Water-soluble vitamin insufficiency, deficiency and supplementation in children and adolescents with a psychiatric disorder: a systematic review and meta-analysis

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I.Baeza had the idea to do this review. She and N.Prades performed the literature search. They and I.Flamarique and E.Varela wrote the draft. All of the authors critically revised the work, read and approved the final manuscript.

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Código de campo cambiado

ABSTRACT

Nutrition is fundamental for brain development, but relatively little is known about water-soluble vitamin (WSV) levels and the effect of supplementation on psychiatry symptoms in children and adolescents (CAD) with psychiatric disorders. Our team systematically reviewed all studies concerning WSV abnormalities or supplementation in CAD with any psychiatric disorder. We searched for original studies published between 1990 and 15/05/2020 which were not based on retrospective chart review and which included WSV blood level measurements or investigated the effect of WSV supplementation on psychiatric symptoms in psychiatric patients aged 18 or under. Forty-two articles were included, 69% of which (N=29) examined Autism Spectrum Disorders (ASD), with most of these assessing folate or vitamin B_{12} supplementation (N=22, 75.9% of ASD studies). Meta-analyses showed significantly lower vitamin B_{12} levels in ASD and ADHD patients vs. healthy controls (HC), while folate levels were higher in ADHD patients vs. HC. Most of the studies (9/10, 90%) showed a decrease in symptoms as measured by clinical scales after supplementation. There was significant heterogeneity between the studies, however many found different types of vitamin abnormalities in CAD with psychiatric disorders.

Keywords: vitamin, nutrition, children and adolescents, psychiatric disorders, psychopathology, supplementation

Introduction

Nutrition is an essential factor for normal brain development, with both micronutrients and macronutrients playing an important role[1,2]. During intrauterine life, and above all from weeks 24 to 40 of gestation, or up until delivery, the developing brain is particularly vulnerable to nutritional alterations because of the immediate impact on several neurologic processes, including synapse formation and myelination[1]. The brain's vulnerability to nutritional insults likely overcomes its plasticity, which may help explain why early nutritional insufficiencies result in brain dysfunction not only while there is a deficiency, but also after repletion[1,2]. All nutrients are important for neuronal cell growth and development, but some appear to have greater effects during the late fetal and early neonatal periods; these include vitamin A, folate and vitamin B_{12}[3]. Although the groundwork for brain development begins just a few weeks after conception and continues through the first years of life, nutrition during middle and late childhood could have a large impact on myelination, and exposure to multiple forms of adversity may affect the development of different cognitive functions[4,5]. Moreover, the biggest shift in both grey and white matter volumes in the brain occurs during the transition to puberty[6]. Thus, well after infancy, numerous environmental factors related to nutrition may still impact brain development during periods of early and middle childhood and adolescence[7,8].

Vitamins are organic compounds that must be supplied to humans through our diet, since we are unable to synthesize them in adequate amounts. Vitamins are classified as water-soluble (B and C) and fat-soluble (A, D, E and K). Most of the nine water-soluble vitamins (WSV) act as coenzymes in metabolic processes while only one (vitamin K) of the four fat-soluble vitamins (FSV) has a coenzyme role[9]. FSV are absorbed and stored within the liver and adipose tissue[9], while WSV generally remain in the body for less time, with vitamin B_{12} being the exception. Specifically, hepatic stores of folic acid are typically sufficient for 3-4 months of normal

physiological needs[10] while B_{12} stores are sufficient for about 3 years[11]. To prevent a variety of medical illnesses caused by vitamin deficiencies, the United States (U.S.) Department of Health and Human Services and the European Food Safety Authority (EFSA) have issued specific recommendations for daily vitamin intake in different periods of life[12,13].

Focusing on WSV, B vitamins play a key role in cellular metabolism, including processes such as transmethylation and oxidation/reduction reactions[14]. Low blood levels of certain B vitamins are a moderately consistent finding in adult patients with schizophrenia versus healthy controls (HC)[15], following the one-carbon cycle hypothesis of schizophrenia[16]. Methyl B_{12} is a vital cofactor for the regeneration of methionine from homocysteine, and methyl B_{12} deficiencies can produce cytotoxic effects[17].

Vitamin C plays an important role as an antioxidant in the central nervous system, but it is also crucial for neurotransmission and neuronal maturation and functioning[18]. Some studies have shown lower vitamin C levels in adults with depressive disorder or generalized anxiety disorder vs. HC[19,20]. Moreover, one study associated vitamin C deficiency with depression and cognitive impairment in adults[21].

Most of the studies examining psychiatric disorders and WSV levels or supplementation have been conducted in adults and have looked at only a scarce number of illnesses, mainly psychotic (for a review in schizophrenia, see[15,22]), and depressive disorders (for a review[23]). In recent years, however, an increasing amount of research has been published about vitamin insufficiencies or deficiencies in the psychiatric child and adolescent population. Thus, the objective of this paper is to systematically review all articles published from 1990 up to 15 May 2020 measuring blood levels of any WSV and/or WSV supplementation treatment in children and adolescents (CAD) with any psychiatric disorder or symptom to address the following questions: 1) Is there any difference in blood WSV levels in CAD with any psychiatric disorder or symptom. vs. HC?; 2) Do CAD with a psychiatric disorder or symptom have more WSV deficiency/insufficiency than the general population (reference WSV levels)?; and 3) Is there any change in symptoms after any WSV supplementation treatment in CAD with any psychiatric disorder or symptom?

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Methods

Literature search

To perform this systematic review, we followed the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines[24]. The systematic review protocol was registered in the International Prospective Register of Systematic Reviews PROSPERO with the number: PROSPERO 2020 CRD42020184366. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020184366 A systematic literature search was carried out in MEDLINE/PubMed/Web of Science databases from 1990 to 15/05/2020, using the following terms: (water-soluble vitamin OR thiamine OR riboflavin OR niacin OR pantothenic acid OR pyridoxine OR folic acid OR folate OR cobalamin Or biotin OR ascorbic acid) AND (psychiatric disorder OR autism OR schizophrenia OR psychosis OR depression OR depressive disorder OR bipolar disorder OR affective disorder OR substance use disorder OR eating disorder OR obsessive-compulsive disorder OR ADHD OR anxiety disorder) AND (child OR adolescent).

Inclusion criteria

The inclusion criteria for selecting the articles were the following: 1) original articles with any WSV blood level measurements or WSV supplementation in patients with any psychiatric disorder or symptom; 2) studies not based on retrospective chart review; 3) mean age of samples ≤ 18 years and 4) written in English.

Exclusion criteria

Studies supplementing with a mixture of multivitamin compounds or other nutrients, apart from any WSV.

Although eating disorders were not excluded a priori from the systematic review, we decided to exclude these disorders a posteriori to avoid possible misinterpretation of the results obtained.

Data systematization

The electronic search was conducted in three steps, in which two researchers (IB and NP) first performed the electronic search. Secondly, both manually reviewed all of the references from the

selected articles using a web platform (www.rayyan.qcri.org) to help classify the studies, and other articles were found from the citations of the selected articles.

The same two authors, NP and IP, extracted the following data from the studies: bibliographic reference, place where the study was mainly conducted, year of publication, type of study, description of the sample (number, sex, age, diagnoses), type of patient (outpatient/inpatient), psychopharmacological treatment and vitamin supplementation, vitamin intervention (if there was one), psychiatric assessment (questionnaires, interviews), vitamin levels assessment and results of the study. The information was verified by both authors, and discrepancies were resolved by agreement between them. The quality of assessment of every study was evaluated with the Newcastle-Ottawa scale for case-control or cohort studies[25] with study-specific criteria, while the *Evidence Project* risk of bias tool[26] was used for intervention studies (Supplemental tables 1, 2 and 3). Finally, NP, IB, IF and EV extracted other relevant data from the selected articles.

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Data analysis

We conducted a meta-analysis when the studies reviewed met the following criteria: five or more studies measured the same vitamin level in a sample with the same psychiatric disorder, a healthy comparison group was included, and results of mean and standard deviation (SD) were published. As a result, only meta-analyses for studies of Autism Spectrum Disorder (ASD) and Attention Deficit and Hyperactivity Disorder (ADHD) patients for folate and vitamin B_{12} levels were performed. Two studies were excluded from the ASD meta-analyses because they either did not show mean and SD vitamin levels[27,28,29] or they had results with a magnitude far different from the others even though they used the same units (Altun et al, 2018 for folate levels[30]; Yektas et al, 2019 for folate and vitamin B_{12} levels[31]). A random-effects model was used to compute the overall mean differences and their confidence interval, taking into account the between-study variability. Statistical heterogeneity among the studies was evaluated using the Cochran's Q test. Risk of bias was assessed with funnel plots, and Egger's tests were used to assess the asymmetry of the funnel

plots. Statistical analyses were carried out using R statistics version 3.6.3 (http://www.r-project.org) and library metafor for v.24-0. p value <0.05 was considered statistically significant.

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Vitamin insufficiency and deficiency levels

Regarding folate, it should be noted that even though folate and folic acid are not the same, the latter being the synthetic form of natural folate[32], it seems that these terms are used indiscriminately in certain articles, and in the authors' explanations of their range levels. We will use the term "folate" throughout the article.

For folate, measured in ng/mL and converted into these units for all of the data reviewed, deficiency has been defined as blood levels lower than 3.0 ng/mL, with insufficiency indicating levels between 3–4.9 ng/mL, and sufficiency corresponding to 5 ng/mL or higher[33,34]. This was the approach followed by Ali et al, 2011 and El Farsi et al (2013)[35,36]. It is also very similar to the definition of sufficient folate used by Sun et al (2016) (2.3-17.5 ng/mL)[37] and other authors (3.1-17.5 ng/mL[38], 3.1–20.5 ng/mL[27,39,31], 4.6–18.7 ng/mL[40] and 6.6-25.2 ng/mL[41]). Some articles measuring this vitamin did not explain what thresholds they were using to define insufficiency[28-31,42-52].

Regarding Vitamin B_{12}, measured in pg/mL and converted to those units for all the studies reviewed, deficiency has been defined as blood levels <187 pg/mL[38], which was followed by Guo et al (2018)[27], while sufficiency has been defined in widely different ways in other studies: 154.5-1074.8 pg/mL[41], 189.6-885.6 pg/mL[37],<200 pg/mL[53], 203.3-881 pg/mL[54], ≥250 pg/mL[42], 250-1250 pg/mL[35,36]. One study separately examined two different levels of B_{12} deficiency: < 200 pg/mL and <300 pg/mL[55]. The other articles measuring vitamin B_{12} levels, did not specify the range which they considered to be normal levels[28-31, 44-46, 48-52, 56,57]. Adams et al (2011a) analyzed both of the vitamins mentioned (folic acid and B_{12}), establishing reference ranges calculated based on the 10th and 90th percentiles of the distribution in neurotypical children[58]. Since very few studies have measured other WSV, we have not included the different definitions of sufficient levels for these vitamins.

A list of the water-soluble vitamins and their biomarkers used to measure their levels in the studies reviewed is shown in Table 1.

Table 1 around here

Psychiatric disorders

We classified the psychiatric disorders into 6 main diagnostic criteria groups to facilitate this review. When a study compared patients with two different disorders, it was grouped according to the disorder that was the most frequent among its sample. The results of the classification were as follows: ASD (N=29), including one study which compared ASD and schizophrenia patients to HC; ADHD (N=7), with three studies comparing ASD and ADHD to HC, and other disorders (N=4). There were also two studies that were conducted on the general population. To facilitate analysis, we divided the studies into groups, separating descriptive studies from those involving intervention.

Results

Of 1,882 articles initially found, 106 potential articles were reviewed and, among them, 42 met the inclusion criteria and were reviewed in depth. Figure 1 shows the steps in the process of selecting the articles and the reasons for exclusion.

Fig. 1 Flow chart of the article screening process

Figure 1 around here

Autism spectrum disorders

Of the 29 studies included, all are focused on outpatients except for Dolske et al (1993)[59], which included residential school children. Twenty studies (69% of the ASD studies reviewed) are descriptive and each of them recruited ASD patients and matched them with HC[27-30,35,36,38,40,42,47,52,54,58,60-64] while Melnyk et al (2012) also included a sample of unaffected siblings[45]. Two interventional studies included a HC group[37, 65]. All studies enrolled males and females.

Regarding the countries where these studies were carried out, eleven studies (37.9%) were conducted in the USA[17,45,47,58-60,65-69], 5 in China (17.2%)[227,37,38,52,64], 2 (6.9%) in Oman[35,36],

Romania[42,56], and Turkey[30,40] and one (3.4%) in each of the following places: Australia[29], Egypt[28], Norway[54], Saudi Arabia[61], Slovakia[63], and United Kingdom[62]. Most of the studies came from groups that have only published a single article on the subject, the exceptions being the Arkansas Children's Hospital Research Institute, Arkansas University Medical Sciences in Little Rock, USA, which has contributed 4 articles[66, 67, 69, 70]; the Department of Children Health and Hygiene, School of Public Health, Harbin Medical University, China with three studies[37,52,64]; and each of the following groups which have published two articles each: the Chongqing Medical University, China[28, 31]; the Department of Child Health at Sultan Qaboos University Hospital, Oman[27, 38]; the Iuliu Haţieganu University of Medicine and Pharmacy, Romania[42,56]; the Autism/Asperger's Research Program at the Arizona State University, Tempe, USA[58, 60]; and the Department of Psychiatry and Behavioural Sciences and the M.I.N.D. Institute at the University of California, Davis Medical Center, Sacramento, USA[17, 68].

Descriptive studies (N=20, Table 2). Eighteen articles (90%) examined vitamin B levels in relation to ASD, with some studies measuring only one vitamin: B_1[62], B_6[60], folate[47] or vitamin B_{12} levels[56]. Twelve studies measured a combination of different B vitamins[27-30,35,36,38,42,45,52,54,64] while two studies examined B vitamins together with FSV[40, 58].

Table 2 around here

Some studies examining both folate and vitamin B_{12} levels found lower levels in ASD compared to HC[28, 30,35,36,52,64]. Studies measuring only vitamin B_{12}[54] or only folate[27] also found significant differences between the samples. However, some studies found no differences between ASD and HC in folate [40,45,47,58] and vitamin B_{12} levels[29,42,58], while one study found no differences between patients and unaffected siblings[45].

Regarding deficiencies, a rate of 0.4% for folate or vitamin B_{12} deficiency has been described in ASD patients vs. none in HC[27], while vitamin B_{12} deficiency in these patients has been found to be as high as 16.7% [53]. Liu et al (2016)[56] found no deficiencies of these vitamins in ASD patients, but neither they nor Pasca et al (2006) compared these groups' levels to the HC sample[38, 56].

A meta-analysis was performed according to the criteria described previously, taking into account that in the study by Paşca et al (2009)[42] only patients with Autism disorder were included, and in the article by Hope et al (2020)[54], only the data for adolescents were used because there was no HC group for children. The results of the meta-analysis indicate that there was no significant overall difference in folate levels between patients and HC: 0.05 ng/mL (95%CI:-1.28, 1.38). In contrast, vitamin B_{12} levels did show a significant overall difference between the groups: -100.38 pg/mL (95%CI:-158.52, -42.24)(Figure 2 and 3, respectively). Begg's funnel plots were drawn for both meta-analyses and showed no asymmetry. Egger's tests were also performed, and no significant asymmetry was found (Supplemental figures 1 and 2).

Fig. 2 Forest plot of descriptive studies measuring plasma/serum folate levels between children and adolescents with autism spectrum disorders and healthy controls

Fig. 3 Forest plot of descriptive studies measuring plasma/serum vitamin B_{12} levels between children and adolescents with autism spectrum disorders and healthy controls

Figure 2 and 3 around here

Regarding other B vitamins, one study found vitamin B_8 to be 20% lower in ASD vs. HC[58]. This study analyzed other B vitamins apart from folate and vitamin B_{12} (B_1, B_2, B_3, B_5 and B_6) and reported only possibly significant lower mean levels in vitamin B_5 in ASD patients compared to HC, after multiple-comparison corrections. However, Anwar et al (2016) studying vitamin B_1 observed that thiamine pyrophosphate was lower in the ASD group compared to HC, while thiamine and thiamine monophosphate were not[62]. Mean vitamin B_2 or riboflavin levels have been found to be higher in ASD patients and their siblings vs. HC, but this difference disappeared after adjustment for multiple comparisons[29]. Looking at vitamin B_6, its inactive form, but not its active form, was found to be higher in ASD patients than in HC[60], although other authors measuring this vitamin have described lower levels in ASD subjects compared to HC[30], or no differences between groups[45].

As for vitamin C, three articles measured levels of this vitamin[58, 61, 63] and mixed results were reported. While one study found that vitamin C levels were not significantly lower in ASD

patients vs. HC[61], Krajcovicova-Kudlackova et al (2009) described higher vitamin C levels in CAD with ASD than in HC, though both groups were above the cutoff point for a free radical disease (>50 µmol/l)[63]. Slightly higher vitamin C levels in ASD children vs. HC have also been reported[58],with 29% of the patients having levels above the reference range. Nevertheless, these findings are tempered by the fact that 13% of the same group of patients presented levels below the reference range[58].

Intervention studies (N=9, Table 3 and 4). We found 5 randomized control trials (RCT), each one assessing the effect of a different vitamin (folate, B_{12}, B_6 and C) (Table 3)[17, 59, 68, 69, 71]. There were also 4 non-RCT open-label trials supplementing with folic acid, B_{12}, a combination of both or B_1 [25, 63-64] (Table 4).

In ASD patients, supplementing with folinic acid, a reduced form of folate, for 12 weeks, was linked to improved verbal communication compared to patients receiving placebo. [69]. In an open-label trial, ASD patients treated with folic acid for 3 months showed an increase in folate levels after the treatment and improvement in some symptoms of autism compared to ASD patients who were not supplemented[37].

Regarding vitamin B_{12}, treatment with methyl B_{12} (every three days for 8 weeks) has been linked to clinical improvement in ASD patients compared to patients treated with placebo, although this was not reported by parents[68]. In a double-blind, placebo-controlled cross-over study, patients were either given placebo for 6 weeks, followed by 6 weeks of methyl B_{12} administered once every 3 days or methyl B_{12} followed by placebo. After the 12 weeks, no overall differences were found between active and placebo groups, even though 30% of patients were considered responders [17].

In two open-label trials which also used methyl B_{12} together with oral doses of folinic acid for 3 months, the same research team described an improvement both in some of the symptoms [66, 67] and in glutathione redox status in ASD patients[66] (Table 4).

A RCT supplementing with pyridoxine orally for 4 weeks at different doses vs. placebo, also looked at B vitamin levels. This study found that ASD patients in the active group showed a significant increase in verbal Intelligence Quotient (IQ) compared to those in the placebo group[71].

Finally, we also found an open label trial using thiamine tetrahydrofurfuryl disulfide, a derivative of vitamin B_1. Eighty percent of ASD patients improved clinically with this supplementation, and this included patients with no B_1 deficit[65] (Table 4).

Table 3 also describes the only RCT study found examining vitamin C supplementation in the CAD psychiatric population. Ascorbic acid or placebo was given for 30 weeks to ASD patients following this pattern: the first 10 weeks all patients received ascorbic acid, after that they were randomized to the active treatment or placebo, and after 10 more weeks, there was a cross-over of treatments. A significant decrease in symptom severity was described in patients when they were on ascorbic acid[59].

Table 3 around here

ADHD

We found only descriptive articles looking at ADHD patients. Seven studies examined vitamins in CAD with ADHD, and three of these also included a sample of ASD patients[31, 56, 57] (Table 2). Some studies found significantly lower folate, vitamin B_6 and vitamin B_{12} levels in ADHD patients vs. HC[46, 51], while others only found significant differences in mean vitamin B_{12} levels[31, 50]. With no comparison group, one study reported vitamin B12 deficiency in 21% of ADHD patients[53].

Comparing subjects with ADHD, ASD and HC, the lowest mean vitamin B_{12} levels were found in ASD patients, followed by ADHD subjects[31,56,57]. Both patient groups had significantly lower B12 levels than HC. In contrast, mean folate levels were not found to differ between these three groups in any of the reviewed studies[31,56,57].

A meta-analysis was performed with the same 5 studies for folate and vitamin B12 levels in ADHD patients vs. HC. For folate levels, a significant overall mean difference between ADHD patients and HC of 0.23 ng/mL (95%CI: 0.17, 0.29) was found (Figure 4).

Figure 5 shows the results of the meta-analysis for vitamin B_{12} levels, which reveal a significant overall difference of -199.14 pg/mL (95%CI: -212.00, -186.28). Begg's funnel plots were drawn for both meta-analyses and showed no asymmetry. Egger's tests were also performed, and no significant asymmetry was found (Supplemental figures 3 and 4).

Fig. 4 Forest plot of descriptive studies measuring plasma/serum folate levels between children and adolescents with attention deficit and hyperactivity disorder and healthy controls

Fig. 5 Forest plot of descriptive studies measuring plasma/serum vitamin B_{12} levels between children and adolescents with attention deficit and hyperactivity disorder and healthy controls

Figure 4 and 5 around here

Regarding possible links between cognition and vitamin levels in ADHD patients, Altun et al (2018b)[46] described a positive correlation between all Weschler Intelligence Scale for Children-Revised (WISC-R) scores and vitamin B_{12} levels. Apart from that, a negative correlation was observed between the psychosomatic subscales of the Conners Parent Rating Scale and vitamin B_{12} levels[5]. In ADHD patients, vitamin B_{12} levels explained 13% of the variance in hyperactivity/impulsivity and oppositionality scores of the DSM-IV scale[31].

Other disorders

Table 2 shows two articles examining outpatients with depressive disorders[39,43], one comparing patients with schizophrenia vs affective disorders [48,] and another looking at patients with obsessive-compulsive disorder (OCD)[44].

Comparing patients with major depressive disorder vs. HC, deficient levels of folate or B_{12} were found in 11.2% and 30.3%, respectively, of patients, , while neither deficiency was found in HC[39]. However, no folate or vitamin B_{12} insufficiency in patients with schizophrenia, affective disorders

or HC were observed by Kevere et al (2014). Regarding mean values, one study described lower folate levels in patients with a major depressive disorder vs. HC[36], though this was not found by the other study reviewed[39].

Table 4 around here

Finally, lower levels of vitamin B_{12} were described in OCD patients compared to HC, while there was no difference between groups regarding folate[44].

Population-based sample

Two studies of the general population from Turkey and Colombia, both longitudinal, were included[49,55] (Table 2).

In the Turkish study, with patients who attended a pediatric outpatient clinic, folate deficiency was found in 2.1% of subjects, while vitamin B_{12} deficiency was set at two different levels. The authors found that 31.7% of subjects had vitamin B_{12} levels <200 pg/mL and that 57.6% had levels < 300 pg/mL. Complaints of anxiety and depression were reported in almost 60% and 44% respectively of patients with vitamin B_{12} deficiency <200 pg/mL, apart from other non-psychiatric symptoms. Fifty-five percent of the sample with vitamin B_{12} levels <200 pg/mL were treated with parenteral or oral vitamin B_{12}. Thirty-four percent of these patients were followed up one month later and all had levels >300 g/mL and their complaints had been resolved[55] (Table 4).

The Colombian study reported that boys with low vitamin B_{12} levels (lowest quartile) at around 8 years had 2.7 times more externalizing behaviour problems and 2.3 times more aggressive

behaviour during adolescence than those within the normal range, while folate levels were not associated with any symptom during the follow-up[49].

Discussion

This is, to our knowledge, the first systematic review with meta-analyses concerning possible WSV deficiencies or insufficiencies in CAD with any psychiatric disorder or symptom and the effects of WSV supplementation on psychiatric symptoms.

We found considerable heterogeneity among the 42 studies reviewed, not only in terms of the type of disorders and the methods used to measure psychopathology, but also in the WSV levels measured and the cut-off levels used to define insufficiency or deficiency. ASD was the most frequently studied disorder, and folate and B_{12} the most frequently analyzed WSV. Meta-analysis revealed that vitamin B_{12} levels were significantly lower in ASD patients and ADHD patients than in HC. No such difference was found in folate levels, except in ADHD, where meta-analysis revealed higher levels in patients than in HC.

Autism spectrum disorders

While ASD is a neurodevelopmental disorder with a wide range of neurological and behavioural symptoms of varying severity, its relationship with diet and nutrition needs to be highlighted. Most studies have shown that both preschoolers as well as older children with ASD have selective eating habits and their dietary intake is often below the recommended daily amounts[72-74]. Low vitamin levels could be the result of such behaviour among ASD patients, however it is also possible that vitamin insufficiency/deficiency is itself linked to the development of the disorder.

In terms of B vitamins, lower levels of folic acid and vitamin B_{12} in ASD patients vs. HC have been the most replicated finding[27, 28, 30, 35, 36, 52, 54, 64], but meta-analyses revealed that only vitamin B_{12} levels were significantly different between the samples. Although neurological symptoms have been described in both children with vitamin B_{12} deficit (hypotonia, neurodevelopmental retardation, seizures, tremor[75]) and in adults (peripheral neuropathies, motor disturbances, visual disturbances and cognitive impairments[76]), none were reported in the reviewed articles.

The possible role of vitamin B_{12} in ASD has been also studied in postmortem frontal cortex, and lower levels of methylcobalamin and adenosylcobalamin have been found in ASD patients (4-9 years) compared to age-matched controls[77].

Regarding supplementation, two RCT studies treating ASD patients with methyl B_{12} found that some children demonstrated improvement on the CGI scale[17, 68]. Moreover, two open-label trials with a combination of methyl B_{12} and folinic acid found an improvement in some ASD symptoms such as intellectual and developmental disabilities[66, 67]. In a model of autism with rats with altered phospholipid metabolism in the brain, increased levels of vitamin B_{12} were found to improve this metabolism[78]. In humans, a meta-analysis of the possible relationship between supplementation with folic acid during pregnancy and ASD in offspring suggested that maternal use of folic acid supplements during pregnancy could significantly reduce the risk of ASD in children regardless of ethnicity[79]. However, in a mother-child pair study conducted at birth[80], mothers with very high levels of plasma folate at birth (≥60.3 nmol/L) showed a 2.5 times greater risk of ASD in children compared to mothers with folate levels in the middle 80th percentile, after adjusting for covariates including MTHFR genotype. The same study found a similar association for mothers with very high B_{12} levels (≥536.8 pmol/L).

Vitamin B_6 levels were measured in four descriptive studies in our review, comparing ASD patients to HC with mixed results (higher levels of total but not phosphorylated form, lower levels and no differences)[28, 30, 58, 60]. However, a RCT study using a high dose of this vitamin for six weeks vs. placebo, reported that ASD patients taking the vitamin experienced an improvement of 6.8 points (95%CI 5.0-8.5) in verbal IQ scores compared to those on placebo[71] A Cochrane review about the usefulness of supplementing with a combination of vitamin B_6 and magnesium vs. placebo or no treatment concluded that no recommendation could be given for using this supplementation as a treatment for autism[81].

Some of the results mentioned above seem to suggest that an alteration of one-carbon metabolism could be implicated in ASD pathogeny through three interdependent pathways: the folate cycle, the methionine cycle (where methionine is transmethylated depending on folate) and

transsulfuration, (which helps synthesize glutathione)[82]. Vitamin B_{12} also participates in these loop reactions as a cofactor of the enzyme methionine synthase both in the folate and the methionine cycles[83]. Homocysteine is a toxic amino acid that could be produced in excess during abnormal methylation processes[83]. The role of vitamin B_6 is to act as a cofactor of the enzymes cystathionine beta synthase and cystathionine gamma lyase in the transsulfuration pathway of homocysteine to cysteine[82]. The one-carbon cycle is key in different functions such as DNA synthesis, epigenetic control of gene expression and, membrane signaling, maintenance of cellular redox homeostasis and detoxification capacity[82]. Apart from that possible biochemical dysfunction, the implication of folate and vitamin B_{12} insufficiencies in disrupting myelinization and inflammation processes has also been described[84]. All of this makes it clear that the roles of folic acid, vitamin B_{12} and even vitamin B_6 need to be further studied to increase our understanding of their possible relationship with the pathophysiology of ASD. Also, the links between vitamin insufficiency and specific life stages (pregnancy[85]; infancy and childhood[83], or adolescence[83]) should be a focus of future study.

Descriptive studies of vitamin C levels have shown mixed results in CAD with ASD vs. HC[58, 61,63]. A significant improvement in some ASD symptoms were found in a RCT study while patients were supplemented with high doses of ascorbic acid, even when their levels before entering the study were within the normal range[59]. In adults, lower vitamin C levels have been reported in patients diagnosed with schizophrenia, depressive disorder and generalized anxiety disorder vs. HC[19,20, 86], which seems to indicate an impaired antioxidant defense system. A recent review noted that high levels of reactive oxygen species, which cause oxidative stress, have been found in ASD patients (adults or CAD), and discussed the potential role of antioxidant treatments such as vitamin C[87]. No studies have been found in adults with ASD and vitamin C supplementation, but as an adjunctive treatment for schizophrenia patients, positive results with amelioration of some symptoms have been reported[88].

Taken together, it seems that different biochemical pathways could be implicated in the WSV abnormalities found in the studies reviewed. Moreover, monitoring certain vitamin levels could

be beneficial from a clinical perspective. Overall, the findings support what other authors have already proposed; namely, that there is a need to identify and develop nutritional assessment indicators in ASD patients which could serve as clinical early warning signs[89]. That said, it is important to take into account the potential limitations of this approach such as the sensitivity and specificity rates of these indicators

ADHD

Meta-analyses showed significant differences in CAD with ADHD vs. HC in both folate and vitamin B_{12} levels. Specifically, patients were found to have higher levels of folate but lower levels of B_{12} than HC. Higher mean folate levels were also described in 32 adults with ADHD compared to HC, but no differences were reported in vitamin B_{12} levels[90]. Also in adults, significantly lower mean levels of B_2, B_6 and folate have been described, but only B_2 levels were associated with ADHD when age and gender were used as covariates[91]. The role of vitamin B_{12} levels in children's cognition is not clear[92], but higher B_{12} levels during early infancy has been associated with better cognitive performance in children 5 years later[93]. The lower vitamin B_{12} levels in ADHD could also be linked to a dysfunction in the one-carbon metabolism cycle, as in ASD, since both are neurodevelopmental disorders. This explanation is supported by Altun et al (2018) and Karababa et al (2014) who found lower homocysteine levels in ASD and abnormal folate levels vs. HC[46, 90].

No studies about WSV supplementation in ADHD were found which met the criteria for this review. However, in adults, Surman et al (2018) carried out a double-blind, placebo-controlled, randomized clinical trial to evaluate the benefits of supplementation with L-Methylfolate in patients with ADHD treated with methylphenidate. L-Methylfolate was associated with no change in efficacy on psychopathology scale scores in adults with ADHD, apart from the possibly reduced efficacy of methylphenidate, since patients on L-methylfolate were on higher doses of the stimulant[94].

Other disorders

No folate or vitamin B_{12} insufficiencies have been found in CAD with schizophrenia[48], and their levels for these vitamins have not been reported to be lower than HC or ASD patients[54]. However, in a retrospective study published in Spanish, 11.2% of CAD inpatients with any psychiatric disorder in a general hospital were found to have a deficit of vitamin B_{12}, serum folate or both. Interestingly, patients with a psychotic disorder had significantly lower mean levels of folate compared to those with an eating disorder[95]. No other studies have been found in adolescents with psychosis related to lower folate or vitamin B_{12} levels, although both of these vitamins are altered in the one-carbon cycle, where elevated levels of homocysteine have been observed in adults with schizophrenia[96]. Also, studies measuring serum folate levels in adult patients with schizophrenia have consistently found significantly lower levels in subjects with the disorder compared to control participants[15], while inconsistent results have been reported in adolescents with schizophrenia. Moreover, Roffman et al (2013) suggest that folate supplementation as an adjunct to antipsychotic therapy may be of benefit for those with a genetic susceptibility[97].

Regarding affective disorders, mixed results were found when looking at folate levels in adolescents with a depressive disorder compared to HC. One study reported lower mean folate levels in patients[43], while another found no such difference in mean levels, but reported folate deficiency rates of 11.2% in patients compared to none in HC[39]. In a meta-analysis performed in adults with the same disorder, subjects with low folate levels had an odds ratio of 1.42 for being diagnosed with depressive disorder[98].

Only one study measured vitamin B_{12} in CAD with affective disorders. It found lower B_{12} levels in patients vs. HC as well as a 30.3% rate of vitamin B_{12} deficiency compared to none in HC[39]. In a retrospective study conducted by our group in 724 CAD inpatients with a psychiatric disorder, almost half of the subjects had folate insufficiency/deficit, 20.3% vitamin B_{12} insufficiency/deficit and 13.1% had both. Patients with depressive disorders showed higher levels of B_{12} insufficiency and lower mean folic acid levels than those in other diagnostic categories[99] . In adults, lower levels of vitamin B_{12} have been linked to melancholic depressive symptoms in a study in the general

population[100] while higher vitamin B_{12} levels have been associated with better 6-month outcomes[101].

Regarding supplementation, in a meta-analysis in adults, folic acid supplements were found to have no efficacy[102]. It has also been reported that folic acid together with vitamin B_{12} did not improve depressive symptoms in patients ≥65 years with a depressive disorder and hyperhomocysteinemia[103]. Recently, in a rat model of depression, it was reported that supplementation with folic acid could play an antidepressant-like role in several pathways involving monoamine neurotransmitters. Overall, the results are mixed and it is uncertain what role these vitamins may play in depression and whether abnormalities in the one-carbon cycle could be implicated[104].

Regarding OCS, two studies in adult patients have analyzed vitamin B_{12} and folic acid in patients diagnosed with this disorder[105,106]. Both found that, among these patients, the rate of vitamin B_{12} deficiency was significantly higher compared to the control group, while folate deficiency was not found in either group. These findings are in line with the study in a pediatric sample reported in this review which also found lower levels of vitamin B_{12}, but not of folates[44]. Consistent with these findings is a study in adults regarding WSV supplementation in OCD patients, which involved adding folic acid or placebo as adjunctive treatment to fluoxetine for 12 weeks. Patients had folate levels within the normal range before starting the trial, and no improvement in symptoms was observed[107]. No studies have been found examining WSV in CAD with this disorder.

Some limitations of this systematic review need to be taken into account. First, the heterogeneity of the samples (ages, questionnaires used to measure psychopathology, diagnosis), cutoff points for defining vitamin insufficiency and deficiency (possibly due to the fact that the WHO has yet to establish clear international recommendations or standards in this area[108]), as well as the doses and duration of supplementation. Specifically, ASD includes a wide range of symptoms, severity

and possible disabilities and this heterogeneity may limit the conclusions that can be drawn from the studies reviewed here. Second, certain vitamins were reviewed in very few studies. Third, there is no gold-standard for measuring WSV. Several decades ago, vitamin $B_{12,}$ like other vitamins, was measured with microbiological methods. In the 1990s, measurements began to be taken with automated competitive binding chemiluminescence assays which allowed for more widespread monitoring[109], however it is still not considered to be a gold standard. Fourth, most of the articles did not mention the psychopharmacological treatment that patients were on, and it is known that some treatments, such as anticonvulsants, could decrease the levels of certain vitamins including folate[110]. Lastly, a fifth limitation is that vitamin supplementation was permitted in 3/33 (9.1%) of the descriptive studies, while in 6/33 (18.2%) data about supplementation was not reported. Nevertheless, despite these limitations, we believe that the review offers valuable information about vitamin insufficiencies/deficiencies in child and adolescent samples with psychiatric disorders.

Summary

We have systematically reviewed 42 articles regarding WSV levels or supplementation in CAD with psychiatric disorders or symptoms, and found considerable heterogeneity among the studies (within the same disorder category, vitamin levels measured, the type, dosage and time of supplementation, etc.). Most of the studies were conducted in patients with ASD, followed by ADHD, with little research having focused on other psychiatric disorders. Folate and vitamin B_{12} were the most frequent vitamin levels measured. Our meta-analysis showed that vitamin B_{12} levels were lower in ASD patients vs. HC. Moreover, we found that supplementation with methyl B_{12} could ameliorate some ASD symptoms, and the use of folinic acid in ASD patients could also be useful, even though folate levels were not significantly different between these patients and HC in the meta-analysis. In ADHD patients, the analysis showed lower B_{12} levels in patients but higher folate levels compared to HC. Both of these nutrients are implicated in brain development, so optimizing folate and B_{12} intake could help prevent and modulate the severity of brain

dysfunction[79]. Considering the impact these nutrients can have on the developing brain and the results of this systematic review and meta-analyses, it is important to increase our knowledge of both the association between folate and vitamin B_{12} levels and different psychiatric disorders in CAD as well as the possible effects of supplementation with these vitamins. The roles of other WSV in this population also need to be further studied.

Disclosure statement

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Data availability statement

The data that support the findings of this systematic review are available on request from the corresponding author [IB].

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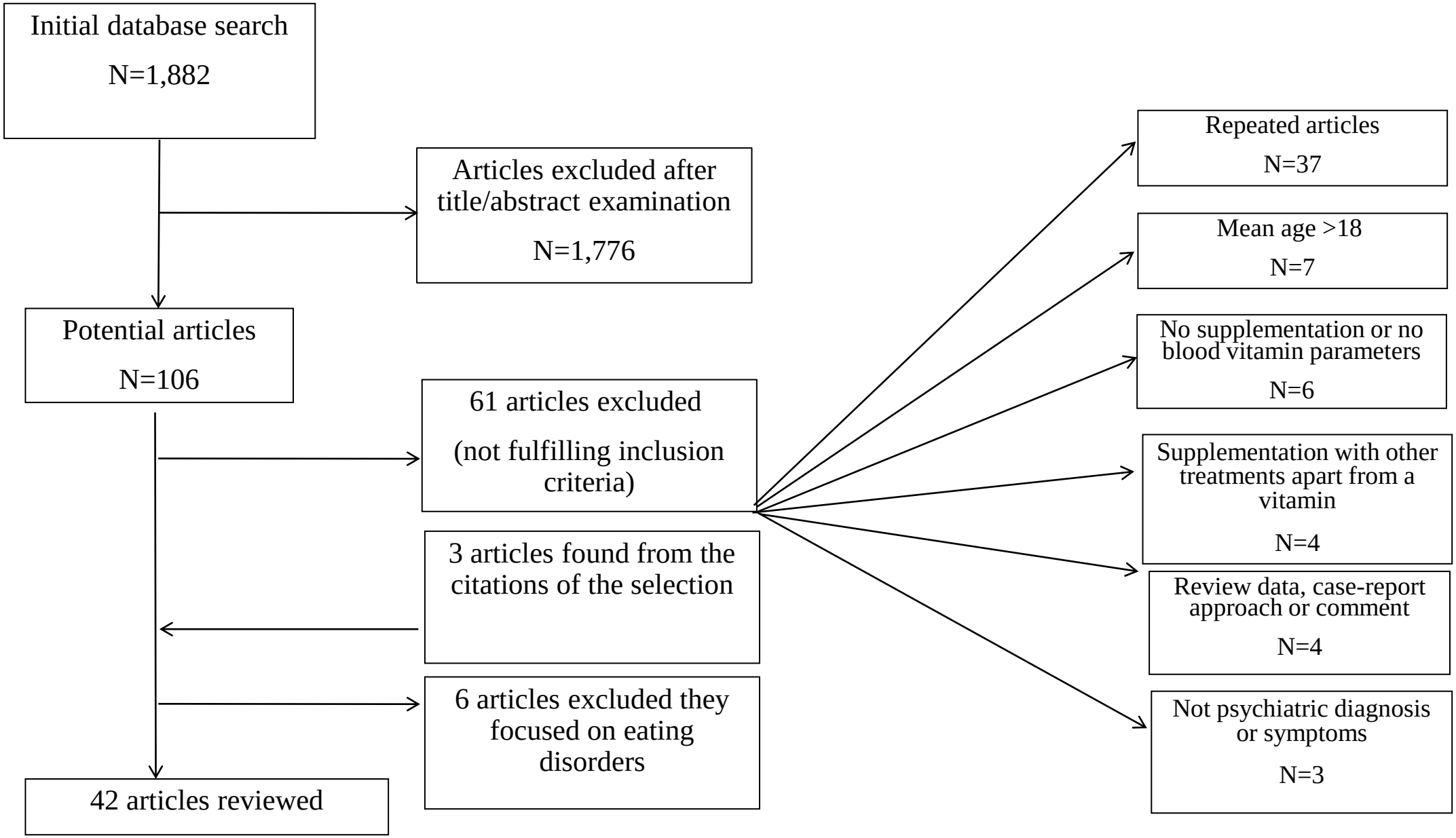
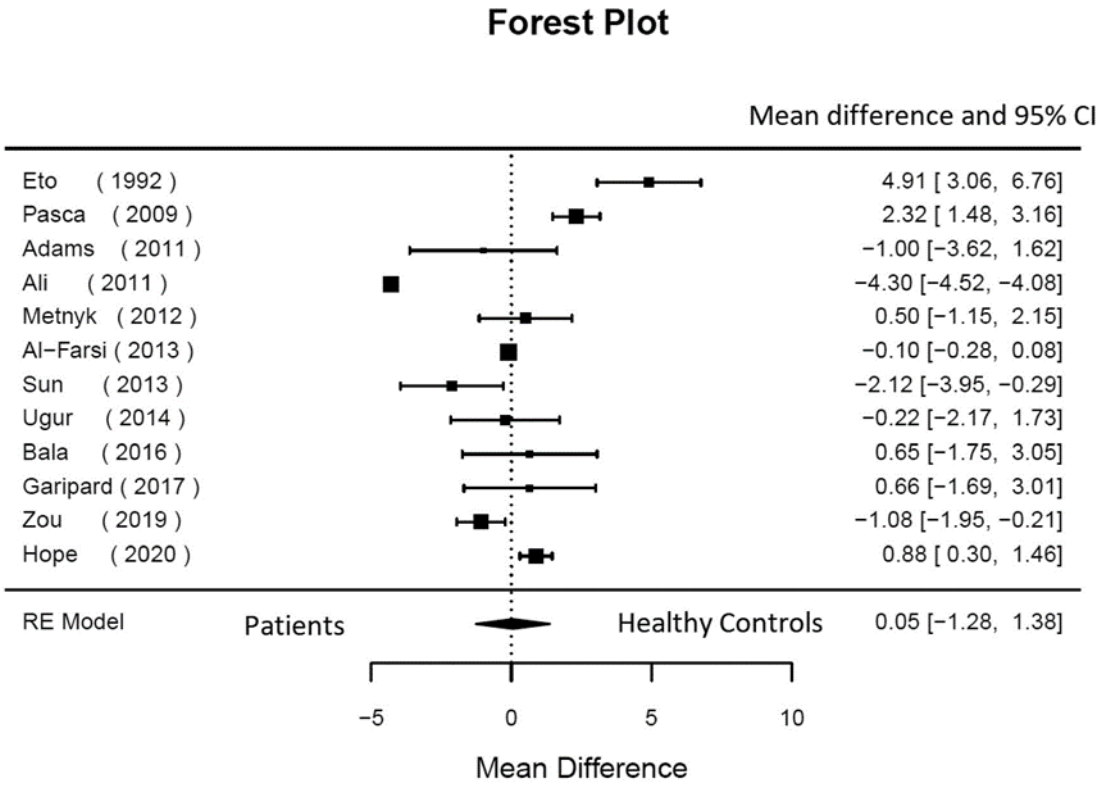

Initial database search
N=1,882
Articles excluded after title/abstract examination
N=1,776
Potential articles
N=106
61 articles excluded
(not fulfilling inclusion criteria)
3 articles found from the citations of the selection
6 articles excluded they focused on eating disorders
42 articles reviewed
Repeated articles
N=37
Mean age >18
N=7
No supplementation or no blood vitamin parameters
N=6
Supplementation with other treatments apart from a vitamin
N=4
Review data, case-report approach or comment
N=4
Not psychiatric diagnosis or symptoms
N=3

Figure 2. Forest plot of descriptive studies measuring plasma/serum folate levels between children and adolescents with autism spec- trum disorders and healthy controls.



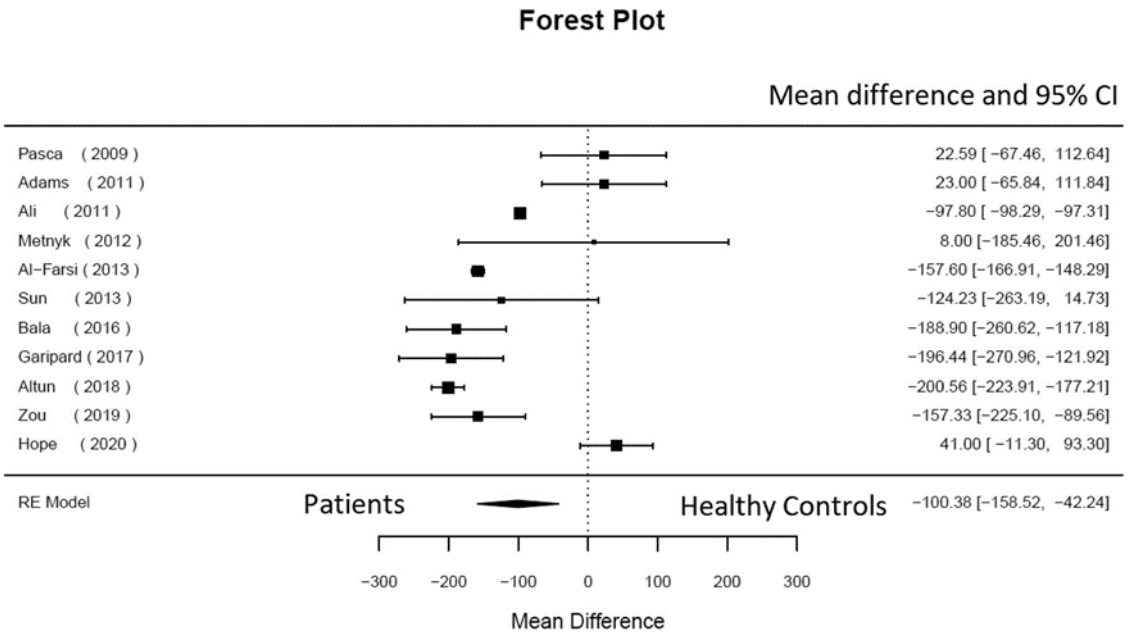
Tests for heterogeneity: $\chi 2=1{,}038.28$, df=11, ($p<0.0001$), $I_2=98.33\%$ (96.28-99.43)

Test for overall effect: Z=-0.077 (p=0.94)

*Negative values indicates that we observed low levels in patients compared to healthy controls

RE Model: Random Effects model

Figure 3. Forest plot of descriptive studies measuring plasma/serum vitamin B_{12} levels between children and adolescents with autism spectrum disorders and healthy controls.



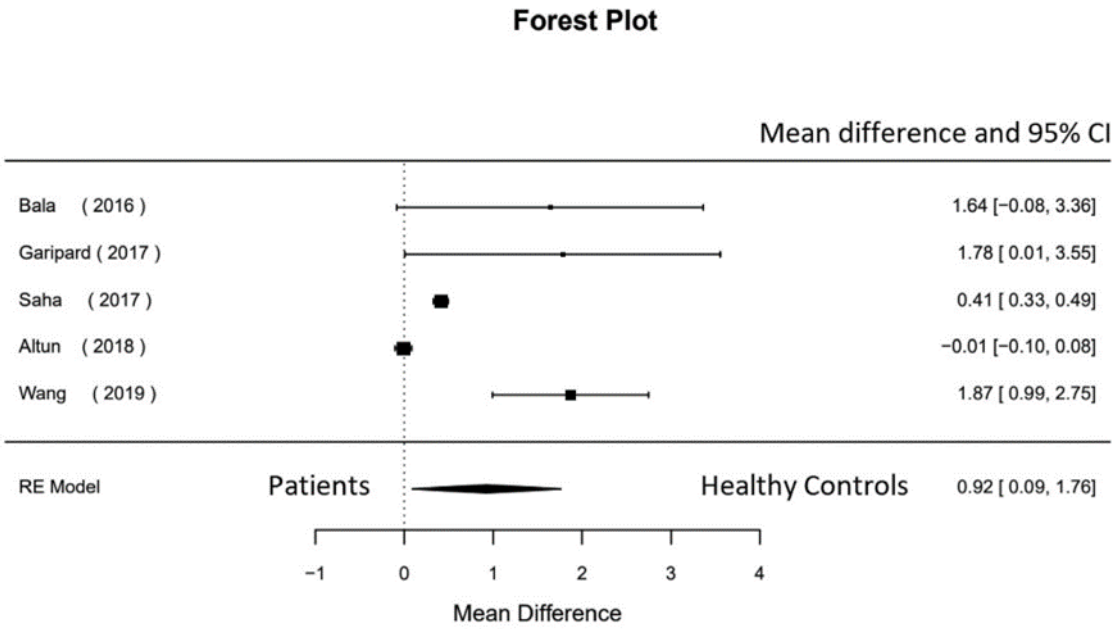
Tests for heterogeneity: $\chi 2=290.51$, df=10 ($p<0.0001$), $I_2=98.9\%$ (97.25-99.68)

Test for overall effect: Z=-3.38 ($p<0.001$)

*Negative values indicate that we observed low levels in patients compared to healthy controls

RE Model: Random Effects model

Figure 4. Forest plot of descriptive studies measuring plasma/serum folate levels between children and adolescents with attention deficit and hyperactivity disorder and healthy controls.



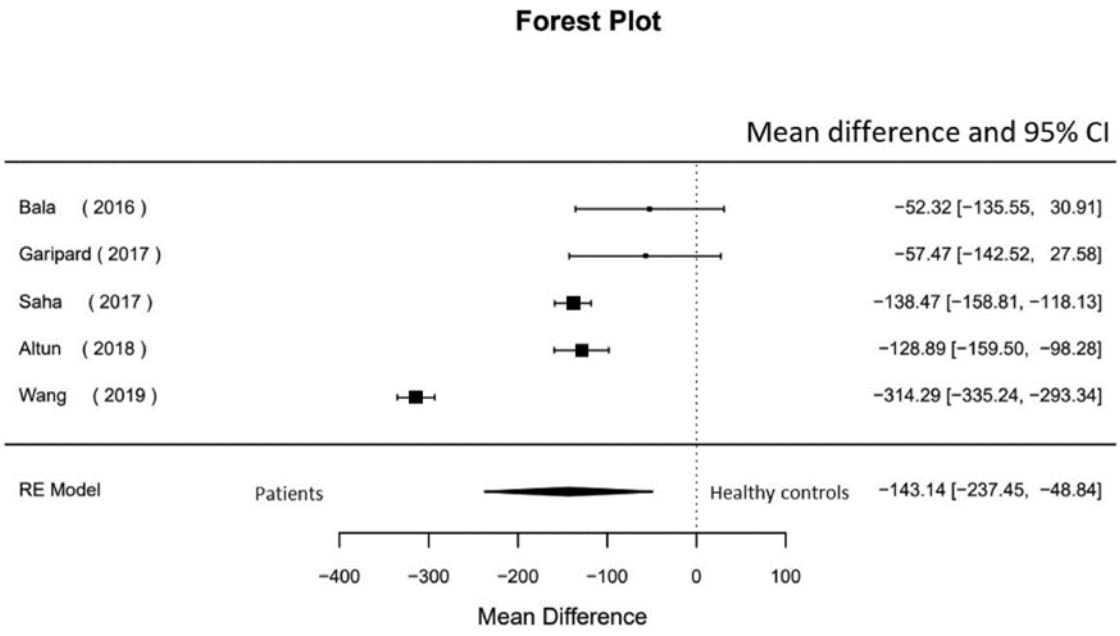
Tests for heterogeneity: $\chi 2=63.42$, df=4 ($p<0.0001$), $I_2=98.85\%$ (93.81-99.87)

Test for overall effect: $Z=7.39$ ($p<0.0001$)

*Negative values indicate that we observed low levels in patients compared to healthy controls

RE Model: Random Effects model

Figure 5. Forest plot of descriptive studies measuring plasma/serum vitamin B_{12} levels between children and adolescents with atten- tion deficit and hyperactivity disorder and healthy controls.



Tests for heterogeneity: $\chi 2=193.11$, df=4 ($p<0.0001$), $I_2=97.66\%$ (93.03-99.72)

Test for overall effect: Z=-30.35 ($p<0.001$)

*Negative values indicate that we observed low levels in patients compared to healthy controls

RE Model: Random Effects model

Table 1. Water-soluble vitamins and their biomarkers in the studies reviewed.

Vitamin	**Biomarker**
B_1 or thiamine	Plasma thiamine, plasma thiamine monophosphate, whole blood thiamine
B_2 or riboflavin	Plasma, erythrocyte and whole blood riboflavin
B_3 or niacin	Whole blood niacin
B_5 or pantothenic acid	Erythrocyte pantothenic acid
B_6 or pyridoxine	Serum pyridoxine, serum pyridoxal, Serum pyridoxamine, and their serum phosphorylated forms
B_8 or vitamin H or biotin	Whole blood biotin
B_9 or folate or folic acid	Serum and plasma folate; serum folic acid; erythrocyte folate
B_{12} or cobalamin	Serum and plasma cobalamin; erythrocyte cobalamin
C or ascorbic acid	Plasma vitamin C; total, reduced and oxidized vitamin C

Table 2. Descriptive studies (N=33), grouped by disorder, arranged according to the number of articles found for each illness (autism spectrum disorder, attention deficit and hyperactivity disorder, affective disorder, psychotic disorder, obsessive-compulsive disorder and others) and listed alphabetically by first author. Where patients with two disorders were included in a study, that study is grouped according to the disorder that had the larger sample size.

	Study/Country/Setting	Year	Type of study	N and diagnosis	Type of patient	Mean age (years)	Psychopharmacological treatment/Vitamin supplementation	Assessment (vitamin levels/ questionnaires)	Results
1	Adams et al/USA/Arizona State University [60]	2006	Cross-sectional	35 ASD 11 HC	Outpatients	ASD 7.2 ± 1.4 HC 7.8 ± 1.2	Not reported	Serum total Vit B_6 (including phosphorilated and unphosphorilated forms)	Children with ASD had 75% higher levels of total vit B_6 than HC, but less PLP (active form). Girls with ASD also had significantly high levels.
2	Adams et al/USA/Arizona State University [58]	2011a	Cross-sectional	55 ASD 44 HC	Outpatients	ASD 10±3.1 HC 11±3.1	29% of ASD on psychopharmaceuticals (mainly risperidone and clonidine); 9% on stimulants; 4% on anticonvulsants/ No vitamin supplements were taken.	Serum vit B_1, B_2, B_3, B_5, B_6, B_8, folic acid, B_{12}, C, FSV, some amino acids, minerals and other biomarkers	Vit B_8 was 20% lower in ASD patients vs. HC, the only clearly significant difference. . There were possibly significantly lower levels of vit B_5. vit C was possibly slightly higher in ASD children.
3	Al-Farsi et al/Oman/Sultan Qaboos University [36]	2013	Cross-sectional	40 ASD 40 HC	Outpatients	ASD 4.8±0.3 HC 4.8±0.3	Not reported	Serum folate and Vit B_{12}	The ASD group had consistently lower levels of folate and vit B_{12}.
4	Al Gadani et al/Saudi Arabia/King Saud University [61]	2009	Cross-sectional	30 ASD 30 HC	Outpatient	Range:3-15	No medication or vitamin supplements were taken	Levels of Vit C, FSV and other biomarkers	Vit C levels were non-significantly lower in ASD patients vs.HC.
5	Ali et al/Oman/Sultan Qboos University [35]	2011	Cross-sectional	40 ASD 40 HC	Outpatients	Range: 3-5	No medication or vitamin supplements were taken	Serum folate and vitamin B_{12}	Significantly lower serum folate and vit B_{12} levels in ASD vs HC children.
6	Altun et al/Turkey/Kahramanmaras Sutcu Imam University [30]	2018a	Cross-sectional	60 ASD 45 HC	Outpatients	ASD 5.8±2.7 HC 6.7±2.5	Not reported/Vitamin supplementation as an exclusion criteria	Serum folate, Vit B_6 and B_{12} CARS	Mean levels of folate, Vit B_6 and B_{12} were significantly lower in ASD vs HC. Total

									CARS score negatively correlated with folate, vit B_6 and B_{12} levels.
7	Anwar et al/United Kingdom/University of Warwick [62]	2016	Cross-sectional	27 ASD 21 HC	Outpatients	ASD 7.4 ± 2.0 HC 8.3 ± 2.12	Not reported/Vitamin supplement as an exclusion criteria	Thiamine and related phosphorylated metabolites in plasma and urine, as well as other biomarkers CARS PEP-3 Leiter-Revised	Plasma thiamine and thiamine monophosphate levels were similar in ASD and HC. Thiamine pyrophosphate was 24% lower in ASD group compared to HC. No correlation was observed between clinical markers and thiamine concentration in plasma and urine.
8	Eto et al/USA/University of Alabama [47]	1992	Cross-sectional	16 ASD 12 HC	Outpatients	ASD 12.3±3.9 HC 10.4±0.9	9/16 (56.3%) on neuroleptics/Some subjects took vitamin supplements	Plasma folate and other biomarkers	No significant differences were found between ASD and HC in folate levels.
9	Guo et al/China/ Chongqing Medical University [27]	2018	Cross-sectional	274 ASD 97 HC	Outpatients	ASD 4.2±1.2 HC 4.2±1.2	Not reported/High-dose vitamin supplementation as an exclusion criteria	Serum folate, vit B_{12}, other FSV and minerals ABC GDS SRS	0,4% of ASD had folate or vit B_{12} deficiency. Significantly lower folate levels were found in ASD vs HC. Folate levels positively correlated with several GDS subscale scores.
10	Hope et al/Norway/University of Oslo [54]	2020	Cross-sectional	222 ASD 401 SCZ 492 HC	Outpatients	ASD 17±11 (Range 2-53) SCZ 30±9 (results not commented due	Not reported/Subjects could take vitamin supplements	Serum folate and vit B_{12}	ASD had significantly higher mean Vit B_{12} levels than HC. No significant interaction effect was reported between age groups and

						to subjects' age) HC 20±10			diagnostic groups on levels of vit B_{12}.
11	Krajcovicova-Kudlackova et al/Slovakia/Slovak Medical University [63]	2009	Cross-sectional	51 ASD (27 children, 24 adolescents) 77 HC	Outpatients	ASD: Children 7.9±0.3 Adolescents: 14.8±0.5 HC: 15±0.2	Not reported/Vitamin supplementation was an exclusion criteria	Vit C and FSV	High mean levels of vit C in ASD v. HC were found.
12	Liu et al/China/Children's Hospital of Chongqing Medical University [38]	2016	Cross-sectional	154 ASD 73 HC (this group did not have blood analysis)	Outpatients	ASD 5.2±1.8 HC 4.8±0.8	No psychopharmacological treatment or vitamin supplementation in the previous 6 months to be included in the study	Folate, Vit B_{12} and FSV CARS	No correlation between vitamin levels and CARS scores.
13	Main et al/Australia/Flinders University [29]	2015	Cross-sectional	35 ASD 27 siblings 25 HC	Outpatients	ASD 7.6±2.9 Siblings 9.3±4.8 HC 8.6±2.8	Medication taken by patients included risperidone (N=1, 2.9%) and lithium oroate (N=1, 2.9%), Multivitamins were taken by 12 patients (34.3%), 9 siblings (33.3%) and 9 controls (36%)	Serum and erythrocyte folate, vit B_2, B_{12} and other biomarkers SCQ VABS PPVT RCPM	Significantly higher mean levels of vit B_2 in ASD and their siblings vs. HC were found before Holm-Bonferroni adjustment. No other significant differences were found between the samples.
14	Meguid et al Egypt/National Research Center [28]	2017	Cross-sectional	80 ASD 80 HC	Outpatients	ASD 3.9±0.72 HC 3.7±0.52	Not reported/Vitamin supplementation was an exclusion criterion	Serum vit B_{12}, folic acid, Vit B_6 and some minerals	The ASD group had lower folic acid and mean Vit B_{12} levels than HC.
15	Metnyk et al/USA/University of Arkansas Medical Sciences[45]	2012	Cross-sectional	68 ASD 40 unaffected siblings	Outpatients	ASD 5.8±2.1 Siblings 5.6±2.3 HC 6.3±2.1	Not reported/35% of ASD, 14% of their siblings and 17% of HC were on Vit supplementation	Plasma vit B_{12}, folate and other biomarkers CARS	No significant differences were found between the groups.

				54 HC					
16	Pașca et al/Romania/ Iuliu Ha¸tieganu University of Medicine and Pharmacy [56]	2006	Cross-sectional	12 ASD 9 HC	Outpatients	ASD 8.3±2.8 HC 8.3±1.8	Not reported, but no drugs interfering with methionine metabolism were permitted/ Vitamin supplementation in the previous 6 months was also an exclusion criterion	Plasma vit B_{12} was measured only in ASD subjects. Other biomarkers were measured in both samples	2 ASD patients (16.7%) had low levels of vit B_{12} and 7 (58.3%) patients had suboptimal levels of vit B_{12}.
17	Pașca et al/Romania/ Iuliu Ha¸tieganu University of Medicine and Pharmacy [42]	2009	Cross-sectional	39 ASD (15 AD, 5 AS, 19 PDD-NOS) 25 HC	Outpatients	AD p/HC: 5.1±0.5/5.9±0.6 AS/HC: 9.2±1.8/10.2±1.1 PDD-NOS/HC: 8.8±0.8/9.1±0.9	Not reported/ Vitamin supplementation was an exclusion criterion	Serum folate, vit B_{12} and the C677T polymorphism of the MTHFR gene	Vit B_{12} and folate levels were within the normal range, but serum folate levels in AS subjects were mildly higher reaching borderline statistical significance. MTHFR gene analysis showed a normal distribution of the C677T polymorphism in children with ASD, but the frequency of the 677T allele was slightly more prevalent in AD patients.
18	Sun et al/China/Harbin Medical University [64]	2013	Cross-sectional	53 ASD 53 HC	Outpatients	ASD and HC 4.9±0.6	Not reported/Vitamin supplementation was an exclusion criterion	Serum folate, vit B_{12} and FSV	Significantly lower mean folate levels in ASD vs HC, but within the normal range.
19	Ugur and Gürkan/Turkey/Ankara University School of Medicine [40]	2014	Cross-sectional	54 ASD 54 HC	Outpatients	ASD 4.96±1.25 HC 4.64±1.15	Not reported/Exclusion criteria included vit D supplementation as well as medication that could affect vit D levels	Serum folate and FSV ABC AbBC CARS	No significant differences were found in folate levels between ASD and HC.
20	Zou et al/China/Harbin Medical University [52]	2019	Cross-sectional	89 ASD 89 HC	Outpatients	ASD 6.7±2.9 HC 7.7±3.0	Not reported/ Vitamin supplementation was an exclusion criterion	Serum folic acid, vit B_{12} and other folate-related metabolism	Mean folic acid and vit B_{12} were lower in ASD vs .HC. A Fisher discriminant analysis

								markers	with 6 folate-related metabolism markers including vit B_{12} detected ASD in 84.3% of subjets.
21	Altun et al./ Turkey/Kahramanmaras Sutcu Imam University [46]	2018b	Cross-sectional	30 ADHD 30 HC	Outpatients	ADHD 9.3±1.8 HC 9.5±1.9	Drug-naïve/Vitamin supplementation was an exclusion criterion	Serum folate, vit B_6, B_{12} and other biochemical parameters CPRS-Revised, Long Form CTRS WISC-R	Significantly lower mean levels of folate, vit B_6 and B_{12} in ADHD vs HC groups. Positive correlation between all WISC-R scores and vit B12 levels.
22	Bala et al/Turkey/Yuzuncu Yil University, School of Medicine [56]	2016	Cross-sectional	34 ADHD 16 ASD 27 HC	Outpatients	ADHD 7.7±3.2 ASD 7.9±5.2 HC	Not reported/Vitamin supplementation was an exclusion criterion	Serum folate,vit B_{12}, FSV and other biochemical and hormonal parameters CARS DBDRS	ASD had the lowest vitamin B_{12} levels, whereas the vitamin B_{12} levels of the ADHD group were significantly lower compared to HC.
23	Garipardic et al./Turkey/Yüzüncü Yil University [57]	2017	Cross-sectional	36 ADHD 18 ASD 25 HC	Outpatients	7.7±3.1 8.1±5.2 9.9±4.1	Not reported, but both long-term use of drugs and vitamin supplementation were exclusion criteria	Serum folate, vit B_{12} and other hematological and biochemical parameters	ASD had the lowest vit B_{12} levels compared to the other groups. ADHD also had significantly lower vit B_{12} levels than HC. No differences in folate levels were found between groups.
24	Saha et al./ India/Manovikas Kendra [50]	2017	Cross-sectional	221 ADHD 286 HC	Outpatients	Not reported	Not reported/Not reported	Plasma folic acid,vit B_{12} , some SNP and other biomarkers	Mean vit B_{12} levels we lower in ASD vs. HC.

25	Unal et al./ South Africa/ Stellenbosch University [53]	2018	Cross-sectional	100 ADHD	Outpatients	9 (range 6-13)	Drug-naïve/Not reported	Vit B_{12} and other haematological and biochemical parameters CPRS	21% had vit B_{12} deficiency. Psychosomatic subscale scores from the CPRS showed an inverse relationship with vit B_{12} levels.
26	Wang et al/Taiwan/Institute of Biomedical Sciences Academia Sinica [51]	2019	Cross-sectional	216 ADHD 216 HC	Outpatients	ADHD 9.2±1.7 HC 9.2±1.8	Not reported/Not reported	Plasma folate , Vit B_6 and Vit B_{12} CTRS WWPAS	ADHD patients had significantly lower levels of folate acid, vit B_6 and B_{12} than HC.
27	Yektas et al/Turkey/ Düzce University Medical Faculty [31]	2019	Cross-sectional	35 ASD 48 ADHD 35 HC	Outpatients	Median: ASD 8.6 ADHD 9.0 HC 6.0	Medication-free subjects/Vitamin supplementation as an exclusion criterion	Serum folate, vit B_{12} and other biomarkers CARS DSM-IV-Based Screening and Assessment Scale for Disruptive Behavior Disorders.	Mean vit B_{12} levels were significantly lower in ASD vs. HC. No significant correlations were found between CARS scores and vit levels. In ADHD subjects, vit B_{12} could explain 13.0% of the variance in hyperactivity/impulsivity and oppositionality scores of the DSM-IV scale.
28	Esnafoglu and Ozturan/Turkey/Ordu university [39]	2020	Cross-sectional	89 DD 43 HC	Outpatients	DD 15.1±1.5 HC 14.4±2.3	Any medical treatment which could affect the biochemical parameters and nutritional supplements were both exclusion criteria	Serum folate, vit B_{12}, FSV and other biomarkers CDI STAI	11.2% and 30.3% of DD subjects had deficient levels of folate and vit B_{12} respectively vs none in the HC group. Vit B_{12} mean levels were

Con formato: Inglés (Estados Unidos)

									significantly lower in patients than HC and these levels negatively correlated with the severity of depression in all subjects.
29	Tsuchimine et al/Japan/Hrosaki University [43]	2014	Cross-sectional	24 DD 26 HC (only female)	Outpatients	DD 16.2±2.2 HC 17.2±2.4	Drug naïve	Serum folate and other biomarkers BDI-II DSRSC	Significantly lower mean folate levels in patients vs HC. No correlation between folate levels and depression scale scores in patients.
30	Kevere et al/Latvia/Riga State University [48]	2014	Cross-sectional	88 SCZ 28 AD 94 HC	Inpatients	SCZ 15.3±2.6 AD 16.5±1.7 HC 14.8±2.8	Drug-free subjects/Not reported	Folic acid and vit B_{12} levels BPRS HDRS HAM-A	Patients had sufficient levels of both vitamins, but the comparison between patients and HC was neither shown nor explained.
31	Esnafoglu and Yaman/Turkey/Ordu University [44]	2017	Cross-sectional	52 OCD 30 HC	Outpatients	OCD 14.7±2.3 HC 14.2±2.6	Not reported /Taking a nutritional support product was an exclusion criterion	Vit B_{12}, folic acid, FSV and other biomarkers Y-BOCS CDI STAI	Lower levels of vit B_{12} in OCD compared to HC group.
32	Kazanci et al/Turkey/ Bakırköy Dr. Sadi Konuk Research and Training Hospital [55]	2017	Cross-sectional	524 pediatric patients (group I:72 from 0-3 years); group II: 240 patients from 3-10 years); group III: 206 patients from 10-16	Outpatients	Total: 8.3 ±4.2 Group I: Group II: Group III:	Taking medication that can cause vit B_{12} deficiency was an exclusion criterion/Not reported	Folate, vit B_{12} and other FSV and haematological parameters Questions about clinical features were made without using scales.	2.1% of all subjects had folate deficiency, but this went up to 5.6% among those with low vit B_{12} levels. 59.7% of patients with vit B_{12} deficiency (<200 pg/mL) complained of anxiety and 43.8% of depression.

Con formato: Italiano (Italia)

				years)					
33	Robinson et al/Colombia/National University of Colombia Medical School[49]	2018	Longitudinal	1042 subjects	General population	8.5±1.6 at baseline 14.7±1.7 at endpoint	Not reported/Not reported	Erythrocyte folate and plasma vit B_{12} as well as other haematological parameters YSR	In boys, low vit B_{12} levels around the age of 8 were associated with increased total externalizing behavior problems measured with YSR scores during adolescence.

ABC: Autism Behavior Checklist; AbBC; Aberrant Behavior Checklist; AD: Autism disorder; ADHD: Attention Deficit and Hyperactivity disorder; AS: Asperger syndrome; ASD: Autism Spectrum Disorder; BDI-II: Beck Depression Inventory-II; CARS: Children Autism Rating Scale; CDI: Children's Depression Inventory; CPRS: Conners Parent Rating Scale; CTRS: Conners Teacher Rating Scale; CYBOCS: The children's Yale-Brown Obsessive Compulsive Scale; ds: disorder; DBDRS: Disruptive Behavior Disorder Rating Scale; DD: Depressive disorder; FSV: Fat-soluble vitamins; GDS: Gesell Developmental Scale; HAM-A: Hamilton Anxiety Scale; HC: Healthy controls; HDRS: Hamilton Depressive Rating Scale; MTHFR: methylenetetrahydrofolate reductase; PEP-3: Psychoeducational Profile, third edition; PDD-NOS: Pervasive Developmental Disorder Not Otherwise Specified; PLP: pyridoxal 5 phosphate; PPVT: Peabody Picture Vocabulary Test; ; RCPM: Raven Coloured Progressive Matrices; SCZ: schizophrenia; SNP: single-nucleotid polymorphism; SRS: Social Responsiveness Scale; STAI: State-Trait Anxiety Inventory; vit: vitamin; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; YSR: Youth Self Report; WWPAS: Werry-Weiss-Peters Activity Scale; WISC-R: Weschler Intelligence Scale for Children-Revised

Table 3: Interventional studies based on Randomized Clinical Trials (RCT) with any Water-Soluble vitamin in children and adolescents with psychiatric disorders (N=5).

	Study/Country/ Setting	Year	N and diagnosis	Type of patient	Mean age (years)	Psycho-pharmacological treatment	Intervention	Assessment (vitamins/ questionnaires)	Results
1	Bertoglio et al/USA/University of California [17]	2010	30 ASD	Outpatients	3-8	Not reported	Double blind, randomly assigned to 6 weeks of PBO and 6 weeks of methyl B_{12} (64.5 µ/kg every third day, subcutaneous) or the opposite order. Following this 12-week study, subjects were given the option of entering a 6-month open-label trial of methyl B_{12} (N=. 22).	Plasma concentrations of glutathione GSH and GSH/GSSG PIA-CV CGI-I CARS PPVT-III ABC CBCL MCDI SB-V	No differences in behavior tests or in glutathione status were identified between active and PBO groups. 9 subjects (30%) demonstrated improvement on the CGI Scale and at least two additional behavioral measures. These responders exhibited increased plasma concentrations of GSH and GSH/GSSG.
2	Dolske et al/USA/University of Alabama [59]	1993	18 ASD	Residential school children	6-19	50% neuroleptics	Double blind PBO controlled asymmetric crossover experimental design	R-F	Changes in R-F total scores and sensory motor scores were found in the active group.

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							18 ASD were assigned to receive ascorbic acid (8g/70kg/day) or PBO during 30 weeks		
3	Frye et al/USA/Arkansas Children's Hospital [69]	2018	48 ASD	Outpatients	Folinic acid treatment: 7.7 PBO: 7.2	26% stimulants, 26% melatonin, 22% alpha-adrenergic agonists, 13% SSRI, 9% antiepileptic	Two-arm double-blind randomized PBO-controlled parallel study. 48 ASD were randomized to receive 12 weeks of high-dose folinic acid (2 mg/kg/d, max 50 mg/d) or PBO Children were subtyped by glutathione and folate receptor-α autoantibody (FRAA) status	ADOS ADI-R OACIS VABS ABC SRS BASC AIM ASQ	FRAA status was predictive of response to treatment. For FRAA-positive participants, improvements in subscales of the VABS, ABC, ASQ and BASC and in verbal communication were greater in the folinic acid group.
4	Hendren et al/USA/University of California [68]	2016	57 ASD	Outpatients	B_{12} treatment: 4.83±1.17 PBO: 5.58±1.33	Not reported	Randomized, PBO-controlled study. 57 ASD were assigned to 8 weeks of treatment with methyl B_{12} (75 ug/kg) or saline PBO every 3	CGI-I ABC SRS Laboratory measures of methionine methylation and antioxidant	CGI-I score was significantly better in the methyl B_{12} group than in the PBO group, but SRS-Social Motivation significantly

							days in a subcutaneous injection	glutathione metabolism were assessed at baseline and 8 weeks	improved in the PBO group. Clinical improvement in the methyl B_{12} group was positively correlated with improvement in cellular methylation capacity.
5	Kuriyama et al/Japan/University of Tohoku [71]	2002	8 ASD	Outpatients	Pyridoxine treatment: 10.6±1.8 PBO group: 10.10±1.00	No treatment	Randomized, PBO-controlled study 8 ASD were assigned to 4 weeks of treatment with pyridoxine (100 mg/d after breakfast for 2 weeks and 100mg after breakfast and after dinner for 2 more weeks) or PBO orally in powder form.	WISC-III SM	Outcome measures were changes in the IQ and SQ scores following treatment. Pyridoxine treatment was associated with a significant increase in verbal IQ scores.

ABC: Aberrant Behavior Checklist; ADI-R: Autism Diagnostic Interview-Revised; ADOS: Autism Diagnostic Observation Schedule; AIM: Autism Impact Measure; ASD: Autism Spectrum Disorder; ASQ: Autism Symptoms Questionnaire; BASC: Behavioral Assessment System for Children 2nd Edition; CGI-I: Clinical Global Impressions-Improvements score; FRAA: folate receptor-α autoantibody; IQ: intelligence quotient; OACIS: Ohio Autism Clinical Impression Scale; PBO: placebo; R-F: Ritvo-Freeman Real Life Rating Scale; SAS: Severity of Autism Scale; SM: Social Maturity Scale test; SRS: Social Responsiveness Scale; SQ: social quotient; VABS: Vineland Adaptative Behavior Scale; WISC-III: Wechsler Intelligence Scale for Children-III; SRS: Social Responsiveness Scale

Table 4: Other interventional studies with any Water-Soluble vitamin that did not use a randomized clinical trial approach in children and adolescents with psychiatric disorders (N=5).

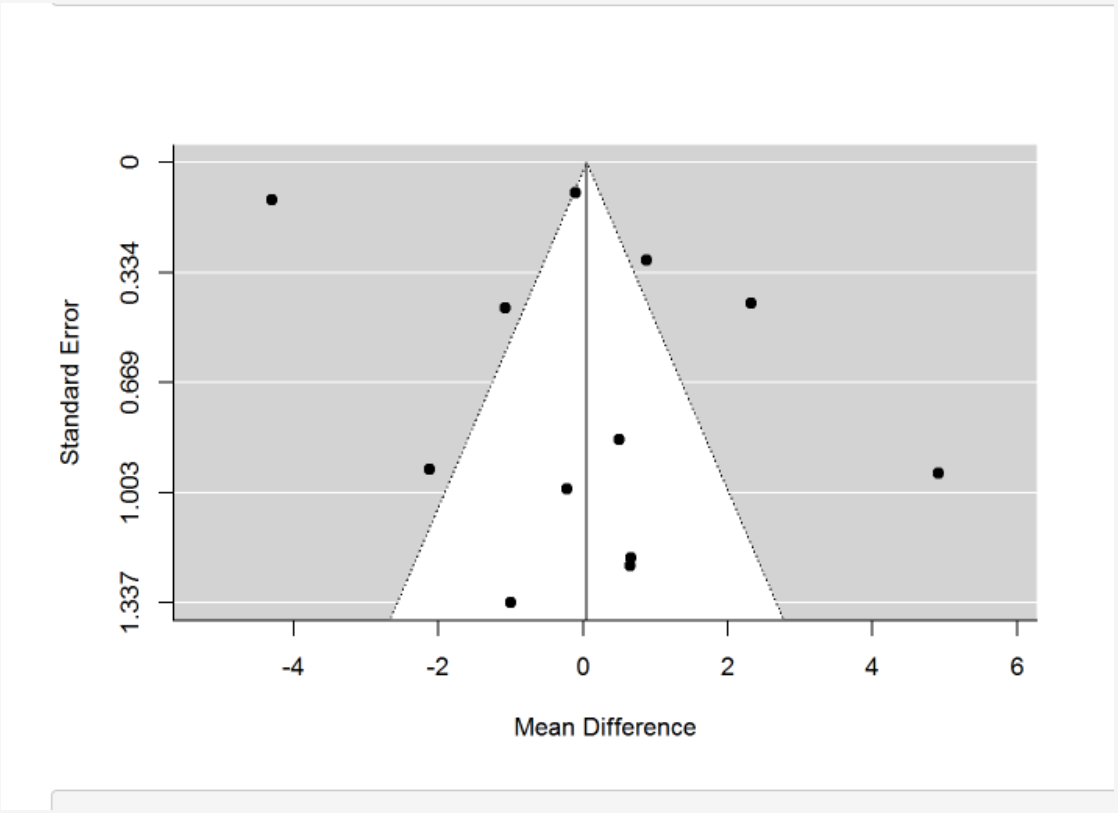
	Study/Country/ Setting	Year	N and diagnosis	Type of patient	Mean age (years)	Psycho-pharmacological treatment	Intervention	Assessment (vitamins/ questionnaires)	Results
1	Frye et al/USA/University of Arkansas Medical Sciences [67]	2013	37 ASD with both abnormal methylation capacity and glutathione redox metabolism	Outpatients	5.1±1.4	Not reported	Open label trial of methyl B_{12} (75µ/kg every third day, subcutaneous) + folinic acid 400 µg/12h for 3 months	Glutathione redox metabolites VABS	All VABS subscale scores significantly increased with an average effect size of 0.59, and an average time of improvement of 7.7 months. A greater improvement in glutathione redox status was associated with a greater improvement in some VABS subscales (expressive communication, personal and domestic daily living skills, and interpersonal, play-leisure, and coping social skills).
2	James et al/USA/University of Arkansas Medical Sciences [66]	2009	40 ASD with abnormal methylation capacity 42 HC	Outpatients	ASD: 4.8±0.8 HC: 4.5±0.9	Not reported	Open-label trial with 400µg folinic acid twice a day + subcutaneous methyB12 (75 µg/Kg) twice a week for 3 months	SAM, SAH, homocysteine and other metabolic parameters VABS	VABS scores improved with the intervention. Significant increase in mean levels of transsulfuration metabolites, cysteine, cysteinylglycine, and GSH, while reducing the concentration of oxidized disulfide GSSG. Plasma levels of methionine and SAM were lower than those in HC.

3	Lonsdale et al/USA/ King James Medical Laboratory [65]	2002	10 ASD	Outpatients	3-8	Not reported	50 mg of TTFD was administered twice daily for 2 months in the form of rectal suppositories.	The concentrations of SH-reactive metals (arsenic, lead, mercury, cadmium, nickel), total protein, sulfate, sulfite, thiosulfate and Thiocyanate in urinary and hair samples, erythrocyte transketolase ATEC	TTFD appears to have a beneficial clinical effect on some autistic children, since 8 of the 10 children improved clinically in speech and behaviour scores. The authors found evidence of an association between this increasingly common disease and the presence of urinary SH-reactive metals, arsenic in particular.
4	Sun et al/China/Harbin Medical University [37]	2016	66 ASD (29 were randomly selected and had metabolic profile analysis) 29 HC (to compare the metabolic profile)	Outpatients	Intervention group: 4.77 ±1.26 Control group: 4.31±1.06	Not reported	Open-label trial with 44 ASD children treated with 400 ug folic acid (twice daily) for a period of 3 months and 22 ASD children who were not given any supplement. Both groups attended structured teaching.	Folic acid, vit B_{12} and other biomarker levels ATEC PEP-3 ABC CARS	Folic acid, but not vit B_{12}, was lower in ASD vs HC before the intervention. There was an improvement in folic acid and homocysteine levels as well as a normalized glutathione redox metabolism after the treatment. Improved subscale scores for sociability, cognitive verbal/ preverbal, receptive language, affective expression and communication were observed after the treatment.
5	Kazanci et al/Turkey/Bakırkoy Dr. Sadi Konuk Research and Training Hospital [55]	2017	524 children and adolescents from the pediatric outpatient clinic	Outpatients	8.3 ± 4.2	Patients receiving any medications causing vit B_{12} deficiency were excluded.	Children and adolescents with vit B_{12} deficiency (< 200 pg/mL) were treated with parenteral or peroral vit B_{12}. Depending on the presence of	Serum vit B_{12}, folic acid, homocysteine No questionnaires, but patients and parents were asked questions.	Symptoms such as forgetfulness, depression, and anxiety were more common in the adolescent group; these symptoms were significantly related to vitamin B_{12} deficiency.

							symptoms, patients with a vit B_{12} levels of 200 - 300 pg/mL also received treatment. Patients with iron deficiency anemia (Hb < 11%) were treated with 8 mg/kg/day of ferrous sulfate.		There was no significant difference between the symptoms of the patients with vit B_{12} < 200 pg/mL and those with Vit B_{12} < 300 pg/mL. Patients who were treated with B_{12} (34% of the sample) normalized their levels and were reported to have no health complaints one month after treatment.

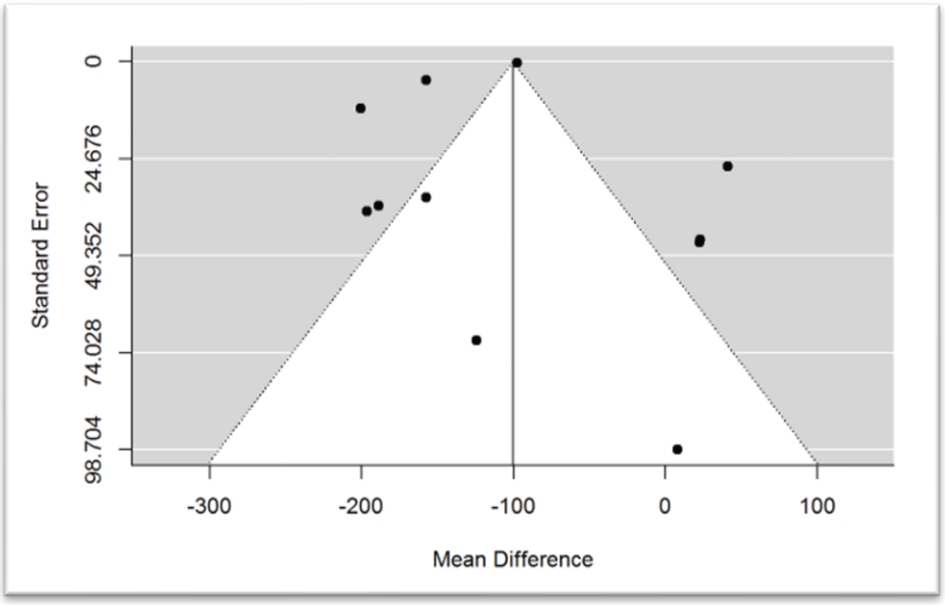
ABC-C: Aberrant Behavior Checklist-Community; ASD: Autism Spectrum Disorder; ATEC: Autism Treatment Evaluation Checklist; CARS: Childhood autism rating scale; CBCL: Child Behavior Checklist; CGI-I: Clinical Global Impression Scale of Improvement; GSH: reduced glutathione; GSSG: oxidized glutathione; HC: Healthy control; MCDI: MacArthur Communication Developmental Inventory; PBO: placebo; PEP-3: Psychoeducational Profile, third edition; PIA-CV: Parent Interview for Autism-Clinical Version; PPVT-III: Peabody Picture Vocabulary Test-Third Edition; SAH: S-Adenosylhomocysteine; SAM: S-Adenosylmethionine; SB-V: Stanford Binet V Edition; SH: sulfhydryl; TKA: erythrocyte transketolase; TPPE: thiamine pyrophosphate effect; TTFD: tetrahydrofurfuryl disulfide; VABS: Vineland Adaptative Behavior Scale; vit: vitamin.

Figure 1. Funnel plot and Egger's test of the meta-analysis includding studies of folate levels in children and adolescents with Autism Spectrum Disorders vs. Healthy controls



Egger's test for funnel plot asymmetry: t = 0.7885, df = 10, p = 0.4487

Figure 2. Funnel plot and Egger's test of the meta-analysis includding studies of vitamin B_{12} levels in children and adolescents with Autism Spectrum Disorders vs. Healthy controls



Egger's test for funnel plot asymmetry: t = -0.9413, df = 9, p = 0.3711

Supplementary Table 1. Description of the Newcastle-Ottawa scale scores for the case-control studies included in the review (N=30).

	SELECTION				COMPARABILITY	OUTCOME			
Study	**Case definition**	**Cases representativeness**	**Control selection**	**Control definition**	**Cases and controls comparability (a-vitamin levels; b-psychopathology scales)**	**Exposure ascertainment**	**Same ascertainment**	**Non-response rate**	**Score**
Adams et al, 2006 [60]	1b	2b	3a	4a	1a	1a	2a	3a	6
Adams et al, 2011 [58]	1b	1b	3a	4a	1a	1a	2a	3a	6
Al-Farsi et al, 2013 [36]	1a	2a	3b	4a	1a	1a	2a	3a	7
Al Gadani et al, 2009 [61]	1a	2b	3c	4a	1a	1a	2a	3a	6
Ali et al, 2011 [35]	1a	2a	3b	4a	1a	1a	2a	3a	7
Altun et al, 2018a [30]	1a	2b	3c	4a	1b	1a	2a	3a	7
Anwar et al, 2016 [62]	1a	2a	3a	4a	1a	1a	2a	3a	8
Eto et al, 1992 [47]	1a	2b	3a	4b	1a	1a	2a	3a	6

Guo et al, 2018 [27]	1a	2a	3a	4a	1a	1a	2a	3a	8
Hope et al, 2020 [54]	1b	2a	3a	4a	1a	1a	2a	3a	7
Krajcovicova-Kudlackova et al, 2009 [63]	1b	2a	3c	4b	1a	1a	2a	3a	5
Liu et al, 2016 [38]	1a	2a	3a	4a	1b	1a	2a	3a	9
Main et al, 2015 [29]	1a	2b	3a	4a	1a	1a	2a	3a	7
Meguid et al, 2017 [28]	1a	2a	3c	4a	1a	1a	2a	3a	7
Metnyk et al, 2012 [45]	1a	2a	3a	4a	1a	1a	2a	3a	8
Paşca et al, 2006 [56]	1a	2b	3c	4a	1a	1a	2a	3a	6
Paşca et al, 2009 [42]	1a	2b	3a	4a	1a	1a	2a	3a	7
Sun et al, 2013 [64]	1a	2a	3a	4a	1a	1a	2a	3a	8
Ugur et al, 2014 [40]	1a	2a	3a	4b	1a	1a	2a	3a	7
Zou et al, 2019 [52]	1a	2a	3a	4a	1a	1a	2a	3a	8

Altun et al, 2018b [46]	1a	2b	3b	4a	1a	1a	2a	3a	6
Bala et al, 2016 [56]	1a	2b	3b	4a	1a	1a	2a	3a	6
Garipardic et al, 2017 [57]	1a	2a	3b	4a	1a	1a	2a	3a	7
Saha et al, 2017 [50]	1a	2b	3c	4b	1a	1a	2a	3a	5
Wang et al, 2019 [51]	1a	2a	3a	4b	1b	1a	2a	3a	8
Yektas et al, 2019 [31]	1a	2a	3b	4a	1a	1a	2a	3a	7
Esnafoglu et al, 2020 [39]	1a	2a	3c	4a	1b	1a	2a	3a	8
Tsuchimine et al, 2014 [43]	1a	2a	3c	4a	1a	1a	2a	3a	7
Kevere et al, 2014 [48]	1a	2a	3a	4b	1a	1a	2a	3a	7
Esnafoglu et al [44]	1a	2a	3b	4b	1b	1a	2a	3a	7

Supplementary Table 2. Description of the Newcastle-Ottawa scale scores for the cohort studies included in the review (N=3).

	SELECTION				**COMPARABILITY**	**OUTCOME**			
Study	**Exposed cohort representativeness**	**Non exposed cohort ***	**Exposure ascertainment**	**Outcome at start (vitamin levels/ psychopathology)**	**Cohorts comparability (a-vitamin levels; b-psychopathology scales)**	**Outcome assessment**	**FU duration (6 months)**	**FU cohort (>80%)**	**Trial score**
Unal et al, 2018 [53]	1b	2d	3b	4b	1b	1b	2b	3d	5
Kazanci et al, 2017 [55]	1b	2d	3b	4b	1a	1b	2b	3d	4
Robinson et al, 2018 [49]	1a	2d	3a	4a	1b	1c	2a	3b	7

FU: follow-up

*In the selection category, an additional response to the second parameter was added (d: non-existence of the non-exposed cohort, rated 0 points) following Pozzi et al, 2020.

Pozzi M, Ferrentino RI, Scrinzi G, Scavone C, Capuano A, Radice S et al. Weight and body mass index increase in children and adolescents exposed to antipsychotic drugs in non-interventional settings: a meta-analysis and meta-regression. Eur Child Adolesc Psychiatry. 2020 Jul 2. doi: 10.1007/s00787-020-01582-9.

Supplemental Table 3: *Evidence Project* risk of bias tool applied to all interventional studies in the review (N=10).

	Study	Cohort	Control of comparison group	Pre/postintervention data	Random assignment of participants to the intervention	Random selection of participants for assessment	Follow-up rate of 80% or more	Comparison groups equivalent on sociodemographics	Comparison groups equivalent on outcome measures
1	Dolske et al, 1993 [59]	Yes	Yes	Yes	Yes	No	Yes	Not reported	Yes
2	Frye et al, 2018 [69]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
3	Hendren et al, 2016 [68]	Yes	Yes	Yes	Yes	No	Yes	Yes	No
4	Kuriyama et al, 2002 [71]	Yes	Yes	Yes	Yes	No	Yes	Yes	Not reported
5	Bertoglio et al, 2010 [17]	Yes	Yes	Yes	Yes	No	Yes	Not reported	Not reported
6	Frye et al, 2013 [67]	Yes	No	Yes	No	No	Yes	Not applicable	Not applicable
7	James et al, 2009 [66]	Yes	No (for the intervention)	Yes	No	No	Yes	Not applicable	Not applicable
8	Lonsdale et al, 2002 [65]	Yes	No	Yes	No	No	Yes	Not applicable	Not applicable
9	Sun et al, 2016 [37]	Yes	No (for the intervention)	Yes	No	No	Yes	Not applicable	Not applicable
10	Kazanci et al, 2017 [55]	Yes	Yes	Yes	No	No	No	Not applicable	Not applicable

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