Review

Vitamins B_9 and B_{12} in children with attention deficit hyperactivity disorder (ADHD)

A systematic review

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Abstract: *Background:* Attention deficit hyperactivity disorder (ADHD) is a common childhood neurodevelopmental disorder that begins before age 12. Given the role of B group vitamins in cell metabolism, synthesis of nucleotides, and neurotransmitters, the present study systematically investigated the plasma levels of vitamins B_9 and B_{12} in children with ADHD. *Methods:* We searched electronic databases including Web of Science, MEDLINE, EMBASE, Scopus, Iran MEDEX, Cochran database, and SID from conception to June 2023. Full-text case-control or cross-sectional studies were included in this study. Participants in the case group were children with ADHD aged 6–12 years. Review Manager Software (RevMan 5.4) was used for statistical analyses. Standardized mean differences (SMD) with 95% CIs were used to determine the differences between the two groups. *Results:* Six studies were included in the present meta-analysis. They included 982 children, of whom, 204 were girls and 744 were boys. The mean age of the children was 8.86±2.03 years. The level of vitamin B_9 was significantly different between children with and without ADHD [SMD −0.80, 95% CI (−1.55, −0.04)]. Vitamin B_{12} was significantly lower in children with ADHD [SMD −0.29, 95% CI (−0.42, −0.16)]. However, due to high heterogeneity (I^2=93%), sensitivity analysis was used, I^2 fell to 21%, and significant difference was observed between the two groups [SMD −0.19, 95% CI (−0.34, −0.04)]. *Conclusion:* The results of this systematic review showed that the level of vitamins B_9 and B_{12} in children with ADHD was significantly lower than that in healthy children.

Keywords: folate, folic acid, vitamin B_{12}, vitamin B_9, attention deficit hyperactivity disorder, systematic review

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common childhood neurodevelopmental disorder that begins before age 12. It has different clinical symptoms such as loss of attention, hyperactivity, and excessive impulsivity, which can affect the child's academic, social, and emotional life in many different ways. In addition to destructive behaviors, ADHD can reduce academic achievement [1, 2]. The worldwide prevalence of ADHD is between 8–12% [3], and its pooled prevalence in children and adolescents is 7.2% [4, 5, 6].

The cause of ADHD is complex and has not yet been completely understood, but findings support multifactorial hypotheses. Various neurochemical, neuroanatomical, genetic, and environmental factors have been reported to play a role in the development of this disorder [7, 8]. Also, it has been shown that there is a relationship between ADHD and poor eating patterns [9], with high consumption of sugar, fried foods, and salt being associated with difficulty in learning, lack of attention, and behavioral problems [10, 11, 12]. Also, dietary patterns rich in fiber, folate, and omega-3 fatty acids are inversely related to ADHD [13].

Vitamin B_{12} and folate (vitamin B_9) play an important role in the function, development, and differentiation of the central nervous system (CNS) [14]. Previous studies have reported the association of folate and vitamin B_{12} with various psychiatric diseases including cognitive disorders, neurological diseases, autism spectrum disorder, and schizophrenia [14, 15, 16, 17, 18, 19]. Also, psychiatric symptoms related to vitamin B_{12} and folate deficiency may include irritability, restlessness, negativity, disorientation, confusion, forgetfulness, concentration and attention problems, and insomnia [20].

B_{12} and folate participate in carbon transfer metabolism (i.e., methylation), which is involved in psychiatric responses. These vitamins also have a key role in the synthesis of catecholamine's, dopamine, serotonin, neurotransmitters, and other monoamines [21]. The basal ganglia, which play a pivotal role in ADHD, may be particularly vulnerable to vitamin B_{12} and folate deficiency [21]. Studies focusing on the relationship of ADHD with folate and associated metabolic pathways on the consequences of prenatal folate deficiency [22]. Also, methyl B_{12} is a critical cofactor in the regeneration of methionine from homocysteine, and a deficiency of methyl B_{12} can cause cytotoxic effects [23].

A previous study demonstrated that Methyl enetetrahydrofolate reductase polymorphism can cause ADHD [24]. Some studies have also found that vitamin B_{12} deficiency and low dietary folate levels are associated with ADHD [25, 26], which is not supported by other studies [4]. Some studies showed that vitamin B_{12} and folate deficiencies are associated with ADHD and that supplementation with these vitamins is effective in improving ADHD symptoms [26, 27]. Also, it was shown that maternal folate deficiency in early pregnancy may cause childhood ADHD [22]. In contrast, a previous study reported that in adult patients with ADHD, the folate level was high and vitamin B_{12} level was normal [28].

Given the importance of this topic and the conflicting results in the literature, we decided to investigate the relationship between the level of vitamins B_9 and B_{12} and development of ADHD in children.

Methods

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines of case-control and cross-sectional studies [29].

Search strategies

We searched electronic databases including Web of Science, MEDLINE, EMBASE, Scopus, Iran MEDEX, Cochran database and SID from conception to June 2023 in order to identify relevant articles according to PECO: [P]: Population "children ADHD"; [E]: Exposure "Vitamin B_9 and B_{12} insufficiency or deficiency", [C]: Comparison group "Healthy children", [O]: Outcome "ADHD".

Some of the search terms used were ("Vitamin B9" OR "Folate" OR "Folic Acid") AND ("ADHD" OR "attention deficit hyperactivity disorder" OR "mental disorder") AND ("child" OR "adolescent")., ("Vitamin B12" OR "Methylmalonic Acid") AND ("ADHD" OR "attention deficit hyperactivity disorder" OR "mental disorder") AND ("child" OR "adolescent").

Inclusion and exclusion criteria

Types of studies

Full-text case-control or cross-sectional studies were included in this study without time, language or place restrictions. Studies with irrelevant data in their titles or abstracts, duplicate studies, articles with minimal critical evaluation index, and those with no full text were excluded from this study.

Types of participants

The eligibility criteria in the case groups were: ADHD children aged 6–15 years. The control groups included age-matched otherwise healthy children.

Exposure

Studies were included in this study if they had assessed the relationship of vitamin B_{12} and B_9 plasma level deficiency with ADHD.

Outcome measures

Outcomes were as follows: A) vitamin B_9 level and ADHD, B) vitamin B_{12} level and ADHD.

Study selection and data extraction

Two authors (FR and AE) screened the title, abstract, and full text of all retrieved records, and then extracted the data separately. In case of any disagreement between these two authors, a third author (PA) helped to resolve the discrepancies. We developed a form in accordance with the data extraction form recommended by the Cochrane Pediatric Group. The following pieces of information were extracted by two authors (FR and AE): First author's name, year of publication, year of search, country of study, sample size, baseline characteristics, ADHD diagnostic tool, and the level of vitamin B_9 and B_{12} in the two independent groups.

Statistical analysis

Statistical analyses were done using Review Manager Software (RevMan 5.4). In order to analyze the data, standardized mean difference (SMD) with 95% confidence intervals (CIs) was used because of the different types of measurement units. The z-test was used to determine the significance level. Fixed effect method was used to show the effect size and CI. Heterogeneity was evaluated by the I-squared index (I^2 index). If the heterogeneity between the studies was statistically significant (I^2>50%), we used random effect method and sensitivity analysis to explore the potential source of heterogeneity [30]. Sensitivity analysis was performed by sequentially removing one

study at a time to test the robustness of uncertainty in the meta-analysis. The level of statistical significance was set at $p<0.05$.

Quality assessment of the included studies

The risk of bias of all selected articles was evaluated by two authors independently using Downs and Black checklist according to which risk of bias was classified as poor, fair, or good. Downs and Black checklist (1998) is used for observational studies such as case-control, cohort, and cross-sectional studies. The checklist contains 27 "yes" or "no" questions distributed in five subscales: 1. Assessment of reporting bias (10 questions), 2. External validity (three questions), 3. Internal validity (seven questions), 4. Confounding and selection bias (six questions), and 5. Power of the study (one question) [31]. Total scores lower than 14 represent poor quality, those between 15 and 19 indicate fair quality, and scores higher than 20 show good quality [32].

Results

Literature search

The PRISMA flowchart shows the searching process and how the studies were selected (Figure 1). Initially, 560 articles were obtained after searching the databases. After screening titles and abstracts, 554 articles were excluded because of irrelevant data (n=90), duplicated data (n=237), protocols (n=4), and lack of full text (n=2). Finally, 6 studies were included in this systematic review and meta-analysis.

Characteristics and quality assessment of the studies

The characteristics of the included studies are shown in Table 1. Six case-control studies [33, 34, 35, 36, 37] and one cross-sectional study [38] were included in this review. They were published between 2016 and 2021 in low- or middle-income countries. The studies included 982 children (495 in the experimental group and 477 in the control group), of whom, 204 were girls and 744 were boys. The mean age of children was 8.86±2.03 years.

Two reviewers (FR & AE) checked the quality of the included studies based on the Downs and Black checklist. As shown in Table 2, all studies had high quality and low risk of bias.

The relationship between ADHD and vitamin B_9

Six studies [33, 34, 35, 36, 37, 38] compared case and control groups in terms of their vitamin B_9 levels. Based on fixed effect analysis, there was a significant relationship between the level of vitamin B_9 and ADHD in children (P=0.04), and vitamin B_9 levels were lower in the ADHD group as compared to the control group [SMD −0.80, 95% CI (−1.55, −0.04)] (Figure 2).

Since we found a high level of heterogeneity (I^2= 96%), we used random effect and sensitivity analysis. After exclusion of four studies [34, 36, 37, 38], the heterogeneity reduced to 29%, and there was a significant relationship between vitamin B_9 level and ADHD in children, with the level of vitamin B_9 in children with ADHD being lower than that in the healthy group [SMD −0.33, 95% CI (−0.60, −0.06)] (Figure 3).

The relationship between ADHD and vitamin B_{12}

Six studies [33, 34, 35, 36, 37, 38] compared the case and control groups regarding their vitamin B_{12} levels. The analysis showed a statistically significant difference between the case and control groups as far as their level of vitamin B_{12} was concerned (P<0.0001). In other words, the level of this vitamin was significantly lower in the case group compared to the control group [SMD −0.29, 95% CI (−0.42, −0.16)] (Figure 4). Due to high heterogeneity (I^2= 93%), we used random effect model and sensitivity analysis. After exclusion of three studies [33, 34, 36], I^2 reduced to 21%, and a significant difference was observed between the two groups in terms of the level of vitamin B_{12} [SMD −0.19, 95% CI (−0.34, −0.04)] (Figure 5).

Discussion

This systematic review aimed to investigate the level of vitamin B_9 and B_{12} in children with ADHD. Six case-control and cross-sectional studies were included in this review. The studies had mostly been conducted in low- or middle-income countries. The levels of B_9 and B_{12} in the ADHD group were significantly lower than those in the healthy group.

The results showed that there was a significant relationship between B_9 level and ADHD. By this mean that the level of vitamin B_9 in children with ADHD was lower than that in the healthy group. Altun et al. [33] and Unal et al. [39] showed that folate levels are lower in children and adolescents with ADHD compared to healthy individuals. Kroll et al. reported that low folate levels were strongly associated with ADHD, regardless of the type of ADHD, age, and gender [40]. Chen et al.'s systematic review reported an inverse relationship between prenatal folic-acid supplementation and the risk of ADHD in the offspring [41]. Also, maternal folate deficiency during pregnancy has been associated with childhood hyperactivity [22]. Studies on the fetal period have also shown that developmental delay, cognitive impairment, and decreased memory

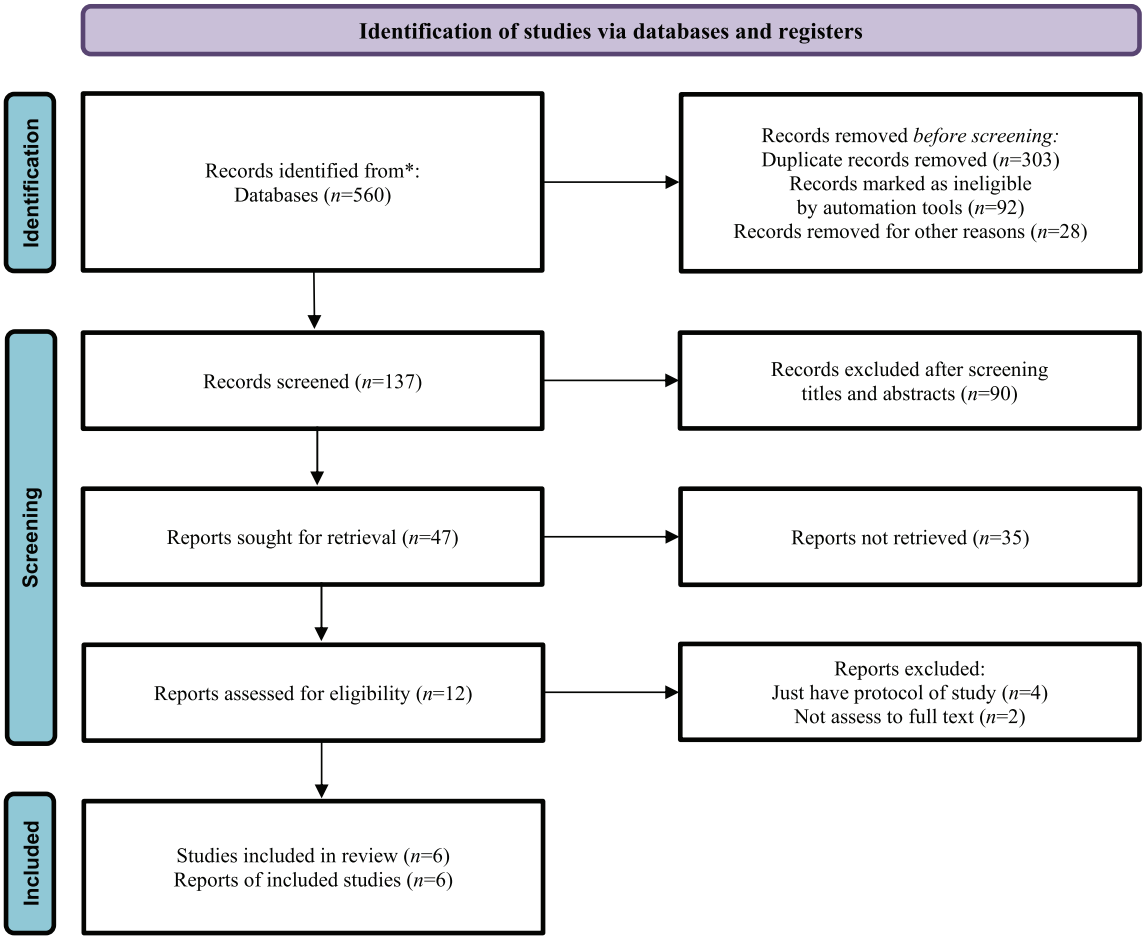

Figure 1. PRISMA flow diagram of selection of study process.

Table 1. Evaluation of quality of included studies

Row	First author	Clarity	External validity	Internal validity	Confounding	Power	Total score
1	Bala et al. [37]	10	2	3	3	1	19
2	Altun et al. [33]	9	3	4	3	1	20
3	Wang et al. [35]	10	2	4	4	1	21
4	Öztürk et al. [38]	9	2	3	3	1	18
5	Yektaş et al. [34]	10	4	3	4	1	22
6	Topal et al. [36]	10	3	4	3	1	21

Notes: 1. Assessment of reporting bias (10 questions), 2. External validity (three questions), 3. Internal validity (seven questions), 4. Confounding and selection bias (six questions), and 5. Power of the study (one question). A total score of less than 14 represents poor quality, those between 15 and 19 indicate fair quality, and scores higher than 20 show good quality.

function are associated with brain folate deficiency due to abnormal transfer of folate to the fetal CNS [42, 43]. However, Surman et al. did not find a relationship between L-Methylfolate supplementation in ADHD patients and improvement of psychopathology scale scores in adults [44]. Prades et al. in their systematic review showed that the level of folate in ADHD is higher than that in the healthy control group [45]. However, according to one study, higher folate levels in ADHD patients could be attributed to two reasons, namely the complex and little-understood pathophysiology of ADHD, and the multi-factorial nature of this disorder [28]. Folate is involved in important biochemical activities such as production of purine, pyrimidine, and methionine amino acids and the metabolism of homocysteine [46]. In a study investigating the role of the homocysteine folate metabolic pathway in the etiology of ADHD, the

Table 2. Characteristics of included studies

Author (reference)	Year	Study type	Population	Age (y) (min–max)	Outcome measures	Results	
						B_9*	B_{12}*
Bala et al. [37]	2016	Case-control	77 children	2–14	DSM-IV, DSM-V	(10.16±2.93, vs. 8.52±3.75) (ng/ml)	(371.72±160.63, vs. 424.04±167.94) (pg/ml)
Altun et al. [33]	2018	Case-control	60 children	6–15	DSM-V	(158.90±20.22, vs. 169.13±16.98) (pg/ml)	(259.75±44.40, vs. 388.64±73.11) (pg/ml)
Wang et al. [35]	2019	Case-control	432 children	8–10	DSM-IV	(15.3±6.3, vs. 19.6±13.6) (nmol/l)	(423.5±150, vs. 462.6±151) (pmol/l)
Öztürk et al. [38]	2019	Cross-sectional	410 children	9–11	DSM-IV	(8.54±2.46, vs. 8.64±2.56) (ng/ml)	(327.84±159.61, vs. 328.28±126.97) (pg/ml)
Yektaş et al. [34]	2019	Case-control	118 children	5–11	DSM-IV	(1129±701, vs. 1139±155) (ng/ml)	(929±774, vs. 1611±357) (pg/ml)
Topal et al. [36]	2021	Case-control	203 children	2–17	DSM-IV	(11.07±3.29, vs. 11.06±4.62) (ug/l)	(239.79±86.43, vs. 210.20±81.17) (ng/l)

Note: *(Intervention vs. Control).

results showed that gene variants of the homocysteine folate pathway can be a cause for ADHD through vitamin B_{12} deficiency and mild hyper-homocysteinemia [46]. Also, folate affects the proliferation of neural stem cells, reduces changes and apoptosis, and alters DNA biosynthesis. Thus, it is an essential substance in tissues where DNA synthesis and degradation are rapid. This includes developing embryos, gastrointestinal mucosa, and hematopoietic tissues [43, 47, 48]. Furthermore, the efficient functioning of the folate cycle is necessary for the synthesis and regeneration of tetrahydrobiopterin (an essential cofactor for enzymes that convert amino acids to monoamine neurotransmitters including serotonin, melatonin, dopamine, epinephrine, and nitric oxide) [49]. All these factors can deteriorate CNS access to folate and play a role in ADHD.

In our study, B_{12} levels in ADHD children were statistically less than those in the control group. A study showed that Turkish children with ADHD had significantly lower vitamin B_{12} levels, and these levels were negatively correlated with teacher-reported psychosomatic symptoms and learning difficulties [39]. Strand et al. also reported that vitamin B_{12} levels in North Indian children were associated with lower scores on the Mental Development Scale [50]. This finding was also confirmed in other studies [33, 37]. By contrast, Karababa et al reported normal vitamin B_{12} levels in adult ADHD patients [28]. Other review studies showed that the level of vitamin B_{12} in children and adolescents with ADHD is lower than that in the healthy control group [45, 51]. Vitamin B_{12} plays a role in brain development, nerve myelination, and cognitive impairments such as mood and dementia disorders [52]. Vitamin B_{12} deficiency in pregnancy and childhood is associated with mental disorders, especially cognitive impairments [52]. Hence, vitamin B_{12} plays a critical role in dopamine-stimulated phospholipid methylation (PLM) by affecting the D4 receptor in the CNS, and this can be linked to ADHD [53]. PLM activity, which differs from D4 gene variants, is involved in neuronal attention and coordination that is impaired in children with ADHD [54]. Also, vitamin B_{12} and folate deficiency may play a role in the pathogenesis of ADHD by reducing methionine synthesis [54].

Folate and vitamin B_{12} are responsible for the acquisition of methyl groups essential for DNA and protein synthesis. Also, they act as a cofactor in the one-carbon metabolism that consists of folate and methionine-homocysteine cycles. One-carbon metabolism contributes to various activities including phospholipid synthesis, protein function, neurotransmitter synthesis, and regulation of DNA/RNA synthesis and metabolism [55, 56, 57]. It also affects epigenetic changes that cause long-term transformations in the brain, learning, cognition, and behavior [58]. These include psychiatric diseases such as schizophrenia, bipolar disorder, autism spectrum disorder (ASD), and depression [59].

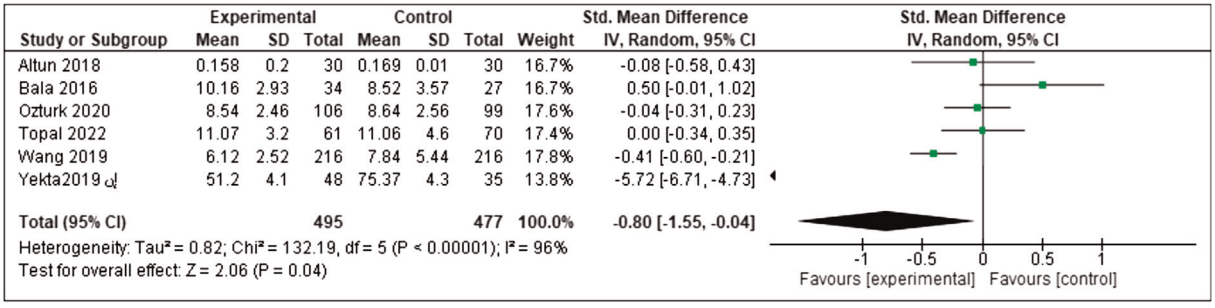

Figure 2. Forest plot of comparison of the level of B_9 in the ADHD children.

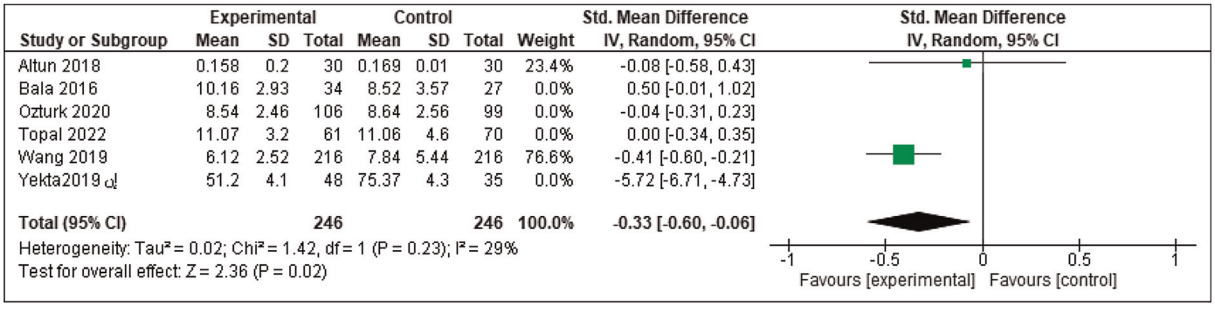

Figure 3. Forest plot of sensitivity analysis of the level of B_9 in the ADHD children.

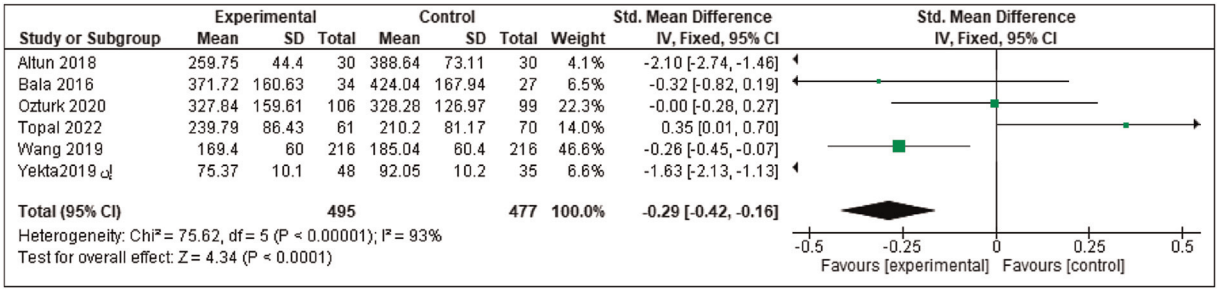

Figure 4. Forest plot of comparison of the level of B_{12} in the ADHD children.

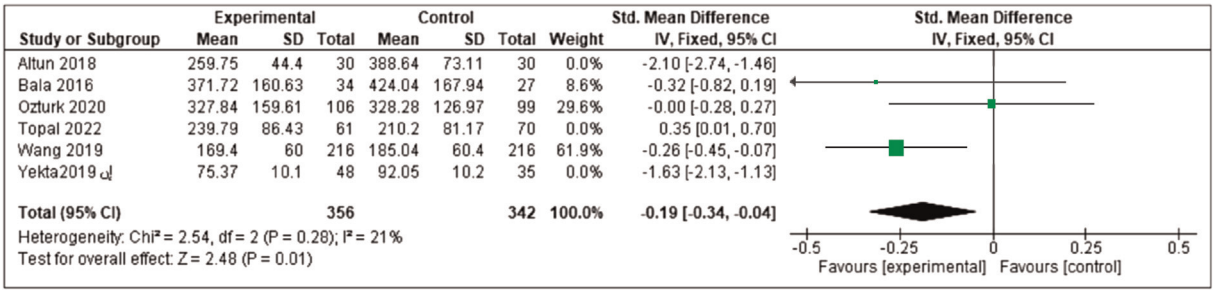

Figure 5. Forest plot of sensitivity analysis of the level of B_{12} in the ADHD children.

Deficiency in B_{12} and B_9 probably contributes to ADHD by impairing the one-carbon metabolism. Furthermore, a study found a relationship between diet-biochemical profile and ADHD [35]. ADHD children prefer non-nutrient foods to nutritious foods. This food pattern matches their food preferences [35]. Previous studies have shown that higher consumption of sugar, fried foods, and salt is positively associated with ADHD, but a balanced diet is inversely related to it [11, 13]. It is difficult to conclude whether children who eat non-nutritious food are more prone to ADHD. Another tentative conclusion would be since these children are impulsive and impatient, they seek quick satisfaction and eat low-density and pleasant food [9]. A nutrient-poor diet leads to unfavorable nutritional blood biochemistry that contributes to the development of ADHD. Lower intake of vegetables/fruits and protein-rich foods and higher consumption of nutrient-poor foods are related to inadequacy of folate and B_{12} (vitamin B factor). Additionally, increased consumption of vegetables/fruits, meat foods, and eggs contributed to better iron status and lower blood phosphate concentrations, while nutrient-poor foods had the opposite effect. Deficiencies and excesses in foods with low nutrient density may compromise children's vitamin and mineral status and are more associated with ADHD characteristics [35].

Limitations of the study

Despite its merits, this study has one major limitation. The unit of measurement of vitamin was different in the studies, and it was necessary to harmonize the unit of measurement. Also, inference of causality from such type of studies is not possible, and further interventional studies are needed to confirm these results.

Conclusion

The results of this systematic review showed that the level of vitamins B_9 and B_{12} in children with ADHD was significantly lower than that in healthy children. Deficiency of vitamin B_{12} and folate should be taken into serious consideration when it comes to ADHD patients since it is one of the medical conditions that can be prevented and treated with careful and informed medical decisions. Therefore, investigating the deficiency of folate and vitamin B_{12} in patients with ADHD can be useful in the process of their diagnosis and treatment. Because this systematic review based on observational studies, further interventional studies are needed to confirm these results.

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FR and PA were responsible for the design. FR was responsible of search. FR, AE, NGh and ShF were involving in data screening and data extraction. FR and PA were responsible in writing of the manuscript. All authors read and approve the final version of the manuscript.

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