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Connections Between Vitamin D Deficiency and Brain Structural Changes: Implications for Neurocognitive Function and Neurodegenerative Disorders

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ABSTRACT

In the general world population, vitamin D insufficiency frequently occurs. Severe vitamin D deficiencies are more common in individuals who also have critical illnesses. Ultraviolet B (UVB) radiation applied to the skin has an impact on the production of vitamin D. Through its anti-inflammatory and anti-autoimmune effects, vitamin D plays an immunomodulatory role. The regulation of calcium-mediated neuronal excitotoxicity, the decrease of oxidative stress, the induction of synaptic structure proteins as well as inadequate neurotransmitters and neurotrophic factors are all aspects of how vitamin D functions in the nervous system. A lack of dietary consumption and inadequate sun exposure can cause vitamin D deficiency. Vitamin D is essential for preserving brain health and function. Vitamin D deficiency can worsen the neurocognitive effects of disorders like Parkinson's disease, Alzheimer's disease, and other dementias. Mild cognitive impairment (MCI) refers to the earliest stage of memory impairment or other cognitive function loss. It has been found that the volume of the hippocampus and white matter integrity are both on the decline which is related to this cognitive impairment. There has been only limited exploration of the brain-specific areas that undergo structural change in response to vitamin D status. The objective of the present article was to review the connections between vitamin D deficiency and structural changes in the brain including implications for neurocognitive and neurodegenerative disorders in order to provide additional understanding, especially of brain areas that are involved with neurocognitive functioning or neurodegenerative disorders.

KEYWORDS vitamin D deficiency, 25-hydroxyvitamin D, 25 (OH)D), vitamin D deficiency and brain image, vitamin D deficiency and neurodegenerative disorders

INTRODUCTION

UVB radiation from sunlight induces 7-dehydrocholesterol (7-DHC) in the epidermis to be converted into pre-vitamin D, the method by which vitamin D is generated endogenously, after which it is then thermally isomerized to generate vitamin D2 and vitamin D3, resulting, through two stages, in an active form of vitamin D. In the liver, vitamin D2 and D3 are first converted into calcidiol (25-hydroxyvitamin D; 25(OH)D), which is the major form of vitamin D in circulating blood, thus serum 25(OH)D concentration is a measure of vitamin D status. The scientific community considers that serum 25(OH)D concentrations <25 or 30 nmol/L (<10 or 12 ng/L) should be prevented and treated. Several guidelines have set targets of serum 25(OH)D concentrations of ≥50 nmol/L (≥20

ng/mL) (1, 2).

Geographic location and demographic factors affect the incidence of severe vitamin D deficiency. Numerous variables, such as the time of day, season, latitude, altitude, extent of cloud cover, level of air pollution, type of clothing, and the use of sunscreen can all affect the level of skin exposure to UVB radiation (1, 3). The extensive benefits of vitamin D as a hormone precursor are becoming more widely recognized (4, 5). According to several studies (6, 7), active vitamin D might influence the brain through a variety of mechanisms, including regulating the activity of neuronal growth factors, reducing inflammation, and preventing thrombosis. In the search for ways to reduce the risk of dementia and stroke, a variety of brain morphometry characteristics have been identified which may indicate a decline in cognition and the onset of neurocognitive disorders.

The author conducted a comprehensive search for references using reputable research databases in the fields of healthcare, medicine, and biomedical research, including PubMed, EMVASE, PMC, Cohhrane Library, Science Direct, and Google Scholar. The search focused on articles published within the previous year and included those from the past 5 years or more as deemed necessary. In compiling information on each topic, the author selected research articles that presented a variety of study designs, including systematic reviews and meta-analyses as well as retrospective, prospective, and cross-sectional studies. The selected articles were then used to consolidate information and provide a robust foundation of content related to various topics. In addition to the research articles, the author also gathered data and statistical information from relevant organizational websites to enhance the depth of information included in this review.

VITAMIN D SOURCES AND BIOSYNTHESIS

Vitamin D is produced in the epidermis layer of the skin and can also be found in foods and dietary supplements such as vitamin D2 (ergocalciferol) and D3 (cholecalciferol). The only form of vitamin D produced through the skin is vitamin D3, which is also found in plants, including potatoes, tomatoes, and peppers. Vitamin D2 is also produced in yeast and fungi through UVB exposure to the steroid ergosterol, a component of the fungi's cell membrane. While farmed mushrooms, which are grown in the dark, do not contain substantial amounts of vitamin D2, UVB-treated vitamin D2-boosted mushrooms are now commercially available. Wild mushrooms are a rich natural source of vitamin D2, containing approximately 13-30 µg (520-1200 IU) per 100 g of fresh weight. Most of the vitamin D in the body is created in the skin through the photochemical reaction of UV light impact on its precursor, 7-dehydrocholesterol (7-DHC), when the skin is exposed to UV radiation from the sun (wave length 290-315 nm) or from artificial UVB light. Previtamin D is created from 7-DHC in the epidermis and reaches its peak level in the skin within a few hours. Even after continuous sun exposure, however, previtamin D production is limited to 12 to 15 percent of the beginning 7-DHC. For those with darker skin pigmentation, cutaneous vitamin D production is less effective (1, 8). Both vitamin D2 and D3 must be transformed twice before becoming physiologically active. The main form of vitamin D that circulates in the blood is calcidiol (25(OH)D), which is first transformed in the liver by an enzyme known as 25-hydroxylase (CYP27A1) and has a half-life of approximately 13-15 days. Several tissues, such as fat tissue, muscle tissue, and the liver, absorb 25(OH)D from the circulation and store it there as well. 25(OH)D is commonly used as a biomarker to assess a person's vitamin D level because it is a particularly stable and frequent vitamin D component in serum. The majority of 25(OH)D is converted to calcitriol (1,25(OH)2D), which is created in the second stage by the kidney enzyme 1-hydroxylase (CYP27B1). While performing its roles, calcitriol interacts with the vitamin D receptor (VDR) in several types of tissues across the body (1, 8-13). The tissues with the highest levels of VDR are the kidney's distal tubules, the islets of Langerhans in the pancreas, intestinal absorptive cells, and osteoblast cells (14). Additionally, a variety of immune cells, including lymphocytes (B and T cells), monocytes, macrophages, and dendritic cells, also contain VDR (15). The nuclear steroid

receptor VDR serves as a functional component in the brain. It has been demonstrated that various parts of the brain are where vitamin D production and destruction take place (16). In the human brain, the location of VDR and an enzyme needed to produce the hormone 1-hydroxylase's active form (CYP27B1) have been identified. Research has also demonstrated that VDR is present in a variety of cells in the brain, including astrocytes, oligodendrocytes, microglia, and neurons (9, 17-19). Active vitamin D may influence the brain through a variety of mechanisms, including the regulation of neurotrophic growth factors, effects on cognitive function, and white matter hyperintensity in patients with mild Alzheimer's disease (20). Brain morphometry can reveal cognitive decline and neurocognitive disorders through numerous methods. Reduced volumes of gray matter in the olfactory and hippocampus are as have been linked to low serum 25 (OH)D in older adults with cognitive impairment (21). The high density of vitamin D receptors (VDR) in the hippocampus, hypothalamus, thalamus, cortex, and substantia nigra suggests the potential of vitamin D to influence neurological conditions (22).

VITAMIN D SUFFICIENCY

Different societies have different minimum standards for adequate serum 25(OH)D. For example, the European Food Safety Authority and the American Institute of Medicine (the National Academy of Medicine) both define sufficiency as >50 nmol/L 25(OH)D, in contrast to the US Endocrine Society's definition of >75 nmol/L (23). The optimum vitamin D level has been determined to be 50 nmol/L (20 ng/mL) by the World Health Organization (WHO) and the Institute of Medicine (IOM) USA in their "Dietary Reference Intakes." A public health plan should likely steer away from vitamin D concentrations <30 nmol/L (or 12 ng/mL) (24-26). Based on 25(OH)D serum levels, vitamin D conditions have been classified into three groups: individuals with sufficient levels of vitamin D (>50 nmol/L), insufficient levels (30-50 nmol/L), and deficient levels (<30 nmol/L). People with adequate vitamin D levels don't require as much vitamin D supplementation as those who are vitamin D deficient.

Vitamin D toxicity is evidenced by hypercalcemia, a serum level of 25(OH)D >250 nmol/L, and hypercalciuria, so it is important to beware of the negative impact of an overdose of vitamin D (27). The <50 nmol/L definition of 25(OH)D inadequacy has a considerable body of evidence to support it in the UK. A "white" and "nonwhite" categorization was used in that analysis as different ethnic categories were used in the population samples. The nonwhite group was comprised of people who were listed as being black, Asian, or other, including mixed race. According to the findings, people with dark skin, including Asians, and other minorities, and people who work in buildings or who get little direct sunlight, are at a much higher risk of insufficiency based on their 25(OH)D serum levels. Insufficiency (<50 nmol/L) has been reported to be present in 45.7% of cases in the summer and 69.3% in the winter, whereas deficiency (<30 nmol/L) was present in 31.8% of cases in the winter and 15.3% in the summer (28). Ninety-two percent of the 6,433 South Asians who live in the UK, based on a recent report from the UK Biobank cohort, have 25(OH)D levels <50 nmol/L (29). Serum 25(OH)D levels <50 nmol/L (<20 ng/mL) have been linked to unfavorable skeletal outcomes, such as fractures and bone loss. The main therapeutic objective is a 25(OH)D level >50 nmol/L (>20 ng/mL), while some studies indicate a benefit from a higher threshold (3).

DEFINITION OF VITAMIN D DEFICIENCY

Low levels of serum 25(OH)D concentrations in the bloodstream indicate a vitamin D deficiency. Estimates of the prevalence of vitamin D insufficiency and, consequently, the magnitude of the low vitamin D status public health problem, are significantly impacted by diverse definitions which are based on different serum 25(OH)D thresholds. It is widely accepted that vitamin D deficiency exists in both high- and low-income nations and that it is necessary to address this deficiency with the strictest serum 25(OH)D criteria of 25 or 30 nmol/L (23). The 2016 report of the Scientific Advisory Committee on Nutrition (SACN) (p. 46, section 6.34) on vitamin D recommendations states that, "In

the UK, the serum 25(OH)D level of 25 nmol/L was defined as a minimum level selected to identify an increased risk of rickets." (1, 30). The vitamin D nutritional guidelines and Nature Reviews Endocrinology agree that blood 25(OH)D concentrations below 25 nmol/L (less than 10 ng/mL) need to be avoided at all ages (31). Severe vitamin D deficiency can be verified using a cutoff of <25 or 30 nmol/L (<10 or 12 ng/ml), a level which considerably increases the risk of nutritional rickets and osteomalacia (13, 32). The Global Consensus Recommendations on Prevention and Management of Nutritional Rickets Research advises categorizing vitamin D status according to 25(OH)D levels as follows: more than 50 nmol/L is sufficient, 30-50 nmol/L is insufficient, and less than 30 nmol/L is deficient (27). Whenever possible, severe vitamin D deficiency that has 25(OH) D concentrations less than 30 nmol/L, should be prevented, as that greatly raises the possibility of mortality, infection, and several other illnesses (3).

VITAMIN D DEFICIENCY ESTIMATES WORLDWIDE

Geographical and demographic factors affect how common vitamin D deficiency is, according to Amrein et al.'s study Vitamin D deficiency 2.0. That study reviewed the current situation globally and found the incidence of severe vitamin D deficiency, defined as 25(OH)D lower than 30 nmol/L, was 5.9% in the US, 7.4% in Canada, and 13% in Europe. An estimated 24% of Americans, 37% of Canadians, and 40% of Europeans had levels of 25(OH)D less than 50 nmol/L. Age, with lower levels in childhood and the elderly, as well as ethnicity, may also affect this. A very high prevalence of low vitamin D status has been reported in several countries, e.g., in India, Tunisia, Pakistan, and Afghanistan it is estimated that >20% of the population has 25(OH)D levels <30 nmol/L. In addition, there is a high prevalence of vitamin D deficiency in some patient subgroups that frequently exhibit organ dysfunction or deficiency affecting the metabolism of vitamin D. The prevalence of vitamin D deficiency in patients with chronic renal failure, who are on hemodialysis, who are renal transplant recipients affected by liver disease, and patients following liver transplantation can range from 85 to 99% (3).

THE FUNCTION OF VITAMIN D ON THE NERVOUS SYSTEM

A research evaluation by Bivona et al. was conducted to provide a summary of the roles that vitamin D plays in the brain as well as to clarify the possibility that it may contribute to neurological illnesses. Vitamin D increases brain function in both embryonic and adult brains, enhancing the connections of neural circuits involved in movement, emotion, and reward-driven behavior. This role appears in the form of interaction between vitamin D and the nervous system. Low vitamin D serum levels have been observed in people with schizophrenia, multiple sclerosis, Parkinson's disease, autism spectrum disorders, and Alzheimer's disease (33). In the neurological system, vitamin D may have an impact on neuronal development, differentiation, neural protection, neurotransmission, and neuroplasticity. Vitamin D also has an impact on how the brain develops and functions. Vitamin D can enhance the expression of synaptic structures of proteins, neurotrophic factors, and can help alleviate the lack of neurotransmitters in some neurodegenerative illnesses (34-37). In a randomized clinical study contrasting vitamin D with a placebo, it was discovered that vitamin D had a significant impact on neuroplasticity as determined by improved corticospinal transmission (38). It has also been reported that vitamin D protects neurons from apoptosis and axon destruction (37, 39). Additionally, vitamin D may also influence intracellular calcium homeostasis by regulating calcium neuronal excitotoxicity (37).

LOW VITAMIN D AND NEUROLOGICAL DISORDERS

The hypothesis that vitamin D is associated with cognitive decline, behavioral abnormalities, and attention deficits has been substantiated by numerous analyses of preclinical research. According to cross-sectional studies, patients with cognitive impairment and Alzheimer's disease have much lower vitamin D levels than healthy individuals. Low vitamin D has also been

linked in longitudinal studies and meta-analyses to cognitive impairment and related neurological illnesses, including Alzheimer's disease (33, 40-43). Cross-sectional studies have suggested a strong link between low vitamin D and mild cognition problems according to systematic reviews and meta-analyses, but interventional studies are still required to demonstrate the specific impacts of vitamin D supplementation on cognition (44). After adjusting for age, educational level, and brain volume, Shivakumar et al. discovered a positive correlation between 25(HO)D level and hippocampus volume in antipsychotic-naive schizophrenic patients, 84% of whom were 25(HO)D deficient (p = 0.018) (45). That research also found a relationship between vitamin D levels and alterations in brain volume in individuals with schizophrenia and bipolar disorder (46, 47). Vitamin D has been shown to promote the growth of neurons by regulating the creation of neurotransmitters including acetylcholine, dopamine, gamma-aminobutyric acid (GABA), and nerve growth factor (NGF) (22, 48). In one study, participants with low levels of vitamin D performed poorly on cognitive tests and processed information more slowly than those with normal vitamin D levels (49). A higher risk of cognitive impairment has been shown to be linked to low vitamin D levels (50). Another study found an independent relationship between olfactory dysfunction and low serum vitamin D concentrations in individuals with Parkinson's disease (51). In subjects with Alzheimer's disease, which is frequently characterized by medial temporal atrophy, it has been discovered that the left parahippocampal gyrus, the fusiform, and the hippocampus are as are positively correlated with 25(OH)D level. The medial and lower parts of the left temporal lobes have been linked to the memory domain of cognitive function. In other words, as the level of atrophy of the medial parts of the temporal lobe, which includes hippocampus, increases, the vitamin D deficiencies in patients with Alzheimer's disease also increases. The concept that vitamin D can help prevent or reduce neurodegenerative processes is supported by these findings. Additionally, as the affected areas are essential to normal cognitive abilities (which include executive functions, memory consolidation, and behavioral regulations), the level of brain atrophy of parts of the brain responsible for neurocognitive functions might be useful in describing cognitive impairment in people with low 25(OH)D levels. The pathogenesis of Alzheimer's disease, which results in neuronal degeneration, may be influenced by vitamin D levels (21). However, despite some encouraging findings, there is still inadequate proof that vitamin D treatment can help treat Alzheimer's disease or reduce its symptoms (52).

LOW VITAMIN D AND BRAIN STRUCTURAL CHANGES

Neurodegenerative processes and decreased neurocognitive performance have both been linked to vitamin D deficiency. According to current research, it is debatable whether vitamin D deficiency has structural correlations in the brain. A study by Terock et al. on the association of vitamin D levels with aging brain imaging patterns was published in 2022. That study investigated correlations between vitamin D status and brain aging imaging patterns obtained from 1,865 individuals from the general population with an average age of 51.6 years and mean vitamin D level of 60.75 nmol/L. Various combinations of covariates were used. Findings from an extensive general population sample composed of adults of various ages supports the concept that vitamin D is crucial for preserving the health of brain neurons. The association of vitamin D deficiency with hippocampus volume was discovered, and the volume of the entire brain and of the gray matter were found to be significantly correlated with linear vitamin D levels. However, as these results are cross-sectional, it would be difficult to establish whether vitamin D levels can be used as an indicator of brain health or as a predictor of the progression of brain aging (53) Table 1. The association between 25(OH)D, neuroimaging features and the likelihood of dementia and stroke was investigated in a study by Navale et al. Prospective data from the UK Biobank were used to examine the relationship between 25(OH)D concentrations and neuroimaging findings, as well as the risk of dementia and stroke. In this observational

research, factors including age, sex, ethnicity, socioeconomic status, lifestyle, sun exposure, and illnesses were included. Out of a total of 427,690 subjects with illness, there were 3,414 occurrences of dementia and 5,339 incidents of stroke. A total of 33,523 people were enrolled in the brain neuroimaging subsample. Low vitamin D status was found to be associated with neuroimaging findings, dementia, and stroke risks, with the strongest associations for those with 25(OH)D less than 25 nmol/L and adjusted HR: 1.79; 95% CI: 1.57, 2.04 (40) Table 1. A study by Lee et al. explored the connection between blood levels of 25(OH)D and structural changes in the brain. That study included 201 participants (10 community-based normal healthy subjects, 33 subjects with subjective cognitive decline, 97 with mild cognitive impairment, and 61 with Alzheimer's disease) and elderly patients with MRI scans. The mean age was 74.91± 9.21 years and the mean 25(OH) D level was 18.05 nmol/L. That study found no correlation between 25 (OH)D levels and white matter area. However, it was found that decreased 25(OH)D levels were linked to smaller right olfactory and rectus gray matter regions. In SCD patients, there was no association between 25(OH)D and total brain volume. The right olfactory, rectus, supplementary motor region, left medial cingulate, superior temporal, and Rolandic operculum areas all showed a positive correlation with 25(OH)D levels in participants with MCI. It has also been demonstrated that the left parahippocampal, fusiform, cerebellum, and hippocampus regions are positively associated with 25(OH)D serum levels in Alzheimer's disease patients (21) Table 1.

Higher levels of vitamin D were found to be associated with increased gray matter volume in a cross-sectional study of 217 Dutch community-dwelling individuals 65 years old and older, but that study did not measure the entire brain volume or white matter volume (54) Table 1. In research on a large sample of healthy Dutch individuals without dementia, vitamin D insufficiency was found to be associated with a reduction in the volume of the hippocampus, white matter, and brain tissue (55) Table 1. The 376 publications chosen were reviewed statistically and systematically for data on the extent and types of morphometric alterations in the brain related to vitamin D deficiency or supplementation. In the studies there were from 20 to 333 clinical patients, all adults. Two studies included young to middle-aged individuals, five studies included elderly people, and 40-79% of the participants in the studies were female. The findings demonstrated that vitamin D deficiency was linked to larger lateral ventricles and reduced brain capacity. The ventricular volume was 1.01 SD greater with vitamin D depletion and the pooled effect size was 1.01 (95% CI: 0.62; 1.41), which is a "large" effect size. In summary, systematic reviews and quantitative syntheses of information on the areas affected and the morphometric alterations in the brain associated with vitamin D depletion or repletion showed that low levels of vitamin D are related to brain atrophy in both parts of the lateral ventricles and throughout the brain (5). There is evidence that vitamin D and its active form can directly affect the health of neurons, the shape of the brain, and memory function in both humans and animals. For example, using structural and diffusion MRI datasets of older patients, Al-Amin et al. conducted a study on people who visited the Memory Clinic at the Konkuk University Hospital (KUH) in South Korea who complained about their memory. A total of 56 MCI patients were divided into serum 25(OH)D deficient (less than 30 nmol/L, n = 27) and not-deficient (>30 nmol/L, n = 29) groups. Voxel-based morphometric analysis was used to examine the relationship between vitamin D levels and focal brain atrophy. The findings revealed that low vitamin D (25(OH) D <30 nmol/L) was associated with decreased hippocampus subfield volume and connection deficits in older MCI patients and may worsen neurocognitive outcomes (56) Table 1. According to Miller et al., accelerated cognitive decline was linked to low vitamin D levels (57). After adjusting for age, education level, and brain volume (p = 0.018), a study by Shivakumar et al. found a positive connection between 25(HO)D level and hippocampus volume in antipsychotic naive schizophrenia patients, 84% of whom were 25(HO)D deficient (45). A blood test and a brain MRI were performed on 215 elderly Caucasian community residents

Table 1. Studies of serum 25(OH)D concentration deficiency and brain volume by magnetic resonance imaging (MRI) scanning

Reference	Design	Population/characteristics	Brain volume areas	Findings
Terock et al. 2022 (53)	Cohort study	1,865 subjects from the general population, age 51.6±13.7 years, 52.3% female	Gray matter and hippocampus	- The average serum 25 (HO)D concentration was 24.3 ng/mL (60.75 nmol/L), range 15.5 to 159.25 nmol/L (6.2 to 63.7 ng/ml) - Increased brain age was strongly linked to vitamin D deficiency and was significantly correlated with the total volume of the brain as well as the gray matter, and the hippocampus volume
Navale et al. 2022 (40)	Cohort study	427,690 subjects; risk of dementia = 3,414 cases, stroke = 5339 cases, age 37-73 years, (99.5% aged 40–69 years), 53.4% female	White matter, gray matter, and hippocampus	The strongest relationships were found in individuals with serum 25(OH)D concentrations < 25 nmol/L compared with 50-75.9 nmol/L and adjusted HR: 1.79; 95% CI: 1.57, 2.04 and HR: 1.40; 95% CI: 1.26, 1.56, respectively, for vitamin D deficiency and a higher risk of dementia and stroke.
Croll et al. 2021 (55)	Cross-sectional study	2,716 individuals without dementia from the Rotterdam population, age 56.6 ± 6.4 years, 55.4% female	White matter, gray matter, and hippocampus	- Serum 25(OH)D average 60.9 nmol/L - Reduced brain tissue volume, white matter, and hippocampus volume were associated with serum 25(OH)D concentrations <30 nmol/L compared to a sufficient vitamin D status (≥50 nmol/L)
Lee et al. 2021 (21)	Cross-sectional study	201 subjects (10 community-based normal healthy subjects, 33 with subjective cognitive decline, 97 with mild cognitive impairment, and 61 with Alzheimer's disease) from the dementia registry database age 74.9 ± 9.2 years, 68.1% female	Gray matter, olfactory areas, cingulate gyrus, temporal lobe, parahippocampus, hippocampus, cerebellum	- The mean serum 25(OH)D was 18.05 nmol/L; reduced brain volume was linked to lower 25(OH)D levels in the right olfactory and rectus gray matter areas, (family-wise error; FWE-corrected, $p < .05$) for all the subjects. - There were no white matter regions associated with 25(OH)D levels. - Left parahippocampus, fusiform, and hippocampal regions had a significant association with 25(OH)D in Alzheimer's disease patients (FWE-corrected, p. 05).
Ali et al. 2020 (59)	Cross-sectional study	53 older adults did not meet the consensus DSM IV criteria for clinical dementia and did not suffer from any neurological, depressive, or orthopedic conditions, age 72±5 years, 38% female	White matter, gray matter	- Serum 25(OH)D levels averaged 67.3 nmol/L - In older individuals, lowered serum 25(OH)D concentrations were linked with atrophy of the calcarine sulcus and a positive correlation was found between serum 25(OH)D and gray matter volume in the left calcarine sulcus ($p < 0.05$), threshold- free cluster enhancement (TFCE), FWE-corrected.

Table 1. Studies of serum 25(OH)D concentration deficiency and brain volume by magnetic resonance imaging (MRI) scanning (continuous)

Reference	Design	Population/Characteristics	Brain volume areas	Findings
Al-Amin et al. 2019 (56)	Cross-sectional study	56 patients who have mild cognitive impairment, age N/A, 67.8% female	White matter, gray matter, hippocampus, dentate gyrus, fimbria	- The average serum 25-OHD concentration was 15.41 ng/mL (37.85 nmol/L) - A significant decrease in the volume of the entire hippocampus, particularly in the dentate gyrus and fimbria, in the serum 25(OH)D deficient group. An absence of connections in 13 areas, with the right hippocampus as the center of the network disruption
Foucault et al. 2019 (58)	Cross-sectional analysis	215 Older Caucasian community-dwellers, age 72.1±5.5 years, 40% female	White matter, gray matter, perigenual anterior cingulate cortex, midcingulate cortex, posterior cingulate cortex	- The total cingulate thickness in subjects with vitamin D insufficiency (<50nmol/L) was lower than that of the other cingulate part (24.6±1.9mm versus 25.3±1.4mm, P=0.001). A significant difference was found for the perigenual anterior (p = 0.011), midcingulate (P=0.013) and posterior cingulate cortex (p = 0.021)
Brouwer-Brolsma et al. 2015 (54)	Cross-sectional study	217 community-dwelling elderly people, age 72± 6 years, 57% male	White matter, gray matter	- The average level of serum 25(OH)D was 61± 23 nmol/L. after adjusting for intracranial volume. Serum 25(OH)D was significantly linked with gray matter volume (β±SE: 0.25 0.09 mL; p = 0.005) and total brain volume (β±SE: 0.26 0.11 mL; p = 0.02) but not with white matter volume.

as part of an investigation by Foucault et al. Using FreeSurfer and T1-weighted MR images, the thickness of the cingulate cortex (perigenual anterior, middle, and posterior) was evaluated. It was found that a smaller cingulate cortex was associated with vitamin D insufficiency (<50 nmol/L, n = 80) in the sample of elderly people studied. A smaller average cingulate thickness was cross-sectionally linked to vitamin D deficiency (β = -0.49, p = 0.028). The thickness of the perigenual anterior, midcingulate, and posterior cingulate cortex was strongly linked with serum 25(OH)D concentration (p = 0.011, p = 0.013, and p = 0.021, respectively) (58) Table 1. In addition, Ali et al. found that in older individuals, a smaller left calcarine sulcus volume was linked to lower serum 25(OH)D levels (59) Table 1.

The upshot is that vitamin D is crucial for the function of various systems such as the skeletal system, nervous system, and immune system, particularly in patients with Alzheimer's disease, Parkinson's disease, and neurocognitive disorders, and results in a decline in the brain's effectiveness. The brain volume also decreases in various areas, resulting in cognitive process being impaired. Cognitive impairment affects daily life and social interaction. Patients with MCI are at a higher risk of vitamin D deficiency, which is associated with focal brain atrophy and reduced brain gray matter volume in the relevant regions, including the hippocampus. Cognitive impairment patients have deficits in perceptual-motor, language, executive function, complex attention, memory and learning, and social cognition.

CONCLUSIONS

Vitamin D deficiency is characterized as a serum 25 (HO)D concentration <30 nmol/L, insufficiency to be between 30 and 50 nmol/L, and sufficiency to be >50 nmol/L. A severe vitamin D deficiency is indicated by serum 25(OH)D levels <25 or <30 nmol/L, which significantly increases the risk of osteomalacia and nutritional rickets. Vitamin D status of 25 (HO)D <30 nmol/L is linked with greater levels of decreased brain tissue volume compared to a sufficient vitamin D status (>50 nmol/L) and is associated with reduced volume of hippocam-

pal subfields and connection deficits in older people with MCI. 25(OH)D level is positively correlated with regions of low gray matter volume. A reduced area of the brain where neurocognitive functions are involved in response, including gray matter, white matter, the hippocampus, the cingulate cortex, the calcarine sulcus, the parahippocampus, cerebral cortex, and the olfactory regions, are associated with a low serum level of 25(OH)D. Additionally, as declining brain regions are responsible for reductions in typical cognitive states (such as executive processes, memory consolidation, and behavioral regulation), it is likely that those individuals have a low serum 25(OH)D concentration resulting in cognitive impairment.

Determination of the adequate intake of vitamin D is an important area for future investigation related to preventing decline in or improvement of neurological function. The results of such a study should be valuable for the general population, the elderly, patients with neurodegenerative disease, and neurocognitive disorders. Dementia is a major neurocognitive disorder. Each of the three categories of dementia (delirium, MCI, dementia), can occur in elderly patients and can cause increased disabilities and dependence which also have a significant impact on families, relatives, caregivers, and a country's health service system. Further investigation is needed to determine the most effective ways to use vitamin D for the prevention, treatment and/or alleviation of neurodegenerative diseases and neurocognitive disorders even though the condition is currently incurable. There are limitations to cross-sectional studies, so longitudinal imaging studies are required as well.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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