East African Journal of Health and Science
eajhs.eanso.org
Volume 8 Issue 1, 2025
Print ISSN: 2707-3912 | Online ISSN: 2707-3920
Title DOI: https://doi.org/10.37284/2707-3920

EAST AFRICAN NATURE & SCIENCE ORGANIZATION

Original Article

Evidence of Dementia Treatment using Vitamin D: A Systematic Review

Micah Nyabiba Asamba[1*]

[1] Kenyatta University, P. O. Box 43844-00100, Nairobi, Kenya.
* Author for Correspondence Email: micahasamba@gmail.com

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

Publication Date:

27 January 2025

Keywords:

Dementia, Vitamin D, Cognitive Function, Alzheimer's Disease, Neuroprotection, Randomized Controlled Trials, Memory Improvement, Neurodegenerative Diseases, Aging Population.

ABSTRACT

Dementia is a progressive cognitive decline that poses significant public health concerns, particularly among the ageing population. Recent evidence highlights vitamin D's neuroprotective roles, including its involvement in neurotransmission, antioxidative processes, and neuronal preservation. This systematic review examined ten studies from 2011 to 2020, including randomized controlled trials (RCTs), cross-sectional studies, and longitudinal studies, to evaluate vitamin D's efficacy in treating dementia. Findings demonstrated that vitamin D supplementation improves cognitive function, particularly in patients with mild cognitive impairment and dementia. High-dose supplementation exhibited enhanced effects on visuospatial memory and executive functions compared to low-dose supplementation in some studies. However, results varied due to differences in study populations, methodologies, and follow-up durations. Despite its limitations, including small sample sizes and short study periods, this review underscores the potential of vitamin D as a complementary intervention in dementia care. Further research is needed to establish optimal dosing and explore its long-term effects on cognitive health.

APA CITATION

M. N., Asamba. (2025). Evidence of Dementia Treatment using Vitamin D: A Systematic Review. *East African Journal of Health and Science*, *8*(1), 62-78. https://doi.org/10.37284/eajhs.8.1.2642

CHICAGO CITATION

Asamba, Micah Nyabiba. 2025. "Evidence of Dementia Treatment using Vitamin D: A Systematic Review". *East African Journal of Health and Science* 8 (1), 62-78. https://doi.org/10.37284/eajhs.8.1.2642.

HARVARD CITATION

Asamba, M. N. (2025) "Evidence of Dementia Treatment using Vitamin D: A Systematic Review". *East African Journal of Health and Science*, 8(1), pp. 62-78. doi: 10.37284/eajhs.8.1.2642.

IEEE CITATION

M. N., Asamba "Evidence of Dementia Treatment using Vitamin D: A Systematic Review", *EAJHS*, vol. 8, no. 1, pp. 62-78, Jan. 2025.

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

MLA CITATION

Asamba, Micah Nyabiba. "Evidence of Dementia Treatment using Vitamin D: A Systematic Review". *East African Journal of Health and Science*, Vol. 8, no. 1, Jan. 2025, pp. 62-78, doi:10.37284/eajhs.8.1.2642

INTRODUCTION

Dementia is a disease characterized by a progressive decline in cognitive function due to brain damage (Buell & Dawson-Hughes, 2008). The disease has a complex pathology that includes various mechanisms such as inflammation, oxidation, genetic vulnerability, and disease-induced neurotoxicity. Dementia is caused by progressive deterioration of cognitive functions such as motor skills, language, and perceptions. It leads to impaired activities of daily living, memory loss, cerebral atrophy, and altered behavioural patterns (Annweiler et al., 2012a). Symptoms depend on the affected area of the brain, and the underlying pathology. The hippocampus, which is the centre of memory and learning, is often involved in the pathology. Worldwide, the diseases affect more than 47 million people, and the number is expected to increase considerably by 2050. Although generally associated with age, dementia can sometimes exhibit early onset (Gangwar et al., 2015). The number of older adults has increased in both developed and developing countries because of improved living standards, longer life expectancies, and reduced fertility.

Dementia essentially results from damage to brain cells which leads to changes in emotional, behavioral, and cognitive functions. All dementias exhibit similar clinical features. They present with a slow loss of cognitive ability, exhibited through impairment of personality, emotions, visuospatial skills, memory, and language (Gangwar et al., 2015). The main difference is in the progression of the disease and the treatment. Various forms of dementia have different causes. The most common form is Alzheimer's Disease (AD) which is age-linked. It affects almost 50% of people aged above 85 years (Annweiler et al., 2014). Another common type is Vascular dementia (VaD) which comprises 20% of all cases reported in the United States. Other less common types are Parkinson's disease, Huntington's disease, frontotemporal dementia, and Lewy body dementia (Lee et al., 2019).

Clinically, degenerative conditions are characterized by loss of neurological function (including paralysis and loss of movement control). Pathologically, they are characterized by loss of neurons. In some dementias, the neuron loss is amid specific histopathological findings, like Lewy bodies and Alzheimer's plaques. In others, there is a gradual neuronal atrophy which is not associated with a specific pathology. Moreover, in others, there are specific anatomical systems involved or an interconnected neuron set. Furthermore, the pathology can either be focal (symmetric and bilateral) or diffuse. Research has shown that many dementias are inherited. Vital to the pathogenesis and pathology of dementias is the deposition of abnormal proteins in the brain.

Currently, no cure exists for dementia. The main goals of the interventions are to improve the quality of life of the patient and to attenuate behavioural disorders. The treatment of dementia entails both non-pharmacological and pharmacological means. The main pharmaceutical interventions include acetylcholinesterase inhibitors (ChELs), which include Exolon, galantamine, Reminly, Aricept, memantine, and Ebixa. Nonpharmaceutical interventions include those that address challenging behaviour, such as Aromatherapy, massage, reminiscence therapy, behavioural therapy, validation therapy, occupational therapy, music therapy, animal-assisted therapy, and multisensory stimulation (D'Onofrio et al., 2016: Berg-Weger & Stewart, 2017; Lee et al., 2019). Research has also shown that nutritional supplementation of vitamin D has a positive effect on dementia (Iacopetta et al., 2018; Byrn et al., 2019). Various empirical studies have been carried out on the role of vitamin D on cognitive function in Dementia. This systematic

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

review provides evidence for the use of Vitamin D in treating dementia.

Vitamin D is a vital micronutrient which helps in calcium homeostasis and bone growth. Apart from born health, it serves other important biological functions, including neurodevelopment. Its primary source is sunlight, but it can also be found in foods. Vitamin D is vital for good health, especially for ageing adults. Recent studies have shown that a deficiency of vitamin D mediates the development of dementia (Miller et al., 2015). According to Chai et al. (2019), vitamin D has a role in neuroprotection, neurotransmission, neurotrophy, and neuroplasticity. Previous studies have reported that low 25(OH) D levels are linked to dementia and cognitive dysfunction. Besides, studies with animal models have shown that there is a therapeutic potential for using vitamin D to prevent and treat dementia and cognitive decline (Dickens et al., 2011). Various RCTs have examined the association of vitamin D with improved cognitive function (Dean et al., 2011; Gangwar et al., 2015; Pettersen, 2017). However, only a few systematic reviews have been conducted on the subject. The purpose of this review, therefore, is to provide evidence for the use of vitamin D for the treatment of dementia.

METHODOLOGY

Study Design

The Review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.

Data Sources and Search Strategy

A computerized search was conducted in January 2020, in four databases: MEDLINE, EMBASE, AMED, and the Cochrane Central database. These databases were selected because they are comprehensive and cover a range of articles related to the study question. A further search was conducted for grey literature using the PsycInfo database for these and dissertations. There was no limit placed on the search in terms of date, subject, or type. The search was limited to human populations, primary studies, and published in the English language. The query consisted of terms that the researcher considered to describe dementia, its treatment, and the role of Vitamin D. The search was divided into two themes.

- For the identification of dementia, a Boolean search was carried out using the term “or” to explore and map the headings shown in the table (S1).
- For the identification of vitamin D, a Boolean search was conducted by using the term “or” to explore and map the headings as shown in the table (S2).
- The two themes S1 and S2 were combined by using the Boolean operator “and” as shown in Table (S3).

The following keywords were used:

Type of Search	Keyword Syntax
S1	“Dementia” OR “Alzheimer’s disease” OR “Lewy body dementia” OR “frontotemporal dementia” OR “vascular dementia” OR “memory” OR “brain” OR “neuropsychological tests”
S2	“Vitamin D” OR “vitamin D2” OR “vitamin D3” OR “cholecalciferol” OR “ergocalciferol” OR “hydroxyvitamin D”
S3	S1 and S2

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

Eligibility Criteria

The relevance of the identified studies was determined using a screening process. Studies were eligible for inclusion if:

- They broadly described the use of vitamin D for the treatment of dementia,
- Were primary studies: randomized controlled trials (RCTS), prospective cohort studies, case-control, cross-sectional studies, and quasi-experiments.
- Participants were adults

Studies were excluded if:

- They were not published in English
- They did not report on primary research

Data Extraction and Management

One reviewer screened the abstracts and full texts by considering the pre-specified criteria. Studies only published as abstracts were not included. A standardized data extraction form was used to gather pertinent information from each study. The data extracted include

- Study information (author, year, setting)
- Study design
- Observation period
- Sample size
- Description of the population: gender, age, type of dementia
- Outcome measurement
- Results.

There was a need for vitamin D measurement to determine the status. As such, the researcher accepted validated neuropsychological tests as measures of cognitive function, including global function, psychomotor speed, intelligence, memory, attention, and executive function.

Assessment of Quality

Methodological quality and risk of bias were conducted following quality assessment tools validated in the study by Balion et al. (2012). Five critical domains were used to determine the quality of studies: the study population selection, statistical power, outcome measure, statistical analysis, and type of randomization (for RCTs). The results of the risk of bias rating for individual studies were reported as either low, medium, or high risk.

Data Analysis

The data extracted from the studies was used to prepare a table which is described in the results section. The extracted data was subjected to content analysis.

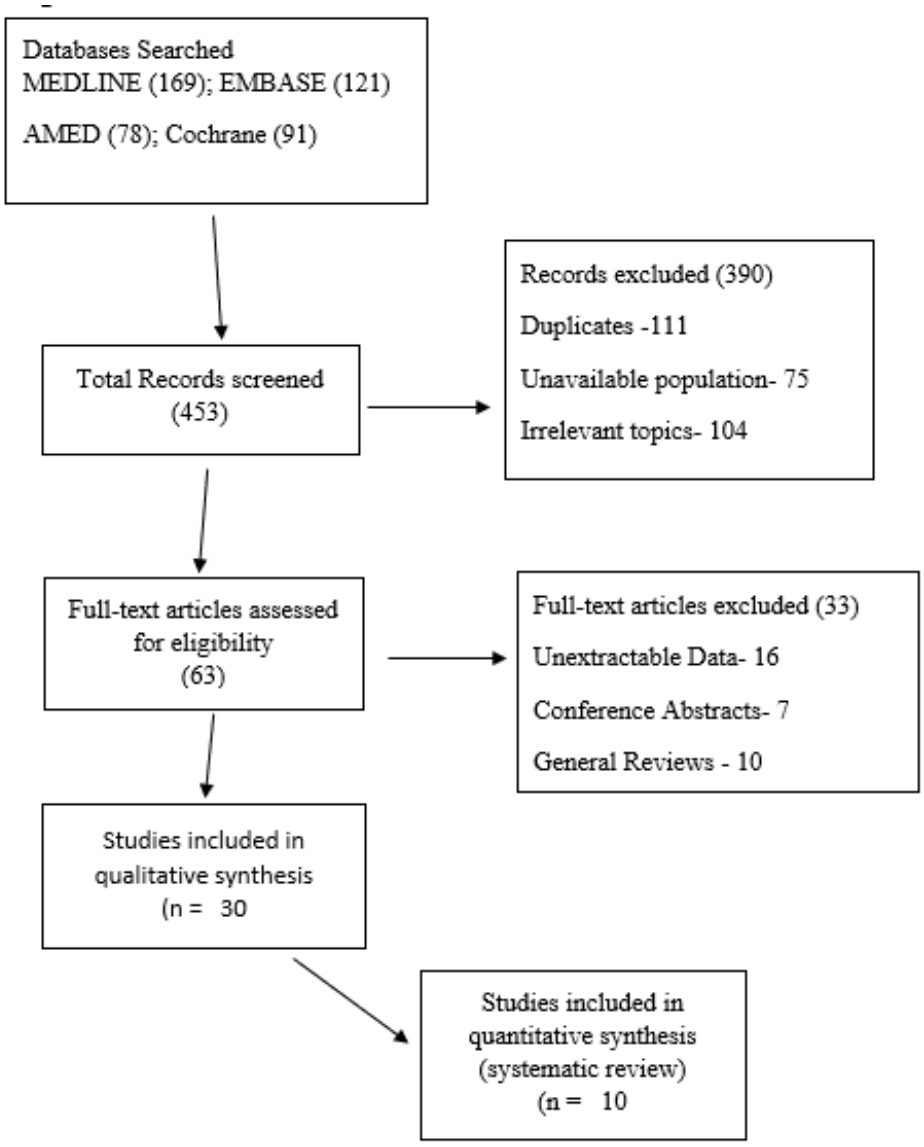
RESULTS

Study Characteristics

Using the inclusion criteria, 10 papers were identified by following the procedure captured by the PRISMA flow chart in Figure 1.

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

Figure 1: PRISMA flow chart: A total of 453 documents were retrieved. However, the inclusion criteria led to the identification of only ten, based on the quality of the articles.



Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

Results Tables

Table 2a: Study characteristics

Author/date	Study Design/ Setting/ Location	Sample size/Baseline characteristics	Outcome measure	Follow-up period
Stein et al., 2011	RCT, Community study, Melbourne, Australia	32 community-dwelling individuals Mean age-77.5 years	MMSE, Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog), Disability Assessment in Dementia, Wechsler Memory Scale-Revised Logical memory (WMS-R LM)	No follow-up
Dean et al., 2011	RCT, Participants were recruited through advertising by the University of Queensland	128 participants Vitamin D-63; placebo-65 Mean age: vitamin D 21.45 (2.96) and placebo 22.06 (2.74) Gender: % female 61.9 in the vitamin D group and 52.3 in the placebo group.	Stop Signal Task, Set shifting task, Peters Delusion Inventory21 (PDI-21), Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), Spectroscopic quantification of 25-hydroxyvitamin D3 (25OHD3.	No follow-up
Annweiler, Fantino, et al., 2012b	RCT in a pre-post design Memory Center of Angers University, France	44 outpatients Case-20 Control-23 Mean age 80.6 (14.0) Female 54.5% 100% Caucasian	MMSE Frontal Assessment Battery (FAB) for executive function. Measurement of 25-hydroxyvitamin D (25OHD) levels.	16-month follow-up.
Annweiler, Herrmann, et al., 2012a	A pre-post RCT Memory Clinic of Angers University Hospital, France	43 white outpatients (memantine 18, vitamin D 17, and combined 8) Mean age 84.7 (6.3) Female-65.1%	MMSE	6 months follow-up
Hooshmand et al., 2014	Cross-Sectional Study Karolinska University Hospital, Sweden	75 patients Subjective cognitive impairment-29 Mild cognitive impairment-28 AD-18. Mean age (standard deviation)-61.6 (9.1), Gender-54.7% female	Plasma 25(OH) D, CSF levels of amyloid β (Aβ1–42), total-tau, brain tissue volumes, phosphorylated tau MRI scanning	No follow-up

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

Gangwar et al., 2015	Cross-Sectional Study Department of Physiology, King George's Medical University	80 subjects Case (A)-40 Control (B)-40 Mean age A: 69.68 (6.45) and B: 66.68 (4.80) Female 22 male 58.	Mini-Mental State Examination (MMSE) score for dementia. Direct Elisa for estimation of vitamin D	6 months
Miller et al., 2015	Longitudinal multiethnic cohort study, An outpatient clinic	382 participants Mean age of 75.5 (7.0), Female-61.8% 17.5% with dementia, 32.7% with mild cognitive impairment, and 49.5% cognitively normal	Serum 25-OHD levels, Spanish and English Neuropsychological Assessment Scales,	8 years of follow up
Petterson et al., 2017	RCT Northern British Columbia, Canada	82 adults Low dose-40 High dose-42	25(OH)D and cognitive performance, Symbol Digit Modalities Test, verbal (phonemic) fluency, CANTAB® computerized battery.	18 weeks
Byrn et al., 2019	RCT, Various hospitals in the USA	20 participants Low dose (15) and high dose (15). Mean age 55.71(9.74) Female-83%; Black-57%,	Serum 25(OH)D measured by LC-MS Executive functioning was measured through the Controlled Oral Word Association Test. Godin Leisure-Time Exercise Questionnaire for measuring the quality of life. CES-D and PHQ-9 assessments for baseline mood Trail Making Test Part B-for cognitive function	12 weeks follow up
Yang et al., 2020	RCT Tianjin, China	183 participants were randomized into: Vitamin D group, 93 and placebo group, 90) Mean age: Vitamin D- 67.22 (6.10) and placebo group 66.59 (5.22) Male-43%	Activities of Daily Living (ADL) score; Diagnostic and Statistical Manual of Mental Disorders-IV; Wechsler Adult Intelligence Scale-Revised; Full-scale intelligence quotient MMSE	12 months follow up

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

Table 2b: Study Objectives and findings

Author year	Objectives	Intervention /groups	Results
Stein et al., 2011	To determine the effect of high-dose vitamin D augmented by nasal insulin on memory in mild-moderate Alzheimer's disease.	Two groups: the Vitamin D group and the control group. In the first 8 weeks (run-in) all participants received a low dose of vitamin D. After 8 weeks, the intervention group received high-dose vitamin D and nasal insulin.	• There was an increase of median 25OHD ($p<0.01$) after the run-in, and a significant increase for the intervention group after that ($p<0.001$). • Neither disability nor cognition changed significantly ($p=0.02$). • The study findings suggest that high-dose vitamin D does not have any benefits on disability or cognition over low-dose vitamin D.
Dean et al., 2011	To examine the effect of vitamin D supplementation on cognitive and emotional functioning in young adults.	Two groups: participants either received Vitamin D (intervention group) or placebo (control). Parallel-arm, double-blind trial. The intervention group received 5000IU cholecalciferol for six weeks.	• Significant increase in vitamin D status for the intervention group • There were no significant changes in cognitive flexibility ($p=0.24$), response inhibition ($p=0.37$), working memory ($p=0.30$), or secondary outcomes. • This means that for healthy young adults, vitamin D does not have any significant effect on cognitive and emotional functioning. • One case of adverse effect was reported: transient rectal bleeding from a participant who received a placebo.
Annweiler, Fantino, et al., 2012b	To examine vitamin D3 supplementation's effect on cognition in older adults.	Two groups. Intervention and control. The intervention group received vitamin D3 supplements. The intervention group received oral vitamin D3 (800IU per day).	• After 16 months, the concentration of 25(OH)D was higher for the intervention group ($P < .001$) than the control ($P < .001$) and the baseline ($P=0.001$). • The vitamin D group had higher scores of FAB (0.02), CAB (0.03), and MMSE (0.047) than control. • Vitamin D supplements were thus associated with medium-term improvement in cognitive performance. • No adverse effects were reported.
Annweiler, Herrmann, et al., 2012a	To compare the treatment with memantine alone with memantine	Three groups: memantine, vitamin D alone, and memantine plus vitamin D Memantine was given orally (20mg/day) for 4 weeks.	• The group that received memantine and vitamin D combined increased the MMSE score by 4.0 ($P=0.034$). No change in those taking memantine alone ($P=0.891$), and those taking vitamin D alone ($p=0.504$).

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

	plus vitamin D for Alzheimer's disease	Vitamin D was given orally (between 400 and 1000 IU daily) for a month.	• It means combining memantine with vitamin D improves clinical outcomes. • No adverse effects were reported.
Hooshmand et al., 2014	To investigate the relationship between vitamin D, Alzheimer's disease, and cognitive impairment.	Subjective cognitive impairment (SCI), Mild cognitive impairment (MCI), AD Various biochemical analyses were done:	• No significant variation in median 25(OH)D concentration by season. (p>0.01) • There was no significant association between tau variables and 25(OH)D, • Higher 25(OH)D levels were associated with greater brain volumes and higher concentrations of CSF Aβ1–42. • AD patients had decreased concentrations of Aβ1–42 and increased p-tau and t-tau compared with MCI and SCI. • The results mean that vitamin D is linked to cognitive status. • No side effects were reported in the study.
Gangwar et al., 2015	To investigate the role of vitamin D in the prevention and treatment of Alzheimer's disease.	Two groups: Case (A) and Control (B) The intervention given to group A was a vitamin D supplement. It was given in the form of oral calcitriol granules. 4000 IU	• Mean levels of vitamin D in serum were lower in Group A than B, but not statistically significant (p>0.05). • There was a significant improvement in the MMSE score for group a (P=0.0001). • Significant changes occurred in both groups from baseline, three months, and six months, but it was higher for group A. • No side effect was reported.
Miller et al., 2015	To assess the association between vitamin D and subdomains of cognitive functions in older adults.	Longitudinal study: Three groups: Cognitively normal, MCI, and Dementia All participants were measured for vitamin D levels and cognitive function.	• The dementia group had significantly lower 25-OHD levels compared to normal and MCI groups. (P=0.06). • There was an association between low vitamin D levels and accelerated decline in cognitive function. • The decline rates of executive function and episodic memory were greater in vitamin D-deficient participants than normal group (P=0.08). • No adverse effects were reported.
Pettersen et al., 2017	To determine whether vitamin D supplementation	Two groups: low-dose and high-dose.	• There was a more significant increase of serum 25(OH)D in high dose (from 67.2 ± 20 to 130.6 ± 26

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

	improved cognition in older adults, and to compare the effect of high dose versus low dose supplementation.	They were given vitamin D supplements as 400 IU (low-dose) or 1000 IU (high dose)	nmol/L) compared to low dose p (60.5 ± 22 to 85.9 ± 16 nmol/L), p = 0.0001. • Performance of high dose group nonverbal memory increased. It means that higher doses of supplementation benefit visual memory. • A higher 25(OH) D is vital for higher-level cognitive functioning. • No adverse effects were reported.
Byrn et al., 2019	To investigate the impact of vitamin D on brain function for patients suffering from diabetes.	Two groups: High dose-50,000IU Low dose: 5,000IU The intervention was carried out for 12 weeks	• No statistically significant difference between high-dose and low-dose supplementation on cognitive measures (p> 0:05) • This result means that higher doses of vitamin D do not necessarily lead to better improvements. • Minimal improvements in Symbol-Digits ((p = 0:001), the Stroop Interference Test (p = 0:01), and the Trail Making Test (p= 0:002) over time. • It means there was an improvement in cognitive functioning for both groups. • Twenty-one participants experienced side effects. Nine in high dose (cold virus), and twelve in low dose groups (nausea).
Yang et al., 2020	To determine the effect of 12-month vitamin D supplementation on cognitive function in elderly participants with mild cognitive impairment	Two groups: Vitamin D and placebo The Vitamin D group received vitamin D 800 IU/day while the placebo group (control) was given matching starch granules.	• The vitamin D group had substantial improvements over the placebo group (p<0.001) in various measures. • There were significantly higher levels of Leucocyte TL. • FSIQ score improved in the vitamin D group compared to placebo (p < 0.001). • Vitamin D supplementation improves cognitive function by reducing oxidative stress. • The interventions had no side effects.

Tables 2a and 2b display the characteristics of the included studies. Differences were observed in terms of sample size, study population, age, setting, outcome measures, and type of dementia.

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

The studies included covered the periods from 2011 to 2020. The use of vitamin D to treat dementia has been gaining a lot of research interest in recent years. Most of the included studies were conducted in community settings. Seven were RCTs, two were cross-sectional studies, and one was a longitudinal cohort study. The sample sizes of the included studies have varied between 20 and 383. The studies included a total of 1083 participants. This small sample size limits the statistical power of the studies. The mean age ranged from 55 to 80 years. Mostly, the participants were older adults. Some studies calculated the mean vitamin D concentration of the participants. Various tests were used to evaluate outcome cognition, the most common one being MMSE (table 2a). Eight studies included a follow-up period, which ranged between 12 weeks to eight years. Two studies did not report any follow-up (Stein et al., 2011; Dean et al., 2011).

Dean et al. (2011), Pettersen et al. (2015), and Yang et al. (2020). conducted randomized trials which explored the effect of dementia on cognition. Pettersen et al. (2015) randomized the participants to low (400IU) and high dose (4000IU). Yang et al randomized participants to either high-dose vitamin D or low-dose weekly for 12 weeks. Dean et al. (2011), on the other hand, provided the experimental group with Vitamin D and placebo for control. Byrn et al. (2019) performed a double-blinded RCT in which subjects were randomized into two groups where they received either weekly vitamin D3 or a matching comparator. The experiment progressed for 12 weeks, during which a battery of neuropsychological tests were conducted.

Miller et al. (2015) conducted a multiethnic cohort study. They conducted the study between 2002 and 2010, with yearly follow-ups after the baseline assessment. They measured D (25-OHD) and subdomains of cognitive function. Houshmand et al. (2014), in a cross-sectional study, investigated the impact of brain volumes and cerebrospinal fluid biomarkers on the association between vitamin D and cognitive function in Alzheimer's disease. Gangwar also conducted a cross-sectional study, which divided participants into two groups, the case and the control. They used the MMSE to assess dementia, and they estimated Vitamin D using a direct ELISA kit.

Study Outcomes

Most studies reported positive outcomes for the use of vitamin D to treat dementia. Higher doses of vitamin D supplementation enhanced nonverbal (visuospatial) memory (Pettersen et al. (2017). The effect was shown to be more pronounced for people whose 25(OH)D levels were insufficient at baseline. Although low doses improved verbal recognition, the effect was more pronounced at high doses. However, there was no improvement in verbal memory and other cognitive aspects. Stein et al. (2011) also found that whereas vitamin D improved outcomes, there was no significant difference between low-dose and high-dose supplementation.

In Yang et al. (2020), vitamin D supplementation was shown to improve cognitive function for individuals with mild dementia. The study showed significant improvement in full-scale intelligence quotient, picture arrangement scores, block design, vocabulary, and digit span in the group that received vitamin D supplements. There was also significantly higher Leukocyte TL, even as serum 8-OXO-dG, OGG1mRNA, and P16INK4amRNA decreased (Yang et al., 2020). Gangwar et al. (2015) reported significant improvement in MMSE score change ($p=0.0001$) from baseline to three months and from three to six months. The group that received vitamin D supplementation showed a higher mean change. They noted that supplementation of vitamin D improved the cognitive performance of subjects with senile dementia. Similar findings were obtained by Annweiler, Fantino, et al. (2012b) who reported a significant increase in the group that received vitamin D3 than in the control.

Some studies did not find a significant association between vitamin D supplementation and dementia. One study reported a significant

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

increase in vitamin D status, without significant changes in working memory, response inhibition, cognitive flexibility, or secondary outcomes (Dean et al., 2011). However, the study was carried out in healthy young adults. Besides, Bryn et al. (2019), although focused only on dementia in diabetes patients, their results showed no significant difference between high-dose and low-dose vitamin D supplementation. However, both studies are limited by their small sample sizes.

According to Miller et al. (2015), accelerated decline in cognitive function was associated with Low Vitamin D status. They showed that significant differences existed in people with dementia, MCI, and normal cognition. The study also reported that variations exist in different races. Moreover, Houshmand et al. (2014) showed that vitamin D impacts CSF Aβ1–42 levels, and brain tissue volumes. Annweiler, Herrmann et al. (2012a) showed that using vitamin D together with memantine improved outcomes better than the drug alone. The Study suggested that vitamin D is a viable augmentation to existing pharmacological interventions.

Risk of Bias Assessment

Table 3: Risk of Bias Assessment

Author/year	Sample selection is unbiased	The sample size is calculated	Validated method of assessing Vitamin D levels	Validated dementia assessment methods	Blind outcome assessment	Appropriate analytic methods	Overall Risk (Low, Medium, High)
Stein et al., 2011	Yes	No	Yes	Yes	Yes	Yes	Low
Dean et al., 2011	Yes	No	Yes	Yes	Yes	Yes	Low
Annweiler, Fantino, et al., 2012b	No	No	Yes	Yes	Partial	Yes	Medium
Annweiler, Herrmann, et al., 2012a	No	No	Partial	Yes	Partial	Yes	Medium
Hooshmand et al., 2014	Yes	No	Yes	Yes	No	Yes	Low
Gangwar et al., 2015	Yes	No	Yes	Yes	No	Yes	Low
Miller et al., 2015	Yes	Yes	Yes	Yes	No	Yes	Low
Pettersen et al., 2017	No	No	Yes	Yes	Yes	Yes	Low
Byrn et al., 2019	Yes	No	Yes	Yes	Yes	Yes	Low
Yang et al., 2020	Yes	No	Yes	Yes	Yes	Yes	Low

DISCUSSION

Synthesis of Study Findings

To our knowledge, this is the first systematic review that examined the treatment of dementia by using vitamin D. Dementia is a common cognitive disorder that mostly affects the elderly. It has become a major public health concern, which has serious implications for the individual, families, and the community. Individuals with an MMSE score of less than 24 are said to be suffering from a cognitive impairment (Gangwar et al., 2015). The role of vitamins in the normal functioning of neural tissue has been previously established (Annweiler et al., 2009; Annweiler et al., 2014; Buell & Dawson-Hughes, 2008). The present review has provided evidence for the use of vitamin D to treat dementia. These findings corroborate earlier studies which have reported a

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

positive relationship between vitamin D and brain function (such as Etgen et al., 2012; Balion et al., 2012).

Some earlier studies have shown that vitamin D influences various metabolic systems in the body (Buell & Dawson-Hughes, 2008; Annweiler et al., 2009). It regulates the absorption of intestinal calcium and contributes to mineral homeostasis (Balion et al., 2012). Moreover, the vitamin D receptor *VDR) binds to 1,25(OH)D, interacting with the nuclear receptor known as retinoic acid X receptor (RXR) (Buell & Dawson-Hughes, 2008). VDR.\/RXR complex, in the presence of 25(OH)D binds small sequence DNA and initiates a series of molecular interactions that lead to the transcription of various genes. It is likely that vitamin D protects against dementia and cognitive deterioration through vasculoprotection, preservation of neurons, and protection against risk factors (Chai et al., 2019). In this review, we have provided current evidence about the role of vitamin D in neuronal health, and a link between vitamin D, dementia, Alzheimer's disease, and cognitive function.

Evidence from the reviewed studies shows that Vitamin D supplementation improves the cognitive functions of the elderly suffering from senile dementia. Various explanations have been provided for the mechanism involved. Gangwar et al. (2015) asserted that vitamin D is critical in the regulation of voltage-caged calcium channels, thereby protecting against necrosis. Vitamin D also has protective properties against toxicity induced by glutamate, thus preventing apoptosis through antioxidant effects. Houshmand et al. (2014) explained that Vitamin D has antioxidative, anti-inflammatory, and anti-ischemic properties which contribute to neuroprotection. This assertion is based on earlier experimental studies which show that 25 (OH)D causes inhibition of nitric oxide synthesis, protection of neuronal integrity, regulation of calcium, and metabolism of neurotransmitters (Annweiler et al., 2009). Moreover, some studies have shown that vitamin D can cause phagocytosis and clearance of amyloid (Masoumi et al., 2009).

The longitudinal study by Miller et al. corroborates the findings of RCTs and cross-sectional studies which show that vitamin D levels vary in individuals with normal cognition, MC, and dementia. Besides, the study showed that differences exist depending on race and ethnicity. While diet is the most common source of vitamin D, the dietary intake is below recommended levels for many people. Vitamin D (25-hydroxyvitamin D or cholecalciferol) circulates in the brain and serves as a precursor for the synthesis of a bioactive substance known as calcitriol. Earlier studies have shown that reduced dietary intake, poor sunlight exposure, and skin impairment can cause a deficiency of vitamin D (Etgen et al., 2012). The important role of vitamin D in the brain has been established in both human and animal model studies.

The findings of this systematic review mirror recent reviews on the effect of vitamin D on cognitive function. For instance, Annweiler et al. (2009) reported on vitamin D and cognitive performance in adults. The review noted that there is a positive relationship between serum 25-hydroxyvitamin D (25OHD) concentration and cognitive function. After reviewing five observational clinical studies, Annweiler et al. (2009) reported that some studies showed a positive association between 250HD concentration and cognition, while in others there was no significant association. However, the systematic review by Annweiler et al. (2009) is limited by the small number of included studies. It only had five studies, especially because it only explored research conducted within the past three years. Our systematic review consists of ten studies: seven RCTs, 2 cross-sectional studies, and one longitudinal study.

Across the RCTs, the supplementation with vitamin D increased cognitive function. However, only a few studies reported significant improvement for high-dose over low-dose supplementation. Significant changes occurred from baseline to the duration of the study. It has

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

been documented that vitamin D causes an increase in pro-inflammation and amyloid burden, which is age-related (Etgen et al., 2012). One study which explored whether vitamin D confers an additional effect on patients undertaking medication showed that it does so. It is postulated that vitamin D regulates the homeostasis of intraneuronal calcium through the regulation of calcium channels. One study focused on the role of vitamin D supplementation for people with type 2 diabetes. While the study reported improvement in the supplementation, there was no significant difference between high-dose and low-dose (Byrn et al., 2019). The study is, however, limited by its small sample size and a lack of a true placebo group.

While the systematic research of current data suggests an association between cognitive function and vitamin D, the studies were underpowered as they had a petite sample size and population. Moreover, all of them, except one (Miller et al., 2015), were conducted within a short study time. Differences in the findings among studies are explained by various methodological issues, including the study population heterogeneity, differences in 25(OH)D status, different forms of assessment, and inconsistent control for confounders. As evidenced in this review, the association between 25(OH)D and structural brain tissue volumes has not been widely examined. Only one study focused on it, and it found a significant association between 25(OH)D and brain volumes (Hooshmand et al., 2014).

The reviewed studies, apart from showing that vitamin D can treat dementia, also showed that the micronutrient is vital for general brain growth and health. The association between vitamin D and brain health was the main outcome in most studies (Byrn et al., 2019; Dean et al., 2011; Miller et al., 2015). Annweiler et al. (2012b) demonstrated that vitamin D's neurosteroid actions help in the regulation of calcium and β-amyloid deposition, and serve as antioxidant and anti-inflammatory components. These roles help in neuroprotection, which serves to prevent the development of neurodegenerative conditions such as dementia. One study in particular, Dean et al. (2011), examined supplementation in young adults without any existing condition. They noted that it led to improvements in various cognitive and emotional functioning measures.

Evidence for the Use of Vitamin D to treat Dementia

Progressive decline in cognition is associated with cardiometabolic risk factors, including diabetes, hypertension, insulin resistance, dyslipidemia, central obesity, and a sedentary lifestyle (Bhatti et al., 2020). As such, the risk of dementia can be reduced through regular exercise, controlling weight, avoiding smoking and alcohol, a healthy diet, and maintaining blood sugar and cholesterol levels. Due to the lack of effective pharmacological treatment for dementia, non-pharmacological interventions are used to reduce the escalation of the condition. In this regard, lifestyle interventions help to reduce morbidity and mortality in the elderly. For instance, healthy nutritional food, with anti-inflammatory and antioxidant properties contributes to a reduction of cognitive impairment.

Nutritional factors are critical in promoting health. Research evidence has shown that deficiencies can exacerbate the deterioration of cognitive function (Buell & Dawson-Hughes, 2008). Vitamin D insufficiency has been associated with dementia and cognitive impairment (Pettersen, 2017). Studies have shown that vitamin D receptors (VDR) are located in the brain ((Stein et al., 2011: van der Schaft et al., 2013). Besides, it has been shown that vitamin D increases the levels of acetylcholine and hippocampal neuron densities (Pettersen, 2017). It also reduces proinflammatory cytokines, augments amyloid--β clearance, and enhances neuroprotection. These are key processes associated with dementia and age-related cognitive decline. As demonstrated in this review, supplementation of vitamin D improves the outcomes for people suffering from dementia. Also, as Gangwar et al. (2015) asserted, the

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

supplementation also offers additional effects for people receiving medical treatment.

Supplementation by vitamin D not only enhances cognition but also improves markers of pathology in lab models of Alzheimer's disease (Pettersen, 2017). Yang et al. (2020) showed that the improvement of recognition comes through a reduction of oxidative stress. Thus, it serves as a neuroprotective hormone. To be effective, it has to undergo hydroxylation which converts it into 25(OH)D. Lower levels of 25(OH)D3 have been reported in cases of neurodegenerative disease. As a steroid hormone, vitamin D exerts its effects through its nuclear hormone receptor (VDR). VDR and associated enzymes are expressed abundantly in various regions of the central nervous system (CNS) (Dursun et al., 2011). Other studies have reported that vitamin D contributes to the homeostasis of calcium on the plasma membranes However, in an RCT, Dean et al. (2011) found out that vitamin D supplementation had no beneficial effects on working memory, ratings of anger, anxiety, and depression, and psychotic-like experiences of hallucination.

Limitations of the Included Studies

The included studies had some limitations that may affect the generalization of the review's findings. The main limitation was the sample size, which was not appropriately powered. Also, there was a lot of heterogeneity in research design, outcome measures, and findings. Some studies included a control group while others did not. Besides, the length of supplementation and follow-up period was short for most studies, except for the one longitudinal study.

CONCLUSION

The current systematic review provides evidence for the use of vitamin D to treat dementia. The analysis has shown a positive relationship between vitamin D and brain function. Furthermore, studies have shown that the risk of dementia is higher in patients with vitamin D deficiency. However, the current literature has not fully established the pathophysiological mechanisms for the effects of vitamin D on dementia. Moreover, the current systematic review did not find any significant difference between high-dose and low-dose vitamin D supplementation. Thus, there is a need for more studies, including longitudinal investigations, to establish the optimal supplementation quantity of vitamin D for dementia patients. Future studies should explore the extent to which vitamin D deficiency leads to cognitive degeneration. It should be noted that the quality of life for older adults depends on their functional ability. As such, dementia is a significant challenge which leads to mortality, morbidity, and institutionalization. The benefits of vitamin D have been reported in this study. Since the study has not found any evidence for optimal vitamin D concentration, it suggests that any levels more than 75nmol/litre are optimal for skeletal and brain health. The elderly should have a dietary intake of between 800 and 1000IU, augmented with adequate sun exposure.

REFERENCES

Annweiler, C., Allali, G., Allain, P., Bridenbaugh, S., Schott, A.-M., Kressig, R. W., & Beauchet, O. (2009). Vitamin D and cognitive performance in adults: a systematic review. *European Journal of Neurology*, *16*(10), 1083–1089. https://doi.org/10.1111/j.1468-1331.2009.02755.x

Annweiler, C., Brugg, B., Peyrin, J.-M., Bartha, R., & Beauchet, O. (2014). Combination of memantine and vitamin D prevents axon degeneration induced by amyloid-beta and glutamate. *Neurobiology of Aging*, *35*(2), 331– 335. https://doi.org/10.1016/j.neurobiolaging.2013.07.029

Annweiler, C., Fantino, B., Gautier, J., Beaudenon, M., Thiery, S., & Beauchet, O. (2012a). Cognitive Effects of Vitamin D Supplementation in Older Outpatients Visiting a Memory Clinic: A Pre-Post Study. *Journal of the American Geriatrics Society*, *60*(4), 793– 795. https://doi.org/10.1111/j.1532-5415.2011.03877.x

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

Annweiler, C., Herrmann, F. R., Fantino, B., Brugg, B., & Beauchet, O. (2012b). Effectiveness of the Combination of Memantine plus Vitamin D on Cognition in Patients with Alzheimer Disease. *Cognitive and Behavioral Neurology*, *25*(3), 121–127. https://doi.org/10.1097/wnn.0b013e31826df647

Balion, C., Griffith, L. E., Strifler, L., Henderson, M., Patterson, C., Heckman, G., Llewellyn, D. J., & Raina, P. (2012). Vitamin D, cognition, and dementia: a systematic review and meta-analysis. *Neurology*, *79*(13), 1397–1405. https://doi.org/10.1212/WNL.0b013e31826c197f

Berg-Weger, M., & Stewart, D. B. (2017). Non-Pharmacologic Interventions for Persons with Dementia. *Missouri Medicine*, *114*(2), 116–119. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6140014/

Bhatti, G. K., Reddy, A. P., Reddy, P. H., & Bhatti, J. S. (2020). Lifestyle Modifications and Nutritional Interventions in Aging-Associated Cognitive Decline and Alzheimer's Disease. *Frontiers in Aging Neuroscience*, *11*. https://doi.org/10.3389/fnagi.2019.00369

Buell, J. S., & Dawson-Hughes, B. (2008). Vitamin D and neurocognitive dysfunction: Preventing "D"ecline? *Molecular Aspects of Medicine*, *29*(6), 415–422. https://doi.org/10.1016/j.mam.2008.05.001

Byrn, M. A., Adams, W., Penckofer, S., & Emanuele, M. A. (2019). Vitamin D Supplementation and Cognition in People with Type 2 Diabetes: A Randomized Control Trial. *Journal of Diabetes Research*, *2019*(1), 1–13. https://doi.org/10.1155/2019/5696391

Chai, B., Gao, F., Wu, R., Dong, T., Gu, C., Lin, Q., & Zhang, Y. (2019). Vitamin D deficiency as a risk factor for dementia and Alzheimer's disease: an updated meta-analysis. *BMC Neurology*, *19*(1). https://doi.org/10.1186/s12883-019-1500-6

D'Onofrio, G., Sancarlo, D., Seripa, D., Ricciardi, F., Giuliani, F., Panza, F., & Greco, A. (2016). Non-Pharmacological Approaches in the Treatment of Dementia. *Update on Dementia*. https://doi.org/10.5772/64232

Dean, A. J., Bellgrove, M. A., Hall, T., Phan, W. M. J., Eyles, D. W., Kvaskoff, D., & McGrath, J. J. (2011). Effects of Vitamin D Supplementation on Cognitive and Emotional Functioning in Young Adults – A Randomised Controlled Trial. *PLoS ONE*, *6*(11), e25966. https://doi.org/10.1371/journal.pone.0025966

Dickens, A. P., Lang, I. A., Langa, K. M., Kos, K., & Llewellyn, D. J. (2011). Vitamin D, Cognitive Dysfunction and Dementia in Older Adults. *CNS Drugs*, *25*(8), 629–639. https://doi.org/10.2165/11593080-000000000-00000

Dursun, E., Gezen-Ak, D., & Yilmazer, S. (2011). A Novel Perspective for Alzheimer's Disease: Vitamin D Receptor Suppression by Amyloid-β and Preventing the Amyloid-β Induced Alterations by Vitamin D in Cortical Neurons. *Journal of Alzheimer's Disease*, *23*(2), 207–219. https://doi.org/10.3233/jad-2010-101377

Etgen, T., Sander, D., Bickel, H., Sander, K., & Förstl, H. (2012). Vitamin D Deficiency, Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis. *Dementia and Geriatric Cognitive Disorders*, *33*(5), 297– 305. https://doi.org/10.1159/000339702

Gangwar, A. K., Rawat, A., Tiwari, S., Tiwari, S. C., Narayan, J., & Tiwari, S. (2015). Role of Vitamin-D in the prevention and treatment of Alzheimer's disease. *Indian Journal of Physiology and Pharmacology*, *59*(1), 94–99. https://pubmed.ncbi.nlm.nih.gov/26571990/

Hooshmand, B., Lökk, J., Solomon, A., Mangialasche, F., Miralbell, J., Spulber, G., Annerbo, S., Andreasen, N., Winblad, B., Cedazo-Minguez, A., Wahlund, L.-O., &

Article DOI: https://doi.org/10.37284/eajhs.8.1.2642

Kivipelto, M. (2014). Vitamin D in Relation to Cognitive Impairment, Cerebrospinal Fluid Biomarkers, and Brain Volumes. *The Journals of Gerontology: Series A*, *69*(9), 1132–1138. https://doi.org/10.1093/gerona/glu022

Iacopetta, K., Collins-Praino, L. E., Buisman-Pijlman, F. T. A., Liu, J., Hutchinson, A. D., & Hutchinson, M. R. (2018). Are the protective benefits of vitamin D in neurodegenerative disease dependent on route of administration? A systematic review. *Nutritional Neuroscience*, *23*(4), 251–280. https://doi.org/10.1080/1028415x.2018.1493807

Lee, G. E., Kim, J. Y., Jung, J. H., Kang, H. won, & Jung, I. C. (2019). Non-pharmacological interventions for patients with dementia. *Medicine*, *98*(38), e17279. https://doi.org/10.1097/md.0000000000017279

Masoumi, A., Goldenson, B., Ghirmai, S., Avagyan, H., Zaghi, J., Abel, K., Zheng, X., Espinosa-Jeffrey, A., Mahanian, M., Liu, P. T., Hewison, M., Mizwicki, M., Cashman, J., & Fiala, M. (2009). 1α, 25-dihydroxyvitamin D3 Interacts with Curcuminoids to Stimulate Amyloid-β Clearance by Macrophages of Alzheimer's Disease Patients. *Journal of Alzheimer's Disease*, *17*(3), 703–717. https://doi.org/10.3233/jad-2009-1080

Miller, J. W., Harvey, D. J., Beckett, L. A., Green, R., Farias, S. T., Reed, B. R., Olichney, J. M., Mungas, D. M., & DeCarli, C. (2015). Vitamin D Status and Rates of Cognitive Decline in a Multiethnic Cohort of Older Adults. *JAMA Neurology*, *72*(11), 1295. https://doi.org/10.1001/jamaneurol.2015.2115

Pettersen, J. A. (2017). Does high dose vitamin D supplementation enhance cognition?: A randomized trial in healthy adults. *Experimental Gerontology*, *90*, 90–97. https://doi.org/10.1016/j.exger.2017.01.019

Stein, M. S., Scherer, S. C., Ladd, K. S., & Harrison, L. C. (2011). A Randomized Controlled Trial of High-Dose Vitamin D2 Followed by Intranasal Insulin in Alzheimr's Disease. *Journal of Alzheimer's Disease*, *26*(3), 477–484. https://doi.org/10.3233/jad-2011-110149

van der Schaft, J., Koek, H. L., Dijkstra, E., Verhaar, H. J. J., van der Schouw, Y. T., & Emmelot-Vonk, M. H. (2013). The association between vitamin D and cognition: a systematic review. *Ageing Research Reviews*, *12*(4), 1013–1023. https://doi.org/10.1016/j.arr.2013.05.004

Yang, T., Wang, H., Xiong, Y., Chen, C., Duan, K., Jia, J., & Ma, F. (2020). 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. *Journal of Alzheimer's Disease*, *78*(4), 1509–1518. https://doi.org/10.3233/jad-200926

