabilization. Furthermore, vitamins may have anti-inflammatory and antioxidant effects; however, the mechanisms underlying their potential antiseizure effects are largely unknown [10,11].

During the past five decades, some investigators have attempted nutritional supplementations in an effort to reduce the seizure frequency in PWE [8]. The purpose of the current study was to systematically review the literature on the clinical trials of vitamin-mineral supplementations in PWE to treat their seizures and improve their seizure control status. We intentionally did not include pyridoxine (vitamin B6) in our study, because pyridoxine-

dependent epilepsy is a specific genetic condition. We specifically intended to investigate the beneficial effects of vitamin-mineral supplementations in PWE, who are not suffering from genetic and metabolic causes of epilepsy that are related to vitamins or trace elements.

2. Methods

The report of the current systematic review was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12,13] (Figure 1). MEDLINE (accessed from PubMed) and Scopus from inception to August 25, 2020 were systematically searched for related published manuscripts. In both electronic databases, the search keywords included “vitamin or folate or folic acid or biotin or thiamine or carnitine or zinc or manganese or selenium or omega-3 fatty acid or linoleic acid or micronutrient or trace element or supplementation (title and abstract)” AND “epilepsy or seizure (title)”. We assumed that with the keywords “vitamin” or “supplementation” or “trace element” we would identify any and all manuscripts of interest; but, in order to ensure the literature saturation, we also included some specific keywords (i.e., folate or folic acid or biotin or thiamine or carnitine or zinc or manganese or selenium or omega-3 fatty acid or linoleic acid) based on the previous review studies [7,8]. Furthermore, to ensure maximum literature saturation, both authors scanned the reference lists of the included studies or relevant reviews identified through the search. The inclusion criteria were articles written in English and human clinical trials. Types of studies included: 1. Randomized controlled trials; 2. Parallel group or crossover studies; 3. Case series, pilot studies, and open label studies. Types of participants were PWE of all types, of any age, and either gender. Types of interventions included: Treatment group will receive one or more vitamins/minerals and controls will receive placebo or no add-on treatment. Types of outcome measures included reduction in seizure frequency. The exclusion criteria were animal studies, studies not

including PWE (e.g., children with febrile seizures), and PWE with specific genetic-metabolic disorders related to vitamins or trace elements [e.g., pyridoxine-dependent epilepsy (B6), Menkes syndrome (Copper), Biotinidase deficiency (Biotin), etc.].

Both authors participated through each phase of the review independently (screening, eligibility, and inclusion). They obtained the full reports for all titles that appeared to meet the inclusion criteria or where there was any uncertainty. Both authors screened the full texts and decided whether these meet the inclusion criteria. They resolved any disagreements through discussions. Neither of the authors were blind to the journal titles or to the study authors or institutions.

The following data were extracted from the included studies: study authors, date, and location, study design, main results, and major limitations. The methodological quality of the included studies was assessed by both authors. The class of evidence was defined as follows [14]:

Class I Evidence: Evidence from one or more well-designed, randomized controlled trials.

Class II Evidence: Evidence from one or more well-designed comparative studies, such as non-randomized cohort studies, case-control studies, and other comparable studies.

Class III Evidence: Evidence from case series, comparative studies with historical controls, case reports, and expert opinion, as well as significantly flawed randomized controlled Trials.

The Shiraz University of Medical Sciences Institutional Review Board approved this systematic review.

Data Availability Statement

Research data sharing is not applicable.

3. Results

Through the search strategy, we could identify 26 related articles [15-40] (Tables 1 and 2). Seventeen studies provided class 2 of evidence and the rest provided class 3 of evidence; none provided class one evidence on the efficacy of nutritional supplementations (vitamins-minerals) in treating seizures in PWE. Eight studies investigated polyunsaturated fats, seven groups studied folic acid, four studies explored the effects of vitamin D, two investigated vitamin E, and three others studied multivitamin cocktails. There was one study on zinc and one on selenium.

Table 3 depicts a picture of the studies providing evidence on the efficacy of nutritional supplementations in treating seizures in PWE. Studies on vitamin E (one positive and one negative studies) and vitamin D (two positive and two negative studies) were conflicting on providing evidence on the efficacy of these nutritional supplementations in treating seizures in PWE. While there were enough studies (6 investigations) refuting the benefits of folic acid supplementation in adults, one study in children suggested that this supplementation would be beneficial in reducing seizures (Table 3). There is some controversial evidence on the efficacy of polyunsaturated fats in treating seizures in PWE (five positive and three negative studies). The evidence on the efficacy of multivitamin cocktails in adults is promising (three positive studies). However, the evidence on the efficacy of zinc and selenium is scarce (Table 3).

Most studies had significant limitations. Only one study calculated the sample size and reached to a desired number of 140 participants [34]. This study had a short duration of 3 months, was not placebo controlled, and was not blinded. All other studies had small sample sizes of below 60 participants. Furthermore, most studies followed their patients for short periods of time (mainly, below six months); only three studies had follow-up durations of at least 12 months [18,24,35]. Seizure freedom after a treatment has started is defined as

freedom from seizures for a minimum of three times the longest preintervention interseizure interval or 12 months, whichever is longer [41]. Therefore, the minimum required follow-up time for evaluating the success and efficacy after any antiseizure intervention has implemented is 12 months. Finally, many studies had other limitations including: not being blinded, not being placebo controlled, and including different epilepsy syndromes (Table 2).

4. Discussion

While high quality data on the efficacy of nutritional (vitamins-minerals) supplementations in treating seizures in PWE is scarce and therefore, performing a meta-analysis is not feasible, we can make the following conclusions based on the available data.

4.1. Type and design of the study: To obtain the desired evidence on the efficacy of nutritional (vitamins-minerals) supplementations in treating seizures in PWE, we need one or more well-designed, randomized controlled trials on any supplementation. In designing such clinical trials, investigators should calculate an appropriate sample size and also should follow their patients for enough period of time (i.e., at least for 12 months). Sample size calculation is one of the first and most important steps in designing any clinical study [42]. Investigators should keep in mind that, in the presence of significant confounding factors (e.g. different etiologies, comorbidities), researchers would need larger sample sizes [42]. All the reviewed studies in the current systematic review suffered from significant limitations and none could provide a strong evidence for or against the efficacy of nutritional supplementations (vitamins-minerals) in treating seizures in PWE.

4.2. Patient population: Epilepsy is not a single disorder, but rather a spectrum of brain disorders. Therefore, it is not expected to find a single therapy that works for all PWE. Generalized epilepsy syndromes differ from focal epilepsies and even focal tumor-

related epilepsies may differ from focal genetic epilepsies (e.g., Rolandic epilepsy) in their underlying physiopathology and response to therapy. With the same logic, it is reasonable to assume that vitamin-mineral supplementation may be efficacious in reducing seizures in some PWE, but not so in others. In designing any clinical trial to assess the efficacy of vitamin-mineral supplementations in PWE to treat their seizures, the investigators should select a uniform population of patients with regard to the etiology. This strategy was not followed in any of the reviewed studies before. While this strategy may cause difficulties in designing studies on some uncommon forms of epilepsy syndromes, for common epilepsy syndromes (e.g., idiopathic generalized epilepsies, focal structural epilepsies, etc.) this is a doable approach that may yield more meaningful and practical results.

4.3. Future trials: Based on the available evidence, it seems that designing future clinical trials of polyunsaturated fatty acid supplementation for drug-resistant epilepsy in adults with focal epilepsy and in children (should be specified more) is justifiable [21,26,27,35,40]. There is some evidence from animal studies that polyunsaturated fatty acids modulate voltage-gated ion channels and neuronal excitation [10]. Another proposed mechanism for the antiseizure effects of polyunsaturated fatty acid supplementation is through membrane stabilization [11]. Polyunsaturated fatty acids are safe and generally well tolerated [26,35]. However, the optimal type of polyunsaturated fatty acid (omega-3 fatty acids or omega-6 fatty acids) and the ideal dose in treating epileptic seizures should be clarified in future studies.

Similarly, designing future trials of multivitamin supplementations in adults with focal epilepsy seems reasonable and promising; while there is no evidence on this in children, designing such studies in children with focal epilepsy is also reasonable

[24,31,37]. Vitamins have anti-inflammatory and antioxidant effects; however, the mechanisms underlying their potential antiseizure effects are largely unknown. While designing future trials on vitamin D and vitamin E supplementation in PWE has some supporting evidence, the outlook is not as promising as for the first two suggested trials above (there are conflicting studies and observations on these nutritional supplements). Folic acid supplementation in adults is most probably not efficacious in reducing seizures [15-18,28,29] and any future trial should be designed cautiously. Evidence on the efficacy of folic acid and zinc supplementation in children [33,34] and selenium supplementation in adults [32] is scarce.

5. Conclusion

High quality data on the efficacy of nutritional (vitamins-minerals) supplementations in treating seizures in PWE is scarce; however, designing future clinical trials of polyunsaturated fatty acid supplementation for drug-resistant seizures in adults with focal epilepsy and in children, and also multivitamin supplementations in adults with focal epilepsy seems reasonable and promising. Such clinical trials should be well-designed, randomized, and placebo controlled, with enough sample size and adequate follow-up time.

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Table 1. The search keywords included "vitamin or folate or folic acid or biotin or thiamine or carnitine or zinc or manganese or selenium or omega-3 fatty acids or linoleic acid or micronutrient or trace element or supplementation (title and abstract)" and "epilepsy or seizure (title)".

	Medline (PubMed)		**Scopus**	
	Primary hints	**Relevant articles**	**Primary hints**	**Relevant articles**
Epilepsy	793	25 (8 duplicates)	1306	20 (20 duplicates)
Seizure	97	7 (4 duplicates)	1534	9 (8 duplicates)
Total	**890**	**32 (12 duplicates)**	**2840**	**29 (28 duplicates)**

Other sources (5): Jensen/ 1970; Ralston/ 1970; Christiansen/ 1974; Gibberd/ 1981; Al Khayat/ 2010.

Table 2. Clinical trials of nutritional supplementations in people with epilepsy.

1st author/ Year/ Country	Study design	Main results	Limitations	Quality
Schlanger/ 2002/ Israel[21]	Non-randomized open assessment of diet enriched with omega-3 fatty acids in adults and adolescents	All five patients exhibited substantial improvement and alleviation in frequency and strength seizures.	Small sample size of 5 patients. Short treatment duration of 6 months. Different epilepsy types. Children and adults were enrolled.	Supporting class III evidence
Yuen/ 2005/ UK[25]	Randomized, double-blind placebo-controlled parallel group trial of omega-3 fatty acids supplementation with 1 g eicosapentaenoic acid and 0.7 g docosahexaenoic acid daily in adults with mainly focal epilepsy	Seizure frequency decreased over the first 6 weeks of treatment in the supplement group, but this effect was not sustained.	Small sample sizes of 29 (drug) and 27 (placebo). Short treatment duration of 12 weeks.	Supporting class II evidence
Bromfield/	Randomized placebo-	There was no significant	Small sample size	Supporting

2008/ USA[22]	controlled trial of polyunsaturated fatty acids for refractory epilepsy in adults	change in seizure frequency	of 21 subjects (12 in treatment and 9 in placebo group). Short duration of 12 weeks. Not blinded.	class III evidence
DeGiorgio/ 2008/ USA[23]	Pilot, randomized, double-blind two-period crossover clinical trial of high-dose fish oil (9600 mg of fish oil/day, 2880 mg of n-3 fatty acids) in 11 adult patients with refractory seizures	No positive effect on seizure frequency was identified.	Small sample size of 11 subjects. Short duration of 12 weeks.	Supporting class III evidence
Yuen/ 2012/ UK[27]	Non-randomized open assessment of eicosapentaenoic acid supplementation 1000 mg daily in adults with focal epilepsy	Six people had fewer seizures (range 12 to 59% reduction)	Small sample size of 10 participants. Short duration of 3 months. Not placebo controlled. Not blinded.	Supporting class III evidence
DeGiorgio/ 2015/	Randomized phase II crossover double-	Low dose fish oil (3 capsules/day, 1080 mg	Small sample size of 24 participants.	Supporting class II

USA[26]	blind placebo-controlled trial of low dose and high dose fish oil in adults with mainly focal epilepsy	eicosapentaenoic acid+docosahexaenoic acid) was associated with a 33.6% reduction in seizure frequency compared with placebo. High dose fish oil was no different than placebo in reducing seizures.	Short duration of exposure (10 weeks).	evidence
Ibrahim/ 2018/ Sudan[35]	A randomized, double-blind, placebo-controlled trial of eicosapentaenoic acid and docosahexaenoic acid on seizure frequency in drug-resistant epilepsy (all ages) (study duration of 12 months)	Both treatment groups had a significantly higher number of seizure-free days compared with the placebo group.	Small sample size of 59 participants. Different epilepsy types. Children and adults were enrolled.	Supporting class II evidence
Al Khayat/ 2010/ Egypt[40]	Non-randomized blinded assessment of polyunsaturated fatty acids for refractory epilepsy in children	Changes in serum levels of polyunsaturated fatty acids were accompanied by decrease in seizure frequency, duration and severity.	Small sample size of 20 participants. Short duration of 6 months. Not placebo controlled.	Supporting class III evidence

			Not randomized.	
Jensen/ 1970/ Denmark[15]	A double-blind cross-over study of the effect of folic acid treatment in adult patients with drug-induced subnormal serum folates	Treatment with massive doses of folic acid (20 mg daily) has no effect on the seizure frequency.	Small sample size of 24 participants. Short duration of exposure of 5 months.	Supporting class II evidence
Grant/ 1970/ UK[16]	Randomized, double-blind, placebo-controlled, clinical trial of 15 mg per day folic acid in adults with epilepsy	There were no significant changes in the frequency of seizures.	Small sample size of 51 participants. Short duration of 26 weeks.	Supporting class II evidence
Norris/ 1971/ Canada[28]	Non-randomized open label cross-over trial of folic acid 5 mg daily in adults with mainly focal epilepsy	There was no significant change in seizure frequency.	Small sample size of 39 participants. Short duration of 3 months. Not blinded.	Supporting class II evidence
Mattson/ 1973/ USA[17]	Double-blind, placebo-controlled trial in adults	Folic acid supplementation at 15 mg per day is not efficacious in seizure control.	Small sample size of 41 participants. Short duration of 6 months.	Supporting class II evidence
Gibberd/	Double-blind,	Folic acid	Small sample size	Supporting

1981/ UK[18]	randomized, placebo-controlled trial in adults	supplementation at 15 mg per day had no significant effect on seizure frequency as compared with placebo.	of 57 participants.	class II evidence
Deopa/ 2018/ India[34]	Non-randomized open label trial of folic acid supplementation in 95 children. Children with serum folate <5 ng/ml were supplemented with 10 mg folic acid daily and children with 5–10 ng/ml were given 5 mg folic acid daily for 3 months.	Children supplemented with folic acid had significant fall in mean seizure frequency	Short duration of 3 months. Not placebo controlled. Not blinded.	Supporting class II evidence
Ralston/ 1970[39]	Double-blind, randomized, placebo-controlled trial of folic acid in adults	No significant changes in seizure frequency were found.	Small sample size of 27 participants. Short duration of 3 months.	Supporting class II evidence
Holló/ 2012/ Hungary[30]	Pilot study of oral vitamin D3 in adults with mainly focal epilepsy	Median seizure reduction was 40%.	Small sample size of 13 participants. Short duration of 3 months.	Supporting class III evidence

			Not placebo controlled. Not blinded.	
Tombini/ 2018/ Italy[36]	Non-randomized open label trial of vitamin D supplementation in adults	No significant change in seizure frequency was found	Small sample size of 48 participants. Short duration of 6 months. Different epilepsy types. Not placebo controlled. Not blinded.	Supporting class III evidence
DeGiorgio/ 2019/ USA[29]	Pilot study of oral vitamin D3 5000 IU/day in adults with mainly focal epilepsy	Median seizure frequency declined from 5.18 seizures per month to 3.64 seizures per month at 6 weeks and to 4.2 seizures per month at 12 weeks.	Small sample size of 9 participants. Short duration of 3 months. Not placebo controlled. Not blinded.	Supporting class III evidence
Christianse n/ 1974/ Denmark[38]	Randomized, double-blind, placebo-controlled, clinical trial of vitamin D2 in adults and children	A reduction in the number of seizures was observed when patients received vitamin D2.	Small sample size of 23 participants. Short duration of 12 weeks.	Supporting class II evidence
Ogunmekan	Randomized, double-	Of the 12 subjects	Small sample size	Supporting

/ 1989/ Canada[19]	blind, placebo-controlled, clinical trial of D-a-Tocopherol (vitamin E) in children with focal or generalized epilepsy	receiving active drug, 10 were responders (i.e., >60% reduction in seizure frequency); 6 had 90%-100% reduction of seizure frequency	of 24 participants. Different epilepsy types. Short duration of 3 months.	class II evidence
Raju/ 1994/ India[20]	Randomized, double-blind, cross-over, placebo-controlled, clinical trial of D-a-Tocopherol (vitamin E) in patients ≥ 12 years of age with focal or generalized epilepsy	No significant change in seizure frequency was observed	Small sample size of 43 participants. Different epilepsy types. Short duration of 3 months.	Supporting class II evidence
Yürekli/ 2013/ Turkey[29]	Pilot study of selenium supplementation in adults; control (n=15), refractory epilepsy (n=15), and refractory epilepsy + selenium (n=8)	3 patients had daily seizures. During the 45-day selenium treatment, the seizure rates in two patients decreased to every week.	Small sample size of 38 participants. Short duration of 45 days. Not placebo controlled. Not blinded.	Supporting class III evidence
Saad/ 2015/	A randomized,	5 of the patients (31%) in	Small sample size	Supporting

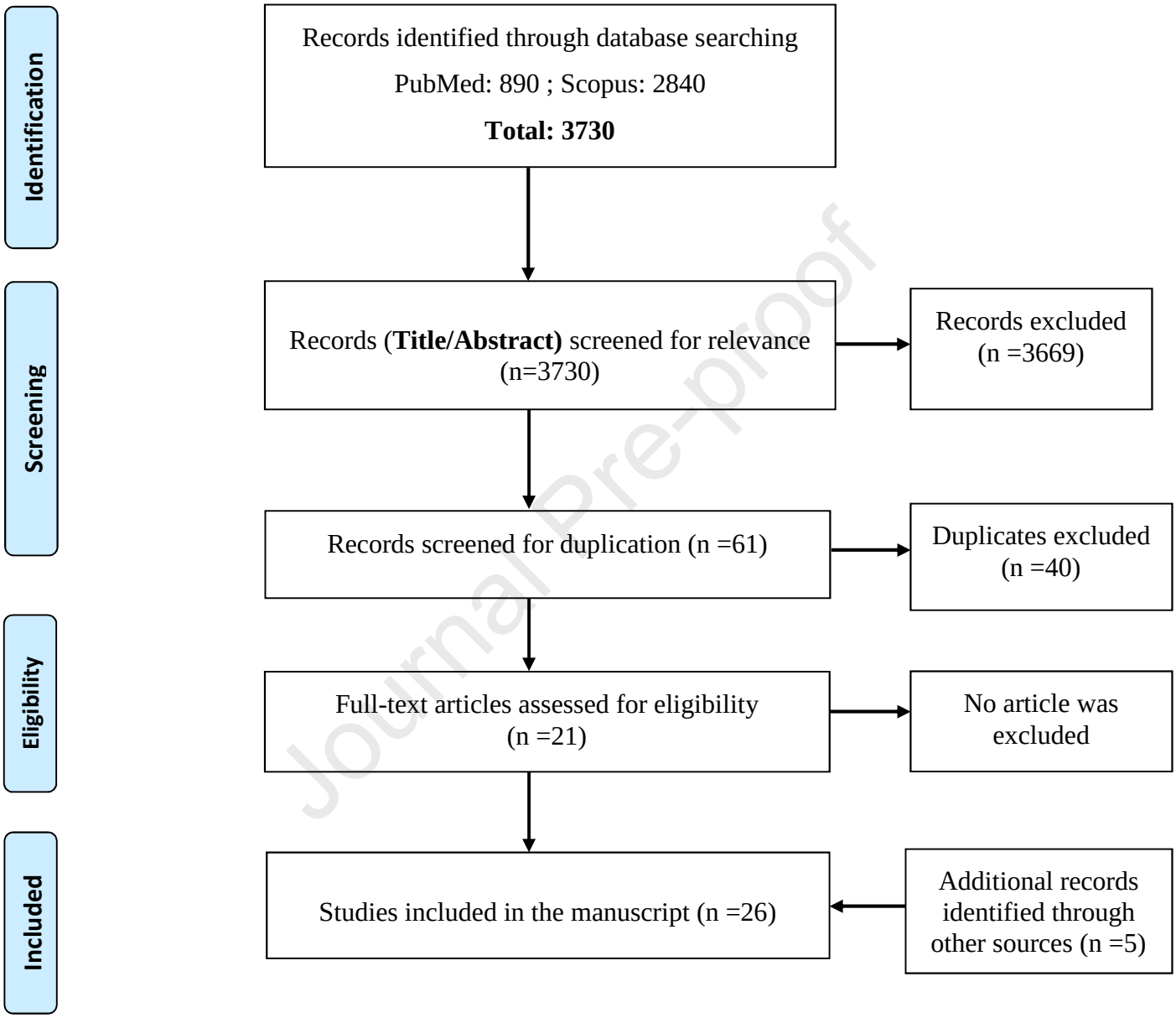
Egypt[33]	double-blind, placebo-controlled clinical trial of treatment with zinc 1 mg/kg/day in children with intractable epilepsy	the intervention group were good responders (>50% reduction in seizure frequency) *vs.* 4.5% of the placebo group.	of 45 participants. Short duration of 6 months.	class II evidence
Zhou/ 2017/ China[24]	Randomized controlled trial of antiepileptic drugs combined with B vitamins in the treatment of epilepsy after stroke in adults (study duration of 12 months)	Anti-epilepsy drugs combined with B vitamins can improve epilepsy control after stroke. Vitamin B12 may be better than vitamin B complex in the treatment of epilepsy after stroke.	Small sample sizes of 30 in each group. Not placebo controlled. Not blinded.	Supporting class II evidence
Chang/ 2020/ Taiwan[31]	Pilot study of oral vitamins (daily dose: B6 100 mg, B9 5 mg, D 1000 IU, E 400 IU and coenzyme Q10 100 mg) in adults with intractable focal epilepsy	The seizure frequency significantly decreased after the six-month supplementation (9.04 ± 18.16/month and 2.06 ± 3.89/month, p = 0.045).	Small sample size of 26 participants. Short duration of 6 months. Not placebo controlled. Not blinded.	Supporting class II evidence
Bochyńska/ 2012/	Non-randomized open label trial of vitamin B	After 1 year of vitamin B supplementation, seizure	Small sample size of 51 participants.	Supporting class II

Poland[37]	supplementation in adult patients with chronic epilepsy	frequency decreased significantly (from 11 per year to 4 per year).	Not placebo controlled. Not blinded.	evidence

Table 3. Summary of evidence on antiseizure effects of vitamin-mineral supplementations in people with epilepsy.

	Evidence supporting antiseizure effects: reference number	**Evidence not supporting antiseizure effects: reference number**
Polyunsaturated fats	Class II: 26 (adults), 35 (all ages) Class III: 21 (all ages), 27 (adults), 40 (children)	Class II: 25 (adults) Class III:22 (adults), 23 (adults)
Vitamin D	Class II: 38 (all ages) Class III: 30 (adults)	Class III: 29 (adults), 36 (adults)
Vitamin E	Class II: 19 (children)	Class II: 20 (mainly adults)
Folic acid	Class II: 34 (children)	Class II: 15 (adults), 16 (adults), 17 (adults), 18 (adults), 28 (adults), 39 (adults)
Multivitamin	Class II: 24 (adults), 31 (adults) , 37 (adults)	
Zinc	Class II: 33 (children)	
Selenium	Class III: 32 (adults)	

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram of the study.



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