

Research article

Vitamin D and the cognitive status: a narrative review

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Abstract: Cognitive disorders and dementia are still one of the most important cause of death and major disability globally, having an enormous financial and social burden on the healthcare system worldwide. Vitamin D is a secosteroid hormone that has anti-inflammatory, antioxidant and regulates neurotransmitters and neurotrophins, by increasing neurotrophic factors such as nerve growth factor which further promotes brain health. Moreover, it is also helpful in the prevention of amyloid accumulation and promotes amyloid clearance. Besides the classical risk factors, vitamin D has been researched and studied as an etiology, prognosis factor and maybe a treatment resource in cognitive disfunctions, especially in dementia and Alzheimer's disease. Its neuroprotective, neuroplasticity and neurotrophic effects have been already demonstrated and so, the aim of this review was to focus on recent studies and trials in order to synthesize the evidence about the possible contribution of low vitamin D in the etiology of cognitive disorders like dementia and Alzheimer's disease and the effect of vitamin D supplementation in prevention and treatment of these conditions.

Keywords: vitamin D, cognition, dementia, Alzheimer's disease

1. Introduction

Cognitive decline has become a serious public health problem today. Many functions in the central nervous system, such as development, growth and cognition can be influenced by some vitamins and minerals, which are known to be capable of supporting the brain health, aging and function throughout life. The definition of cognition is related to knowledge, the process of learning and understanding, the ability of making decisions and solving problems. It consists of cognitive areas that should act in synergy, in order to maintain and develop intellectual and social skills. It is the result of several complex systems involving many neuronal circuits and is divided in 4 main domains: attention, intelligence, memory and decision-making or executive function.

Cognitive disorders are one of the leading causes of death and disability throughout the world. Currently, almost 48 million people around the world are suffering from severe cognitive impairment, dementia and related disorders and this number is expected to increase 2.73 times by 2050. [1]. Roughly 10 million people progress from mild cognitive impairment to dementia each year with the median age of diagnosis being about 80 years old [2]. All this has an enormous burden on any healthcare system, therefore many researchers have focused on exploring relevant preventive interventions to delay the development of dementia and cognitive impairment.

There are already several relevant modifiable risk factors been identified such as being overweight, smoking, diabetes mellitus, hypertension, hypercholesterolemia, and cardiovascular diseases, but also a potential prognostic role of vitamin D deficiency has been proposed and researched [3]. The aging population is predicted to increase in the nearby future, and also a large population of elderly is vitamin D-deficient, there is an important need to determine whether improving the vitamin D status can impact the cognitive decline. Due to the important role of vitamin D in neurotrophicity, neurotransmission, neuroprotection and neuroplasticity, various studies and scientists have suggested that vitamin D deficiency may play a key role in the progression of cognitive disorders, particularly dementia and Alzheimer's disease (AD).

2. Vitamin D and the brain

In the past years, there is considerable research showing that vitamin D deficiency is a pandemic throughout the entire global population and it is associated with many neurodegenerative diseases [4]. Vitamin D is a group of liposoluble secosteroids which plays a crucial role in bone physiology and in the homeostasis of Ca²⁺-phosphate metabolism, but has also multiple other biological effects known as "non-calcemic" [5]. Vitamin D is found in only a few food sources, like fish (salmon, mackerel, tuna, sardines), eggs, beef liver, cereals, walnuts, apples, dairy products, but the main natural source remains its synthesis when the skin is exposed to sun (specifically to ultraviolet B) [6, 7]. In humans, the most important forms of vitamin D are D₂ (ergocalciferol) and D₃ (cholecalciferol). After dietary intake or exposure to sun, vitamin D is biologically inactive and requires activation through hydroxylation in the liver and kidney. In the liver, ergocalciferol is converted to its hydroxylated form and cholecalciferol is converted to calcifediol, which undergoes another hydroxylation process in the kidney resulting in calcitriol (1,25-(OH)₂D₃). This is the active form of vitamin D, i.e. the one which produces the many biological effects in different locations. This active form of vitamin D binds to the VDR (vitamin D receptor), which belongs to the steroid hormone receptors superfamily and is expressed in the nuclei of more than 30 human tissues such as the skin, heart, brain, prostate, gonads, breast and blood cells. The activation of VDR maintains the levels of calcium and phosphorus in the blood stream, promotes calcium absorption, bone formation and remodeling [8, 9].

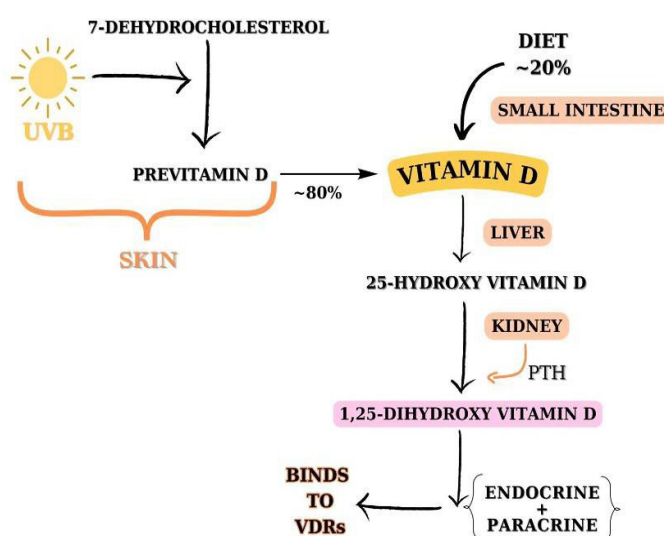


Figure 1. Vitamin D pathway

Despite its classical role, current research is focused on the "non-calcemic" effects of vitamin D, suggesting wider biological roles for this vitamin. Studies link its deficiency with the development and progression of autoimmune diseases and diabetes mellitus, with cardiometabolic pathologies, with infectious diseases and to some extent also with obesity and cancer [10-12]. The major cause of vitamin D deficiency is an inadequate diet and lack of or low sun exposure. This is why in the case of vitamin D, one should take into consideration some geographic characteristics, like latitude. Latitudes between 40° parallel North and south offer greater sun exposure, while there is relatively less sunlight available at higher latitudes. Somewhere about 15% of the global population lives in higher latitudes and therefore lower ability to convert pre-vitamin D and depends on the diet and supplements. Also, UV radiation is reduced by melanin, so dark skinned color people have a reduced capacity to synthesize vitamin D in the skin [13].

Although current public health strategies recommend moderate sun exposure and foods that are fortified with vitamin D, both these sources are often inadequate and do not satisfy the requirements of vitamin D for a child or an adult [14]. The World Health Organisation accepts a value of 50ng/ml as the optimal blood level for vitamin D, but the level of 30 ng/ml is preferred by several specialist guidelines (endocrinologists, rheumatologists) [15-17].

The role of vitamin D within the nervous system and in neurological pathologies is suggested and sustained by many researchers [18,19]. Degenerative neurological pathologies, characterized by progressive dysfunction and neuronal loss in the central nervous system, have an increasing prevalence in the last decade with an important socioeconomic impact. A meta-analysis of 127 studies of the last 20 years concluded that vitamin D acted like a neurosteroid hormone within the central nervous system, especially in the areas for neurotransmission, neuroprotection and neuromodulation, and that decreased levels were associated with neuromuscular disorders, dementia, Parkinson's and Alzheimer's disease, psychiatric pathology, type 1 and 2 diabetes and neoplasms [20].

Vitamin D can be locally produced and activated in the brain, independently of the plasma concentrations. This is because not only VDR is expressed in the brain, but also the activation and degradation enzymes for vitamin D, especially 1 α hydroxylase, are expressed in the neurons and glial cells, mainly in the temporal lobe, cingulate, thalamus, accumbens nucleus, amygdala, hippocampus [21-23]. In this way vitamin D plays a neurotrophic and neuroprotective role through effects on cell proliferation and differentiation, plasticity of synapses, promoting neurotransmission, neurogenesis and increasing amyloid metabolism [24].

The non-genomic effects of vitamin D in the brain are rapid, non-transcriptional and occur at the plasma membrane level through a membrane associated receptor (1,25-MAARS), thus influencing neuronal maturation in the development and neuroprotection phase [14]. The cerebral local production of vitamin D after binding to VDR is responsible for almost 2000 genes in the upregulating process, thus being involved in many metabolic pathways. There is evidence that vitamin D has also an immune modulatory effect in the brain by influencing the production and activity of anti-inflammatory cytokines like IL-4 and IL-5, macrophages, lymphocytes T and B, conferring a neuroprotective effect [25].

In rodents, studies found that the brain function and behavioral outcome is affected by vitamin D deficiency and inactivated vitamin D receptor. The research was conducted on mice with prenatal deficiency of vitamin D and vitamin D knock-out mice. Rats born to vitamin D3-deficient mothers demonstrated a reduction in the nerve growth factor and

glial-derived neurotrophic factor compared to control rats [26]. Another study on 10-week-old rats with vitamin D deficiency demonstrated enlarged lateral ventricle volume and reduced nerve growth factor compared to controls [27]. The amount of evidence regarding the impact of vitamin D deficiency on the behavior of mice which developed later in life is not so much, but one study reported a subtle effect on attentional tasks in 16–20-week-old rats with a vitamin D-deficient diet given for 10 weeks compared to control rats [28].

The neuroprotective effect is correlated with the role of vitamin D in inhibiting the synthesis of inducible nitric oxide synthase (iNOS), and by this lowering the production of nitric oxide, which damages both neurons and oligodendrocytes if produced in high levels [29]. Also, vitamin D controls the brain detoxification processes through the glutathione cycle, various studies demonstrating that calcitriol can modulate the production of neurotrophins correlated with a neuroprotective effect [30,31].

3. Vitamin D, cognitive impairment and dementia

Mild cognitive impairment (MCI) involves the onset and evolution of cognitive impairments beyond those expected based on an individual's age and education, but which are not significant enough to interfere with the individual's daily activities. It may occur as a transitional stage between normal aging and dementia, more than half of individuals with MCI convert to dementia in 5 years from the onset (especially the amnesic type of MCI) [32]. Although there are many predisposing factors and pathogenic theories, the most common etiology of MCI is degenerative, which makes it more prone to prevention than to treatment. Research in the field of neurogenetics states that the vitamin D receptor begins to develop in the twelve day of embryo transfer, in its central area, and that it plays an important role in the metabolism of neurotransmitters like acetylcholine, dopamine, serotonin and GABA [33]. Due to the fact that VDR is expressed in the cerebellum, cortex and the limbic system, specific areas where the behavioral and memory processes are integrated, low levels of vitamin D lead to cognitive impairment, irritability, anxiety, depression and even psychosis [34–36]. Moreover, the existing literature associates vitamin D with higher executive functions like memory and processing speed and studies state that increasing the intake of vitamin D can increase cognitive performance evaluated through different scales [37, 38]. Concerning the neuropsychiatric symptoms that appear in MCI, researchers show that lower vitamin D levels in individuals over 65 years old can lead to mood disorders and depression and supplementing the diet with vitamin D improves these conditions [39]. The literature consists of a lot of studies associating vitamin D with cognitive impairment as it is shown in the below table.

Table 1. Prospective studies on association between vitamin D status and cognitive decline.

Study	Study design and follow up	Number of participants	Methods of assessment	Conclusion
Littlejohns, 2014, USA [40]	Prospective Cardiovascular Health Study, a large, population-based study Follow-up 5.6 years	N = 1658 subjects Both men and women, both black and white	Cognitive status-tests not reported Serum 25(OH)D concentration (LC-MS) VDD cutoff 50 nmol/L	Vitamin D deficiency increases the risk of developing AD
Afzal, 2014,	Prospective Follow-up 30 years	N = 10,186 subjects Danish	Cognitive status-tests not reported Serum 25(OH)D	Lower vitamin D concentrations

Denmark [41]		general population	concentration (ECLIA method) VDD cutoff < 25 nmol/L	increase the risk of developing AD
Licher, 2017, Netherlands [42]	Prospective Follow-up 13.3 years	N = 6220 subjects aged >55 years, 6087 nondemented at baseline	Cognitive status-MMSE, GMS Serum 25(OH)D concentration (ECLIA method) VDD cutoff < 25 nmol/L	Lower vitamin D concentrations increase the risk of developing AD
D Lee et al., 2020, Korea [43]	Prospective Korean frailty and aging cohort study Duration of follow-up not reported	N = 2990 subjects (1415 men and 1575 women) 2 years of baseline data	Assessment of cognitive status-tests not reported Serum 25(OH)D concentration (CMIA method) VDD cutoff: 10 nmol/L	No direct correlation between vitamin D levels and cognition
Laughlin, et al., 2017, USA [44]	Longitudinal. Follow-up 12 years.	N=1,058 (median 75 years of age). Healthy.	MMSE; and Trail Making Test B.	Vitamin D deficiency was associated with poorer cognitive performance in multiple areas.

Alzheimer's disease (AD) is a neurodegenerative disorder, clinically characterized by irreversible and progressive cognitive impairment, memory loss and behavioral alteration. Although the etiology is still unknown and many factors are being researched, it is known that its pathogenesis involves accumulation of extracellular amyloid beta plaques and intraneuronal neurofibrillary tangles. These changes can damage the synapses that mediate memory and cognition, resulting in neuronal and synaptic loss, leading to the behavioral symptoms and loss of memory that happens in a patient with AD [45]. Currently, the AD management includes many treatment strategies including an anti-amyloid beta therapy, which is expected to be the most effective approach. The evolution and progression of AD is devastating for the patient and his/her caregiver. Vitamin D plays an important role in AD through stimulating the neuronal growth factor and neurotransmitters pathways, increasing the amyloid metabolism, anti-inflammatory effect and promoting calcium homeostasis [46]. Chai et al aimed to explore the associations between vitamin D deficiency and the risk of dementia and Alzheimer's disease (AD) by doing a meta-analysis on 12 prospective cohort studies and 4 cross-sectional studies. The conclusion was that there are significant associations between vitamin D deficiency and both dementia and AD. They found stronger associations between severe vitamin D deficiency (< 10 ng/ml) and both dementia and AD compared to moderate vitamin D deficiency with serum levels of 10–20 ng/ml [47].

Seventy to 90% of the AD patients have low levels of vitamin D [48]. Many epidemiological studies have highlighted an association between low serum vitamin D levels and an increased risk of AD. It is already proven that vitamin D regulates gene expression via the vitamin D receptor, a nuclear ligand-dependent transcription factor, however, the molecular mechanism underlying the pathogenic and therapeutic effects of vitamin D on AD is not fully understood yet. Kang et al performed a study on mice, where they induced vitamin D deficiency with a vitamin-D-deficient diet and observed the changes in the

mRNA level of genes related to β -amyloid processing, which resulted in an increase in the β -amyloid load in the brain. Moreover, the vitamin D-deficient diet suppressed the expression of genes for microglial β -amyloid phagocytosis, thus accumulating inside the central nervous system. Also, they administered vitamin D intraperitoneally to mice with a normal diet and found lower β -amyloid levels with the suppressed expression of genes for β -amyloid generation and observed improved memory function. All these findings support the role of vitamin D as a crucial disease-modifying factor that may modulate the amyloid pathology with regard to reducing AD symptoms [49].

The Cardiovascular Health Study followed the participants for up to 5 years and observed that 171 subjects developed dementia and 102 developed AD. All these patients had levels of vitamin D lower than 25 nmol/L; subjects with a level of vitamin D below 50 nmol/L had a much higher risk of developing AD. There is a therapeutic window (during the preclinical phase or the MCI phase) in which administration of vitamin D can improve cognitive performances. Also, many studies show that supplementation (either dietary or oral) with vitamin D in patients with AD can improve the overall quality of life, the rate of deterioration and also the memory deficit in some areas [40]. The In Chianti study followed 858 adults for up to 6 years, and concluded that low levels of vitamin D were associated with cognitive decline and a dietary increase of vitamin D lowered the risk for AD [50,51].

Besides all the positive correlations between vitamin D deficit and cognitive functions, there is also a research group from Taiwan, who suggests that vitamin D deficiency may be caused by AD rather than caused by a lack of dietary vitamin D. Conducting a study on AD mice fed with vitamin D-supplementation diet, they reached the conclusion that vitamin D might have a potentially damaging effect on neuronal cells exposed to amyloid beta and after 3 months they found more severe amyloid beta plaque deposits and reactive gliosis in the hippocampus compared to controls, thus exacerbating the AD. Also, they have performed an epidemiological study using two nationwide longitudinal cohorts, in which they found that long term supplementation with vitamin D in dementia-free older adults increased the risk with 1.8 for developing dementia and among those with pre-existing dementia the risk of mortality increased by 2.17. The underlying mechanism is supposed to be that the dementia-related toxic amyloid formation elicits xenobiotic responses through non-genomic VDR signaling. These findings are surprising and the researchers recommend that the use of vitamin D supplementation to prevent dementia should be reconsidered [52,53].

The current literature already states that patients with type 2 diabetes have an increased risk of cognitive decline and dementia, which can adversely impact their quality of life and self-management of the disease. Byrn et al assessed vitamin D supplementation with 50.000 IU/day and 5000 IU/day for 3 months, on cognitive executive function in these patients. The primary outcome was a battery of neuropsychological tests which were collected over 12 weeks using alternative testing forms to minimize practice effects. In the end, there was no statistically significant finding between participants who received high-dose vitamin D supplementation and those who received low-dose supplementation. However, when assessing cognitive function in both groups over time, minimal improvement on the Symbol-Digits, the Stroop Interference Test, and the Trail Making Test Part B was observed. In the end, this study does not support the idea that vitamin D supplementation might improve the cognitive status in people with high risk for cognitive decline, hence a larger randomized control trial with longer period of observation is recommended [54]. In the Vital clinical trial, done in Boston, USA, the supplementation with vitamin D and its effects on cognitive decline was studied. The participants were

aged over 60 years, free of cardiovascular disease and cancer, and were randomised on vitamin D 2000 IU/day and fish oil supplements. 3424 had cognitive assessments by phone (eight neuropsychologic tests; 2.8 years follow-up) and 794 had in-person assessments (nine tests; 2.0 years follow-up). The primary outcome was to evaluate the decline over two assessments in global composite score and the pooled mean difference in annual rate of decline for vitamin D3 versus placebo was 0.01 (95% CI - 0.01, 0.02; $p = 0.39$), so not so significantly, meaning that vitamin D may provide modest cognitive benefits, especially among black participants assigned to vitamin D who had better cognitive maintenance versus placebo (MD = 0.04, 95% CI 0.01, 0.08) [55].

Yang et al wanted to determine whether a 12-month vitamin D supplementation improves cognitive function in elderly subjects with mild cognitive impairment (MCI) in a double-blind, randomized, placebo-controlled trial in China. Participants were aged 65 years and older with MCI of which 183 subjects were randomized to an intervention group with supplementation of vitamin D 800 IU/day or a placebo group (with administration of matching starch granules). All participants were followed up for 12 months and evaluated at baseline, 6 and 12 months with tests of cognitive function. The results showed significant improvements in the full scale intelligence quotient (FSIQ), information, digit span, vocabulary, block design, and picture arrangement scores in the vitamin D group over the placebo group ($p < 0.001$), for 12 months, so they concluded that vitamin D supplementation for 12 months appears to improve cognitive function and that vitamin D may be a promising public health strategy to prevent cognitive decline [56].

In another study, Buell, et al. studied 318 participants who had vitamin D levels, MRI measures of cerebral vascular disease and who developed dementia during a four-year study. 25(OH) D levels were deficient in 14.5% and insufficient in 44% of the participants, 23% developed dementia, one half were probable Alzheimer's disease. There was a much higher prevalence of dementia among those with vitamin D insufficiency: 30% vs. 14% and these levels were associated with increased white matter hyper-intensity and prevalence of white matter infarcts (10% vs. 7%). Overall, this study suggested a vascular protected role of vitamin D and its role in reducing hippocampal degenerative processes, the involvement in detoxification by interacting with reactive oxygen and nitrogen species, improving neuronal survival [57]. Moreover, studies divided the relationship of vitamin D improving the cognitive status on sexes. A group from Turkey aimed to determine if there is a link between vitamin D and cognitive functioning in women with vitamin D deficiency. They included 90 female patients, with a wide range of age between 25 and 45 years old, who were assessed with the MoCA scale and were divided in 3 subgroups according to their vitamin D levels. The medical staff reevaluated the patients after 3 months when they received oral vitamin D supplementation, both for serum levels and cognitively. In the end they found a positive correlation between low vitamin D and poor performances in the MoCA test and better scores after supplementation [58].

Although many researchers and studies favor the supplementation of vitamin D both in healthy adults, but mainly in cognitive disorders and dementias, there are contradictive opinions stating that there is no benefit from adding vitamin D to daily intake of nutrients. Some of these opinions are presented in the below table.

Table 2. Studies that showed no benefit from supplementation of vitamin D

Name of the study and year	Design of the study	Population	Intervention	Conclusion
Rossum et al., 2012, USA [59]	RCT Double blind, placebo controlled WHI Calcium and Vitamin D Trial and Memory Study	N = 4143 women aged 65 and older without probable dementia at baseline Follow-up 7.8 years	Group 1: 1000 mg of calcium carbonate combined with 400 IU of vitamin D (3) (treatment) Group 2: placebo.	No association between treatment assignment and incident cognitive impairment.
DO-HEALTH Trial Bischoff Ferrari et al., 2020, Multicenter study [60]	RCT to test whether vitamin D, omega-3s, and an exercise program, alone or in combination, improved health outcomes among older adults.	N = 2157 adults recruited aged >70 years Follow up 3 years	Eight groups: 2000 IU/d of vitamin D3 1 g/d of omega-3s + a training exercise program (n = 264); vitamin D3 + omega-3s (n = 265); vitamin D3 + exercise (n = 275); vitamin D3 alone (n = 272); omega-3s + exercise (n = 275); omega-3s alone (n = 269); exercise alone (n = 267); placebo (n = 270).	No significant difference in improvement in systolic or diastolic BP, physical performance, infection rates, or cognitive function after treatment with vitamin D3, omega-3s, or a strength-training exercise
Owusu, et al., 2019, USA [61]	RCT	N=260 (post-menopausal African-American women without cognitive impairment, mean age 68 years of age).	2,400 – 4,800 IU/day (adjustable to 25(OH)D levels) + 1,200 mg calcium/day Follow up 3 years	No improvement of cholecalciferol, compared to placebo, in MMSE score
Schietzel, et al., 2019, Switzerland [62]	RCT	N=273 (N=136, with 800 IU D3; N=137, with 2,000 D3).	800 or 2,000 IU D3/day Follow up 1 year	No differences in cognitive tests (MMSE, Stroop, digit span, verbal fluency and memory) between different doses or by age range.
Ates Bullut, et al., 2019, Turkey [63]	Pre-post comparative OR (three groups).	Institutionalised, of which 86 with dementia (N=560, mean age 75 years of age). Three groups according to 25(OH)D levels.	50,000 IU/D3/ week, 6 weeks, and 5,000 IU/D3/ week, up to 6 months.	No cognitive test (MMSE, MOCA, Clock Test, BADL, IADL, CDRS) scores improved.

As with other pathologies, there is no consensus stating the dosage and administration of vitamin D in AD, but the recommendation for adults aged 70 and younger is 600 IU daily and for adults over 70 years old is 800 IU daily. Some studies recommend that middle aged and older adults should keep their vitamin D blood levels in the higher range

of normal (175–200 nmol/l) due to the probable protective effect on neurodegeneration. For this blood level to be reached an intake of 10,000 IU/day (250 mcg) or more is required, but vitamin D level should be monitored in order to ensure that toxicity does not occur [64]. Researchers from China even found that daily oral vitamin D supplementation decrease amyloid related serum biomarkers (like A β 42, APP, BACE1), together with the cognitive function [65]. Besides the dosage and prophylaxis, the route of administration seemed to be important; a systematic review compared the effect of vitamin D endogenously produced from sunlight exposure to supplementation from synthetic exogenous vitamin D and acknowledged the neuroprotective role of vitamin D in neurological pathologies, but without stating recommendations for dosage and route of administration [66]. It remains the issue of cause and effect: does low vitamin D contribute to cognitive deterioration or does cognitive deterioration involve disability and short sun exposure time which leads to hypovitaminosis D?

4. Conclusions

The aim of this review was to focus on recent studies and trials in order to understand the biology of vitamin D in the nervous system, but also to look for evidence of the multiple roles for vitamin D in the brain function and neurodegenerative disorders. Also another goal was to synthesize the evidence about the possible contribution of low vitamin D in the etiology of cognitive impairment and dementia and the effect of vitamin D supplementation in prevention and treatment of neurological conditions.

Epidemiological studies agree that vitamin D deficiency has become a global health problem, leading to a pandemic deficiency with important consequences in many areas. There is important evidence from literature that indicates the presence of decreased levels of vitamin D in patients with cognitive impairment and dementia, especially Alzheimer's disease, but also in other neurological pathology such as multiple sclerosis, Parkinson disease and ALS. Most studies found an immunomodulatory and neuroprotective effect of vitamin D supplementation in these pathologies. Cross-sectional studies have consistently found that vitamin D levels are significantly low in individuals with Alzheimer's disease and cognitive impairment compared to healthy adults. Longitudinal studies and meta-analysis have also exhibited an association of low vitamin D with cognitive impairment and Alzheimer's disease.

A consensus regarding the dosage and way of administration is not yet established by a protocol, but supplementation in aged adults is recommended, via oral administration or dietary intake. Also moderate sun exposure is suggested. The association between vitamin D supplementation and cognition remains controversial. The results from interventional studies have produced mixed results on the role of vitamin D supplementation in the prevention and treatment of cognitive impairment and dementia. The truth is that there is not enough information to predict hypovitaminosis D related to cognitive impairment. The biggest problem of the existing studies is their quite small sample size, the heterogeneity of the studied population, lack of consensus over the dose and the methods of determination and age of initiation of vitamin D supplements to prevent cognitive impairment. Also, vitamin D receptor genotype has not been addressed in many studies, and gene polymorphism may exist for responders and non-responders and it is possible that some allele combination offer greater protection against cognitive decline. Therefore, there is a need for large double-blind randomized control trials to assess the benefits of vitamin D supplementation in the prevention and treatment of cognitive impairment.

It is imperative to define the timing and duration of the ‘critical window’ during which low vitamin D status is associated with differential and adverse brain outcomes, in order to establish a standard protocol for supplementation in neurological pathologies. Also, further research is needed to clear the role of vitamin D in disorders that involve the cognitive status, whether it is a contributing factor to the etiology or it is a consequence of the disease and it can be used as a treatment tool. Future research will improve the knowledge to determine if cost effective preventative treatments, such as vitamin D supplementation, would be a beneficial addition to the treatment plan of patients who are at risk for cognitive impairment or dementia.

Conflicts of Interest: The authors declare no conflict of interest

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used “Conceptualization, C.G. and B.E.I.; methodology, C.G.C.; software, A.F.C.; validation, C.G., D.A. and A.F.C.; formal analysis, A.G.; investigation, A.C.O.; resources, D.A.; data curation, A.G.; writing—original draft preparation, C.G.; writing—review and editing, B.E.I.; visualization, C.G.C.; supervision, A.C.O.; project administration, C.G.; funding acquisition, B.E.I. All authors have read and agreed to the published version of the manuscript.” Please turn to the [CRediT taxonomy](#) for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

References

1. Haapasalo, A.; Hiltunen, M. A report from the 8th Kuopio Alzheimer symposium. *Neurodegener Dis Manag.* 2018;8(5):289–99.
2. Wolters, F.J.; Ikram, M.A. Erratum to: epidemiology of dementia: the burden on society, the challenges for research. *Methods Mol Biol.* 2018; 1750: E3.
3. Anjum, I. et al. The role of vitamin D in brain health: a mini literature review. *Cureus.* 2018;10(7): e2960
4. Hossein-Nezhad A, Holick MF. Vitamin D for health: a global perspective. *Mayo Clin Proc* 2013; 88(7): 720–755.
5. DeLuca HF. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 2004; 80(6 Suppl): 1689S–1696S.
6. Autier, P.; Boniol, M.; Pizot, C.; Mullie, P. Vitamin D status and ill health: a systematic review. *Lancet Diab Endocrinol* 2014; 2(1): 76–89.
7. Tangpricha, V.; Pearce, E.N.; Chen, T.C.; Holick, M.F. Vitamin D insufficiency among free-living healthy young adults. *Am J Med* 2002; 112(8): 659–662.
8. Jones, G.; Prosser, D.E.; Kaufmann, M. Cytochrome P450-mediated metabolism of vitamin D. *J Lipid Res* 2014; 55(1): 13–31.
9. Pop, G.D.; Duncea, I.; Georgescu, C.; Hazi, G.; Dragotoiu, G.; Leucuta, D.C. Estimation of 25(OH)D levels required for maintaining a normal bone turnover in healthy aging men. *Acta Endo (Buc)* 2007; 3(1): 31–44.
10. Cui, X.; Gooch, H.; Groves, N.J.; Sah, P.; Burne, T.H.; Eyles, D.W.; McGrath, J.J. Vitamin D and the brain: Key questions for future research. *J Steroid Biochem Molec Biol* 2015; 148: 305–309.
11. Garland, C.F.; Garland, F.C.; Gorham, E.D.; Lipkin, M.; Newmark, H.; Mohr, S.B.; Holick, M.F. The role of vitamin D in cancer prevention. *Am J Public Health* 2006; 96: 252–261.
12. Radulian, G. (coordinator). Managementul nutritional în diabetul zaharat, bolile metabolice și alte patologii. Editura Universitară “Carol Davila” București 2015, vol.1, pp 55–56.
13. Ghareghani, M.; Reiter, R.J.; Zibara, K.; Farhadi, N. Latitude, Vitamin D, melatonin and gut microbiota act in concert to initiate multiple sclerosis: a new mechanism pathway. *Front Immunol* 2018;9:2484.
14. Holick, M.F.; Chen, T.C. Vitamin D deficiency: A worldwide problem with health consequences. *Am J Clin Nutr* 2008; 87(4): 1080S–1086S.
15. Pludowski, P.; Holick, M.F.; Grant, W.B.; Konstantynowicz, J.; Mascatengas, M.R.; Haq, A.; Povoroznyuk, V.; Balaska, N.; Barbosa, A.P.; Koronova, T. et al. Vitamin D supplementation guidelines. *J Steroid Biochem Mol Biol* 2018; 175: 125–135.
16. Vieth, R.; Bischoff-Ferrari, H.; Boucher, N.J.; Dawson-Hughes, B.; Garland, C.; Heaney, R.; Holick, M.F.; Hollis, B.W.; Lambert-Allardt, C.; McGrath, J.J. et al. The urgent need to recommend an intake of vitamin D that is effective. *Am J Clin Nutr* 2007; 85(3): 649–650.

17. Wolpowitz, D.; Gilchrist, B.A. The vitamin D questions: how much do you need and how should you get it? *J Am Acad Dermatol* 2006; 54(2): 301–417.
18. Cui, X.; Gooch, H.; Petty, A.; McGrath, J.J.; Eyles, D. Vitamin D and the brain: Genomic and non-genomic actions. *Mol Cell Endocrinol* 2017; 453: 131–143.
19. Mpandzou, G.; Ait Ben Haddou, E.; Regragui, W.; Benomar, A.; Yahyaoui, M. Vitamin D deficiency and its role in neurological conditions: A review. *Rev Neurol (Paris)* 2016; 172(2): 109–22.
20. Annweiler, C.; Montero-Odasso, M.; Llewellyn, D.J.; Richard-Devantoy, S.; Duque, G.; Beauchet, O. Meta-analysis of memory and executive dysfunctions in relation to vitamin D. *J Alzheimers Dis* 2013; 37(1): 147–171.
21. Zhender, D.; Bland, R.; Williams, M.C.; McNinch, P.W.; Howie, A.J.; Stewaer, P.M.; Hewison, M. Extrarenal expression of 25-hydroxyvitamin D₃-1 α hydroxylase. *J Clin Endocrinol Metab* 2001; 86(2): 888–894.
22. Orme, R.P.; Middleditch, C.; Waite, L.; Fricker, R.A. The role of Vitamin D₃ in the Development and Neuroprotection of Midbrain Dopamine Neurons. In: Litwack G, ed. *Vitamine D Hormone*. Amsterdam: Elsevier Vitamines & Hormones vol 100, 2016:273–297.
23. Stumpf, W.E.; Clark, S.A.; O'Brien, L.P.; Reid, F.A. 1,25(OH)₂ vitamin D₃ sites of action in spinal cord and sensory ganglion. *Anat Embryol* 1988; 177: 307–310.
24. Garcion, E.; Wion-Barbot, N.; Montero-Menei, C.N.; Berger, F.; Wion, D. New clues about vitamin D functions in the nervous system. *Trends Endocrinol Metab* 2002; 13(3): 100–105.
25. Wimalawansa, S.J. Non-musculoskeletal benefits of vitamin D. *J Steroid Biochem Mol Biol* 2018; 175: 60–81.
26. Eyles D., Brown J., Mackay-Sim A., McGrath J., Feron F. Vitamin D₃ and brain development. *Neurosci-ence*. 2003;118(3):641–653.
27. Féron F., Burne T. H. J., Brown J., et al. Developmental vitamin D₃ deficiency alters the adult rat brain. *Brain Research Bulletin*. 2005;65(2):141–148.
28. Byrne J. H., Voogt M., Turner K. M., et al. The impact of adult vitamin D deficiency on behaviour and brain function in male Sprague-Dawley rats. *PLoS One*. 2013;8(8)
29. Dulla, Y.A.; Kurauchi, Y.; Hisatsune, A.; Seki, T.; Shudo, K.; Katsuki, H. Regulatory Mechanisms of Vitamin D₃ on Production of Nitric Oxide and Pro-inflammatory Cytokines in Microglial BV-2 Cells. *Neurochem Res* 2016; 41(11): 2848–2858.
30. Gil, A.; Plaza-Diaz, J.; Mesa, M.D. Vitamin D: Classic and Novel Actions. *Ann Nutr Metab* 2018; 72: 87–95.
31. Kuzumaki, N.; Ikegami, D.; Tamura, R.; Hareyama, N.; Satohchi, I.; Narita, M.; Torigoe, K.; Niikura, K.; Takeshima, H.; Ando, T. et al. Hippocampal epigenetic modification at the brain-derived neurotrophic factor gene induced by an enriched environment *Hippocampus* 2011; 21(2): 127–132.
32. DeCarli, C. Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. *Lancet Neurol* 2003; 2(1): 15–21.
33. McGrath, J.; Saari, K.; Hakko, H.; Jokelainen, J.; Jones, P.; Jarvelin, M.R.; Chant, D.; Isohanni, M. Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. *Schizophr Res* 2004; 67(2–3): 237–245.
34. Annweiler, C.; Fantino, B.; Gautier, J.; Beaudenon, M.; Thiery, S.; Beauchet, O. Cognitive effects of vitamin D supplementation in older out patients visiting a memory clinic: A pre–post study. *J Am Geriatr Soc* 2012; 60(4): 793–795.
35. Annweiler, C.; Beauchet, O. Vitamin D and cognition: Recommendations for future trials. *J Am Geriatr Soc* 2013; 61: 1049–1050.
36. Ristic, S.; Kocic, S.S.; Milovanovic, D.R.; Mihajlovic, G.; Mihailovic, N.; Lucic, A.T.; Zivanovic, S. Vitamin D Status in Patients with Mental Disorders: a Cross-Sectional Analysis of Single Cohort from Routine Practice. *Acta Endo (Buc)* 2017; 13(1): 40–46.
37. Llewellyn, D.J.; Langa, K.M.; Lang, I.A. Serum 25-hydroxyvitamin D concentration and cognitive impairment. *J Geriatr Psychiatry Neurol* 2009; 22(3): 188–195.
38. Annweiler, C.; Dursun, E.; Féron, F.; Gezen-Ak, D.; Kalueff, A.V.; Littlejohns, T.; Llewellyn, D.; Millet, P.; Scott, T.; Tucker, K.L. et al. Vitamine D et cognition chez la personne âgée: consensus et recommandations d'un groupe d'experts internationaux. *Geriatr Psychol Neuropsychiatr Vieil* 2016; 14(3): 265–273.
39. Wilkins, C.H.; Sheline, T.I.; Roe, C.M.; Birge, S.J.; Morris, J.C. Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. *Am J Geriatric Psychiatry* 2006; 14(12): 1032–1040.
40. Littlejohns, T.J.; Henley, W.E.; Lang, I.A.; Annweiler, C.; Beauchet, O.; Chaves, P.H.M.; Fried, L.; Kestenbaum, B.R.; Kuller, L.H.; Langa, K.M. et al. Vitamin D and the risk of dementia and Alzheimer disease. *Neurology* 2014; 83: 920–928.
41. Afzal, S.; Bojesen, S.E.; Nordestgaard, B.G. Reduced 25-hydroxyvitamin D and risk of Alzheimer's disease and vascular dementia. *Alzheimer's Dement*. 2014, 10, 296–302.
42. Licher, S.; De Bruijn, R.F.A.G.; Wolters, F.J.; Zillikens, M.C.; Ikram, M.A.; Ikram, M.K. Vitamin D and the Risk of Dementia: The Rotterdam Study. *J. Alzheimer's Dis*. 2017, 60, 989–997.
43. Lee, D.H.; Chon, J.; Kim, Y.; Seo, Y.K.; Park, E.J.; Won, C.W.; Soh, Y.; Bush, E. Association between Vitamin D deficiency and cognitive function in the elderly Korean population: A Korean frailty and aging cohort study. *Medicine* 2020, 99, e19293.

44. Laughlin, G.A.; Kritz-Silverstein, D.; Bergstrom, J.; Reas, E.T.; Jassal, S.K.; Barrett-Connor, E.; McEvoy, L.K. Vitamin D Insufficiency and Cognitive Function Trajectories in Older Adults: The Rancho Bernardo Study. *J Alzheimers Dis.* 2017;58(3):871-883.
45. Bloom, G.S. Amyloid- β and tau: the trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurol* 2014; 71(4): 505-508.
46. Moon, M.; Song, H.; Hong, H.J.; Nam, D.W.; Cha, M.Y.; Oh, M.S.; Yu, J.; Ryu, H.; Mook-Jung, I. Vitamin D-binding protein interacts with A β and suppresses A β -mediated pathology. *Cell Death Differ.* 2013; 20: 630-638.
47. Chai, B.; Gao, F.; Wu, R. et al. Vitamin D deficiency as a risk factor for dementia and Alzheimer's disease: an updated meta-analysis. *BMC Neurol* 19, 284 (2019).
48. Annweiler, C.; Llewellyn, D.J.; Beauchet, O. Low serum vitamin D concentrations in Alzheimer's disease: A systematic review and meta-analysis. *J Alzheimers Dis.* 2013; 33(3): 659-674.
49. Kang, J.; Park, M.; Lee, E.; Jung, J.; Kim, T. The Role of Vitamin D in Alzheimer's Disease: A Transcriptional Regulator of Amyloidopathy and Gliopathy. *Biomedicines* 2022, 10, 1824.
50. Feart, C.; Helmer, C.; Merle, B.; Herrmann, F.R.; Annweiler, C.; Dartigues, J.F.; Delcourt, C.; Samieri, C. Associations of lower vitamin D concentrations with cognitive decline and long-term risk of dementia and Alzheimer's disease in older adults. *Alzheimer Dement* 2017; (11): 1207-1216.
51. Annweiler, C.; Rolland, Y.; Schott, A.M.; Blain, H.; Vellas, B.; Hermann, F.R.; Beauchet, O. Higher Vitamin D dietary intake is associated with lower risk of Alzheimer's Disease: A 7-year follow-up. *J Geron* 2012; 67(11): 1205-1211.
52. Stein, M.S.; Scherer, S.C.; Ladd, K.S.; Harrison, L.C. A randomized controlled trial of high-dose vitamin D2 followed by intranasal insulin in Alzheimer's disease. *J. Alzheimers Dis* 2011; 26(3): 477-484.
53. Lai, R.H.; Hsu, C.C.; Yu, B.H.; Lo, Y.R.; Hsu, Y.Y.; Chen, M.H.; Juang, J.L. (2022). Vitamin D supplementation worsens Alzheimer's progression: Animal model and human cohort studies. *Aging Cell*, 21, e13670.
54. Byrn, M.A.; Adams, W.; Penckofer, S.; Emanuele, M.A. Vitamin D supplementation and cognition in people with type 2 diabetes: a randomized control trial, *J Diab Res*, 2019;1-14. ID 5696391.
55. Kang, J.H.; Vyas, C.M.; Okereke, O.I. et al. Effect of vitamin D on cognitive decline: results from two ancillary studies of the VITAL randomized trial. *Sci Rep* 11, 23253 (2021).
56. Yang, T.; Wang, H.; Xiong, Y.; Chen, C.; Duan, K.; Jia, J.; Ma, F. Vitamin D Supplementation Improves Cognitive Function Through Reducing Oxidative Stress Regulated by Telomere Length in Older Adults with Mild Cognitive Impairment: A 12-Month Randomized Controlled Trial. *J Alzheimers Dis.* 2020;78(4):1509-1518.
57. Buell, J.S.; Dawson-Hughes, B., et al 25Hydroxy vitamin D, Dementia and Cerebral Vascular Pathology in Elders receiving Home Services. *Neurology* 74: 18-26, 2010.
58. Balbalogu, O.; Tanik, E. The effect of vitamin D on cognitive functions in young female patients: a prospective controlled study using the Montreal Cognitive Assessment; *Arq. Neuro-Psiquiatr.*;2019: 77 (1).
59. Rossom, R.C.; Espeland, M.A.; Manson, J.E.; Dysken, M.W.; Johnson, K.C.; Lane, D.S.; Leblanc, E.S.; Lederle, F.A.; Masaki, K.H.; Margolis, K.L. Calcium and vitamin D supplementation and cognitive impairment in the Women's health initiative. *J. Am. Geriatr. Soc.* 2012, 60, 2197-2205.
60. Bischoff-Ferrari, H.A.; Vellas, B.; Rizzoli, R.; Kressig, R.W.; Da Silva, J.A.P.; Blauth, M.; Felson, D.T.; McCloskey, E.V.; Watzl, B.; Hofbauer, L.C.; et al. Effect of Vitamin D Supplementation, Omega-3 Fatty Acid Supplementation, or a Strength-Training Exercise Program on Clinical Outcomes in Older Adults: The DO-HEALTH Randomized Clinical Trial. *JAMA J. Am. Med. Assoc.* 2020; 324:1855-1868.
61. Owusu, J.E.; Islam, S.; Katumuluwa, S.S.; Stolberg, A.R.; Usera, G.L. et al. (2019) Cognition and Vitamin D in Older African American Women- Physical performance and Osteoporosis prevention with vitamin D in older African Americans Trial and Dementia. *J Am Geriatr Soc* 67(1): 81-86.
62. Schietzel, S.; Fischer, K.; Brugger, P.; Orav, E.J.; Renerts, K.; Gagesch, M.; Freystaetter, G.; Stähelin, H.B.; Egli, A.; Bischoff-Ferrari, H.A. Effect of 2000 IU compared with 800 IU vitamin D on cognitive performance among adults age 60 years and older: a randomized controlled trial. *Am J Clin Nutr.* 2019 Jul 1;110(1):246-253.
63. Ates Bulut, E.; Soysal, P.; Yavuz, I.; Kocyigit, S.E.; Isik, A.T. Effect of Vitamin D on Cognitive Functions in Older Adults: 24-Week Follow-Up Study. *Am J Alzheimers Dis Other Demen.* 2019 Mar;34(2):112-117.
64. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010.
65. Jia, J.; Hu, J.; Huo, X. et al. Effects of vitamin D supplementation on cognitive function and blood A β -related biomarkers in older adults with Alzheimer's disease: a randomized, double-blind, placebo-controlled trial. *Journal of Neurology, Neurosurgery & Psychiatry* 2019;90:1347-1352
66. Iacopetta, K.; Colins-Praino, L.E.; Buisman-Pijlman, F.T.A.; Liu, J.; Hutchinson, A.D.; Hutchinson, M.R. Are the protective benefits of vitamin D in neurodegenerative disease dependent on route of administration? A systematic review. *Nutr neurosci* 2018; 9: 1-30.