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REVIEW ARTICLE

Vitamin D and cognitive performance in adults: a systematic review

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Chronic low serum 25-hydroxyvitamin D (25OHD) concentrations are common in adults and are associated with numerous non-skeletal diseases. Vitamin D receptors (VDR) are located in the human cortex and hippocampus, which are key areas for cognition. The objective of this study was to systematically review all published data from the past 30 years which examined the association between serum 25OHD concentrations and cognitive performance in adults. An English and French Medline, PsycINFO® and Cochrane Library search ranging from 1979 to 2008 indexed under the Medical Subject Heading (MeSH) terms 'Vitamin D' or 'Hydroxycholecalciferols' combined with the terms 'Dementia' or 'Cognition' or 'Cognition Disorders' or 'Delirium' or 'Memory' or 'Memory Disorders' or 'Orientation' or 'Executive Functions' or 'Attention' or 'Brain' or 'Neuropsychological Tests' was performed. Of the 99 selected studies, five observational studies met the selection criteria and were included in the final analysis. No prospective cohort study was found. The number of participants ranged from 32 to 9556 community-dwelling older adults (45–65% women). Three studies showed four significant positive associations between serum 25OHD concentrations and global cognitive functions, whereas three other studies exploring specific aspects of cognition showed 11 non-significant associations. This systematic review shows that the association between serum 25OHD concentrations and cognitive performance is not yet clearly established. The inconclusive results of the reviewed studies could be due to methodology, types of the cognitive tasks used and/or the cellular mechanisms of vitamin D.

Introduction

Chronic low serum vitamin D concentration in the elderly is an important public health concern due to its high prevalence of 50–80% and to the increased incidence of related adverse health events such as bone, cardiovascular, epileptic, neoplasic, or infectious diseases [1–4]. Indeed, vitamin D is not only involved in bone metabolism. It has multiple biological targets mediated by vitamin D receptors (VDR) present in many cells [4,5], including neurons and glial cells [4]. In both humans and animals, vitamin D is a neurosteroid hormone which may regulate neurotransmission, neuroprotection, neuroimmunomodulation and brain processes [4,5].

VDR have been located in the human cortex and hippocampus [4], which are key areas for cognitive functioning, and their absence has been associated with neurodegenerative dementia such as Alzheimer's disease (AD) [6]. The relationship between serum 25-hydroxyvitamin D (25OHD) concentration and cognitive function was uncertain until the recent position paper by Buell and Dawson-Hughes which supported a potentially beneficial role of 25OHD on cognitive functioning [5]. Based on these results [5] and on the knowledge that low serum 25OHD concentrations are associated with an increased risk of developing several diseases including AD [7], we performed a systematic review of all published data over the past

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30 years which examined the association between serum 25OHD concentrations and cognitive performance in adults.

Methods

Literature search

An English and French systematic Medline literature search of cohort, case–control and transverse studies on humans aged 19 years and older, published from January 1979 to December 2008, using the Medical Subject Heading (MeSH) terms 'Vitamin D' or 'Hydroxycholecalciferols' combined with the terms 'Dementia' or 'Cognition' or 'Cognition Disorders' or 'Delirium' or 'Memory' or 'Memory Disorders' or 'Orientation' or 'Executive Functions' or 'Attention' or 'Brain' or 'Neuropsychological Tests' was performed. The search also included the Cochrane Library, the PsycINFO® database of the American Psychological Association, and the reference lists of the retrieved articles. In order to ensure a comprehensive approach, additional key studies known to the authors that did not meet the search criteria were lastly included.

Study selection and analysis

Abstract selection was based on the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist which describes items that should be included in reports of cohort studies [8]. Abstracts identified with the literature search were independently evaluated by two reviewers (CA and OB). From abstracts which fulfilled the initial inclusion criteria (data collection of serum 25OHD concentration and either cognitive status or diagnosed dementia as outcomes), full articles were obtained for the final analysis. Since subjects cannot be their own controls in cross-sectional observational studies, a control group was required to assess the association of vitamin D deficiency with cognitive impairment. To improve the quality of the review, we only included studies which used a regression model to explore the association between serum 25OHD concentrations and cognitive performance. Final selection criteria were therefore applied when serum 25OHD concentration and cognitive performance were provided, when the association between serum 25OHD concentrations and cognitive performance was analyzed and when a healthy control group was included. The study selection is shown on a flow diagram (Fig. 1).

Of the 99 originally identified abstracts, 13 met the initial inclusion criteria. Thorough examination excluded eight of those 13 studies [9–16] because the control group was not healthy (n = 2) and no association between serum 25OHD concentrations and cognitive performance or status was analyzed (comparison demented/non-demented, n = 5; association between vitamin K and cognition, n = 1). The remaining five studies were included in this review [17–21].

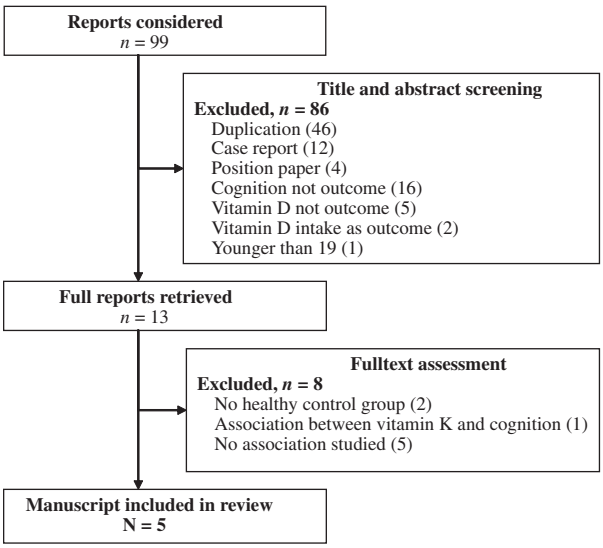

Figure 1 Flow diagram of selection of studies focusing on vitamin D concentration.

Results

Table 1 summarizes the five observational studies included in this review [17–21]. The number of participants ranged from 32 to 9556 [19,20]. Women represented 45–65% of the studied populations [17,21]. All studies examined the association between serum 25OHD concentration and cognitive performance in community-dwelling older adults [17–21]. Data collection was based on a case–control [17] or cross-sectional design [18–21], and linear regression models were used to explore the association between serum 25OHD concentrations and cognitive performance. No longitudinal prospective cohort study was found. Regarding the outcomes, three studies used the serum 25OHD concentration as a continuous variable in the regression [17,19,21], whereas the other two [18,20] used a categorized variable (insufficiency/deficiency for 25OHD concentrations lower than 20 and 10 ng/ml respectively, and quintiles). Although two studies did not take any confounders into account [17,19], three accounted for age, gender, ethnicity, solar exposition, educational level, and serum concentrations of vitamin B1, B6 and B12 [18,20,21]. Tests evaluating global cognitive function (Mini Mental State Examination (MMSE),

Table 1 Main characteristics of the five observational studies exploring the association between 25OHD concentrations and cognitive performance using a linear regression analysis

Study			Outcomes			Result
Reference	Design	Setting/Population	25OHD	Adjustment for potential confounders	Cognitive performance	Significant positive association between 25OHD concentration and cognitive performance?
Jorde *et al.* [17]	Case–control study	Community-dwelling n = 148, 45.9% women Mean age: 62.1 ± 13.6 years	Mean 25.4 ± 7.2 ng/ml Continuous variable	No adjustment	Working memory capacity (Digit Span forward[a], Seashore Rhythm test[b]) Speed of information processing (Trail Making test A, Stroop test part 1 and 2, Digit Symbol test, CalCAP) Memory (Verbal Recall, Visual Recall[a], Word list test[c]) Language (Controlled Oral Word Association test) Cognitive flexibility/executive function (Stroop test part 3, Trail Making test B) Intelligence (Vocabulary[d])	No No No No No No
Wilkins *et al.* [18]	Cross-sectional study	Community-dwelling n = 80, 62.5% women Mean age: 74.8 ± 7.7 years 40 with mild AD, and 40 non-demented subjects	Mean 18.6 ± 7.6 ng/ml Categorized variable: Insufficiency < 20 ng/ml Deficiency < 10 ng/ml	Age Gender Ethnicity Season of vitamin D determination	Short Blessed test Clinical Dementia Rating, Sum of boxes Mini Mental State Examination Psychometric battery factor score (Mental Control[a], Logical Memory[a], Digit Span Forward and Backward[a], Associate Learning[a], Information[d], Block Design[d], Digit Symbol[d], Boston Naming test, Benton Visual Retention test Form C and D, Trail Making test Part A, Word Fluency for S and P, Crossing-off)	Yes Yes No No
Przybelski *et al.* [19]	Cross-sectional study	Community-dwelling n = 32 Mean age: 79.5 ± 1.6 years	Mean 21.6 ± 1.6 ng/ml Continuous variable	No adjustment	Mini Mental State Examination	Yes
McGrath *et al.* [20]	Cross-sectional study	Community-dwelling n = 9 556 Middle-aged [20–59 years], n = 4 747 Elderly [60–90 years], n = 4 809	Categorized variable: Middle-aged quintiles: <15.8, 15.8–21.1, 21.2–26.7, 26.8–33.9, >33.9 ng/ml Elderly quintiles: <17, 17–22.2, 22.3–27.6, 27.7–34.1, >34.1 ng/ml	Age Gender Ethnicity Activity	Middle-aged Symbol-digit Substitution Coding Speed Serial Digit Learning Trials To Criterion Elderly Memory and Learning score	 No No No
Oudshoorn *et al.* [21]	Cross-sectional study	Community-dwelling n = 225, 65% women Mean age: 77.7 ± 7.3 years	Mean 18.2 ± 9.1 ng/ml Continuous variable	Age Gender Total mobility score Action radius Years of education Serum vitamin B1, B6, B12 concentrations	Mini Mental State Examination	Yes

25OHD, 25-hydroxyvitamin D; AD, Alzheimer's Disease; CalCAP, California Computerized Assessment Package.

[a] Subtest from Wechsler Memory Scale-Revised; [b] subtest from Halstead-Reitan test battery; [c] subtest from California Verbal Learning Test; [d] subtest from the Wechsler Adult Intelligence Scale.

Clinical Dementia Rating (CDR), Short Blessed Test (SBT)) [18,19,21] and tasks assessing specific cognitive functions (executive function, speed of information processing, language, verbal fluency, intelligence, learning and memory) [17,18,20] were used as outcome measures. Due to the heterogeneity of the methods, the results could not be meta-analyzed. Wilkins *et al.* [18], Przybelski *et al.* [19] and Oudshoorn *et al.* [21] showed four significant positive associations between global cognitive efficiency measures and serum 25OHD concentrations, whereas Jorde *et al.* [17], Wilkins *et al.* [18] and McGrath *et al.* [20] showed, mainly with specific cognitive measures, 11 results without significant positive association.

Discussion

Incongruous results were observed in the five observational clinical studies analyzed in this systematic review: some found a significant positive association between serum 25OHD concentrations and cognitive performance, whereas others failed to show any significant association. These inconclusive findings raise a number of issues that mainly concern the choice of cognitive tasks, the heterogeneity of studied populations, the lack of control of confounders, the methodology of reviewed studies, and the cellular mechanisms of vitamin D.

Inconsistent findings may be partially due to the choice of the cognitive tasks used to assess cognitive performance. The studies which failed to show any significant association between 25OHD concentrations and cognitive performance (Table 1) used tasks that explored specific aspects of cognition [17,18,20], whereas those which showed significant positive associations (Table 1) examined global cognitive function using composite neuropsychological tests [18,19,21]. For example, Wilkins *et al.* [18] found a significant positive association between low serum 25OHD concentrations and low scores on the SBT and the CDR. Przybelski *et al.* [19] and Oudshoorn *et al.* [21] highlighted a significant positive linear correlation between serum 25OHD concentrations and MMSE scores. It should be noted that the only non-significant positive association with MMSE score [18] should be mitigated because of a controversial threshold for low serum 25OHD concentrations. 25OHD insufficiency was defined as serum concentrations lower than 20 ng/ml, although six international experts proposed a consensual threshold of 30 ng/ml in 2005 [22]. Furthermore, serum 25OHD concentrations did not appear to be associated with the specific cognitive tasks used so far. Wilkins *et al.* [18] and McGrath *et al.* [20] also found no significant positive association between serum 25OHD concentrations and executive and learning functions. What is more, Jorde *et al.* failed to highlight any significant association with various specific cognitive tasks, but their results were less reliable as no adjustment for confounders was made [17]. It therefore remains unclear which specific cognitive functions are affected in vitamin D deficiency. Some authors have suggested that vitamin D insufficiency could be associated with AD [5,6]. Since AD patients typically exhibit deficits in explicit episodic memory [23], it could be argued that impairment of this specific cognitive domain may be associated with low serum 25OHD concentrations. Exploring the association between serum 25OHD concentration and explicit episodic memory might thus be useful in addressing the heterogeneity of cognitive impairment in vitamin D deficient elderly and in predicting cognitive outcomes in vitamin D insufficiency. In our opinion, further studies are needed to explore the relationship between 25OHD insufficiency and cognition in normal and pathological aging using cognitive tasks that assess specific cognitive processes.

Discrepant results amongst observational studies may also result from their small sample size, as only one of the five studies analyzed in this review included more than 250 subjects [20]. A further limitation is the heterogeneity of the studied populations. As an example, only patients with elevated serum parathyroid hormone (PTH) were tested in the Jorde *et al.* study [17], although specific roles of vitamin D and PTH on cognition have not yet been fully elucidated. It has indeed been suggested that the non-skeletal effects of 25OHD insufficiency could be due to PTH and not to a direct action of vitamin D [3,24]. 25OHD insufficiency indeed triggers a series of reactions, including elevation of serum PTH concentrations [3,24]. The association of such increased PTH levels with cognition has been known for a long time in patients with primary hyperparathyroidism. The clinical features of hyperparathyroidism include dementia [25], which was reversed in one study after parathyroidectomy [25]. Moreover, only AD patients were selected in Oudshoorn *et al.*'s study [21], whilst Wilkins *et al.* [18] compared groups of AD patients to a group of non-demented subjects. In addition, Pryzbelski *et al.* [19] examined only older adults referred to a clinic for memory disorders, whilst McGrath *et al.* [20] reviewed adults of all ages that were part of large epidemiological survey.

Differences of methodology in the studies analyzed in this review may also partly explain the inconclusive results. Firstly, the study designs were limited to case–control and cross-sectional studies, providing not only a low level of proof in exploring an association between two variables, but do not allow any causal inference compared to prospective longitudinal cohort studies [26]. Secondly, the conditions of serum preservation

might account for potential conflicting results. All studies stated that serum 25OHD concentrations were assayed with identical radioimmunoassay kits (Diasorin, Stillwater, MN, USA) [17–21]. However, amongst the five studies, none indicated the duration and methods of serum collection and preservation before 25OHD assay. The effects of temperature, light and long-term serum storage on measurements are not certain, especially regarding 25OHD stability. Serum 25OHD rate may therefore not always be 100% safe and conduct to divergent conclusions.

Another explanation of inconclusive results may be due to normal human VDR gene polymorphism [3]. Indeed, the latest experimental publications suggest that this gene polymorphism could explain the existence of responders and non-responders to vitamin D substitution [27] and could also be involved in neuronal damage and neurodegenerative diseases. As an example, Poduslo *et al*. [28] demonstrated that three markers on chromosome 12, on which the VDR gene is located, were associated with the development of late-onset AD. To the best of our knowledge, three studies addressed the relationship between VDR gene polymorphism and neurodegenerative diseases with mixed results [29–31]. Although late-onset AD was associated with neither the *Foq*I genotype [29] nor the *Taq*I genotype [30], Gezen-Ak *et al*. [30] showed, amongst 104 AD cases and 109 aged-matched controls, a significant association between AD and the *Apa*I polymorphism, with the presence of the '*Aa*' genotype associated with a 2.3-fold higher risk developing AD compared to the '*AA*' genotype. Also in this study, the '*AATT*' combined genotype was more often present in healthy controls than in patients with AD, suggesting a protective effect on AD [30]. Moreover, *Bsm*I polymorphism has recently been associated with Parkinson's disease, the allele '*b*' and homozygosity '*bb*' being more frequent amongst 85 cases compared to 231 controls [31]. The impact of VDR genetic polymorphism on cognition is still far from being completely defined. As a consequence, it should be systematically taken into account when assessing the neurological and cognitive effects of vitamin D on individuals or populations.

It is now better recognized that vitamin D could play a part in the nervous system. In animal experiments, vitamin D has antiepileptic, neuroprotective and immunomodulating properties and is involved in neurotransmitter metabolism and the synthesis of certain growth factors such as GDNF [4]. Vitamin D is also involved in the development and maturation of the brain [32]. In addition to this central action, vitamin D also acts on the peripheral nervous system. A reduction of nerve conduction velocity is reportedly associated with vitamin D deficiency [33]. As in other non-skeletal targets, vitamin D exerts its effects along genomic and non-genomic pathways [4]. VDR have also been characterized in some brain regions, especially in the hippocampus, hypothalamus, limbic system as well as in cortical, subcortical and spinal motor areas [4,5]. At the cellular level, these receptors are present on both neurons and glial cells [4,5]. VDR-knockout mice models have shown that the genetic ablation leading to expression of non-functional VDR in the brain was associated with anxiety and motor disorders such as a decreased swimming capacity and an increase in uncoordinated swimming movements, suggesting the essential role of vitamin D in motor control [34,35].

In humans, indirectly via an improvement of attentional capacities and independently of an action on muscle, vitamin D appeared to stabilize postural equilibrium in the elderly [36]. Dhesi *et al*. have also demonstrated that vitamin D supplementation in older adults with a history of falls significantly decreased reaction times to stimuli and improved postural equilibrium independently of any effect on muscle [36].

To be fully comprehensive, it should be noted that intervention studies, like observation studies, have demonstrated inconsistent results concerning the effects of vitamin D supplementation on cognitive functions. Even if Rondanelli *et al*. [37] showed a significant negative correlation between dietary intake of vitamin D and poor performance on cognitive tests ($r = 0.35$, $P < 0.01$) amongst 69 community-dwelling healthy elderly people (mean age 84 ± 7 years), the only recent prospective clinical trial found no cognitive efficacy of a short course, high dose, oral vitamin D supplementation of 25 vitamin D deficient nursing home residents (mean age 86.2 ± 2.3 years) [38] compared to the non-supplemented controls. The failure to demonstrate an effect of vitamin D on cognitive performance could be related to the short follow-up of less than 4 months after starting treatment [38], and to the effects of confounders such as the serum PTH levels [3,24], the presence of medical conditions which may preclude the possibility of a response [3], or the cognitive and mental conditions of the nursing home residents which were not given in this study, other that they could walk and give consent [38].

In conclusion, this systematic review shows that the association between 25OHD concentrations and cognitive performance remains uncertain because of inconclusive results. The choice of cognitive tasks, the methodology of the reviewed studies and the cellular mechanisms of vitamin D may explain such discrepancies. We suggest that 25OHD insufficiency likely negatively affects specific cognitive functions, such as explicit episodic memory, which have not yet been sufficiently investigated. Well-designed longitudinal

prospective cohort studies are required to determine such associations.

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Author contributions

Annweiler has full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Study concept and design: Annweiler and Beauchet. Acquisition of data: Annweiler and Beauchet. Analysis and interpretation of data: Annweiler, Beauchet, Allain, Allali, Schott, Kressig, Bridenbaugh. Drafting of the manuscript: Annweiler, Allain, Allali, Bridenbaugh and Beauchet. Critical revision of the manuscript for important intellectual content: Schott and Kressig. Obtained funding: not applicable. Administrative, technical, or material support: Annweiler and Beauchet. Study supervision: Beauchet.

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