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The role of vitamin D in reducing risk of Alzheimer’s disease

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**Abstract**

**Introduction**

Alzheimer’s disease (AD) is a progressive neurodegenerative disease characterized by the accumulation of amyloid β in the form of extracellular plaques and by intracellular neurofibriliary tangles, with eventual neurodegeneration and dementia (Kunkle, Grenier-Boley et al. 2019).

In the U.S., approximately 6.08 million Americans had either clinical AD or [mild cognitive impairment](https://www.sciencedirect.com/topics/medicine-and-dentistry/mild-cognitive-impairment" \o "Learn more about mild cognitive impairment from ScienceDirect's AI-generated Topic Pages) due to AD in 2017 and that will grow to 15.0 million by 2060. In 2017, 46.7 million Americans had preclinical AD (amyloidosis, [neurodegeneration](https://www.sciencedirect.com/topics/medicine-and-dentistry/neurodegeneration" \o "Learn more about neurodegeneration from ScienceDirect's AI-generated Topic Pages), or both), although many may not progress to clinical disease during their lifetimes. (Brookmeyer, Abdalla et al. 2018).

It is estimated that 1.73% of the population of the European Union countries have AD

https://www.alzheimer-europe.org/sites/default/files/alzheimer\_europe\_dementia\_in\_europe\_yearbook\_2019.pdf

AD rates increase rapidly with age above 70 years.

Table 4 – M ale age speci­ c prevalence rates of dementia in Europe Age Range Prevalence 60–64 0. 2 65–69 1 . 1 70–74 3 . 1 75–79 7 . 0 80–84 10 . 7 85–89 16 . 3 90+ 29 . 7 Table 5 – Female age speci­ c prevalence rates of dementia in Europe Age Range Prevalence 60–64 0. 9 65–69 1 . 5 70–74 3 . 4 75–79 8 . 9 80–84 13 . 1 85–89 24 . 9 90+ 44 . 8

Thus, given that AD is a debilitating disease affecting a sizable number of people and having a significant economic impact, it is worthwhile to try to find ways to reduce the risk of developing AD. One way, first proposed by the author in 1997, is to eat a diet that reduces risk (Grant 1997). However, that is not always possible due to cultural and economic constraints. Another way that is easier and much less expensive to implement is to raise serum 25-hydroxyvitamin D [25(OH)D] concentrations. This brief review presents the evidence that vitamin D reduces risk of AD and makes recommendations on its use.

**Method and materials**

The approach taken is to use Hill’s criteria for causality in a biological system as a framework to organize the evidence. In 1965, A.B. Hill outlined the criteria for causality in his President’s Address to the Royal Medical Society (Hill 1965). The criteria of most interest regarding vitamin D include strength of association, consistency, temporality, biological gradient, plausibility, coherence with known facts of the natural history and biology of the disease, experiment, and analogy. Hill’s criteria have been used to evaluate the evidence regarding vitamin D and several health outcomes including cancer (Grant 2009, Mohr, Gorham et al. 2012) and cardiovascular disease (Weyland, Grant et al. 2014).

Publications to include in this review were found through searchers of both Scholar.Google.com and Pubmed.gov. Search terms included Alzheimer’s disease, vitamin D, mechanisms, Mendelian randomization.

**Results**

Four of Hill’s criteria can be combined in the analysis: strength of association, biological gradient, consistency, and temporality since the studies used are primarily prospective observational studies. The fact that they are prospective rather than cross-sectional establishes temporality. The only caveat would be if serum 25(OH)D concentration was found to be a marker for another risk factor such as non-vitamin D effects of solar UVB exposure.

Observational studies satisfy these four criteria. Table 1 presents findings from observational studies for studies of incidence of AD and vascular dementia available by 2017 as determined by (Jayedi, Rashidy-Pour et al. 2019). In a recent review (Grant, Boucher et al. 2022), these results were plotted in order to estimate the 25(OH)D concentration-risk relationship in Figures 1 and 2. The assumption was made that each study represented the risk expressed as hazard ratio (HR) for the mean 25(OH)D concentration of the study. The study by Littlejohns (Littlejohns, Kos et al. 2016) was omitted from the graphs since it was an outlier from the relationships determined from the other studies. The plots suggest that vascular dementia has a stronger correlation with 25(OH)D concentration than does AD; also, that the optimal 25(OH)D concentration is greater than 30 ng/mL. It should be noted that the HRs determined in all of these studies very likely underestimate the effect of 25(OH)D concentration nearer to the time of incidence due to changes in 25(OH)D concentration with time. This effect has been discussed regarding all-cause mortality rate (Grant 2012) and cancer (Grant 2015).

Table 1. Data associated with the observational studies for AD and vascular dementia in the meta-analysis by Jayedi and colleagues (Jayedi, Rashidy-Pour et al. 2019).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Country** | **Mean 25(OH)D (ng/mL)** | **Follow-up (yrs)** | **Vascular Dementia, HR (95% CI)**  **for 10 ng/mL** | **Alzheimer’s, HR (95% CI) for 10 ng/mL** | **Author** |
| US | 12 | 5.6 | 0.57 (0.34*–*0.97) | 0.61 (0.41*–*0.93) | Littlejohns et al., (Littlejohns, Kos et al. 2016) |
| France | 14 | 11.4 | 0.60 (0.47*–*0.78) | 0.60 (0.47*–*0.78) | Feart et al., (Feart, Helmer et al. 2017) |
| Finland | 16 | 17.0 | 0.77 (0.62*–*0.92) |  | Knekt et al., (Knekt, Saaksjarvi et al. 2014) |
| Denmark | 16 | 21.0 |  | 0.91 (0.82*–*1.02) | Afzal et al., (Afzal, Brondum-Jacobsen et al. 2014) |
| Netherlands | 20 | 13.3 | 0.77 (0.63*–*0.95) | 0.73 (0.59*–*0.93) | Licher et al., (Licher, de Bruijn et al. 2017) |
| US | 22 | 16.6 | 0.93 (0.79*–*1.07) |  | Schneider et al., (Schneider, Lutsey et al. 2014) |
| US | 25 | 9.0 | 1.01 (0.88*–*1.14) | 1.09 (0.95*–*1.12) | Karakis et al., (Karakis, Pase et al. 2016) |
| Sweden | 28 | 12.0 | 1.04 (0.93*–*1.17) | 0.95 (0.81*–*1.12) | Olsson et al., (Olsson, Byberg et al. 2017) |

Abbreviations: 95% CI, 95% confidence interval; 25(OH)D, 25‑hydroxyvitamin D; HR, hazard ratio.

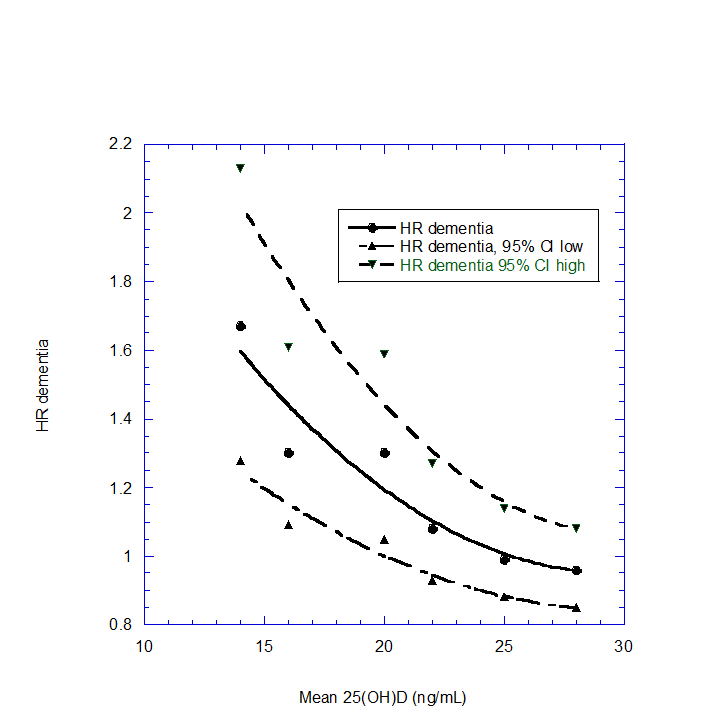
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Figure 1. Hazard ratio (HR; mean and 95% confidence interval [CI]) for dementia versus mean 25‑hydroxyvitamin D [25(OH)D] concentration seven of the studies included in meta-analysis (Jayedi, Rashidy-Pour et al. 2019).

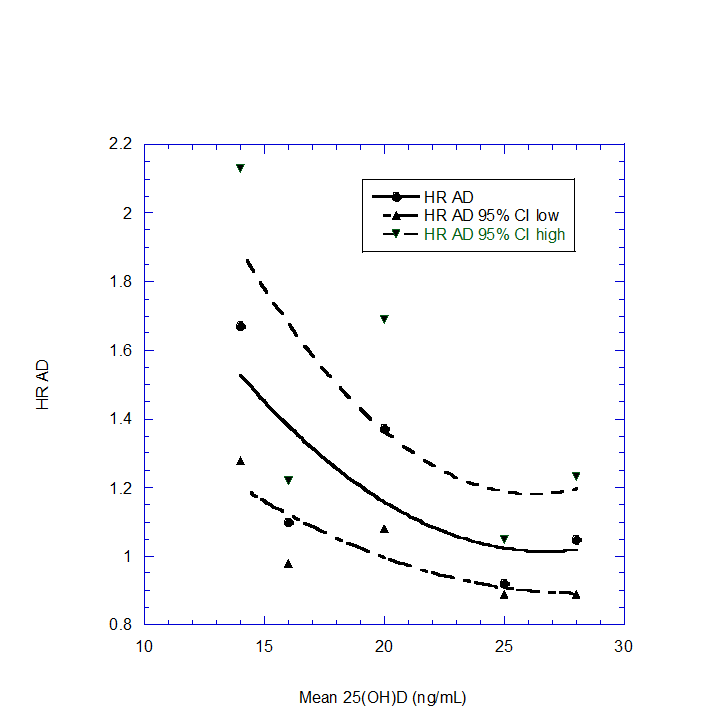


Figure 2. Hazard ratio (HR; mean and 95% confidence interval [CI]) for Alzheimer’s disease (AD) versus mean 25‑hydroxyvitamin D [25(OH)D] concentration for each of the seven studies included in meta-analysis (Jayedi, Rashidy-Pour et al. 2019).

**Mendelian randomization studies**

Mendelian randomization (MR) studies are now being used to evaluate whether vitamin D can be considered to affect health outcomes in a causal manner. In MR studies, data for alleles of genes involved in the vitamin D pathway are used to estimate genetic variations in serum 25(OH)D [genome-wide association studies (GWAS)] using perhaps 100,000 participants, and have then examined health outcomes with those gene variants in large study populations. The assumption is that, since individuals are randomized into study groups by the genetic variants they carry, bias due to confounding and reverse causation is avoided (Hyppönen, Vimaleswaran et al. 2022). Four MR studies found that genetically-predicted serum 25(OH)D concentrations were inversely correlated with AD (Mokry, Ross et al. 2016, Larsson, Traylor et al. 2018, Wang, Qiao et al. 2020, Meng, Wang et al. 2022) while one MR study found vitamin D-binding proteins inversely correlated with AD (Zhang, Wang et al. 2020). Two of the MR studies (Mokry, Ross et al. 2016, Larsson, Traylor et al. 2018) used GWAS data for vitamin D from the (the Study of Underlying Genetic Determinants of Vitamin D and Highly Related Traits [SUNLIGHT] Consortium (Wang, Zhang et al. 2010) Given these important advantages, we elected to perform an MR study using SNPs from the largest genome-wide association study (GWAS) for vitamin D (the Study of Underlying Genetic Determinants of Vitamin D and Highly Related Traits [SUNLIGHT] Consortium; N 5 33,996) (Wang, Zhang et al. 2010) and summary statistics from the largest GWAS to date for AD (the International Genomics of Alzheimer’s Project [IGAP]; N 5 17,008 AD cases and 37,154 controls) (Lambert, Ibrahim-Verbaas et al. 2013). One used data from IGAP and the UK Biobank (Wang, Qiao et al. 2020), while one from China used data from two vitamin D GWAS (Meng, Wang et al. 2022)

Coherence: cause-effect relationship should not seriously conflict with the known facts of the natural history and biology of the disease

**Experiment**

There have been both human and animal experiments to evaluate the effect of vitamin D on risk of AD. A clinical study conducted in the U.S. with nine AD patients and three controls examined the effect of 1,25-dihydroxyvitmin D [1,25(OH)2D3] on clearance of amyloid-beta (Masoumi, Goldenson et al. 2009). Accumulation of amyloid-beta in the brain results in amyloidosis, a hallmark of AD. 1,25(OH)2D3 was found to strongly stimulate amyloid-betaphagocytosis (ingestion by phagocytes) and clearance through the genomic pathway, thus demonstrating that an important function of vitamin D in reducing risk of AD is reducing risk of amyloidosis.

Cognitive impairment can be an early indicator of risk for AD. An RCT was conducted in China to see whether supplementation with 800 IU/day vitamin D3 could improve cognitive function of participants with mild cognitive impairment (Yang, Wang et al. 2020) As explained in the article, telomeres are DNA-protein structures located at 57 the ends of linear eukaryotic chromosomes that pro58 tect chromosomal ends from DNA damage (Aubert and Lansdorp 2008). 59 Studies have discovered telomere length (TL) might 60 be a critical factor in predicting the rate of mild cognitive impairment or AD progression (Scarabino, Broggio et al. 2017). Thus, a potential beneficial 62 method for improving cognitive function is to maintain or enhance TL to protect neurons. The further biochemical reaction is oxidative stress (OS). Ninety participants were in each of the vitamin D treatment and placebo groups. Mean 25(OH)D concentration in each group was near 19 ng/mL at baseline, increasing to 23 ng/mL after 12 months in the treatment group. Telomere length increased from 1.42±24 to 1.60±0.24 in the treatment group while remaining unchanged in the placebo group. A measure of OS decreased by 15% in the treatment group but was unchanged in the placebo group.

However, most vitamin D RCTs regarding risk of cognitive impairment or AD have not found beneficial effects (Sultan, Taimuri et al. 2020). This review suggested that there were many limitations of such RCTs including small sample size, lack of consensus over vitamin D dose, and age of initiation of vitamin D supplementation to prevent cognitive impairment. In addition, most vitamin D RCTs reported to date have not found beneficial effects of vitamin D in preventing or treating disease due to poor design, conduct, and analysis of results (Grant, Boucher et al. 2022). Vitamin D RCTs should be based on the guidelines for nutrients as proposed by Heaney (Heaney 2014) and based on 25(OH)D concentrations rather that vitamin D dose. Thus, lack of positive results from most vitamin D RCTs regarding cognitive impairment or AD should not be considered as evidence that vitamin D supplementation would not be beneficial. “Absence of evidence is not evidence or absence.”

Animal models are also very useful for experiments on vitamin D effects on AD. Mouse and rat models are frequently used since laboratory strains have been developed with AD-related genes and can develop AD symptoms rapidly. A brief overview of mouse model studies of vitamin D and AD is given in a recent paper (Morello, Landel et al. 2018). That article also presented results of their mouse model studies of neurogenesis and cognition related to vitamin D supplementation. Improved working memory and neurogenesis were observed when high vitamin D supplementation was administered during the early phases of the disease, while a normal dose of vitamin D increased neurogenesis during the late phases. Conversely, an early hypovitaminosis D increased the number of amyloid plaques in AD mice while a late hypovitaminosis D impaired neurogenesis in AD and wild type mice.

A rat model study showed that vitamin D supplementation improves the impaired amyloid-beta induced memory and that, by acting as a strong antioxidant, it can attenuate the stress oxidative biomarkers in hippocampus and serum of rats with AD (Mehri, Haddadi et al. 2020).

Interestingly, an observational study conducted in Taiwan reported that vitamin D supplementation worsens AD progression (Lai, Hsu et al. 2022). However, it was not vitamin D supplementation but, rather calcitriol (1,25-(OH)2D3] supplementation, for which data on prescription used is maintained in a national database. However, as Vieth pointed out, calcitriol is not vitamin D but, instead, a hormone, and is largely used for treatment of impaired kidney ability to convert 25(OH)D to calcitriol (Vieth 2022).

Analogy

Other diseases related to vitamin D deficiency were listed in a review regarding vitamin D and AD in 2009 (Grant 2009). By that time, observational studies found that 25(OH)D had been associated with increased risk for cardiovascular diseases, diabetes mellitus, depression, dental caries, osteoporosis, and periodontal disease, all of which are either considered risk factors for dementia or have preceded incidence of dementia. Of course the list is much longer now.

Summary

Evidence regarding vitamin D satisfies the criteria for causality in a biological system for reducing risk of cognitive function, AD, and vascular dementia. Thus, vitamin D supplementation can be recommended as an additional way to reduces risk of these diseases. It should also be useful for reducing the rate of progression of these diseases. It is unlikely that vitamin D supplementation is of much use for treating advanced stages of these diseases, although it would be useful in reducing risk of other vitamin D-sensitive adverse health outcomes.

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