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Original article

Association between mental disorders, cognitive disturbances and vitamin D serum level: Current state

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SUMMARY

Background & aims: Vitamin D deficiency has been identified as a global problem. Approximately 14% of the world population has inadequate vitamin D levels. This vitamin has been usually associated with bone disorders such as rickets, osteomalacia, and osteoporosis. However, these disorders present only a small part of all the disturbances which can be induced by its deficiency. Low serum vitamin D is associated with development of cardiovascular diseases, hypertension, neurodegenerative diseases, diabetes mellitus, metabolic syndrome and even cancer. This vitamin may be an important factor in the development of psychiatric illnesses, therefore clinicians should not leave this serious issue unresolved. The aim of this review is to describe the current data concerning the association between vitamin D serum levels, cognition and mental disorders.

Methods: We conducted a systematic bibliographical research, of PubMed, MedLine literature and Cochrane database without language restriction to identify all publications concerning this issue from 1995 to the first quarter of 2017.

Results: We found 48,937 articles concerning vitamin D, published during the last 22 years and 3 months (1995–2017). We selected only those publications focused on the association between vitamin D serum deficiency and mental disturbances (depression, schizophrenia, cognitive disturbances, attention deficit disorder, and autism). One hundred and sixty-seven papers were found suitable to our selection criteria. Careful evaluation of the relevant literature demonstrates that addition of vitamin D to conventional antidepressive agents can improve antidepressive effect in contrast to placebo. Regarding other mental conditions there are no clear-cut conclusions.

Conclusions: An association between low vitamin D serum levels and different mental disorders was found. Yet, nonetheless there is no clear consensus that addition of vitamin D improves or is related to a beneficial effect on mental health. More randomized clinical control trials should be performed in order to reach evidence based conclusions.

1. Introduction

Since the discovery of vitamin D in 1922 by an American researcher Elmer McCollum, its role in calcium homeostasis and bone health was well established. Vitamin D is a secosteroid, fat-soluble vitamin as well as a hormone precursor that plays an important role in bone metabolism and seems to have some anti-inflammatory and immune-modulating properties. It exists in two forms: ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) [1]. Vitamin D_2 is synthesized by plants. Vitamin D_3 is synthesized by humans in the skin when it is exposed to ultraviolet-B (UVB) rays from sunlight. Vitamin D from sun exposure, food, and supplements is not biologically active. To become biologically active, this vitamin must undergo two hydroxylation steps: first-in the liver, cholecalciferol (vitamin D_3) is converted to calcidiol (25-hydroxyvitamin D_3). Next, part of the calcidiol is converted by the kidneys to calcitriol, the biologically active form of vitamin D [1,2].

Vitamin D deficiency has been identified as a global problem with an estimated one billion people worldwide suffering from

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vitamin D deficiency or insufficiency [3]. According to Dickens et al., about 14% of the world population has inadequate vitamin D low levels [4]. Among different researchers there is no consensus concerning the optimal serum levels of 25-hydroxyvitamin D. Nevertheless vitamin D deficiency is defined by most experts as lower than 20 ng/mL [4–9]. Studies performed in different countries found that 30%–50% of children and adults have low levels of vitamin D(<20 ng/mL) [6]. Other studies demonstrate that 40%–100% of U.S. and European elderly men and women who live in the community (not nursing homes), have vitamin D deficiency [10].

Vitamin D is highly active in regulating cell differentiation, proliferation, and peroxidation in a variety of structures. Receptors for vitamin D are present in most cells of the body including the brain [11–14]. This means that vitamin D deficiency is not only associated with bone disease, but also may play a role in other body systems as well, including cardiovascular diseases, several autoimmune diseases, cancer, infections, and diabetes [15–17].

Since the discovery of vitamin D, its role in calcium homeostasis and bone health was well established. Inadequate levels of vitamin D have been usually associated with bone disorders such as rickets, osteomalacia, and osteoporosis [18]. However, these disorders can be considered as “the tip of vitamin D deficiency iceberg” [6].

During the last years the number of publications about this topic has significantly increased. A little over half of all articles regarding vitamin D since its discovery in 1922 were published only in the last 10 years (34,679 of 68,473 articles). A preliminary search of literature shows that only during the 2016, there already were 4239 publications. These researches show a growing body of knowledge regarding vitamin D and also highlight its role in brain development and function, as well as stir interest in the investigation of its role in the pathogenesis of mental disorders. For example, some studies demonstrated a connection between the lack of vitamin D supplementation in the first year of life and increased risk of schizophrenia in males [19], while another study found a nonlinear increase in the risk of schizophrenia in patients with low levels of the vitamin [20]. Furthermore, several studies demonstrated a link between vitamin D and depression [21–23].

Vitamin D deficiency is a very common disturbance but often clinically invisible, therefore the clinicians may be unaware to it. It may be an important point in psychiatric illnesses development [24–26], and according to the Bradford Hill criteria [27], clinicians should not leave this serious issue without an attention.

The aim of this literature review is to describe the current knowledge about the association between vitamin D deficiency, cognition, and mental disorders. The authors summarized all relevant publications during the last 22 years and 3 months (1995–2017). We believe that a better understanding of this issue can help clinicians' efforts to correctly diagnose and treat these disturbances.

2. Methods

We conducted a bibliographical research of various medical databases such as PubMed, MedLine literature and Cochrane database without language restriction to identify all studies concerning the association (or absence of such association) between vitamin D deficiency and mental disorders. Additional publications were hand searched from the reference lists of every primary study.

Two independent researchers (PL and CM) investigated the library databases in order to reduce errors/bias in accessing evidence. Relevant publications were identified from the title, abstract and study descriptions by one researcher; the decision to include was independently validated by a second and disagreements were referred to a third researcher for an independent ruling. We included only publications which specifically investigated the association between mental disturbances and vitamin D deficiency.

Since the association between vitamin D and psychiatric phenomena, is a relatively new researchable issue, the current review is integrative and includes clinical as well as animal trials. In this review the following Medical Subject Heading (MeSH) terms using both common and chemical names for vitamin D, such as ‘Vitamin D’ OR 'ergocalciferol' OR 'vitamin D_2' OR 'cholecalciferol' OR 'vitamin D_3' OR 'calcitriol' OR 'vitamin 1,25 D_3' OR 'vitamin 25 D' OR 'hydroxy vitamin D' OR '25-OHD' AND 'Alzheimer's disease', 'Attention deficit hyperactivity disorder', 'ADHD', 'autism', 'autism spectrum disorder', 'ASD', 'Asperger', 'bipolar disorder', 'bipolar affective disorder', 'cognition' ‘cognitive impairment’, ‘cognitive decline’, 'delusional disorder', 'depression', ‘dementia’, 'depressive disorder', 'depressive mood disorder', 'memory', 'psychosis', 'seasonal affective disorder', 'schizoaffective disorder', 'schizophrenia' were used.

Case reports and open treatment studies were not included in this review. Additionally, the initial search of publications with the mentioned above keywords yielded a large number of works due to brief mentions of vitamin D in various articles without examination of-vitamin D levels and/or its association with the mental disorder/cognitive disturbance. Thus the actual number of relevant articles concerning our specific subject is significantly lower. For example: a preliminary search for “vitamin D deficiency” and “schizophrenia” yielded 91 articles, but only 38 of them were relevant for future review (the other 53 articles were not suitable according to the inclusion criteria).

Electronic databases and bibliographies were searched and identified for articles to be evaluated for this work. In this review, the included studies were grouped according to the association between serum level vitamin D deficiency and specific mental disturbances.

3. Vitamin D and mental disorders

3.1. Vitamin D and depression

The association between the lack of sun exposure and mood changes was first described about two thousand years ago [28]. Some recent reports demonstrate that vitamin D deficiency is associated with an increased risk of depression from 8% to 14% [29,30] and a 30% increased risk of suicide [31].

The idea about the relationship between the deficiency of vitamin D and depression comes from studies dealing with seasonal affective disorder. This phenomenon describes rhythmic decreases of mood during the same season each year. Usually, these mood changes occur during autumn and winter months, when the days are shorter and there is less sunlight.

The researchers assumed that a low exposure to sunlight produces a low formation of vitamin D_3 in winter. One study demonstrated that there are seasonal variations in the plasma levels of precursor 25-hydroxyvitamin D_3 ($25(OH)D_3$) (the inactive precursor for active vitamin D), with peak values occurring during autumn. At the same time, there was no seasonal change in the serum concentrations of 1,25-$(OH)_2D_3$ [32]. Low serotonin (5-HT) levels in the brain have been linked to the symptoms of seasonal affective disorder and it has been suggested that vitamin D may play a role in seasonal mood cycles due to dysregulation of 5-HT [33,34]. Vitamin D deficiency or low serum levels of $25(OH)D_3$ are associated with low mood and depression in humans and vice versa [35–38]. Supplementation with vitamin D for 5 days during late winter had a significant positive effect on mood in healthy subjects [39] and on the well-being of endocrine outpatients with low serum $25(OH)D_3$ levels [40]. In a pilot study, 8 subjects with seasonal depression received 100,000 IU of vitamin D over a month, while 7 others were treated only with phototherapy during the same period. Vitamin D treatment was associated with improved

depression symptoms measured by the Hamilton Depression scale, while phototherapy was not effective [41].

Clinical trials support the hypothesis that vitamin D of supplementation may be effective not only in seasonal affective disorder. Wilkins et al. [37] examined the relationship among vitamin D status, cognitive performance, mood, and physical performance in 80 subjects aged 65 years and older living at home. The authors found that 58% of the participants had abnormally low vitamin D levels defined as less than 20 ng/mL. Additionally, the mean level of the vitamin in the total sample was 18.58 ng/mL (SD = 7.59). After adjusting for age, race, gender, and season of vitamin D determination, vitamin D deficiency was significantly associated with low mood ($p = 0.022$). Other authors have also demonstrated that lower serum 25-OHD_2 and 1,25-$(OH)_2D_3$ concentrations were observed in depressive subjects compared to healthy subjects [30,35,42].

In a recent exploratory study, the authors investigated the relationship between frequency and severity of specific psychiatric diagnoses and vitamin D deficiency. The trial included 82 subjects with mood disorders, schizophrenia and schizoaffective disorders. Serum vitamin D level was significantly lower in patients with mood disorders than in schizophrenia patients [43].

There are many studies, some systematic reviews and meta-analyses, regarding the relationship between vitamin D and depression. However, these reports provide conflicting results [28,29,31,44–53]. Most of the studies indicate a direct association between vitamin D deficiency and depression.

Two prospective large cohort studies (n = 954 adults, aged 65 years and n = 1892, aged 18–65 years) found that low levels of 25(OH)D were associated with presence and severity of depression. The authors suggest that hypovitaminosis D may represent an underlying biological vulnerability for depressive disorder [23,54]. Another large, population-based survey of elderly subjects (n = 2070 participants, aged 65 years and older) reported a significantly increased risk of depressive symptoms in those persons with vitamin D deficiency [55].

Using a UK-based birth cohort at the mean ages of 10.6 years (n = 2759) and 13.8 years (n = 2752), Tolppanen et al. [56] found a significant association between low serum vitamin D measured at age 9.8 years, and higher scores on depressive symptoms assessed at age 13.8 year but not at age 10.6 years. Higher socioeconomic position of the parents was associated with lower risk of depressive symptoms at age 10.6 years.

In a cross-sectional, randomized double-blind controlled trial, 441 subjects (aged 21–70 years) were divided into three groups. During a period of 1 year, one group received 20,000 IU of vitamin D, the second group 40,000 IU per week and the third received placebo. Subjects with baseline serum 25(OH)D levels of less than 40 nmol/L had significantly higher scores (more depressive traits) on the Beck Depression Inventory (BDI) scale, than those with more than 40 nmol/L. Both groups, which received vitamin D had a significant improvement in BDI scores after 1 year in contrast to the placebo group [57]. In another 8 week, randomized, double-blind controlled trial, performed on 42 major depressive disorder patients, the researchers compared the therapeutic effects of 1500 IU vitamin D_3 combined with 20 mg fluoxetine in contrast to fluoxetine-placebo combination. The results of this study demonstrated that vitamin D + fluoxetine combination was significantly better than fluoxetine-placebo from the fourth week of treatment. The authors reported that supplemental vitamin D is a safe, effective adjunctive treatment in major depressive disorder [58].

Recent findings from randomized trials suggest that high doses of supplemental vitamin D may improve mild depressive symptoms. A meta-analysis performed by Spedding which included 15 randomized double-controlled trials, demonstrated that in subjects with low levels serum 25(OH)D, vitamin D supplementation was effective for treatment of depression. On the other hand, in subjects with a normal range of vitamin D, its supplementation showed no significant effect [28]. Another systematic review and meta-analysis examined three cohort studies, ten cross-sectional studies and one case–control study. In total, 31,424 participants were included. The cohort studies showed a significantly increased hazard ratio of depression for the persons with the lowest versus highest serum levels of vitamin D. These findings are consistent with the hypothesis that low serum level of vitamin D is associated with depression. The authors highlight the need for randomized controlled trials of vitamin D supplementation for prevention and treatment of depression in order to determine whether this association is causal [44]. Additional 2 meta-analyses included 16 trials with a total of 8114 participants [46,53].

Gowda et al. [46] conducted a meta-analysis of 9 randomized controlled trials which included in total 4923 subjects. The trials were concerned with vitamin D supplementation for reducing depression or depressive symptoms. This meta-analysis showed no significant reduction in depression after vitamin D supplementation ($P = 0.19$). However, the authors emphasize that most of the studies included participants with sufficient vitamin D serum levels at the baseline and low levels of depression.

Shaffer et al. performed a systematic review and meta-analysis of randomized controlled trials which dealt with the effect of vitamin D supplementation on depression or depressive symptoms. In this review, the authors demonstrated that vitamin D supplementation had no overall effect on depressive symptoms ($P = 0.16$). A subgroup analysis showed that vitamin D supplementation for participants with clinically significant depressive symptoms or depressive disorder had a moderate, statistically significant effect ($P = 0.046$). No effect of vitamin D supplementation was found in subjects without clinically significant depression ($P = 0.61$) [53].

A meta-analysis performed by Ju et al. based on 11 cross-sectional studies and 5 cohort studies (n = 55,785) demonstrated an inverse association between serum 25(OH)D levels and the risk of depression. An increase of vitamin D level by10 ng/mL was associated with an 8% decrease in the risk of depression in cohort studies while only a 4% decrease in cross-sectional studies. The authors conclude that the association was somewhat stronger in the elderly and in cases with clinically diagnosed depression. At the same time they suggest that further studies are warranted to establish whether this association is causal [48].

A number of cross-section studies have reported an association between low vitamin D level and depression [36,37,59]. However, these studies are difficult to interpret, as the findings may simply reflect the altered behavior of depressed individuals (e.g. reverse causality – less outdoor activity and thus lower level of vitamin D).

In contrast to the above mentioned publications, some authors believe that there are not enough data to establish whether and when vitamin D supplementation should be considered as an effective augmentation strategy to antidepressants [60]. Li et al. analyzed six randomized controlled trials. Five of them involved adults at risk of depression (total number = 1203, 72% were females) and one trial included 71 depressed patients. Researchers assessed the efficacy of oral vitamin D supplementation compared to placebo. The authors concluded that the differences between the groups treated with placebo versus vitamin D were minimal and non-significant. According to their opinion, there is insufficient evidence to support the efficacy of vitamin D supplementation in depression symptoms [50]. Some researchers believe that although cross-sectional studies have identified associations between depression and low vitamin D levels, they failed to clarify whether vitamin D deficiency is an antecedent cause, correlate or consequence of depression. While vitamin D deficiency and insufficiency

have been linked with seasonal affective disorder, these suggested associations have not been rigorously tested [60]. Dumville et al. [61] did not observe any improvement in quality of life scores following 6 months of vitamin D supplementation in 1621 women aged 70 years and older. However, it should be noted that the authors did not take into account the initial vitamin D status and used different vitamin D doses. Oren et al. [62] found no significant differences between serum vitamin D concentrations in 15 depressed subjects compared to 15 healthy controls.

Recently, a large population-based study which included 35,651 participants aged 55 and older was conducted. During a follow-up for depression a cross-sectional yet not prospective association between serum vitamin D levels and depression was found. The authors suggest that a cross–sectional association in the absence of a longitudinal association can mostly be attributed to reverse causality or residual confounding. According to their opinion, vitamin D deficiency is not an independent risk factor for depression but co-occurs with late-life depression [63].

Some researchers believe that the relationship between vitamin D deficiency and mood is still unclear [64–66]. Moreover, there are other important questions which remain unclear, such as: how does vitamin D affect monoamine function and hypothalamic-pituitary-adrenal axis response to stress? Whether vitamin D supplementation can improve mood in individuals with moderate-to-severe depression? Whether vitamin D sufficiency is protective against depression incidents and their recurrence?

Many authors believe that the best way to define the link between vitamin D levels and depression is by conducting well designed adequately powered randomized controlled trials. According to their opinion, the limited number of such researches has not produced encouraging results, since it is premature to conclude that vitamin D status is related to the occurrence of depression. Additional prospective studies need to prove this relationship [67,68]. The main studies, summarizing the relation between serum vitamin D levels and depression, are presented in Table 1.

3.2. Vitamin D and suicide

Suicide is a global health concern and takes approximately one million lives every year worldwide. Some psychiatric researches report about an asymmetry in the seasonal distribution of suicides, with a peak in the late spring months for both sexes [69,70]. Moreover, some authors connect the increased risk of suicide in areas with less sun exposure, and in the spring with low vitamin D serum level [69,71,72].

We found only 2 studies concerning this issue [31,73]. In a prospective, case-controlled study 25(OH)D serum level in verified suicide cases (n = 495) were examined and matched to control subjects (n = 495) by age and sex. It was found that over 30% of all subjects had 25(OH)D values below 20 ng/mL. Although mean serum 25(OH)D concentrations did not differ between suicide cases and controls, risk estimates indicated that subjects with vitamin D serum level less than 15.5 ng/mL had the highest risk of suicide. The authors conclude that the lowest 25(OH)D levels are associated with an increased risk for suicide [31].

In another research, vitamin D levels in suicide attempters (n = 59), non-suicidal depressed patients (n = 17) and healthy controls (n = 14) were compared. The authors found that suicide attempters had significantly lower mean levels of vitamin D than depressed non-suicidal patients and healthy controls. Fifty eight percent of the suicide attempters were vitamin D deficient according to the clinical standard (<20 ng/mL) while only 29% in the healthy and non-suicidal depressed groups [73].

Although only 2 studies concerning the relationship between vitamin D levels and suicide were performed, however the both concluded that vitamin D low levels associated with suicide. More randomized clinical control trials should be performed for reaching evidence based conclusions, but even on these preliminary data we recommend to clinicians to examine vitamin D levels in depressed patients.

3.3. Vitamin D and schizophrenia

Schizophrenia is a chronic and severe mental disorder characterized by abnormal social behavior and effects on a persons' thinking and feelings. The development of schizophrenia is probably more complex than was proposed over 50 years ago. According to modern knowledge, schizophrenia may originate by a combination of multiple factors which include: genetic vulnerability, changes in neurodevelopmental activity, lowered prenatal vitamin D exposure, viral infections, smoking, intelligence coefficient, cannabis use, social defeat, nutrition and childhood trauma. All of these may culminate in the expression of disease state [74].

In addition to the conventional theories of schizophrenia, there is a hypothesis concerning vitamin D as a component of its pathogenesis [75]. In order to prove this theory, animal models were developed [76]. In these models, it has been shown that vitamin D receptors are directly involved in the regulation of dopaminergic-associated genes expression, which in turn affect dopamine production [77]. Vitamin D deficiency during embryonic development has been proposed as a risk factor for schizophrenia as part of the neurodevelopmental hypothesis for this disorder [75,78]. An epidemiological link has been observed between the season of birth, latitude, and the occurrence of schizophrenia [75]. The schizophrenia subjects were found to be born significantly more frequently during winter time, in the higher areas, and in urban zones. The common denominator is a lower maternal serum 25-OHD_2 concentration [79].

Recent studies have suggested a potential role of vitamin D in the development of schizophrenia. It was found that neonatal vitamin D status is associated with the risk of developing schizophrenia in later life. The biological mechanism is most likely related to vitamin D's action on the regulation of inflammatory and immunological processes, consequently affecting the manifestation of clinical symptoms and treatment response of schizophrenia [80]. McGrath et al. examined the association between neonatal vitamin D status and risk of schizophrenia. The authors performed an individually matched case–control study which included 424 schizophrenia patients and a control group of identical number matched for sex and date of birth. It was found that people with neonatal levels of vitamin D in the lower 3 quintiles had a 2-fold increased risk of schizophrenia. Unexpectedly, those in the highest quintile also had a significantly increased risk of schizophrenia [20].

Yan et al. described in their study on schizophrenic patients three novel structural variants of vitamin D receptors [81]. They have been identified in the hamster [82] rat [83,84] and human [85] brains. The distribution of vitamin D receptors in certain brain regions suggested that vitamin D may influence particular neurotransmitters and cortical function. In the adult human brain, vitamin D receptors are present in neurons and glia of the prefrontal cortex, hippocampus, hypothalamus, amygdala, substantia nigra and other regions and are implicated in a range of neuropsychiatric disorders [85]. Subsequent research has provided robust evidence linking vitamin D related mechanisms and dopaminergic neurotransmission [11,86].

Following vitamin D deficiency during embryogenesis protein changes were found in the frontal cortex and the hippocampus. These proteins are involved in diverse pathways including mitochondrial function, cytoskeletal control, synaptic plasticity,

Table 1
Cohort studies, RCT, major reviews and meta-analyses assessing the relationship between serum vitamin D levels and depression.

No. Reference	Design	No. of patients/No. of studies	Main conclusion
Milneschi et al. (2014) [23]	Cohort study	Current depressive disorder (N = 1102); Remitted depressive disorder (N = 790); Healthy controls (N = 494).	Low levels of vitamin D were associated to the presence and severity of depressive disorder
Spedding (2014) [27]	Systematic review and meta-analysis	15 Randomized control trials	All studies demonstrated a statistically significant improvement in depression with vitamin D supplements
Gangi et al. (2010) [28]	National Health and Nutrition Examination Survey	7970 non-institutionalized US residents	The likelihood of having depression in persons with vitamin D deficiency is significantly higher compared to those with vitamin D sufficiency
Umhau et al. (2013) [30]	Prospective, nested, case −control study	495 suicide cases; 495 control group (by rank, age and sex)	The lowest vitamin D levels are associated with an increased risk for suicide
Wilkins et al. (2006) [36]	Cross-sectional study	40 with mild Alzheimer disease; 40 non-demented persons	Vitamin D deficiency was associated with low mood and with impairment on two of four measures of cognitive performance
Anglin et al. (2013) [43]	Systematic review and meta-analysis	10 cross-sectional studies; 3 cohort studies; 1 case−control study a total of 31,424 participants	Low vitamin D concentration is associated with depression
Gowda et al. (2015) [45]	Meta-analysis of vitamin D supplementation randomized controlled trials	9 trials with a total of 4923 participants	No clear conclusion; The studies included used different vitamin D doses with a varying degree of intervention duration
Ju et al. (2013) [47]	Systematic review	11 cross-sectional studies (43,137 participants); 5 cohort studies (12,648 participants)	An inverse association between serum vitamin D levels and the risk of depression.
Kjaerjaar et al. (2011) [48]	Longitudinal, population-based, multipurpose study	10,086 participants of the sixth Tromso study	Low serum vitamin D levels were found to be a significant predictor of depressive symptoms in both smokers and non-smokers. The association seemed to be stronger in women
Li et al. (2014) [49]	Meta-analysis of vitamin D supplementation randomized controlled trials	6 Randomized control trials (1203 participants)	There is insufficient evidence to support the efficacy of Vitamin D supplementation in depression symptoms
Murphy and Wagner (2008) [51]	Integrative review	6 quantitative research studies (578 participants, of them 528 females)	4 of the 6 studies show a significant association between mood disorders and low vitamin D levels
Shaffer et al. (2014) [52]	Meta-analysis of vitamin D supplementation randomized controlled trials	7 randomized controlled trials	Vitamin D supplementation may be effective for reducing depressive symptoms in patients with clinically significant depression
Milneschi et al. (2010) [53]	Population-based cohort study	531 women and 423 men	Hypovitaminosis D is a risk factor for the development of depressive symptoms in older persons. The prospective association is higher in women
Stewart and Hirani (2010) [54]	National Health Survey	2070 participants who had participated in the 2005 Health Survey for England	Vitamin D deficiency is associated with late-life depression in northern latitudes
Tolppanen et al. (2012) [55]	Prospective cohort study	10.6 years (2759 participants); 13.8 years (2752participants)	There is an association which emerges in childhood between vitamin D concentrations and depression
Jorde et al. (2008) [56]	Cross-sectional, randomized double blind controlled trial	159 men and 282 women	Supplementation with high doses of vitamin D seems to ameliorate symptoms of depression
Khoraminya et al. (2013) [57]	Double-blind, randomized, placebo-controlled trial. Vitamin D as add on to fluoxetine treatment	42 patients	Vitamin D + fluoxetine combination was superior to fluoxetine alone in controlling depressive symptoms
Hoang et al. (2011) [58]	Cross-sectional study	12,594 participants	Low vitamin D levels are associated with depressive symptoms, especially in persons with a history of depression
Parker and Brotchie (2011) [59]	Clinical overview	N/A	There is currently insufficient evidence to argue strongly for vitamin D supplementation in patients with depression
Dumville et al. (2006) [60]	Randomized control study	2117 women (1205 in the control group and 912 in interventional group)	Supplementing elderly women with 800 IU of vitamin D daily did not lead to an improvement in mental health scores.
Nanri et al. (2009) [62]	Health survey	527 municipal employees	Overall, depressive symptoms were not appreciably associated with serum vitamin D concentrations
Pan et al. (2009) [63]	Population-based cross-sectionall study	3262 community residents	Depressive symptoms are not associated with vitamin D concentrations in middle-aged and elderly Chinese
Zhao et al. (2010) [64]	A cross-sectional, population-based study	3916 participants	No significant associations were found between serum concentrations of vitamin D and the presence of moderate-to-severe depression, major depression or minor depression among US adults
Jovanova et al. (2017) [65]	Population-based study	35,651 participants	Probably, vitamin D deficiency is not an independent risk factor for depression, but co-occurs with late-life depression.

chaperoning and neurotransmission. The authors emphasize that of the 36 proteins found to change, 13 have been linked with schizophrenia [87]. Screening for alterations in gene expression in the brain following embryonic vitamin D deficiency found changes in 74 genes (two-fold or more) involved in the same pathways [88]. Sixteen of them were genes linked with schizophrenia [38]. However, it is difficult to build up a case of linkage and perhaps further investigations on the matter are necessary.

Shivakumar et al. examined the potential association between serum vitamin D level and hippocampal gray matter volume in 35 antipsychotic-naïve or antipsychotic-free schizophrenia patients. The authors found that 34 schizophrenia patients (97%) had suboptimal levels of serum vitamin D (83%, deficiency; 14%, insufficiency). A significant positive correlation was seen between vitamin D and regional gray matter volume in the right hippocampus after controlling for age, years of education and total intracranial volume. Lower levels of serum vitamin D levels were associated with decreased gray matter volume in the right hippocampus in schizophrenia patients. These findings support the theory that vitamin D deficiency has a potential role in mediating hippocampal volume deficits, possibly through neurotrophic, neuroimmunomodulatory and glutamatergic effects [89].

Jamilian et al. performed a cross-sectional study, it included 100 schizophrenia patients and 100 with major depression. A serum sample was taken and levels of vitamin D, calcium, phosphorus and parathyroid hormone were assessed and then compared between the three groups. The authors found that vitamin D affects the brain independently of hormonal pathways which regulate serum level of calcium. Non-significant differences in the serum level of vitamin D between the schizophrenics and the depressed patients suggest that the independent effect of vitamin D in brain is a general effect and is not specialized to a specific region or pathway in the brain; however, differences between psychiatric and non-psychiatric patients might result from differences in psychosocial backgrounds [90].

Studies undertaken in the UK, the Netherlands and Nordic countries, demonstrated that the incidence of schizophrenia is significantly higher in dark-skinned migrants compared to the native born [91]. In an epidemiological study performed on two separate data sets (Australia and the Netherlands) an association between perinatal sun exposure and schizophrenia birth rates was found in males, but not females [92]. The authors could not explain these findings and did not discuss them; however, they emphasized the importance of replication of these results.

Mackay-Sim et al. suggested that low 25-OHD_2 levels during embryonic neuroformation could interact with susceptible genes and modifying the development of the brain through epigenetic regulation, which may induce predisposition to the appearance of psychosis [93]. Animal trials support this hypothesis. Moreover, apolipoprotein (apo) E, which was identified in these model rats, and is considered a risk factor for schizophrenia [87]. Similarly, Burne et al. [94] demonstrated that chronic pre- and postnatal vitamin D deficiencies in animals, unlike the deficiency observed in the early days of life, were risk factors for developing schizophrenia. In humans, low serum 25-OHD_2 concentrations have been reported in patients with schizophrenia [95,96]. Such observations are consistent with the findings of the prospective study of McGrath et al. [19] who described a decreased incident risk of long-term schizophrenic psychosis in 9114 subjects supplemented with vitamin D over the first year of life. A meta-analysis of observational studies, performed by Valipour et al., demonstrated that vitamin D-deficient persons were 2.16 times more likely to have schizophrenia than those without it. The authors note a strong association between vitamin D deficiency and schizophrenia [97]. In a recent study titled "Low vitamin D levels predict clinical features of schizophrenia", the authors demonstrated that 91% of patients had deficient or insufficient vitamin D levels, which were associated with excitement and grandiosity, social anhedonia, and poverty of speech. Sex-specific analyses showed strong associations of hypovitamintosis D to negative symptoms and decreased premorbid adjustment in males. Additionally, they also found a relation to lesser intensity of hallucinations and emotional withdrawal, but increased anti-social aggression in females. Moreover, this study demonstrated a relationship of low vitamin D levels with increased cellular aging in females [98]. Graham et al. [99] compared vitamin D plasma levels of 20 recent onset schizophrenia patients and 20 control subjects. No significant difference in the vitamin levels was found. However, an interesting finding was that the severity of negative symptoms correlated with lower vitamin D levels ($P = 0.012$). Additionally, it was found that the correlations of the severity of positive symptoms and overall symptom severity with 25 OH vitamin D levels approached significance ($P = 0.12$, $P = 0.07$ respectively).

In a study comparing vitamin D serum concentrations in patients with major depression, schizophrenia and healthy control lower levels of the vitamin were demonstrated in schizophrenia patients. The authors did not find a correlation between disease severity measured by The Positive and Negative Syndrome Scale and vitamin D levels [100].

In two other studies, low serum 25-OHD_2 concentration has also been reported in schizophrenia patients [95,96]. These results were supported by findings from a Finnish birth cohort study ($n = 9114$), where vitamin D supplementation to neonates was associated with a reduced risk for schizophrenia in males, but not females [19]. However, another study which examined the association between vitamin D levels in maternal serum during third trimester of pregnancy, and the development of schizophrenia in their offspring, failed to find such a significant relationship [101]. In a large and well-controlled study the McGrath et al. examined the relationship between vitamin D levels in archived neonatal blood and the subsequent development of schizophrenia. Unexpectedly, the authors found that both low and high levels of neonatal vitamin D were associated with an increased risk for schizophrenia. However, in their opinion, the low vitamin D hypothesis should be potentially accounted for by some of the important epidemiological, neurophysiological, and clinical features of schizophrenia [20,102]. In addition, vitamin D serum levels in 26 mothers whose children developed schizophrenia, were not significantly lower than in 51 control mothers, whose children did not develop the disease [101]. The authors believe that below a certain critical threshold, low levels of maternal vitamin D may be associated with an increased risk of schizophrenia [101]. Furthermore, these studies suggest that vitamin D is not the sole factor in schizophrenia's origin.

In addition to the risk of schizophrenia, there is preliminary evidence linking vitamin D intake with risk of isolated psychotic (subclinical) symptoms. A large population-based study of Swedish women ($n = 33,623$) reported a significant association between low vitamin D consumption and increased endorsement of psychotic-like symptoms [103]. This finding suggests that vitamin D status during adulthood may also influence the risk of psychosis.

In a nationally representative sample, Partti et al. examined broadband ultrasound attenuation and speed of sound. The trial included 48 schizophrenia subjects, 56 patients suffered from other nonaffective psychosis, 37 patients with affective psychosis, and 6100 population controls. In addition, serum vitamin D level was measured. It was found that women with schizophrenia and men with affective psychosis had significantly lower bone ultrasound values as compared with the age- and sex-matched population controls. Significantly lower vitamin D levels were observed in subjects with schizophrenia in comparison with the general population [104].

Concerning the ethical issue regarding treatment or withholding vitamin D in pregnant women, until now it remains not clear. There are no definite controlled results in order to create guidelines. In our opinion continuation of placebo control studies should be warranted.

Many authors have come to the same conclusion that future well-designed observational studies and, more importantly, randomized clinical trials of vitamin D supplementation both during pregnancy and post-partum are clearly warranted to clarify whether the level of maternal vitamin D is a cause for concern [68].

In an open parallel label randomized clinical trial, vitamin D was added to the standard therapeutic regimen of schizophrenic male patients with inadequate vitamin D status in order to examine its effect on positive and negative symptoms in schizophrenia. The researchers did not find a relationship between serum vitamin D level changes and the improvement of negative and positive symptoms. Further randomized clinical trials are required to confirm these findings [105].

In order to recommend supplementation of vitamin D as a standard therapeutic attitude, more randomized placebo-controlled studies should be performed with definite results showing its efficacy.

The main studies, which summarize the relation between serum vitamin D levels and schizophrenia, are presented in Table 2.

3.4. Vitamin D and cognitive disturbances

More than 10% of people over 65 years and 50% of people over 85 years develop dementia [106]. Alzheimer's disease (AD) represents 60–70% of these cases. It is a chronic neurodegenerative disease with insidious evolution caused by complex interactions of genetic, environmental factors [107], and potentially includes hypovitaminosis D. Laboratory evidence include several findings on the role of vitamin D in neuroprotection and reducing inflammation [26].

Experimental studies revealed abnormal brain morphology in the setting of vitamin D deficiency. These animals had a longer cortex, enlarged lateral ventricles, increased brain size, reduced expression of nerve growth factors and increased cellular proliferation [108]. Most publications based on clinical studies during the past decade demonstrated that hypovitaminosis D is associated with a 2.4 times higher risk of cognitive impairment as a whole [3,109,110], and specifically with AD compared to healthy controls [4,111,112]. Subjects older than 50 years were found especially susceptible. This information may be stipulated by different factors such as reduced intake, absorption, and decreased exposure to sunlight [6,113–117]. According to a study by Soni et al., the risk of cognitive impairment was up to four times greater in the severely deficient elders (25(OH)D < 25 nmol/L (2.5 nmol/L = 1 ng/mL)) in comparison with individuals with adequate levels (≥75 nmol/L) [118]. In another study, subjects with vitamin D serum level of less than 50 nmol/L, were more than twice as likely to have all-cause dementia/AD, than those with a concentration more than 50 nmol/L after adjustment for age, race, sex, body mass index and education [119]. Similarly, several cross-sectional studies from Europe [120,121] and US [37,113,122] suggest a linkage between low vitamin D serum level and poor global cognitive function. The risk of cognitive impairment was up to four times greater in persons

Table 2
Cohort studies, RCT, major reviews and meta-analyses assessing the relationship between serum vitamin D levels and schizophrenia.

No. Reference	Design	No. of patients	Main conclusion
McGrath et al. (2010) [20]	Individually matched case–control study drawnfrom a population-based cohort	424 individuals with schizophrenia; 424 controls (matched for sex and date of birth)	Both low and high concentrations of neonatal vitamin D are associated with increased risk of schizophrenia
Jamilian et al. (2013) [90]	Cross-sectional study	100 patients with schizophrenia 100 patients with depression	The independent effect of vitamin D in brain is not specialized to a specific region or pathway in the brain
McGrath et al. (2002) [91]	Ecological analysis	Australia 6630 participants; The Netherlands 24,474 participants	A measure of long-term trends in perinatal sunshine duration was associated with two epidemiological features of schizophrenia in two separate data sets
Valipour et al. (2014) [96]	Systematic review and a meta-analysis	19 observational studies that were included in 3 separate meta-analyses	A strong association between vitamin D deficiency and schizophrenia was found.
Ciesak et al. (2014) [97]	A pilot study exploring the association between vitamin D levels and illness features in schizophrenia	22 schizophrenia patients	Low Vitamin D in males with schizophrenia was associated with increased overall negative symptoms and decreased premorbid adjustment. Among females, decreased Vitamin D was associated with lesser hallucinatory behavior and emotional withdrawal
Graham et al. (2015) [98]	Comparison of plasma levels of vitamin D between schizophrenia patients and healthy control	20 recent onset schizophrenia patients; 20 control subjects	Lower vitamin D levels in schizophrenia subjects were associated with more severe negative symptoms and overall cognitive deficits.
Itzhaky et al. (2012) [99]	Comparison of serum levels of vitamin D in patients with major depression, schizophrenia and healthy controls	50 patients with schizophrenia; 33 patients with major depression; 50 control (no major psychopathology)	Serum vitamin D levels were lower in patients with schizophrenia as compared to patients with depression and to healthy controls. No correlation was found between serum concentration and disease severity
McGrath et al. (2003) [100]	Comparison of serum levels of vitamin D in mothers of individuals with schizophrenia or schizoaffective disorders versus mothers of unaffected controls	26 mothers of affected individuals; 51 control group	Maternal vitamin D does not operate as a continuous graded risk factor for schizophrenia, however, the results in the black subgroup raise the possibility that below a certain critical threshold, low levels of maternal vitamin D may be associated with an increased risk of schizophrenia
Sheikhmoonesi et al. (2016) [103]	An open parallel label randomized clinical trial	80 patients	No relationship was found between serum vitamin D level changes and the improvement of negative and positive symptoms in schizophrenic patients
Partti et al. (2010) [104]	Nationally representative sample	48 schizophrenia subjects, 56 patients with other nonaffective psychosis, 37 patients with affective psychosis, and 6100 population controls.	Significantly lower vitamin D levels were observed in subjects with schizophrenia in comparison with the general population

with vitamin D serum level less than 25 nmol/L compared to those who had serum concentrations more than 75 nmol/L [122].

Vitamin D's relationship to cognitive impairment in elderly adults may have significant implications for geriatric care and long-term care facility planning. Cross-sectional and longitudinal studies of older adults from the United States and Europe have generally found that low serum vitamin D levels are associated with greater odds of cognitive impairment [4,109,120–128]. Recent studies indicate that the association between hypovitaminosis D and AD can be partly explained by the onset of executive dysfunction [3,113,124,129].

A multiethnic cohort study included 382 older adults (a mean (SD) age of 75.5 (7.0) years). The study assessed associations between serum vitamin D levels and cognitive function. Miller et al. found that low vitamin D level was associated with accelerated decline in cognitive function domains in ethnically diverse older adults, including African American and Hispanic individuals who exhibited a high prevalence of vitamin D insufficiency or deficiency. However the researchers did not examine whether vitamin D supplementation slows cognitive decline [130].

Two recent large, prospective studies suggest a temporal association between low baseline vitamin D status and subsequent cognitive decline. Elderly Italian adults (65 years or older), with serum 25-hydroxyvitamin D level lower than 25 nmol/L had a 60% increased relative risk of substantial cognitive decline over a 6-year period compared with those who had 75 nmol/L and higher [124]. A German study which included elderly general population (1639 participants) aged 65+ years, demonstrated that low levels of vitamin D may be associated with reduced cognitive functioning [123]. In a cross-sectional study of 80 participants, 40 with mild AD and 40 non demented persons, vitamin D deficiency was associated with the presence of an active mood disorder and with worse cognitive performance in 2 out of 4 measurements [37]. From a chart review of 80 patients, serum 25(OH)D concentrations showed a significant positive correlation with Mini-Mental Status Examination (MMSE). The authors suggest that vitamin D may play a specific role in cognitive function of older adults [125]. A significant negative correlation between dietary intake of vitamin D and poor performance on cognitive tests was also observed in a study of 69 free-living urban healthy elderly [131]. In a study performed by Tofanello et al., 1927 community dwelling elderly individuals with a mean (SD) age of 73.9 (6.7) years were examined. Vitamin D deficiency (25(OH)D, lower than 50 nmol/L) was identified in approximately 28% of the whole sample, and the deficiency was severe (lower than 25 nmol/L) only in 6.5% of cases. The authors found an independent association between low 25(OH)D levels and cognitive decline in elderly individuals. In cognitively intact elderly subjects, 25(OH)D levels below 75 nmol/L were already predictive of global cognitive dysfunction in the next 4.4 years [132].

Furthermore, in a recent meta-analysis based on 37 studies, the authors concluded that lower vitamin D concentrations are associated with poorer cognitive function and a higher risk of AD. Nevertheless, the researchers note that further studies are required to determine the significance and potential public health benefit of this association [133].

There are also controversial data which didn't support the relationship between low levels of vitamin D and cognitive impairment. Two different trials included a total sample of more than 10,000 participants, the results were similar and did not find significant associations between lower levels of 25(OH)D with impaired performance of cognitive tests. The first trial included participants with mean age of 62 years [134]. The researchers did not find significantly associated with lower cognitive test scores at baseline or with greater decline in cognitive test score over time. Lower levels of 25(OH)D measured in late middle age were also not significantly associated with increased dementia risk during a median of 16.6 years of follow-up. In the second trial there were 3 groups of patients according to their age without mention of gender: adolescent group (12–16 years, n = 1676), adult group (20–59 years, n = 4747), and elderly group (60–90 years, n = 4809) [135]. In the adolescent and adult groups, none of the psychometric measures were associated with vitamin D levels. In the elderly group there was a significant difference Ws2QAZSbetween 25(OH)D quintiles performance on a learning and memory task. The authors concluded that lower 25(OH)D levels were not associated with impaired performance on various psychometric measures. While it remains to be seen if chronic exposure to low 25(OH)D levels alters brain function in the long term, this cross-sectional study suggests that 25(OH)D levels do not influence neurocognitive performance. Additional study performed in the US on elderly men (65 years or older) over a mean of 4.6 years found little evidence of independent associations between lower 25-hydroxyvitamin D level and baseline global and executive cognitive function or incident cognitive decline [136]. It is important to note that the same research group which didn't find a relation between vitamin D levels and cognitive impairment in men, found a positive association in elderly women (over 65 years old) in another study [137].

In a randomized double-blind placebo control trial performed on mental health group of 50 adolescents, the effect of vitamin D supplementation on vitamin D status, executive functioning and self-perceived mental health during winter time were investigated. The participants were exposed to a test procedure, consisting of blood draw, and completion of cognitive tests. The participants with low vitamin D status scored demonstrated worse results on cognitive tests. The addition of vitamin D improved their performance on the most demanding tests and may be important for both executive functioning and mental health [138].

We found one study that aimed to examine whether vitamin D supplementation led to improvements in diverse measures of cognitive and emotional functioning. In this study, the researchers performed a parallel-arm, double-blind trial. One hundred and twenty-eight subjects were randomly allocated to receive vitamin D 5000 IU or identical placebo capsules for six weeks. The mean age of participants was 21.8 years (18–30), and more than half were female (57%). All participants and outcome assessors were blinded to the group assignment. The findings of this study did not demonstrate that vitamin D supplementation had influence on cognitive or emotional functioning in healthy young adults [139].

Such conflicting data could be explained by differences in methodology, participants' age, gender, type of cognitive tasks used in the studies and definition of vitamin D deficiency. Also, it remains unclear which specific cognitive functions are affected in vitamin D deficiency and explain the link with impaired global composite cognitive scores.

The laboratory evidence which support the connection between low levels of vitamin D and cognitive impairment include several findings on the role of the vitamin in neuroprotection and reducing inflammation. Although this evidence is supportive, we could not find any observational studies referring to incidence of dementia associated with prediagnostic serum 25(OH)D and improvement after vitamin D supplementation. Such studies now appear to be warranted [140]. Vitamin D insufficiency may be a modifiable risk factor for dementia as the role of vitamin D in brain function is becoming clearer [141,142].

Although it is known that low levels of vitamin D are associated with cognitive impairment, it is unknown if high or optimum levels will lessen cognitive loss. It also remains unclear whether giving vitamin D will help patients to regain some of the impaired high-level functions.

The main studies, summarizing the relation between serum vitamin D levels and cognitive disturbances, are presented in Table 3.

3.5. Vitamin D and autism

Autism spectrum disorder (ASD) is a neurodevelopmental disorder caused by a complex interaction between genetic and environmental risk factors and is characterized by impaired social interaction, impaired verbal and non-verbal communication, and is accompanied by restricted and repetitive behavior patterns [143,144]. ASD is relatively common. Studies performed in Asia, Europe and North America have identified an approximate prevalence of 6/1000 to over 10/1000 children [145]. The etiology of ASD remains poorly understood. Among the environmental factors, vitamin D seems to play a significant role in the etiology of ASD as this vitamin is important for brain development. Lower concentrations of vitamin D may lead to increased brain size, altered brain shape, and enlarged ventricles, which have been observed in patients with ASD. Moreover, epidemiologic data on seasonal

Table 3
Cohort studies, RCT, major reviews and meta-analyses assessing the relationship between serum vitamin D levels and cognitive impairment.

No. Reference	Study Design	No. of patients	Main conclusion
Annweiler et al. (2014) [3]	Cross sectional study	100 Caucasian older community dwellers	Vitamin D deficiency was associated with poorer mental flexibility among older community dwellers with memory complaint
Etgen et al. (2012) [107]	Systematic literature research and meta-analysis	5 cross-sectional and 2 longitudinal studies (7688 participants)	No clear conclusions due to methodological limitations
Oudshoorn et al. (2008) [108]	Cross sectional study	225 individuals having probable Alzheimer's disease	A relationship exists between vitamin D status and cognition in patients with probable AD. However, given the cross-sectional design of this study, no causality can be concluded
Annweiler et al. (2013) [109]	Meta-analysis	14 observational studies (including 3 prospective cohort studies) and 3 interventional studies	Lower serum vitamin D concentrations predict executive dysfunctions, especially on mental shifting, information updating and processing speed
Buell et al. (2010) [117]	Cross sectional investigation	318 participants	Vitamin D insufficiency and deficiency was associated with all-cause dementia, Alzheimer disease, stroke (with and without dementia symptoms), and MRI indicators of cerebrovascular disease
Annweiler et al. (2010) [118]	Cross-sectional population-based study	752 women	Vitamin D deficiency was associated with cognitive impairment in this cohort of community-dwelling older women
Llewellyn et al. (2009) [119]	Nationally representative population-based study	1766 adults living in private households and older residents in institutions	Low serum 25-hydroxyvitamin D is associated with increased odds of cognitive impairment
Llewellyn et al. (2011) [120]	Nationally representative cross-sectional study	3325 adults of the U.S. non-institutionalized population	Vitamin D deficiency is associated with increased odds of cognitive impairment in the elderly U.S. population
Breitling et al. (2012) [121]	Population-based study	1639 participants of epidemiological ESTHER study	Low levels of vitamin D may be associated with reduced cognitive functioning in the elderly
Llewellyn et al. (2010) [122]	Population-based study	858 adults participating in the InCHIANTI population-based study	Low levels of vitamin D were associated with substantial cognitive decline in the elderly population
Peterson et al. (2012) [126]	Community-based cohort study	159 participants from “Intelligent Systems for Assessment of Aging Changes” study	Vitamin D concentrations correlated with cognition and falls
Annweiler et al. (2012) [127]	Pre–post study	20 participants in “vitamin D3 group”; 24 participants in a control group	The use of vitamin D3 supplements, was associated with medium-term improvement in cognitive performance in older adults and in particular with better executive functioning
Miller et al. (2015) [128]	Multiethnic cohort study	382 participants	Low vitamin D status was associated with accelerated decline in cognitive function domains in ethnically diverse older adults
Toffanello et al. (2014) [129]	Population-based cohort study	1927 Italian elderly subjects, part of Progetto Veneto Anziani study	The study supports an independent association between low vitamin D levels and cognitive decline in elderly individuals. In cognitively intact elderly subjects, the vitamin levels below 75 nmol/L are already predictive of global cognitive dysfunction at 4.4 years
Balion et al. (2012) [130]	Meta-analysis	37 studies	Lower vitamin D concentrations are associated with poorer cognitive function and a higher risk of AD
McGrath et al. (2007) [131]	Cross-sectional study	Participants from population-based NHANES III survey. Adolescent group (n = 1676, age range 12–17 years); adult group (n = 4747, 20–60 years); elderly group (n = 4809, 60–90 years)	Lower vitamin D levels were not associated with impaired performance on various psychometric measures
Schneider et al. (2014) [132].	Prospective cohort analysis	1652 participants	No significant associations between lower levels of vitamin D with lower cognitive test scores at baseline were found
Slinin et al. (2010) [133]	Cohort study	1604 men	Little evidence of independent associations between lower vitamin D level and baseline global and executive cognitive function or incident cognitive decline
Slinin et al. (2012) [134]	Prospective cohort study	6257 community-dwelling elderly women	Low vitamin D levels among older women were associated with a higher odds of global cognitive impairment and a higher risk of global cognitive decline
Grung et al. (2017) [135]	Randomized double-blind placebo control trial	50 healthy volunteers 25 in vitamin D group; 25 in placebo group	Vitamin D status in adolescents may be important for both executive functioning and mental health
Dean et al. (2011) [136]	Parallel-arm, double-blind trial	128 healthy young adults 63 in vitamin D group 65 in placebo group	Vitamin D supplementation does not influence cognitive or emotional functioning in healthy young adults

variation in birth rates and prevalence of autism suggest that maternal vitamin D deficiency is a risk factor for ASD [146,147]. Reduced serum vitamin D levels have been associated with alexithymia, a condition that shows high comorbidity with autism [148]. One of the theories regarding the development of autism is connected to vitamin D deficiency. Since activated vitamin D up regulates DNA-repair genes, its deficiency during development may inhibit the repair of de novo DNA mutations in fetuses and infants thus contributing to the risk of autism. Vitamin D supplementation may influence and decrease the risk or severity of autism. Its mechanism of action includes anti-inflammatory activity and anti-autoimmune effects. It increases seizure threshold, and T-regulatory cells, protects the mitochondria, and up regulates glutathione, which scavenges oxidative by-products and chelates (captures and excretes) heavy metals.

A difference in the season of birth was found between ASD and non-ASD siblings. However, these findings are still controversial. Hebert et al. performed a study including a total of 86 children with ASD. The authors found some evidence that a larger number of children with ASD are born during the summer months. However, in their review of 13 studies, in 8 of them a corresponding peak was found in spring births. Another 5 sufficiently large studies failed to replicate any season effect of birth [149]. A recent clinical review, included 35 publications from 1995 to 2011 performed by Kosovska et al., concluded that low vitamin D levels in utero or early postnatal life might interact with other factors to increase the risk for development of ASD [150]. Some studies found that vitamin D levels are significantly lower in children with ASD in contrast to healthy control group from the community [151–153]. Furthermore, 2 of these studies also demonstrated that the severity of ASD is conversely correlated with vitamin D levels [151,153].

Some ecological studies support the findings that ASD prevalence is increased in children born at higher latitudes [147] and in infants of dark skin migrant mothers compared to offspring of lighter skin migrants [154–156]. However, when serum levels of $25(OH)D_3$ were measured they were equivalent among children with and without ASD [156]. Fernell with coworkers analyzed serum levels of 25(OH)D in 58 Swedish-born different origin sibling pairs, in which one child had ASD and the other did not. The authors found that children with ASD had significantly lower vitamin D levels in comparison to their siblings. According to researchers' opinion, the difference was also related to a difference in season of birth between ASD and non-ASD siblings, since the mean 25(OH)D levels differed between the sibling pairs born during winter and summer. All children from African/Middle East origin, both the children with ASD and their non-ASD siblings, had vitamin D deficiency. The authors concluded that low prenatal vitamin D may be a risk factor for ASD. However, replications with larger samples are needed [157].

In the recent research by Kosovska et al., a cross-sectional population in the Faroe Islands was examined. The group included a cohort of 40 individuals with ASD (aged 15–24 years). They had significantly lower $25(OH)D_3$ level, than their 62 healthy siblings and their 77 parents. Furthermore, the vitamin D level was also significantly lower than in the 40 healthy, age and gender matched control. There was a trend for males having lower level of $25(OH)D_3$, in comparison with females. The effects of month/season of birth, current age, IQ, various subcategories of ASD and Autism Diagnostic Observation Schedule scale were also investigated, however, no association was found. Nevertheless the researchers suggest that in the ASD group the very low serum level of $25(OH)D_3$ has some underlying pathogenic mechanism [158] such as a result of autism impacting on a family/child's lifestyle and/or diet (indoor activities, selective eater, etc.) and/or hormonal imbalance [6,159].

One hundred and six patients, having ASD with serum levels of 25-OHD lower than 30 ng/mL, received vitamin D_3 (300 IU/kg/day not to exceed 5000 IU/day) in an open label mode for 3 months. The researchers found that 80.72% (67/83) of subjects had significantly improved aberrant behavior, stereotypy, eye contact, and attention span outcome. They concluded that vitamin D may have beneficial effects in ASD subjects, especially in those who have final serum level more than 40 ng/mL [160]. The study performed by Benner et al., examined 254 children with autism and showed that 14.2% had severe vitamin D deficiency (<10 ng/mL), 43.7% had moderate insufficient levels (between 10 and 20 ng/mL), 28.3% had mild insufficient levels (between 20 and 30 ng/mL), and only 13.8% of subjects had sufficient levels (>30 ng/mL). The authors demonstrate that vitamin D deficiency was higher in autism children compared to healthy children and supplementing infants with vitamin D might be a safe and more effective strategy for reducing the risk of autism [161].

Up to date there is no medication for treating the core symptoms of autism. However, according to some researchers, it is possible that pharmacological doses of vitamin D may have a therapeutic effect [162]. Since many of the relevant studies are underpowered, it is difficult to come to a specific conclusion [163].

3.6. Vitamin D and attention deficit hyperactivity disorder

Attention-deficit-hyperactivity disorder (ADHD) is one of the most common psychiatric disorders of childhood. It has an early onset and is affecting 2–18% of children worldwide [164]. The pathophysiology of ADHD is complex and not well understood. There is no specific etiology identified for this entity, and findings are consistent with a multifactorial hypothesis [165–167]. Vitamin D takes an important part in cerebral function and might play a role in the etiopathogenesis of ADHD [59]. Recent studies suggest that vitamin D stimulates neurogenesis, so its deficiency during prenatal brain development might harm neuronal development and function in the early stages of life, thus increasing the risk of ADHD symptoms in childhood [68,168]. Vitamin D receptors and metabolizing enzymes are found in different parts of the brain that might have causal relationships in the pathophysiology of ADHD [169]. Up to date there are only limited data associating hyperactivity, behavioral problems and vitamin D deficiency in children.

In a prospective study 1650 mother–child pairs were analyzed. The researchers examined whether maternal vitamin D status in pregnancy was associated with risk of ADHD-like symptoms in offspring. They found that higher maternal circulating serum levels of $25(OH)D_3$ in pregnancy was associated with lower risk of developing ADHD-like symptoms in childhood [168].

4. Resume

The main studies presented in this review summarize the relation between serum vitamin D levels and depression, schizophrenia and cognitive disturbances. According to the Bradford Hill nine criteria, there is evidence of causal relationship between low serum vitamin D level, different mental and cognitive disorders and the effect of vitamin D treatment [27].

Clinicians prior to taking any therapeutic decision, clinicians should evaluate two parameters: a) the patients' vitamin D serum levels; and b) if there is a low level concentration, the severity and its sequelae should be evaluated including toxic overdose effect; c) the cost-effectiveness of vitamin D supplementation should be considered. Last, but not least, clinicians should be aware of the harmful consequences of vitamin D deficiency. We came to the conclusion that in those patients who have low vitamin D serum level, supplementation of vitamin D should be given. From our everyday clinical practice we paid attention that sometimes some general physicians prescribe vitamin D once a month or even once a

week in very high dose such as 30,000 or 40,000 IU. Once the physician decides to prescribe supplementation of vitamin D, toxic overdose effect should be taken in account. Toxicity is associated only with excessive supplemental intake (usually well above 20,000 IU/day) [170].

Vitamin D may cause hypercalcemia when the "free" concentration of 1,25-dihydroxyvitamin D is inappropriately high. Plasma concentrations of unmetabolized vitamin D during the first days after an acute, large dose of vitamin D can reach the micromolar range and cause acute symptoms of hypercalcemia. The availability of synthetic 1α-OH-D_3 in recent years has reduced the risks of hypervitaminosis [2]. According to the Institute for Medicine for the Dietary Reference Intakes, doses higher than 4000 IU/day should be considered as potentially dangerous. Nevertheless, there is evidence from some clinical trials that shows that a prolonged intake of 250 mcg (10,000 IU)/day of vitamin D_3 is likely to pose no risk of adverse effects in almost all individuals in the general population. This dose meets the criteria for a tolerable upper intake level [171,172]. It is recommended that the available safety information be interpreted cautiously [173].

Once again, as with so many other presumed associations of vitamin D and different maladies, there is no clear consensus that vitamin D improves or is related to mental health. There is some evidence that supplementation of vitamin D, especially in depressive subjects, combined with antidepressive agents is more effective than combination with placebo. Future clinical and basic science researches should be focused on vitamin D deficiency in mental health to clarify its mechanism and obtain strong proof of its efficacy. Greater samples and more randomized clinical placebo-controlled studies are needed [174].

Disclosure statement

None to declare.

Author contributions

CM – conception and design of the study; PL and CM investigated the library databases; PL - acquisition and analysis of data; LS - drafting the manuscript and Tables.

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