ADHD Attention Deficit and Hyperactivity Disorders
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REVIEW ARTICLE

Vitamin D levels in children and adolescents with attention-deficit hyperactivity disorder (ADHD): a meta-analysis

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Abstract

The aim of this article was to assess the differences in serum 25(OH)D levels between children and adolescents with attention-deficit/hyperactivity disorder (ADHD) and healthy controls. We used the PubMed (1966–2017), Scopus (2004–2017), ClinicalTrials.gov (2008–2017), Cochrane Central Register of Controlled Trials CENTRAL (2000–2017), and Google Scholar (2004–2017) databases. Statistical meta-analysis was performed with RevMan 5.3. Eight studies were finally included in the present meta-analysis with a total number of 11,324 children. Among them, 2655 were diagnosed with ADHD, while the remaining 8669 were recruited as healthy controls. All eight trials reported significantly lower serum concentrations of 25(OH)D in patients diagnosed with ADHD compared to healthy controls. The pooled data showed that there was a significant difference between the ADHD group and the control group (SMD = − 0.73, 95% CI [− 1.00, − 0.46]). The systematic review and meta-analysis of observational studies demonstrated an inverse association between serum 25(OH)D and young patients with ADHD. Large cohort studies are required to investigate whether vitamin D-deficient infants are more likely to develop ADHD in the future. Also, whether children with ADHD should be supplemented with higher doses of vitamin D3 remains to be confirmed through long-term controlled clinical trials.

Keywords Vitamin D · ADHD · Children · Adolescents · Attention-deficit hyperactivity disorder

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in childhood, with a reported prevalence of 3–4% in children worldwide (Feldman and Reiff 2014). It is characterized by hyperactivity/inattention and impulsivity, and a minimum of six symptoms from at least one category must be present for diagnosis (Subcommittee on Attention-Deficit/Hyperactivity Disorder et al. 2011). Diagnosis in childhood is associated with poor academic and social outcomes, including learning disabilities; impaired social functioning; low self-esteem; and emotional dysregulation. Many of these symptoms persist through childhood and adolescence, and into adult life, and lead to poor quality of life (Dopfner et al. 2015; Klein et al. 2012; Coghill and Hodgkins 2016; Mulraney et al. 2017). Existing therapy, including the stimulant medication, is often inadequate (Subcommittee on Attention-Deficit/Hyperactivity Disorder et al. 2011; Childress and Sallee 2014). Furthermore, a number of studies suggest that ADHD imposes a significant burden on multiple public services with overall national costs ranging from $143 to $266 billion in the USA, £ 670 million in the UK, and €1041–€1529 million in other European countries (Doshi et al. 2012; Le et al. 2014; Telford et al. 2013). Although genetic factors are found to play a prominent role in the etiology of ADHD, the exact pathogenic mechanisms are not comprehensively understood (Gallo and Posner 2016). Vitamin D deficiency has recently been identified as a potential etiologic factor in several neuropsychiatric disorders, including Parkinson's disease, Alzheimer's disease, multiple sclerosis, depression, schizophrenia, and autism spectrum disorder (ASD). This implies that the vitamin plays a pivotal role in ensuring that the central nervous system (CNS) functions properly as well as in supporting good mental health (Eyles et al. 2013; Kaneko et al. 2015; Ascherio et al. 2010; Autier et al. 2014). Cumulative data suggest that decreased levels of vitamin D may also be a significant risk factor for developing ADHD. In

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the present meta-analysis, we sought to investigate whether children and adolescents with ADHD have lower levels of vitamin D compared to healthy controls.

Materials and methods

Study design

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to design this systematic review (Liberati et al. 2009). Eligibility criteria and the assessed outcomes were predetermined. Language or date restrictions were avoided during the literature search. The study selection was conducted in three consecutive stages. First, we screened the titles and/or abstracts of all electronic articles to evaluate their eligibility. In a second stage, we retrieved the articles that met or were supposed to meet the criteria, and in the third stage, we chose to include all observational studies (both prospective and retrospective) that reported serum vitamin D concentration among ADHD children and adolescents and healthy controls. Case reports and review articles were excluded. Two authors performed the electronic search of articles and tabulated the data in structured form, and afterward, all authors reviewed the selected indices. In case of discrepancy regarding the evaluation of the methodology, retrieval of articles, and statistical analysis, we resolved all matters with consensus of all authors.

Literature search and data extraction

We used the PubMed (1966–2017), Scopus (2004–2017), ClinicalTrials.gov (2008–2017), Cochrane Central Register of Controlled Trials CENTRAL (2000–2017), and Google Scholar (2004–2017) databases in our primary search along with the reference lists of electronically retrieved full-text papers. The date of our last search was set on December 31, 2017. Search strategies and results are shown in Fig. 1. Our search strategy included the words vitamin D, 25(OH)D, cholecalciferol, vitamin D_3, ADHD, attention-deficit/hyperactivity disorder, attention-deficit/hyperactivity symptoms. The PRISMA flow diagram depicts the stages of article selection (Fig. 1).

Quality assessment

We assessed the methodologic quality of all included studies using the Oxford Levels of Evidence and the GRADE list. The Newcastle-Ottawa Scale (Klein et al. 2012) was used to evaluate the quality of our nonrandomized studies (Stang 2010). Specifically, a "star system" has been developed in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case–control or cohort studies, respectively. There is an adjustment for cross-sectional studies as well. The two first raters conducted the NOS assessment independently. Any discrepancies between their scores were solved by discussion.

Statistical analysis

Statistical meta-analysis was performed with RevMan 5.3. Confidence intervals were set at 95%. Since the studies did not use the same laboratory technique to measure the serum 25(OH)D concentration, we calculated standardized mean differences (SMD) to assess the association between vitamin D status and ADHD. We calculated the pooled SMD and 95% confidence intervals (CI) with the DerSimonian–Laird random-effects model as a result of the significant heterogeneity in the methodologic characteristics of included studies (DerSimonian and Kacker 2007). Subgroup meta-analyses stratified studies by assay method and sample size. Due to the significant heterogeneity and small number of included studies, publication bias was not tested (Souza et al. 2007).

Sensitivity analysis

Sensitivity analysis was also conducted by omitting one study at a time to assess the effect of each study on the outcomes of the meta-analysis. The forest plots of the "leave-one-out" meta-analysis were produced with Open Meta-Analyst. We also performed a random-effects meta-regression analysis using latitude gradient as a moderator, again produced with Open Meta-Analyst.

Results

Included studies

Eight studies were finally included in the present meta-analysis with a total number of 11,324 children (Bala et al. 2016; Bener et al. 2014; Garipardic et al. 2017; Goksugur et al. 2014; Kamal et al. 2014; Meyer et al. 2017; Shang-Guan and Zhao 2015; Sharif et al. 2015). Among them, 2655 were diagnosed with ADHD, while the remaining 8669 were recruited as healthy controls. The design of each study, its classification according to the Oxford Level of Evidence, the patient eligibility criteria, as well as the instrument/measure for diagnosis and evaluation of ADHD symptoms are summarized in Table 1. Table 2 presents the patient characteristics including their number, patient age, gender, BMI, and household income.

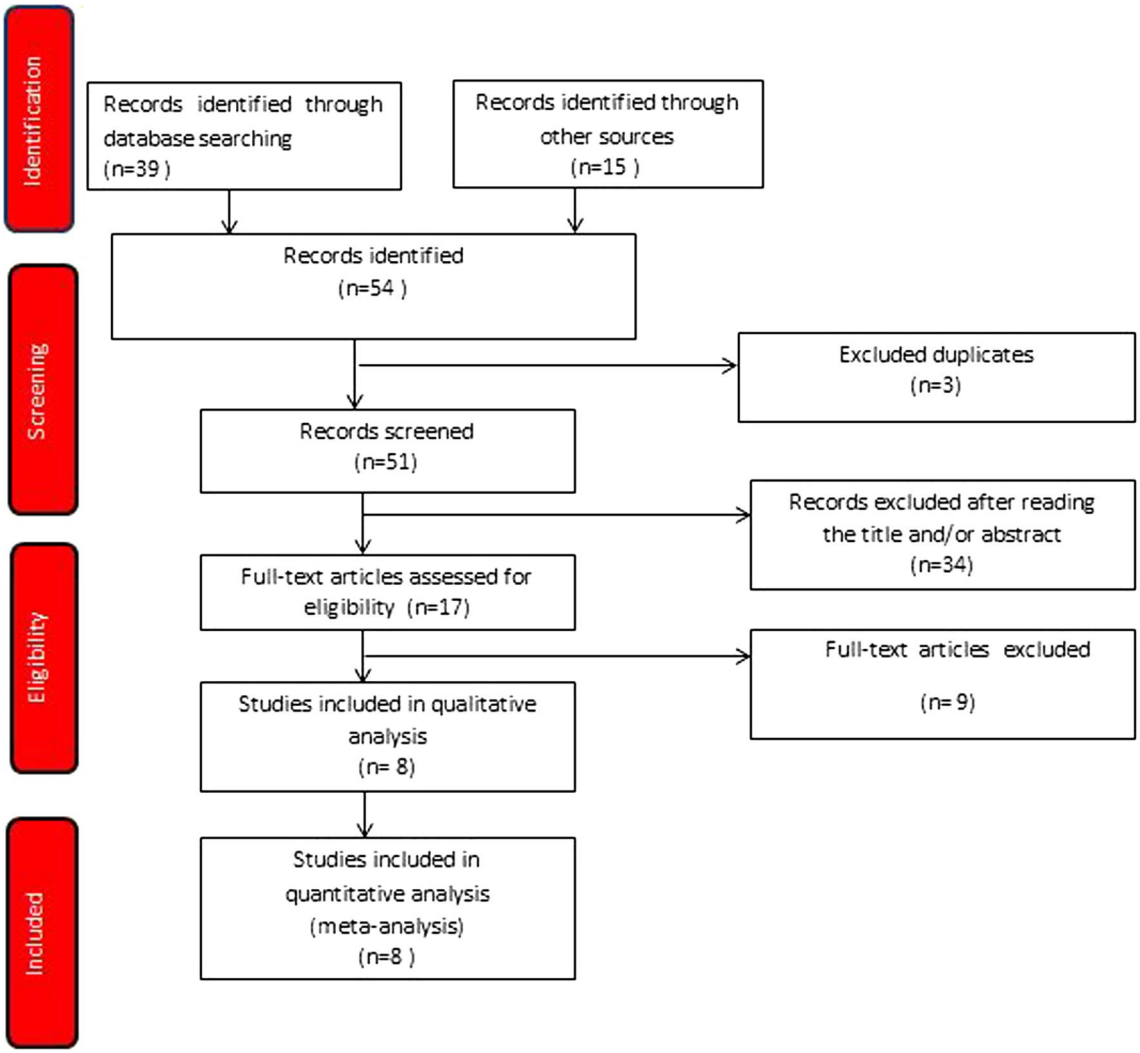


Fig. 1 Search flow diagram

Excluded studies

Eight studies were excluded after reading the full text (Strom et al. 2014; Morales et al. 2015; Daraki et al. 2018; Gustafsson et al. 2015; Mossin et al. 2017; Holton et al. 2018; Humble et al. 2010; Avcil et al. 2017). Seven of them did not report the outcomes of interest, since three of them measured the maternal vitamin D levels during pregnancy, the other two measured the vitamin D concentration from umbilical cord blood samples, another one measured the reported vitamin D intake and did not provide data of the serum vitamin D levels, and the last one measured the vitamin D levels in adults. The last one was excluded, as we could not retrieve it in full text.

Outcomes

In our meta-analysis, heterogeneity was present; therefore, we employed a random-effects model. All eight studies reported significantly lower serum concentrations of 25(OH) D in patients diagnosed with ADHD compared to healthy controls. The pooled data showed that there was a significant difference between the ADHD group and the control group (SMD = −0.73, 95% CI [−1.00, −0.46], $p < 0.00001$, Fig. 2). To explore the sources of heterogeneity ($I^2 = 94\%$), we performed a subgroup analysis of the assay methods used in the included studies, separated into enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and chemiluminescence immunoassay (CLIA) (Fig. 3). The

Table 1 Study characteristics

References	Study type, Country	Exclusion criteria	ADHD instrument/measure	OLE	NOS
Bala et al. (2016)	Case–control, Turkey	Age > 18 years, known genetic or metabolic disorder, head injury, infection on admission, abnormal renal or hepatic test results, chronic use of medication, vitamin supplements	DSM-5, DSM-4 Turkish version, DBDRS	4	6
Bener et al. (2014)	Case–control, Qatar	Age < 6 or > 18 years, known metabolic disorder, other acute or chronic disorder, epilepsy or antiepileptic drugs, calcium or vitamin D supplements during the last 6 months before study, systematic sunblock use, pubertal age, hemoglobin < 10 g/dL	DSM-4 TR, CPRS, CTRS, SNAP	3b	8
Garipardic et al. (2017)	Case–control, Turkey	Age > 18 years, known genetic or metabolic disorder, head injury, infection on admission, other chronic disorder, abnormal renal or hepatic test results, chronic use of medication, vitamin supplements	DSM-5, DSM-4 TR, DBDRS	4	6
Goksugur et al. (2014)	Case–control, Turkey	Age < 7 or > 18 years, mental retardation, autistic spectrum disorders, psychotic disorders, other chronic physical or neurological disorders, BMI < 5th or > 85th	DSM-4 TR, T-DSM-4-S	4	4
Kamal et al. (2014)	Case–control, Qatar	Age > 18 years, epilepsy or antiepileptic drug, calcium or vitamin D supplements during the last 6 months before study, systematic sunblock use, pubertal age	Physician diagnosis, CPRS, CTRS, SNAP	3b	8
Meyer et al. (2017)	Cross-sectional, Germany	Not in KiGGS study	Healthcare professional report before study, SDQ	4	9
Shang-Guan and Zhao (2015)	Case–control, China	Age > 18 years, known comorbidity (e.g., neuropsychiatric, neurodevelopmental, neurological disorder), sexually transmitted disease, vitamin D supplements	DSM-5	4	5
Sharif et al. (2015)	Case–control, Iran	Age > 18 years, known metabolic, liver or kidney disorder, mental retardation, epilepsy, autistic spectrum disorders, vitamin D supplements	DSM-4	4	4

ADHD, attention-deficit/hyperactivity disorder; OLE, Oxford Levels of Evidence; 3b, individual case–control study; 4, poor quality case–control/cohort study or case series, DSM, Diagnostic and Statistical Manual of Mental Disorders DSM-4; TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision; CPRS, Conners' Parents Rating Scale; CTRS, Conners' Teachers Rating Scale; SNAP, Swanson, Nolan and Pelham (SNAP) *Questionnaire*; T-DSM-4-S, Turgay DSM-4-based Child and Adolescent Behavioral Disorders Screening and Rating Scale; DBDRS, Disruptive Behavior Disorders Rating Scale; SDQ, Strengths and Difficulties Questionnaire; KiGGS, German Health Interview and Examination Survey for Children and Adolescents, conducted by the Robert Koch Institute, Germany

pooled SMD for serum vitamin D levels using ELISA was −0.77, 95% CI [−1.10, −0.45], using RIA was −0.73, 95% [−0.91, −0.55], while using CLIA was −0.76, 95% CI [−1.32, −0.20]. We also separated the studies into two independent groups according to the total sample size: small sample size ($n < 200$) and large sample size studies ($n > 1000$) (Fig. 4). The pooled SMD in studies with small sample size was −0.87, 95% CI [−1.06, −0.68], while for the large sample size studies was −0.53, 95% CI [−0.95, −0.11].

The leave-one-out meta-analysis did not affect the statistical significance of the overall estimated pooled data (Fig. 5).

Table 2 Patient characteristics

References	Patients no.	Age (years)	Gender male/female	BMI (kg/m^2)	Household income low/high
ADHD versus control					
Bala et al. (2016)	34 vs 27	7.68 ± 3.20 vs 9.80 ± 4.01	23/11 vs 13/14	17.4 vs 17.5	N/A
Bener et al. (2014)	630 vs 630	5–18 vs 5–18	315/315 vs 313/317	544 vs 500Ŧ 28 vs 65ŦŦ*	200/212 vs 194/177*
Garipardic et al. (2017)	36 vs 25	7.67 ± 3.13 vs 9.90 ± 4.13	24/12 vs 12/13	17.2 vs 18.1	N/A
Goksugur et al. (2014)	60 vs 30	9 ± 2.2 vs 10.1 ± 3.3	40/20 vs 17/13	17.73 ± 2.67 vs 18.06 ± 3.38	11/14 vs 3/8
Kamal et al. (2014)	1331 vs 1331	5–18 vs 5–18	963/368 vs 766/565*	1168 vs 1104Ŧ 61 vs 102ŦŦ*	393/418 vs 447/370*
Meyer et al. (2017)	430 vs 6492	14.4 ± 2.0 vs 14.6 ± 2.0*	351/79 vs 3103/3389*	21.2 ± 4.4 vs 21.1 ± 4.0	134/82 vs 1623/1616*
Shang-Guan and Zhao (2015)	97 vs 97	8.7 ± 1.7 vs 8.5 ± 1.5	N/A	N/A	N/A
Sharif et al. (2015)	37 vs 37	9.13 ± 2.37 vs 9.40 ± 2.19	23/14 vs 18/19	N/A	N/A

*Statistically significant difference

Ŧ < 85th percentile of BMI

ŦŦ > 95th percentile of BMI

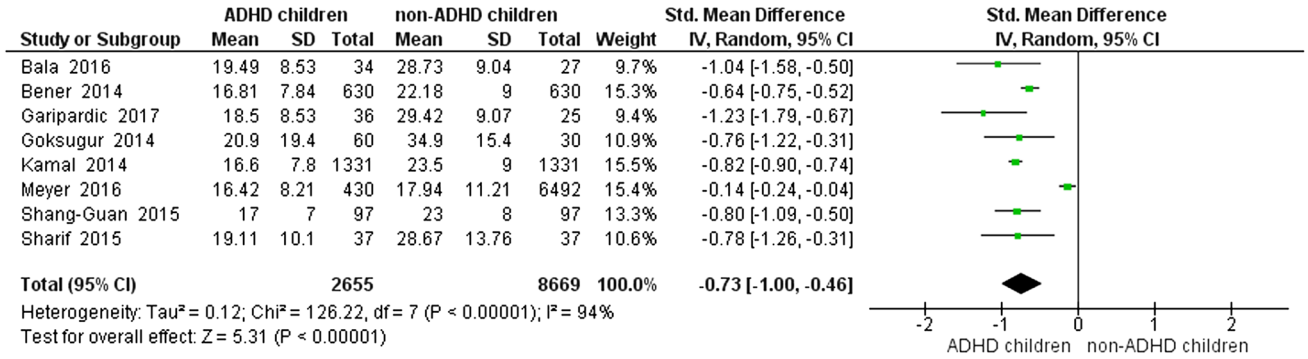


Fig. 2 Forest plot of the serum vitamin D concentration in ADHD and healthy controls

The meta-regression analysis on the latitude gradient of the country of each study showed a statistically significant correlation ($p = 0.034$) (Figs. 6, 7). Mean age and gender could not be used as moderators, since we had a small number of included studies and we missed values (Table 2).

Discussion

The present meta-analysis shows that 25(OH)D serum concentrations are significantly lower in children and adolescents with ADHD compared to healthy control subjects. Our results are based on observational studies conducted with children aged 5–18. Given that sunlight directly influences vitamin D levels and increasing latitude equates to less sunlight exposure, we conducted a meta-regression analysis to investigate the influence of latitude on the findings of our meta-analysis and observed a statistically significant correlation (Webb et al. 1988; Leary et al. 2017) (Figs. 6, 7). This means that vitamin D levels were found to be lower in young ADHD patients compared to healthy controls and that depended on the latitude of the country performing the study. In other words, the latitude gradient was found to influence the mean difference of vitamin D levels between the ADHD group and the control group (Fig. 6). Figure 7 depicts the relationship between the standardized mean difference of vitamin D levels between the two groups (ADHD, control) and the latitude. Each study is represented by a circle which shows the actual coordinates for that study. The area of each circle is proportional to that study's weight to the analysis. The center line shows the predicted values. Visual inspection of the graph was not suggestive of an association between

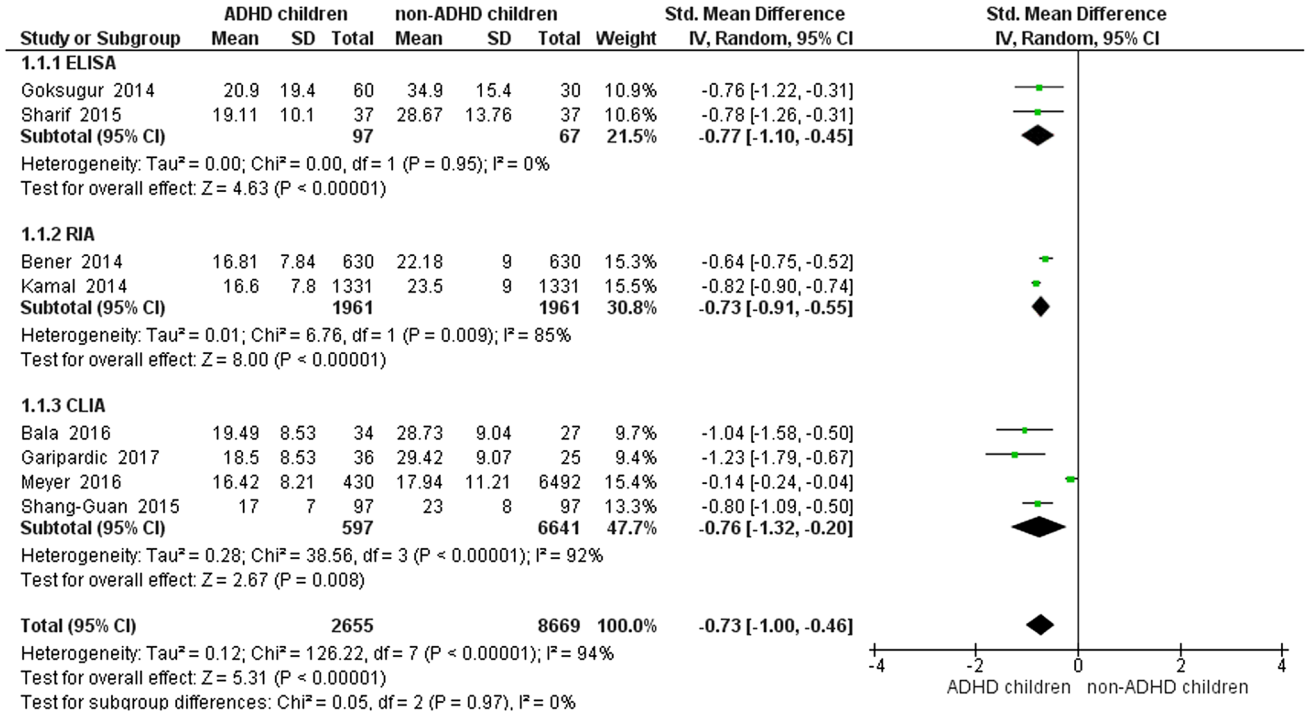


Fig. 3 Forest plot in subgroup analysis according to the assay method

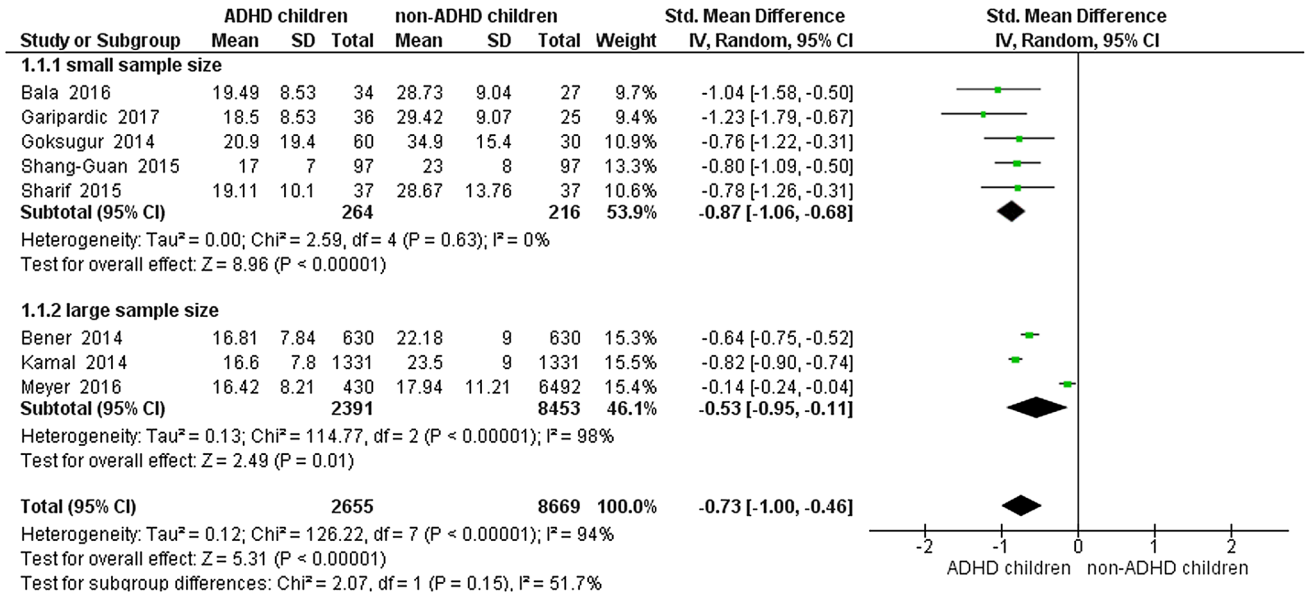


Fig. 4 Forest plot in subgroup analysis according to the sample size

the latitude and the mean difference; however, a statistical test by meta-regression analysis was significant ($p = 0.034$).

Vitamin D is widely acknowledged as a steroid hormone that plays a key role in calcium and phosphorous homeostasis, and hence bone metabolism and muscular growth. For humans, the main source is vitamin D3 which is synthesized in the skin from the provitamin D3 by exposure to ultraviolet B rays (UVB, 290–315 nm) (Holick 1987). Vitamin D is present in very few foods, largely only in oily fish such as salmon, mackerel, and sardines. The active form of vitamin D, i.e., 1,25-dihydroxyvitamin D, is an unreliable indicator of vitamin D status, as it is kept within reference range as

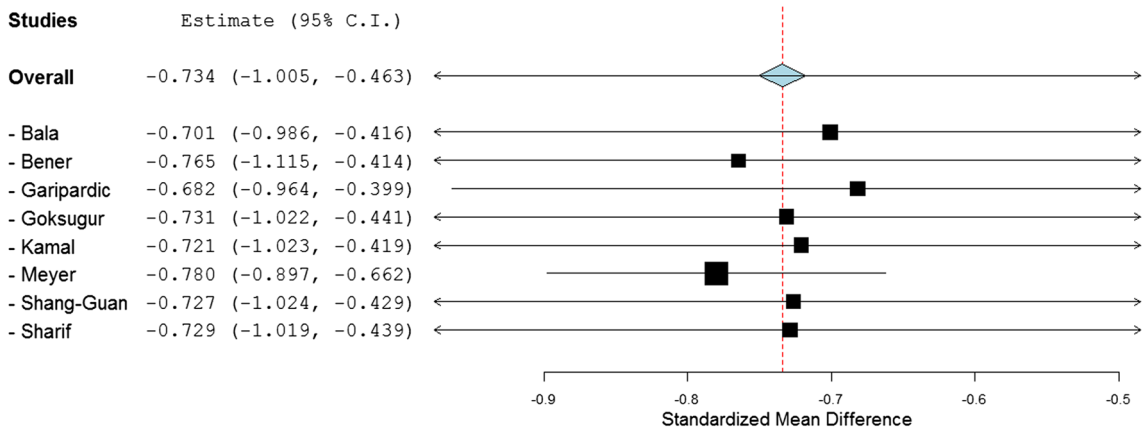
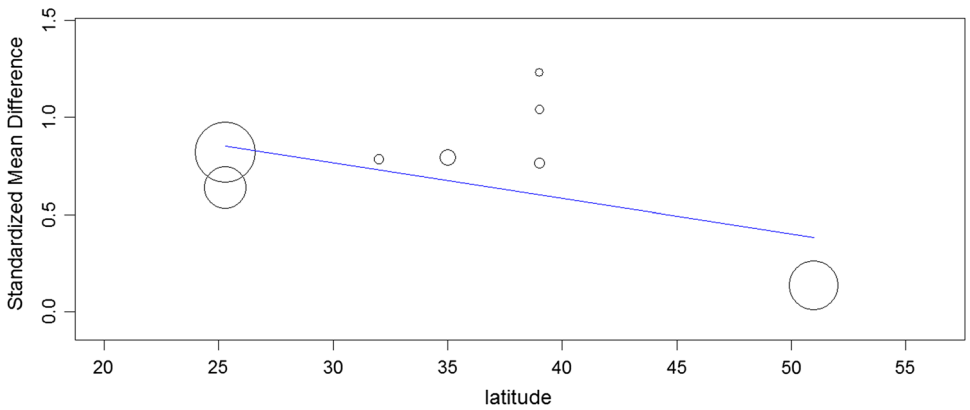


Fig. 5 Leave-one-out forest plot

study name	year	Control N	Control mean	Control SD	ADHD N	ADHD mean	ADHD SD	SMD	lower	upper	latitude (c)
Bala	2016	27	28.730	9.040	34	19.490	8.530	1.042	0.504	1.579	39.000
Bener	2014	630	22.180	9.000	630	16.810	7.840	0.636	0.523	0.749	25.300
Garipardic	2017	25	29.420	9.070	36	18.500	8.530	1.232	0.676	1.787	39.000
Goksugur	2014	30	34.900	15.400	60	20.900	19.400	0.764	0.311	1.216	39.000
Kamal	2014	1331	23.500	9.000	1331	16.600	7.800	0.819	0.740	0.898	25.300
Meyer	2017	6492	17.940	11.210	430	16.420	8.210	0.138	0.040	0.235	51.000
Shang-Guan	2015	97	23.000	8.000	97	17.000	7.000	0.795	0.503	1.087	35.000
Sharif	2015	37	28.670	13.760	37	19.110	10.100	0.784	0.311	1.257	32.000

Fig. 6 Meta-regression analysis on latitude gradient

Fig. 7 Meta-regression plot on latitude gradient



long as possible by hormonal mechanisms and is measured only in disorders of 1a-hydroxylation, vitamin D receptor defects, and extrarenal 1a-hydroxylation (Braegger et al. 2013). The most reliable indicator is the serum concentration of 25(OH)D and is measured in blood using several assay methods. ELISA, RIA, and CLIA were used in the studies included in this meta-analysis. Different assays may have different results, with inter-assay variation reaching up to 25% at low serum 25(OH)D levels (15 nmol/L), while the intra-assay variation can reach up to 10% at 15 nmol/L, even when quality controls and standardization programs are enforced. This could be explained by the fact that 25(OH)D assays have different affinities for vitamin D2 and D3 (Health Quality 2010; Le Goff et al. 2015; Snellman et al.

Table 3 Comparison of the laboratory techniques used in the included studies

Characteristics	ELISA	RIA	CLIA
Principle	The antibody is linked to an enzyme; after incubation with the antigen, the unbound antibody is washed away; the bound antibody-enzyme attached to the target antigen is observed by adding a substrate to the solution; the enzyme catalyzes a chemical reaction of the substrate to produce a quantifiable color change detected by simple photometer	A radioisotope (I^{125}) is attached to an antigen of interest and binds with its complementary antibody; then a sample with the antigen to be measured is added; it competes with the radioactive agent and replaces it in the binding spot; after washing away unbound antigens, the radioactivity of the sample is measured using a gamma-detector; the amount of the radioactive signal is inversely related to the amount of target antigen; the accuracy of the method will depend on the specificity of the antibody used	Chemical reaction between an emitter and a coreactant results in an electron moving to a higher energy state and emitting a photon; the electromagnetic radiation emitted as light is measured by luminometers; accuracy of the method will depend on the specificity of the antibody used
Time of experiment	Very short	Time-consuming	Short
Limitations	Low or no signal, high background, inconsistent results between replicate samples or controls	Requires the use of radionuclides, efficient and highly skilled personnel	High costs, limited tests panel, closed analytical systems
Benefits	Rapid results, minimal skill, and knowledge required	Requires small sample size, not subjected to nonspecific interference	Easy performance, low cost, high sensitivity, high degree of automation

ELISA enzyme-linked immunosorbent assay, *RIA* radioimmunoassay, *CLIA* chemiluminescence immunoassay

2010; Wallace et al. 2010). Table 3 depicts some basic characteristics of these methods. While there are no universally accepted reference values of 25(OH)D levels, nonetheless, vitamin D deficiency is defined by most experts as a serum 25(OH)D level of less than 20 ng/mL (50 nmol/L) (Holick 2007). Vitamin D insufficiency has been defined as a serum 25(OH)D level of 21–29 ng/mL (52–72 nmol/L) (Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium et al. 2011). This is based on the observed physiological changes in calcium absorption and parathyroid hormone levels that occur with changes in vitamin D levels. Vitamin D sufficiency has been defined as serum 25(OH)D levels of 30 ng/mL (75 nmol/L) and above, based on the analysis of observational studies of vitamin D and various health outcomes (Holick 2007).

Growing scientific evidence identifies the importance of vitamin D in various diseases including cardiovascular diseases; cancer; metabolic disorders; infectious and autoimmune diseases; as well as in brain development; neurodegenerative and neuropsychiatric disorders, although highly convincing evidence of clear associations does not yet exist (Wacker and Holick 2013; Pludowski et al. 2013). Vitamin D receptors are expressed in almost every organ and tissue, including the brain where they are especially present in the hypothalamus, the substantia nigra, and also the hippocampus (Wang et al. 2012; Eyles et al. 2014).

A strong relationship between vitamin D deficiency and neurocognitive function and behavior has been reported both in animal models and in observational studies. Studies using genetically modified mice have allowed greater understanding of the physiology and functioning of vitamin D in the brain. In experiments conducted by Eyles et al., it became clear that vitamin D-deficient rats (DVD rats) are characterized by brain distortion, reduced expression of nerve growth factors, sensitivity to agents that induce psychosis (NMDA antagonist MK-801) as well as poor attentional processing, changes which persist in the adult rat brain (Eyles et al. 2009). DVD rats also appear to have increased impulsivity as well as a lack of inhibitory control (Turner et al. 2013). Furthermore, it is shown that prenatal vitamin D deficiency leads to alterations in genes related to neuronal survival, speech and language development, and dopamine synthesis (Hawes et al. 2015). Likewise, vitamin D deficiency has been hypothesized as an increased risk factor for schizophrenia (Kesby et al. 2013; Schoenrock and Tarantino 2016). A possible component could be that vitamin D potentially plays a key role in various important molecular processes as discussed by Morales et al. and Eyles et al. (2011, 2013). Specifically, vitamin D regulates calcium transients in the brain and neuronal development, by participating in neuronal migration and growth; differentiation; neurotransmission; cell interaction; and synaptic function. It also protects against reactive oxygen species, alters neurotrophic factors and monoamine levels, and regulates hormonal and serotonin pathways within the CNS (Partonen 1998; Cass et al. 2006). Thus, vitamin D contributes to the DNA repair of de novo mutations, and it can also decrease inflammation and act immunoprotectively (Fleet et al. 2012; Carvalho et al. 2017).

In clinical studies, there seems to be a correlation between the vitamin D status of the mother during pregnancy and the brain development of the fetus, bearing in mind that the mother is the only source of vitamin D substrate for the fetus. Higher concentrations of the vitamin have been found to provide protection for the neuronal development of the fetus (Shin et al. 2010).

It is not currently known whether vitamin D insufficiency is a risk factor for developing ADHD, a simple mediator of the disease or a result of the severity of the illness. Two prospective studies performed by Strøm et al. and Morales et al. in 2014 and 2015, respectively, had inconsistent results regarding the association between maternal 25(OH)D levels and future prediction of ADHD symptoms in children (Strom et al. 2014; Morales et al. 2015). Morales et al. confirmed that reduced maternal 25 (OH)D levels in plasma in the 13th week of pregnancy were associated with ADHD-like symptoms in 4- to 5-year-old children (Morales et al. 2015). Specifically, it is stated that the number of total ADHD-like symptoms in children decreased by 11% per 10 ng/ml increase in 25(OH)D3 concentration (incidence rate ratio [IRR] = 0.89, 95% confidence interval [CI] = 0.80, 0.98). A twenty-two-year follow-up study by Strøm et al., however, did not, however, show any association between serum levels of 25(OH)D in the 30th week of pregnancy and ADHD symptoms in children. Gustafsson et al. also reported that cord blood vitamin D concentration did not differ among children with ADHD (median 13.0 ng/ml) and controls (median 13.5 ng/ml) ($p = 0.43$) (Gustafsson et al. 2015). On the other hand, Mossin et al. detected an inverse association between cord 25(OH)D and ADHD symptoms in toddlers, with higher prenatal vitamin D concentrations protecting against early ADHD symptoms (Mossin et al. 2017). The recent Rhea mother–child cohort study in Greece found a relationship between high maternal vitamin D concentrations (> 50.7 nmol/L) and a reduction in the number of hyperactivity-impulsivity and total ADHD-like symptoms, as well as a reduction in overall behavior difficulties at 4 years of age, with a female predominance after adjusting for several confounders (Daraki et al. 2018). Therefore, the authors suggest that appropriate supplementation during pregnancy should be considered, especially in countries with higher prevalence of vitamin D deficiency, in order to reduce the potential incidence of ADHD-like symptoms later in life. Similarly, a recent systematic review and meta-analysis has demonstrated an inverse association between serum concentration of 25-hydroxyvitamin D and ASD (Wang et al. 2016). Possible molecular mechanisms in which vitamin D deficiency is linked to these specific neurodevelopmental disorders have been discussed lately by Berridge (2018). Both ADHD and ASD are characterized by abnormal brain developmental processes, with vitamin D playing a key role in these processes. Specifically, vitamin D deficiency leads to reduced expression of tryptophan hydroxylase 2 (TPH2) and as a result to decreased serotonin synthesis. A decline in serotonin levels is related to both ADHD and ASD, and it is worth bearing in mind that serotonin modulates neurogenesis, axon branching, and the formation of dendrites, processes that have been found to be abnormal in these disorders. Furthermore, vitamin D modulates the Wnt/beta-catenin signaling pathway that contributes to early brain development by promoting the expression of DKK-1 which inhibits the Wnt/beta-catenin signaling pathway. As a result of vitamin D deficiency, this specific pathway does not function properly, leading to neurodevelopmental disorders. Another way in which vitamin D deficiency could lead to neurodevelopmental disorders is through distortion of the Ca^{2+} transients which regulate brain development. Also, it is suggested that vitamin D deficiency causes low levels of antioxidants such as glutathione and glutathione peroxidase, provoking oxidative stress which is common in neuropsychiatric disorders.

Limitations

It is important to know that there are some limitations in our study. First of all, the findings are based on data from relatively heterogeneous studies as shown in Table 1, which may contribute to the fact that serum vitamin D concentrations may not be comparable between studies. The ADHD instrument/measure varied from study to study which might result in slightly different definitions of diagnosis of ADHD in each study. Furthermore, different assay techniques were used in the included studies and therefore could have resulted in variable findings. Also, our meta-analysis did not investigate the difference in vitamin D levels in specific populations (e.g., stratification with gender, age, BMI, socioeconomic status of the family). Although we performed a random-effects model, subgroup analysis, and meta-regression analysis, we failed to identify the factors leading to heterogeneity. Only the latitude gradient of the countries performing the studies was found to significantly influence our results. Lastly, our study included only case–control studies which are inferior in reliability compared to cohort studies. For all these reasons, our results should be interpreted cautiously.

Implications for future research and clinical practice

Current evidence suggests the potential interplay between vitamin D levels and ADHD. However, the causality and association between the two conditions remain unknown given the nature of studies published in the field (case–control studies cannot explain the underlying pathophysiology).

Given that adequate doses of vitamin D can partially reverse the brain damage and the fact that it has already

been used to improve cognition and memory in traumatic brain injury and ASD, there is discussion around whether young ADHD patients would benefit from vitamin D3 supplements (Lawrence and Sharma 2016). The value of vitamin D supplementation in ADHD has also been supported by a randomized double-blind placebo-controlled trial which reported the effect of vitamin D supplementation as adjunctive therapy to methylphenidate (Mohammadpour et al. 2018). After 8 weeks of adjunctive therapy, the study reported a decrease in evening symptoms of ADHD such as difficulty in completing homework, running excessively, inattentiveness in doing tasks, and getting ready for sleeping, according to WPREMB scale (Weekly Parent Ratings of Evening and Morning Behavior scale). To date, to the best of our knowledge, this is the only published study on the use of vitamin D alone; other interventions have included a combination of vitamin D and several other micronutrients which also showed a remission in many ADHD symptoms. Assessing the effect of vitamin D supplementation without methylphenidate (as monotherapy) on ADHD symptoms is strongly suggested for future research in this field in order to ascertain the therapeutic effects. Studies investigating the effectiveness of vitamin D supplementation in this patient group appear to be underway.[1]

Although we have clear evidence suggesting that vitamin D levels are lower in ADHD children and adolescents, the clinical meaning of our results has yet to be clarified—that means whether deficient or insufficient vitamin D levels can cause symptoms of hyperactivity/inattention and impulsivity. Furthermore, the actual prevalence of vitamin D deficiency in this particular population is still unknown as is the benefit of vitamin D supplementation for this group. To confirm this, large high-quality long-term clinical trials using the same assay techniques are requested. Furthermore, as already stated, cohort studies are required to investigate whether vitamin D-deficient infants are more likely to develop ADHD in the future or not. Given that vitamin D deficiency has been identified in pregnant women and infants across a number of populations, should a direct link be established, action to address this issue should be taken (Cashman et al. 2016; Dawodu and Nath 2011). Finally, a distinct definition of vitamin D deficiency as well as its prevalence in the general population needs to be assessed.

Compliance with ethical standards

Conflicts of interest None to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statement on the welfare of animals This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in all studies in our review.

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