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Vitamin D, cognitive dysfunction and dementia in older adults

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Abstract

The physiologically active form of vitamin D, 1,25-dihydroxyvitamin D3, is a fat-soluble steroid hormone with a well established role in skeletal health. A growing body of evidence suggests that low vitamin D levels also play a role in the pathogenesis of a wide range of non-skeletal age-associated diseases such as cancer, heart disease, type 2 diabetes and stroke. Low serum 25-hydroxyvitamin D (25(OH)D) levels, a stable marker of vitamin D status, are also associated with increased odds of prevalent cognitive dysfunction, Alzheimer's and all-cause dementia in a number of studies, raising the possibility that vitamin D plays a role in the aetiology of cognitive dysfunction and dementia. So far the majority of human studies reporting associations between vitamin D and cognition or dementia have been cross-sectional or case-control designs that are unable to exclude the possibility that such associations are a result of disease progression rather than being causal. Animal and in-vitro experiments have identified a number of neuroprotective mechanisms that might link vitamin D status to cognitive dysfunction and dementia including vasoprotection and amyloid phagocytosis and clearance, but the clinical relevance of these mechanisms in humans is not currently clear. Two recent large prospective studies go some way to establish the temporal relationship with cognitive decline. The relative risk of cognitive decline was 60% higher (relative risk 1.60, 95% CI 1.2-2.0) in elderly Italian adults who are severely deficient (<25 nmol/L) when compared them with those sufficient (>75 nmol/L). Similarly the odds of cognitive decline were 41% higher (odds ratio 1.41, 95% CI 0.9-2.2) when elderly US men in the lowest quartile (<50 nmol/L) were compared with those in the highest quartile (>74 nmol/L). To our knowledge no prospective studies have examined the association between 25(OH)D levels and incident dementia or neuroimaging abnormalities. The possible therapeutic benefits of vitamin D have attracted considerable interest as over 1 billion people worldwide are

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thought to have insufficient 25(OH)D levels, which can be increased using inexpensive well-tolerated dietary supplements. However, no large randomized controlled trials have yet examined the effect of vitamin D supplements upon cognitive decline or incident dementia. Further studies are urgently needed to establish which mechanisms may have clinical relevance in human populations and whether vitamin D supplements are effective at minimizing cognitive decline or preventing dementia.

Introduction

The physiologically active form of vitamin D, 1,25-dihydroxyvitamin D3, is a fat-soluble steroid hormone with a well established role in skeletal health.[1, 2] Meta-analyses of randomized controlled trials suggest that vitamin D supplementation reduces the risk of fractures,[3] falls,[4] and mortality.[5] A growing body of evidence suggests that low vitamin D levels also play a role in the pathogenesis of a wide range of non-skeletal age-associated diseases such as various cancers,[6] type 2 diabetes,[7] cardiovascular disease,[8] hypertension[9] and stroke.[10] Low serum 25-hydroxyvitamin D (25(OH)D) levels, a stable marker of vitamin D status, are also associated with increased odds of prevalent cognitive dysfunction and dementia in a number of studies, raising the possibility that vitamin D plays a role in the aetiology of cognitive dysfunction, Alzheimer's disease and all-cause dementia.[11, 12]

In 2005 it was estimated that 24.3 million people worldwide were affected by dementia, and this was predicted to rise to 81.1 million people by 2040.[13] The majority of people with dementia exhibit clinically significant neuropsychiatric symptoms, and in the later stages dementia results in total dependency, frailty and death.[14] The impact on families can be devastating and caregiving is associated with substantial psychological and physical morbidity.[15, 16] Drugs such as donepezil hydrochloride result in modest symptomatic improvements for some patients but do not modify the underlying disease processes and can have troubling side-effects.[17-19] Insufficient evidence currently exists to support the use of any medication or intervention for the primary prevention of dementia.[20] The identification of cost-effective well-tolerated disease modifying treatments that are effective at preventing or treating cognitive impairment and dementia would have a striking population impact given their high population prevalence.[21]

This review provides an overview of the emerging literature linking vitamin D status with cognitive dysfunction and dementia in older adults. Key findings, potential mechanisms and the limitations of existing studies are addressed, and recommendations are made for future research addressing key areas of uncertainty.

Vitamin D

Sources and metabolism

Vitamin D is a fat-soluble steroid prohormone produced in skin through UVB irradiation of 7-dehdrocholesterol, dietary sources such as oily fish, and dietary supplements.[22] Vitamin D is inert until it is metabolised in the liver to form 25-hydroxyvitamin D (25(OH)D) and

subsequently metabolised primarily in the kidneys, producing the physiologically active hormonal form of 1,25-dihydroxyvitamin D ($1,25(OH)_2D_3$). Once activated, $1,25(OH)_2$ D facilitates calcium and phosphorous absorption and regulates gene transcription through vitamin D receptors (VDR) that are present in many organs, including the brain.[2, 23]

Sunlight exposure

In most individuals more than 90% of serum vitamin D is produced by the skin in response to sunlight exposure, as dietary sources such as oily fish contain only modest amounts.[24, 25] At latitudes less than 37°, sunlight exposure for 5-15 minutes on the arms and legs between 10am and 3pm between spring and autumn is thought to be adequate to prevent vitamin D inadequacy with skin types II (strong tendency to burn and rarely tans) and III (sometimes burns, sometimes tans).[26] Sunlight exposure has often been discouraged due to concerns over skin cancer, and have prompted major public health and mass media campaigns such as those in Australia encouraging safe sunlight exposure.[27] However, the risks associated with excessive UVB radiation exposure may need to be balanced by the need for sensible sunlight exposure in order to maintain adequate vitamin D levels.[28] Reduced sunlight strength at latitudes further away from the equator, and reduced hours of sunlight in winter months, result in insignificant levels of cutaneous vitamin D production.[29, 30] In addition, certain population groups are less able to synthesize vitamin D from sunlight exposure. Homebound and older adults are at risk of Vitamin D deficiency due to minimal sunlight exposure [31] and the declining capacity of skin to produce vitamin D with age.[32, 33] Ethnic minority groups are also more likely to be vitamin deficient as a result of darker skin pigmentation,[34-36] as are those who cover their skin when outdoors.[37-39]

Definitions of vitamin D status and deficiency

Serum 25-hydroxyvitamin D (25(OH)D) levels are widely used as an indicator of vitamin D status as it provides a relatively stable and accurate indicator of bioavailability.[40] Serum 25(OH)D levels are either expressed as ng/mL or as nmol/L (to convert ng/mL to nmol/L multiply by 2.496).[41] Thresholds used to define vitamin D deficiency (hypovitaminosis D) are typically based upon traditional thresholds thought to be adequate to maintain skeletal health, and their relevance to non-skeletal diseases has yet to be fully established. A common cut-point to define deficiency is <50 nmol/L, although other cut-points used range from <25 nmol/L to <64 nmol/L.[22, 42] Definitions of insufficiency range from 25-50nmol/L[43] to 65-74nmol/L[42]. Sufficiency has been defined as >50nmol/L,[44, 45] although there is increasing consensus that serum 25(OH)D levels should be at least 75nmol/L for optimal health.[3, 22, 46] Some authors have also proposed a further distinction between deficiency (25-50 nmol/L) and severe deficiency (<25 nmol/L).[22, 47] While there is clear consensus regarding the use of 25(OH)D levels as an indicator of vitamin D status, it is also clear that the cut-points used to define deficiency and sufficiency remain disputed.

Population levels of vitamin D

Population-based studies of older adults in Europe and the US suggest that vitamin D deficiency is common although may vary by country of residence.[48, 49] For example, data from the nationally representative Health Survey for England (HSE) 2005 revealed a

substantial proportion of people aged 65 or above (n=2070) with serum 25(OH)D levels <50 nmol/L (men: 49%, women: 58%), and <25 nmol/L (men: 8%, women: 14%).[50] In the Netherlands, blood samples were collected from respondents aged 65 or above (n=1319) participating in the Longitudinal Aging Study Amsterdam (LASA).[51] In this sample, serum 25(OH) levels was <50 nmol/L in 48.4%, and <25 nmol/L in 11.5% of participants. US population-based data (n=5555 aged ≥50 years) from the National Health and Nutrition Examination Survey (NHANES) 2000-2004 showed approximately one quarter of males (50-69 years: 27%; ≥70 years: 27%) and a third of females (50-69 years: 36%; ≥70 years: 34%) had serum levels <50nmol/L.[52] The prevalence of 25(OH)D levels <25 nmol/L was low (50-69 years: 4%; ≥70 years: 4%). Levels of vitamin D deficiency appear to vary by country according to latitude, sunlight exposure, clothing habits, skin pigmentation, age, the fortification of staple foods such as milk, and the use of sun block and vitamin D supplements.[48, 49] Thus latitude is not the only factor in determining population vitamin D levels, and social, demographic and behavioural factors are also important. It is estimated that over 1 billion people worldwide are thought to have insufficient 25(OH)D levels (<75 nmol/L).[53]

Vitamin D intake and dietary supplementation

The Western diet does not protect from Vitamin D deficiency. On the contrary, reduced Vitamin D levels found in the rising numbers of morbidly obese subjects are thought to be primarily attributed to insufficient intake of micronutrients.[54] Whilst the association of 25(OH)D levels and body mass index is a consistent finding,[55] a study from Norway found that 1 in 3 women and 1 in 2 men with a BMI ≥40 were Vitamin D deficient.[56] Dietary supplements may be required for the maintenance of sufficient 25(OH)D levels, particularly those living at high latitudes (37°+) and high risk groups such as ethnic minority groups and older adults.[57, 58] Supplements containing 400 International Units (IU) are likely to result in a stable increase of serum 25(OH)D levels by 7 nmol/L.[59] The Institute of Medicine (IoM) recently updated their guidance and increased the recommended daily intake of vitamin D to 600 IU for those aged 1-70 years and 800 IU for those over 70 years of age, assuming minimal sunlight exposure.[60] Their guidance also stipulates a Tolerable Upper Intake Level (TUIL), the higher boundary of intake associated with no adverse events, of 4000 IU per day. The IoM recommendations are largely based on studies of skeletal health, in part because of the comparatively limited evidence for other health outcomes. Reviews that have also considered the existing evidence for non-skeletal health have proposed higher intake levels of 1000 IU/d and 2000 IU/d,[53, 61, 62] hence it is possible that IoM recommended daily intake levels are insufficient.[63] Future studies of non-skeletal diseases, including Alzheimer's disease and dementia, may therefore support the argument to further increase the recommended daily intake of vitamin D. The optimal dose of vitamin D in relation to cognitive outcomes is unknown, although supplements are inexpensive and well-tolerated.[64] Extremely high doses present a risk of vitamin D toxicity (hypervitaminosis D), which can cause hypertension and hypercalcemia. Some argue that the TUIL of 4000 IU/d is too low to allow supplementation at levels beneficial to public health.[65, 66] Authors of a review of 21 clinical trials of vitamin D supplementation proposed the TUIL be increased to 10000 IU/d on the basis that no adverse events had been reported in trials using this dose.[64] Total-body sun exposure quickly provides the

equivalent of 10000 IU/d, suggesting that this is a physiologic limit.[67] Hypervitaminosis has only been reported with serum 25(OH)D levels of >374nmol/L[22] and >500nmol/L, [68] levels that are considerably higher than those observed in study participants receiving 10000 IU/d (213 to 220 nmol/L).[64]

Neuroprotective properties of vitamin D

The hormonally active form of vitamin D, $1,25(OH)_2D_3$, is the key mediator of the vitamin D endocrine system which produces biological effects in over 50 tissues.[69] It is well established that vitamin D is involved in mammalian brain functioning, and vitamin D deficiency in mice impairs learning.[70, 71] An early study of Alzheimer's disease patients revealed the gene expression of VDR in humans.[72] It was subsequently confirmed that the VDR, and the enzyme responsible for formation of the active vitamin in the human brain, 1α-hydroxylase, are widespread in both neurons and glial cells within brain regions critical for cognition.[23, 73] Furthermore, recent evidence has revealed that gene variations of the VDR, such as Bsml, Taql polymorphisms, influence the likelihood of cognitive impairment. [74]

$1,25(OH)_2D_3$ strongly stimulates amyloid beta (Aβ; a hallmark pathological lesion in Alzheimer's disease) phagocytosis and clearance whilst protecting against apoptosis in the macrophages of patients with Alzheimer's disease.[75] In primary cortical neurons Aβ triggered neurodegeneration by dramatically suppressing VDR gene expression.[76] Administration of $1,25(OH)_2D_3$ to this model protected neurons by preventing cytotoxicity and apoptosis, and downregulating L-type voltage sensitive calcium channels A1C (LVSCC A1C) and upregulating VDR. $1,25(OH)_2D_3$ treatment protects against glucocorticoid-induced apoptosis in hippocampal cells, likely to represent a mechanism of vitamin D-mediated neuroprotection.[77] This may have important implications in disorders with dysregulated glucocorticoid signaling, including Alzheimer's disease.[78] Vitamin D upregulates the production of several neurotrophin factors, such as glial cell line derived neurotrophic factor (GDNF) and neurotrophin-3 (NT-3), which promote the survival, development and function of neurons.[79, 80] Chronic $1,25(OH)_2D_3$ treatment protects against the neurotoxicity of glutamate exposure by upregulating VDR gene expression in cultured rat cortical neurons.[81] Vitamin D also has direct antioxidant effects, for example, $1,25(OH)_2D_3$ prevents zinc-induced oxidative injuries and apoptosis in vivo.[82] $1,25(OH)_2D_3$ reduces nitric oxide synthesis and inhibits the production of inducible nitric oxide synthase,[83] an enzyme upregulated during ischemic events and in Alzheimer's disease.[84, 85]

A previously unrecognized consequence of vitamin D deficiency may be reduced endogenous neuroprotection against calcium toxicity. Alzheimer's disease and cognitive impairment are associated with altered neuronal CA^{2+} homeostasis, and $1,25(OH)_2D_3$ is the major CA^{2+} regulatory hormone in the periphery.[86-88] Evidence from a rodent study suggests a direct neuroprotective action of $1,25(OH)_2D_3$ at relatively low concentrations (1-100 nM).[89] Similarly treatment with 500 ng/kg of $1,25(OH)_2D_3$ over 7 days reduced Ca^{2+} mediated biomarkers of ageing in rat hippocampal neurons.[90]

Vitamin D and cerebrovascular pathology

In a cross-sectional study of 318 US elders receiving home care severe 25(OD)D deficiency (<25 nmol/L) was associated with greater white matter hyperintensity volume (4.9 vs. 2.9 mL), white matter hyperintensity grade (3.0 vs. 2.2), and the prevalence of large vessel infarcts (10.9% vs. 6.9%) in comparison with elders with higher levels (>50 nmol/L).[43] To our knowledge no prospective study in humans has examined the association between serum 25(OH)D levels and neuroimaging abnormalities such as white matter hyperintensities and infarcts. However, the risk of clinically defined cerebrovascular accident was considerably higher in 26025 US adults with low levels of 25(OH)D (<37.5 nmol/L) in comparison with those with sufficient levels (≥75 nmol/L) over a mean follow-up of 1.3 years (HR=1.78, p=0.004).[10] Similarly low 25(OH)D was independently predictive of fatal stroke in a study of 3316 coronary angiography patients over a mean of 7.8 years (OR per seasonally adjusted z value=0.67, 95% CI 0.46-0.97).[91] As $1,25(OH)_2D_3$ modulates the immune system it may also protect against the spread of ischemic injury.[92] Administration of $1,25(OH)_2D_3$ for eight days attenuated cortical infarction induced by middle cerebral arterial ligation in rats.[93] Low 25(OH)D levels may also increase the risk of cerebrovascular pathology indirectly by increasing hypertension, diabetes and cardiovascular disease.[94]

Serum 25(OH)D levels and Dementia

Several studies have explored the association between vitamin D and all-cause dementia or Alzheimer's disease in older people.[42, 43, 95] A US case-control study reported that samples of Alzheimer's (n=97) and community control (n=99) participants had comparable serum 25(OH)D levels (p=0.30), whereas those with Parkinson's disease had significantly lower levels than controls (p=0.01).[42] A Japanese study reported that in comparison with community controls (n=100), participants with Alzheimer's disease (severe: n=58; mild: n=42) had significantly lower levels of vitamin D (p<0.001).[95] In a study of US community-dwelling participants, those with all-cause dementia (n=76), and sub-groups of participants with Alzheimer's disease (n=41) and vascular dementia (n=21) were all reported to have lower serum 25(OH)D levels than controls (n=211) (p<0.01 for all comparisons).[43] Logistic regression modeling in the latter study indicated that, after adjustment for age, race, sex, body mass index and education, participants with vitamin D insufficiency (<50 nmol/L) were more than twice as likely to suffer from all-cause dementia (OR: 2.3, 95% CI 1.2 to 4.2) and from Alzheimer's dementia (OR: 2.5, 95% CI 1.0 to 6.1), than those with 25(OH)D levels ≥50 nmol/L. To our knowledge no prospective study has investigated the associations between 25(OH)D levels and incident Alzheimer's disease, vascular dementia or all-cause dementia.

Serum 25(OH)D levels and Cognitive Dysfunction

Several cross-sectional studies from Europe[47, 96, 97] and the US[98, 99] have explored the association between vitamin D and global cognitive function. Analysis of data on community-dwelling older women (n=752) aged 75 or above in France showed those with deficient 25(OH)D levels (<25 nmol/L) were twice as likely to be cognitively impaired (OR=2.0, 95% CI 1.1 to 3.5; p=0.02) as those with levels ≥25 nmol/L.[96] A study of US

community-dwelling participants (n=1080) aged 65 and above also defined vitamin D deficiency as <25 nmol/L, and reported a significant association with cognitive impairment (β coefficient=0.01, p=0.05).[99] Analysis of data from older people referred to a US geriatric outpatient clinic with a diagnosis of probable Alzheimer's disease (n=225) demonstrated a significant association between vitamin D deficiency (<50 nmol/L) and cognitive impairment (β coefficient=0.05, p=0.01).[97] In a US community sample of older people (n=3396), those with severe deficiency (<25 nmol/L) were four times as likely (OR=3.9, 95% CI 1.4 to 10.4) to be cognitively impaired compared with those with serum levels of ≥75 nmol/L (p-value for linear trend=0.02).[98] Analysis of data from a sample of community-dwelling older people and care home residents (n=1766) in England found that participants with serum 25(OH) levels in the lowest quartile of measurements were more than twice as likely (OR=2.3, 95% CI 1.4 to 3.8) to be cognitively impaired compared with those in the highest quartile (p-value for linear trend=0.001).[47] An important limitation of these cross-sectional and case-control studies is that are unable to exclude the possibility that such associations are a result of disease progression rather than being causal.

Two recent large prospective studies go some way to establish the temporal relationship with cognitive decline. In a population of community-dwelling older Italian adults (n=858), those identified as severely 25(OH)D deficient (<25 nmol/L) were at increased risk of substantial cognitive decline over a six-year period compared with those with sufficient (≥75 nmol/L) levels (RR=1.6, 95% CI 1.2 to 2.0).[98] Similarly in community-dwelling older US males (n=1136), those in the lowest 25(OH)D quartile (<50 nmol/L) had borderline increased odds of cognitive decline (OR=1.4, 95% CI 0.9-2.2) in comparison with those in the highest quartile (>74 nmol/L).[100] The small difference in these results may reflect the cut-points used to define vitamin D status (a priori groups vs. quartiles) or genuine differences between the countries or studies (possibly reflecting latitude, sociodemographic or behavioural factors). Median 25(OH)D levels were 41.4 nmol/L in Italian older adults (unpublished data) and 62.6 nmol/L in US older males,[100] although differences in the assays and laboratories used make direct comparisons problematic. Further studies are therefore needed to clarify if the association between 25(OH)D levels and cognitive decline are stronger at lower concentrations and whether there is a threshold below which the risk of cognitive decline markedly increases. (We hypothesize that such a threshold may lie in the 25 to 50 nmol/L range.) In the meantime these recent prospective studies provide preliminary evidence to suggest an association between low 25(OH)D levels and an increased risk of cognitive decline.[100, 101]

Three randomized controlled trials have assessed the treatment effect of vitamin D on cognitive function with mixed results, although all are of insufficient methodological quality due to small sample size (n=82[102], n=96[103]) and/or the use of very low daily doses of vitamin D taken in combination with other nutrients (160 IU/d[103], 520 IU/d[104]). One trial observed no improvement in mental state although the authors did not report the p-value,[102] one observed an improvement in overall cognitive function,[103] while the third trial only observed improved overall cognitive function in a subanalysis of lean individuals.[104] However, one trial[103] was subsequently retracted due to concerns regarding the methodology and analysis employed.[105]

Limitations of the current evidence

Studies of the association between 25(OH)D and cognitive dysfunction and dementia have used a variety of assays to measure serum 25(OH)D, including radioimmunoassay (RIA), competitive protein binding assay (CPBA), enzyme-linked immunoassay (ELISA) and, liquid chromatography–tandem mass spectrometry (LC-MS/MS). 25(OH)D levels are known differ by assay and laboratory,[106] which has led to calls for a standardisation of methods.[107, 108] LC-MS/MS methods are currently considered to be the most accurate, particularly at lower concentrations.[109]

Heterogeneity in relation to the 25(OH)D cut-points used to define vitamin D status and differences in the outcome measures for cognitive function and diagnostic criteria for dementia also make it difficult to compare results between studies. The inability to directly compare vitamin D status and outcome measures hampers attempts to synthesize results and will make future meta-analyses methodologically challenging.

Given the known associations between 25(OH)D levels and a wide range of health conditions, such as various cancers,[6] type 2 diabetes,[7] cardiovascular disease,[8] hypertension,[9] obesity,[110] and stroke,[10] it could be argued that vitamin D status is simply a marker for poor health status. However, vitamin D may increase the risk of cognitive dysfunction and dementia indirectly by increasing the risk of non-skeletal diseases that are themselves associated with dementia. For example, there is preliminary evidence to suggest that cerebrovascular disease[43] or type 2 diabetes[98] may partially mediate the association between 25(OH)D levels and cognitive dysfunction. Randomized controlled trials are therefore needed to establish whether improving vitamin D levels reduces the risk of dementia.

The possibility of reverse causation remains a concern[111] given that the majority of existing studies have been cross-sectional or case-control in design. Reverse causation is a particular concern in studies of vitamin D status and dementia where disease progression may lead to reduced mobility and outdoor activity, which may reduce 25(OH)D levels due to restricted sunlight exposure.[112, 113] However, prospective designs help to establish the temporal relationship between 25(OH)D levels and cognitive decline and dementia.

While animal and in-vitro experiments have identified a number of neuroprotective mechanisms that might link vitamin D status to cognitive dysfunction and dementia their clinical relevance in human populations has yet to be fully established. To our knowledge no prospective studies or randomized controlled trials have investigated the association between 25(OH)D levels and dementia subtypes, such as Alzheimer’s disease, or neuroimaging abnormalities which might provide important new aetiological insights.

Implications for future research

1) Large prospective studies of human populations are needed to provide new information about the effect size that could reasonably be expected in future trials and the dose of vitamin D likely to result in a clinically meaningful difference in underlying cerebrovascular and neurodegenerative mechanisms.

2) Prospective studies of incident Alzheimer's disease, all-cause dementia and neuroimaging abnormalities are a particular priority.

3) In an attempt to address the possibility of reverse causation prospective analyses should be statistically adjusted for baseline cognitive function, physical function/impairment and other potential confounders. Participants with dementia at baseline may also be excluded in primary or secondary analyses.

4) Investigators should also consider the possibility of inappropriate adjustment for covariates. For example, latitude is an important influence upon 25(OH)D levels,[48, 49] although it is not clear how this could confound an association between 25(OH)D levels and cognitive decline or dementia.

5) Large well-designed randomized controlled trials will ultimately be necessary to determine whether vitamin D supplementation is effective at minimizing cognitive decline or preventing dementia. However, prospective studies will provide vital information to refine the design and reduce the cost of these trials.

6) Steps to standardize laboratory methods and assays are needed to ensure comparability of 25(OH)D levels.[107, 108] Further research is therefore warranted to investigate whether the strength of observation observed is partially dependent upon 25(OH)D assay used.

7) Further prospective research is needed to investigate associations in key subgroups at risk of 25(OHD)D deficiency (e.g. homebound older adults[31], ethnic minority groups[34-36] and obese subjects[110]).

Conclusions

Cross-sectional and case-control studies have established that low 25(OH)D levels are associated with prevalent cognitive dysfunction and dementia, however these studies are prone to the possibility of reverse causation. Animal and in vitro experiments suggest that vitamin D has therapeutic potential for the prevention and treatment of cognitive decline and dementia. Two recent prospective studies also suggest that low 25(OH)D levels increase the risk of substantial cognitive decline. To our knowledge no prospective studies or randomized controlled trials have examined the association with dementia or associated neuroimaging abnormalities. Large prospective studies of human populations and randomized controlled trials are urgently needed to clarify the temporal and causal relationships between vitamin D status and cognitive dysfunction and dementia. If we confirm that low 25(OH)D levels are a potentially modifiable risk factor for cognitive decline and dementia then this would represent an important breakthrough as vitamin D deficiency is common in older adults and supplements are inexpensive and well-tolerated.

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