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Vitamin D status is associated with executive function a decade later: Data from the Women's Healthy Ageing Project

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ABSTRACT

Objectives: Vitamin D deficiency has been associated with cognitive decline and dementia in older adults. However, there is a paucity of studies assessing whether this association manifests from midlife. Given the long prodromal stage of dementia, we investigated the association between midlife vitamin D and cognition 10 years later.

Study design: 252 participants (aged 55–67 years) from the Women's Healthy Ageing Project had baseline (2002) vitamin D and neuropsychological measures assessed. Of these, 170 (aged 65–77 years) had follow-up neuropsychological testing (2012).

Outcome measures: Serum 25-hydroxyvitamin D (25[OH]D) was measured using an automated chemiluminescence system. The neuropsychological tests used were: Consortium to Establish a Registry for Alzheimer's Disease (CERAD), California Verbal Learning Test Second Edition (CVLT-II), verbal fluency and Trail Making Test-B (TMT-B). Composite scores for verbal episodic memory (CERAD and CVLT-II) and executive function (verbal fluency and TMT-B) were obtained by summating standardized scores for each test.

Results: Analyses were adjusted for age, education and body mass index (BMI). Further adjustment for physical activity, depression, vascular risk factors, supplementation and *APOE4*-genotype did not materially change the results. At baseline, those with vitamin D > 25nmol/L performed better on verbal fluency (β = 2.46, 95%CI = 0.53,4.40) and TMT-B time (β = -18.23, 95%CI = −32.86, −3.61), with higher executive function (β = 1.40, 95%CI = 0.44,2.37). These relationships persisted 10 years later for TMT-B (β = -15.38, 95%CI = −30.82,0.07) and executive function (β = 1.05, 95%CI = 0.14,1.95). There were no associations with tests of verbal episodic memory.

Conclusion: Midlife vitamin D > 25nmol/L is associated with improved aspects of executive function in ageing. Findings highlight a potential therapeutic age window where midlife vitamin D repletion could be neuroprotective against cognitive decline.

1. Introduction

As the population ages, the imminent rise in cognitive impairment and dementia is a significant public health concern. With numerous drug trials failing to reverse or improve clinical symptoms of dementia [1], preventative therapy targeting people at risk of developing this disease remains an essential goal for research. Although risk factors such as diabetes, smoking, physical inactivity, low education and cognitive stimulation contribute to half of the risk of developing dementia [2], compliance to programs aimed at modifying these factors is poor. Observational evidence has demonstrated a relationship between vitamin D deficiency and reduced cognitive health [3], highlighting the potential for a readily available and modifiable target for risk reduction. Population rates of vitamin D deficiency or insufficiency (< 25 and 50 nmol/L respectively) range between 31%-42% [4,5], with older women at greatest risk of deficiency [4]. Despite women also being

Abbreviations: APOE4, Apolipoprotein E4; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CESD-10, Center for Epidemiological Studies Depression Scale-10 item; CVLT-II, California Verbal Learning Test Second Edition; TMT-B, Trail Making Test B

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more likely to develop cognitive decline and dementia [6], there is a lack of research examining sex-specific risk factors for disease.

Currently, there is limited evidence from long-term prospective studies and randomized control trials (RCTs) [3] to support a protective effect of vitamin D on cognitive health. Considering the long prodromal stage of cognitive decline [7], longitudinal studies in this field can provide valuable information about "critical windows" where intervention for risk reduction and prevention could be most beneficial. Much of the observational evidence to date demonstrating a relationship between vitamin D and cognition has primarily been conducted in older adults (≥ 65yrs) [8,9], which may increase the likelihood of reverse causality. Given the pathophysiology of cognitive decline and dementia precedes clinical symptoms by decades [7], identifying and modifying risk factors should focus on the early prodromal stages, before irreversible neuronal loss.

Most longitudinal studies conducted from midlife [10] and for durations over 10-years [11–13] have not found consistent associations between vitamin D and cognition. However, these studies have been mixed sex [10–12] or male-only [13]. Although there is some evidence to suggest a more pronounced effect of vitamin D status on cognitive processes in women [14], no study has yet followed this association from midlife to late-life in a female-only cohort. The objective of this study was therefore to investigate the role of midlife vitamin D levels and late-life cognition in women, over a 10-year follow-up.

2. Methods

2.1. Study design and cohort

Participants were recruited from the Women's Healthy Ageing Project, which is an ongoing longitudinal cohort of 438 Australian women, aged 45–55 years at baseline. Details of the cohort and protocol have been previously described [15]. The present study has received approval from the University of Melbourne Human Research Ethics Committee (HREC: 931149X, 010528, 010411, 1034765 and 1647448) and was carried out in accordance with the Declaration of Helsinki. All participants signed written informed consent prior to participation.

2.2. Measurement of serum 25-hydroxyvitamin D

Serum 25-hydroxyvitamin D (25[OH]D) was measured at one timepoint (baseline, 2002). Following an overnight fast, 80 ml of venous blood was collected via the median cubital vein. Within an hour of collection, samples were centrifuged and a 1 ml aliquot was used for 25[OH]D analysis. Serum 25[OH]D was analyzed using the DiaSorin Liaison assay (Liaison) automated chemiluminescence system (interassay C.V = 10.3% at 29 nmol/L). Serum 25[OH]D results were multiplied by 2.496 to convert from conventional units (ng/ml) to International System of Units (SI).

2.3. Neuropsychological assessment

Neuropsychological assessments were performed at baseline (2002) and follow-up (2012). Verbal episodic memory was assessed via the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) and the California Verbal Learning Test Second Edition (CVLT-II) word list recall. Specifically, three trials of immediate recall and a three minute delayed recall were administered. For the CERAD, participants were read 10 unrelated words, with the presentation of words in a different order for each trial. The maximum score for each trial is 10 with a total sum of immediate recall trial score of 30. For the CVLT-II, 16 words belonging to one of four categories (List A: furniture, animals, vegetables, vehicles) were read to participants. For this study, the three immediate recall trials and 20 min delayed free recall from list A was used, as per a previously described protocol [16].

Executive function was assessed via the Trail Making Test B (TMT-B) and semantic (animal) verbal fluency task. The TMT-B required participants to draw a line to connect numbers (1–13) and letters (A-L). Participants were required to switch between numbers to letters as quickly as possible whilst maintaining pen-paper contact. The number of errors and time to completion were recorded. The semantic verbal fluency task required participants to name as many animals as they could think of within one minute. The total number of animals verbalized (minus repetitions) within one minute was recorded.

2.4. Covariates

Covariates included participant demographics (age in years, level of education [< 12, 12 or > 12 years], and body mass index [BMI]), lifestyle factors (self-reported physical activity, current smoking status, alcohol intake and taking vitamin D supplementation [yes/no]), depression (Center for Epidemiologyical Studies Depression Scale [CESD-10] score) comorbidities (self-reported, current diagnosis [yes/no] of diabetes, heart disease and hypertension) and genetic factors (apolipoprotein E4 [*APOE4*] risk variant carrier). Physical activity was self-reported relating to their physical activity levels for recreation and leisure (≤1d/wk, 2–3d/wk, 4–6d/wk and daily). Alcohol intake was measured as the average number of drinks in the preceeding week (none, 1–2, 3–7 and > 7d/wk).

2.5. Data analyses

To account for the seasonal variation in vitamin D, serum 25[OH]D was deseasonalized using a sinusoidal regression function which has been previously described [17]. The estimated annual 25[OH]D level was used for all analyses thereafter. Serum 25[OH]D was analyzed as a categorical variable, dichotomized at 25nmol/L cut-off for deficiency, as outlined by the World Health Organization [18].

Composite scores for verbal episodic memory and executive function were calculated by generating z-scores equal to the standard deviation of the total sample mean for each test. Specifically, both total immediate recall (sum of trials 1–3) and delayed recall scores for the CERAD and CVLT-II were summated for verbal episodic memory and verbal fluency, TMT-B errors and TMT-B times were summated to form the executive function composite score. Change in all neuropsychological outcome measures were calculated as the difference in scores between 2002 and 2012, divided by the duration (10-years) between measures, then multiplied by 10 to restore the scale.

2.6. Statistical analyses

Differences in baseline characteristics between vitamin D categorical groups were quantified using one-way ANOVA and Pearson Chi Square for continuous and categorical variables respectively. Paired *t*-tests were used to compare differences in demographics for individuals who did not have follow-up neuropsychological testing in 2012, compared to individuals with neuropsychological testing in both 2002 and 2012. All data was tested for normality. Where raw neuropsychological test scores were highly skewed, Box-Cox regression was used to identify the optimal transformation. To allow for clinical interpretation, the coefficients presented in text and tables have been transformed back to their original scale.

Multivariable linear regression was used to assess the effect of vitamin D level (≤ 25 and > 25nmol/L) and relevant covariates on neuropsychological test scores and standardized cognitive composite scores at baseline (2002) and follow-up (2012). Cognitive decline was evaluated as a dichotomous term, defined by whether the participants' change from, 2002–2012 was greater than 1 SD from the mean change of the sample. The association between vitamin D level and the risk of cognitive decline was assessed by log-binomial regression. Multivariable models were adjusted for all covariates which were significant independent predictors of neuropsychological tests and composite scores. All analyses were conducted using STATA/SE 14.0 (StataCorp, College Station, TX USA) and confidence intervals (CI) presented as 95%.