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Vitamin D-Mentia: Randomized Clinical Trials Should Be the Next Step

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Vitamin D intake · Neurosteroid hormone · Trials · Cognition · Alzheimer's disease · Older adults

Abstract
Hypovitaminosis D is highly prevalent in the elderly. Its possible role in the pathogenesis of Alzheimer's disease (AD) is particularly important, as AD remains a public health concern with no current efficient treatment. Vitamin D administration could be a multitarget stabilizing treatment for AD since vitamin D simultaneously targets several factors leading to neurodegeneration through immunoregulatory, antioxidant and anti-ischemic actions, as well as the regulation of neurotrophic factors, acetylcholine neurotransmitter and clearance of amyloid beta peptide, and the avoidance of hyperparathyroidism. By preventing neuronal loss, the question is whether correcting hypovitaminosis D among older adults could also prevent AD-related cognitive decline. The cross-sectional associations between the vitamin D intakes – whether from diet, sun exposure or drug supplements – and cognition strengthened this hypothesis, but prevented the finding of a cause and effect link. Pre-post studies showed an improvement of cognition concomitant with the increase in 25-hydroxyvitamin D concentrations. One randomized trial found that supraphysiological doses of vitamin D were not better than physiological doses at improving cognition in AD. At this stage, only clinical trials testing vitamin D supplements versus placebo can further determine the impact of vitamin D administration on cognition and AD with higher levels of evidence.

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Introduction

Alongside its long-known effects on phosphocalcic metabolism and bone, vitamin D exhibits neurosteroid properties indispensable to physiological functioning and protection of the central nervous system (CNS) [1–3]. Around one billion people are currently insufficient in vitamin D worldwide [4]. Most of them are older adults, with a prevalence ranging from 50 to 80% [4]. Since both hypovitaminosis D and cognitive decline/dementia are common in older adults, the involvement of age-related hypovitaminosis D in 'D-mentia' has recently been questioned [5].

Vitamin D Status and Cognition

The specific association of serum vitamin D status with cognition has been questioned repeatedly in recent years [6, 7] until the publication of a systematic review in

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2009, which provided elements of response [8]. More precisely, the authors underlined an association between hypovitaminosis D and global cognitive impairment measured with composite scores among older adults. They subsequently confirmed this association in a population-based sample consisting of more than 750 community-dwelling women aged 75 and older [9]. In this cross-sectional study, vitamin D deficiency <10 ng/ml doubled the risk of presenting with cognitive impairment measured with Pfeiffer's Short Portable Mental State Questionnaire (SPMSQ; odds ratio, OR = 2.03; 95% confidence interval (CI) = 1.17–3.53, p = 0.01). Similarly, in the same year, two works reported higher risks of global cognitive decline in older adults with hypovitaminosis D compared to those with normal 25-hydroxyvitamin D (25OHD) status. First, Slinin et al. [10] highlighted an independent association between lower 25OHD levels and odds of cognitive decline by Modified Mini-Mental State Examination (3MS) performance among 1,138 men aged ≥65 years and followed for 4.6 years on average (p = 0.04 after adjustment for age, center and season tested). Second, Llewellyn et al. [11] showed a 1.60-fold risk of losing at least 3 points on Mini-Mental State Examination (MMSE) in 6 years among 175 older adults with baseline 25OHD <10 ng/ml (mean, 77.5 years; 80.0% women) compared to 157 subjects with 25OHD ≥30 ng/ml (mean, 71.6 years; 39.5% women). Compared to previous cross-sectional studies, these longitudinal works established the temporal sequence of events and determined that low baseline vitamin D status may predict incident cognitive decline in the elderly.

Particularly, in the case of severe chronic hypovitaminosis D, the lack of vitamin D appears to be associated with dementia-level cognitive impairment [12], with a 2.4-fold risk for moderately severe to severe all-cause dementia (95% CI = 1.1–5.1, p = 0.02) in case of serum 25OHD <10 ng/ml compared to normal vitamin D status (mean, 86.0 ± 0.4 years; 66.1% women). More precisely, hypovitaminosis D may contribute to Alzheimer's disease (AD) since lower 25OHD concentrations were found among AD patients compared to controls [13, 14] and since an association of vitamin D insufficiency ≤20 ng/ml with the diagnosis of AD (OR = 2.51, 95% CI = 1.04–6.09, p = 0.04) was recently described among 318 older community-dwellers (mean, 73.5 ± 8.1 years; 72.6% women) [15].

Most recent works showed that the association between hypovitaminosis D and AD could be specifically explained by the occurrence of episodic memory disorders as well as executive dysfunction in the case of hypovitaminosis D. Indeed, both hypovitaminosis D and AD are characterized by these specific cognitive disorders. First, episodic memory is impaired among AD patients, but has also been associated with hypovitaminosis D [16]. Second, impaired executive functions are usually described in AD [17]. Executive functions refer to the heterogeneous set of high-level functions (i.e., mental shifting, cognitive inhibition and information updating) required for flexible and appropriate behavior [18]. Interestingly, impairment of executive functions – and more particularly of mental shifting assessed with Trail Making Test part B – has been associated with hypovitaminosis D among community-dwelling older adults in cross-sectional studies [19] as well as in longitudinal studies [11], with deleterious effects on information processing speed [19]. The involvement of hypovitaminosis D in AD-related cognitive decline could be of particular importance since AD remains a public health concern with no current efficient treatment.

AD: Underlying Mechanisms and Treatments

AD is the leading cause of dementia, loss of autonomy and independency in the elderly. This public health problem will grow in coming decades. In order to delay this period for as long as possible and thus reduce its impact at an individual level and in terms of health costs, the development of efficient therapeutic strategies proves necessary.

Underlying Mechanisms

Although the pathophysiological bases of AD remain not fully understood, three main neurodegenerative mechanisms are likely to explain AD (fig. 1):

(1) Senile plaques (or amyloid plaques), corresponding to the extracellular aggregation of amyloid beta 42 (Aβ42) peptide [20]. They create inflammatory and oxidant stress resulting in the death of the affected neurons. In addition, they overactivate the MAP kinase responsible for controlling the phosphorylation of Tau proteins.

(2) Neurofibrillary degeneration, due to the increase in the phosphorylation of Tau disassembling from microtubules and aggregating in neurofibrillary tangles [20]. The consequence is neuron degeneration.

(3) Glutamatergic neuronal excitotoxicity, likely due to the preferential localization of amyloid beta peptides and phosphorylated Tau in glutamatergic synaptosomes [21, 22], leads to excessive calcium entry into the postsynaptic neuron, ending in neuronal necrosis and apoptosis [23, 24].

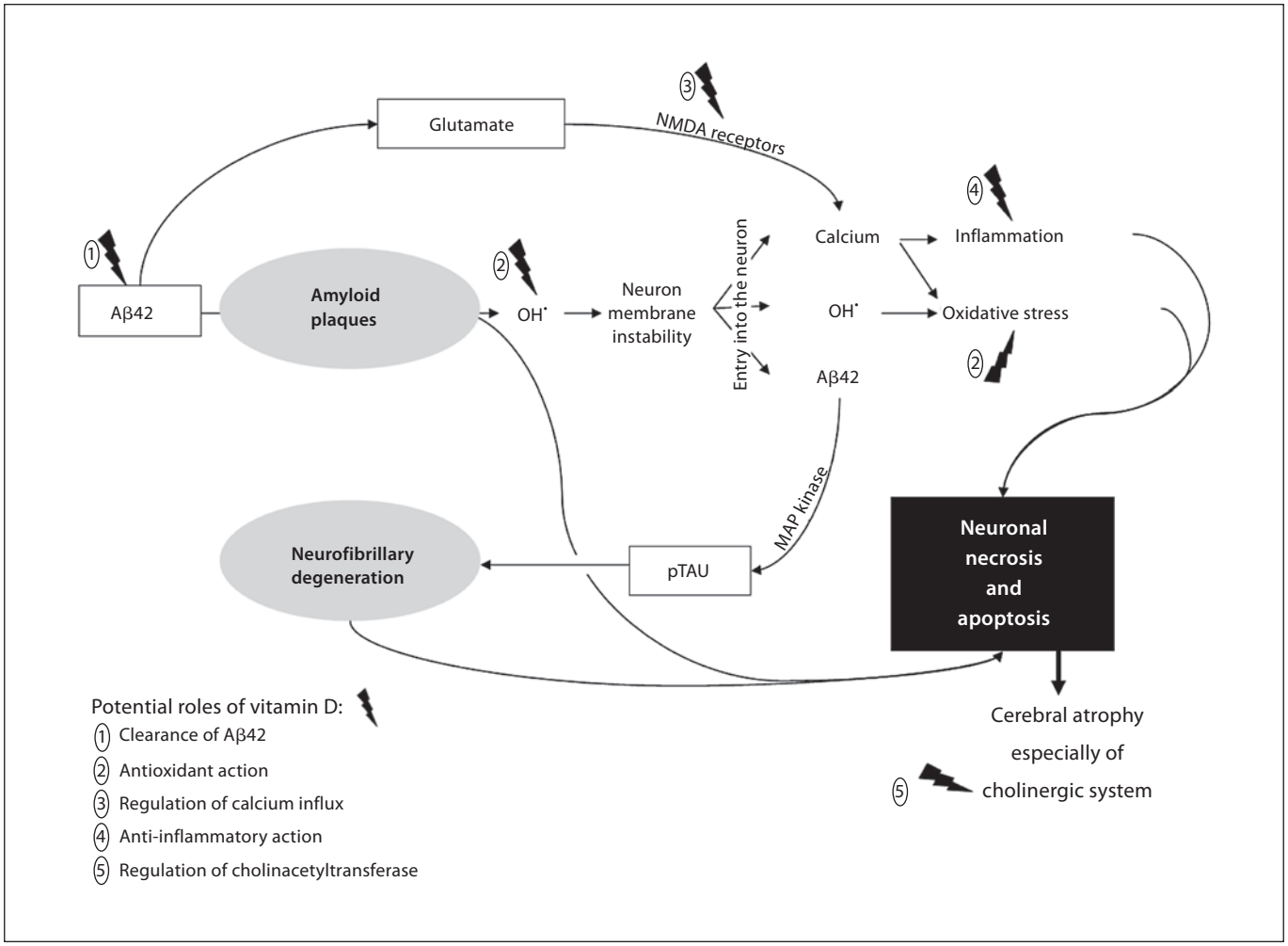

Fig. 1. Potential targets and neuroprotective mechanisms of vitamin D in AD. OH^- = Superoxide anion; NMDA = N-methyl D-aspartate; pTAU = phospho-tubule associated unit.

The clinical consequence of these degenerative processes is a decline in cognitive function that mainly leads to learning and memory difficulties.

The Need for Multitarget Drugs in AD

The drugs currently available (i.e., anticholinesterasics and memantine) are symptomatic and can only temporarily slow down AD symptoms [25, 26]. Because of their symptomatic action, they are intended only for patients with mild to severe AD.

One of the main AD challenges over the coming decade lies in the finding of a curative drug that could modify the neurodegenerative process [25, 26]. This strategy requires patients with no neurodegenerative lesions and thus at the earliest stages of AD, which leads to a very limited selection of patients. For instance, the French National Centre for the Management of Trials on Healthcare Products (CeNGEPS), which involves more than ten university memory centers in France, included in 2009 only 260 patients in clinical trials for curative drugs, although there were potentially 24,000 subjects available in these centers [26]. In other words, curative drugs are addressing only 1.1% of AD patients followed in French university memory centers.

The question is then what can be offered to the other AD patients. A particularly attractive approach is the multitarget drugs approach, meaning that the treatment administered to the AD patient simultaneously targets several factors leading to neurodegeneration [25, 26]. This last approach offers the opportunity to stabilize pa-

tients at later stages of AD, thus reducing chance inequalities between AD patients. This question is central since it could benefit a larger number of patients. Due to its numerous neurosteroid properties that regulate multiple brain targets (fig. 1) [1–3], we suggest that vitamin D could be a new multitarget therapy for AD.

Neuroprotective Properties of Vitamin D

Exactly how vitamin D and cognition are associated and if this association is causal has not been fully elucidated. On the one hand, low cognitive function could lead to low dietary intakes of vitamin D or a lack of sunlight exposure, which in turn lead to low vitamin D serum concentrations [4]. Most recent studies found yet a significant association of vitamin D with cognition even while adjusting for nutritional and physical status [9, 11, 16, 19, 27–29]. A scenario of reverse causation is thus plausible and should be considered: the association of hypovitaminosis D with AD could be a causal relationship explained by the neuroprotective properties of vitamin D. Vitamin D is a neurosteroid hormone the action of which is mediated by the vitamin D steroid receptors (VDR) present in neurons and glial cells of the CNS including hippocampus, hypothalamus, cortex and subcortex [1, 3]. The binding of 1,25-dihydroxyvitamin D on VDR triggers protective mechanisms against degenerative processes implicated in AD (fig. 1) [3].

Firstly, VDR-dependent immunoregulatory effects permit an increase in the number of macrophages and polymorphonuclear leukocytes [30, 31]. It has been proposed that vitamin D may reduce the accumulation of Aβ42 peptide in stimulating the innate immune system, specifically the phagocytosis and clearance of amyloid β peptide by macrophages [32].

Secondly, the neuroprotective effect of vitamin D also results from intraneuronal calcium homeostasis being maintained via the regulation of voltage-dependent calcium channels in the hippocampus, and via the synthesis of calcium-related cytoplasmic proteins such as parvalbumin or calcium-binding protein [3, 33].

Thirdly, vitamin D plays a part in the cerebral processes of detoxification by interacting with reactive oxygen and nitrogen species, especially in case of excessive entry of calcium into brain neurons [3]. Calcium not stored in the endoplasmic reticulum causes the activation of nitric oxide synthase and the synthesis of nitric oxide (NO′) or the stimulation of phospholipase A2, the generation of superoxide anion (O_2^-) [23, 24]. NO′ can interact with O_2^- to form peroxynitrite ($OONO^-$). Oxy-reduction reactions resulting from free radicals induce dose-dependent neuronal damage to deoxyribonucleic acid, membrane lipid by peroxidation, and enzyme inactivation. The consequences are cell contraction, relocation of organelles, condensation of chromatin, nuclear fragmentation, and production of apoptotic bodies containing fragments of cytoplasm and kernel, that defines neuronal apoptosis [23, 24]. The action of detoxification of vitamin D was described on cultured rat mesencephalic cells, with an efficient protection against the superoxide ion, hydrogen peroxide, and intracellular free radicals generated by reactive oxygen species [34]. In addition, it has been demonstrated that vitamin D inhibits the synthesis of inducible nitric oxide synthase, an enzyme produced in CNS cells in response to stress, the high-dose action of which results in neuronal cell alteration [30]. The consequence of vitamin D administration is an increase in the number of survival neurons after exposure to cytotoxic stimuli.

Fourthly, besides neuronal protection, vitamin D may help in fighting brain atrophy via the control of neurotrophin levels and the number of mitoses [35]. In vitro, vitamin D increases the synthesis of neurotrophic agents such as nerve growth factor, glial cell line-derived neurotrophic factor, neurotrophin 3, as well as the synthesis of low-affinity $p75_{NTR}$ receptors [1, 35]. It also accelerates neuronal growth in a dose-dependent way in rodent hippocampal cell cultures [35]. Vitamin D-related trophic induction seems to play a neuroprotective role in cerebral ischemia [36], as well as an antineurodegenerative role for dopaminergic cells in experimental animal models of Parkinson's disease [30]. The latter observation could be particularly interesting for secondary prevention and treatment of neurodegenerative diseases such as AD.

Fifthly, experimentation found that vitamin D supplementation in rats caused an increase in choline acetyltransferase activity (thus an increase in acetylcholine availability) in several specific brain areas, with potential applications during AD [37].

Finally, it has also been proposed that the avoidance of hyperparathyroidism in the case of normal vitamin D status may prevent the occurrence of cognitive and neuropsychiatric effects specifically induced by parathormone receptors in the brain [8, 38].

These multitarget mechanisms of protection could prevent at least part of the neuronal death and dysfunction, with subsequent benefits in terms of learning ability and memory. The question is whether correcting hypovitaminosis D among older adults can prevent neuronal death and hence cognitive decline.

What about Vitamin D Intake?

In addition to these neurosteroid 'multitarget' effects, testing vitamin D therapy sounds interesting in that vitamin D could be associated with current antidementia drugs as part of a 'multi-drug' regimen. This is an important point when considering randomized controlled trials (RCT), since it seems almost impossible to get an RCT approved to examine the efficacy of vitamin D alone in AD patients after having removed standard therapies. In addition, supraphysiological doses of vitamin D are not likely necessary to obtain an effect, and it is probably sufficient to use consensual supplementation schemes with the sole purpose of raising the serum 25OHD concentrations above 30 ng/ml (i.e., 75 nmol/l) [39]. Such therapeutic schemes do not reach toxic doses (i.e., higher than 10,000 IU per day) [39–41], which is of prime importance since hypervitaminosis D-induced hypercalcemia may increase AD risk [42]. Furthermore, conducting a placebo-controlled clinical trial in subjects with overt hypovitaminosis D for a 6-month period is acceptable because of the absence of expected accidents linked to vitamin D deficiency within this short period [43]. Despite all these facilitating arguments and the growing interest in vitamin D nonskeletal effects, no randomized placebo-controlled trial on the efficacy of vitamin D in AD patients has been conducted yet.

As a first approach, it seems useful to examine the impact of vitamin D intake on cognition (table 1). Vitamin D is a fat-soluble vitamin which exists in two forms: vitamin D_2 produced by irradiation of ergosterol by the action of ultraviolet (UV) radiation in the skin, and vitamin D_3 provided directly by foods or produced by the action of UV from cholesterol after transformation to 7-dehydrocholesterol [4]. Three sources of vitamin D can therefore be distinguished: dietary intake, sun exposure, and drug supplements.

Dietary Intake of Vitamin D and Cognition

An association was recently highlighted between the weekly dietary intake of vitamin D and global cognitive performance ($\beta = 0.002$, 95% CI = 0.001–0.003, $p < 0.001$; table 1) [44]. The findings showed, among 5,596 community-dwelling older women (mean, 80.4 years), that inadequate vitamin D dietary intake was associated with cognitive impairment (OR = 1.30, 95% CI = 1.04–1.63, $p = 0.024$) [44]. The latter result was obtained after exclusion of women having used vitamin D drug supplements during the past 18 months, and after adjustment for self-reported sun exposure at midday as well as age, body mass index, disability level, the number of comorbidities, hypertension, depression, use of psychoactive drugs, education level and season of assessment. Although this association could be explained in a more general way by a healthy lifestyle illustrated by a rich and varied diet and by regular physical activity, it was coherent with the previous literature. In particular, a pilot study published in 2007 found a correlation between the 3-day vitamin D dietary intake and cognitive impairment on the MMSE score ($r = 0.35$, $p < 0.01$) among 69 community-dwellers aged 84 years on average (59.4% women; table 1) [45]. This work proposed a precise quantification of the dietary intake of vitamin D, but was restricted to a limited size. Despite these methodological divergences, both studies found that high dietary intake of vitamin D was associated with high cognitive performance assessed with global composite cognitive scores [44, 45].

Vitamin D Intake Related to Sun Exposure and Cognition

Sun exposure of the skin is the second natural source of vitamin D [4]. To the best of our knowledge, no study has explored yet the effect of solar radiation on cognition. Only the study cited above assessed the link between sun exposure and cognitive status of older women [44]. In this study, the authors found an unadjusted association between sun exposure of the hands and face at least 15 min per day between 11 a.m. and 3 p.m., and global cognitive performance assessed with Pfeiffer's SPMSQ ($\beta = 0.248$, 95% CI = 0.183–0.313, $p < 0.001$; table 1) [41]. In addition, sun exposure protected against cognitive impairment (OR = 0.641, 95% CI = 0.542–0.758, $p < 0.001$) [44]. Nevertheless, both associations were not significant after adjustment for age, disability level, and other covariates ($\beta = 0.037$ with $p = 0.282$, and OR = 0.944 with $p = 0.552$, respectively), which was consistent with the observations that skin synthesis of vitamin D from UVB decreases with age [46] and that the effect of sun exposure is minor in the elderly compared to the other sources of vitamin D.

Vitamin D Drug Supplements and Cognition

The third source of vitamin D in the elderly is drug supplementation. To date, two studies have examined the effects of the use of vitamin D supplements on cognition (table 1) [47, 48]. The first one, by Przybelski et al. [47], failed to find a greater improvement of cognitive performance after the oral administration of 50,000 IU vitamin

Table 1. Main characteristics of the studies exploring the association between vitamin D intakes and cognitive performance

Study			Outcomes			Results
Reference	Design	Setting/population	Vitamin D intake	Adjustment for potential confounders	Cognitive performance	Significant positive association between vitamin D intakes and cognitive performance?
Dietary intakes of vitamin D						
Annweiler et al. [44]	cross-sectional study	community-dwelling high-functioning older women n = 5,596; 100% female mean age: 80.5 ± 0.1 years mean BMI: 25.6 ± 0.1 kg/m^2 Europe	dietary intake estimated from a self-administered food frequency questionnaire mean intake = 62.7 ± 0.4 μg/week continuous variable or categorized variable inadequate <35 μg/week recommended ≥35 μg/week	age BMI sun exposure at midday season disability number of chronic diseases hypertension depression use of psychoactive drugs education level	cognitive performance as a whole – Pfeiffer's SPMSQ	linear regression – unadjusted model: yes – fully adjusted model: yes logistic regression – unadjusted model: yes – fully adjusted model: yes
Rondanelli et al. [45]	cross-sectional study	community-dwelling older adults with no medication and no disabling condition n = 59; 59.4% female mean age: 84 ± 7 years range: 70–89 years mean BMI: 23.7 ± 4.2 kg/m^2 Europe	dietary intake dietary history over the 3 days preceding study entry mean intake = 7.9 ± 2.4 μg/day continuous variable	no adjustment	cognitive performance as a whole – MMSE	correlation : yes
Vitamin D intakes related to sun exposure						
Annweiler et al. [44]	cross-sectional study	community-dwelling high-functioning older women n = 5,596, 100% female mean age: 80.5 ± 0.1 years Europe	sun exposure of hands and face at least 15 min/day between 11 a.m. and 3 p.m. estimated from a standardized health questionnaire categorized variable (yes/no)	age BMI dietary intakes of vitamin D season disability number of chronic diseases hypertension depression use of psychoactive drugs education level	cognitive performance as a whole – Pfeiffer's SPMSQ	logistic regression – unadjusted model: yes – fully adjusted model: no

Table 1 (continued)

Study			Outcomes			Results
Reference	Design	Setting/population	Vitamin D intake	Adjustment for potential confounders	Cognitive performance	Significant positive association between vitamin D intakes and cognitive performance?
Vitamin D drug supplements						
Przybelski et al. [47]	pre-post study	frail nursing home residents n = 63; 74.6% female intervention group: – 25OHD ≤25 ng/ml – n = 25; 68.0% female – mean age: 86.2 ± 2.3 years control group: – 25OHD >25 ng/ml – n = 38; 78.9% female – mean age: 87.4 ± 0.9 years – may receive vitamin D routinely USA	nonrandomized vitamin D_2 supplementation in a group with vitamin D insufficiency intervention group: – unblinded supplementation – 50,000 IU vitamin D_2 3 times weekly for 4 weeks – NB: mean serum 25OHD concentration increased from 17.3 to 63.8 ng/ml control group: – no increase of vitamin D supplementation over what they were receiving at baseline – no placebo – NB: mean serum 25OHD concentration remained stable at around 34 ng/ml	not applicable	visuospatial and constructional abilities – CDT animal naming – SFT behavioral disorders – NPI	improvement of NPI and CDT scores within the intervention group no differences between the intervention group and the control group for any of these parameters after the intervention
Stein et al. [48]	pre-post 'pilot' study	community-dwelling older adults with mild to moderate AD n = 13 Age ≥60 years Australia	open-label 3,000 UI/day vitamin D_2 for 8 weeks – NB: median serum 25OHD concentration increased from 66 to 140 nmol/l	not applicable	cognitive performance as a whole – ADAS-cog score	improvement of ADAS-cog score
Stein et al. [48]	RCT	community-dwelling mild to moderate AD – n = 32; 74.6% female intervention group: – n = 16; 56.3.0% female – median age: 75 years control group: – n = 16; 50.0% female – median age: 79 year Australia	randomized intervention group: – 1,000 IU/day vitamin D_2 for 8 weeks – then 7,000 IU/day for 8 weeks – then nasal insulin for 2 days – NB: median serum 25OHD concentration increased from 49 to 187 nmol/l control group: – 1,000 IU/day vitamin D_2 for 8 weeks – then 1,000 IU/day for 8 weeks – then nasal insulin placebo for 2 days – NB: median serum 25OHD concentration increased from 49 to 72 nmol/l	not applicable	cognitive performance as a whole – ADAS-cog score logical memory – WMS-LM immediate and delayed scores	no between-group difference regarding the change in ADAS-cog score after the intervention no between-group difference regarding the changes in WMS-LM immediate and delayed scores after the intervention

ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive subscale; BMI = body mass index; NB = nota bene; SFT = Semantic Fluency Task; WMS-LM = Wechsler Memory Scale-Revised Logical memory.

D_2 3 times a week for 4 weeks among 25 older residents with hypovitaminosis D (mean age, 86.2 years; 68% women), compared to 38 residents with a normal vitamin D status who did not receive any vitamin D supplements (mean age, 87.4 years; 78.9% women; mean baseline 25OHD, 34.8 ± 1.8 ng/ml; table 1) [47]. In particular, no significant between-group difference was observed after 4 weeks of treatment with regards to the performance on Semantic Fluency Task, Clock Drawing Test (CDT) and Neuropsychiatric Inventory (NPI). Nevertheless, this pre-post study also showed that the increase in serum 25OHD concentrations among the treatment group (from 17.3 to 63.8 ng/ml, $p < 0.0001$) was coupled with an improved NPI score (from 7.3 ± 2.0 before vitamin D supplementation to 5.5 ± 1.9 after treatment; lower scores indicate reduced intensity and/or frequency of neuropsychiatric symptoms) and an improved CDT score (5.7 ± 0.5 after treatment vs. 5.1 ± 0.5 before treatment; table 1) [47]. The scores were also improved among the group with a normal vitamin D status (NPI score changing from 7.4 ± 1.6 to 6.4 ± 1.6; and CDT score from 4.6 ± 0.6 to 5.7 ± 0.5), but the authors did not provide the degree of significance of these differences. Anyway, the improvement of the neuropsychiatric symptoms among participants with no hypovitaminosis D was interestingly concordant with previous experiments in rodents proposing that hypovitaminosis D could be involved in the occurrence of behavioral disorders. In particular, the model of resistance to vitamin D (similar to avitaminosis D) provided by the transgenic VDR knockout (VDR-KO) mouse showed a deleterious impact on behavior, primarily marked by excessive stress, motor disorders [49], aberrant maternal behaviors and aggressiveness [50]. Since behavioral disorders are common in the course of AD and are often a challenging issue due to the use of chemical restraints and the need for institutionalization [51], this finding may be of prime importance and should be investigated in more depth.

The second study on this topic, by Stein et al. [48], had two phases. First, the authors conducted a feasibility pilot study, consisting in a pre-post study based on the open supplementation of 3,000 IU vitamin D_2 per day for 8 weeks in 13 older patients with mild to moderate AD (table 1). In line with the study by Przybelski et al. [47], the increase in serum 25OHD concentration from 66 to 140 nmol/l was accompanied by a 6-point improvement of the ADAS-cog score (range: 4.5–8.5, $p < 0.001$) [48]. The second phase of the study by Stein et al. [48] consisted in a randomized control trial designed to correct hypovitaminosis D among 32 AD participants with open-label 1,000 IU vitamin D_2 per day for 8 weeks, and then to examine the cognitive effectiveness of supraphysiological doses of vitamin D_2 in 16 AD patients (i.e., 7,000 IU/day) compared to 16 other AD patients receiving physiological doses of vitamin D_2 (i.e., 1,000 IU/day; table 1). The authors failed to find a significant between-group difference regarding the change in ADAS-cog and WMS-LM scores on the whole cohort (table 1), highlighting the fact that supraphysiological doses of vitamin D were not more efficient in improving cognitive abilities than physiological ones [48].

These two studies, whether by Przybelski et al. [47] or by Stein et al. [48], had yet a number of methodological problems that limited their conclusions. For instance, they were both limited by the use of vitamin D_2 supplements which are generally less efficient than vitamin D_3 for repletion [52], and by the short duration of the follow-up that did not exceed 16 weeks, while the effects of vitamin D can be observed after a longer period [43]. Additionally, none of these studies assessed executive functions or episodic memory as outcome measures, although serum 25OHD concentrations are likely associated with these domain-specific cognitive functions, as described above. It should also be mentioned that no stratification was made on the stages of AD by Stein et al. [48], although the preventive effects of vitamin D may be more evident in the early stages of the dementia process than in later stages. This should have justified a separate analysis for each AD stage; and most importantly, both studies compared participants who received vitamin D supplements to participants who had already a normal vitamin D status, which did not allow drawing conclusions about the cognitive effectiveness of the correction of hypovitaminosis D.

In conclusion, it appears that cognitive decline in AD and hypovitaminosis D have a partially common pathophysiological pathway based on impaired protection against oxidative stress, accumulation of β amyloid protein and calcium excitotoxicity. On the contrary, vitamin D experimentally protects neurons against degenerative mechanisms implicated in AD and could be a new multitarget therapy for AD both easily applicable and inexpensive. The previously described cross-sectional associations between vitamin D intakes – whether from diet, sun exposure or drug supplements – and cognition strengthened this hypothesis, but prevented determining whether cognitive decline precipitated low intakes of vitamin D due to disability, or whether low intakes of vitamin D had a role in precipitating cognitive decline. In this regard, pre-post studies suggest an improvement of cog-

nition concomitant with the increase in 25OHD concentrations, even if supraphysiological doses of vitamin D seemed not better than physiological doses at improving cognition in the only RCT conducted to date. This observation is consistent with the recent conclusions of the Institute of Medicine highlighting that available evidence in favor of the nonskeletal effects of vitamin D are still limited [53]. At this stage, only RCTs testing the effectiveness of vitamin D supplements versus placebo on the evolution of cognition as a whole, and specifically of episodic memory and executive functions, can further determine the impact of vitamin D repletion in AD with a higher level of evidence.

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