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A review focus on the latest research progress of vitamin D in brain science

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Abstract. Vitamin D is a hormone precursor that is increasingly recognized for its broad impact, including on brain health. Vitamin D regulates neurotrophic growth factors and influences inflammation and thrombosis; all of which affect neurocognition. Lack of vitamin D can cause osteoporosis, decreased bone density, and fractures. The flesh of fatty fish and fish liver oils are the finest sources of vitamin D. Any mixture of calcifediol, obtained from vitamin D3, and ercalcidiol, derived from vitamin D2, is known as 25-hydroxyvitamin D, also known as 25(OH)D. Loss of cognitive abilities including thinking, remembering, and reasoning is referred to as dementia. Some dementia patients have emotional instability and personality changes. The most common type of dementia is Alzheimer's disease. The condition is gradual, starting with minor memory loss and potentially progressing to the loss of communication and environmental awareness. One of the characteristics of Alzheimer's disease, amyloid beta (Aβ) aggregates, are known to be cleared by vitamin D. Additionally, vitamin D may offer neuroprotection against tau hyperphosphorylation brought on by A. As a result, dementia and Alzheimer's disease are more likely to develop in those with low vitamin D levels. A stroke, also known as a brain attack, happens when a blood artery in the brain breaks or when something stops the flow of blood to a specific area of the brain. Parts of the brain suffer harm or degeneration in either scenario. In addition, the risk of stroke may be raised by vitamin D deficiency.

Keywords: Vitamin D (VD); 25-hydroxyvitamin D (25(OH)D); Dementia; Alzheimer's disease; Stroke.

1. Introduction

Vitamin D is both a nutrient that we consume and a hormone that our bodies synthesize. It is a fat-soluble vitamin that has long been recognized for assisting the body's absorption and retention of calcium and phosphorus, two nutrients necessary for bone development. The substance is anti-inflammatory, antioxidant, and neuroprotective. It is a vitamin that we ingest as well as a hormone that our bodies make. It is a fat-soluble vitamin that has long been recognized for assisting the body's absorption and retention of calcium and phosphorus, both of which are necessary for bone development. The substance is anti-inflammatory, antioxidant, and neuroprotective [1]. To further support brain health, it enhances neurotrophic factors including nerve growth factor. According to recent research, VD may help to lessen the symptoms of Alzheimer's disease [1]. Numerous preclinical research provide credence to the idea that low VD levels are linked to cognitive decline, attention deficit disorders, and behavioral issues. Patients with Alzheimer's disease and cognitive impairment regularly have much lower levels of VD than healthy adults, according to cross-sectional research. Low VD levels may be linked to Alzheimer's disease and cognitive decline, according to studies and analysis [1]. Numerous processes, such as the control of neurotrophic growth factors, inflammation, and thrombosis, may cause VD to have an impact on the brain. Since supplementation, food, and solar exposure may all maintain adequate serum concentrations of VD, it has become more important to identify modifiable risk factors for dementia and stroke [1]. VD comes in the form of 25-hydroxyvitamin D.

Although the results of some studies did not find a clear mechanism between 25(OH)D and the risk of frailty, an aging-related physical decline syndrome characterized by an apparent susceptibility to adverse health outcomes, in some other studies, older adults with low 25(OH)D were found to be more susceptible to frailty than those with high D levels [2]. Additionally, the findings of certain meta-analyses have demonstrated a strong correlation between decreased 25(OH)D levels and higher

frailty severity [2]. High blood VD concentrations may both prevent and lessen the emergence of frailty [2]. VD is a neurosteroid hormone that is also linked to cognitive decline and neurodegenerative illnesses [2]. It is necessary for optimal brain function and development. According to epidemiological data, VD is a reliable indicator of dementia or cognitive deterioration in older persons [2]. In a population-based longitudinal research, older persons with low baseline VD levels were strongly linked to cognitive deterioration, as measured by a straightforward mental status evaluation at age 2 years, and even with a risk of Alzheimer's disease [2]. Previous research has mostly concentrated on the link between frailty and cognitive performance, with little attention paid to the underlying processes or putative mediators of this correlation. Large epidemiological cohorts of older persons have also seldom been employed in these investigations. Furthermore, the findings of research that may be utilized to pinpoint the precise connection between VD and frailty and cognitive function have not been agreed upon [2].

2. Body Paragraph

There is a consensus about the association between low VD and brain health. At the same time, there are conflicting opinions about the association between low VD and brain health. Age affects the brain in different ways. Aging affects the formation of 25(OH)D, the active form of VD. Due to age-related decline in renal function, 25(OH)D production is reduced by 50%, although 25(OH)D levels are partially maintained through secondary hyperparathyroidism. Since 25(OH)D is dependent on an adequate supply of the substrate VD, the development of VD deficiency leads to a further reduction in 25(OH)D formation and therefore may have a greater impact on brain health [3]. There is growing evidence that low prenatal VD levels are associated with an increased risk of neurodevelopmental disorders such as schizophrenia [4]. It is thought that the mechanism linking developmental VD deficiency to neurodevelopmental disorders may be related to the pro-differentiation and anti-proliferative properties described for the active form of VD [4]. Thus, VD deficiency deprives the developing brain.

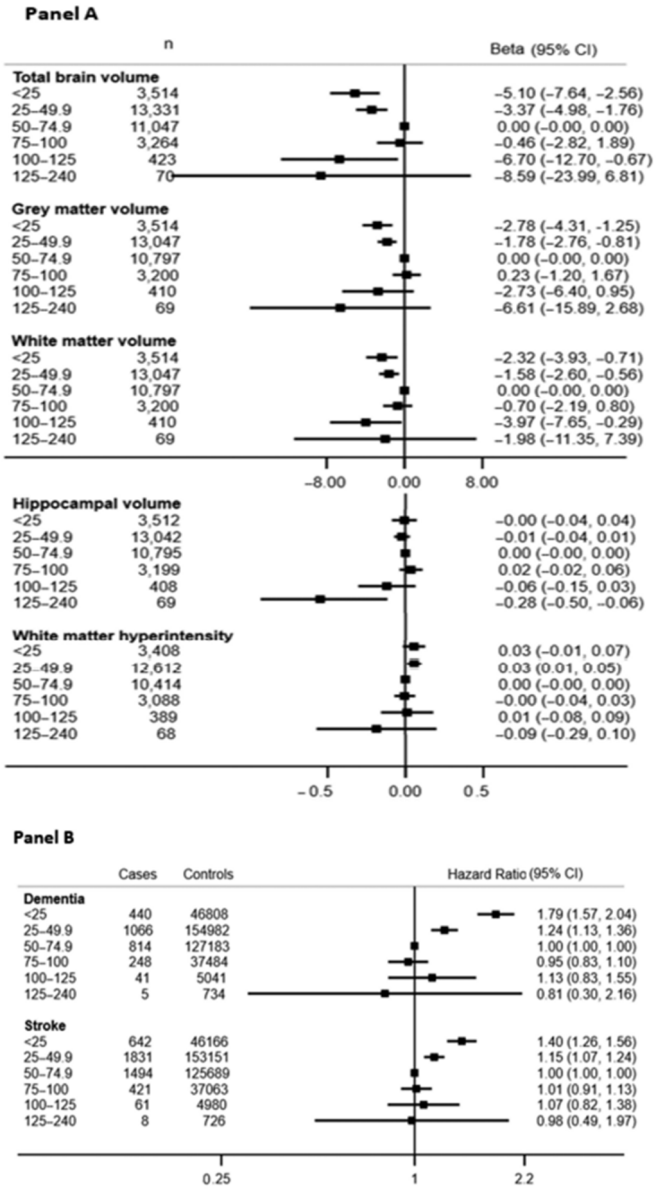
Factors such as age, education, physical activity, diabetes, hypertension, hypercholesterolemia, and season may have a significant impact on the results of cohort studies. However, most studies do not take into account confounding factors, such as depression. In longitudinal follow-up, several studies have shown no correlation between low blood VD levels and CI and dementia, although others have reported a substantial correlation ($p=0.001$) [5]. The size and follow-up of the studies that discovered a meaningful connection, however, were modest. A Swedish study with a longer follow-up (18 years) in a large sample (2,841) found no association. Confounding variables in this investigation included overall dietary consumption of VD, physical exercise, and sun exposure [5]. Nevertheless, frequent blood tests and food evaluations increased exposure information accuracy, which was absent in this investigation [5].

Another US research with a sizable sample (13,044 people) and lengthy follow-up (20 years) did not find any such association [5]. The previously noted relationship between low 25(OH)D levels and cognitive impairment might be the result of reverse causality, where people with poor health (such as cognitive impairment) engage in less physical activity and get less sun exposure, which results in lower VD concentrations, rather than a causal factor in the pathogenesis of cognitive impairment and dementia. Since 25(OH)D was measured at midlife and changes in cognition were assessed over 20 years, it can be assumed that this study is less prone to reverse causality [5]. The use of a single serum 25(OH)D test at baseline to represent all long-term exposure studies [5] is another methodological error that compromises the validity of the findings.

The UK Biobank is an ongoing prospective cohort study comprising 502,504 people between the ages of 37 and 73. Using prospective data from the UK Biobank, the relationship between 25(OH)D concentrations and neuroimaging findings as well as the risk of dementia and stroke is examined. The UK Biobank study found that hypovitaminosis D status continued to be associated with neuroimaging outcomes and risk of dementia and stroke even after extensive adjustment for covariates. For

dementia and stroke incidence, the median follow-up time was 10.9 years [6]. In the table, there was a U-shaped relationship between total brain, gray matter, and white matter volumes and 25(OH)D concentrations. Lower brain volumes were associated with both low and high 25(OH)D concentrations, but only at the high end for hippocampal volumes (Figure 2). Lower 25(OH)D concentrations were associated with greater white matter volumes, according to the American Biobank study (25-49.9 nmol/L vs. 50-74.9 nmol/L; adjusted. 0.03; 95% CI: 0.01, 0.05) (Table 2A). The risk of dementia and stroke was highest among patients with the lowest 25(OH)D concentrations (50 nmol/L), with no change in risk with increasing concentrations (Figure 2B). The combined risk of dementia was 5,467,740.9 years, while the combined risk of stroke was 5,371,196.5 years. A causal relationship between a VD deficit and dementia was established by Mendelian randomization (MR) study, but not by research on the risk of stroke. The majority of individuals were female, between the ages of 60 and 73 at baseline, without a history of chronic disease or depression, and of British, Irish, or white descent [6]. Type of physical activity, time spent outdoors, sun protection, intake of oily fish, and dietary restriction were similarly linked to brain volume, incidence of dementia, and stroke, and 25(OH)D concentrations varied by social and lifestyle factors [6].

Table 1. [6] The adjusted observational relationships between 25(OH)D) category and illness outcomes are shown in (A) and (B), respectively. Reference participants are those with 25(OH)D levels of 50–74.9 nmol/L. Estimates derived from Cox proportional hazards modeling for illness outcomes and from linear regression for neuroimaging outcomes [6]



Recent studies conducted have shown that VD has an impact on brain development early in life. In May 2018, a research by Yates et al. revealed that VD deficit in mothers and offspring was connected to a range of early-life abnormalities, including learning and memory issues and grooming habits [7]. Additionally, there is some evidence that suggests autism and schizophrenia-like diseases, including increased lateral ventricular enlargement and altered brain expression of genes associated to dopamine and glucocorticoid pathways [7]. A comprehensive evaluation of prenatal nutrition and children's emotional development and subsequent mental illnesses was carried out in March 2018 by Freedman et al. [7]. According to the findings, pregnant women require prenatal vitamins, such as vitamins A and D, to lower their baby's chance of developing schizophrenia and other psychiatric illnesses later in life [7]. In February 2018, Stutsman completed a study revealing that pregnant moms are at increased risk of VD insufficiency. VD plays a critical role in newborn hypoxic-ischemic brain damage. Children born to moms who lacked VD experienced hypoxic-ischemic brain damage [8].

3. Discussion/Conclusion

The UK Biobank analysis using a large number of UK participants provides some evidence that adequate 25(OH)D concentrations are beneficial for brain health. Low 25(OH)D concentrations were found to increase the risk of dementia and stroke as well as variations in a number of brain morphometric variables in observational investigations [6]. The study did find evidence of a non-linear causal association between 25(OH)D and dementia risk in MR analyses, despite its inability to conclusively link the two variables to impacts on brain volume or stroke risk. The study emphasizes the significance of diagnosing, treating, and avoiding VD deficiency [6].

The UK Biobank project has the advantage of being the biggest population-based prospective and magnetic resonance imaging (MR) study examining the relationship between 25(OH)D and brain health, and the study has superior statistical power in all respects. The abundance of data also allowed analyses of the impact of extremely low 25(OH)D concentrations and complete confounder correction [6]. Our MR findings were less impacted by confounding variables and adverse causation because of the nature of MR investigations. The UK Biobank study further conducted the first non-linear MR analysis and revealed causal support for the contribution of 25(OH)D, even though the risk of dementia appeared to be just below the deficit threshold [6].

The UK Biobank study also has limitations. Despite using a sophisticated adjustment method, the study was unable to completely eliminate the impact of residual confounding in the observational analysis. Despite the UK Biobank cohort's diversity, bias in healthy volunteers was still a possibility because the baseline population was primarily low-poverty, moderately to tertiary educated, and BMI-wise, normal to overweight [6]. These results might not apply to other populations since the MR study was restricted to participants from white British communities. The study cannot totally rule out the possibility of horizontal pleiotropy, where the genetic variant of interest impacts the outcome through a different channel, even though all of the genetic tools included in the analysis had repeated relationships with 25(OH)D concentrations [6].

In conclusion, VD is necessary to preserve vital bodily processes such as calcium homeostasis, skeletal integrity preservation, and neurodevelopment. Numerous issues, including dementia, depression, type 2 diabetes, autism, and schizophrenia have been associated with its lack [7]. This subject has to be highlighted since addressing the deficient status can assist in avoiding a number of harmful health effects [7]. Currently, the lack of data induce to insufficient understanding of the effects of vitamins on the brain health. Therefore, in the future, there should be more investigation and testing to prove the association between VD and brain health.

4. Objective

This review paper's objective was to evaluate the relationship between Vitamin D and mental health, including the risk of dementia and stroke.

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