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The Effect of Vitamin D Supplementation on Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective: A systematic review and meta-analysis of randomized controlled trials (RCTs) were conducted to assess the benefits and harms of vitamin D supplementation for attention-deficit/hyperactivity disorder (ADHD) patients.

Methods: We followed the standard methodological procedures of the Cochrane Handbook for Systematic Reviews of Intervention. PubMed, Embase, the Cochrane Central Register of Controlled Trials, Science and Conference Proceedings Citation Index-Social Science and Humanities (Web of Science), ClincalTrials.gov, and World Health Organization's International Clinical Trials Registry Platform were searched for RCTs in January 2019. Independently, two authors (J.G., T.X.) extracted data, assessed the risk of bias, combined the data, and graded evidence quality using the Grading of Recommendations Assessment, Development, and Evaluation approach. Our primary outcomes were assessed through rating scales of ADHD severity. Secondary outcomes measured were the possible adverse effects of vitamin D supplementation and vitamin D status after supplementation for ADHD.

Results: We included four RCTs with 256 children addressing vitamin D supplementation as adjunctive therapy to methylphenidate on ADHD symptoms. Vitamin D supplementation demonstrated a small but statistically significant improvement in ADHD total scores, inattention scores, hyperactivity scores, and behavior scores. The improvement was likely limited due to the low to very low quality of evidence in the literature. There was no statistically significant improvement in oppositional scores. Reported adverse events in the vitamin D group were mild and not significantly different from the control group. Vitamin D supplementation increased serum vitamin D levels and the ratio of patients with sufficient vitamin D levels.

Conclusions: Vitamin D supplementation as adjunctive therapy to methylphenidate appeared to reduce ADHD symptoms without serious adverse events, associated with improved vitamin D status. However, considering the generally low strength of evidence, well-designed RCTs are needed to determine the efficacy and safety of vitamin D supplementation for both children and adults with ADHD, especially in the setting of a combination of vitamin D and other ADHD treatments.

Keywords: vitamin D, attention-deficit/hyperactivity disorder, supplementation, effect, meta-analysis

Introduction

Attention-deficit/hyperactivity disorder (ADHD), characterized by inattention and hyperactivity/impulsivity, is a chronic neurological condition with considerably high prevalence worldwide. It has been reported that 5.3%–9.5% of children and 2.5%–5% of adults have ADHD, with increasing incidence and a higher susceptibility in males (Feldman and Reiff 2014; Thapar and Cooper 2016). Although the etiology is still unknown, it is widely held that the disorder can stem from multiple complicated interactions between genes, environmental factors, brain injuries, or pregnancy problems (Belanger et al. 2018; Demontis et al. 2019). Individuals with the disorder not only display impaired social function and cognitive development, but also a significant increase in mortality rates (Dalsgaard et al. 2015). Furthermore, comorbidities (oppositional defiant disorder, depression, anxiety, etc.) are commonly presented in patients with ADHD, making symptoms harder to treat (Belanger et al. 2018; Craig et al. 2019). Not

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surprisingly, it has been identified as one of the leading causes of academic underachievement and disruptive behaviors in school (Feldman and Reiff 2014; Voigt et al. 2017). The negative effects often extend to family members, friends, and teachers of affected patients (Storebo et al. 2011; Feldman and Reiff 2014), causing significant economic and social burdens (Feldman and Reiff 2014; Chan et al. 2016).

Comprehensive multimodal treatment is currently recommended for treating ADHD (medication, parent training, skills training, counseling, behavioral therapy, massage, educational support, education regarding ADHD, etc). (Feldman and Reiff 2014; Chan et al. 2016). Although there are emerging treatment options for ADHD, pharmacological therapies (Food and Drug Administration [FDA]-approved agents: methylphenidate hydrochloride, atomoxetine, clonidine; FDA-nonapproved agents: tricyclic antidepressants, modafinil, magnesium pemoline, etc.) continue to play important roles, especially for patients who cannot tolerate or do not respond to nonpharmacological therapy or suffer from a comorbid condition (Lichtenstein et al. 2012; Briars and Todd 2016; Chan et al. 2016; Storebo et al. 2016). Unfortunately, despite treatment advancements only 30%–70% of patients respond to currently available ADHD therapies (Spencer et al. 2005; Chan et al. 2016).

In addition, some pharmacological treatments for ADHD are associated with cardiovascular risks and suicide thoughts (Wilens et al. 2005). Moreover, the potential for abuse and dependence of many of these pharmacological treatments has alarmed many physicians (Storebo et al. 2016). To boost the effect and minimize side effects of pharmacological treatments, physicians often consider nutrient supplementation for ADHD treatment such as single-ingredient interventions (vitamins, minerals, amino acids, essential fatty acids), botanicals (pycnogenol, *Hypericum perforatum*, *Panax quinquefolium*, and *Ginkgo biloba*), and multiingredient formulas (Rucklidge et al. 2009; Abdullah et al. 2019).

Vitamin D has a major role in bone and calcium homeostasis by increasing intestinal absorption of calcium and phosphate (Grant and Holick 2005; Rosen et al. 2012). It has been regarded as a versatile hormone, playing a role in the neurological system, cardiovascular system, immune system, endocrine system, cancer diseases, and psychiatric diseases (Slavov et al. 2013; Bener et al. 2014; Jozefowicz et al. 2014; Tagliabue et al. 2015; Chiang et al. 2016; Meyer et al. 2017; Apostolakis et al. 2018). Deficiency of vitamin D can cause cerebral dysfunction related to neuropsychiatric disease in humans (Eyles et al. 2013; Groves et al. 2013). In ADHD, vitamin D supplementation is thought to decrease symptoms through several possible mechanisms.

Vitamin D receptors and its active enzyme are widely distributed in the brain, especially in areas related to the pathogenesis of ADHD such as the hippocampus, hypothalamus, substantia nigra, prefrontal cortex, and cingulated gyrus (Ellison-Wright et al. 2008). With the capacity of passing the blood–brain barrier, vitamin D could bind to its receptor in the brain and regulate the development of the central neural system. A deficiency of vitamin D results in an imbalance of neurotransmitters in dopaminergic pathways responsible for the pathophysiology of ADHD (Eyles et al. 2009; Orme et al. 2013; Sharma and Couture 2014; Villagomez and Ramtekkar 2014; Cui et al. 2015; Patrick and Ames 2015). Moreover, vitamin D deficiency reduces the production of acetylcholine, which helps maintain attention and executive functions (Elshorbagy et al. 2018).

The prevalence of vitamin D deficiency in children is high worldwide, especially in developing countries (Al-Alyani et al. 2018; Kamboj et al. 2018). Serum vitamin D concentrations in children and adolescents with ADHD are also significantly lower than healthy populations (Khoshbakht et al. 2018). Additionally, there may be a negative correlation between perinatal and childhood vitamin D status and the likelihood of developing ADHD (Gustafsson et al. 2015; Morales et al. 2015; Garcia-Serna and Morales 2019). Thus, vitamin D supplementation may compensate for its deficiency and possibly alleviate ADHD symptoms. In the last 2 years, clinical trials have aimed at evaluating the effectiveness of vitamin D supplementation in patients with ADHD (Elshorbagy et al. 2018; Mohammadpour et al. 2018; Dehbokri et al. 2019; Naeini et al. 2019). For clinicians and patients and their families, this novel supplementation treatment may provide an effective, safe, and nonaddictive treatment option. To assess the available clinical data, this article reviews and analyzes existing published evidence.

Methods

We conducted this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al. 2009) and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green 2008). We performed the analyses using Review Manager 5.3 (RevMan 5.3) and Gradepro. This systematic review has been registered on PROSPERO (Registration No. CRD42019125698).

Eligibility criteria

Types of studies. We included randomized controlled trials (RCTs), quasirandomized trials, and cluster randomized trials.

Types of participants. Participants included in the studies fulfilled the inclusion criteria as patients with a diagnosis of ADHD, according to one of the following: (1) The *Diagnostic and Statistical Manual of Mental Disorders* [*Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed. (American Psychiatric Association 1980), *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed., Text Revision (American Psychiatric Association 1987), *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (DSM-IV, American Psychiatric Association 1994), *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision (American Psychiatric Association 2000), or *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (American Psychiatric Association 2013); (2) International Classification of Diseases ninth or tenth revisions (ICD-9 or ICD-10 codes). Patients who received any medical-based treatments or studies which are not associated with ADHD were excluded.

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

Types of comparators. Acceptable comparators were no treatment or any type of placebo intervention. We investigated the following comparisons in patients with ADHD: (1) Vitamin D only versus no treatment; (2) Vitamin D only versus placebo treatment; (3) Vitamin D plus baseline treatment versus the same baseline treatment alone; (4) Vitamin D plus baseline treatment versus placebo treatment plus the same baseline treatment.

Types of outcomes. The primary outcomes were ADHD symptom severity level measured by validated clinician, teacher, or parent report using the following scales: Conners Parent Rating Scale (CPRS), Conners Parent Questionnaire (CPQ), Conners Teacher Rating Scale, ADHD rating scale-IV (ADHD-RS), Weekly

Parent Ratings of Evening and Morning Behavior (WPREMB), Social Skills Rating Scale, Strengths and Difficulties Questionnaire by parents (SDQP), Strengths and Difficulties Questionnaire by teachers, Continuous Performance Test, Baecke International Questionnaire, Wisconsin's Card Sorting Test, Wechsler Intelligence Scale for children, Mothers' Objective Method for Subgrouping, and Teacher-rated General Behavior. Secondary outcomes were the adverse effects of vitamin D supplementation for ADHD and vitamin D status after supplementation for ADHD.

Search strategy

We followed the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green 2008). Two authors (J.G. and T.X.) independently conducted an electronic search of the following databases in January 2019: MEDLINE (PubMed), Embase, The Cochrane Central Register of Controlled Trials, Science, and Conference Proceedings Citation Index-Social Science and Humanities (Web of Science), ClincalTrials.gov, and World Health Organization's International Clinical Trials Registry Platform. Research studies' listed symptoms of ADHD were screened and reviewed. In addition, we reviewed the references of previous trials and review articles to identify trials which may have been missed during initial searches. After contacting the specialists in relevant fields, we searched for gray literature as much as possible (See Appendix Table A1 for the search strategy in detail).

Study selection

Two authors (J.G. and T.X.) with knowledge of systematic review methodology independently extracted data according to inclusion. Disagreements were resolved through discussion or through the third reviewer (D.M.) by performing an additional independent evaluation. Full-text studies failing to meet the inclusion criteria were ruled out. The search results have been reported in full in the final report with a PRISMA flow diagram.

Data collection

Before input into Excel spreadsheet and the RevMan 5.3, data were independently extracted and verified from the eligible articles by J.G. and T.X. Disagreements were solved by consensus of a third author (D.M.). The extracted data included: first author name, study setting, participant characteristics, intervention and control conditions, methodology, information for assessment of the risk of bias, recruitment and study completion rates, outcomes, and implications for clinicians. We wrote to original authors of RCTs for clarification if the information was not provided in the published articles.

Risk of bias assessment

The risk of bias and methodological quality of each included study was assessed by J.G. and T.X. independently through the Cochrane Collaboration's tool for several aspects, including allocation concealment, blinding, incomplete outcome data, selective reporting, differential noncompliance in vitamin D and control groups, number of dropouts, and lack of details on controls. One of three grades (either unclear, low risk, or high risk) were awarded to each trial. Discrepancies between two researchers were solved by consulting a third reviewer (D.M.) through discussion. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was applied to evaluate the quality of evidence for each outcome of interest with the following criteria: quality of primary studies, the design of primary studies, consistency, and directness.

Analysis and synthesis of results

We performed data synthesis according to recommendations in Version 5.1.0 of the Cochrane Handbook for Systematic Reviews of Interventions. After data extraction, the RevMan 5.3 was used for data analysis and a meta-analysis was performed. For dichotomous data, risk ratio (RR) and odds ratio (OR) were used for analysis. For continuous data, mean difference (MD) or standardized mean difference (SMD) with 95% confidence intervals (CIs) were used to represent the summary statistics of the outcome with the same units and different scales, respectively.

We assessed statistical heterogeneity by examining χ^2 and I^2. We used the χ^2 test ($p \leq 0.1$ showed substantial or considerable heterogeneity) to determine whether statistically significant heterogeneity was present. We also assessed the degree of statistical heterogeneity by examining I^2. Data were pooled by applying a fixed-effects model following $I^2 \leq 50\%$ or a random-effects model. In the case of outcome data that only provided p-values in trials, we performed a narrative description of the results.

Subgroup analysis and sensitivity analyses. Subgroup analyses were conducted to investigate any potential factors that could influence the interventions and outcome measurements within the respective trials. We performed three subgroup analyses according to the following categories: (1) The dose of vitamin D (low dose was the daily equivalent of 400–2000 IU per day and high dose was more than 2000 IU per day); (2) The frequency of vitamin D administration (daily doses and weekly bolus doses); and (3) The baseline vitamin D status (sufficient baseline vitamin D level, insufficient baseline vitamin D level, and deficient baseline vitamin D level).

We also performed sensitivity analyses using different statistical models to evaluate the robustness of the results (fixed-effect or random-effects model).

Quality of evidence. The GRADE was used to evaluate the overall quality of evidence for the primary outcome (Dijkers 2013). The GRADE approach categorizes evidence from systematic reviews and meta-analyses into four levels, namely, ''high,'' ''moderate,'' ''low,'' or ''very low'' quality. Study design of RCTs dictates a high baseline quality of evidence. However, the quality of evidence could be downgraded to ''moderate,'' ''low,'' or ''very low'' due to five aspects: study limitation, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, and high probability of publication bias.

Results

Study selection

The study review process is summarized in the PRISMA flow diagram (Fig. 1). For this review, our search yielded 1550 records after removing duplicates. We excluded 1244 records on the first pass, leaving 306 records eligible for the title and abstract screen. After discarding records of conference abstracts, reviews, non-English records, and non-human research, we retrieved 30 full-text articles for further inspection. There were 10 articles irrelevant to ADHD or vitamin D (Humble et al. 2010; Arab Ameri et al. 2012; Tolppanen et al. 2012; Andreeva et al. 2014; Fernell et al. 2015; Gordon et al. 2015; Lehti et al. 2016; Ghaderi et al. 2017; Chen

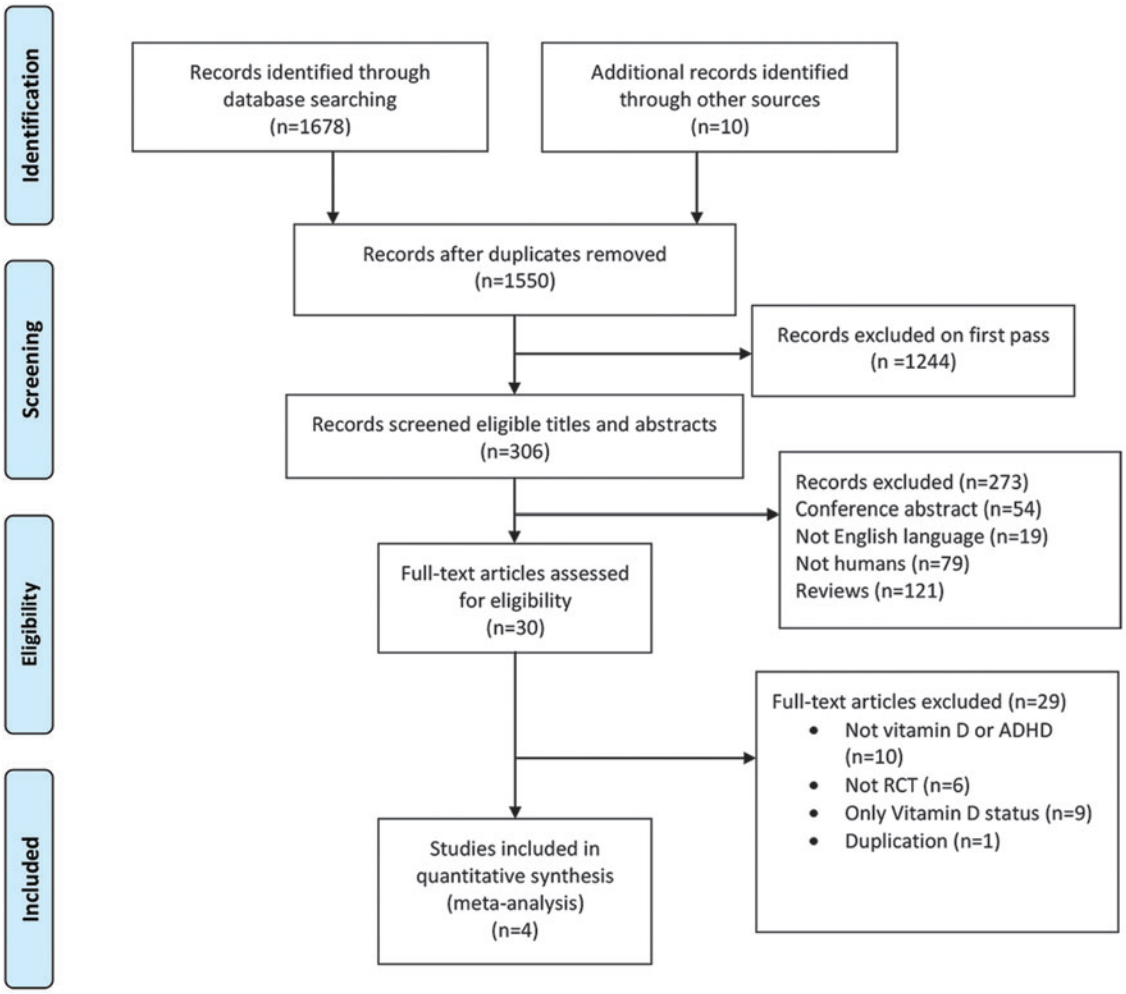


FIG. 1. The flow diagram of selected studies.

et al. 2019; Mazahery et al. 2019), 6 were not RCTs (Rucklidge et al. 2009; Villagomez and Ramtekkar 2014; Heilskov Rytter et al. 2015; Focker et al. 2017; Nct 2017; Khoshbakht et al. 2018), 9 were only vitamin D serum levels rather than vitamin D treatment issues (Ritterhouse et al. 2011; Morales et al. 2015; Shang-Guan and Zhao 2015; Sharif et al. 2015; Bala et al. 2016; Meyer et al. 2017; Noorazar et al. 2018; Reinehr et al. 2018; Sahin et al. 2018), and 1 was a duplication of the included trials (Elshorbagy et al. 2018). Consequently, four trials met the inclusion criteria of this study.

Characteristics of included studies

Characteristics of the included studies are listed in Table 1. In the review, we included four RCTs with a total of 256 children with ADHD (Elshorbagy et al. 2018; Mohammadpour et al. 2018; Dehbokri et al. 2019; Naeini et al. 2019). The diagnosis of ADHD was generally taken according to DSM-IV criteria. All four trials were double-blinded placebo-controlled among which only two mentioned the placebo in detail (Miglyol neutral oil or Starch) (Mohammadpour et al. 2018; Dehbokri et al. 2019). In three of the trials, the ratio of girls to boys was 1:3 or 1:4 (Mohammadpour et al. 2018; Dehbokri et al. 2019; Naeini et al. 2019), and in one trial the ratio of girls to boys was nearly 1:1.3 (Elshorbagy et al. 2018). Each of these studies was performed in the Middle East (three in Iran and one in Saudi Arabia). The ethnicity of participants was not mentioned in the articles.

Vitamin D supplementation was combined with methylphenidate for ADHD treatment in all four trials, and duration ranged from 6 to 12 weeks. The doses of vitamin D supplementation were between 1000 IU/day and 50,000 IU/week. All trials included ADHD-related outcomes. The scales chosen to measure ADHD symptoms varied among studies (Appendix Table A2). All studies, however, used parents' scales or questionnaires to assess ADHD severity. Only one study used both parent and teacher scales and questionnaires in their assessments (Naeini et al. 2019). We chose to only analyze the parents' scales and questionnaires to maintain consistency among all of the studies. A description of each scale's items and scoring is included in Appendix Table A3.

Quality assessment

We attempted to contact all authors of the included RCTs to retrieve any potential data that were unprovided in their respective articles. The correspondence author of Dehbokri et al. (2019) responded on the diagnostic criteria, the compliance of groups, and random sequence generation and allocation concealment methodology. All other authors did not reply. Consequently, only Dehbokri et al. (2019) trial had a low risk of allocation sequence and

Table 1. Characteristics of Included Studies

Study	*Region*	*Age range (year)*	*Study design*	*Diagnostic criteria*	*Number (M/F)/ dropout*	*VD Baseline EG; CG (ng/mL)*	*Intervention (VD supplementation)*	*Comparator*	*Basic medicine*	*Study duration*	*Rating*	*Subscales*
Mohammadpour et al. (2018)	Tehran, Iran	5–12	Permuted-block randomization, double-blind	DSM-IV	54 (46/16)/6	15.792 ± 5.259; 12.979 ± 5.804*	2000 IU/day	Placebo (Starch)	Methylphenidate	8 Weeks	CPRS, ADHD-RS, WPREMB	O, CG, H, ADHD INDEX, I, Morning and Evening symptoms, TOTOL SCORE
Dehbokri et al. (2019)	Tabriz, Iran	2–18	Block randomization, double-blind	NA	96 (80/16)/6	17.50 ± 6.98; 17.71 ± 6.01*	50,000 IU/week	Placebo (Miglyol-neutral oil)	Methylphenidate	6 Weeks	CPRS	IA, H/I, C
Elshorbagy et al. (2018)	Saudi Arabia	7–14	Permuted-block randomization, double-blind	DSM-IV	35 (NA)/5	NA	3000 IU/day	Placebo (NA)	Methylphenidate	12 Weeks	CPRS, WCST	IA, H, IM, O, CL, CC
Naeini et al. (2019)	Isfahan, Iran	6–13	Double-blind	DSM-IV	71 (50/12)/13	47.01 ± 17.05; 59.63 ± 25.88 (IU)*	1000 IU/day	Placebo (NA)	Methylphenidate	3 Months	CPQ, SDQT, SDQP, CPT	E, R, S, B, H

*$p < 0.05$.

RCT, randomized controlled trial; M/F, male/female; EG, experimental group; CG, control group; VD, vitamin D; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.; NA, not applicable; ADHD, attention-deficit/hyperactivity disorder; CPRS, Conners parent rating scale; CPQ, Conners Parent Questionnaire; WPREMB, Weekly Parent Ratings of Evening and Morning Behavior; WCST, Wisconsin's Card Sorting Test; WLSC, Wechsler Intelligence Scale for children; SDQT, Strengths and Difficulties Questionnaire by teachers; SDQP, Strengths and Difficulties Questionnaire by parents; CPT, Continuous Performance Test; ADHD-RS, ADHD rating scale; E, emotion; R, relationship; S, social; H, hyperactivity; IA, inattention; H/I, hyperactivity/impulsive; C, combination; IM, impulsive; CC, categories completion; CL, conceptual level; O, oppositional; CG, cognitive.

concealment, whereas the other three studies had an unclear risk of bias in these factors due to the lack of description of their methodology. Nevertheless, all four included trials were double blind and placebo controlled, and thus had a low-risk bias related to blinding. To ensure complete outcome data, all participants who dropped out of the studies were excluded from the analysis. One trial had a nearly 12% dropout rate in the placebo group without any statement of explanation; consequently, this could have induced clinically relevant bias into the observed effect size. Thus, a high risk of bias on incomplete outcome data was assigned (Dehbokri et al. 2019).

Based on the adequately stated information about participants lost to follow-up of all three other studies, a low risk of bias for incomplete data was assigned (Elshorbagy et al. 2018; Mohammadpour et al. 2018; Naeini et al. 2019). We considered the selective reporting in all four studies to be at a low risk for bias. Three of the four trials had protocols. All the trials reported on all expected outcomes, including those that were prespecified in the Methods paragraph or protocols. All trials were at little risk of vested interest bias, as all funding and financial support was stated and not provided by any interested party. No trial had early treatment termination. Two trials did not specify placebo information, and we assigned an unclear risk of other biases as well (Elshorbagy et al. 2018; Naeini et al. 2019). The other two studies appeared to have no additional potential sources of bias and thus were at low risk of other biases (Mohammadpour et al. 2018; Dehbokri et al. 2019) (Fig. 2).

Synthesis of the results

We presented the results for each of the five primary outcomes and the three secondary outcomes below. The analysis was organized by parent-rated scales.

Primary outcome: ADHD symptoms. ADHD symptoms were evaluated according to five aspects, including ADHD total scores, inattention scores, hyperactivity scores, behavior scores, and oppositional scores. The resulting forest plots (Fig. 3) demonstrate that vitamin D as an adjunctive treatment to methylphenidate may improve all measured ADHD symptoms, except for those pertaining to oppositional scores. We added an evaluation of our primary outcomes following the GRADE system to ensure quality judgment concerning the risk of bias (Fig. 4), as well as other factors affecting the quality of evidence (Higgins and Green 2008).

SMD and MD were used to represent effect sizes. There would be no meaningful clinical effect with an SMD effect size of <0.15, a meaningful but small clinical effect with an SMD effect size of 0.15–0.40, and a moderate-to-large clinical effect with an SMD effect size of 0.40–0.75 and greater, respectively (Thalheimer and Cook 2002).

ADHD total scores. Three articles, including a total of 221 children with ADHD, investigated ADHD total scores based on CPRS or CPQ at the end of treatment (Mohammadpour et al. 2018; Dehbokri et al. 2019; Naeini et al. 2019). A fixed-effects model illustrated a clinically meaningful but small effect of vitamin D supplementation as an adjunctive treatment to methylphenidate on ADHD total scores (SMD 0.39; 95% CI 0.12–0.65, $I^2 = 41\%$, $p = 0.005$; Fig. 3A).

Inattention scores. Three articles, including a total of 185 children with ADHD, investigated inattention scores based on CPRS or ADHD-RS at the end of treatment (Elshorbagy et al. 2018; Mohammadpour et al. 2018; Dehbokri et al. 2019). A random-effects model displayed a significant moderate effect of vitamin D supplementation as an adjunctive treatment to methylphenidate on inattention scores (SMD 0.67; 95% CI 0.12–1.23, $I^2 = 67\%$, $p = 0.02$; Fig. 3B).

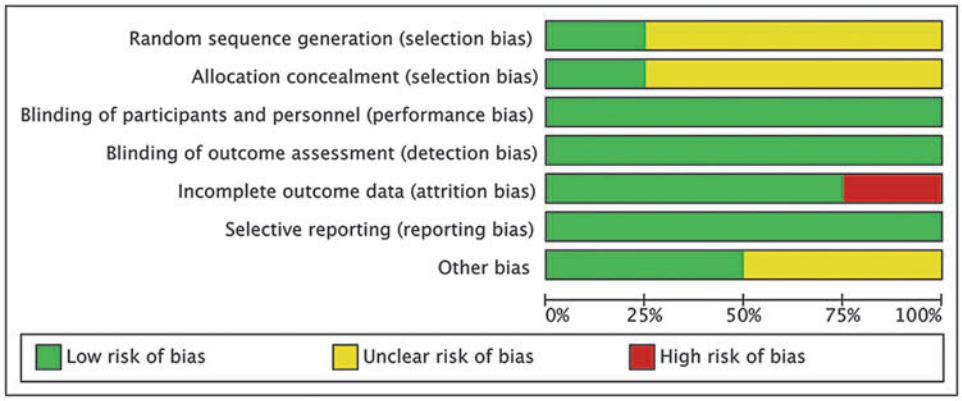
Hyperactivity scores. Four articles, including a total of 256 children with ADHD, investigated hyperactivity scores based on CPRS, ADHD-RS, or SDQP at the end of treatment (Elshorbagy et al. 2018; Mohammadpour et al. 2018; Dehbokri et al. 2019; Naeini et al. 2019). A random-effects model illustrated a significant moderate effect of vitamin D supplementation as an adjunctive treatment to methylphenidate on hyperactivity scores (SMD 0.60; 95% CI 0.07–1.13, $I^2 = 75\%$, $p = 0.03$; Fig. 3C).

Behavior score. Only two articles, including a total of 125 children with ADHD, investigated behavior scores based on WPREMB-TOTAL or SDQP at the end of treatment (Mohammadpour et al. 2018; Naeini et al. 2019). A fixed-effects model demonstrated a significant moderate effect of vitamin D supplementation as an adjunctive treatment to methylphenidate on behavior scores (SMD 0.54; 95% CI 0.18–0.90, $I^2 = 0\%$, $p = 0.003$; Fig. 3D).

Oppositional scores. Only two articles, including a total of 89 ADHD children, investigated oppositional scores based on CPRS at the end of treatment (Elshorbagy et al. 2018; Mohammadpour et al. 2018). Due to statistical heterogeneity ($I^2 = 81\%$), a random-effects model was selected. The result revealed a pooled MD of 9.76 (95% CI −0.62 to 20.13, $p = 0.07$; Fig. 3E) suggesting that vitamin D supplementation as an adjunctive treatment to methylphenidate may not improve oppositional symptoms.

Secondary outcome: adverse events. Only one RCT provided the number of adverse events in the vitamin D group and placebo group (Mohammadpour et al. 2018). There was no significant difference between the vitamin D group and placebo group in specific adverse events (such as headache, weight, etc.) and the total number of adverse events (OR 1.53; 95% CI 0.86–2.72; one trial, $n = 54$; Fig. 3F). Another study reported that 15% of the participants with ADHD experienced some form of side effect (vitamin D and placebo group) (Elshorbagy et al. 2018). The adverse effects were in the form of mild abdominal pain, loss of appetite, or diarrhea. However, there was no information distinguishing these effects between the vitamin D and placebo group.

Secondary outcome: vitamin D status. Three RCTs, including a total of 221 ADHD children, investigated serum vitamin D level at end of treatment (Mohammadpour et al. 2018; Dehbokri et al. 2018; Naeini et al. 2019). A random-effects model displayed a significant effect of vitamin D supplementation treatment on serum vitamin D level (SMD 2.26; 95% CI 1.46–3.06, $I^2 = 81\%$, $p = 0.005$; Appendix Table A4) compared with placebo. Only one trial reported the ratio of patients with sufficient vitamin D level after intervention (Dehbokri et al. 2019). The trial further demonstrated that vitamin D supplementation could increase the ratio of patients with sufficient vitamin D level after intervention versus placebo treatment (RR 0.14; 95% CI 0.07–0.29, $p < 0.00001$; Appendix Table A4) (Dehbokri et al. 2019).



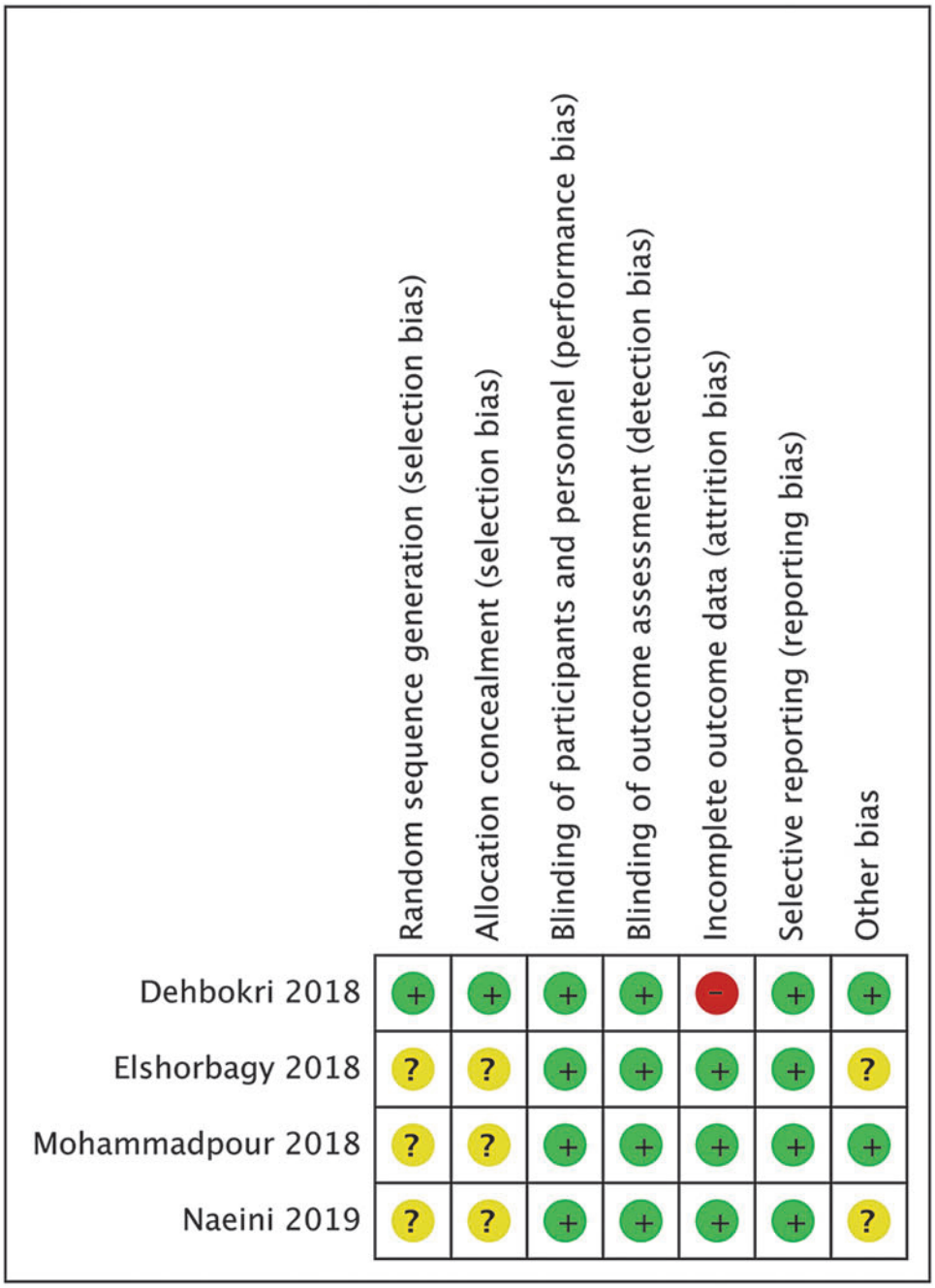


FIG. 2. The results of quality evaluation of randomized controlled trials.

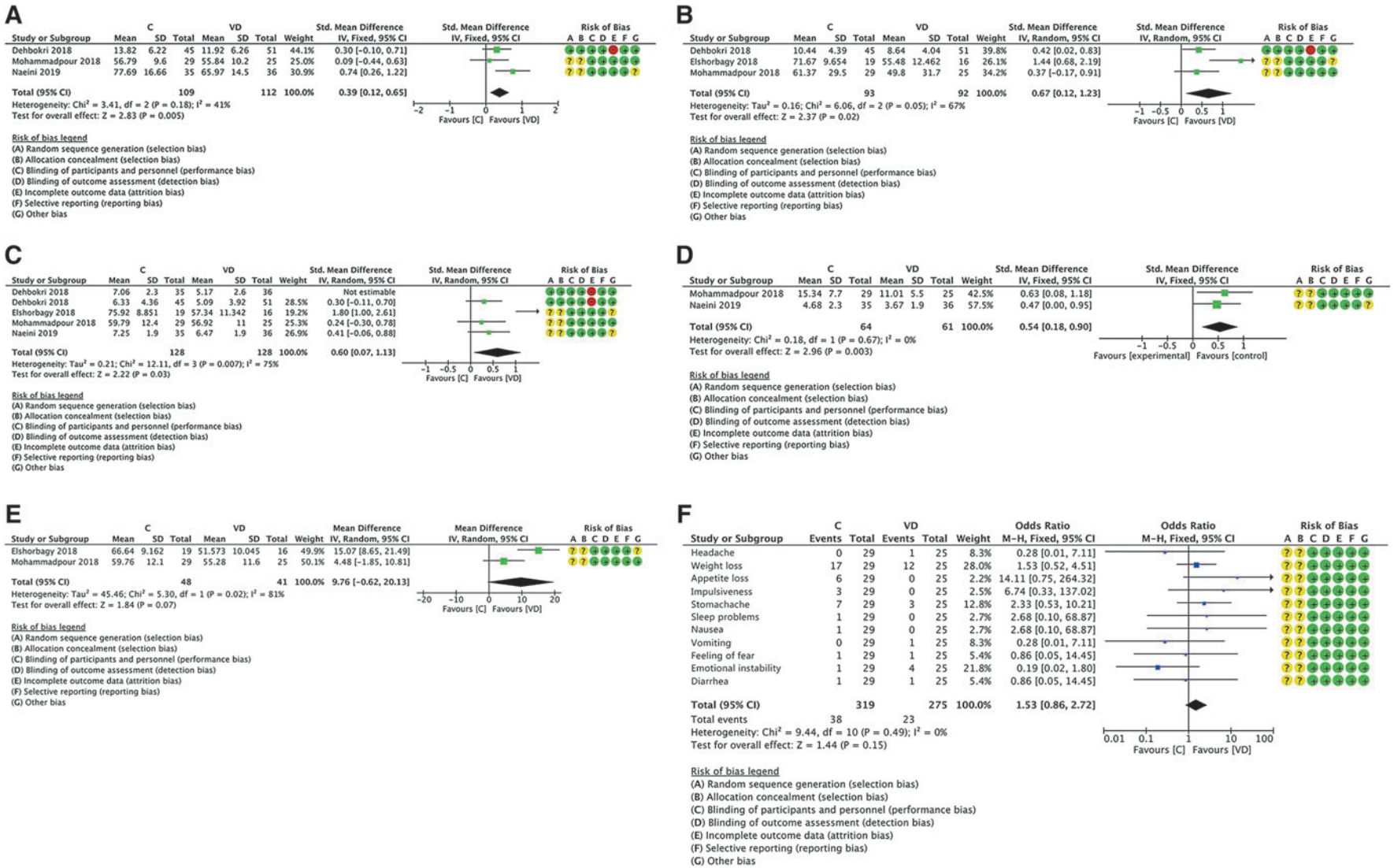


FIG. 3. Forest plots of vitamin D versus placebo. **(A)** Forest plots of vitamin D versus placebo for ADHD total scores. The fixed-effects model was selected because the I^2-value <50% and p-value >0.05; SMD = 0.39 (95% CI 0.12–0.65) indicates a clinical meaningful but small effect of the vitamin D supplementation treatment as an add-on to methylphenidate for ADHD total scores compared with placebo. **(B)** Forest plots of vitamin D versus placebo for inattention scores. The random-effects model was selected because the I^2-value >50%; SMD = 0.67 (95% CI 0.12–1.23) indicates a significant moderate effect of the vitamin D supplementation treatment as an add-on to methylphenidate for inattention scores compared with placebo. **(C)** Forest plots of vitamin D versus placebo for hyperactivity scores. The random-effects model was selected because the I^2-value >50% and p-value <0.05; SMD = 0.60 (95% CI 0.07–1.13) indicates a significant moderate effect of the vitamin D supplementation treatment as an add-on to methylphenidate for hyperactivity scores compared with placebo. **(D)** Forest plots of vitamin D versus placebo for behavior scores. The fixed-effects model was selected because the I^2-value <50% and p-value >0.05; SMD = 0.54 (95% CI 0.18–0.90) indicates a clinical meaningful but small effect of the vitamin D supplementation treatment add-on to methylphenidate for behavior scores compared with placebo. **(E)** Forest plots of vitamin D versus placebo for oppositional scores. The random-effects model was selected because the I^2-value >50% and p-value <0.05. SMD = 9.76 (95% CI –0.62 to 20.13) indicates that vitamin D supplementation treatment add-on to methylphenidate may not improve the oppositional symptoms compared with placebo. **(F)** Forest plots of vitamin D versus placebo for adverse events. CI, confidence interval; ADHD, attention-deficit/hyperactivity disorder; SMD, standardized mean difference.

Vitamin D supplementation for ADHD

Patient or population: Children with ADHD

Settings: Adjunctive therapy to methylphenidate

Intervention: Vitamin D supplementation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Vitamin D supplementation				
ADHD IN TOTAL CPRS, CPQ Follow-up: mean 8.7 weeks		The mean ADHD in total in the intervention groups was **0.39 standard deviations higher** (0.12 to 0.65 higher)		221 (3 studies)	⊕⊕⊖⊖ **low**[1,2]	SMD 0.39 (0.12 to 0.65)
Inattention CPRS, ADHD-RS, Follow-up: mean 8.7 weeks		The mean inattention in the intervention groups was **0.67 standard deviations higher** (0.12 to 1.23 higher)		185 (3 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	SMD 0.67 (0.12 to 1.23)
Hyperactivity CPRS,ADHD-RS,SDQP Follow-up: mean 9.5 weeks		The mean hyperactivity in the intervention groups was **0.6 standard deviations higher** (0.07 to 1.13 higher)		256 (4 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	SMD 0.6 (0.07 to 1.13)
Oppositional O-CPRS Follow-up: mean 10 weeks		The mean oppositional in the intervention groups was **0 higher** (0.62 lower to 20.13 higher)		89 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	MD 9.76 (-0.62, 20.13)
Behavior WPREMB-TOTAL, SDQP-behavioral Follow-up: mean 10 weeks		The mean behavior in the intervention groups was **0.54 standard deviations higher** (0.18 to 0.9 higher)		125 (2 studies)	⊕⊕⊖⊖ **low**[1,2]	SMD 0.54 (0.18 to 0.9)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; ADHD, Attention-Deficit/Hyperactivity Disorder; CPRS,Conners parent rating scale; CPQ,Conners Parent Questionnaire; WPREMB,Weekly Parent Ratings of Evening and Morning Behavior; SDQT,Strengths and Difficulties Questionnaire by teachers; SDQP,Strengths and Difficulties Questionnaire by parents ;ADHD-RS,ADHD rating scale.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1]Selection bias may exit due to an unclear risk of random sequence generation and allocation concealment

[2]The total population size is less than 400.

[3]I^2 is more than 50%

FIG. 4. Quality evaluation by Grading of Recommendations Assessment, Development, and Evaluation tool for vitamin D versus placebo.

Subgroup analysis

We performed subgroup analyses based on differing dose and dosing frequency (Table 2). The majority of subgroup analyses did not indicate a statistical significance between the vitamin D and placebo group, except in the cases of weekly doses of vitamin D for inattention scores, high doses of vitamin D for oppositional scores, and low doses of vitamin D for behavior scores. The only significant difference found between subgroups was between low and high vitamin D dose for oppositional scores ($p = 0.02$).

Only one RCT separately reported vitamin D intervention among children with different vitamin D baseline statuses (sufficient, insufficient, and deficiency) (Dehbokri et al. 2019). In this RCT, no standard deviation was provided, only MD and p-values. As a result, we were unable to perform a meta-analysis. Generally, before treatment, there was no significant difference regarding ADHD baseline scores among all subgroups (sufficient, insufficient, and deficient serum levels). However, after 6 weeks of vitamin D supplement, children with a previous insufficient level of vitamin D displayed significantly decreased ADHD/total Conners scores and all subscale scores compared with the corresponding placebo group. Children with a deficient level of vitamin D also had a significantly lower Conners H/I score compared with the corresponding placebo group. However, children with a sufficient level of vitamin D did not express any statistically significant improvement in ADHD scores.

Publication bias. A funnel plot requires 10 or more studies for detecting publication bias. As there was an insufficient number of trials included in our study, we did not create funnel plots to assess publication bias.

Table 2. The Results of Subgroup Analysis

Outcome and subgroups	*Number of studies*	*Participants*	*Statistical method*	I^2 *(%)*	p-*Values for heterogeneity*	*Effect estimate [95% CI]*	*Test for subgroup differences*	
							I^2 *(%)*	p-*Values*
1. ADHD-TOTAL scores								
Dose								
Low-dose vitamin D	2	125	SMD (IV, random, 95% CI)[a]	68	0.08	0.43 [–0.21 to 1.06]	0	0.74
High-dose vitamin D	1	96	SMD (IV, random, 95% CI)[a]	NA	NA	0.30 [–0.10 to 0.71]		
Dosing frequency								
Daily dose	2	125	SMD (IV, random, 95% CI)[a]	68	0.08	0.43 [–0.21 to 1.06]	0	0.74
Weekly dose vitamin D	1	96	SMD (IV, random, 95% CI)[a]	NA	NA	0.30 [–0.10 to 0.71]		
2. Inattention scores								
Dose								
Low-dose vitamin D	1	54	SMD (IV, random, 95% CI)[a]	NA	NA	0.37 [–0.17 to 0.91]	0	0.38
High-dose vitamin D	2	131	SMD (IV, random, 95% CI)[a]	81	0.02	0.88 [–0.11 to 1.86]		
Dosing frequency								
Daily dose	2	89	SMD (IV, random, 95% CI)[a]	80	0.02	0.87 [–0.17 to 1.91]	0	0.43
Weekly dose vitamin D	1	96	SMD (IV, random, 95% CI)[a]	NA	NA	0.42 [0.02–0.83]		
3. Hyperactivity scores								
Dose								
Low-dose vitamin D	2	125	SMD (IV, random, 95% CI)[a]	0	0.65	0.33 [–0.02 to 0.69]	0	0.38
High-dose vitamin D	2	131	SMD (IV, random, 95% CI)[a]	91	0.001	1.01 [–0.46 to 2.48]		
Dosing frequency								
Daily dose	3	160	SMD (IV, random, 95% CI)[a]	82	0.004	0.76 [–0.04 to 1.55]	1.1	0.31
Weekly dose vitamin D	1	96	SMD (IV, random, 95% CI)[a]	NA	NA	0.30 [–0.11 to 0.70]		
4. Oppositional scores								
Dose								
Low-dose vitamin D	1	54	MD (IV, random, 95% CI)	NA	NA	4.48 [–1.85 to 10.81]	81.1	0.02
High-dose vitamin D	1	35	MD (IV, random, 95% CI)	NA	NA	15.07 [8.65–21.49]		
5. Behavior scores								
Dose								
Low-dose vitamin D	1	54	SMD (IV, random, 95% CI)[a]	NA	NA	0.63 [0.08–1.18]	0	0.67
High-dose vitamin D	1	71	SMD (IV, random, 95% CI)[a]	NA	NA	0.47 [0.00–0.95]		

[a]The random effects model was selected because the I^2 value >50% or p-value <0.05.

RCT, randomized controlled trial; NA, not applicable; MD, mean difference; SMD, standard mean difference; CI, confidence interval; ADHD, attention-deficit/hyperactivity disorder.

Sensitivity analysis. Sensitivity analysis revealed that our results were not influenced by differing models to pool the data, which demonstrates the robustness of the primary analysis, including ADHD total scores (by random-effects model, SMD 0.39; 95% CI 0.03–0.74, $I^2 = 41\%$, $p = 0.03$), inattention scores (fixed-effects model, SMD 0.57; 95% CI 0.27–0.86, $I^2 = 67\%$, $p = 0.0002$), hyperactivity scores (fixed-effects model, SMD 0.47; 95% CI 0.21–0.72, $I^2 = 75\%$, $p = 0.0003$), behavior scores (random-effects model, SMD 0.54; 95% CI 0.18–0.90, $I^2 = 0\%$, $p = 0.003$), and vitamin D status (fixed-effects model, SMD 2.21; 95% CI 1.87–2.55, $I^2 = 81\%$, $p = 0.005$).

Discussion

Main findings

Vitamin D deficiency is prevalent in ADHD patients (Villagomez and Ramtekkar 2014; Focker et al. 2017; Khoshbakht et al. 2018), and vitamin D treatment is considered safe, economical, and simple to apply. To our knowledge, this is the first systematic review and meta-analyses to examine the effect of vitamin D supplementation for ADHD patients.

We found that vitamin D supplementation may alleviate ADHD symptoms, which were supported by improvements in ADHD total scores, inattention scores, hyperactivity scores, and behavior scores. Improvements in oppositional measures were not observed. Furthermore, vitamin D supplementation appears safe, as no significant difference in adverse events was found between the vitamin D and placebo groups, although most studies did not prospectively monitor adverse events or other safety measures. Vitamin D supplementation also significantly increases the vitamin D levels in patients with ADHD. In summation, the findings of our meta-analysis conclude that there is clinical evidence that vitamin D supplementation may improve the ADHD symptoms without any obvious side effects.

Currently, there are only a small number of trials assessing vitamin D supplementation treatment for ADHD patients. In this meta-analysis, the four trials included 256 participants with ADHD, all of which were pediatric patients from the Middle Eastern countries. No data from adult patients or those from other countries were available. Additionally, this study has only investigated the effect of vitamin D supplementation as add-on therapy to methylphenidate. No evidence could be gathered or accurately extrapolated about the effect of vitamin D as monotherapy for ADHD symptoms or the effect of vitamin D supplementation as adjunctive treatment to other classic ADHD medicines. Therefore, the applicability of evidence presented in this study should be met with caution beyond these settings.

According to current guidelines, it is recommended that daily vitamin D doses should range between 400 and 2000 IU depending on age, body weight, disease status, and ethnicity (Pludowski et al. 2018; Randev et al. 2018). Individuals with insufficient and deficient vitamin D require 1000 IU per day or 50,000 IU per week intake orally, respectively (Alshahrani and Aljohani 2013). Dosage can even reach levels as high as 10,000–50,000 IU daily in cases of gastrectomy or malabsorption history (Alshahrani and Aljohani 2013). It has been reported that severe adverse effects could occur only 12–52 weeks after consumption of $\sim$40,000 IU/day. Consequently, dosage and duration in our included RCTs were within safe and acceptable ranges: dosage was between 1000 IU per day and 3000 IU per day or 50,000 IU per week and the duration of vitamin D therapy was at or below 3 months.

A range of symptoms due to vitamin D toxicity have been documented, such as diarrhea, nausea, vomiting, anorexia, bone pain, loss of appetite, weakness, headaches, and drowsiness (Alshahrani and Aljohani 2013; Randev et al. 2018), some of which were reported in our included studies. However, it may be inappropriate to attribute these adverse effects to vitamin D therapy as no significant difference was found between the vitamin D and placebo groups. A plausible explanation is that those adverse effects were due to methylphenidate administration (Elshorbagy et al. 2018). Limited by the sample size, it is hard to discriminate the advantages and disadvantages of different doses and frequency of vitamin D administration.

Interestingly, in our subgroup analyses of baseline vitamin D status, the results from one RCT indicated that only ADHD children with insufficient or deficient vitamin D levels would benefit from vitamin D supplementation. No benefit was observed for ADHD children with sufficient baseline vitamin D levels. This may indicate that only patients with vitamin D deficient/insufficient levels benefit from vitamin D supplementation. Therefore, future studies need to explore whether the effectiveness of vitamin D on ADHD symptoms is based on the deficiency of vitamin D, whether it is necessary to routinely monitor concentrations in children with ADHD before vitamin D treatment, and whether patients with normal vitamin D status benefit from vitamin D supplementation.

Considering the safety of vitamin D and its general deficiency in ADHD patients (Alshahrani and Aljohani 2013; Villagomez and Ramtekkar 2014; Focker et al. 2017; Khoshbakht et al. 2018), vitamin D supplementation has strong potential as an adjunctive therapy for ADHD treatment. To date however, the current evidence is not strong enough. To confirm these findings, further research requires multicentered, higher-quality RCTs with broader geographical representation, a greater age range (children and adults), and a longer range of follow-up. These future RCTs could confirm the studies reviewed and analyzed in this study and demonstrate conclusively the potential therapeutic effectiveness and safety of vitamin D supplementation as a monotherapy or add-on therapy to traditional ADHD pharmacological treatment.

Strength and limitation

The present review has several strengths. Our meta-analysis is the first systematic review to summarize the evidence regarding vitamin D supplementation as adjunctive medicine for ADHD treatment. We registered this systematic review on PROSPERO. Two authors (J.G. and T.X.) independently applied comprehensive searches in relevant databases. We finished article selection, data extraction, and bias risk evaluation according to the Cochrane Handbook for Systematic Reviews of Intervention. A third author (D.M.) resolved the disagreements. After we contacted the authors and were informed of any missing data, some of the biases, such as the allocation sequence generation and the allocation concealment, could be eliminated. Sensitivity analysis revealed that our results were not influenced by different models used to pool the data.

Forthrightly, this review has some limitations. Our study was based on only four trials with a limited number of participants ($n = 256$) only in Middle East countries. Three trials were prone to selection bias due to an unclear generation of allocation sequence and concealment. One trial was at high risk of bias of incomplete outcome due to the high dropout rate in the placebo group without explanation. This missing outcome data could plausibly have had a large enough effect to induce clinically relevant bias in observed effect size. Due to the limited number of included trials, we could not investigate the risk publication through funnel plot or other analyses.

Generally, we rated the quality of the evidence as low to very low mainly due to three reasons: (1) selection bias may exist due to an unclear risk of random sequence generation and allocation concealment; (2) the total population size is <400; (3) I^2 is more than 50%. We considered low-quality evidence for ADHD total scores and behavior scores, and very low-quality evidence for inattention, hyperactivity, and oppositional scores (Fig. 4). Additionally, we only searched studies published in English. There are potentially other relevant articles published in other languages that were consequently missed.

Conclusions

In summary, our meta-analyses from limited evidence indicate that vitamin D supplementation for ADHD treatment may safely alleviate ADHD symptoms with no significant adverse events. Considering the wide use of vitamin D and the general deficiency in ADHD patients, vitamin D is indeed a potential and feasible agent that may contribute to the treatment of ADHD.

Clinical Significance

This study, for the first time, examined available clinical data to assess the efficacy and safety of vitamin D supplementation versus placebo as adjunctive to methylphenidate for patients with ADHD. According to our study, the available data support the use of vitamin D for the therapy of ADHD as a supplementation agent. This review highlights the need for future studies on the efficacy of vitamin D for ADHD symptoms as monotherapy. Moreover, future studies should consider baseline vitamin D levels and address different dosing (low or high dose) and the frequency of vitamin D supplementation.

Authors' Contributions

The study was conceived by J.G., P.G., D.M., C.C., and T.X. J.G. and T.X. developed the eligibility criteria, search strategy, assessment of methodological quality, data extraction, and data summary plan with guidance from J.G., D.M., and T.X. J.G. and P.G. wrote the article, to which all authors J.G., P.G., D.M., C.C., and T.X. contributed.

Disclosures

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(*Appendix follows*→)

Appendix Table A1. Search Strategy of the Following Databases in January 2019: PubMed, Embase, The Cochrane Central Register of Controlled Trials, Web of Science, ClincalTrials.gov, and World Health Organization's International Clinical Trials Registry Platform

#	*Searches*	*Results*
Platform: PubMed		
1	vitamin D	79,557
2	vitamin D2	5109
3	vitamin D3	32,057
4	1-alpha hydroxyvitamin D3	1378
5	1-alpha-hydroxy-vitamin D3	49
6	1-alpha hydroxycalciferol	4
7	1-alpha-hydroxy-calciferol	1
8	1,25 dihydroxyvitamin D3	22,234
9	1,25-dihydroxy-vitamin D3	601
10	1,25 dihydroxycholecalciferol	21,071
11	1,25-dihydroxycholecalciferol	21,071
12	25-hydroxycholecalciferol	4573
13	25 hydroxycholecalciferol	4573
14	25 hydroxyvitamin D	15,498
15	25-hydroxy-vitamin D	1803
16	Alfacalcidol	1237
17	Calcidiol	4112
18	Calcitriol	20,545
19	Calcifediol	3861
20	Calciferol	4407
21	Ergocalciferol	4501
22	Cholecalciferol	26,488
23	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	84,042
24	Attention Deficit Disorder	36,144
25	Adhd	36,179
26	Addh	33,844
27	Hyperactivity	50,767
28	Hyperkinesia	5104
29	hyperactiv*	62,292
30	hyperkinesis*	4667
31	Attention Deficit Disorder* with Hyperactivity	26,625
32	Attention Deficit Disorders with Hyperactivity	34,081
33	Attention Deficit*Hyperactivity Disorder*	22,480
34	Attention Deficit Disorder*	27,158
35	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	69,417
36	#23 AND #35	113
Platform: OVID (Database: Embase 1974 to Present with Daily Update)		
1	Vitamin D/explode.mp.	20,900
2	vitamin D.mp.	113,072
3	vitamin D2.mp.	1630
4	vitamin D3.mp.	14,841
5	1-alpha hydroxyvitamin D3.mp.	109
6	1-alpha-hydroxy-vitamin D3.mp.	27
7	1-alpha hydroxycalciferol.mp.	1
8	1-alpha-hydroxy-calciferol.mp.	6450
9	1,25 dihydroxyvitamin D3.mp.	588
10	1,25-dihydroxy-vitamin D3.mp.	1300
11	1,25 dihydroxycholecalciferol.mp.	1300
12	1,25-dihydroxycholecalciferol.mp.	1236
13	25-hydroxycholecalciferol.mp.	1236
14	25 hydroxycholecalciferol.mp.	22,751
15	25 hydroxyvitamin D.mp.	2952
16	alfacalcidol.mp.	4503
17	calcidiol.mp.	1508
18	calcitriol.mp.	31,865
19	calcifediol.mp.	8505
20	calciferol.mp.	333

(*continued*)

Table AT1. (Continued)

#	Searches	Results
21	ergocalciferol.mp.	8750
22	cholecalciferol.mp.	3891
23	OR/1–22	141,353
24	exp Attention Deficit Disorder/	54,424
25	adhd.mp.	32,399
26	addh.mp.	151
27	exp Hyperactivity/	19,132
28	Hyperkinesia/	4428
29	(attention adj3 deficit).mp.	59,837
30	hyperactiv*.mp.	77,601
31	hyperkinesis*.mp.	897
32	(minimal adj brain adj3 disorder*).mp.	19
33	(minimal adj brain adj3 dysfunction*).mp.	1577
34	(minimal adj brain adj3 damage*).mp.	117
35	OR/24–34	108,562
36	23 and 35	328
Database: The Cochrane Central Register of Controlled Trials		
1	MeSH descriptor Attention Deficit Disorder with Hyperactivity explode all trees	38
2	adhd or addh or adhs	3261
3	attention near/3 deficit	4351
4	hyperactiv*	5174
5	hyperkinesis*	510
6	attention deficit*	5926
7	MeSH descriptor Hyperkinesis explode all trees	11
8	minimal brain near/3 disorder*	67
9	minimal brain near/3 dysfunction* or minimal brain near/3 damage*	175
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	7961
11	vitamin D	11,562
12	vitamin D2	272
13	vitamin D3	2098
14	1,25 dihydroxyvitamin D3	230
15	1,25 dihydroxycholecalciferol	69
16	25 hydroxycholecalciferol	107
17	25 hydroxyvitamin D	2061
18	Alfacalcidol	295
19	Calcidiol	62
20	Calcitriol	1598
21	Calcifediol	513
22	Calciferol	49
23	Ergocalciferol	290
24	Cholecalciferol	1879
25	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	13,541
26	#10 AND #25	107
Platform: Science and Conference Proceedings Citation Index-Social Science and Humanities (Web of Science)		
1	TS = (''ADHD'' or ''ADDH'' or ''ADHS'' or ''AD/HD'')	39,581
2	TS = ((attention* or behav*) NEAR/3 (defic* or dysfunc* or disorder*))	759,223
3	TS = (((disrupt* NEAR/3 disorder*) or (disrupt* NEAR/3 behav*) or (defian* NEAR/3 disorder*) or (defian* NEAR/3 behav*))	17,432
4	TS = (impulsiv* or inattentiv* or inattention* or hyperactiv* or hyperkine*)	189,644
5	TS = (''minimal brain disorder*'')	7
6	TS = (vitamin d2 OR vitamin d 2 OR hydroxyvitamin* OR cholecalciferol* OR calciferol* OR calcitriol* OR calcifediol* OR dihydrotachysterol* OR alfacalcidol* OR alphacalcidol* OR colecalciferol*)	130,395
7	#1 OR #2 OR #3 OR #4 OR #5	888,065
8	TS = (random* or control* or trial* or groups or effectiveness or evaluation or placebo*)	30,355,853
9	#6 AND #7 AND #8	1153
Platform: ClincalTrials.gov		
1	Attention Deficit Disorder OR adhd OR addh OR Hyperactivity OR Hyperkinesia OR hyperactiv* OR hyperkinesis* OR Attention Deficit Disorder* with Hyperactivity OR Attention Deficit Disorders with Hyperactivity OR Attention Deficit*Hyperactivity Disorder* OR Attention Deficit Disorder*	1184

(*continued*)

Table AT1. (Continued)

#	Searches	Results
2	vitamin D OR vitamin D2 OR vitamin D3 OR 1,25 dihydroxyvitamin D3 OR 1,25 dihydroxycholecalciferol OR 25 hydroxycholecalciferol OR 25 hydroxyvitamin D OR alfacalcidol OR calcidiol OR calcitriol OR calcifediol OR calciferol OR ergocalciferol OR cholecalciferol OR	543
3	#1 and #2	2
Platform: WHO's International Clinical Trials Registry Platform		
1	Attention Deficit Disorder OR adhd OR addh OR Hyperactivity OR Hyperkinesia OR hyperactiv* OR hyperkinesis* OR Attention Deficit Disorder* with Hyperactivity OR Attention Deficit Disorders with Hyperactivity OR Attention Deficit*Hyperactivity Disorder* OR Attention Deficit Disorder*	2680
2	vitamin D OR vitamin D2 OR vitamin D3 OR 1,25 dihydroxyvitamin D3 OR 1,25 dihydroxycholecalciferol OR 25 hydroxycholecalciferol OR 25 hydroxyvitamin D OR alfacalcidol OR calcidiol OR calcitriol OR calcifediol OR calciferol OR ergocalciferol OR cholecalciferol OR	3683
3	#1 and #2	6

WHO, World Health Organization.

Appendix Table A2. Attention-Deficit/Hyperactivity Disorder Symptom Severity Scales Used in Included Trials

Scales/measures	*Mohammadpour et al. (2018)*	*Dehbokri et al. (2019)*	*Elshorbagy et al. (2018)*	*Naeini et al. (2019)*
Conners parent rating scale	Yes	Yes	Yes	—
ADHD rating scale-IV	Yes	—	—	
Strengths and Difficulties Questionnaire by parents/teachers	—	—	—	Yes
Continuous Performance Test	—	—	—	Yes
Weekly Parent Ratings of Evening and Morning Behavior	Yes	—	—	—
Conners Parent Questionnaire	—	—	—	Yes

ADHD, attention-deficit/hyperactivity disorder.

Appendix Table A3. Description of Scales Used in Included Studies

Scales/measures	*Number of items*	*Scoring*
Conners parent rating scale	A 27-item scale that is usually scored by patents, consisting of four subsocres: oppositional, cognitive/inattentive problems, hyperactivity, and ADHD index or total scores. Ratings on the questionnaire ranged from 0 (never or rarely) to 3 (very often).	A total score is derived from the scale, and the cutoff score of 15 has been established. Raw scores were converted to T-scores based on gender and age.
ADHD rating scale-IV	18-Item questionnaire classified into three subgroups: hyperactivity/impulsivity, inattention, and total. Nine questions each on inattention and hyperactivity/impulsivity, where the odd-numbered items represent the inattention subscale, and the even-numbered items represent the hyperactive/impulsive subscale.	Items were scored from 0 (never or rarely) to 3 (very often) and scoring was in T-score format.

(*continued*)

Table AT3. (Continued)

Scales/measures	*Number of items*	*Scoring*
Strengths and Difficulties Questionnaire by parents/teachers	This questionnaire includes 25 questions and was completed by parents (SDQP) and teachers (SDQT), with results being obtained numerically. The questionnaire has five scales each constituted by five questions, and included; emotional problems, behavioral problems, hyperactivity, problems with peers, and social behavior scales.	The score of each scale ranges between 0 and 10, and each question is assigned a score between 0 and 2.
Continuous Performance Test	The test is conducted by computer and its length of time is adjustable; in this research it was adjusted to take 5 minutes. In the test, 120 images were shown on the monitor; each image lasted for 8 seconds after which another image was substituted. 15 of the 120 images were repeated, and on seeing an image shown before, the respondents were to tab the space bar. The Game Card and Joystick versions were used in this research.	Correct detection: This indicates the number of times the client responded to the target stimulus. Higher rates of correct detections indicate better attentional capacity; Commission errors: This score indicates the number of times the client responded but no target was presented. A fast reaction time and high commission error rate points to difficulties with impulsivity. A slow reaction time with high commission and omission errors, indicates inattention in general.
Weekly Parent Ratings of Evening and Morning Behavior	WPREMB questionnaire includes 11 items; 3 questions for morning symptoms and 8 questions pertinent to late afternoon and evening symptoms. Morning questions were asked about behaviors before taking the first dose of methylphenidate and evening items were specifically about behaviors 2–3 hours after taking the last dose of medication, to ensure that symptoms are not mainly affected by the methylphenidate consumption.	Responses to each item were a Likert-type scale; 0 (none), 1 (a little), 2 (a moderate amount), and 3 (a lot). Values for the WPREMB questionnaire were defined in three subscores: morning symptoms, late afternoon and evening symptoms, and total. The higher the score, the stronger the disorder.
Conners Parent Questionnaire	The Conners Parent Questionnaire has 26 questions and has been validated by the Iranian Institute of Cognitive Sciences.	The total score of the test ranges from 26 to 104. If the obtained score is higher than 34, it can be concluded that there exists a case of attention deficit disorder. The higher the score, the stronger the disorder.

ADHD, attention-deficit/hyperactivity disorder; WPREMB, Weekly Parent Ratings of Evening and Morning Behavior; SDQP, Strengths and Difficulties Questionnaire by parents; SDQT, Strengths and Difficulties Questionnaire by teachers.

Appendix Table A4. Secondary Outcome of Trials with Vitamin D Supplementation Compared with Trials with Placebo Intervention, Including the Ratio of Patients with Sufficient Vitamin D Level and the Vitamin D Level of Patients' Level After Intervention

Outcome and Subgroups	*RCT*	*Participants*	*Statistical method*	I^2 *(%)*	p-*Values*	*Effect estimate*
The vitamin D level of patients' level after intervention	3	221	SMD (IV, random, 95% CI)[a]	81	0.005	2.26 [1.46, 3.06]
The ratio of patients with sufficient vitamin D level after intervention	1	96	RR (M-H, fixed, 95% CI)	NA	NA	0.14 [0.07, 0.29]

RR <1 indicates that compared with placebo, vitamin D could increase the ratio of patients with sufficient vitamin D level after intervention.
[a]The random effects model was selected because the I^2 value >50% or p-value <0.05.
RCT, randomized controlled trial; NA, not applicable; SMD, standard mean difference; CI, confidence interval; RR, risk ratio.