Review Article

Low Vitamin D and Its Association with Cognitive Impairment and Dementia

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Vitamin D is a neurosteroid hormone that regulates neurotransmitters and neurotrophins. It has anti-inflammatory, antioxidant, and neuroprotective properties. It increases 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. Emerging evidence suggests its role in the reduction of Alzheimer’s disease hallmarks such as amyloid-beta and phosphorylated tau. Many preclinical studies have supported the hypothesis that vitamin D leads to attentional, behavioral problems and cognitive impairment. 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. Despite such evidence, the causal association cannot be sufficiently answered. In contrast to observational studies, findings 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 biggest issue of the existing RCTs is their small sample size, lack of consensus over the dose, and age of initiation of vitamin D supplements to prevent cognitive impairment. 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.

1. Background

Vitamin D is a fat-soluble steroid vitamin with a definitive role in bone health. Beyond its role in the regulation of bone health, it also plays an important role in the functioning of other systems such as cardiovascular, endocrine, and nervous systems [1]. Ultraviolet radiation (UVR) is the major source of vitamin D. The two forms of vitamin D are ergocalciferol (D2) and cholecalciferol (D3). It undergoes two hydroxylation processes, first in the liver by enzyme 25 hydroxylase to produce 25(OH)D and second in the kidney to produce active form of 1,25(OH)D [2, 3]. An estimated one billion people worldwide suffer from hypovitaminosis D. There is no worldwide consensus regarding the cutoff value for definition of vitamin D deficiency. Typically, vitamin D deficiency is defined as a 25(OH)D level of less than 50 nmol/L, with severe deficiency defined as less than 25 nmol/L and insufficiency between 50 and 75 nmol/L [4]. Vitamin D can reach the brain by crossing the blood-brain barrier (BBB) through passive diffusion. The active form, 1,25(OH)D, binds to the vitamin D receptor (VDR) and influences gene expression. Vitamin D exerts its action via VDR present in neurons, glial cells of the hippocampus, orbitofrontal-cortex, cingulate, amygdala, and thalamus [5–7]. Its neuroprotective, anti-inflammatory, and antioxidant effect on neurons promotes brain health [8–10]. Vitamin D promotes the production of neurotrophic factors such as nerve growth factor (NGF). Many studies have consistently reported the increase in neuronal growth in rat hippocampal cell cultures enriched with vitamin D [8, 9]. The NGF and other neurotrophic factors promote the survival of both hippocampal and cortical neurons [10, 11]. Vitamin D is also implicated in regulating the gene expression of various neurotransmitters such as acetylcholine,
Studies - the association of low vitamin D and global cognitive deficit is established through many cross-sectional and longitudinal studies. Nevertheless, the issue of reverse causality remains to be answered [21]. Table 1 shows a summary of evidence demonstrating an association between serum 25(OH)D, CI, and dementia [9, 21, 22, 23–26]. Many studies have shown an association of low vitamin D with CI at a cross-sectional level although the same studies with longitudinal follow-ups did not replicate the association [21, 23, 24]. All included studies showed a difference in the study population, sample size, participants’ age, follow-up time, vitamin D exposure, method used for estimation for vitamin D, criteria used to diagnose dementia and CI, and methods of assessment of cognition. Most studies adjusted for confounders like age, education, physical activity, diabetes, hypertension, hypercholesteremia, and season. However, most studies did not consider confounders like depression. Four studies [9, 22, 23, 25] found no association between low serum vitamin D levels and CI and dementia in a longitudinal follow-up, whereas two studies [21, 24] found a significant association (P = 0.001). However, the studies which found a significant association were smaller in size and duration of follow-up. A Swedish study [22] done on a large sample (2,841) for a longer follow-up (18 years) did not find an association. This study took into account the confounders like common dietary intake of vitamin D, physical activity, and sun exposure. However, repeated blood sampling and dietary assessments improve the precision of exposure information, the study lacked in doing so. Similarly, another American study [25] done on a large sample (13,044) with a long follow-up (20 years) did not report any such association. The previously reported associations between 25(OH)D concentrations and cognitive impairment may be a result of reverse causation—whereby low 25(OH)D is a marker of poor health (resulting from those in poor health (e.g., those with cognitive impairment) doing less physical activity and having less sun exposure and thereby having lower vitamin D concentrations) rather than a causative factor in cognitive impairment and dementia pathogenesis. This study can be considered less susceptible to reverse causation as 25(OH)D was measured in midlife, and cognitive change was evaluated over 20 years. Another methodological shortcoming compromising the validity of the data is the use of single serum 25(OH)D measurements taken at baseline to represent long-term exposure in all studies [9, 21, 22, 23–25]. A prospective study with two follow-ups, each at 5 years, conducted to examine the association of dietary and supplemental vitamin D intake and cognitive decline showed an association between high intake and a slower decline in the cognitive domains of verbal fluency. Those with supplemental intake also exhibited a slower decline in the cognitive domain of verbal fluency although the effect on visual and verbal memory was less in magnitude [26]. Similarly, a study on participants (age 55–67 years) with levels >25 nmol/l has demonstrated better verbal fluency and executive functioning both at baseline and at a 10-year follow-up [27].

In contrast to the existing body of literature demonstrating a positive correlation between cognitive function and vitamin D status, Lam et al. [28] reported a negative association between vitamin D levels and verbal episodic

2. Vitamin D and Brain-Evidence through Animal Studies

Developmental vitamin D deficiency and inactivated vitamin D receptor gene affect brain functioning and behavioral outcome in rodents. The studies which support this hypothesis were 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 [17]. Similarly, a study on 10-week-old rats with transient vitamin D deficiency during the early developmental stage demonstrated enlarged lateral ventricle volume and reduced nerve growth factor compared to controls [18]. The evidence concerning the impact of vitamin D deficiency on the behavior of mice which developed later in life is sparse. However, a study investigating the effect of vitamin D-deficient diet for 10 weeks on 20-week-old mice reported behavioral and neurochemical changes [19]. Similarly, another 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 [20].

2.1. Evidence through Cross-Sectional and Longitudinal Studies. The association of low vitamin D and global cognitive deficit is established through many cross-sectional and longitudinal studies. Nevertheless, the issue of reverse causality remains to be answered [21]. Table 1 shows a summary of evidence demonstrating an association between serum 25(OH)D, CI, and dementia [9, 21, 22, 23–26]. Many studies have shown an association of low vitamin D with CI at a cross-sectional level although the same studies with longitudinal follow-ups did not replicate the association [21, 23, 24]. All included studies showed a difference in the study population, sample size, participants’ age, follow-up time, vitamin D exposure, method used for estimation for vitamin D, criteria used to diagnose dementia and CI, and methods of assessment of cognition. Most studies adjusted for confounders like age, education, physical activity, diabetes, hypertension, hypercholesteremia, and season. However, most studies did not consider confounders like depression. Four studies [9, 22, 23, 25] found no association between low serum vitamin D levels and CI and dementia in a longitudinal follow-up, whereas two studies [21, 24] found a significant association (P = 0.001). However, the studies which found a significant association were smaller in size and duration of follow-up. A Swedish study [22] done on a large sample (2,841) for a longer follow-up (18 years) did not find an association. This study took into account the confounders like common dietary intake of vitamin D, physical activity, and sun exposure. However, repeated blood sampling and dietary assessments improve the precision of exposure information, the study lacked in doing so. Similarly, another American study [25] done on a large sample (13,044) with a long follow-up (20 years) did not report any such association. The previously reported associations between 25(OH)D concentrations and cognitive impairment may be a result of reverse causation—whereby low 25(OH)D is a marker of poor health (resulting from those in poor health (e.g., those with cognitive impairment) doing less physical activity and having less sun exposure and thereby having lower vitamin D concentrations) rather than a causative factor in cognitive impairment and dementia pathogenesis. This study can be considered less susceptible to reverse causation as 25(OH)D was measured in midlife, and cognitive change was evaluated over 20 years. Another methodological shortcoming compromising the validity of the data is the use of single serum 25(OH)D measurements taken at baseline to represent long-term exposure in all studies [9, 21, 22, 23–25]. A prospective study with two follow-ups, each at 5 years, conducted to examine the association of dietary and supplemental vitamin D intake and cognitive decline showed an association between high intake and a slower decline in the cognitive domains of verbal fluency. Those with supplemental intake also exhibited a slower decline in the cognitive domain of verbal fluency although the effect on visual and verbal memory was less in magnitude [26]. Similarly, a study on participants (age 55–67 years) with levels >25 nmol/l has demonstrated better verbal fluency and executive functioning both at baseline and at a 10-year follow-up [27].

In contrast to the existing body of literature demonstrating a positive correlation between cognitive function and vitamin D status, Lam et al. [28] reported a negative association between vitamin D levels and verbal episodic
| Study          | Study design     | Sample size | Study period | Population                        | Cognitive test                      | Vitamin D levels                          | Outcomes                                                                                     |
|---------------|------------------|-------------|--------------|-----------------------------------|-------------------------------------|------------------------------------------|---------------------------------------------------------------------------------------------|
| Schneider et al. [25] | Longitudinal study | 13,044      | 20 years     | Mean age 57 years From USA         | DWRT, DSST, WFT                      | Insufficiency 20–30 ng/ml                | No significant association with cognitive decline for deficient versus sufficient: –0.035 (95% CI – 0.104 to 0.033) and intermediate versus sufficient: –0.029 (95% CI – 0.080 to 0.233). |
| Olsson et al. [22] | Longitudinal study | 2,841       | 18 years     | Mean age 68 years From Sweden      | MMSE                                | Deficient < 50 nmol/L Sufficient > 75 nmol/L | Cox proportional hazards regression (95% CI: 0.59, 1.31) in men with plasma 25(OH)D concentrations 50 compared with 0.75 n·mol/L (95% CI: 0.63, 1.32). |
| Feart et al. [21] | Longitudinal study | 916         | 12 years     | Mean age 65 years and more From France | MMSE visual retention test Trail making test | Sufficient > 50 nmol/L Insufficient 25–50 nmol/L Deficiency < 25 nmol/L | Multivariate analysis Vitamin D deficiency and insufficiency had double the risk of all cause dementia with 95% CI (1.21–3.71) for deficiency and 95% CI (1.17–3.36) for insufficiency. |
| Beydoun et al. [26] | Longitudinal study | 1,803       | 10 years     | Age (30–64 years) From USA White urban adults African-Americans | MMSE CVLT TMT-B BVRT CDT DF-S and DFS-B AF | Linear regression Higher aseline serum 25OHD was linked toa slower decline in verbal fluency (p < 0.001). Higher intake of vitamin D was associated with a slower rate of decline constructive ability (p < 0.001). Use of vitamin D supplements during follow-up was related to slower rate of decline in verbal fluency among older individuals. |
| Goodwill et al. [27] | Longitudinal study | 252         | 10 years     | Age (55–67 years) From Australia   | CVLT-11 TMT-B CERAD,                | Deficient < 25 nmol/L                   | One-way ANOVA and Pearson Chi square Vitamin D > 25n·mol/L performed better on verbal fluency (95% CI = 0.53, 4.40) and TMT-B time (95% CI = –32.86, –3.61), with higher executive function (95% CI: 0.44,2.37). These relationships persisted 10 years later in the follow-up. |
| Laughlin et al. [9]  | Longitudinal study | 1,058       | 12 years     | MMSE TMT Halstead–Reitan neuropsychological test Animal naming category test, fluency test | MMSE TMT Halstead–Reitan neuropsychological test Animal naming category test, fluency test | Insufficiency > 30 ng/ml                  | Linear mixed effect regression model. Vitamin D insufficiency associated with poor performance on MMSE(p = 0.013). No association found on follow-up. |
| Jorde et al. [23]   | Longitudinal study | 4,624       | 13 years     | Age 54.9 years From Norway          | MMSE                               | Continuous variable                      | Linear regression Association of low vitamin D and CI found in older, more than 65 years (p = 0.001) at cross-sectional level; no association found on follow-up. |
| Study | Study design | Sample size | Study period | Population | Cognitive test | Vitamin D levels | Outcomes |
|-------|--------------|-------------|--------------|------------|----------------|-----------------|----------|
| Moon et al. [24] | Longitudinal study | 412 | 5 years | Mean age 74 From Korea | MMSE | Deficiency 25–49 nmol/L | One-way ANOVA Severe Vitamin D deficiency was associated with future risk of MCI and dementia. 95% CI (1.46–14.8) |
| Lam et al. [28] | Longitudinal study | 179 | — | Mean age 74 From Korea | MMSE and RAVLT | 31–334.4 mol/L (mean 84.7 nmol/L) | Bayesian mixed model 25(OH)D levels were negatively associated |
| First author, year | Inclusion criteria | Outcomes | Assessment of dementia | Number of articles included | Number of patients | Design of the included articles | Main conclusion |
|-------------------|--------------------|----------|------------------------|----------------------------|-------------------|-------------------------------|----------------|
| Goodwill, 2017 [31] | Longitudinal, cross-sectional, and interventional studies. Data of serum 25OHD in healthy adults and its correlation with CI and dementia | Dementia and MCI | Cognitive function tests (e.g., MMSE, Boston naming test, Stroop test, Raven’s progressive matrices, clock drawing; block) | 41 studies | 9,556 | Cross-sectional (n = 20) Longitudinal (n = 18) Interventional (n = 3) | Significant association in cross-sectional studies (95% CI 1.09 to 1.23) and weak association in longitudinal studies. No benefit with vitamin D supplementation (95% CI −0.05 to 0.46) |
| Sommer, 2017 [3] | Prospective and retrospective studies with data on serum vitamin D and dementia | Dementia: Alzheimer’s disease vascular, frontotemporal, Lewy body | Diagnostic criteria (e.g., ICD10, DSM4, NINCDS-ADRDA) | 6 studies | 18,933 | Prospective (n = 5), Retrospective (n = 1) | Low evidence of vitamin D deficiency increasing the risk of dementia (95% CI 1.19 to 1.99) |
| Kuzma, 2016 [32] | Prospective studies with data on serum 25OHD and subsequent development of dementia, visual and verbal memory loss | Dementia, Visual and verbal memory | Diagnostic criteria (e.g., NINCDS-ADRDA criteria). Cognitive function tests (MMSE, Benton visual retention test, Reys auditory verbal learning test) | 2 studies | 1,291 | Prospective studies (n = 2) | Those moderately and severely deficient individuals with serum 25(OH)D changed (95% CI: −0.06 to 0.01) and (95% CI: −0.19 to −0.02) per year, respectively, in visual memory compared to those sufficient serum 25(OH)D were associated with a mean change of 0.01 SD (95% CI: −0.01 to 0.02) and (95% CI: −0.04 to 0.02) per year, respectively, in verbal memory compared to sufficiency |
| Shen, 2015 [33] | Data on 25(OH)D concentration and Alzheimer’s disease or dementia | Alzheimer’s disease and dementia | Diagnostic criteria (e.g., ICD-10, DSM-4NINCDS-ADRDA criteria) | Alzheimer’s disease: 5 studies, 5 studies | Dementia: 5 studies, 4 studies | Alzheimer’s disease: cross-sectional (n = 1), prospective (n = 4) Dementia: cross-sectional (n = 3), prospective (n = 2) | Lower 25(OH)D status is associated with increased risk of developing AD and dementia (OR = 1.63, 95% CI 1.01–1.40) |
| Lopes da Silva, 2014 [34] | Data on any type of plasma nutrient status and Alzheimer’s disease | Alzheimer’s disease | Diagnostic criteria (e.g., NINCDS-ADRDA, DSM III or IV) | 5 studies | 865 | Case-control (n = 5) | No association between low levels of 25(OH)D and Alzheimer’s disease (95% CI −12.11 to 0.58) |
| Annweiler, 2013 [30] | Any type of observational study, data on 25(OH)D and cognition | Memory and executive dysfunction | Cognitive function tests (e.g., word list recall, serial digit recall frontal assessment battery, TMT, DST) | 17 studies | 39,975 | Cross-sectional (n = 11), prospective (n = 1) | Low serum 25(OH)D concentration found in AD when compared to controls. No association found in longitudinal study and inconsistencies in results seen with 3 case control studies (95% CI 0.26–2.56) |
Table 2: Continued.

| First author, year | Inclusion criteria                                                                 | Outcomes | Assessment of dementia                                                                 | Number of articles included | Number of patients | Design of the included articles | Main conclusion                                                                 |
|--------------------|------------------------------------------------------------------------------------|----------|----------------------------------------------------------------------------------------|----------------------------|-------------------|-------------------------------|---------------------------------------------------------------------------------|
| van der Schaft, 2013 [35] | Observational studies with data on vitamin D (serum concentration or dietary intake and cognition) | Cognition | Cognitive function tests (e.g., MMSE, TMT, DST, n-back test, block design test)        | 8 studies                  | 59,576            | Cross-sectional \( (n = 25) \), prospective \( (n = 6) \) | Low serum 25(OH)D was associated with higher frequency of dementia on follow-up of 4–7 years |

NINCDS-ADRDA: National Institute Neurological and Communicative Disorders and Stroke-Alzheimer Disease and Related Disorders Association, ICD-10: International Classification of Disease, DSM4: Diagnostic and Statistical Manual for Mental Diseases, CDR: clinical dementia rating, MCI: mild cognitive impairment, MMSE: Mini-Mental Status Examination, TMT: trial making test, CI: cognitive impairment, AD: Alzheimer's disease, and DST: digit symbol test.
| Author, year | Study design | Sample size | Study period | Population characteristics | Intervention | Outcome measures | Findings |
|--------------|--------------|-------------|--------------|---------------------------|--------------|------------------|----------|
| Przybelski et al., 2008 [39] | Prospective Pre-post interventional study | 63 | 4 weeks | USA-nursing home residents Intervention groups N = 25 Mean age = 86.2 females 68% Deficiency defined as 25(OH)D < 25 ng/mL Comparison group N = 38 Mean age = 87.4, female 78.9% Serum 25(OH)D < 25 ng/mL | Unblinded study Intervention group 50,000 IU of Vit D2, 3 times per week for duration of 4 weeks Comparison group No placebo | Cognitive test Clock drawing test Semantic fluency test | No significant difference in cognitive outcome measures, although significant change (p = 0.0001) in serum 25(OH)D levels from 17.3 to 63.8 ng/mL |
| Stein, et al., 2011 [36] | Randomized controlled trial | 32 | 6 weeks | Australia-community dwellers with mild-to-moderate dementia High dose group N = 16 Mean age 79 Females 50% Low dose group N = 16 | First 1,000 IU Vit D2 daily for 8 weeks Then, 6,000 IU Vit D2 daily for 8 Intranasal insulin (60 IU/4 times/day) and 50% randomized to placebo Comparison group 1,000 IU Vit D2 daily for 16 weeks Finally, 50% randomized to Intranasal insulin (60 IU/4 times/day) and 50% randomized to placebo for 2 days | Alzheimer assessment scale-cognitive subscale (ADAS memory scale-revised logical memory (WSM-RLM)) Minitab release 13.1 used to calculate CI. Significant median increase in serum 25(OH)D concentrations in the high dose group (187 nM) No significant differences (p = 0.02) on any of the outcome measures) between groups. ADAS-Cog (95% CI-5 to 3) WSM-RLM (95% CI −1 to 3) |
| Annweiler, et al., 2012 [40] | Prospective Pre-post interventional study | 44 | 16 months | France-outpatient from memory clinic Intervention group N = 20 Mean age 81.9 females 55% Comparison group N = 24 Mean age 75. Females 54.2% | Unblinded Unrandomized intervention group = 800 IU/day or 1,000,000 IU of Vit D3/ month comparison group = no placebo | MMSE Frontal assessment battery Cognitive assessment battery | Over the 3-year period, MMSE scores increased in both groups (p < 0.001), although change over time was not significantly different between the groups |
| Owusu et al., 2018 [37] | Randomized controlled trial | 390 | 3 years | USA-healthy African-American postmenopausal women Intervention group N = 130 Mean age 67.8 Control group N = 130 | Double-blind randomized placebo-controlled trial Intervention Vit D3 (2,400 IU–3,600 IU or 4,800 IU/day) which maintained 25(OH)D level of 30 ng/mL Control group Placebo follow-up of 3 years | MMSE Every 6 months > 27 | No difference in cognition over time between older African-American women with serum concentrations of 25(OH)D of 30 ng/mL and greater than those taking placebo |
memory. In a prospective (3-year follow-up), population-based study of older adults aged 85+, it was found that both low and high season-specific quartiles of 25(OH)D were associated with higher odds of prevalent cognitive impairment (assessed by MMSE), poorer attention reaction times/processing speed and focused attention/concentration, and greater attention fluctuation [29].

2.2. Evidence through Meta-Analysis and Systematic Review. Several systematic reviews and meta-analysis of cross-sectional studies, case-control studies, and observation prospective studies have suggested an association between low vitamin D, cognitive impairment, and dementia. Moreover, a meta-analysis on vitamin D levels and specific cognitive domains have suggested a strong association between low vitamin D and a range of executive dysfunction, such as impaired processing speed, mental shifting, and information updating. Only a modest association was noted with episodic memory [30]. Several such systematic reviews and meta-analysis in the last 6 years are depicted in Table 2 [30–34].

2.3. Vitamin D Supplementation and Cognition. Five studies have investigated the effects of vitamin D supplementation on cognitive outcomes in elderly individuals (see Table 3); three were RCT’s [36–38] and two had pre-post study design [8, 37]. Overall, three studies found that vitamin D supplementation did not improve either cognitive outcomes [36, 38, 39] or reduce the risk of dementia/MCI compared to controls. A prospective pre-post interventional study [39] on nursing home residents with a mean age (86 years) reported no significant change in cognitive outcome with oral vitamin D2 (50,000 IU 3 times/week) for 4 weeks. On the contrary, another prospective pre-post intervention study [37], which included 80-year-old subjects from memory clinic, found that those who received oral vitamin D3 supplementation (800 IU per day or 100,000 IU per month) experienced improved global cognition and executive functioning abilities over a 16-month follow-up period compared to controls [40]. Nevertheless, the pre-post design (without randomization) of the study and small sample size and shorter duration of treatment limit the exploration of cognitive effect of vitamin D. A randomized trial [38] found that visual memory improved in the high dose group (4,000 IU per day for 18 weeks of oral vitamin D supplementation) when compared to the low dose group (400 IU per day) in healthy adults, although verbal memory and other cognitive domains did not improve. On the contrary, Stien et al. [36] reported no significant change in cognition with higher doses of vitamin D followed by intranasal insulin (nasal insulin improves cognition, and vitamin D increases insulin receptor expression) when compared to lower dose of vitamin D and intranasal insulin in subjects diagnosed with mild-to-moderate AD. A more recent double-blind, randomized, placebo-controlled trial showed no significant difference in cognition over time (3 years) according to the MMSE score (assessed every 6 months) between older postmenopausal African-American women who took vitamin D (orally in doses of 2,400, 3,600, and 4,800 which maintained serum level of >30 ng/mL) than those who did not [37]. However, methodological weaknesses such as small sample sizes [36, 38, 39], short follow-up periods [36, 38, 39], and lack of participant randomization [39, 40], as well as heterogeneous doses of vitamin D supplementation and baseline vitamin D levels make it difficult to interpret the results of the interventional studies. Another limitation found in most studies was the use of MMSE for cognitive testing. This test is best used as a screening tool and not for diagnosis. There is no clear idea of when vitamin D is most effective in the pathogenesis of cognitive decline and particularly the advent of AD. Therefore, the supplementation of vitamin D after the advent of CI or AD might not have helped the already existing neurological insult which could have been the reason for the failure of such a treatment. Larger trials over a longer period in patients at risk for, but has not yet progressed to cognitive decline or dementia, may be more capable of demonstrating an impact. Identifying such individuals using CSF biomarkers such as amyloid-beta and phosphorylated tau may help. Future studies directed towards finding the effect of vitamin D on biomarkers of AD would further clarify the role of vitamin D and its disease-modifying effect. Pharmacogenomic studies to identify the individuals who could benefit from such a therapy may further help.

3. Conclusion

Evidence from animal and cellular studies suggests that vitamin D has multiple functions throughout the central nervous system and could be implicated in the prevention

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**Table 3: Continued.**

| Author, year | Study design | Sample size | Study period | Population characteristics | Intervention | Outcome measures | Findings |
|-------------|--------------|-------------|--------------|---------------------------|--------------|------------------|---------|
| Petterson Trial, 2017 [38] | Randomized controlled trial | 82 | 18 weeks | Canada-healthy adults | High dose group N = 42 Mean age = 56.7 Low dose group N = 40 Mean age = 52.6 Females = 65% | Randomized and blinded to high dose High dose group Vit D3 4,000 IU/day Low Dose group Vit D3 400 IU/day | Pattern recognition memory task Paired associate learning task | Visual memory benefit with high dose (p = 0.005) in those who are insufficient (<75 nmol/L) No change in verbal memory |
| [8, 37] | | | | | | | |

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and treatment of disorders such as dementia and AD. Cross-sectional and case-control studies confirm that vitamin D concentrations are lower in individuals with cognitive impairment and dementia although reverse causality remains a possibility. Few longitudinal studies have found that low vitamin D concentrations are associated with an increased risk of cognitive decline, all-cause dementia, and AD, but those with a bigger sample size and longer (18–20 years) follow-up time did not find such an association. Future neuroimaging studies may uncover a link with specific abnormalities that could explain the observed associations between vitamin D concentrations and dementia-related disorders. Clinical trials investigating the effect of vitamin D supplementation on cognitive outcomes have produced mixed findings; however, a variety of methodological weaknesses limit the interpretability of these findings. Lack of consensus over the exact dosage of vitamin D to be used and optimal age of treatment initiation of individuals at risk remains unidentified. Furthermore, large double-blind, randomized, placebo-controlled trials with appropriate dosage and duration may provide conclusive results. Taken together, this body of evidence suggests that vitamin D may be a new paradigm for therapy in the prevention and treatment of dementia and AD. Although vitamin D may be considered as a modifiable risk factor, the causal relationship between vitamin D deficiency and CI so far remains inconclusive.

**Abbreviations**

- 25(OH)D: 25 hydroxyvitamin D
- Aβ: Amyloid-beta
- AD: Alzheimer’s disease
- AMSTAR: Assessing the methodological quality of systematic reviews
- BBB: Blood-brain barrier
- BDNF: Brain-derived neurotrophic factor
- CDR: Clinical dementia rating
- CI: Cognitive impairment
- CKD: Chronic kidney disease
- CSF: Cerebral spinal fluid
- DSM4: Diagnostic and Statistical Manual for Mental Disease
- DSST: Digit symbol substitution test
- DST: Digit symbol test
- DWRT: Delayed word recall test
- GM: Grey matter
- HPV: Hippocampal volume
- ICD: International Classification of Disease
- ICV: Intracranial volumes
- IOM: Institute of medicine
- LTP: Long-term potentiation
- MCI: Mild cognitive impairment
- MMSE: Mini-Mental Status Examination
- NGF: Nerve growth factor
- NINCDS-ADRDA: National institute neurological and communicative disorders and stroke-Alzheimer disease and related disorders
- NMDA: N-Methyl d-aspartate
- RCT: Randomized controlled trials
- RDA: Recommended daily allowances
- TMT: Trial making test
- UVR: Ultraviolet radiation
- VDR: Vitamin D receptor
- WFT: Word fluency test
- WM: White matter
- WMA: White matter abnormalities
- WMH: White matter hyperintensities

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

**Authors’ Contributions**

Dr. S. Sultan, MD, substantially contributed to conception or design of the work, finally approved the version to be published, and was responsible for agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Miss Uzma Taimuri, Miss SA Basnan, Miss W K A Orabi, Miss A Awadallah, Miss F Almowald, and A Hazazi substantially contributed to conception and design of the work. All authors read and approved the manuscript.

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