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Vitamin D Deficiency, Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis

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Key Words

Cognitive impairment · Dementia · Vitamin D · Etiology · Prevention

Abstract

Background: Recent preventive strategies for patients with cognitive impairment include the identification of modifiable somatic risk factors like vitamin D deficiency. ***Methods:*** A systematic literature research and meta-analysis were conducted to assess the association of cognitive impairment and vitamin D deficiency. ***Results:*** Data from cross-sectional and longitudinal studies suggest an association between cognitive impairment and vitamin D deficiency. Meta-analysis of 5 cross-sectional and 2 longitudinal studies comprising 7,688 participants showed an increased risk of cognitive impairment in those with low vitamin D compared with normal vitamin D (OR 2.39, 95% CI 1.91–3.00; $p < 0.0001$). ***Conclusions:*** Methodological limitations of these studies comprise heterogeneity of study populations, different forms of cognitive assessment, the problem of reverse causality, different definitions of vitamin D deficiency and inconsistent control for confounders. As the value of vitamin D substitution in cognitive impairment remains doubtful, a long-time major placebo-controlled randomized trial of vitamin D supplementation in participants with mild cognitive impairment (MCI) should be started.

Introduction

Recent preventive strategies among patients with cognitive impairment and dementia include the identification of risk factors and predictors [1, 2]. As somatic co-morbidity often contributes to dementia and somatic risk factors are modifiable, the early detection and treatment of these risk factors offers important opportunities to delay and to avoid the manifestation of cognitive impairment and dementia [2–4].

Vitamin D (25-hydroxyvitamin D or cholecalciferol) serves a circulating pool from which the bioactive form calcitriol (1,25-dihydroxycholecalciferol) is synthesized. Restricted sunlight exposure, impaired capacity of the skin to produce vitamin D, and reduced dietary vitamin D intake can lead to vitamin D deficiency in the elderly, which affects nearly 50% of older adults [5]. Evidence from animal and in vitro studies suggests an important role of vitamin D in brain function. Vitamin D receptors have been identified in the brain [6]. Vitamin D is linked with the synthesis of neurotrophic factors and neurotransmitters [7], is involved in the down-regulation of receptors in memory-relevant regions and is linked with amyloid phagocytosis and clearance [8, 9] (fig. 1).

Vitamin D deficiency has emerged as a possible somatic risk factor and a few recent reviews have already provided some evidence for an association between vitamin D deficiency and cognitive impairment [10–12].

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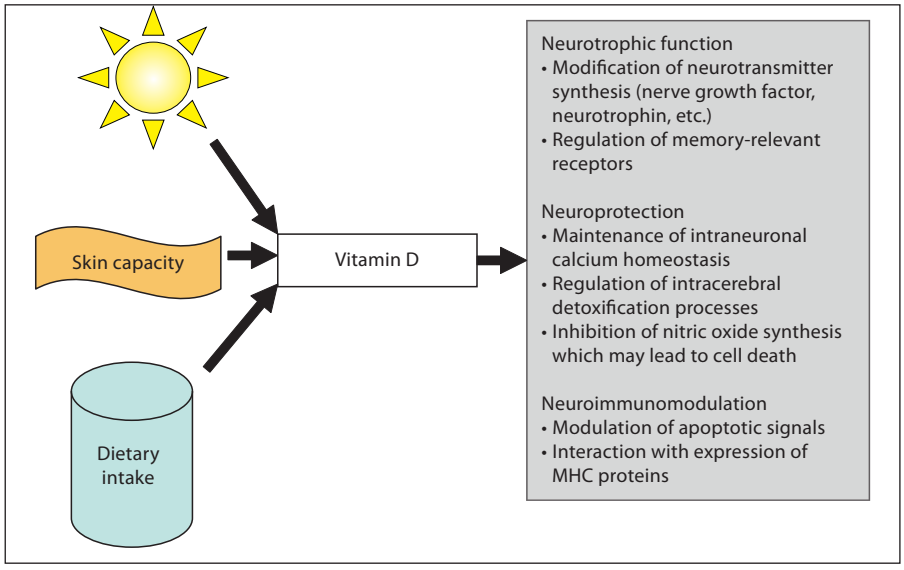

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Fig. 1. Factors influencing vitamin D level and potential central nervous effects of vitamin D (modified after [10]).

Several recent studies contributed even more intriguing data regarding this relationship. This systematic review provides an up-to-date overview of vitamin D and the association with cognitive impairment. Based on the evidence available today the value of possible therapeutic interventions is discussed and proposals for future research are developed.

Methods

A systematic bibliographical research of MedLine literature and Cochrane database of case-control, cross-sectional, longitudinal or prospective and interventional studies in human subjects was performed. This research included the period from 1980 to April 2012 and used the following Medical Subject Heading (MeSH) terms 'Vitamin D', 'Dementia', 'Cognitive Impairment' and 'Cognitive Decline'. Abstracts were screened for further items as 'serum vitamin D concentration' and 'cognitive assessment'.

We assessed all potentially relevant articles for eligibility. Inclusion or exclusion of studies was decided hierarchically on the basis of the (1) study title, (2) the abstract and (3) completeness of the study. Studies were included if they fulfilled all the following criteria: (1) either cross-sectional or longitudinal study, (2) at least 100 participants, (3) association of vitamin D and cognitive impairment as primary or secondary outcome, and (4) results presented by odds ratio (OR) or hazard ratio (HR) values or sufficient data to calculate these parameters (fig. 2). The primary outcome for this meta-analysis was cognitive impairment. The meta-analysis to pool results from the individual studies was done with Review Manager (RevMan; version 5.1 for Macintosh; Copenhagen, Denmark). Pooled results are reported as OR and are presented with 95% CI with two-sided p values using a random effects model. $p < 0.05$ was considered to be statistically significant. Statistical heterogeneity was evaluated using the I^2 statistic, which assessed the appropriateness of pooling the individual study results. The I^2 value provides an estimate of the amount of variance across

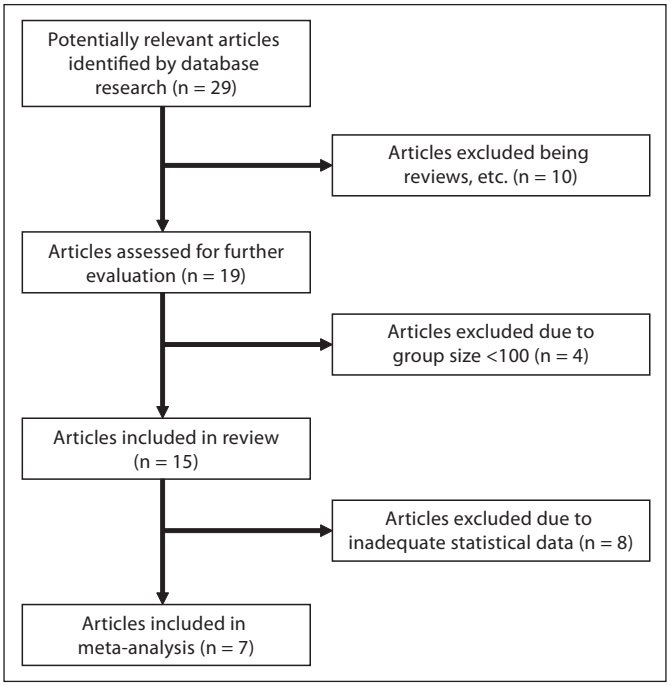

Fig. 2. Flow chart of search strategy.

studies because of the heterogeneity rather than chance. Where I^2 was greater than 50%, heterogeneity was considered to be high. Moreover, to further investigate the heterogeneity across studies, we performed sensitivity analyses by dividing studies into groups according to their main characteristics. Subgroup analyses were then performed according to age, physical activity, gender, method used to evaluate cognitive function, mean sample size of the study populations (less than/at least 500) and different study populations (community-dwelling/inpatients). Publication bias was appraised by visual inspection of the funnel plot of effect size against standard error.

A number of studies used the conventional unit (ng/ml) and others the SI unit (nmol/l). To convert from the conventional unit to the SI unit, multiplication by the conversion factor 2.496 is required.

Results

Small-Scale, Case-Control and Cohort Studies

The majority of case-control and small cohort studies in the field suggest that a low serum 25-hydroxyvitamin D concentration is associated with dementia and cognitive impairment. Among 20 women with mild dementia, 25-hydroxyvitamin D was significantly lower compared with 40 age-matched cognitively normal female controls [13]. A decrease of 25-hydroxyvitamin D was observed in a Japanese study of 58 patients with severe and 42 patients with mild Alzheimer's disease in comparison with 100 age-matched community dwelling controls [14]. In a group of 40 persons with mild Alzheimer Dementia (AD) compared with 40 non-demented persons, vitamin D deficiency was associated with worse performance on the Short Blessed Test ($p = 0.044$) and higher Clinical Dementia Rating ($p = 0.047$) [15]. One study of 21 persons with secondary hyperparathyroidism compared with 63 healthy controls reported an association between a deranged calcium metabolism and impaired neuropsychological function tests [16]. Among 32 patients attending a memory clinic, a positive correlation between vitamin D concentration and Mini-Mental State Examination (MMSE) was detected [17]. In a cross-sectional study of 60 older American adults, participants with low vitamin D showed worse results in the Short Blessed Test [18]. However, one of the first studies which compared 16 elderly persons with dementia, who still lived independently, with a gender- and age-matched control group, reported no significant difference in vitamin D levels [19].

Problems of these studies consisted in a small sample size (<100 participants), different definitions of normal vitamin D level, lack of population-based participants and lack of adjustment for important confounders.

Cross-Sectional Studies

In recent years, larger cross-sectional studies have been published (table 1): among 225 older outpatients with probable AD, an association of lower serum 25-hydroxyvitamin D(3) levels and MMSE test scores was observed [20]. An investigation of 713 patients receiving home care revealed an association of 25-hydroxyvitamin D insufficiency with impaired executive function and attention/processing speed factors, but not with memory factors even after multiple adjustments [21]. In a subset (n = 318) of this study population, an association of 25-hydroxyvitamin D insufficiency with all-cause dementia (OR: 2.5; 95% CI 1.2–4.2) and also with MRI indicators of cerebrovascular disease was reported [22]. Among 4809 elderly participants from the 'National Health and Nutrition Examination Survey (NHANES III)', lower vitamin D levels were not associated with impaired performance on various psychometric measures [23]. An updated analysis of this study with 3325 NHANES III participants aged >65 years employed a different adjustment for potential confounders and incorporated the full range of NHANES III cognitive measures which might reflect a more stable representation of cognitive function [24]. Therefore and in contrast to the first NHANES III study, this group reported an association of severe vitamin D insufficiency (<25 nmol/l) and cognitive impairment (OR 3.9; 95% CI 1.5–10.4) [24]. A large British population-based study ('Health Survey for England 2000') examined the association of cognitive impairment and vitamin D in 1,766 persons aged >65 years. Cognitive impairment was assessed using the Abbreviated Mental Test that has a high correlation with the more common MMSE. After adjusting for multiple other risk factors, the lowest serum 25-hydroxyvitamin D quartile (8–30 nmol/l) was associated with cognitive impairment (OR 2.3; 95% CI 1.4–3.8) [25]. In a population-based cross-sectional study including 3,133 men with a mean age of 60 years ('European Male Ageing Study) lower 25-hydroxyvitamin D levels were associated with poorer performance on one cognitive subtest ('Digit Symbol Substitution Test'), but not any other cognitive function test [26]. In another population-based study with 752 women aged ≥75 years from the 'Epidemiologie de l'Osteoporose' (EPIDOS) cohort, after adjustment for multiple confounders, an association of deficient vitamin D concentration (<10 ng/ml) with cognitive impairment assessed by Pfeiffer Short Portable Mental State Questionnaire was reported (OR 1.99; 95% CI 1.13–3.52) [27]. An Irish multicenter study among 387 elderly healthy

Table 1. Major (>100 participants) cross-sectional studies of the association between vitamin D and cognitive impairment

Study	Participants	Mean age years	Classification of vitamin D deficiency	Cognitive assessment	Confounder	Result/ association with cognitive impairment
McGrath, 2007 [23]	4,809 noninstitutionalized persons	range 60–90	sufficient (>50 nmol/l) insufficient (25–50 nmol/l) deficient (<25 nmol/l)	Learning and Memory task	age, race, sex, physical activity	no clear association
Oudshoorn, 2008 [20]	225 persons with Alzheimer dementia	77.6	<50 nmol/l	MMSE	age, sex, total mobility score, action radius, education, vitamin B_1, B_6 and B_{12} levels	positive association (β = 0.05)
Buell, 2009 [21]	703 with homecare service	75.7	sufficient (>50 nmol/l) insufficient (25–50 nmol/l) deficient (<25 nmol/l)	MMSE, trail A+B, digit symbol coding, matrix reasoning, block design, WMS-recall + logical memory recognition, Digit span, etc.	age, race, sex, BMI, smoking, alcohol, physical activity, ApoE allele status, nutritional covariates, diabetes, hypertension, homocysteine, CKD	executive function (β = 0.01) attention/ processing speed (β = 0.01)
Lee, 2009 [26]	3,133 noninstitutionalized men	59.9	suboptimum (50–75 nmol/l), insufficient (25–49 nmol/l), deficient (<25 nmol/l)	Rey-Osterrieth Complex Figure, Camden Topographical Recognition Memory Test, Digit-Symbol Substitution Test (DSST)	age, smoking, alcohol, age left education, depression, physical activity, BMI	association with vitamin D <35 nmol/l
Llewellyn, 2009 [25]	1,766 institutionalized persons	78.2	insufficient (≥50 and <75 nmol/l) deficient (≥25 and <50 nmol/l) severely deficient (≥25 nmol/l)	Abbreviated Mental Test	age, sex, education, ethnicity, season of sample, smoking, alcohol, psychiatric morbidity, hypoalbuminemia, self-reported medical history, impaired mobility	insufficient or 0.9 (0.5–1.6) deficient or 1.4 (0.8–2.3) severely deficient OR 2.7 (1.5–5.0)
Annweiler, 2010 [27]	752 community-dwelling women	80.2	<25 nmol/l	SPMSQ <8	age, body mass index, number of chronic diseases, hypertension, depression, use of psychoactive drugs, education level, regular physical activity, serum intact parathyroid hormone and calcium	OR 2.0 (1.1–3.5)

Table 1. (continued)

Study	Participants	Mean age years	Classification of vitamin D deficiency	Cognitive assessment	Confounder	Result/ association with cognitive impairment
Llewellyn, 2011 [24]	3,325 noninstitutionalized persons	73.7	insufficient (≥50 and <75 nmol/l) deficient (≥25 and <50 nmol/l) severely deficient (≥25 nmol/l)	global cognitive function score from 6 tests	age, sex, ethnicity, education, season of sample, smoking, BMI, alcohol, vitamin E, family income, mobility, physical activity, diabetes, hypertension, stroke	insufficient OR 0.9 (0.6–1.3) deficient OR 1.4 (1.0–2.1) severely deficient OR 3.9 (1.5–10.4)
Annweiler, 2011 [29]	288 patients of geriatric acute care unit	86.0	severely deficient (≥25 nmol/l)	clinical diagnosis based on DSM-IV	age, sex, pulse pressure, number of acute and chronic diseases, use of psychoactive drugs, albumin, CKD	OR 2.4 (1.1–5.1)
Seamans, 2011 [28]	387 healthy adults	range 55–87	tertiles (<48, 48–86 and >86 nmol/l)	Cambridge Neuropsychological Testing Automated Battery	age, sex, BMI, zinc status, season of sample	spatial working memory associated with low vitamin D tertile in women

MMSE = Mini Mental Status Examination; SPMSQ = Pfeiffer Short Portable Mental State Questionnaire; ApoE=Apolipoprotein E; CKD = chronic kidney disease; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; WMS = Wechsler Memory Scale.

participants reported an association of vitamin insufficiency and impaired spatial working memory, especially in women [28]. Annweiler et al. [29] found in 288 older patients of a French geriatric acute care unit a significant association between severe vitamin D deficiency (<10 ng/ml) and moderately severe to severe dementia (OR 2.57; 95% CI 1.05–6.27).

Longitudinal Studies

The majority of prospective studies found an association between low vitamin D level and cognitive impairment: in a cohort of 1,604 men enrolled in the 'Osteoporotic Fractures in Men Study', after more than 4 years men with lower 25(OH)D levels (<50 nmol/l) showed a nonsignificant association with cognitive impairment [30]. One problem of this study included a limited study population of only white elderly community-dwelling men. A second limitation consisted of a possible bias by a high-rate of participants lost at follow-up (about 30%) who were older and had initially lower levels of vitamin D and cognitive function. The cognitive testing used the Modified MMSE (3MS) and trail B but for the latter no definition of cognitive impairment exists. Important and new confounders of cognitive impairment as depression and chronic kidney disease were not included in this study.

The prospective Italian population-based InCHIANTI study with 858 adults aged ≥65 years, found an association between a severe deficiency of 25-OH-D (<25 nmol/l) at baseline with an increased risk of a substantial cognitive decline in the following six years measured by MMSE (OR 1.61; 95% CI 1.19–2.01) [31]. Limitations of this study are its confinement to exclusively white elderly participants from a geographically confined area; and a lack of control for potential for calcium, parathyroid hormone and chronic kidney disease as potential confounders [27, 32].

The French 'Epidemiology of Osteoporosis Tolouse Cohort Study (EPIDOS)' assessed 498 community-dwelling elderly women free of vitamin D supplements for 7 years. After adjustment for several confounders, the authors found a significant association between the highest quintile of baseline vitamin D intake and a lower risk of developing AD (OR 0.23; 95% CI 0.08–0.67) [33]. In a substudy of EPIDOS, among 40 high-functioning older women an association between vitamin D deficiency at baseline (<10 ng/ml) and the onset of non-Alzheimer dementia (adjusted OR 19.57, p = 0.042), but not with AD was reported [34]. Problems of this study comprised the restriction to well-functioning women, the use of a self-administration of the food frequency questionnaire and the lack of a more detailed diagnosis of dementia.

Among a subgroup of 1,639 elderly participants of the large epidemiology ESTHER study (mean age 74 years), after multiple linear regression low vitamin D level at baseline was associated with worse cognitive functioning after 5 years [35]. Limitations included lack of baseline cognitive assessment and possible self-selection bias.

In the 'Study of Osteoporotic Fractures' with 6,257 community-dwelling elderly women, those with low vitamin D level (<25 nmol/l) at baseline showed an increased risk of global cognitive decline after 4 years (OR 1.58; 95% CI 1.12–2.22) [36]. Problems incorporated a selected study population (healthy Caucasian women) and extrapolation of completion time for one cognitive test.

Interventional Studies

In a randomized, double-blind, placebo-controlled study of 139 elderly persons with a history of falls and low serum level of 25-hydroxyvitamin D (≤12 μg/l), a single intramuscular injection of 600,000 IU ergocalciferol led to a significant improvement of choice reaction time (–0.06 s vs. +0.41 s; $p < 0.01$) compared with placebo [37]. In a prospective study among 63 nursing home residents, 25 persons with low vitamin D status (serum vitamin D ≤25 ng/ml) received oral ergocalciferol 50,000 IU three times weekly for 4 weeks whereas the remaining individuals received no active medical intervention apart from their routine care. Although vitamin D concentration increased in the treatment group, neurocognitive performance (clock-drawing test and verbal fluency) did not improve significantly [38].

Meta-Analysis

Five cross-sectional studies including 5,686 participants could be included in the meta-analysis. Five cross-sectional could not be included as they did not report OR or HR values or sufficient data to calculate these parameters. For all studies, only the baseline data were used. If the data were given for quartiles of vitamin D, the first and fourth quarter were compared. Meta-analytic pooling using a random-effects model showed that participants with a lower vitamin D concentration (n = 2,518) had a significantly increased risk of cognitive impairment compared with those with a normal vitamin D concentration (n = 3,168) (OR 2.37; 95% CI 1.77–3.17; $p < 0.0001$) (fig. 3). However, there was a significant heterogeneity amongst the studies (d.f. = 4; p = 0.02).

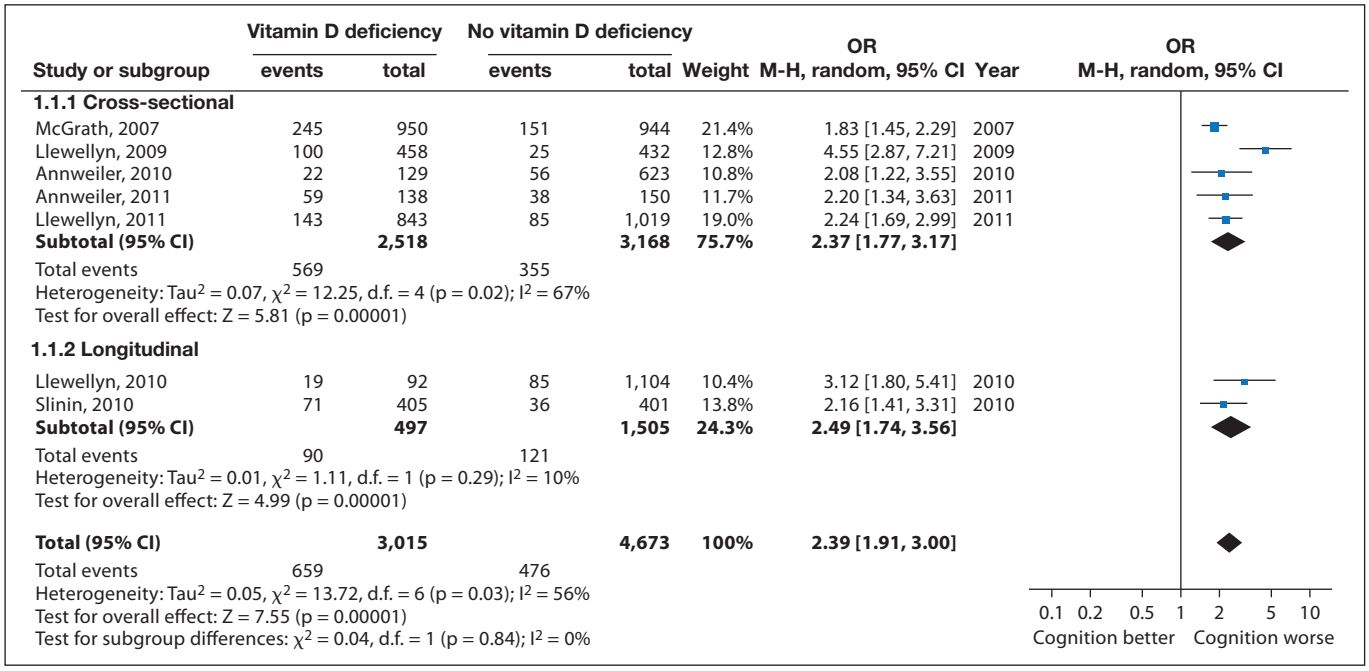

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Fig. 3. Forest plot of cross-sectional and longitudinal studies assessing vitamin D concentration and cognitive impairment.

With longitudinal studies, only two studies could be included in the meta-analysis. Three studies could not be included as they did not report OR or HR values or sufficient data to calculate these parameters. Meta-analytic pooling using a random-effects model also revealed that participants with vitamin D deficiency had a significantly increased risk of incident cognitive impairment at follow-up compared with those with normal Vitamin D concentration (OR 2.49; 95% CI 1.74–3.56; $p < 0.0001$) (fig. 3). No significant heterogeneity amongst the studies was observed (d.f. = 1; $p = 0.29$). To investigate the possible differences across studies, we performed sensitivity analyses by grouping studies according to various characteristics (sex, method used to evaluate cognitive function, mean sample size of the study populations [less than/at least 500] and different study populations [community-dwelling/inpatients]). We observed no significant change in the results. In contrast, age and physical activity contributed significantly to the observed heterogeneity between the studies.

Funnel plots of effect size versus standard error to investigate possible publication bias were broadly symmetrical, suggesting the absence of publication bias.

Discussion

Systematic research of current data from cross-sectional and longitudinal studies suggests an association between cognitive impairment and vitamin D deficiency. This result is supported by a meta-analysis suggesting a more than doubled risk of cognitive impairment in vitamin D deficiency. Interventional studies of vitamin D supplementation were underpowered (small study population, short study time).

Differences among the studies may be partially explained by several methodological problems, which include heterogeneity of study populations, different forms of cognitive assessment, the problem of reverse causality, different definitions of vitamin D insufficiency and inconsistent control for confounders.

Several studies examined selected groups of in- or out-patients with either mild cognitive impairment (MCI) or dementia [20, 21, 29] whereas in other studies community-dwelling noninstitutionalized participants were reviewed [23, 24, 26, 27].

The assessment of cognitive function showed a great variability between the different studies and may further contribute to the divergent results. Studies with subtests exploring specific aspects of cognition, such as learning

or memory tasks did not show any association with vitamin D concentrations [23] whereas studies assessing global cognitive performance (Clinical Dementia Rating or MMSE) reported a significant association with vitamin D insufficiency [11]. Another problem of cognitive assessment consisted of the employment either as a categorical variable [23] or as a continuous score without checking for the normality of its distribution [15, 17].

Reverse causality represents another problem, as cross-sectional studies cannot determine whether low levels of vitamin D cause cognitive impairment. Instead, cognitive impairment may lead to reduced outdoor activity with impaired sunlight exposure and reduced oral intake of vitamin D, both leading to vitamin D insufficiency. Several studies considered this by using confounders as season of sampling and physical activity level [24].

As there is no established definition of vitamin D deficiency, different threshold values of vitamin D deficiency have been used throughout the studies, which may also explain conflicting results. Several studies used a threshold of 50 nmol/l [20, 30] whereas in most other studies levels below 25 nmol/l were defined as deficient or even severe deficient [21, 23–26, 29]. According to an international expert panel, the minimum desirable concentration level of 25-hydroxyvitamin D for the skeleton and for fracture prevention varied between 50 (preferably 70) and 80 nmol/l [39] but levels for cognitive function have not been defined.

The different inclusion of potential confounders is another critical point. A number of studies have used only a few confounders [20, 26], whereas others considered many confounding factors (table 1) [24, 27]. Confounders which received increasing attention over recent years had been left out before: depression and chronic kidney disease.

In summary, due to the methodological problems of the cross-sectional and longitudinal studies, an association between serum vitamin D deficiency and cognitive impairment is not yet clearly established despite the results of our meta-analysis. There is a strong need for a major prospective study which should include all possible and new confounders (depression, chronic kidney disease, etc.). As earlier stages of dementia as for example mild cognitive impairment are more likely to benefit from therapeutic interventions [40], more data about the association of mild cognitive impairment and vitamin D would be useful. Therefore, future prospective studies should also address incident dementia and incident prestages of dementia (e.g. mild cognitive impairment). This would also require a more detailed focus on early forms of vitamin D insufficiency, for example the classification used in Europe ('Health Survey for England' [25] and US ('NHANES III') [24]: insufficient (50–75 nmol/l), deficient (25–49 nmol/l) and severely deficient (<25 nmol/l). Finally, a placebo-controlled randomized trial of vitamin D supplementation in a larger number of participants with mild cognitive impairment and dementia followed up over a longer period of time would be able to shed more light on vitamin D deficiency as potentially modifiable risk factor for cognitive impairment.

Disclosure Statement

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