ARTICLE

Effects of Vitamin D supplementation on Pediatric Attention Deficit Hyperactivity Disorder: a meta-analysis and systematic review

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OBJECTIVE: Attention Deficit Hyperactivity Disorder (ADHD) is a common mental disorder in children. It is unclear how nutrition and dietary components relate to ADHD. Some studies suggest that children with ADHD have lower serum levels of vitamin D than healthy controls. In the current study, the effects of Vitamin D supplementation on ADHD were reviewed and analyzed using available literature.

MATERIALS AND METHODS: A meta-analysis and systematic review were performed. Children less than 18 years old diagnosed with ADHD given Vitamin D supplementation or placebo were included. A search was performed in PubMed/MEDLINE, EMBASE, Scopus, Cochrane, and Google Scholar databases from inception to August 2024 using the MeSH keywords: "Vitamin D" AND (ADHD OR Attention Deficit Hyperactivity Disorder) AND (children OR pediatric OR adolescents) AND randomized controlled trial. Standardized Mean Difference (SMD) was used as an effect measure and pooled using random effects meta-analysis.

RESULTS: The pooled SMS showed significantly lower ADHD scores (SMD=-0.59, 95%CI=-1.06 to -0.11, p=0.01), lower inattentive scores (SMD=-0.61, 95%CI=-1.00 to -0.23, p=0.002), and lower hyperactivity scores (SMD=-0.64, 95%CI=-1.08 to -0.20, p=0.004) in children given Vitamin D supplementation. The adverse events reported were minor only and did not vary significantly between intervention and control groups.

CONCLUSION: Vitamin D treatment as an adjuvant to methylphenidate alleviated ADHD symptoms without significant adverse effects, correlating with enhanced vitamin D levels. Given the robust evidence and well-structured randomized controlled trials, we strongly advocate for the integration of vitamin D supplementation with ADHD treatment.

Keywords: Pediatric ADHD, Vitamin D, meta-analysis, systematic review

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The authors affirm that this manuscript is original, has been read and approved by all contributing authors, that each author meets the established criteria for authorship, and that the content represents a truthful and accurate account of the work conducted.

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental condition that has been known to affect children's ability to function worldwide. People with this disorder show traits of developmentally inappropriate levels of inattentiveness, hyperactivity, or impulsivity. It is associated with cognitive and functional deficits that relate to diffuse abnormalities in the brain.[1] ADHD has been identified as one of the leading causes of academic underachievement and disruptive behaviors in school. Its negative effects extend to family members, friends and teachers of affected patients, causing significant economic and social burdens. [2] ADHD has also been associated with long term adverse outcomes including increased risk for substance abuse, reduced vocational opportunities, and increased criminal activity. It is also often comorbid with other conditions like oppositional defiant disorder, conduct disorder, depression and anxiety. [5] Comprehensive multimodal treatment is currently recommended in managing ADHD. Despite emerging treatment options for this disorder, pharmacologic therapies continue to play an important role for individuals who cannot tolerate nonpharmacologic therapy or have comorbid conditions. However, almost 25-30% of ADHD cases are nonresponsive to psychostimulants and report poor adverse events, such as increased resting heart rate and systolic blood pressure, insomnia, and decreased appetite. Vitamin D has been known for skeletal effects, but recent literature explored its functions in immunomodulation, diabetes, cancer, cardiovascular diseases, and hypertension.[2] It has been regarded as a versatile hormone playing a role in neurological system, cardiovascular system, immune system, endocrine system, cancer diseases, and psychiatric diseases. Hence, Vitamin D supplementation is thought to decrease symptoms through several possible mechanisms.[3] Vitamin D deficiency results in imbalance of neurotransmitters in the dopaminergic pathways responsible for the pathophysiology of ADHD. In addition, it has been reported that Vitamin D deficiency in effect reduces the production of acetylcholine which helps in maintaining attention and executive function. Studies illustrated that serum vitamin D concentrations in children and adolescents with ADHD are also significantly lower than healthy populations. Consequently, Vitamin D supplementation may compensate for its deficiency and possibly reduce ADHD symptoms.[4] With the emerging studies determining the possible effects of Vitamin D supplementation in cognitive function of children with ADHD, collating the data reported through a meta-analysis would be beneficial in the future management of ADHD.

In the interest of conveying the possible benefit of Vitamin D supplementation in managing ADHD in children, studies have been performed to test this hypothesis. A randomized control trial done in Iran have used Vitamin D supplementation as adjunct in treatment of ADHD. It showed that after 8 weeks of supplementation, evening symptoms and total score of WPREMB scale were significantly different between the two groups at weeks 4 and 8. [2] Another double-blind, randomized clinical trials were done in Iran including 96 children aged 2-18 years old with ADHD. In this study, after 6-week supplementation, Conners ADHD, Inactivity and Hyperactivity/Impulsivity were reduced compared to baseline values in the Vitamin D group. [6] Similar study was also done in Egypt wherein they showed that there is a statistically significant lower values of serum Vitamin D levels in children with ADHD compared with controls. After 12 weeks of Vitamin D supplementation, there was a significant increase in serum levels of Vitamin D in the supplemented group. Subsequently, children with ADHD who received Vitamin D supplementation exhibited a significant improvement in conceptual level, inattention, and opposition as well as hyperactivity and impulsivity. [4] The effects of Vitamin D supplementation on ADHD in 6-13 students were done by Naeini, et.al in Iran. In this double-blind parallel clinical trial, findings showed that the mean scores of Conners Parent Questionnaire (CPQ) were significantly lower in the intervention group compared to the control group after the intervention. In addition, the mean score of Strengths and Difficulties Parent Version (SDQP) was also significantly lower in the intervention group compared to the control group at the end of the study. [7] On another study done last 2020, Vitamin D supplementation was compared with neurofeedback therapy as management of ADHD. Analysis of the data showed that there was lower Attention Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) score in the combined group compared with the other 3 groups. [8]

This study aims to compare the effects of Vitamin D supplementation as primary or adjunct treatment to ADHD versus established modes of therapy. Specifically, it aims to collate, summarize, and re-analyze results and conclusions of published studies regarding the use of Vitamin D as treatment or treatment adjunct to ADHD using a systematic literature search method.

Materials and Methods

The Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) declaration was used to create this meta-analysis and systematic review.

Inclusion and Exclusion Criteria

1. Types of Studies

Only randomized controlled trials with published English version were included in

this meta-analysis. There were no limitations to date.

2. Types of Participants

Children less than 18 years old who have been diagnosed with ADHD based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV or DSM-V) Criteria. Children with co-morbidities were excluded.

3. Types of Interventions

Vitamin D supplementation as the only treatment or as an adjunct therapy in treatment of ADHD.

4. Types of Comparators

Comparator included was any type of placebo intervention. This meta-analysis included studies comparing Vitamin D to placebo treatment, baseline treatment, or neurofeedback therapy.

5. Types of Outcomes

The primary outcome that was measured in this meta-analysis was ADHD symptoms severity using different psychometric scales such as Conners Parent Rating Scale, Conners Parent Questionnaire, Conners Teacher Rating Scale, ADHD rating scale, Weekly Parent Ratings of Evening and Morning Behavior, Strengths and Difficulties Questionnaire by Teachers, Continuous Performance Test, Wisconsin's Card Sorting Test, and Wechsler Intelligence Scale for Children. The secondary outcome was adverse effects of Vitamin D supplementation on children with ADHD.

A search was performed in PubMed/ MEDLINE, EMBASE, Scopus, Cochrane, and Google Scholar databases from inception to August 2024 using the MeSH keywords: "Vitamin D" AND (ADHD OR Attention Deficit Hyperactivity Disorder) AND (children OR pediatric OR adolescents) AND randomized controlled trial.

The titles and abstracts obtained from the electronic search were examined separately by the primary investigator. If the title or abstract of a report is found to meet the inclusion criteria, the full paper was retrieved. Relevant studies were assessed completely. Following the PRISMA criteria, a search and selection process flow diagram was created.

Full text articles of studies that met the inclusion criteria were used to fill a standardized extraction form. The following were extracted by the principal investigator: study name (along with the name of the first author and year of publication), country where the study was conducted, patient characteristics (age, sex), source from which patients or study participants were selected, study design, intervention and control groups, reported outcomes, number of children per study group, and total number of participants.

The quality of the studies was assessed by the primary investigator using the Cochrane's Collaboration risk of bias tool for several aspects including sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, differential

differential noncompliance in Vitamin D and control groups, dropout rate, and lack of details on controls. Each methodology was graded as high, low, or unclear to show the risk of bias.

Review Manager version 5.4 was used for data analysis and performing the meta-analysis which was summarized in ad-hoc tables and forest plots. Standardized Mean Difference with 95% Confidence Intervals was used to determine effect of Vitamin D supplementation in management of ADHD in children.

Statistical heterogeneity was determined using X^2 and I^2 wherein $p < 0.10$ or I^2 greater than 60% was considered as substantial heterogeneity. Data were also analyzed using a random-effect model.

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system was used to determine the overall quality of evidence for the primary outcome. It categorized evidence into four levels with evaluation process starting from quality of evidence until determination of strength of recommendations.

Results

A total of 245 studies were identified using the search strategy (Figure 1), of which 192 were eliminated from title and abstract screening because of duplicate and non-relevant study population or treatment groups. From the remaining 8 studies, 2 were further excluded because they had no control groups. Overall, 6 studies were included in the systematic review, and one was excluded (Mirhosseini 2024) in the meta-analysis because the data on mean values cannot be extracted from the study.

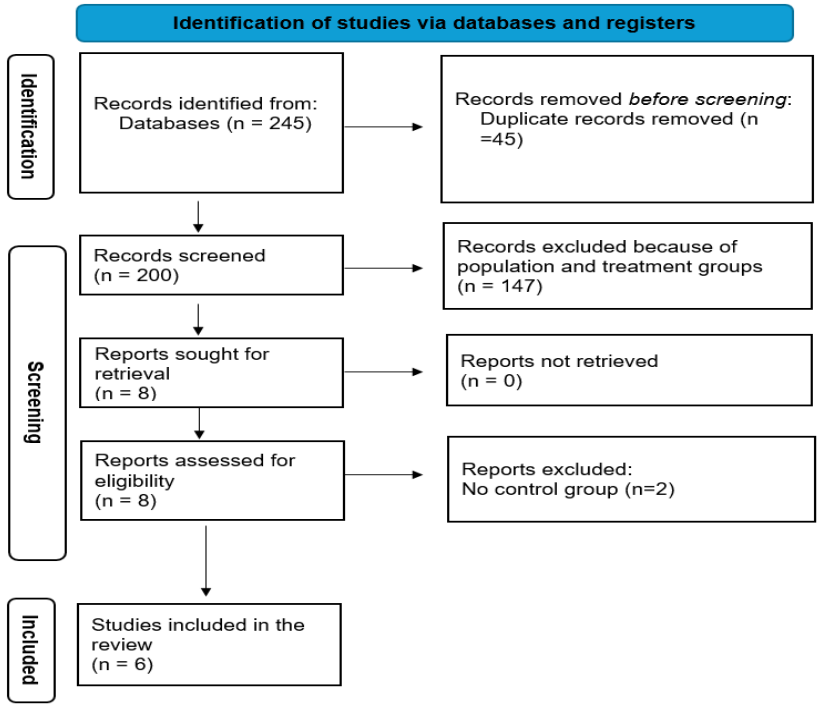


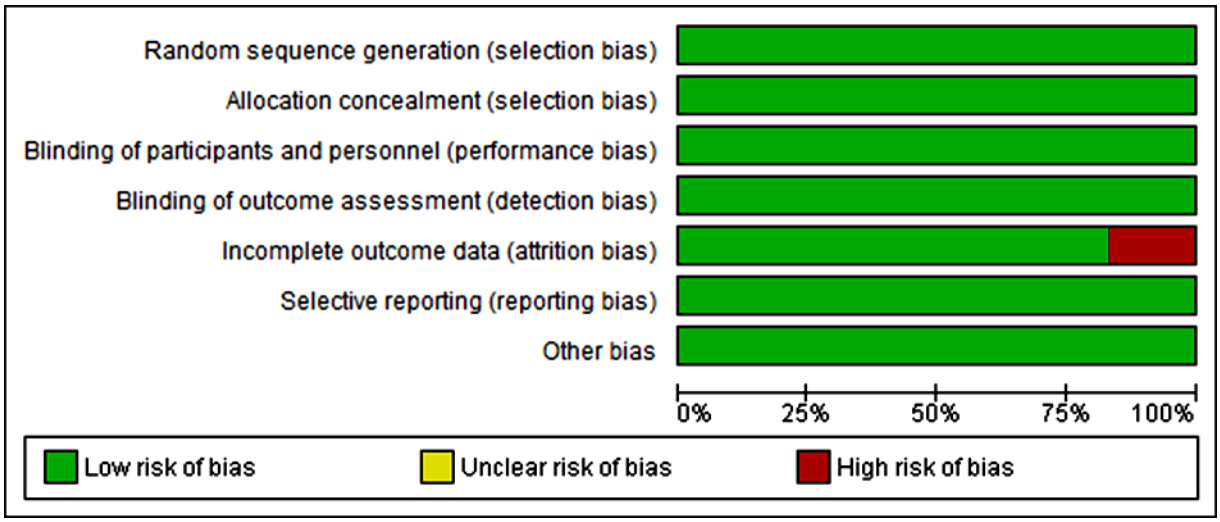
Figure 1. PRISMA flow chart shows the study selection process for meta-analysis.

All studies were conducted in the Middle East and were published between 2018 and 2024 (Table 1). The age range varied across studies and majority were males. Vitamin D dosage also varied with most studies reporting 50,000 IU/ week supplementation. The duration of supplementation across studies varied between 6 to 12 weeks. The most used ADHD rating scale was the Conners parent rating scale.

Table 1. Characteristics of included studies

Author year, country	Demographics (age range, male:female sex)	Vitamin D dosage	Comparator	Study duration	Rating scale used
Dehbokri et al. (2019) Iran	2 to 18 years 80:16	50,000 IU/week	Placebo	6 weeks	Conners parent rating scale
Elshorbagy et al. (2018) Saudi Arabia	7 to 14 years Not reported	3,000 IU/day	Placebo	12 weeks	Conners parent rating scale Wisconsin's Card Sorting Test
Mirhosseini et al. (2024) Iran	7 to 13 years 10:25	50,000 IU/week	Placebo	8 weeks	Conners parent rating scale
Mohammadpour et al. (2018) Iran	5 to 12 years 46:16	2,000 IU/day	Placebo	8 weeks	Conners parent rating scale ADHD rating scale Weekly Parent Ratings of Evening and Morning Behavior
Naeini et al. (2019) Iran	6 to 13 years 50:12	1,000 IU/day	Placebo	12 weeks	Conners Parent Questionnaire Continuous Performance Test Strengths and Difficulties Questionnaire
Rahmani et al. (2022) Iran	6 to 15 years Not reported	50,000 IU/week	Placebo	12 weeks	ADHD rating scale

All studies were of good methodological quality with low risk of selection bias, detection bias, and reporting bias. The study of Dehboki et al 2018 is at risk for attrition bias given the more than 10% drop-out rate and small sample size in this study (Figure 2).



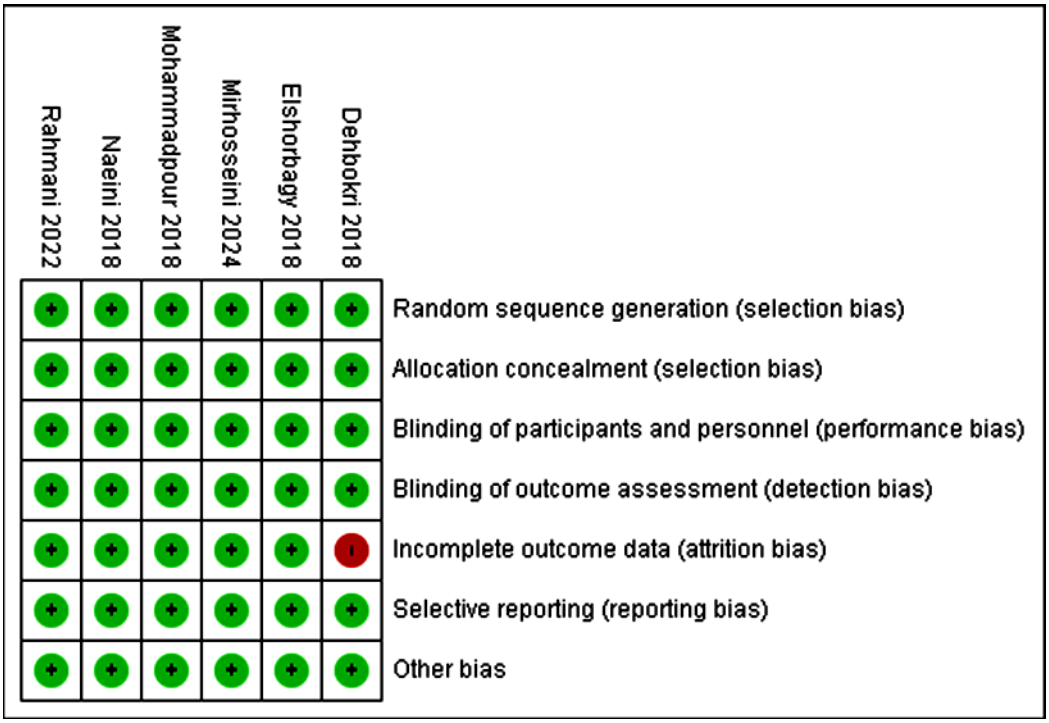


Figure 2. Risk of bias assessment of included studies

Four of four studies showed lower ADHD scores in patients given Vitamin D supplementation compared to placebo by the end of the intervention period. The overall pooled SMD showed significantly lower ADHD scores in patients given Vitamin D supplementation (SMD=-0.59, 95%CI=-1.06 to -0.11, p=0.01). The studies showed considerable heterogeneity (I^2=72%) (Figure 3).

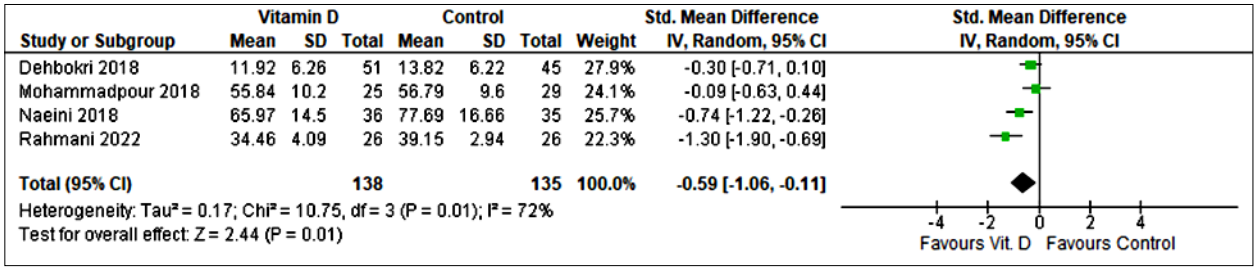


Figure 3. Meta-analysis on the effect on total ADHD score

Four of four studies showed lower inattentive scores in patients given Vitamin D supplementation compared to placebo. The overall pooled SMD showed significantly lower inattentive scores in patients given Vitamin D supplementation (SMD=-0.61, 95%CI=-1.00 to -0.23, p=0.002). The studies showed moderate heterogeneity (I^2=51%) (Figure 4).

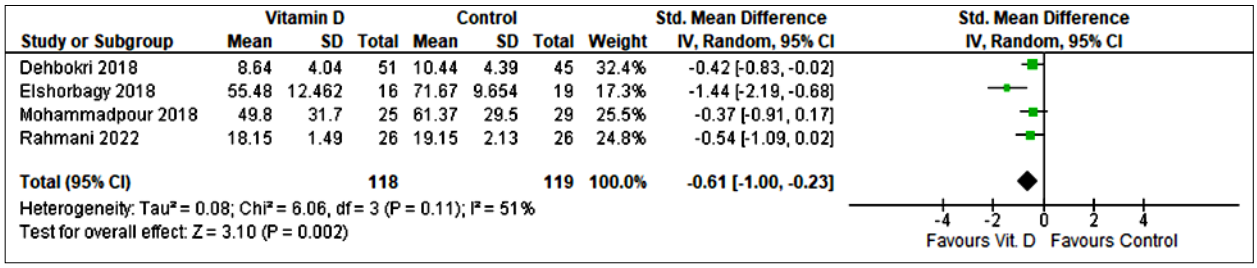


Figure 4. Meta-analysis on the effect on inattention score

Five of five studies showed lower hyperactivity scores in patients given Vitamin D supplementation compared to placebo. The overall pooled SMD showed significantly lower hyperactivity scores in patients given Vitamin D supplementation (SMD=-0.64, 95%CI=-1.08 to -0.20, p=0.004). The studies showed considerable heterogeneity (I^2=70%) (Figure 5).

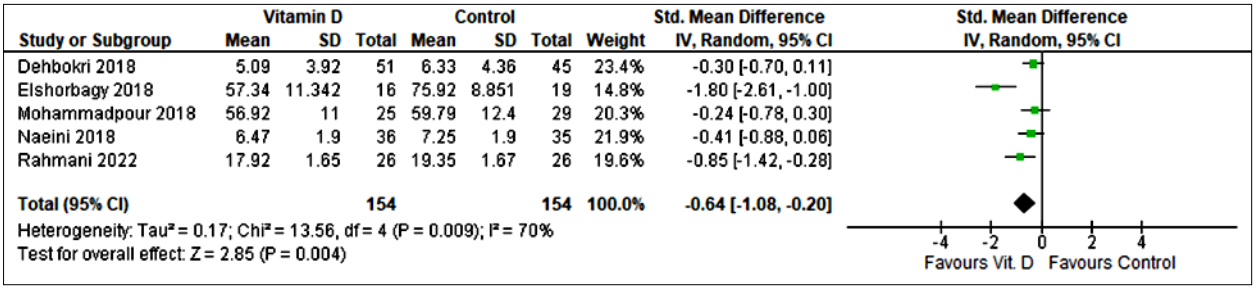


Figure 5. Meta-analysis on the effect on hyperactivity score

Four studies reported on adverse events associated with Vitamin D supplementation and placebo use. Elshorbagy et al. 2018 reported non-significant difference in the incidence rates of adverse events between the intervention and control groups (15% versus 5%, respectively). The reported cases were minor gastrointestinal related events. Naeini et al. 2018 and Rahmani et al. 2022 both reported absence of adverse events in all patients. Mohammadpour et al. 2018 reported the most common adverse events which included weight loss (48% in intervention and 58.6% in control), appetite loss (0% in intervention and 20.7% in control), and stomach-ache (12% in intervention and 24.1% in control). All these did not vary significantly between groups.

Discussion

Consistently, the studies show positive effect of Vitamin D in children with ADHD. This may be attributed to several reasons. ADHD is a complex condition which has many underlying causes, including a reduction in fast brain waves in the cerebellum, basal ganglia, and prefrontal cortex. [8] Vitamin D supplementation may play a role in this. In the study of Mirhosseini, brain map data shows that when eyes are closed and open, the power of theta spectra decreases in the left and right temporal lobes, but only significantly in the Vitamin D3 group. Theta power also decreases in the left frontal region when eyes are closed. Theta/beta and theta/alpha ratios only decrease when eyes are open and in the left temporal and right frontal areas of the vitamin D3 group. [9] It has been suggested that enhanced cognitive processing is linked to a decline in the theta/beta ratio (TBR) values, while an increase in the theta/alpha ratio (TAR) in the temporo-frontal region was linked to a decline in cognitive ability, particularly memory. [10,11]

Although not included in the meta-analysis, Mirhosseini et al. (2024) was considered relevant since they observed that vitamin D supplementation was associated with better electrophysiological outcomes and improved Connors scores in children with ADHD compared to placebo.

in symptoms. It was concluded that Vitamin D supplementation as an adjunctive therapy improved ADHD evening symptoms. [2]

The study of Naeini et al. (2018) involved 71 children who were divided into two groups: those who received Vitamin D3 supplements of 1000 IU (n=36) or placebo (n=35) given daily for three months. The results showed significant differences in mean scores of the Conners Parent Questionnaire (CPQ), Strengths and Difficulties Questionnaire Teacher Version (SDQT), and Strengths and Difficulties Questionnaire Parent Version (SDQP) scores after the intervention. The impulsivity mean scores of the CPT after intervention showed statistical significance ($p = 0.002$), but the attention ($p = 0.11$) and mean reaction time ($p = 0.19$) mean scores did not. The study concluded that Vitamin D supplementation not only improved some behavioral problems but may prevent exacerbation of some symptoms of the disorder and reduce impulsivity. [7]

In the study of Rahmani et al. (2022), 120 patients were randomized into three experimental groups, along with a control group. For a period of 12 weeks, the first group had vitamin D pearl, neurofeedback plus vitamin D, and neurofeedback; the control group got no treatment at all. The combined group had a lower mean score than the individual groups, with significant differences in mean scores observed between them. Over the course of the 12-week trial, no serious side effects were recorded; instead, all side effects were mild to moderate in nature. The study found that receiving treatment in combination was more beneficial than receiving it separately. [8]

Furthermore, in the case of ADHD, studies have shown that nutrition plays a significant role. Studies have shown that there has been evidence of an association between nutritional deficiencies and the intensity of ADHD symptoms. [12,13] From a physiological point of view, several nutrients are required for the biological process since they have been shown to support the Krebs and methylation cycles. Combining nutrients could also be a remarkable strategy to enhance metabolic function. [14]

The effects of Vitamin D supplementation on ADHD may also be explained by the relationship between brain dopamine levels and vitamin D. Via the calcium transition, its antioxidant qualities, gene expression, and other mechanisms, vitamin D can affect the neurological system. The genesis of ADHD is most likely due to a dopamine deficit. Another explanation by which vitamin D elevates dopamine levels is by stimulating the expression of glial cell line-derived neurotrophic factor (GDNF). The survival and development of dopaminergic neurons depend heavily on GDNF. [2,9]

Furthermore, Vitamin D promotes the production of glutathione, a significant

antioxidant in the brain. A lack of vitamin D can enhance the oxidative stress response and modify neuroendocrine transmitters. [9] Vitamin D plays a crucial role in controlling serotonin synthesis and calcium transmission, which can be harmful if elevated levels are present. By lowering the elevated amount, vitamin D aids in preventing this occurrence. [15] Cognitive impairments have been linked to vitamin D insufficiency, but the underlying mechanisms remain unclear. Vitamin D is involved in mediating long-term potentiation (LTP) in ADHD, which is a critical component of brain data retention. LTP is correlated with the rise in calcium in the postsynaptic cell via voltage-gated calcium channels or N-methyl-D-aspartate receptors. [15,16] Deficiency in vitamin D can negatively impact neuron differentiation, brain structure, axon synapses, and function during fetal life and youth. [9]

The study also has limitations. The studies included looked at the supplementation of Vitamin D within a relatively short period with the majority utilizing low levels of Vitamin D only. It is assumed that more significant changes in symptoms would occur with appropriate vitamin D levels. Nevertheless, the use of different tools to evaluate the changes in symptoms of ADHD is one of the strengths of this meta-analysis that provides a more comprehensive understanding of the effects of Vitamin D supplementation on ADHD. Also, we determined the level of evidence generated from this meta-analysis to be of high quality given the randomized study design, good methodological quality, and consistency of findings across studies (Table 2).

Table 2. Summary of findings and level of evidence

Outcome	Effect Measure	Heterogeneity	GRADE level of evidence
Total ADHD scores	SMD=-0.59, 95%CI=-1.06 to -0.11, p=0.01	I^2=72%	High
Inattentive scores	SMD=-0.61, 95%CI=-1.00 to -0.23, p=0.002	I^2=51%	High
Hyperactivity scores	-0.64, 95%CI=-1.08 to -0.20, p=0.004	I^2=70%	High
Adverse events	Cannot be pooled. Four studies reported no significant difference in adverse events.	n/a	n/a

Conclusion

Vitamin D treatment as an adjuvant to methylphenidate alleviated ADHD symptoms without significant adverse effects, correlating with enhanced vitamin D levels. Given the robust evidence and well-structured randomized controlled trials, we strongly advocate for the integration of vitamin D supplementation with ADHD treatment. Furthermore, the potential benefits of vitamin D supplementation extend beyond symptom relief, as it may also improve overall cognitive function and behavior in individuals with ADHD. This holistic approach to treatment could lead to more comprehensive and effective management of the disorder. Further research should explore the long-term benefits and optimal dosages of vitamin D supplementation in this population.

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