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Vitamin D and Memory Decline: Two Population-Based Prospective Studies

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Abstract.

Background: Vitamin D deficiency has been linked with dementia risk, cognitive decline, and executive dysfunction. However, the association with memory remains largely unknown.

Objective: To investigate whether low serum 25-hydroxyvitamin D (25(OH)D) concentrations are associated with memory decline.

Methods: We used data on 1,291 participants from the US Cardiovascular Health Study (CHS) and 915 participants from the Dutch Longitudinal Aging Study Amsterdam (LASA) who were dementia-free at baseline, had valid vitamin D measurements, and follow-up memory assessments. The Benton Visual Retention Test (in the CHS) and Rey's Auditory Verbal Learning Test (in the LASA) were used to assess visual and verbal memory, respectively.

Results: In the CHS, those moderately and severely deficient in serum 25(OH)D changed -0.03 SD (95% CI: –0.06 to 0.01) and –0.10 SD (95% CI: –0.19 to –0.02) per year respectively in visual memory compared to those sufficient ($p = 0.02$). In the LASA, moderate and severe deficiency in serum 25(OH)D was associated with a mean change of 0.01 SD (95% CI: –0.01 to 0.02) and –0.01 SD (95% CI: –0.04 to 0.02) per year respectively in verbal memory compared to sufficiency ($p = 0.34$).

Conclusions: Our findings suggest an association between severe vitamin D deficiency and visual memory decline but no association with verbal memory decline. They warrant further investigation in prospective studies assessing different memory subtypes.

Keywords: Cognition, memory, prospective studies, vitamin D

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INTRODUCTION

Recent meta-analyses confirm low serum vitamin D concentrations are linked with prevalent Alzheimer's disease [1] and global cognitive decline [2]. A range of neuroprotective (e.g., increased phagocytosis of amyloid-β peptide, regulation of neurotrophins and calcium homeostasis, anti-inflammatory and antioxidant action) mechanisms have been identified suggesting vitamin D may play a substantial role in preventing dementia [3–5]. However, the relationship with specific cognitive domains remains largely unknown. It has previously been hypothesized that vitamin D may be primarily associated with cognitive domains other than memory [6]. Our previous systematic review identified no prospective studies investigating the relationship between vitamin D and memory [7]. Cross-sectional studies suggested the association between vitamin D and memory may be less consistent than that observed for executive dysfunction [7]. Recent cross-sectional studies indicate a potential link with visual memory [8, 9], but not with verbal memory [9]. We therefore updated our systematic review to identify any new prospective studies and analyzed data from two large prospective population-based studies.

Systematic review

We updated our systematic review on vitamin D, memory, and executive dysfunction (conducted May 2012) [7] focusing specifically on the prospective association with memory. Following a predefined protocol, we searched MEDLINE and PsycINFO from 2012 onwards without language restrictions using subject headings and free text terms, with forward and backward citation searching of included studies (Supplementary Figure 1). We included prospective observational or interventional studies with a mean follow-up of $\geq$1 year investigating the association between serum vitamin D concentrations and memory in adults aged 65 and over. We excluded publications without objectively assessed memory, conference abstracts, and manuscripts that did not include original research. Titles, abstracts, and full-texts were screened independently by two reviewers (EK and JMR). Any discrepancies were resolved by discussion with a third reviewer (DJL).

Our searches yielded a total of 397 references. After removing 90 duplicates, 295 records were excluded after title and abstract screening. We conducted a full-text review of 12 publications though none met our inclusion criteria (Supplementary Figure 2). Our systematic review established that no previous study had investigated the relationship between vitamin D and long-term memory decline in older adults. Therefore, we identified through prior publications and existing collaborations two prospective population-based studies including vitamin D measurements and memory assessments: the US Cardiovascular Health Study (CHS) [10] and the Dutch Longitudinal Aging Study Amsterdam (LASA) [11]. We did not conduct a meta-analysis due to heterogeneous outcomes included in each study (visual versus verbal memory).

METHODS

Data and study populations

We used data from the CHS and LASA to investigate the relationship between vitamin D and memory. The CHS recruited 5,201 older adults in 1989-1990 and an additional 687 African-American participants in 1992-1993 from four communities in the US and assessed them annually through 1999 [10]. Serum 25-hydroxyvitamin D (25(OH)D) concentrations were measured in blood samples collected at the 1992-1993 study visit (baseline for the current study) in 2,312 participants free from cardiovascular disease and with sufficient serum volumes ($\geq$500 ul) [12]. The LASA was initiated in 1992 and included 3,107 adults from three geographic regions in the Netherlands [11]. Participants were assessed every three to four years thereafter. Blood samples for measurement of 25(OH)D were collected in 1995-1996 (baseline for the current study) from 1,352 participants aged 65 and older and valid vitamin D measurements were obtained from 1,320 samples [13]. The end of follow-up for the current study was the 2008–2009 study visit. We restricted both samples to dementia-free participants [14, 15] aged 65 and older at baseline with valid vitamin D assessment and $\geq$2 cognitive assessments. In the CHS, dementia status was adjudicated according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [14] whereas in the LASA probable dementia (persistent cognitive decline of more than two standard deviations (SD) below the mean decline with continued decline during follow-up) was identified based on available data as previously described [15]. We also excluded those with baseline memory scores that precluded substantial decline defined as $\geq$1 SD decrease greater than the mean change score from

baseline to final assessment [16] (scores <3 and <8 in the CHS and LASA, respectively). Baseline global cognitive scores did not preclude substantial decline defined as a decline of ≥5 points on the Modified Mini-Mental State Examination (3MSE) [17] and ≥3 points on the Mini-Mental State Examination (MMSE) from baseline to final assessment [18] for any participants. This resulted in 1,291 CHS and 915 LASA participants in analyses of memory decline (primary outcome), and 1,612 and 1,074, respectively, for global cognitive decline (secondary outcome).

Ethical approval and informed consent

Institutional review boards at CHS participating institutions approved research protocols. The LASA study protocol was approved by the Medical Ethics Committee of the VU University Medical Center. All participants provided written informed consent.

Serum 25(OH)D measurement

In the CHS, serum samples were collected in 1992–1993 and stored at –70°C [12]. In 2008, 25(OH)D was measured using high-performance liquid chromatography-tandem mass spectrometry on a Waters Quattro micro mass spectrometer (Waters Corporation, Milford, Massachusetts) with the inter-assay coefficient of variation of <3.4% [12]. The assay was validated using the Standard Reference Material 972 developed by the National Institute of Standards and Technology [19].

In the LASA, serum samples were obtained in 1995-1996 and stored at –20°C until 25(OH)D measurement in 1997-1998. A competitive protein binding assay (Nichols Diagnostics, San Juan Capistrano, CA) was used to determine 25(OH)D concentrations with an inter-assay coefficient of variation of 10% [20].

In both cohorts, serum 25(OH)D concentrations were divided into clinically relevant categories: sufficient (≥50 nmol/L), moderately deficient (≥25 to <50 nmol/L), and severely deficient (<25 nmol/L) [21]. We also analyzed serum 25(OH)D concentrations as a standardized continuous variable with a mean of zero and a SD of one.

Cognitive assessment

In the CHS, visual memory was assessed by the Benton Visual Retention Test (BVRT) [22] consisting of ten designs one, two, three, four, and six years after the study baseline [17]. Scores range from 0 to 10 with higher scores representing better visual memory. Global cognition was assessed annually using the 3MSE (range 0 to 100) [23] with higher scores representing better global cognition [17].

In the LASA, cognition was assessed at baseline and after three, six, ten, and thirteen years [16]. Verbal memory was assessed using immediate (three trials) and delayed (one trial) recall of 15 words on an abbreviated Dutch version of the Rey's Auditory Verbal Learning Test [24]. In addition to immediate word recall (score on the third trial, range 0 to 15) and delayed word recall (range 0 to 15), we derived a total verbal memory score as the sum of immediate and delayed recall (range 0 to 30) with higher scores representing better verbal memory. Global cognition was assessed with the MMSE (range 0 to 30) with higher scores representing better global cognition [25]. The 3MSE and the MMSE are highly correlated measures of global cognition [26].

Substantial memory decline was defined as ≥1 SD decrease greater than the mean change score in both cohorts from baseline to final assessment [16]. Substantial global cognitive decline was defined as a decline of ≥5 points on the 3MSE [17] and ≥3 points on the MMSE from baseline to final assessment [18].

Covariates

Analyses were adjusted for covariates previously identified as potential confounders [1, 5, 7, 27] and to address the possibility of reverse causation [5]: age in years, season of blood collection (March-May, June-August, September-November, December-February), education (CHS: did not finish high school, finished high school/some college/vocational qualifications, completed college/professional qualifications; LASA: in years), gender, income (low, middle, high, and missing; in the CHS: <$25,000, $25,000–$49,999, and ≥$50,000 per annum [28]; in the LASA: <€1,134, €1,135-€1,816, >€1,816 per month [29]), body mass index (BMI in kg/m^2), smoking (non-smoker, current smoker), alcohol consumption (US National Institute on Alcohol Abuse and Alcoholism guidelines for older adults: non-drinkers, moderate drinkers [≤7 drinks per week], heavy drinkers [>7 drinks per week]), depressive symptoms (CHS: ≥8 on the revised 10-item Center for Epidemiologic Studies Depression Scale (CES-D) [30]; LASA: ≥16 on the 20-item Dutch version of the CES-D [31]), and gait impairment (gait speed <0.5 m/s and/or use of assistive devices [32]).

Statistical analyses

We summarized baseline characteristics of the CHS and LASA samples across vitamin D categories using percentages for categorical variables, means and standard deviations for normally distributed continuous variables, and medians and interquartile ranges for skewed continuous variables.

Linear mixed-effects regression models were fitted to estimate the mean difference in annual change in memory and global cognition (outcomes) between vitamin D deficient categories and the sufficient (reference) category. Data were reshaped into *long* format so that all responses (at baseline and follow-up) for a given outcome were analyzed as a single variable with a *time* variable indicating when the outcome was measured. Basic adjusted models included the covariates: time, vitamin D category, interaction term between vitamin D category and time, baseline age and season of blood collection. Coefficients for the interaction variable indicate mean differences in annual change between vitamin D deficient categories and the sufficient category. Fully adjusted models additionally included baseline education, gender, income, BMI, smoking, alcohol consumption, depressive symptoms and gait impairment. Linear mixed-effects regression models with random intercept and random slope for the time variable, specifying the study participant as the *grouping* or *clustering* variable, were fitted as they allow for correlation between responses over time from the same participant. Mean differences in memory and global cognition were converted to SD units by dividing the raw score differences by the baseline SD of each test in the analytic sample in each study in order to aid interpretability and comparability.

We used Poisson regression models with a robust error variance [33] to estimate relative risk (RR) of substantial memory and global cognitive decline associated with baseline vitamin D categories. In basic adjusted models, we controlled for age, season of vitamin D collection, baseline memory or global cognitive score and years of follow-up. In fully adjusted models, we also included baseline education, gender, income, BMI, smoking, alcohol consumption, depressive symptoms, and gait impairment.

In sensitivity analyses, we first repeated the above analyses using attrition weighting to assess the potential influence of differential loss to follow-up. Weights were defined as the inverse probability of having completed at least one follow-up cognitive assessment and calculated by fitting logistic regression models to follow-up status (outcome) using key predictors (25[OH]D category, age, gender, education, income, season of vitamin D collection, baseline cognition, BMI, smoking, alcohol consumption, depressive symptoms, and gait impairment). Since there was little difference between findings from the non-weighted and weighted analyses the former are reported here. We then analyzed serum 25(OH)D concentrations as a continuous rather than a categorical variable. Furthermore, we repeated the main analyses adjusting for ethnicity (white/black) in the CHS and excluding non-white participants in the LASA as they represented only 1% of the sample. In the LASA we also repeated the main analyses to investigate the association between vitamin D categories and immediate and delayed word recall separately.

RESULTS

Results from the CHS

Baseline characteristics of CHS participants included in analyses of memory are presented in Table 1. We present here only fully adjusted results as there was little difference between basic and fully adjusted models (Tables 3 and 4).

For visual memory, those moderately and severely deficient in serum 25(OH)D changed –0.03 SD (95% CI: –0.06 to 0.01) and –0.10 SD (95% CI: –0.19 to –0.02) per year, respectively, compared to those sufficient ($p = 0.02$; Table 3). The RR for substantial decline in visual memory in those moderately and severely 25(OH)D deficient was 1.08 (95% CI: 0.87 to 1.34) and 1.32 (95% CI: 0.87 to 2.01), respectively, compared to those sufficient ($p = 0.37$; Table 3).

For global cognition, those moderately and severely deficient in serum 25(OH)D changed –0.01 SD (95% CI: –0.04 to 0.03) and –0.05 SD (95% CI: –0.13 to 0.02) per year, respectively, compared to those sufficient ($p = 0.37$; Table 4). The RR for substantial decline in global cognition in those moderately and severely 25(OH)D deficient was 1.22 (95% CI: 0.97 to 1.53) and 1.73 (95% CI: 1.22 to 2.45), respectively, compared to those sufficient ($p = 0.007$; Table 4).

Sensitivity analyses with continuous serum 25(OH)D concentrations yielded similar results. Every SD increase in 25(OH)D concentrations was associated with a slower rate of decline in visual memory of 0.02 SD (95% CI: 0.004 to 0.03, $p = 0.01$) per year. The association between 25(OH)D concentrations and substantial memory decline was not significant (RR = 0.97, 95% CI: 0.87 to 1.07, $p = 0.53$). For global cognition, every SD increase in 25(OH)D

Table 1
Baseline characteristics of CHS participants included in analyses of memory by serum 25(OH)D category

Characteristic		Serum 25(OH)D, nmol/L		
	All *N* = 1,291	≥50 *N* = 937	≥25 to <50 *N* = 309	<25 *N* = 45
Age (y), median (IQR)	72 (70–75)	72 (70–75)	72 (70–75)	72 (70–76)
Female, *n* (%)	875 (67.8)	601 (64.1)	236 (76.4)	38 (84.4)
Season tested, *n* (%)				
Dec–Feb	266 (20.6)	157 (16.8)	93 (30.1)	16 (35.6)
Mar–May	298 (23.1)	166 (17.7)	114 (36.9)	18 (40.0)
Jun–Aug	370 (28.7)	319 (34.0)	45 (14.6)	6 (13.3)
Sep–Nov	357 (27.7)	295 (31.5)	57 (18.5)	5 (11.1)
Education (*N* = 1,289), *n* (%)				
Did not finish high school	216 (16.8)	151 (16.1)	56 (18.2)	9 (20.0)
Finished high school/some college/vocational	740 (57.4)	537 (57.4)	176 (57.1)	27 (60.0)
College/professional	333 (25.8)	248 (26.5)	76 (24.7)	9 (20.0)
BMI, mean(SD)	26.6 (4.5)	26.1 (4.1)	27.9 (5.1)	27.9 (5.7)
Income, *n* (%)				
Low	618 (47.9)	435 (46.4)	155 (50.2)	28 (62.2)
Middle	395 (30.6)	303 (32.3)	83 (26.9)	9 (20.0)
High	207 (16.0)	160 (17.1)	42 (13.6)	5 (11.1)
Missing	71 (5.5)	39 (4.2)	29 (9.4)	3 (6.7)
Current smoker (*N* = 1,257), *n* (%)	112 (8.9)	74 (8.1)	34 (11.2)	4 (9.1)
Alcohol use (*N* = 1,289), *n* (%)				
Non-drinkers	649 (50.4)	459 (49.0)	164 (53.3)	26 (59.1)
Moderate drinkers	485 (37.6)	353 (37.7)	115 (37.3)	17 (38.6)
Heavy drinkers	155 (12.0)	125 (13.3)	29 (9.4)	1 (2.3)
Depressive symptoms, n (%)	247 (19.1)	164 (17.5)	71 (23.0)	12 (26.7)
Gait impairment (*N* = 1,288), *n* (%)	31 (2.4)	24 (2.6)	7 (2.3)	0 (0.0)
White, *n* (%)	1,156 (89.5)	888 (94.8)	241 (78.0)	27 (60.0)
Visual memory score[a], mean (SD)	5.6 (1.6)	5.6 (1.6)	5.4 (1.6)	5.2 (1.8)
Global cognitive score[b], median (IQR)	95 (91–98)	95 (92–98)	94 (91–97)	94 (91–98)
Years of follow-up, median (IQR)	5 (5-5)	5 (5-5)	5 (5-5)	5 (3–5)

CHS, Cardiovascular Health Study; 25(OH)D, 25-hydroxyvitamin D; BMI, Body Mass Index; SD, Standard Deviation; IQR, Interquartile Range. [a]Benton Visual Retention Test (range 0–10; higher scores represent better visual memory). [b]Modified Mini-Mental State Examination (range 0–100; higher scores represent better global cognition).

concentrations was associated with a mean change of 0.01 SD (95% CI: –0.01 to 0.02, $p = 0.37$) per year. The association between 25(OH)D concentrations and substantial global cognitive decline was not significant (RR = 0.96, 95% CI: 0.85 to 1.07, $p = 0.44$). Additional adjustment for ethnicity did not change the pattern of results for either outcome (Supplementary Tables 1 and 2).

Results from the LASA

Baseline characteristics of LASA participants included in analyses of memory are presented in Table 2. In the LASA, there was also little difference between basic and fully adjusted models (Tables 3 and 4) therefore we present fully adjusted results.

For verbal memory, moderate and severe deficiency in serum 25(OH)D was associated with a mean change of 0.01 SD (95% CI: –0.01 to 0.02) and –0.01 SD (95% CI: –0.04 to 0.02) per year respectively compared to sufficiency ($p = 0.34$; Table 3). The RR for substantial decline in verbal memory in those moderately and severely 25(OH)D deficient was 0.83 (95% CI: 0.63 to 1.11) and 1.04 (95% CI: 0.62 to 1.76), respectively, compared to those sufficient ($p = 0.42$; Table 3).

For global cognition, those moderately and severely deficient in serum 25(OH)D changed –0.03 SD (95% CI: –0.05 to –0.004) and –0.08 SD (95% CI: –0.12 to –0.04) per year, respectively, compared to those sufficient ($p < 0.001$; Table 4). The RR for substantial decline in global cognition in those moderately and severely 25(OH)D deficient was 0.94 (95% CI: 0.77 to 1.14) and 1.12 (95% CI: 0.84 to 1.48), respectively, compared to those sufficient ($p = 0.43$; Table 4).

Sensitivity analyses revealed continuous 25(OH)D concentrations in SD units were not associated with annual change in verbal memory (0.0002 SD, 95% CI: –0.01 to 0.01, $p = 0.97$) or substantial verbal memory decline (RR = 1.04, 95% CI: 0.90 to 1.20, $p = 0.58$). For global cognition, every SD increase in 25(OH)D concentrations was associated with a slower rate of decline in global cognition of 0.02 SD (95% CI: 0.01 to 0.03,

Table 2
Baseline characteristics of LASA participants included in analyses of memory by serum 25(OH)D category

Characteristic		Serum 25(OH)D, nmol/L		
	All *N* = 915	≥50 *N* = 515	≥25 to <50 *N* = 326	<25 *N* = 74
Age (y), mean (SD)	74.1 (6.0)	72.6 (5.3)	75.5 (6.2)	78.6 (6.4)
Female, No. %	505 (55.2)	245 (47.6)	212 (65.0)	48 (64.9)
Season tested, No. (%)				
Dec–Feb	225 (24.6)	105 (20.4)	94 (28.8)	26 (35.1)
Mar–May	239 (26.1)	124 (24.1)	100 (30.7)	15 (20.3)
Jun–Aug	204 (22.3)	141 (27.4)	48 (14.7)	15 (20.3)
Sep–Nov	247 (27.0)	145 (28.2)	84 (25.8)	18 (24.3)
Education (y, *N* = 914), mean (SD)	9.1 (3.2)	9.2 (3.1)	8.9 (3.3)	8.6 (3.5)
BMI (*N* = 911), mean (SD)	27.0 (4.0)	26.5 (3.6)	27.6 (4.3)	27.8 (4.9)
Income, *n* (%)				
Low	460 (50.3)	228 (44.3)	185 (56.8)	47 (63.5)
Middle	255 (27.9)	158 (30.7)	84 (25.8)	13 (17.6)
High	148 (16.2)	95 (18.5)	44 (13.5)	9 (12.2)
Missing	52 (5.7)	34 (6.6)	13 (4.0)	5 (6.8)
Current smoker, *n* (%)	152 (16.6)	77 (15.0)	54 (16.6)	21 (28.4)
Alcohol use (*N* = 914), *n* (%)				
Non-drinkers	197 (21.6)	84 (16.3)	94 (28.8)	19 (25.7)
Moderate drinkers	475 (52.0)	265 (51.6)	165 (50.6)	45 (60.8)
Heavy drinkers	242 (26.5)	165 (32.1)	67 (20.6)	10 (13.5)
Depressive symptoms (*N* = 907), *n* (%)	123 (13.6)	58 (11.4)	51 (15.7)	14 (19.2)
Gait impairment (*N* = 905), *n* (%)	81 (9.0)	22 (4.3)	38 (11.8)	21 (28.4)
White, *n* (%)	906 (99.0)	510 (99.0)	324 (99.4)	72 (97.3)
Verbal memory score[a], mean (SD)	15.2 (4.6)	15.6 (4.6)	15.0 (4.6)	14.1 (4.1)
Immediate word recall[b], mean (SD)	8.7 (2.3)	8.8 (2.3)	8.6 (2.4)	8.0 (2.2)
Delayed word recall[c], mean (SD)	6.6 (2.6)	6.7 (2.6)	6.4 (2.6)	6.1 (2.2)
Global cognitive score[d], median (IQR)	28 (27–29)	28 (27–29)	28 (26–29)	28 (26–29)
Years of follow-up, median (IQR)	10 (6–13)	10 (6–13)	6 (6–13)	6 (3–10)

LASA, Longitudinal Aging Study Amsterdam; 25(OH)D, 25-hydroxyvitamin D; BMI, Body Mass Index; SD, Standard Deviation; IQR, Interquartile Range. [a]Rey's Auditory Verbal Learning Test (range 0–30; sum of immediate and delayed recall; higher scores represent better verbal memory). [b]Rey's Auditory Verbal Learning Test (range 0–15; third trial score on immediate recall; higher scores represent better immediate word recall). [c]Rey's Auditory Verbal Learning Test (range 0–15; delayed recall; higher scores represent better delayed recall). [d]Mini-Mental State Examination (range 0–30; higher scores represent better global cognition).

$p = 0.001$) per year. 25(OH)D concentrations were not associated with the risk of substantial global cognitive decline (RR = 1.00, 95% CI: 0.91 to 1.09, $p = 0.93$). Excluding non-white participants did not change the pattern of results for either outcome (Supplementary Tables 1 and 2). The same pattern of results was also observed for both immediate and delayed word recall (Supplementary Table 1).

DISCUSSION

Our systematic review confirms no previous long-term population-based studies of older adults have investigated the association between vitamin D and memory decline. In the CHS, severe vitamin D deficiency was significantly associated with greater decline in visual memory compared to sufficiency. In the LASA, there was no significant association with verbal memory. For global cognition, severe vitamin D deficiency was significantly linked with increased risk of substantial decline in the CHS whereas in the LASA, moderate and severe vitamin D deficiencies were significantly associated with greater decline compared to sufficiency.

Our results add to the ongoing debate on the association between vitamin D and specific cognitive domains. A recent prospective study of 318 older adults observed that those moderately and severely deficient in serum 25(OH)D (30 to <50 and <30 nmol/L, respectively) experienced significantly greater annual decline in verbal memory (immediate and delayed word list recall) compared to those sufficient (50 to <125 nmol/L) over a mean of 4.8 years [34]. In the LASA, a similar measure of verbal memory was used, but we did not find a significant association. This may result from substantial methodological differences: Miller and colleagues [34] incorporated participants from a community outreach study and memory clinic referrals, had a shorter follow-up period, and used a competitive immunoassay with different cut points to measure serum 25(OH)D. They

Table 3
Estimates of standardized mean differences in change in memory and relative risk of substantial memory decline by serum 25(OH)D categories

			Serum 25(OH)D, nmol/L			
	No. of participants	No. of cases	≥50	≥25 to <50	<25	*p*-value
Standardized mean difference (95% CI) in change in memory						
CHS (visual memory)						
Model A[a]	1,291	NA	reference category	–0.03 (–0.06; 0.01)	–0.10 (–0.18; –0.02)	0.03
Model B[b]	1,250	NA	reference category	–0.03 (–0.06; 0.01)	–0.10 (–0.19; –0.02)	0.02
LASA (verbal memory)						
Model A[a]	915	NA	reference category	0.01 (–0.01; 0.02)	–0.01 (–0.04; 0.02)	0.41
Model B[b]	897	NA	reference category	0.01 (–0.01; 0.02)	–0.01 (–0.04; 0.02)	0.34
Relative risk (95% CI) of substantial memory decline						
CHS (visual memory)						
Model A[c]	1,291	336	reference category	1.12 (0.91; 1.37)	1.42 (0.96; 2.09)	0.16
Model B[d]	1,250	320	reference category	1.08 (0.87; 1.34)	1.32 (0.87; 2.01)	0.37
LASA (verbal memory)						
Model A[c]	915	183	reference category	0.85 (0.64; 1.13)	1.02 (0.62; 1.69)	0.51
Model B[d]	897	183	reference category	0.83 (0.63; 1.11)	1.04 (0.62; 1.76)	0.42

CHS, Cardiovascular Health Study; LASA, Longitudinal Aging Study Amsterdam; 25(OH)D, 25-hydroxyvitamin D; NA, Not Applicable; CI, Confidence Interval. [a]Model A includes baseline age, season of vitamin D collection, time and interaction term between vitamin D categories and time. [b]Model B includes Model A and baseline education, gender, income, body mass index, smoking, alcohol consumption, depressive symptoms and gait impairment. [c]Adjusted for age, season of vitamin D collection, baseline memory score and years of follow-up. [d]Adjusted for Model A and education, gender, income, body mass index, smoking, alcohol consumption, depressive symptoms and gait impairment.

Table 4
Estimates of standardized mean differences in change in global cognition and relative risk of substantial cognitive decline by serum 25(OH)D categories

			Serum 25(OH)D, nmol/L			
	No. of participants	No. of cases	≥50	≥25 to <50	<25	*p*-value
Standardized mean difference (95% CI) in change in global cognition						
CHS						
Model A[a]	1,612	NA	reference category	–0.01 (–0.04; 0.03)	–0.04 (–0.11; 0.03)	0.52
Model B[b]	1,564	NA	reference category	–0.01 (–0.04; 0.03)	–0.05 (–0.13; 0.02)	0.37
LASA						
Model A[a]	1,074	NA	reference category	–0.02 (–0.05; –0.001)	–0.08 (–0.12; –0.03)	0.001
Model B[b]	1,044	NA	reference category	–0.03 (–0.05; –0.004)	–0.08 (–0.12; –0.04)	<0.001
Relative risk (95% CI) of substantial global cognitive decline						
CHS						
Model A[c]	1,612	337	reference category	1.18 (0.95; 1.47)	1.65 (1.17; 2.34)	0.01
Model B[d]	1,564	324	reference category	1.22 (0.97; 1.53)	1.73 (1.22; 2.45)	0.007
LASA						
Model A[c]	1,074	356	reference category	0.95 (0.79; 1.14)	1.22 (0.94; 1.59)	0.17
Model B[d]	1,044	346	reference category	0.94 (0.77; 1.14)	1.12 (0.84; 1.48)	0.43

CHS, Cardiovascular Health Study; LASA, Longitudinal Aging Study Amsterdam; 25(OH)D, 25-hydroxyvitamin D; NA, Not Applicable; CI, Confidence Interval. [a]Model A includes baseline age, season of vitamin D collection, time and interaction term between vitamin D categories and time. [b]Model B includes Model A and baseline education, gender, income, body mass index, smoking, alcohol consumption, depressive symptoms and gait impairment. [c]Adjusted for age, season of vitamin D collection, baseline global cognitive score and years of follow-up. [d]Adjusted for Model A and education, gender, income, body mass index, smoking, alcohol consumption, depressive symptoms and gait impairment.

did not include a measure of visual memory, so it was not possible to compare with our CHS results. Taken together, these results suggest that there may be an association between low vitamin D levels and memory decline which is weaker than that observed for other cognitive domains [6]. We therefore hypothesize that the previously observed relationship between low vitamin D and an increased risk of Alzheimer's disease [27, 35] is driven by non-amnestic cognitive decline, and in particular executive dysfunction. Further prospective

studies incorporating multiple measures of memory are needed to confirm whether there is a differential pattern of association between visual and verbal memory. Our findings for global cognition are consistent with previous prospective studies showing increased global cognitive decline [2] and risk of all-cause dementia [27, 35, 36].

Several neurodegenerative and vascular mechanisms have been identified explaining the association between vitamin D, cognition and dementia [3–5]. Executive dysfunction is more strongly linked with cerebrovascular disease than neurodegeneration [37]. Low 25(OH)D levels are associated with an increased risk of stroke, particularly ischemic [38]. Given that stroke is an important dementia risk factor [39], vascular mechanisms may drive the association with dementia. Cross-sectional neuroimaging studies indicate the link with cerebrovascular abnormalities may be stronger than with neurodegeneration, including hippocampal atrophy [4]. However, the only prospective neuroimaging study found no association between vitamin D and white matter hyperintensities or infarcts [40]. Future prospective neuroimaging studies are warranted to establish whether vascular abnormalities mediate the association between low vitamin D and dementia to a greater degree than neurodegenerative markers.

Our study has several strengths. We incorporate a systematic review and analyses of two large prospective population-based studies including both men and women in the US and Europe. The long follow-up and the exclusion of participants with prevalent dementia in both studies make reverse causation less likely. Sensitivity analyses using attrition weighting suggest that it is unlikely that non-random attrition accounts for the associations observed. Our study also has several limitations. While the CHS included white and African-American elders, it did not incorporate other ethnicities, and the LASA sample was predominantly white. The competitive protein-binding assay used in the LASA is less accurate than the liquid chromatography-tandem mass spectrometry used in the CHS, which may have contributed to the heterogeneity of results [41]. A previous meta-analysis of vitamin D and prevalent Alzheimer's disease observed significant heterogeneity depending on the assay used [1]. Different aspects of memory were assessed in each cohort using a single test making comparisons more challenging and further large population-based or well-designed interventional studies are needed to exclude the possibility of chance findings. Results may have been attenuated in the LASA due to regression dilution bias linked to the longer follow-up period [42], and in the CHS due to the exclusion of participants with cardiovascular disease at baseline.

CONCLUSIONS

Our systematic review establishes no previous long-term population-based studies of older adults have investigated the association between vitamin D and memory decline. Our findings suggest an association between low vitamin D levels and decline in visual memory in the CHS, but no association with verbal memory in the LASA. Clarification of the mechanisms mediating the associations with vitamin D deficiency will inform the design of future vitamin D supplementation trials to prevent or delay cognitive decline and dementia.

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SUPPLEMENTARY MATERIAL

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