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

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Abstract
Alzheimer's disease (AD) is a devastating disease that affects many elderly people. Observational studies and Mendelian randomization analyses find that higher 25-hydroxyvitamin D [25(OH)D] concentrations are causally associated with lower risk of developing AD as well as dementia in general. The mechanisms identified include reduced brain aging, cellular senescence, mitochondrial dysfunction and oxidative stress as well as higher high-density lipoprotein. Analyses of observational study findings indicate that serum 25(OH)D concentrations above 30 ng/mL (75 nmol/L) reduce the risk of AD and dementia by 40±20% for dementia and 30±15% for AD compared to 25(OH)D = 12 ng/mL (30 nmol/L).

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 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, 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 has AD https://www.alzheimer-europe.org/sites/default/files/alzheimer_europe_dementia_in_europe_yearbook_2019.pdf

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 for brain health 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) (reproduced from (Grant, Boucher et al. 2022).

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.

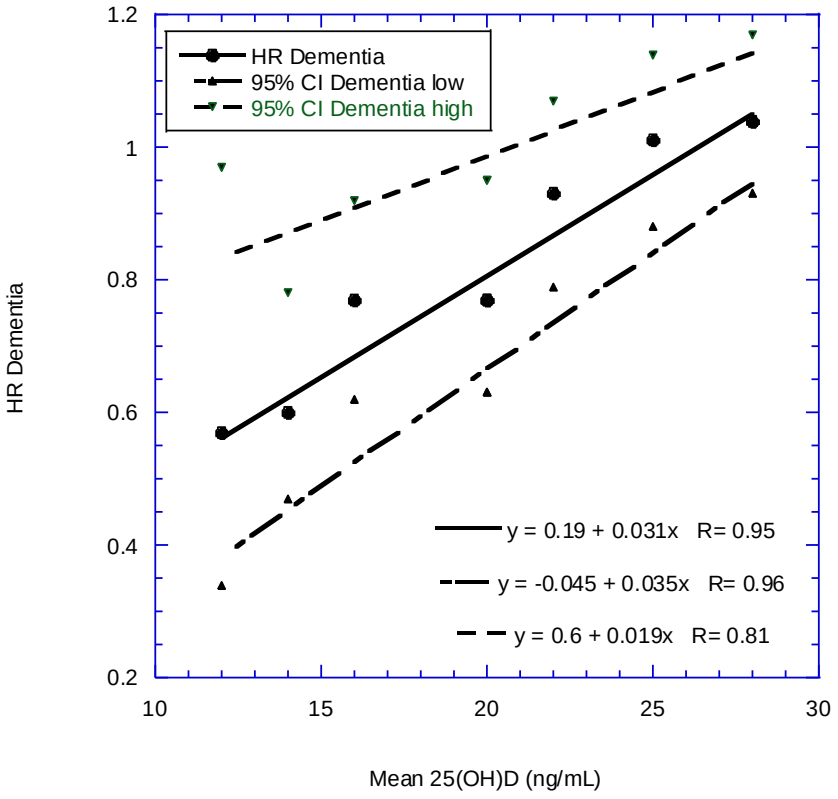

Figure 1. Hazard ratio (HR; mean and 95% confidence interval [CI]) for dementia versus mean 25-hydroxyvitamin D [25(OH)D] concentration seven of the studies included in meta-analysis (Jayedi, Rashidy-Pour et al. 2019) (reproduced from (Grant, Boucher et al. 2022).

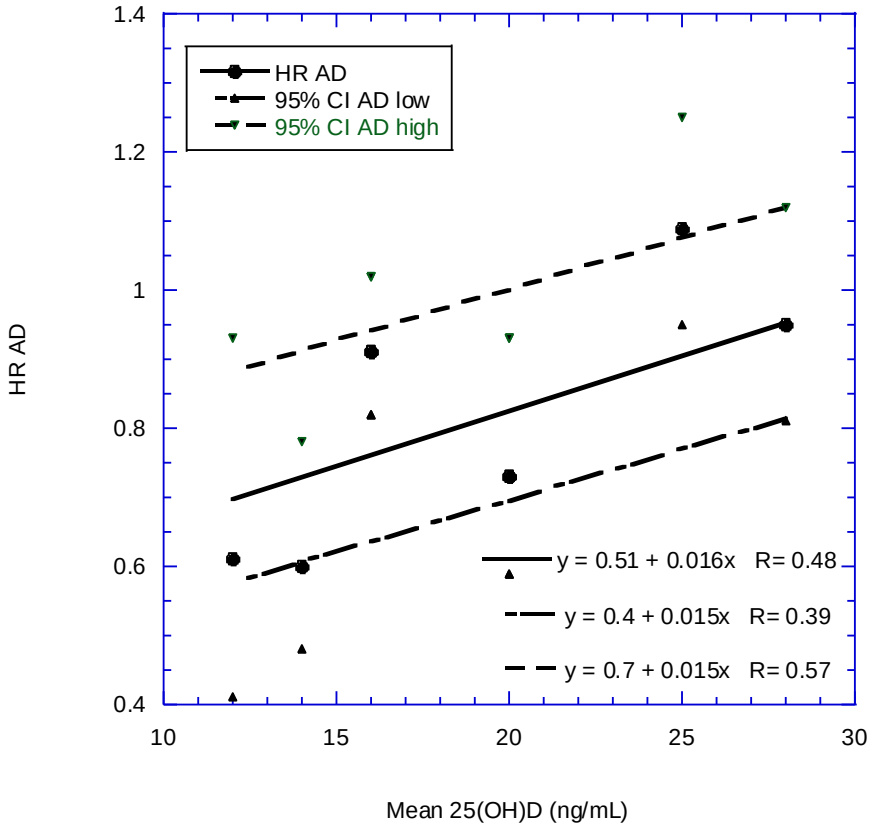

Figure 2. Hazard ratio (HR; mean and 95% confidence interval [CI]) for Alzheimer's disease (AD) versus mean 25-hydroxyvitamin D [25(OH)D] concentration for each of the seven studies included in meta-analysis (Jayedi, Rashidy-Pour et al. 2019) (Grant, Boucher et al. 2022).

A recent observational study was published regarding the associations between serum 25(OH)D_3 concentrations and cognitive decline (Shea, Barger et al. 2022). Data for 289 participants enrolled in the Rush Memory and Aging Project free of known dementia at time of enrollment were included. Annual diagnoses of cognitive function as well as brain autopsies were used to classify participants as dementia, mild cognitive impairment, or no cognitive impairment. The mean age of death was 92 years (SD, 6 years). The odds of having dementia or MCI at the last cognitive assessment before death were 25% to 33% lower per doubling of 25(OH)D_3 in the four brain regions measured (Table 2 in that article) (OR 0.67 to 0.75, all p's $\leq$ 0.03). Higher brain 25(OH)D_3 concentrations in all regions were also associated with better ante-mortem global

cognitive function scores (all p's ≤ 0.03), and in the anterior watershed, was also associated with a slower rate of cognitive decline ($p = 0.04$) (Table 2 in that article).

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)] based on data from tens of thousands of participants. These findings are then used to assign genetically-predicted 25(OH)D concentrations to participants in large databases, such as the UK Biobank. 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). The health outcomes of interest are then compared statistically with the genetically-predicted 25(OH)D concentrations.

The first MR study to find that vitamin D was causally linked to AD was published in 2016 (Mokry, Ross et al. 2016). It used GWAS data from four single nucleotide polymorphisms (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 data on 17,008 clinically determined AD patients and 37,154 controls from the International Genomics of Alzheimer's Project [IGAP] (Lambert, Ibrahim-Verbaas et al. 2013). The MR analysis demonstrated that a 1-standard deviation decrease in natural log–transformed 25OHD increased AD risk by 25% (odds ratio 1.25, 95% confidence interval 1.03–1.51, p = 0.02). (A 1-standard deviation of 25(OH)D is approximately ten ng/mL.)

Another one used data from IGAP and the UK Biobank (Wang, Qiao et al. 2020). It was found that the MR analysis using IGAP data found significant inverse correlations between both genetically-determined and measured 25(OH)D concentrations with AD while neither 25(OH)D concentration was inversely correlated with AD in the UK Biobank dataset. The proposed reason was that the IGAP AD data were based on clinical diagnoses while the UK Biobank AD data were based on self-report AD-by-proxy related to family members.

An analysis of modifiable pathways in AD using MR analyses was published in 2017 (Larsson, Traylor et al. 2017). It used GWAS data from many data sets and AD data from IGAP. The odds ratio for each factor was calculated independently of the others. Factors found significantly associated with reduced risk of AD were years of education, college/university, intelligence, smoking quantity and a 20% increase of 25(OH)D concentration [OR = 0.92 (95% CI, 0.85-0.98), p = 0.01], while coffee consumption was associated with increased risk.

MR studies have also examined whether 25(OH)D concentration is causally linked to serum lipid concentrations. One such study was conducted in Norway involving 56,435 adults and three vitamin D-increasing alleles (Mai, Videm et al. 2019). It found that a genetically-determined 10 ng/mL increase in 25(OH)D concentration was associated with a 2.5% (95% CI, 0.8 to 4.3%) increase in high-density cholesterol. The analyses for other cholesterol concentrations were not significant.

Mechanisms for development of Alzheimer's disease
Several mechanisms have been identified that support the development of AD. They are listed here, along with evidence that vitamin D reduces the magnitude of the effect.

Brain aging (Swerdlow, Burns et al. 2014)
Cellular senescence (Sikora, Bielak-Zmijewska et al. 2021)
Low HDL (Mai, Videm et al. 2019)
Mitochondrial dysfunction (Swerdlow, Burns et al. 2014, Wang, Wang et al. 2014, Weidling and Swerdlow 2019)
Oxidative stress (Tonnies and Trushina 2017)

Vitamin D affects the mechanisms causally linked to development of AD
Brain aging (Terock, Bonk et al. 2022)
Cellular senescence (Sosa-Diaz, Hernandez-Cruz et al. 2022)
Low HDL (Mai, Videm et al. 2019)
Mitochondrial dysfunction (Wimalawansa 2019)
Oxidative stress (Wimalawansa 2019, Mehri, Haddadi et al. 2020), (Mehrabadi and Sadr 2020, Bivona, Lo Sasso et al. 2021)

Thus, these studies satisfy this Hill criterion:
Coherence: cause-effect relationship should not seriously conflict with the known facts of the natural history and biology of the disease.

Experiment
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 D_3 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 the ends of linear eukaryotic chromosomes that protect chromosomal ends from DNA damage (Aubert and Lansdorp 2008). Studies have discovered telomere length (TL) might be a critical factor in predicting the rate of mild cognitive impairment or AD progression (Scarabino, Broggio et al. 2017). Thus, a potential beneficial 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 nutrient studies 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 the 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-$(OH)_2D_3$] 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 as well as stronger, such as for cardiovascular disease (Weyland, Grant et al. 2014, Zhou, Selvanayagam et al. 2022)

Drs. Dursun and Gezen-Ak published a review of the evidence regarding vitamin D and AD in 2019 (Dursun and Gezen-Ak 2019). They considered evidence from several approaches. First was the genetic background. There were at least two important points. One is that many studies found genetic links between vitamin D receptor (VDR) genes to be highly correlated with AD and cognitive decline. A list of selected genetic studies was given in Table 1 of that review. The second was that genes for AD and the vitamin D pathway are linked evolutionary such that those with higher risk of late-onset AD have higher 25(OH)D concentrations if they also have the ApoE epsilon4 allele (Dursun, Alaylioglu et al. 2016). Next was pathological approach. One mechanism relates to amyloid beta clearance, but the evidence for this mechanism is not yet

clear. Then there is biochemistry and neurochemical approach. This topic includes the link between genes related to ApoE epsilon 4 and vitamin D pathway as well as correlations between serum 25(OH)D concentrations and cognitive impairment and AD. Table 1 in that review lists a number of such observational studies. Intervention studies have found some beneficial effect related to cognitive impairment and AD as listed in Table 1 of that review. Finally, the role of vitamin D in modifying the immune system was discussed in light of the fact that inflammation is a risk factor for AD.

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 reduce 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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