Is Vitamin D Supplementation of Potential Benefit for Community-living People with Alzheimer's disease?

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Abstract

Background & Objective: Vitamin D is associated not only with its known effects on calcium and bone metabolisms but also with many chronic diseases. Low vitamin D levels in patients with Alzheimer's disease have been widely reported in the literature in recent years. The purpose of this study was to critically review the potential benefit of vitamin D supplementation in individuals with Alzheimer's disease in the community.

Methods: A systematic literature search was conducted using – PubMed, CINAHL, EMBASE, and Cochrane using appropriate MeSH search terms, for papers published between 2011-2018. The application of a sophisticated literature search strategy allowed the selection of seven relevant studies.

Results: Seven papers were selected, consisting of one clinical trial, five cohort studies and one systematic review. All reviewed studies published in a good quality peer-reviewed journal. Studies showed an association only between vitamin D deficiency and lower attention in elderly. None of the reviewed studies provided evidence of a positive impact of vitamin D supplementation on cognitive function in the elderly with Alzheimer's disease.

Conclusion: There was no evidence that vitamin D supplementation has a potential benefit directly on Alzheimer's disease. The review synthesized the existing body of knowledge concluded that; optimum levels of vitamin D scores required for efficient patient care as well as for quality of life. Despite all, it is still unclear why vitamin D intake is inadequate with aging. Further research is needed to clarify vitamin D-related aspects of Alzheimer's disease.

Keywords: Alzheimer's disease, vitamin D, supplementation, cognitive function.

INTRODUCTION

Chronic diseases not only threaten the quality of life but also impose a significant burden on the economy in terms of health expenditure [1]. These diseases are also seen to have slow progression and a long duration. Alzheimer's disease is described as an irreversible brain disorder that is slow progressing, leads to memory loss and deteriorating thinking skills over a long period of time. [2]. According to recent evidence, vitamin D is associated not only with its known effects on calcium and bone metabolisms but also with many chronic diseases due to the widespread presence of vitamin D receptors in the body [3-5]. In addition, inadequate vitamin D intake with aging has been reported and vitamin D deficiency is presumed to be associated with Alzheimer's disease [6]. Reduced outdoor activities, skin wrinkles or poor skin integrity and malabsorption disorders with aging are held responsible for low vitamin D in patients with Alzheimer's disease [6]. In the context of vitamin classifications, scientists have concluded that vitamin D usually acts as a hormone rather than a vitamin [7, 8]. Vitamin D in the nervous system participates in calcium-mediated neuronal activities and neurotransmitter metabolism [9]. The aim of this paper is to carry out and report on a thorough literature review on the potential benefit of vitamin D supplementation in individuals with Alzheimer's disease in the community and to identify implications for practice and further research.

BACKGROUND TO THE TOPIC OF INTEREST

Increased age may result in significant changes, such as the accumulation of harmful substances and the lack of essential vitamins and minerals in the body [10, 11]. Alzheimer's disease primarily manifests itself with cognitive impairment. In this paper, the potential benefits of vitamin D supplementation and the effects of vitamin D directly on cognitive functions and indirectly on quality of life in Alzheimer's disease were investigated. According to Tamura and Yaffe [12], patients with cognitive impairment and dementia have a higher risk of death. In a

controlled trial study, Sato *et al*. [13] reported that 80% of 46 women with Alzheimer's disease had vitamin D deficiency; the sample shared a common characteristic – old age, which indicated an increased risk of cognitive impairment accompanied by the lack of vitamin D in the elderly. Although that study is a small sample and very old, the determined percentage is still significant. Furthermore, more recent research has provided evidence that vitamin D has a positive effect on many chronic diseases. However, detrimental effects of vitamin D also reported. Alshahrani and Aljohani [14] indicating that serum vitamin D (25[OH]D) levels have a level of toxicity (over 150 ng/ml) which occurs after consumption of 40,000 IU / day. Thus, excessive increases may lead to different side effects and deterioration of health. Hypercalcemia caused by vitamin D toxicity is held responsible for symptoms including irregular heartbeat, muscle pain and kidney stones. Nevertheless, Schlögl and Holick [15] suggested an association between vitamin D and many chronic diseases, including neurocognitive failure [16, 17]. Furthermore, vitamin D receptors (VDR) have been found in more than 200 genes and 37 different tissues, including the brain [18]. Although the presence of a vitamin D receptor in the brain is known, the role of vitamin D and how it works in the brain is still unclear [19, 20]. A deeper understanding of this process may suggest whether vitamin D supplementation has an impact on the maintenance of cognitive function in patients with Alzheimer's disease.

THE ROLE OF VITAMIN D IN THE NERVOUS SYSTEM

In order to guide this literature review, the results of current researches trying to explain the presence of vitamin D in the nervous system need to be synthesized briefly. Firstly, Latimer *et al*. [21] who studied synaptic functions in animals to explain the role of vitamin D in nervous system, concluded that the important role of contactin complex in anchoring myelin to the axons provided by vitamin D mediated processes. Additionally, basis of neuronal communication is dependent on nerve conduction provided through axons and insulated by myelin, a fatty white

substance, which needs vitamin D to be anchored to the axon (see Figure 1) [21]. The model indicates that the human brain may be affected by the lack of vitamin D. Then, further evidence supporting Latimer *et al*. may lie in the findings of Landel *et al*. [22], who tried to explain the complexity of vitamin D-mediated processes in Alzheimer's disease in compliance with another well-known effect of vitamin D which relates to neurotransmitter release. Landel *et al*. defined new mechanisms explaining the role of vitamin D-mediated processes in Alzheimer's disease including oxidative stress, inflammatory processes and neurotransmission which needs optimum levels of vitamin D (*see* Figure 2) [22]. Next, Littlejohns *et al*. [23] emphasized that *in vitro* axon degeneration models in cell cultures induced by β-amyloid peptide and glutamate showed a significant recovery after vitamin D supplementation. Moreover, phagocytic clearance of amyloid plaques was increased by the presence of vitamin D in culture dishes of tissue samples taken from Alzheimer-diagnosed patients. After that, the absence of vitamin D, as was first demonstrated by Eyles *et al*. [24] and subsequently verified by Gezen-Ak *et al*.

[25], results in a decreased nerve growth factor (NGF), which means that optimum level vitamin D is essential for mental health. Finally, optimum vitamin D levels are crucial for proper vascular processes, neurotransmission, protein accumulation, oxidative stress, inflammation and the immune system [22]. Researchers have focused whether vitamin D has an impact on nervous system both in human and animal studies as well as *in vitro* models. All models provided valid results as specified by each study, but Landel *et al.*'s paper is noteworthy as it is not only focusing experimental results but also indicates that the effects of vitamin D on mental health are multifactorial and depend on genetic, immune-mediated, environmental, nutritional and hormonal factors. Cultural factors are also significant on maintaining vitamin D levels. For example, the clothing style, which is common in Muslim society, is held responsible for low vitamin D levels in women. Overall, all authors have proposed a role for vitamin D in mental health but the exact mechanisms of action are still unclear.

PEOPLE LIVING IN THE COMMUNITY WITH ALZHEIMER'S DISEASE

Alzheimer's disease primarily manifests itself with cognitive impairment and it is known as the most common type of dementia [26]. According to World Alzheimer Report (2016) more than 47 million people live with dementia across the world, and this number is estimated to increase up to 131 million by 2050 [27]. Most people with Alzheimer's and dementia in the community live with others, Lepore *et al*. [28] reported that only one-fifth of people with Alzheimer's and dementia live in residential care settings or nursing homes. Most people with Alzheimer's disease live in the community but are often dependent on others for their day-to-day care. The number of people living alone is approximately 30% and it is higher than those living in residential care settings or nursing homes. [28]. Caregivers are often family members or spouses who need to provide average 24.4 hours of care per week and have difficulty in performing their nursing duties [29]. The difficulty in carrying out nursing tasks stems from the fact that caregivers are more likely to have other caring roles; approximately one-third of caregivers are over 65 years old, and one-fourth is defined as "sandwich" carers facing both parents and children care under 18 years old [28]. The burden of dealing with Alzheimer's and dementia can be greater than expected as it has both financial and emotional impact on family. In a survey conducted by the Alzheimer Association in 2014 revealed that approximately 10% of caregivers have quit their jobs and 13% of caregivers turn their full-time jobs in to part-time. For people living in the community with Alzheimer's disease, both pharmacological and non-pharmacological interventions may reduce the burden of disease.

Why vitamin D supplementation might be useful is that it is a pharmacological method that is cheap, practical and easy to apply at home by both caregivers and patients. The benefits and potential risks of vitamin D supplementation may only be demonstrated by long-term studies.

If the potential benefits of vitamin D supplementation in patients with Alzheimer's disease were known, multifactorial risks associated with vitamin D involving oxidative stress, inflammatory processes and vascular processes can be better explained and eliminated. In the light of current knowledge, evidence suggests that improving vitamin D levels in people living with Alzheimer's disease could potentially improve their cognitive ability, patient care and quality of life.

FORMULATING THE QUESTION

Given the evidence cited above, vitamin D supplementation may impact on cognition and may be beneficial to people living with Alzheimer's disease. The rationale for this literature review is, therefore, to summarise and synthesize the existing evidence of vitamin D supplementation on cognition in the elderly in the community. The PICO tool was used to formulate a research question (*see* Table 1.) [30]. This literature review is therefore driven by the following research question:

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METHODOLOGY

The current inquiry is driven by the purpose of investigating the relationship between vitamin D supplementation and its potential benefits on Alzheimer's disease. Driven by this research pursuit, this study was designed to carefully examine the existing knowledge base for the findings of intelligence tests, brain imaging, and blood and spinal fluid tests in relation to individuals' consumption of vitamin D supplementation in the community [31]. In line with the research purpose, a literature review was chosen as a method enabling a review of the current

state of the relevant science, a summary of the existing points, a new angle of view, and an evaluation of the applicability of theoretical foundations to the current practice [32]. Aveyard emphasizes that, hand searching the reference list for each selected article in the literature review and selection of most commonly cited papers will allow access to the maximum amount literature, thus preventing the 'cherry-picking' which means choosing the first relevant one or choosing what you want from the literature [32]. Despite being a secondary research technique, a literature review can be instrumental in summarising, synthesizing and re-evaluating the existing body of knowledge and practice in order to identify areas for improvement of the current practice, patient care and further research [33]. It was decided to study the assumed association by reviewing peer-reviewed scholarly articles citing evidence from intelligence tests, brain imaging, and blood and spinal fluid test results for people in the community exposed to vitamin D supplementation or not. A set of inclusion and exclusion criteria were applied to limit the potential set of articles to the most relevant ones. The overall process of the application of methodology is explained and justified below.

ELECTRONIC DATABASE SEARCH

The pursuit of attaining credible peer-reviewed journal articles informed the decision to turn to the major medical databases to gain access to the required data and scholarship. PubMed, EMBASE, Cochrane, and CINAHL were finally determined as the most appropriate data sources. They are recommended as a huge reputable electronic database of clinical trials and other medical data for "Systematic Reviews and Meta-Analysis*"* by Harvard Library [34] (*see* Table 2). These medically-specific databases provide references to health care, nursing and medical journals with a continuous update of the latest findings in the field of current practice. In addition, they are convenient to navigate, which streamlines the search and selection processes.

SEARCH TERMS

The initial overview of the academic field regarding the current research interest enabled the researcher to define the search terms and keywords which were applied to find and retrieve data using digital search engines. The list of the developed search words included but was not limited to: 'Vitamin D', 'supplementation', 'Alzheimer's disease', 'cognitive functions' and 'mental health'. For instance, MeSH (Medical Subject Headings) terms used to identify the relevant keywords for vitamin D. Search terms expanded as vitamin D deficiency, vitamin D receptors, cholecalciferol, ergocalciferols, and calcitriol. The application of Boolean operators such as 'AND' and 'OR' allowed expanding the search capacity and systematizing the process. The procedure involved dividing the search terms by themes and offered alternative keywords in each theme thereby simplifying the search process and ensuring its accuracy (*see* Table 3).

INCLUSION CRITERIA

The keyword-based search through the four selected medical databases was highly productive and resulted in a large volume of peer-reviewed articles being obtained. However, the research method of a literature review implies a narrow-focused analysis of the most relevant evidence of a given issue in order to produce a credible answer to the central research question. In respect of this, therefore, the scope of potentially relevant articles was subject to further refinement to remove duplicates. Firstly, all results transferred to Endnote X8 and duplicates were removed. Ross [35] claim that generally academic works written in the last decade is considered up-to-date, however, even the ideas that have been proposed in the past five years can be out-of-date. For this reason, although the threshold limit is shown between 2011 and 2018, preference has been used in current publications. After their exclusion, the rest were analyzed in compliance with the formulated inclusion criteria:

1) Publication date (the period from 2011-2018);

2) Access to full copy of paper

3) Papers with a focused research question evaluating cognitive abilities with intellectual tests, brain imaging or use of blood and spinal fluid tests consuming vitamin D supplementation.

4) English language of the publication.

Correspondingly, studies; (i) published in a language other than English (ii) or addressing the issue of Alzheimer's disease without any reference to cognition measurement tools (iii) case reports/conference papers were excluded from the list. Furthermore, the volume of potentially relevant articles was further reviewed by reference to the abstract and the full content in order to define a final set for analysis and avoiding bias [36]. PRISMA flow diagram of article screening has then enabled to reach seven peer-reviewed articles (*see* Graphic 1 and Table 4)

CRITIQUE TOOLS

Whereas the literature search strategy which was developed ensured the accuracy and systematics of the selection process, the use of critical appraisal tools enabled the justification of the value of each article for accomplishing the research goal [37]. Critical Appraisal Skills Programme (CASP, 2017) [38] is a commonly used tool for critically appraising the literature chosen for a systematic review and Moule & Goodman [39] emphasizes the need for using a critical appraisal tool for reliable academic studies. The CASP tool offers different checklists to evaluate the quality of randomized controlled trials, case-control studies, cohort studies, systematic reviews and other academic endeavors. The CASP tool is convenient and easily accessible, and this shaped the researcher's decision to use this critical appraisal tool for

verifying the relevance of the chosen peer-reviewed articles. The use of the developed search strategy contributed to a non-biased and transparent manner of selection of articles, and the CASP checklists ensured the researcher's objectivity in evaluating the credibility and quality of the selected papers.

HOW VARIABLES AND OUTCOMES WERE INVESTIGATED

The comprehensive literature search strategy described above enabled the collection of an appropriate and anticipated amount of data for analysis. In line with the formulated research pursuit, the planned literature review required identifying ways of assessing cognitive functions. The available scope of cognitive assessment tools divided into three categories, intellectual tests, brain imaging, and blood and spinal fluid testing [40]. In practice, these tests are also classified as invasive and non-invasive. The application of invasive procedures requires special ethical considerations in Alzheimer's patients rather than healthy people. However, no ethical principles regarding patient safety have been stated in any study. Littlejohns *et al*., [23] Granic *et al*., [41] Miller *et al*.,[42] and Hooshmand *et al.* [43] reported only getting an ethical approval from an institutional review boards. Firstly, Mini-Mental State Examination (MMSE), which was first developed in 1975 by Folstein *et al.,* is one of the most frequently used tools in clinical practice to assess the cognitive impairment [44]. Therefore, MMSE scores and vitamin D levels were taken into account with studies assessing cognitive impairment. Secondly, brain imaging, an alternative to intellectual tests, is a useful method for diagnosing cognitive impairments or revealing changes in the brain [45]. Research in this field identified the role of proteins called Tau protein and β-amyloid in reducing neurological function [46]. A decreased mass of cerebral cortex and dead nerve cells surrounded by β-amyloid protein are primary symptoms of declining cognition (see Figure 3). Therefore, monitoring visible changes in the brain allows the identification of affected areas which is critical for cognitive assessment and diagnosis [46].

The study conducted by Hooshmand *et al*. [43] revealed a relationship between higher 25 (OH) D levels and larger brain volumes as well as for white matter and temporal lobe. These findings are taken into account for distribution of VDR in the brain. It has, therefore, been suggested that decreased temporal lobe functions exposed to low vitamin D may be related to performing poor speech, impaired memory and hearing loss in Alzheimer's patients. Finally, the findings of blood and spinal fluid tests may offer early signs of neurodegenerative diseases [47]. A study conducted by Bredesen [48] showed that the nature of and disparity in the underlying processes of different forms of cognitive impairment could be monitored and observed through the plasma and spinal fluid sampling [49]. When investigating the studies, the relationship between the β-amyloid levels in cerebrospinal fluid and serum vitamin D levels were considered. Given the efficiency of these three approaches to cognitive assessment, this literature review research paid particular attention to the measurement tool used when investigating the potential benefit of vitamin D on the cognitive function.

RESULTS AND DISCUSSION

The comprehensive screening process resulted in the selection of seven peer-reviewed journal articles, one was clinical trial, five were cohort studies and one was systematic review. Table 4. summarises the selected papers' titles, years and the authors (*see* Table 4.) All of them were thoroughly evaluated regarding quality using the CASP critical appraisal tools for randomized-controlled trials (*see* Appendix 1), cohort studies (*see* Appendix 2) and systematic reviews (*see* Appendix 3). Except for some points, all reviewed studies produced credible findings by following academic guidelines for problem development, research methods, participant sampling and selection, research procedures, outcomes measurement, and reporting. However, it was challenging to limit the literature review research specifically to Alzheimer's disease as the prevailing amount of primary research studies had examined the role of vitamin

D in cognitive performance in several cognition-related illnesses characteristic for the elderly, namely community dwelling healthy older adults, Alzheimer's disease, dementia and mild cognitive impairment. It is important to note that the population of the clinical pilot trial carried out by Aspell *et al*. [50] was community-dwelling healthy older adults. The purpose of inclusion of Aspell *et al*.'s pilot study is that it is the most up-to-date study and the pilot studies may have parallel results with the following cohort studies and randomized controlled trials. In addition, Aspell *et al*. did not confirm a positive association between vitamin D concentrations and cognitive function in older adults whereas the cohort studies of Tofanello *et al*. [51], Littlejohns *et al*. [23], Hooshmand *et al*. [43], Miller *et al*. [42] and Granic *et al*. [41], along with the systematic review of Annweiler *et al*. [52], illustrated the prevalence of dementia, mild cognitive impairment and Alzheimer's disease among those elderly with low 25-OHD (25-hydroxyvitamin D) scores. Except for the systematic review article, all of the studies included in the review used intellectual test scores to measure individuals' global cognitive function, attention, and executive cognition. Blood testing for measuring vitamin D scores was also a widespread measurement. This method is indispensable for determining the serum level of vitamin D but, in the near future, the forms of measurement of vitamins D that can make a differential diagnosis such as; measurement of only skin derived or only dietary intake of vitamin D level may replace this method. Furthermore, Hooshmand *et al*. assessed cognition through cerebrospinal fluid (CSF) biomarkers and brain volumes and concluded a significant reduction of brain mass in patient with Alzheimer's disease. In addition, an in-depth analysis of these data may suggest that the reduction in brain mass not only leads to a decrease in cognition but also decreases the quality of life. Overall, the literature review revealed the prevalence of Alzheimer's disease, dementia and mild cognitive impairment in the elderly defined with vitamin D deficiency or insufficiency. However, none of the reviewed studies provided evidence of a positive impact of vitamin D supplementation on cognitive function in the elderly with

Alzheimer's disease or dementia, and this requires further discussion of the literature review findings.

VITAMIN D AND COGNITIVE FUNCTIONS

In the findings of Sato *et al*., Latimer *et al*., Schlögl and Holick and others, a linear association between vitamin D deficiency and delayed cognition in patients diagnosed with dementia and Alzheimer's disease was suggested. The role of vitamin D in the vascular processes, β-amyloid and Tau accumulation, neurotransmission and inflammation and immune system suggested the idea that the natural decline in vitamin D levels may contributes to the development of Alzheimer's disease [22]. In this respect, it was assumed that vitamin D supplementation is likely to maintain and sustain cognitive function in people diagnosed with Alzheimer's disease. However, the reviewed studies did not prove this point. Orally administered supplements may not absorb enough from the intestine with aging or there may be a deficiency in the amount of skin-derived form with aging. Therefore, a more focused research question is required for understanding of vitamin D-related aspects of Alzheimer's disease, such as: to distinguish the insufficient skin-derived and inadequate dietary intake of vitamin D. More precisely, Annweiler *et al*., Littlejohn *et al*., Tofanello *et al*. and Miller *et al*. illustrated the prevalence of vitamin D deficiency in Alzheimer's disease cases by comparing 25-OHD blood samples and intellectual test scores but the mechanism of causation is still unclear. Hooshmand *et al*. measured the association between vitamin D and cognition through the coincidence of low 25-OHD scores and lower brain volumes and abnormal proteins. In the context of the relationship between the mass of the cerebral cortex in *Figure 3* outlined by Jin [46], the findings of Hoshmand *et al*. may contributed to the assumed association between vitamin D levels and cognitive function. At the same time, the cohort study by Granic *et al*., which was based on a Standardized Mini-Mental State Examination (SSME), assessment of

global cognitive function and attention in compliance with 25-OHD scores, showed that excessive increase in vitamin D level is associated with poor attention and concluded that global cognitive functions are maintained at optimum levels, not at low or high 25 (OH) D concentrations. These findings may oppose the suggested benefit of vitamin D supplementation for improving cognition, but it should be noted that supplements may be beneficial in the optimum dosage and/or optimum vitamin D levels may be beneficial, otherwise intoxication dosage of vitamin D is considered as 150 ng/ml [14]. Contrary, a pilot clinical trial by Aspell *et al*. rejected a relationship between vitamin D levels and cognitive performance in the elderly. As mentioned, pilot studies may have parallel results with the originals but, how reliable these results are depends on its feasibility, duration, cost, and sample size. After all, the articles included in the review were evaluated for their quality in accordance with the CASP critical appraisal checklists. And it is possible to conclude that the general view in literature opposes the relevance of prescribing vitamin D supplementation to individuals with Alzheimer's disease in favor of their cognitive performance. It has been widely reported that low 25-OHD scores in Alzheimer's disease should be considered as biomarkers of the disease. So far existing knowledge does not have a scientific position regarding a positive association between vitamin D scores and cognitive functions in Alzheimer's disease. It is, therefore, irrational to prescribe vitamin D for sustaining cognitive functions. However, Annweiler *et al*., Littlejohn *et al*., Tofanello *et al*., Hooshmand *et al*. and Miller *et al*. have stressed the association between vitamin D deficiency and lower attention. Lower attention in patient with Alzheimer's disease may potentially impact the quality of life regarding fulfilling their daily needs and being dependent on others. For instance, patients who could not provide the necessary attention to cross a road would be reluctant to operate outdoor activities and may suffer from physical and mental health thus, cannot live without assisted living. By highlighting the association between vitamin D deficiency and lower attention in elderly, those studies could not identified a potential

benefit for supplementing Alzheimer's disease with vitamin D in terms of improving memory and cognition.

CONCLUSIONS, LIMITATIONS AND IMPLICATIONS FOR PRACTICE

This work has synthesised the current knowledge about the potential benefit of vitamin D supplementation in patient with Alzheimer's disease in favour of their cognitive performance. The vast majority of studies have highlighted the role of vitamin D contributing to the neurocognitive processes in Alzheimer's disease, and suggested that optimum vitamin D levels are essential in maintaining cognition [15, 41]. Due to complex vitamin D-mediated processes in Alzheimer's disease, low vitamin D scores may be indirectly responsible for reduced quality of life [22]. The majority of reviewed studies also stressed an association between vitamin D deficiency and lower attention [41, 50, 52]. However, the association between lower vitamin D scores and lower intellectual test scores does not imply the ability of vitamin D to sustain or increase cognitive function. Similarly, the relationship between vitamin D levels and brain volumes and CSF biomarkers, do not guarantee the ability of vitamin D supplementation to sustain cognition [43]. The articles were found to be of good quality through critical review with the CASP-based critical appraisal process; however, their findings represent value for the current research rather than current practice. In current practice, studies measuring 25(OH) vitamin D levels are widely performed, but it is not known which form is deficient in production. Theoretically, it is still unclear whether or not there is a conversion disorder due to skin wrinkles, impaired absorption from the gut or inadequate vitamin D intake with aging. This is significant because understanding which form of vitamin D is missing and which way of administration is beneficial may allow us to choose the correct form and correct route of administration. The idea of distinguishing between insufficiency of skin-derived and dietary intake of vitamin D in

elderly may ease the understanding of which route of supplementation would be more useful in practice. Due to the lack of consensus among the reviewed studies regarding supplementing Alzheimer's disease with vitamin D, this literature review did not answer clearly any potential positive or negative outcomes on cognitive function. It is possible to conclude that, so far, low vitamin D scores can be only interpreted as early symptoms of dementia, mild cognitive impairment, and Alzheimer's disease [17]. This literature review was limited by the secondary nature of the data and the scarcity of clinical trials addressing a potential benefit of vitamin D supplementation to sustaining cognitive function in Alzheimer's disease. Limitations were mitigated in this current review by the use of the CASP appraisal tool to verify the quality and credibility of the selected sources of data. The most significant limitation of this research is revealing the relationship between vitamin D deficiency and lower attention in elderly without explaining the exact mechanisms in the light of current literature. Therefore, further research is needed to clarify vitamin D-related aspects of Alzheimer's disease. The key recommendation for further studies would be to distinguish between insufficiency of skin-derived and dietary intake of vitamin D in elderly in order to understand which route of supplementation is best for Alzheimer's patients in practice. While investigating the effects of skin-derived vitamin D in the elderly, studies should be carried out to allow individuals to take advantage of the sunlight on a regular basis.

ACKNOWLEDGMENTS

Master's Degree funding was supported by the Republic of Turkey, Ministry of National Education (MoNE) Study-Abroad Program.

CONFLICT OF INTEREST/DISCLOSURE STATEMENT

The authors have no conflict of interest to report. This project was submitted as a dissertation by Mehmet Karaoglan at the University of Southampton.

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Tables

Table 1.

PICO	
Population	Patients with Alzheimer’s disease in the community
Intervention/**I**ndicator	Benefit of Vitamin D supplementation

Comparison	Patients with Alzheimer's disease without supplementation
Outcome	Possible positive or negative outcomes on cognitive function?

PICO Sections in Formulating Research Question.

Table 2.

Database	**Full Name**	**Provider**
PUBMED	Public MEDLINE	National Institutes of Health
EMBASE	*Excerpta Medica* database	Elsevier

CINAHL	Cumulative Index to Nursing and Allied Health Literature	EBSCO (United States)
COCHRANE LIBRARY	Name of Archie Cochrane	John Wiley & Sons

Selected Databases.

Table 3.

Vitamin D OR	AND	Alzheimer's disease/syndrome OR	AND	Memory facilitation OR

Vitamin D Supplementation OR Vitamin D deficiency OR Vitamin D receptors OR Cholecalciferol/ Ergocalciferols	Neurocognitive disease/ disorders OR Neurodegenerative disease/disorder OR Memory Impairment	Improved neuronal communication OR Neurotransmission OR Cognitive functions OR Cognition

Boolean Search Terms.

Table 4.

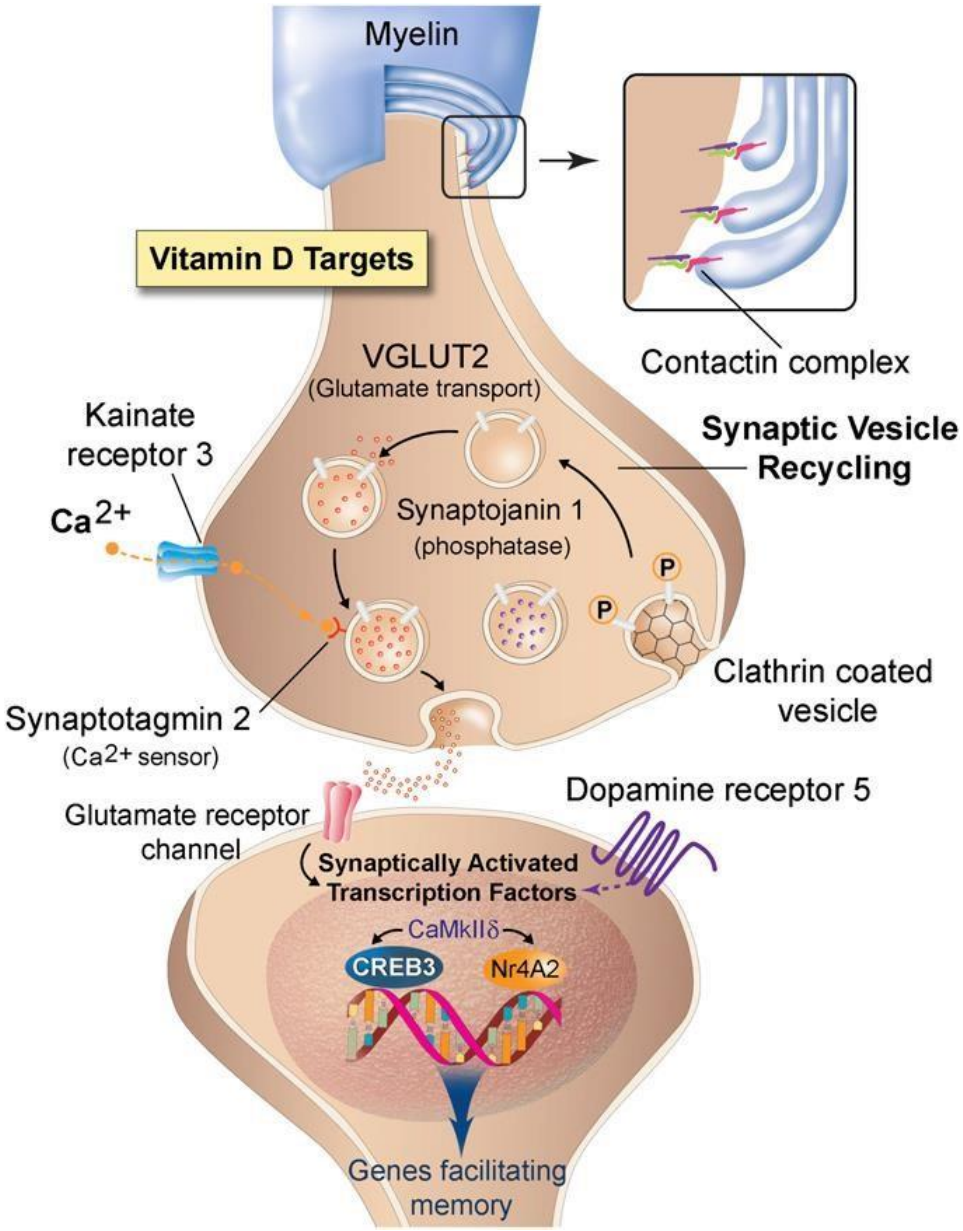
Author(s) and Years	Title of Article

Aspell *et al*., (2017) [50]	Effects of vitamin D supplementation on cognitive function in healthy, community-dwelling older adults: Results from a randomized double-blind placebo-controlled pilot trial.
Granic *et al*., (2015) [41]	Serum 25-hydroxyvitamin D and cognitive decline in the very old: The Newcastle 85+ study.
Hooshmand *et al*., (2014) [43]	Vitamin D in relation to cognitive impairment, cerebrospinal fluid biomarkers, and brain volumes.
Littlejohns *et al*., (2014) [23]	Vitamin D and the risk of dementia and Alzheimer disease.
Miller *et al*., (2015) [42]	Vitamin D status and rates of cognitive decline in a multiethnic cohort of older adults.
Tofanello *et al*., (2014) [51]	Vitamin D deficiency predicts cognitive decline in older men and women.
Annweiler *et al*., (2013) [52]	Low serum vitamin D concentrations in Alzheimer's disease: A systematic review and meta-analysis.

Selected papers.

Figures

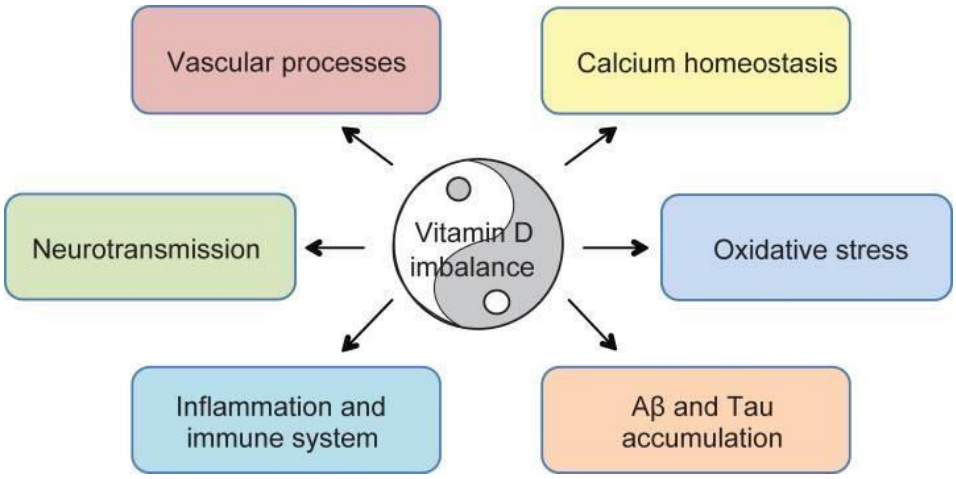
Figure 1.



Proposed Model of Vitamin D Targets between Myelin and Axon. (Latimer *et al*., 2014.) [21]

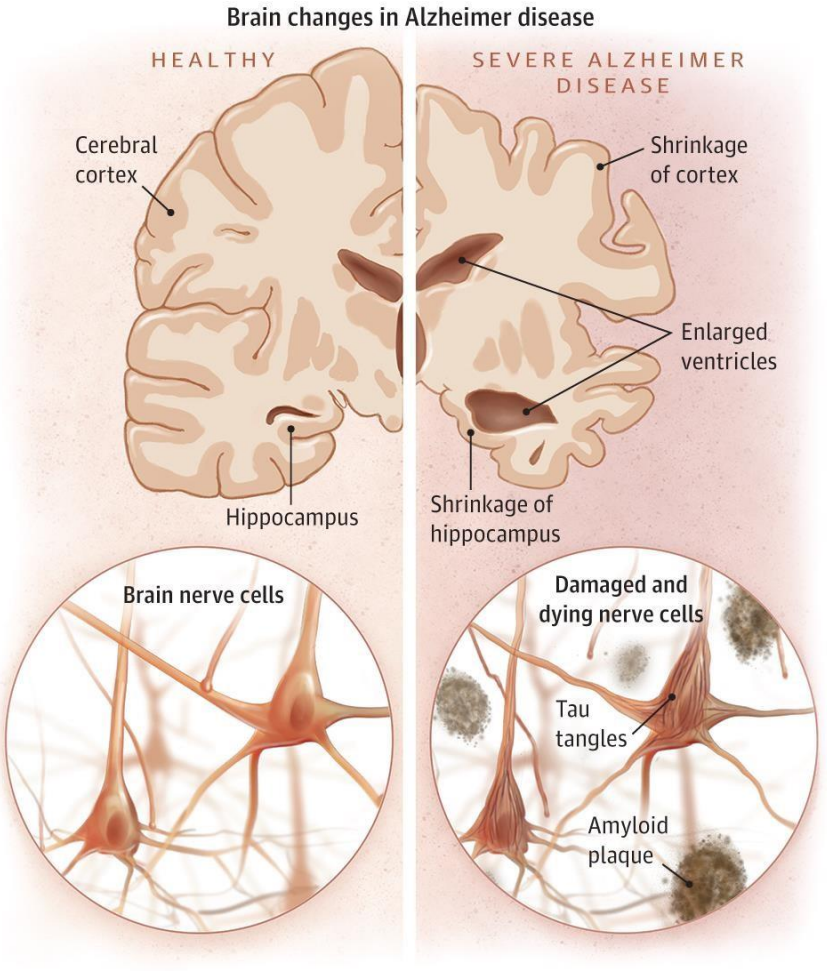
Fig.1. Pivotal role of the contactin complex in anchoring the myelin to the axon in the presence of vitamin D [21].

Figure 2.



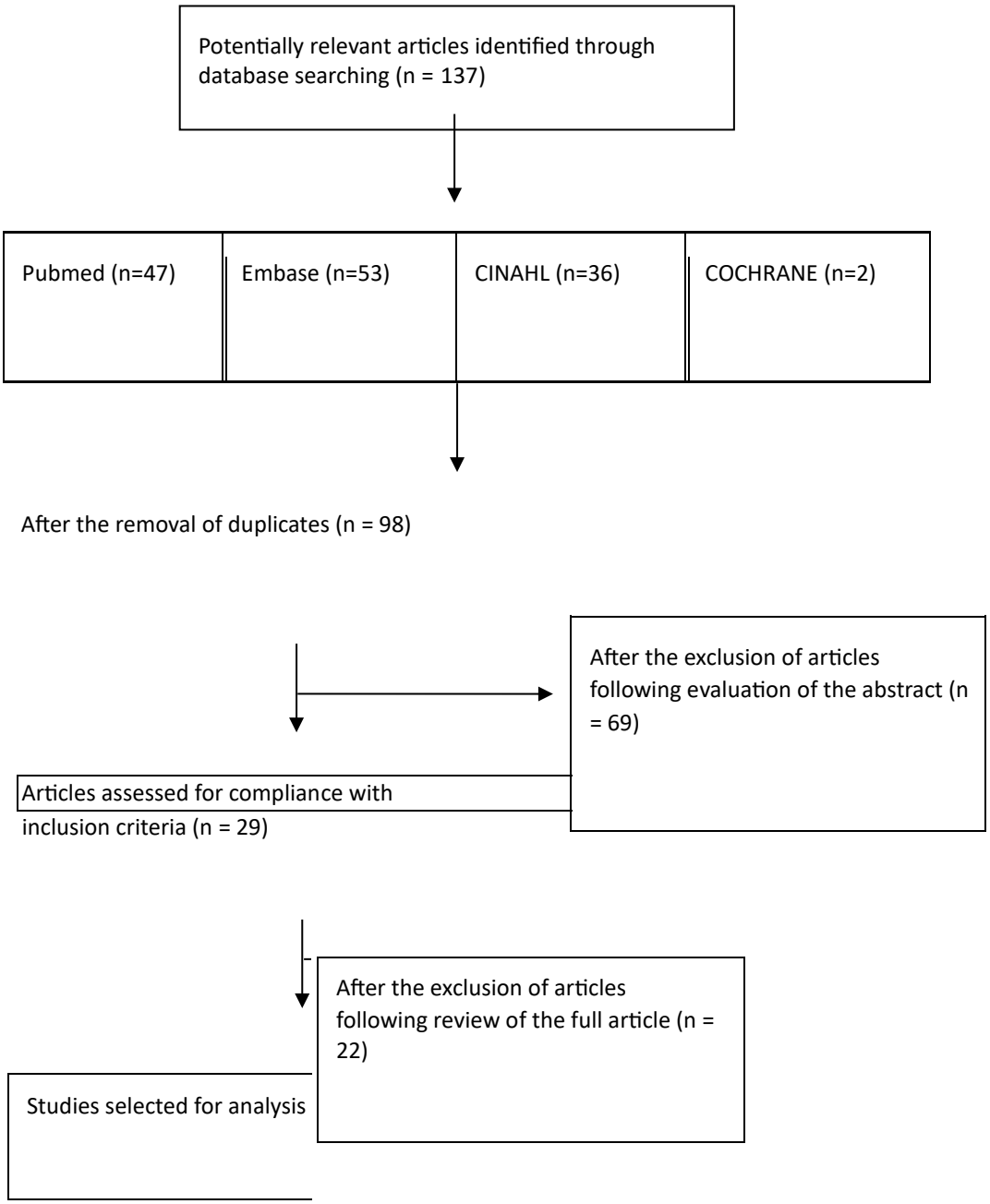
Vitamin D-Mediated Processes in Alzheimer's Disease. (Landel *et al.*, 2016.) [22]

Figure 3.



Brain changes in Alzheimer diseases. (Jin, 2015.) [46]

Graphic 1.



Modified PRISMA flow diagram of article screening and selection.

Appendix A CASP Appraisal for Randomised Controlled Trials

Article title	Did the study ask a clearlyfocused question?	Was this a randomised controlled trial and was it appropriately so?	Were participants appropriately allocated in intervention and control groups?	Were participants, staff and study personnel 'blind' to participants' study group?	Were all of the participants who entered the trial accounted for at its conclusion?	Were the participants in all groups followed up and data collected in the same way?	Did the study have enough participants to minimise the play of chance?	How are the results presented, and what is the main result?	How precise are these results?	Were all important outcomes considered so the results can be applied?
Aspell *et al*., 2017	Yes. It studied the impact of vitamin D supplementation on the cognitive function of healthy older adults.	Yes. It was a randomised double-blind placebocontrolled pilot trial.	Yes. The samples of 60 participants were randomly assigned to the experiment group exposed to daily vitamin D3 supplementation and the control group were exposed to placebos.	Yes. The investigators were blind regarding the sample randomisation.	Yes. The sample of 60 participants was measured at baseline, 3 and 6 months.	Yes. The intention-totreat approach was applied to all participants to measure global cognitive function, attention and executive function with intellectual tests.	The sample was enough for a pilot trial, but requires extension for further trial.	At 6 months., 25OHD scores were higher in the experimental group. However, no significant difference was found between global cognitive function, executive function and attention.	Results are not statistically significant p=.051.	No. further research is required with an expanded sample.

Appendix B CASP Appraisal for Cohort Studies

Article title	Did the study address a clearly focused issue?	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confoundin g factors?	Was the followup of subjects complete and long enough?	What are the results of this study?	How precise are the results?	Do you believ e the result s?	Can the results be applied to the local populatio n?	Do the results fit with other available evidence ?	What are the implication s for practice?

Granic *et al*., 2015	Yes. It studied the relationship between 25OHD levels among the elderly (85+) and cognitive impairment.	Yes. The sample of 775 participants was recruited from the Newcastle 85+ Study with the authorities' permission.	Yes. Standardised Mini-Mental State Examination screened participants for mild cognitive impairment. Cognitive Drug research measured attention. Morning blood samples were measured for 25-OHD levels.	Yes. KruskalWallis tests measured ordered and abnormally distributed variables with adjustment to confounding factors.	Yes. Sociodemographic factors, health and morbidity and lifestyle factors were included in the analytical model.	Yes. Baseline assessment of 20062007 of was followed up in 1.53 years.	The lowest and highest 25-OHD scores were associated with cognitive impairment and poorer attention.	Results are statistically significant with $p<.05$.	Yes.	Yes. To people aged 85 years and above.	Partially. While proving the relationship between low 25-OHD level and cognitive impairment, it did not correlate with global cognitive decline and incident impairment.	It is reasonable to sustain medium vitamin D score in the elderly to maintain attention.

Hooshmand *et al*., 2014	Yes. It examined an association between 25OHD scores and cerebrospinal fluid biomarkers and brain volumes reflecting cognitive function.	Yes. A sample of 75 patients referred to the Memory Clinic at Karolinska University Hospital, Huddinge, Sweden was recruited.	Yes. Blood samples were measured for 25-OHD levels, and CSF scores were measured through amyloid $^{\beta}$ ($A^{\beta}1$-42), total tau and phosphorylated tau. Brain volumes were measured with brain imaging.	Yes. Analysis of variance and linear regression analysis determine the distribution of variables and measured their relationships respectively.	Yes. Age, gender, the season of blood draw and kidney function were considered.	Cannot say. There was no follow-up assessment.	Higher vitamin D scores were associated with higher levels of CSF and volumes of brain.	Yes. Results were presented as odd ratios with 95% confidence intervals.	Yes.	Yes. To the elderly aged 61 years and above.	Cannot say. They offer an insight into the proven association between 25-OHD scores and cognitive function.	Yes. When detecting a lowering in brain volumes and CSF values, it is relevant to prescribe vitamin D treatment.

Littlejohns *et al*., 2014	Yes. With the high incidence of dementia and Alzheimer's disease among the elderly, the authors associated the risk of these illnesses with the natural lowering of vitamin D concentrations.	Yes. The sample of 658 elderly ambulatory patients was retrieved from the US populationbased Cardiovascular Health Study between 1992-1993 and 1999.	Yes. Patient blood samples for 1992-1993 were examined with liquid chromatography-tandem mass spectrometry to determine levels of serum 25OHD.	Yes. The 5-6-year follow-up was assessed using National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and related Disorders Association criteria.	No. Cox proportional hazards model calculated multivariate-adjusted hazard ratios for dementia and Alzheimer's disease in severely deficient and deficient patients compared with non-deficient ones.	Yes. The mean follow-up was 5.6 years.	Out of 658 patients, 102 developed Alzheimer's disease, which prevailed in vitamin D-deficient patients.	The incidence of Alzheimer's disease in vitamin D-deficient patients was 2.22 compared with 1.69 in nondefinition patients.	Yes.	Yes. They are applicable to the general population of the elderly, who at high risk of dementia and Alzheimer's disease.	Yes. They are consistent with those of Latimer *et al*. (2014) and Landel *et al*. (2016).	It is relevant to preventing vitamin D decline to reduce the risk of dementia and Alzheimer's disease.

Miller *et al.*, 2015	Yes. The authors assumed an association between low vitamin D concentrations and brain structural abnormalities and cognitive decline.	Yes. The sample of 382 outpatient clinic patients was enrolled for baseline and follow-up assessments in Feb 2002 and Aug 2010.	Yes. Levels of 25-OHD were measured to distinguish patients with deficient, insufficient, adequate, and high concentration.	Yes. English and Spanish Neuropsychological Assessment Scales measured early follow-up cognitive function.	Yes. Participants' age, gender, body mass index, ethnicity, seasonal blood draw, apolipoprotein E4 genotype, and vascular risk were considered.	Yes. The follow-up was around 4.8 years and covered multiple factors.	Yes. Low Vitamin D scores were lower at baseline and follow-up assessments for participants defined with mild cognitive impairment. Ethnic minority groups appeared at higher risk of cognitive dysfunction because of low vitamin D score,	Results are statistically significant with p< .05	Yes.	Yes. To the elderly at an increased risk of cognitive impairment.	Yes. They echo the findings of Latimer *et al*. (2014) and Landel *et al*. (2016).	The proven association suggests the need for sustaining vitamin D scores in the elderly.
Tofanello *et al*., 2014	Yes. It tested the assumed association between vitamin D deficiency	Yes. As a part of the *Progetto Veneto Anziani* populationbased cohort	Yes. Plasma 25-OHD were measured at baseline along with global cognitive function	Yes. MMSE scores at baseline and follow-up were compared between patients with 25-OHD	Yes. The analytical model was adjusted to measure health and	Yes. The mean follow-up was 4.4 years.	Results indicate a positive association between 25-OHD score	Yes. They are statistically significant with p<.05.	Yes.	Yes. They are applicable to the population of adults aged 73	Yes. They support the arguments of Latimer	Monitoring of vitamin D levels in the elderly is likely to predict cognitive

	and an increased risk of cognitive decline.	study, this research recruited a sample of 1,927 older adults.	measured with the MiniMental State Examination.	deficiency/insufficiency and adequacy.	performance status.		lower than 75 nmol/L and global cognitive dysfunction at 4.4 years.			years and above.	*et al*. (2014) and Landel *et al*. (2016).	decline and perform early diagnosis of neurocognitive illness.

Appendix C CASP Appraisal for Systematic Reviews

Article title	Did the review address a clearly focussed issue?	Did the authors look for the appropriate sort of papers?	Do you think the important, relevant studies were included?	Did the review's authors do enough to assess the quality of the included studies?	If the results of the review have been combined, was it reasonable to do so?	What is the overall result of the review?	How precise are the results?	Can the results be applied to the local population?	Were all the important outcomes considered?	Are the benefits worth the harms and costs?

Annweiler, Llewellyn and Beauchet, 2013	Yes. It explored the existing body of knowledge regarding an association between vitamin D and cognitive function in the elderly.	Yes. They searched Medline and PsycINFO databases for peerreviewed scholarly articles.	Yes. Out of 284 obtained studies, ten were included in the review (nine casecontrol and one cohort study).	Yes. The quality of papers was assessed regardless of the publication date.	Yes. Data from seven case-control studies were subject to fixed and random-effects metaanalyses of biascorrected effect size of the disparity in 25 OHD levels between AD cases and controls through an inversevariance method.	25-OHD scores were lower in AD cases compared to controls.	Results are statistically significant with $p<.05$.	Yes. They are relevant to the elderly, predominantly females.	Vitamin D scores can serve as a biomarker of AD.	Yes. The association between lower 25OHD levels and AD cases was confirmed.