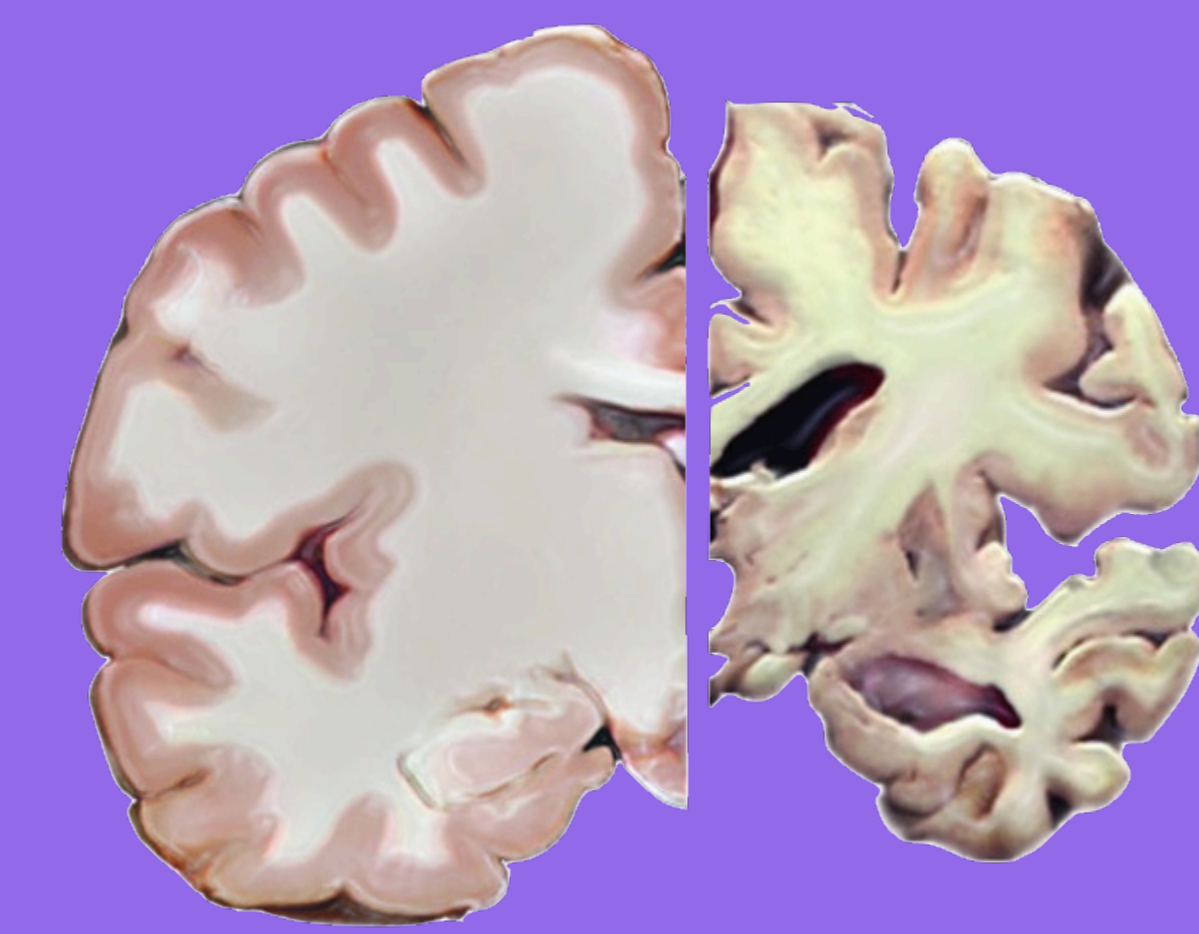


Is Vitamin D Deficiency Associated with an Increased Risk of Alzheimer's Disease in the Elderly?

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ABSTRACT

Background: Alzheimer's Disease is the most prevalent neurodegenerative disease amongst the elderly, affecting 6% of individuals aged 65 years and older, and it also causes inevitable psychological and physical dependency. Symptoms progress slowly and include impairment of memory and executive function, speech and comprehension difficulties, as well as psychological symptoms such as hallucinations, delusion, and depression. Although the exact causes of AD are currently unknown, research has shown that both genetic and environmental factors, including diet, play a role. Specifically, there has been a greater interest in whether vitamin D deficiency increases the risk of developing Alzheimer's disease in the elderly population. Processes that are affected in Alzheimer's include calcium homeostasis, neurotransmission, $\alpha\beta$ and tau protein accumulation, oxidative stress, and inflammation, which are all influenced by vitamin D levels.

Objective: To evaluate the association between vitamin D deficiency and the risk of developing Alzheimer's disease in the elderly.

Methods: A structured literature review was conducted using the PubMed and Scopus databases. Relevant studies were obtained using the following keywords: "Alzheimer's Disease", "vitamin D", "deficiency", "dementia", and "elderly". Only peer-reviewed articles published within the last 15 years were used.

Results: The keyword searches identified 43 potentially relevant reports, which were screened against the exclusion criteria to obtain the 8 articles which were analyzed, including 4 meta-analyses.

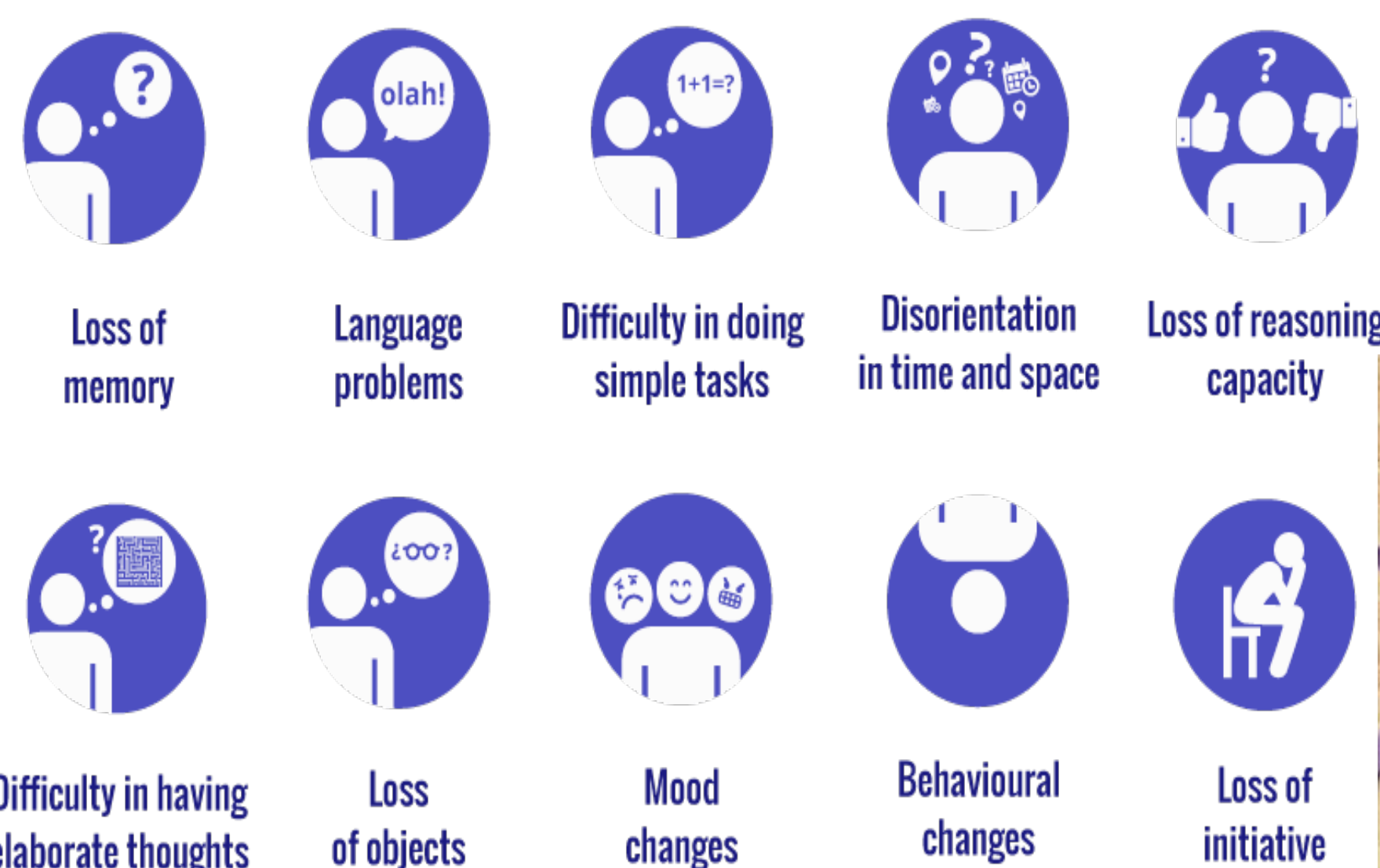
Conclusion: The evidence strongly supported an association between vitamin D deficiency and an increased risk of developing Alzheimer's disease, in individuals aged 65 years and over. Further research is required to confirm the relationship and assess the potential advantages of vitamin D supplementation in reducing the risk of developing Alzheimer's disease.

OBJECTIVE

To evaluate the association between vitamin D deficiency and the risk of developing Alzheimer's disease in the elderly.

BACKGROUND

Dementia is an umbrella term that encompasses several brain diseases that cause a decline in cognitive function and disruption to everyday life. Currently, 47.5 million people worldwide suffer from dementia, with Alzheimer's disease (AD) accounting for 60-70% of cases [9]. Alzheimer's Disease is the most prevalent neurodegenerative disease amongst the elderly, affecting 6% of individuals aged 65 years and older, and causes inevitable psychological and physical dependency [10]. The pathogenesis of the disease involves the proliferation of neurofibrillary tangles and amyloid plaques in the brain, which are two abnormal protein structures [11].



Psychological symptoms

- Personality changes
- Hallucinations
- Delusions
- Confusion
- Depression
- Aggression

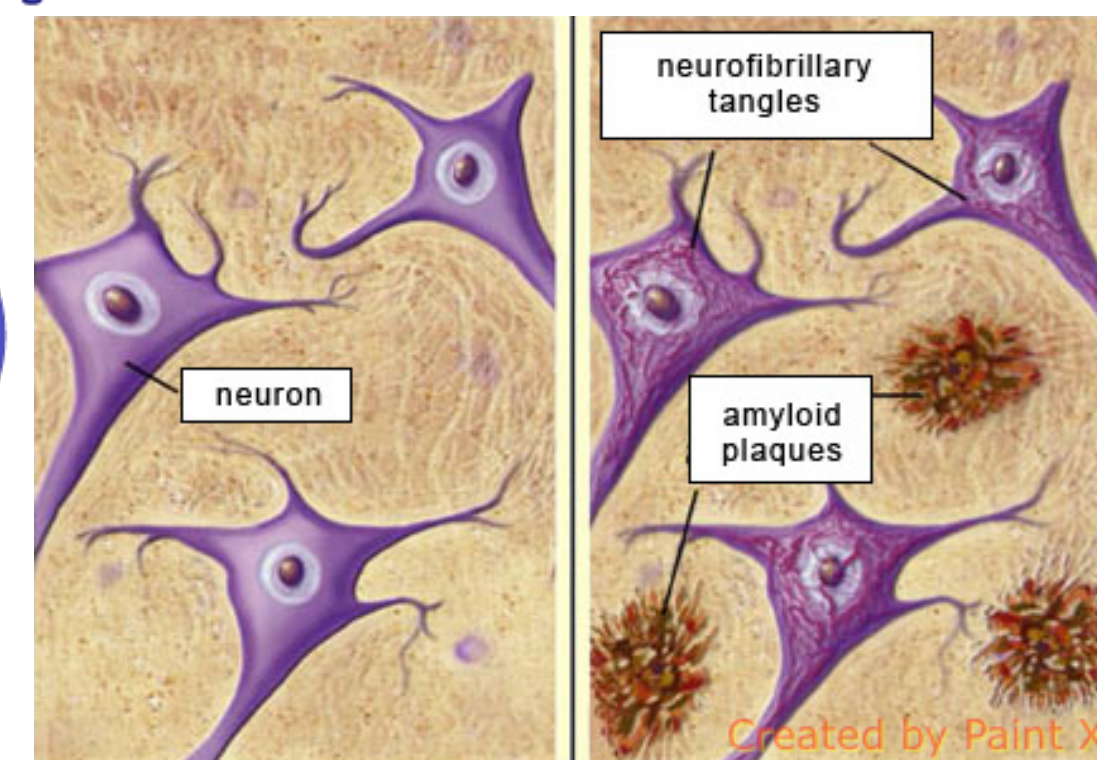


Figure 2. Normal brain vs. Alzheimer's brain

Although the exact causes of AD are currently unknown, research has shown that both genetic and environmental factors, including diet, play a role. Specifically, there has been a greater interest about whether vitamin D deficiency increases the risk of developing Alzheimer's disease in the elderly population. Vitamin D has been found to play an important role in the brain, by stimulating macrophages to increase the phagocytic removal of amyloid plaques [2], which is one of the hallmarks of Alzheimer's disease. Vitamin D is also beneficial through its actions in vasculoprotection, the preservation of neurons [13], and the regulation of nerve growth factor (NGF), choline acetyltransferase, and neurotrophin production - which are all neuroprotective substances [7]. Furthermore, Vitamin D levels influence calcium homeostasis, neurotransmission, $\alpha\beta$ and tau protein accumulation, oxidative stress, and inflammation, which are some of the affected processes in Alzheimer's disease [7]. Therefore, deficiency in this vital substance has been linked to a higher prevalence of Alzheimer's disease in the elderly.

METHODS

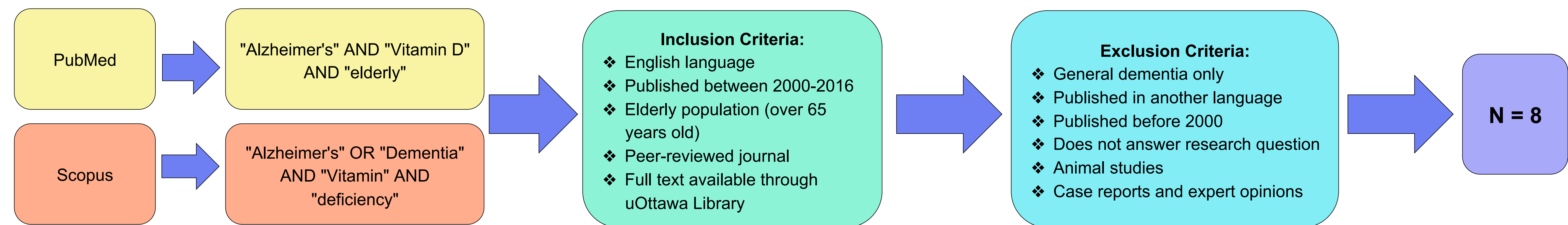


Figure 3. Methodology of the structured literature review of the association between Alzheimer's disease and vitamin D deficiency in the elderly

RESULTS

Table 1. Results of the structured literature review of the association between Alzheimer's disease and vitamin D deficiency in the elderly

Study	Population	Methodology & Design	Findings
Shen et al. (2015) ¹	• 5 study populations from 3 studies • n = 10,019 • Mean age 73.6 years	• PRISMA guidelines • MEDLINE database	• Subjects with deficient vitamin D status were at increased risk of developing AD, compared to those with 25(OH)D level > 50 nmol/L • Overall OR = 1.21, 95% CI 1.01 to 1.40, I ² = 0.0% (no significant heterogeneity)
Littlejohns et al. (2014) ²	• 1658 elderly US residents • Mean age 73.6 years • Participants of the "Cardiovascular Health Study" • Free of dementia, CVD, and any history of heart attacks or stroke	• Determined serum 25 hydroxyvitamin D (25(OH)D) concentrations in 1992-1993 • Assessed AD status at follow up in 1998-1999 • Cox proportional hazards models used to assess the association	• 102 participants had developed AD at follow up • Compared with participants who had sufficient 25(OH)D concentrations, the hazard ratio for AD was 2.22 in participants who were severely deficient, and the hazard ratio was 1.69 in those who were deficient • Vitamin D may be neuroprotective against AD • "Sufficiency" is 50 nmol/L, in the context of dementia risk
Afzal et al. (2014) ³	• 10 186 white individuals, Danish population • Free of any dementia diagnosis at baseline	• Plasma samples of 25(OH)D collected at baseline in 1981-1983 • AD diagnoses collected from the national Danish patient registry • Cox proportional hazards regression	• 418 cases of AD during 30 years of follow-up • Adjusted hazard ratios for AD increased as levels of 25(OH)D decreased • Association between reduced plasma 25(OH)D levels and an increased risk of AD
Zhao et al. (2013) ⁴	• 6 studies • 319 patients and 573 controls total • Mean age of each study population at least 66.4 years	• MEDLINE database, literature search from 1983 to 2012 • Only used papers showing comparative analyses of individuals with AD against healthy populations	• Patients with AD had lower levels of 25(OH)D, as compared to healthy controls • Summary standardized mean difference of -1.39, 95% CI -2.79 to 0.01 • Six study results showed statistically significant heterogeneity
Buell et al. (2010) ⁵	• 318 elders receiving home care • Participants of the Nutrition and Memory in Elders (NAME) study • Mean age 73.5 years	• Phlebotomy (fasting blood sample analyzed for 25(OH)D concentration) • Dementia classification by a team of neurologic exam + MRI • Logistic regression used to examine associations between AD and 25(OH)D concentration	• 25(OH)D concentrations deficient (<10ng/mL) in 14.5% and insufficient (10-20 ng/mL) in 44.3% of participants • 25(OH)D insufficiency was associated with more than twice the risk of all-cause dementia (AD, stroke with dementia, and other) after adjusting for confounders • 25(OH)D deficiency was associated with a higher prevalence of AD (17.4% vs 6.9%, p < 0.01)
Annweiler et al. (2012) ⁶	• 498 community-dwelling women • Mean age 79.8 years • From the EPIDemiology of Osteoporosis Toulouse cohort study • Free of vitamin D supplements	• Self-report questionnaires used to estimate baseline dietary vitamin D intakes • 4 to 7 year follow-up • Cognitive status assessed using Mini-Mental Status Examination at the 7th year of follow-up • Two logistic regression models used to examine association	• 14.1% of participants had AD at follow-up • Subjects who developed AD had lower baseline vitamin D intakes than women who did not develop AD • Higher vitamin D dietary intake was associated with a lower risk of developing AD among older women • Dietary intake of vitamin D was inversely associated with the onset of AD (OR = 0.99, 95% CI 0.98 to 0.99) • The highest consumption of dietary vitamin D was associated with a decreased incidence of AD by 4.35 times.
Balton et al. (2012) ⁷	• 37 studies (21 cross-sectional, 10 case-control, 1 before-after with comparison group, 2 prospective cohort, and 3 RCTs) • 30 studies included only elderly participants (65+ years)	• Medline, Embase, Amed, PsycINFO and Cochrane Central databases • Any published English-language study examining relationship between vitamin D and cognition • Used random-effects models for the weighted mean difference and Hedge's g	• Individuals with AD had lower 25(OH)D concentrations compared to those without AD • Mini Mental State Examination scores were lower in individuals with lower 25(OH)D concentrations • Lower vitamin D concentrations are associated with poorer cognitive function and a higher risk of AD
Annweiler et al. (2012) ⁸	• 10 observational studies (9 case-controls, 1 cohort)	• MEDLINE and PsycINFO databases, no date or language restriction for literature search • Serum concentration of 25(OH)D used as the indicator for Vitamin D status • Determined effect size of the difference between 25(OH)D concentrations in cases vs. controls	• 6 out of 9 case-control studies found that AD cases had significantly lower levels of serum vitamin D concentrations, compared to controls • One study found a decreasing trend of 25(OH)D concentrations among severe AD cases, as compared to mild AD cases • Cross-sectional analysis showed a higher prevalence of AD among participants with serum 25(OH)D < 10ng/mL, as compared to subjects with 25(OH)D > 20ng/mL

DISCUSSION

Key Findings

- Deficiency in 25(OH)D serum concentration is associated with a higher prevalence of Alzheimer's disease.
- Vitamin D sufficiency is suggested to be 50nmol/L, in the context of dementia risk.
- Higher vitamin D intake is inversely associated with the onset of Alzheimer's disease.

Limitations

- **Confounding variables** (gender differences in AD incidence, skin pigmentation, anti-AD drugs, genetic factors, amount of sunlight exposure, older age, lifestyle factors) → overestimation of association
- Cannot assume **causality** → individuals with AD are less likely to spend time outdoors and more likely to have poor nutrition → lower vitamin D levels
- **Misclassification bias** → measurement of vitamin D status is not consistent between all of the chosen studies
- **Confirmation bias** → searched for data to confirm the association rather than disprove it
- **Foreign language exclusion bias, rhetoric bias, ease of access**

Considering that AD is a multifactorial disease, it is not surprising that dietary factors may play a role in its development, particularly vitamin D deficiencies.

Future research should investigate:

- Potential advantages of vitamin D supplementation in reducing the risk of developing Alzheimer's disease in healthy individuals, as well as in slowing the progression in diagnosed individuals
- Benefits of vitamin D administration as part of a treatment plan
- Other dietary factors that may interact with vitamin D deficiency to further exacerbate the disease

CONCLUSION

Results of the structured literature review, n = 8, showed that there is an association between vitamin D deficiency and an increased risk of developing Alzheimer's disease amongst the elderly.

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REFERENCES

- Shen, L., & Ji, H.-F. (2015). Vitamin D deficiency is associated with increased risk of Alzheimer's disease and dementia: evidence from meta-analysis. *Nutrition Journal*, 14, 76. Doi: 10.1186/s12937-015-0063-7
- Littlejohns, T. J., Henley, W. E., Lang, I. A., Annweiler, C., Beuchet, O., Chaves, P. H. M., ... Llewellyn, D. J. (2014). Vitamin D and the risk of dementia and Alzheimer disease. *Neurology*, 83(10), 920-928. Doi: 10.1212/WNL.0000000000000755
- Zhao, Y., Bogaesen, S. E., Nordestgaard, B. G. (2014). Reduced 25-hydroxyvitamin D and risk of Alzheimer's disease and vascular dementia. *Alzheimer's & Dementia*, 10(3), 296-302. Doi: 10.1016/j.jalz.2013.05.1785
- Zhao, Y., Sun, Y., Ji, H. F., Shen, L. (2013). Vitamin D levels in Alzheimer's and Parkinson's diseases: A meta-analysis. *Nutrition*, 29(6), 828-832. Doi: 10.1016/j.nut.2012.11.018
- Buell, J. S., Dawson-Hughes, B., Scott, T. M., Weiner, D. E., Dallal, G. E., Qui, W. Q., ... Tucker, K. L. (2010). 25-Hydroxyvitamin D, dementia, and cerebrovascular pathology in elders receiving home services. *Neurology*, 74(1), 18-26. Doi: 10.1212/WNL.0b013e3181b0c6c7
- Annweiler, C., Roland, Y., Schott, A. M., Blain, H., Vellet, B., Herrmann, F. R., Beuchet, O. (2012). Higher Vitamin D Dietary Intake is Associated With Lower Risk of Alzheimer's Disease: A 7-Year Follow-up. *Journals of Gerontology*, 67(11), 1205-1211. Doi: 10.1093/geronj/gls107
- Balton, C., Griffith, L. E., Stricker, L., Henderson, M., Patterson, C., Heckman, G., ... Raina, P. (2012). Vitamin D, cognition, and dementia: A systematic review and meta-analysis. *Neurology*, 79(13), 1397-1405. Doi: 10.1212/WNL.0b013e31821926c197f
- Annweiler, C., Llewellyn, D. J., Beuchet, O. (2013). Low Serum Vitamin D Concentrations in Alzheimer's Disease: A Systematic Review and Meta-Analysis. *Journal of Alzheimer's Disease*, 33(3), 659-674. doi: 10.3233/JAD-2012-121432
- World Health Organization. (2016, April). Dementia. Retrieved from <http://www.who.int/mediacentre/factsheets/fs362/en/>
- Solfrizzi, V., Capurso, C., D'Itrono, A., Colacicco, A., Santamato, A., Ranieri, M., Fiore, P., Capurso, A., & Panza, F. (2008). Lifestyle-related factors in pre-dementia and dementia syndromes. *Expert Review of Neurotherapeutics*, 8(1), 133-58. doi: 10.1586/14737175.8.1.133
- Hasegawa, M. (2016). Molecular Mechanisms in the Pathogenesis of Alzheimer's disease and Tauopathies-Prion-Like Seeded Aggregation and Phosphorylation. *Biomolecules*, 6(2), 24. Doi: 10.3390/biom602024
- Sampson, E. (2010). Palliative care for people with dementia. *British Medical Bulletin*, 96(1), 159-174. doi: 10.1093/bmb/ldq024
- Buell, J. S., & Dawson-Hughes, B. (2008). Vitamin D and Neurocognitive Dysfunction: Preventing "D"efine? *Molecular Aspects of Medicine*, 29(6), 415-422. Doi: 10.1016/j.mam.2008.05.001
- Alzheimer's disease [Digital image]. (2013). Retrieved from <https://iqr.nlm.nih.gov/condition/alzheimer-disease>
- Alzheimer's Disease: Definition, Causes, Symptoms and Treatment - Doctor's Advice [Digital image]. (2016). Retrieved from <http://www.doc-advice.com/alzheimers-disease>
- Amyloid Plaques and Neurofibrillary Tangles [Digital image]. (2016). Retrieved from <http://www.brightfocus.org/alzheimers/info/amyloid-Plaques-and-neurofibrillary-tangles>
- Mayer, M. J. [Weblog post] (2015). Alzheimer's Disease. Retrieved from <https://www.thermofisher.com/blog/thermofisher.com/alzheimers-disease-sulforaphane-inhibits-peptide-aggregation/>