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Vitamin D insufficiency and cognitive impairment in Asians: a multi-ethnic population-based study and meta-analysis

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Abstract

Background. The relationship between vitamin D insufficiency and cognitive impairment remains equivocal in Asians. We examined the association between circulating 25-hydroxyvitamin D (25OHD) concentration and cognitive performance in a large multi-ethnic Singaporean population-based study. We also conducted a meta-analysis of 25OHD concentrations among cognitively impaired older adults in Asia.

Methods. Our population-based cross-sectional study included 2273 persons ≥ 60 years of age from the Singapore Epidemiology of Eye Diseases (SEED) study (mean $\pm$ SD age 70.4 $\pm$ 6.2 years; 44.7% female), who were categorized according to 25OHD concentration (i.e. ≤ 10 , 10.1–20, and >20 ng/mL). 25OHD concentration was measured and adjusted to reflect a deseasonalized value. Cognition was assessed using the total and domain scores of the Abbreviated Mental Test (AMT). Global cognitive impairment was defined as AMT score of ≤ 6 if 0–6 years of education and AMT score of ≤ 8 if >7 years of education. Fully adjusted multivariate models were used. We included seven studies in a meta-analysis of 25OHD and cognition in Asia (6068 participants; 1179 cognitively impaired cases).

Results. Participants with 25OHD levels >20 ng/mL ($n = 1302$) had higher AMT total scores (mean $\pm$ SD 8.5 $\pm$ 1.9) and were less likely to have cognitive impairment (14.1%) than participants with lower 25OHD levels (overall $P < 0.001$, P -trend < 0.001). Deseasonalized 25OHD concentration was associated with AMT score ($\beta=0.10$ per 10 ng/mL, $P = 0.035$). Vitamin D insufficiency (25OHD ≤ 20 ng/mL) was associated with global cognitive impairment (OR 1.56, $P = 0.028$). Specifically, 25OHD concentration correlated with semantic memory ($r = 0.08$, $P = 0.009$) and orientation in time ($r = 0.09$, $P = 0.003$). In the meta-analysis, the pooled mean 25OHD difference was -6.83 ng/mL (95% confidence interval -11.36;-2.30), indicating lower 25OHD concentrations among cognitively impaired compared to cognitively healthy participants in Asia.

Conclusion. Vitamin D insufficiency is associated with a greater likelihood of and more severe cognitive impairment in Asian populations.

Keywords: Asia, cognition, older adults, vitamin D.

Introduction

Cognitive disorders in older adults are becoming a worldwide concern, due to their increasing prevalence and adverse consequences on health [1]. Vitamin D, a hormone classically recognized for its involvement in bone and calcium metabolism, has been extensively studied as a risk factor for cognitive impairment [2–7]. It has been suggested that vitamin D influences brain health and function [5–7]. Specifically, the hippocampus, hypothalamus, cortex, and subcortex possess vitamin D receptors (VDRs) [6], which allow vitamin D to exert various neuroprotective effects in brain areas essential for cognition [7]. Neuropidemiology has consistently revealed a strong association between vitamin D status and cognition in older adults [2–5]. Indeed, epidemiological studies have shown an increased prevalence of Alzheimer’s disease (AD), dementia, and cognitive impairment among European and US older community dwellers with low serum 25-hydroxyvitamin D (25OHD) concentrations [2–4]. In the same countries, older adults with vitamin D insufficiency experience greater cognitive decline [4] and are at higher risk of dementia [8] than those with normal levels. Nevertheless, to the best of our knowledge, little is known about these relationships in Asian populations [9–14]. It is well recognized that populations in Asia are ageing [15]. As a decreasing proportion of adults are able to maintain normal vitamin D status with advancing age [16], cognitive disorders and vitamin D insufficiency are among the challenges that will be encountered in the coming years in Asia. Furthermore, significant regional differences in vitamin D levels around the world have been highlighted, with particularly low levels in Asia [17]. Vitamin D insufficiency has been reported in older individuals in Singapore [18], but the potential consequences for cognition are not known. The aim of the present study was to examine the relationship between vitamin D status and cognitive performance (overall and domain-specific) in multi-ethnic Asian older community dwellers in Singapore. In addition, the 25OHD concentrations among cognitively impaired and cognitively healthy Asian older adults were investigated in a meta-analysis including the present and previous studies.

Methods

Study population

Data for the current analysis were derived from a case–control study (Singapore Kidney Eye Study; $n = 2944$) nested within the Singapore Epidemiology of Eye Diseases (SEED) study, comprising data from three large major ethnic groups: Malays (Singapore Malay Eye Study, 2004–2006), Indians (Singapore Indian Eye Study, 2007–2009), and Chinese (Singapore

Chinese Eye Study, 2009–2011). All studies were conducted in the same clinic (Singapore Eye Research Institute), according to the same protocol; adults aged 40–80 years residing in the south western region of Singapore were recruited through an age-stratified random sampling method (latitude, 1.35°N). Details of the methodology and population characteristics of the SEED study have been reported previously [19, 20]. All participants attended an interview and underwent clinical and laboratory examination at the study clinic. For the current analysis, we included only individuals aged ≥ 60 years ($n = 2273$) as cognitive status was assessed only among these participants.

Assessment of cognitive performance

Cognition was assessed using the Abbreviated Mental Test (AMT), a reliable, standardized, validated screening test for cognitive impairment [21]. Of note, the AMT is sensitive (91.5%) and specific (82.4%) for dementia in adults aged ≥ 60 years [22]. It consists of 10 items scored 0 or 1 (correct answer). Global cognitive performance was explored using the total AMT score, which ranges from 0 (no correct answers) to 10 (all answers correct). Decreasing AMT score is synonymous with increasing severity of cognitive impairment. Global cognitive impairment was defined as AMT score of ≤ 6 if 0–6 years of education, or AMT score of ≤ 8 if >7 years of education [19, 20]. The number of years of education was determined from a standardized questionnaire.

In addition, domain-specific cognitive performances were separately analysed by decoupling AMT items referring to anterograde episodic memory (recall of memory phrase), retrograde episodic memory (date of birth, home address), semantic memory (name of prime minister, picture recognition), working memory (serial subtraction from 20), and orientation in space (place) and time (hour, year). Each performance domain was considered impaired if one or more items were not answered correctly.

Assessment of circulating 25OHD concentration

Circulating 25OHD concentration was measured from venous blood collected in the non-fasting state at baseline and stored at -80°C . The collection and storage process was the same for all study participants. Serum samples were used for measuring 25OHD levels in Chinese and Indian participants and plasma samples were used in Malay participants. Circulating 25OHD levels were measured using an electrochemiluminescence immunoassay (ECLIA) at the National University Hospital Referral Laboratory. ECLIA is comparable for quantification of 25OHD levels to the gold standard high-performance liquid chromatography [23]. The

lower limit of detection of 25OHD in the current study was 4 ng/mL. The coefficient of variation of the assay ranged from 4.7% to 11.5% for the concentration range 10.3–57.5 ng/mL.

Deseasonalized 25OHD concentrations were calculated by regression of the measured 25OHD concentrations (in ng/mL) according to the periodic function:

$$y_t = \beta_0 + \beta_1 \sin\left(\frac{2\pi t}{365}\right) + \beta_2 \cos\left(\frac{2\pi t}{365}\right)$$

where y_t denotes as-measured 25OHD concentration, t denotes the day of the year the sample was collected and β_j ($j=0,1,2$) are estimated regression coefficients; the residuals are then added to the seasonal average to create a deseasonalized 25OHD concentration for each individual [24]. This provides a way to adjust for the seasonal variation of 25OHD concentration given that blood samples were collected throughout the year; ‘1 January’ deseasonalized values were arbitrarily chosen for analysis [24], though in a periodic function any date would be expected to have been equally informative. Given the assumptions and limitations inherent in deseasonalized analysis, we also performed parallel analyses using as-measured 25OHD values.

Vitamin D status was categorized as follows: 25OHD ≤ 10 , 10.1–20, and >20 ng/mL (reference group) based on conventional cut-off values for deficiency (≤ 10 ng/mL) and insufficiency (≤ 20 ng/mL) [16], and consistent with previous evidence that sufficiency in the context of cognitive risk may be in the region of 20 ng/mL (to convert to nmol/L, multiply by 2.496) [8].

Assessment of covariates

The following covariates were assessed: age, gender, smoking, alcohol consumption, education, ethnicity, body mass index (BMI), mean arterial pressure (MAP), wearing glasses, gait disorders, anxiodepressive disorders, glycosylated haemoglobin (HbA1c), LDL cholesterol, and estimated glomerular filtration rate (eGFR).

An interviewer-administered standardized questionnaire was used to obtain information on age, gender, ethnicity, history of regular smoking, alcohol consumption, highest education level attained, whether the participant was wearing glasses, motor skills, and mood. A high education level was defined as ≥ 6 years of education; regular alcohol consumption was defined as consumption on ≥ 5 days per week; gait disorders were defined as problems walking about, or being confined to bed; and anxiodepressive disorders were defined as self-reported moderate to extreme anxiety or depression. Clinical covariates were obtained from a

standardized physical examination. Systolic (SBP) and diastolic blood pressure (DBP) were measured using a digital automatic blood pressure monitor after the participant had rested sitting down for at least 5 min, and an average of two measurements were taken as the blood pressure value for that individual. MAP was calculated as: $\frac{SBP+2\ DBP}{3}$. Circulating creatinine, HbA1c, and LDL cholesterol were determined using automated standard laboratory methods at the National University Hospital Referral Laboratory. eGFR was determined from the standardized serum creatinine level using the CKD-EPI equation [25].

Statistical analysis

Participants' characteristics were presented as mean $\pm$ SD or frequency and percentage, as appropriate. As the number of observations was higher than 40, comparisons were not affected by the shape of the error distribution and no transformation was applied [26]. First, comparisons between participants separated into three groups based on 25OHD concentration (i.e. ≤ 10 , 10.1–20, and >20 ng/mL) were performed using the chi-squared test or ANOVA, as appropriate. Further *post hoc* analyses were performed using Fisher's least significant difference test. The Jonckheere–Terpstra test was used to assess trends in total AMT score across groups. Secondly, univariate and multiple linear regressions were used to examine the association between 25OHD concentration (independent variable) and the total AMT score (dependent variable), while adjusting for potential confounders. Separate models were used for as-measured and deseasonalized 25OHD concentrations. Thirdly, Pearson correlation matrices were used to determine which domain-specific cognitive performance correlated with as-measured and deseasonalized 25OHD concentrations. Finally, multiple logistic regression models were used to examine the risk of global cognitive impairment according to the participants' characteristics. *P*-values <0.05 were considered significant. All statistical analysis was performed using SPSS (v15.0, IBM Corporation, Chicago, IL, USA).

Ethics

All subjects provided written informed consent before participating in the study. The study was conducted in accordance with the Declaration of Helsinki (1983). The SEED study and Singapore Kidney and Eye Study were approved by the Singapore Eye Research Institute Institutional Review Board.

Meta-analysis

The meta-analysis was performed according to the MOOSE guidelines [27]. To summarize results from the present and previous studies in Asia, we systematically identified relevant peer-reviewed, population-based, prospective, cross-sectional, and patient-based studies on the association between 25OHD concentration and cognitive impairment in Asia using an electronic literature search of Medline until April 2015 without language restriction, with combinations of key words (Fig. 1), and by scanning relevant reference lists. Studies using both cognitive impairment (i.e. abnormal cognitive score or mild cognitive impairment) and AD as the outcome were included. This search strategy identified six previous studies [9–14] as well as the present one; all included cross-sectional analyses.

All results were expressed as mean difference in as-measured 25OHD concentration (ng/mL) between cognitively impaired and cognitively healthy participants. Fixed- and random-effects meta-analyses were performed to generate summary values (Review Manager v5.1, The Nordic Cochrane Centre, Copenhagen, Denmark). Results are presented as forest plots. Heterogeneity was evaluated using Cochran's chi-squared test and I^2 statistics.

Results

A total of 2273 participants were recruited for this analysis (mean age 70.4 ± 6.2 years; 44.7% female; mean AMT score 8.2 ± 2.1). Overall, the mean measured 25OHD concentration was 23.3 ± 10.8 ng/mL; vitamin D deficiency (≤ 10 ng/mL 25OHD) was observed in 232 of the participants (10.2%) and vitamin D insufficiency (≤ 20 ng/mL 25OHD) in 971 participants (42.7%). Information on the season of blood test was available for 1121 participants; thus deseasonalized values of 25OHD were calculated for these participants.

As illustrated in Table 1, the mean AMT score differed according to 25OHD status (overall $P < 0.001$, P -trend < 0.001). Participants with 25OHD levels > 20 ng/mL had higher AMT scores than those with 25OHD ≤ 10 ng/mL ($P < 0.001$) or between 10.1 and 20 ng/mL ($P < 0.001$), although there was no difference between the latter two groups ($P = 0.067$).

Similarly, the proportion of participants with cognitive impairment differed across the groups ($P < 0.001$); individuals with 25OHD levels > 20 ng/mL were less likely to show cognitive impairment than those with 25OHD ≤ 10 ng/mL ($P < 0.001$) or between 10.1 and 20 ng/mL ($P < 0.001$). Again there was no difference between the latter two groups ($P = 0.264$).

Participants with cognitive impairment had lower 25OHD concentrations than those who were cognitively healthy (20.9 ± 10.8 vs. 23.8 ± 10.7 ng/mL, $P < 0.001$).

Table 2 shows univariate and multiple linear regressions between 25OHD concentration and total AMT score as a quantitative variable (on a scale of 0–10). Increased 25OHD

concentration was associated with an increase in total AMT score (unadjusted $\beta=0.26$ per 10 ng/mL 25OHD, $P \leq 0.001$), even after adjustment for demographic characteristics (adjusted $\beta=0.08$ per 10 ng/mL 25OHD, $P = 0.030$), additional adjustment for clinical factors (adjusted $\beta=0.08$ per 10 ng/mL 25OHD, $P = 0.029$), and further adjustment for blood measures (adjusted $\beta=0.08$ per 10 ng/mL 25OHD, $P = 0.029$). Using deseasonalized 25OHD values did not alter the association with AMT score (adjusted $\beta=0.10$ per 10 ng/mL 25OHD, $P = 0.035$). Table 3 shows the correlations between impairments of domain-specific cognitive performance and as-measured (Table 3A) or deseasonalized (Table 3B) 25OHD concentrations. As-measured 25OHD concentration correlated negatively with impairments of retrograde episodic memory ($r = -0.12$, $P < 0.001$), semantic memory ($r = -0.12$, $P < 0.001$) and orientation in time ($r = -0.13$, $P < 0.001$). Conversely, as-measured 25OHD did not correlate with any of the other domain-specific cognitive impairments. Regarding deseasonalized values, 25OHD correlated only with semantic memory impairment ($r = -0.08$, $P = 0.009$) and disorientation in time ($r = -0.09$, $P = 0.003$), and not with the other domain-specific cognitive impairments.

Lastly, Fig. 2 shows the association between vitamin D insufficiency (25OHD ≤ 20 ng/mL) and cognitive impairment. We found that vitamin D insufficiency was associated with cognitive impairment in the studied sample using as-measured or deseasonalized 25OHD (OR 1.35, $P = 0.020$ and OR 1.56, $P = 0.028$ respectively).

In a meta-analysis involving seven studies with a total of 6068 participants including 1179 cognitively impaired cases, the summary random mean 25OHD difference between cognitively impaired and cognitively healthy participants was -6.83 ng/mL [95% confidence interval (CI) -11.36;-2.30] (Fig. 3). This result indicates that cognitively impaired participants had lower 25OHD concentrations than their healthy counterparts in Asia. A sensitivity analysis stratifying by type of cognitive outcome demonstrated a summary random mean 25OHD difference of -14.9 ng/mL (95% CI -15.8;-14.0) ($\chi^2 = 0.7$, $P = 0.39$, $I^2 = 0.0\%$) while focusing on the diagnosis of AD [9, 10].

Discussion

The main finding of the present study was that among community dwelling Asian older adults in Singapore, independent of measured potential confounders, vitamin D insufficiency was associated with more frequent and more severe cognitive impairment, specifically affecting semantic memory and orientation in time. This finding was substantiated in a meta-analysis in

which the present study contributed 36% of all cognitively impaired participants. Taken together, our results provide strong evidence that vitamin D is important for cognitive function in Asians, and that Asian older adults with vitamin D insufficiency are particularly prone to cognitive impairment for which vitamin D may be a modifiable risk factor. The biological mechanisms linking vitamin D to brain health and function have been extensively studied, although not fully elucidated. It has been demonstrated that vitamin D (i) acts in the brain through VDRs present in neurons and glial cells [6], (ii) regulates the gene expression of various neurotrophins and protects neural networks by controlling the rate of mitosis and neuronal growth [6, 7], (iii) regulates inflammatory changes in the brain [28], promoting neuron viability and function, (iv) exerts neuroprotective effects against glutamate toxicity through the upregulation of VDR expression together with antioxidant and anti-ischaemic effects [6, 7], and (v) attenuates amyloid- β 42 accumulation by stimulating the phagocytosis of the amyloid- β peptide and by enhancing brain-to-blood amyloid- β efflux across the blood–brain barrier, with fewer amyloid plaques as a result [29]. However, causality cannot be inferred from our cross-sectional study. It is possible that, inconsistent with our hypothesis, impaired cognitive performance may lead to reduced mobility, lower sun exposure and limited access to vitamin D-rich foods; this may be responsible for vitamin D insufficiency, rather than vice versa. However, this possibility is mitigated by the relatively high BMI of 25.4 ± 4.9 kg/m² in our study population, which indicates overweight according to the National Heart, Lung, and Blood Institute [30]. Moreover the association between vitamin D insufficiency and cognition was significant even after adjustment for BMI and other factors (Table 2, Fig. 2).

The results of our original study, although attenuated, are in agreement with the overall finding from the meta-analysis. The definition of cognitive disorders differed in some of the included studies, and was based on an abnormal cognitive score as in our study [11–13], a diagnosis of mild cognitive impairment [14], or a diagnosis of AD [9, 10]. Despite the variety of cognitive outcomes, which is likely to account for the high degree of heterogeneity of the meta-analysis, our results are consistent with recent neuroepidemiological evidence of an association between decreased 25OHD concentrations and reduced global cognitive performance among older adults in Europe and the USA [2–5, 8]. Our results also show that 25OHD concentration correlated positively with impairments of semantic memory and orientation in time (Table 3). These additional analyses, though not definitive, allow us to explore which domain-specific cognitive functions explain the impairment of cognition as a whole in the case of vitamin D insufficiency. The finding of memory impairments

accompanying vitamin D insufficiency is consistent with the results of some previous European and US studies [4].

The present results provide evidence that decreased 25OHD concentration (i.e. ≤ 20 ng/mL) is associated in Asian older adults with worse cognitive performance, specifically semantic memory and orientation in time. This has many implications for practice and research. First, our results are consistent with the notion that age-related vitamin D insufficiency may explain part of the cognitive changes during aging. Secondly, they reinforce the idea that vitamin D insufficiency is a biological characteristic of older adults with cognitive impairment, suggesting that cognitively impaired older adults may benefit from vitamin D supplements in clinical routine to prevent the bone and non-bone adverse events that accompany vitamin D insufficiency. Thirdly, our results provide a strong rationale for conducting clinical trials in older adults with impaired cognition to assess whether vitamin D supplementation may affect cognition. In particular, future clinical trials should recruit older adults with both cognitive impairment (notably impaired semantic memory and impaired orientation in time) and an initial concentration of 25OHD ≤ 20 ng/mL, which is expected to reveal a potential cognitive effect of vitamin D supplements based on our results. For instance, it appears from the two studies with inconclusive results included in our meta-analysis [11, 12] that the mean 25OHD concentration above 20 ng/mL was already sufficient to meet the physiological needs associated with cognition, and thus detection of vitamin D effects was less likely in participants in these studies. From a clinical perspective, our findings contribute to further elucidating the profile of ideal target populations, which is the first step toward effective guidelines on the proper use of vitamin D supplements for the prevention of cognitive impairment in the elderly.

In our study, and as previously described [31], female gender was associated with cognitive impairment. There are several possible explanations for this finding, including sex-specific differences in education level ($P < 0.001$), age-related hormone reduction, genetics, comorbidities such as depression ($P < 0.001$), and brain glucose metabolism [31]. Another explanation may rely on the greater prevalence of vitamin D insufficiency in women compared to men in the present study ($P < 0.001$), likely due to a higher BMI in women (27 vs. 24 kg/m², $P < 0.001$) [32].

Strengths of our study include the relatively large size of the sample of older participants recruited from three different population-based cohorts in Singapore, a country in which the association between vitamin D and cognition has not yet been studied. Additionally, 25OHD concentration was measured using a standardized and validated automated technique, and

both as-measured and deseasonalized values of 25OHD were used in parallel analyses. Beside global cognitive performance, the use of AMT subscores enabled specific aspects of cognition to be assessed in relation to vitamin D. Finally, both linear and logistic regression models were applied to measure adjusted associations.

A number of limitations should also be considered. First, the study cohort was restricted to community dwelling adults who might not be representative of all older adults in Singapore, despite the fact that participants of three different ethnicities were included. Secondly, no information was available on possible history of vitamin D supplementation in the study participants. Thirdly, a selection bias is possible as data were derived from a case-control study designed to examine the association between novel biomarkers, including 25OHD, and both renal and retinal diseases [19, 20]. However controls had similar 25OHD concentrations compared to cases with age-related macular degeneration ($P = 0.2$) and cases with chronic kidney disease ($P = 0.8$), thus it was possible to use data from this population to examine the association between 25OHD concentration and cognition. Fourthly, the use of AMT subscores, which consist of one or two items, is a limitation as they provide a lower degree of proof compared to memory-dedicated tests; however they were used to identify areas warranting future study. Finally, the use of a cross-sectional design prevented any causal inference.

In conclusion, we observed an association between vitamin D insufficiency and overall and domain-specific cognitive impairment among community dwelling Asian older adults in Singapore. These findings were substantiated in a meta-analysis. Our findings contribute to the understanding of the involvement of vitamin D in cognitive function, and suggest that vitamin D supplements may prevent cognitive decline in Asians.

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None.

Author contributions

CS has full access to all of the data, takes responsibility for the data, the analyses and interpretation, and the conduct of the research and has the right to publish any and all data, separate and apart from the attitudes of the sponsor.

Study concept and design: CS and CA.

Acquisition of data: CYC, ELL, and CS.

Analysis and interpretation of data: CA, DM, ELL, and CS.

Drafting of the manuscript: CA, DM, CYC, ELL, and CS.

Critical revision of the manuscript for important intellectual content: HEW, TYW, and MKI.

Obtained funding: TYW, ELL, and CS.

Statistical expertise: CA, CYC, and CS.

Meta-analysis: CA.

Administrative, technical or material support: TYW, ELL, and CS.

Study supervision: CS.

Conflict of interest statement

None of the authors has any conflicts of interest to disclose.

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Table 1 Participants’ characteristics

	25-hydroxyvitamin D concentration				P-value ^a			
	Entire cohort (<i>n</i> = 2273)	≤10 ng/mL		>20 ng/mL	Overall	≤10 versus	≤10 versus	10.1–20 versus
		(<i>n</i> = 232)	10.1–20 ng/mL (<i>n</i> = 739)	(<i>n</i> = 1302)		10.1–20 ng/mL	>20 ng/mL	>20 ng/mL
Demographic characteristics								
Age, years	70.4±6.2	69.2±6.1	70.1±6.3	70.8±6.1	<0.001	0.047	<0.001	<0.001
Female gender, <i>n</i> (%)	1016 (44.7)	170 (73.3)	431 (58.3)	415 (31.9)	<0.001	<0.001	<0.001	<0.001
Regular smoking, <i>n</i> (%)	807 (35.5)	45 (19.4)	207 (28.0)	555 (42.6)	<0.001	0.009	<0.001	<0.001
Regular alcohol consumption ^b , <i>n</i> (%)	21 (0.9)	1 (0.4)	2 (0.3)	18 (1.4)	0.029	0.701	0.227	0.014
High education level ^c , <i>n</i> (%)	609 (26.8)	55 (23.7)	172 (23.3)	382 (29.3)	0.006	0.892	0.080	0.003
Indian ethnicity, <i>n</i> (%)	535 (23.5)	72 (31.0)	197 (26.7)	266 (20.4)	<0.001	0.194	<0.001	0.001
Clinical characteristics								
Body mass index, kg/m ²	25.4±4.9	27.1±6.2	26.4±5.0	24.5±4.3	<0.001	0.057	<0.001	<0.001
Mean arterial pressure, mmHg	102.03±13.07	104.36±14.29	102.76±13.17	101.19±12.71	0.001	0.104	0.001	0.009
Wearing glasses, <i>n</i> (%)	1663 (73.2)	166 (71.6)	517 (70.0)	980 (75.3)	0.029	0.643	0.230	0.009
Gait disorders, <i>n</i> (%)	559 (24.6)	77 (33.2)	206 (27.9)	276 (21.2)	<0.001	0.120	<0.001	0.001
Anxiodepressive disorders, <i>n</i> (%)	679 (29.9)	87 (37.5)	242 (32.8)	350 (26.9)	0.001	0.182	0.001	0.005
Neuropsychological characteristics								

Abbreviated Mental Test								
Score (/10)	8.2±2.1	7.7±2.5	7.9±2.3	8.5±1.9	<0.001	0.067	<0.001	<0.001
Cognitive impairment ^d , n (%)	425 (18.7)	64 (27.6)	177 (24.0)	184 (14.1)	<0.001	0.264	<0.001	<0.001
Blood measures								
25-hydroxyvitamin D concentration, ng/mL								
As-measured values	23.3±10.8	7.33±1.77	15.35±2.86	30.65±7.98	<0.001	<0.001	<0.001	<0.001
Deseasonalized values ^e	25.41±11.12	7.56±1.78	15.46±2.87	31.68±8.31	<0.001	<0.001	<0.001	<0.001
Glycosylated haemoglobin, %	6.5±1.4	6.8±1.5	6.7±1.6	6.4±1.2	<0.001	0.313	<0.001	<0.001
LDL cholesterol, mmol/L	3.27±1.03	3.33±1.13	3.35±1.04	3.22±0.99	0.012	0.725	0.142	0.004
Estimated glomerular filtration rate, mL/min	65.1±20.0	62.4±23.3	65.9±20.3	65.1±19.2	0.063	-	-	-

Data are presented as mean $\pm$ SD, unless otherwise indicated. ^a Comparisons based on one-way ANOVA, Fisher's least significant difference or chi-squared test, as appropriate; ^b ≥ 5 days a week; ^c ≥ 6 years; ^d defined as AMT score of ≤ 6 if 0–6 years of education, or AMT score of ≤ 8 if > 7 years of education; ^e data available for 1121 participants (25OHD ≤ 10 , 10.1–20, and > 20 ng/mL in $n = 82$, 311, and 728 respectively). Significant *P*-values (i.e. < 0.05) indicated in bold.

Table 2 Univariate and multiple linear regressions showing the cross-sectional association between 25-hydroxyvitamin D concentration (independent variable) and the Abbreviated Mental Test score (dependent variable), adjusted for participants' characteristics ($n = 2273$)

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Abbreviated Mental Test score										
	Model 1		Model 2		Model 3		Model 4		Model 5	
	β [95% CI]	<i>P</i> -value	β [95% CI]	<i>P</i> -value	β [95% CI]	<i>P</i> -value	β [95% CI]	<i>P</i> -value	β [95% CI]	<i>P</i> -value
25-hydroxyvitamin D concentration ^a	0.26 [0.18;0.34]	< 0.001	0.08 [0.01;0.16]	0.030	0.08 [0.01;0.16]	0.029	0.08 [0.01;0.16]	0.029	0.10 [0.01;0.19]	0.035
Demographic characteristics										
Age	-0.08 [-0.10;-0.07]	< 0.001	-0.08 [-0.09;-0.07]	< 0.001	-0.07 [-0.08;-0.06]	< 0.001	-0.07 [-0.08;-0.06]	< 0.001	-0.07 [-0.09;-0.06]	< 0.001
Female gender	-1.58 [-1.74;-1.42]	< 0.001	-1.38 [-1.58;-1.19]	< 0.001	-1.37 [-1.56;-1.17]	< 0.001	-1.37 [-1.57;-1.17]	< 0.001	-1.10 [-1.29;-0.91]	< 0.001
Regular smoking	0.78 [0.60;0.96]	< 0.001	-0.09 [-0.28;0.10]	0.368	-0.07 [-0.26;0.11]	0.446	-0.06 [-0.25;0.12]	0.500	0.49 [0.28;0.70]	< 0.001
Regular alcohol consumption ^b	0.53 [-0.37;1.44]	0.249	-0.14 [-0.93;0.64]	0.723	-0.25 [-1.01;0.51]	0.517	-0.30 [-1.06;0.46]	0.433	0.02 [-0.73;0.76]	0.964
High education level ^c	1.74 [1.55;1.92]	< 0.001	1.11 [0.92;1.29]	< 0.001	0.87 [0.69;1.05]	< 0.001	0.87 [0.68;1.05]	< 0.001	1.40 [1.22;1.59]	< 0.001
Indian ethnicity	0.39 [0.19;0.60]	< 0.001	0.19 [0.01;0.37]	0.045	0.19 [0.01;0.37]	0.044	0.18 [-0.01;0.36]	0.061	-0.29 [-0.49;-	0.004

Clinical characteristics

Body mass index	0.001	0.950	-	-	0.03	<0.001	0.04	<0.001	-0.02	0.104
	[-0.02;0.02]				[0.02;0.05]		[0.02;0.05]		[-0.04;0.00]	
Mean arterial pressure	-0.01	<0.001	-	-	-0.01	0.014	-0.01	0.034	-0.001	0.787
	[-0.02;-0.01]				[-0.01;-0.00]		[-0.01;0.00]		[-0.01;0.01]	
Wearing glasses	1.28	<0.001	-	-	0.91	<0.001	0.93	<0.001	0.92	<0.001
	[1.10;1.47]				[0.74;1.08]		[0.76;1.10]		[0.69;1.16]	
	-0.83	<0.001	-	-	-0.31	0.001	-0.30	0.001	-0.77	<0.001
	[-1.03;-0.63]				[-0.48;-0.13]		[-0.48;-0.12]		[-1.00;-0.53]	
Gait disorders										
Anxiodepressive disorders	-0.50	<0.001	-	-	-0.22	0.010	-0.21	0.012	-0.31	0.007
	[-0.69;-0.31]				[-0.38;-0.05]		[-0.38;-0.05]		[-0.54;-0.09]	

Blood measures

	-0.03	0.420	-	-	-	-	0.02	0.468	-0.10	0.028
Glycosylated haemoglobin	[-0.09;0.04]						[-0.04;0.08]		[-0.20;-0.01]	
LDL cholesterol	-0.17	<0.001	-	-	-	-	-0.05	0.206	0.05	0.394
	[-0.25;-0.08]						[-0.12;0.03]		[-0.06;0.16]	
Estimated glomerular	0.01	0.001	-	-	-	-	0.002	0.259	0.01	0.003

filtration rate

[0.00;0.01]

[-0.002;0.006]

[0.00;0.01]

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Model 1: unadjusted; Model 2: adjusted for demographic characteristics; Model 3: model 2 + adjustment for clinical characteristics; Model 4: model 3 + adjustment for blood measures; Model 5: using deseasonalized 25-hydroxyvitamin D concentration ($n = 1121$). β , coefficient of regression corresponding to a change in Abbreviated Mental Test score (/8); CI, confidence interval. ^a Change per 10 ng/mL 25-hydroxyvitamin D; ^b ≥ 5 days a week; ^c ≥ 6 years; Significant P -value (i.e. <0.05) indicated in bold.

Table 3 Correlation matrix of 25-hydroxyvitamin D and subscores of the Abbreviated Mental Test score

A. As-measured 25-hydroxyvitamin D concentration (*n* = 2273)

Characteristic	1.	2.	3.	4.	5.	6.	7.
1. 25-hydroxyvitamin D concentration	–	-0.03	-0.12***	-0.12***	-0.04	-0.02	-0.13***
2. Anterograde episodic memory impairment		–	0.33***	0.28***	0.30***	0.15***	0.31***
3. Retrograde episodic memory impairment			–	0.41***	0.45***	0.26***	0.50***
4. Semantic memory impairment				–	0.38***	0.24***	0.38***
5. Working memory impairment					–	0.26***	0.48***
6. Disorientation in space						–	0.26***
7. Disorientation in time							–

B. Deseasonalized 25-hydroxyvitamin D concentration (*n* = 1121)

Characteristic	1.	2.	3.	4.	5.	6.	7.
1. 25-hydroxyvitamin D concentration	–	-0.01	-0.04	-0.08**	0.00	-0.03	-0.09**
2. Anterograde episodic memory impairment		–	0.30***	0.30***	0.30***	0.11***	0.30***
3. Retrograde episodic memory impairment			–	0.35***	0.40***	0.16***	0.40***
4. Semantic memory impairment				–	0.36***	0.16***	0.32***
5. Working memory impairment					–	0.21***	0.42***
6. Disorientation in space						–	0.21***

* $P < 0.05$ (two-tailed); ** $P < 0.01$ (two-tailed); *** $P \leq 0.001$ (two-tailed).

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Fig. 1 Flow diagram of the selection of studies focusing on vitamin D and cognition in older adults in Asia.

Fig. 2 Fully-adjusted odds ratio of cognitive impairment according to participants' characteristics and vitamin D insufficiency, using either as-measured ($n = 2273$) or deasonalized ($n = 1121$) vitamin D concentration. Cognitive impairment was defined as Abbreviated Mental Test (AMT) score of ≤ 6 if 0–6 years of education, or AMT score of ≤ 8 if >7 years of education; vitamin D insufficiency was defined as 25-hydroxyvitamin D ≤ 20 ng/mL. CI, confidence interval; eGFR, estimated glomerular filtration rate.

Fig. 3 Meta-analysis of studies comparing as-measured 25-hydroxyvitamin D concentrations in cognitively impaired and cognitively healthy participants in Asia. In the forest plot, the area of the black box is proportional to the sample size of each study, and horizontal lines correspond to the 95% confidence interval (CI). Black diamond represents the summary value. The vertical line corresponds to a mean difference of 0.0 ng/mL (i.e. equivalent to no difference). IV, inverse variance.

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