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Vitamin D Levels and Cognition in the Elderly Population in China

Choy-Lye Chei, PhD[1,2], **Prassanna Raman, MSc**[1], **Zhao-Xue Yin, PhD**[3], **Xiao-Ming Shi, PhD**[3], **Yi Zeng, PhD**[4,5], and **David B. Matchar, MD**[1,6]

[1]Health Services and Systems Research, Duke-NUS Graduate Medical School Singapore, Singapore

[2]Department of Public Health Medicines, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

[3]Division of Non-Communicable Disease Control and Community Health, Chinese Center for Disease Control and Prevention, Beijing, China

[4]Center for the Study of Aging and Human Development and the Geriatric Division of School of Medicine, Duke University, Durham, NC, USA.

[5]Center for Study of Healthy Aging and Development Studies, National School of Development, Peking University, Beijing, China

[6]Center for Clinical Health Policy Research and Department of Medicine, Duke University School of Medicine, Durham, NC, USA

Abstract

Objectives—To evaluate the association between vitamin D status and cognitive impairment (CI) in elderly aged 60 years and above

Design—Cross-sectional cohort study

Setting—Chinese Longitudinal Healthy Longevity Survey, a community-based cohort study in longevity areas in China

Participants—Individuals with mean age of 84.9 (± 12.7) (n=2004)

Measurements—Participants' cognitive state was evaluated using the Mini-Mental State Examination (MMSE). Vitamin D in plasma was measured using enzyme-linked immunoassay.

Results—The cross-sectional association between quartiles of plasma vitamin D level and CI (MMSE score <18) was modeled using logistic regressions. Plasma vitamin D levels were lower in individuals with CI compared to those without (31.9 (±15.3) versus 45.6 (±19.6)nmol/L). There

Corresponding authors: David B. Matchar, Professor and Director, Program in Health Services & Systems Research, Duke-NUS Graduate Medical School, Singapore, 8 College Road Singapore 169857, Tel: (65) 6601-2296, Fax: (65) 6534-8632, david.matchar@duke-nus.edu.sg, Yi Zeng, Professor, zengyi68@gmail.com.

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Author Contributions" C.L. Chei and D.B. Matchar designed or conceptualized the study; C.L. Chei and P. Raman analyzed or interpreted the data; C.L. Chei, P. Raman, Z.X. Yin, X.M. Shi, Y. Zeng and D.B. Matchar drafted or revised the manuscript. All authors read and approved the final manuscript.

was a reverse association between plasma vitamin D and CI. After adjusting for age, gender, chronic conditions, smoking and drinking habits, outdoor activities, depression, and Activities of Daily Living limitations, the association remained significant. The multivariable adjusted odds ratio for lowest versus highest vitamin D levels was 2.15 (1.05–4.41) for CI, and the multivariable odds ratio associated with 1-SD decrement of plasma vitamin D was 1.32 (1.00–1.74) for CI.

Conclusion—In our sample population, low plasma vitamin D levels were associated with increased odds of CI. Further prospective studies in Asian populations are needed to examine the causal direction of this association.

Keywords

Vitamin D; cognition; elderly; oldest old; China

INTRODUCTION

Approximately 14% of the world has insufficient vitamin D levels[1]. 1,25-dihydroxyvitamin D regulates more than 200 genes, and is responsible for musculoskeletal health and the protection of the nervous system[2]. Inadequate levels of vitamin D lead to a higher risk of mortality, fractures and chronic disease in the elderly[2, 3]. Vitamin D deficiency also increases the probability of stroke, diabetes, and hypertension, which leads to dementia[3–6], and may also be directly associated with the onset of neurodegenerative diseases[1]. Vitamin D's neuroprotective effect stems from its roles in calcium homeostasis, neurogenesis, immunomodulation, antioxidant defense, and amyloid beta clearance[2, 7, 8]. Vitamin D's relationship to cognitive impairment (CI) in the elderly may have significant implications for geriatric care and long-term care facilities planning.

Cross-sectional and longitudinal studies of older adults from the United States and Europe generally observe that low serum vitamin D levels are associated with higher odds of CI[1, 7, 9–17]. Single gender studies report that in women, a negative relationship exists betweenvitamin D levels and CI[11, 13, 18]. Chan et al[19]found no such association in their sample of older Chinese men. In samples with both men and women, the results are mixed[12, 20].

Besides gender, the type of cognitive assessment used in studies affects the relationship between vitamin D levels and cognitive performance. Wilkins et al[21]highlighted that while their population's performance on the Short Blessed Test and the Clinical Dementia Rating supported the negative relationship between vitamin D levels and the odds of CI, their Mini-Mental State Examination (MMSE) scores failed to reveal any cognitive differences between vitamin D groups.

Country- and ethnicity-specific analyses are imperative because the factors affecting vitamin D levels are diverse: variables associated with differential sunlight exposure (skin pigmentation, sunscreen use, latitude, and seasons), age, obesity, and presence of chronic diseases[22]. A previous study found significant regional differences in vitamin D levels across the world, and highlighted particularly low levels in the Middle East and Asia[23].

Research on vitamin D and cognition in elderly Asian populations is scarce. Chan et al[19] analyzed vitamin D levels in older Chinese men in Hong Kong and found that while vitamin D levels were inversely related to depression, they were not associated with CI. A study of elderly Japanese men observed that Japanese men with low vitamin D levels had lower MMSE scores[20].

Our study addresses the dearth of evidence on vitamin D levels and CI in Asian populations. We used data from the 2012 wave in the Chinese Longitudinal Healthy Longevity Survey (CLHLS), a community-based study in longevity areas in China. Using the MMSE to assess CI in our population, we hypothesized that, consistent with evidence of vitamin D's neuroprotective effect, participants with lower vitamin D levels would have higher odds of CI.

METHODS

Subjects

CLHLS is an ongoing longitudinal data collection and research project established in 1998. The baseline and follow-up surveys were conducted in half of the counties and cities in the selected 22 provinces in 1998, 2000, 2002, 2005, 2008–09 and 2011–12. Details of this survey have been described elsewhere[24]. In 2012, a biomarker sub-study of 2011–12 CLHLS was conducted in eight longevity areas: Laizhou City of Shandong Province, Xiayi County of Henan Province, Zhongxiang City of Hubei Province, Mayang County of Hunan Province, Yongfu County of Guangxi Autonomous Area, Sanshui District of Guangdong Province, and Chengmai County of Hainan Province and Rudong County of Jiangsu Province.

2378 subjects aged 60 years and above were recruited in the biomarker sub-study. Written informed consent was obtained from all participants or their proxies. The Ethics Committees of Peking University and National University of Singapore approved this study.

Cognitive function

Cognitive function was measured using the Chinese version of the MMSE[25], which is widely used to assess cognitive status. The MMSE consists of 30 items, with scores ranging from 0 to 30. Higher scores indicate better cognition. The MMSE assesses participants' orientation, memory, attention, calculation, language, and written and visual construction. As previously described, we used a cutoff of <18 to categorize subjects as cognitively impaired[26–28].

Plasma 25(OH)D_3 concentration

Fasting venous blood was collected in heparin anticoagulant vacuum tubes, and then centrifuged at 20°C, 2500rpm for 10 minutes. The plasma was isolated and frozen in −20°C, shipped on wet ice to the central laboratory at Capital Medical University in Beijing, and then stored at −80°C until analysis.

Plasma 25(OH)D_3 levels were measured using an enzyme-linked immunosorbent assay (Immunodiagnostic Systems Limited, Bolton, UK). The inter- and intraassay coefficients of variation were less than 10% and less than 8%, respectively.

Determination of independent covariates

Home interviews were conducted to collect data on demographics (age, gender, and education), lifestyle (smoking and drinking), outdoor activities (gardening), and disability (Activity of Daily Living [ADL] limitations). Height and weight were measured and body mass index (BMI) was calculated as weight (kg)/height (m^2). Blood pressure measurements and phlebotomy were performed by trained medical personnel. Fasting plasma glucose and plasma creatinine was measured by an Automatic Biochemistry Analyzer (7180; Hitachi, Tokyo, Japan) using commercially available diagnostic kits (Roche Diagnostic, Mannheim, Germany). Estimated glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD) equation: estimated GFR (ml/min/1.73m^2) = 186 × (creatinine / 88.4)$^{-1.154}$ × (age) $^{-0.203}$ × (0.742 if female) (Leveyet al[29]). Depression was determined by two questions: 1. In the last 12 months, have you felt sad, blue or depressed for two weeks or more? 2. In the last 12 months, have you lost interest in things like hobbies, work, or activities that usually give you pleasure? Subjects were defined to have depressive symptoms if they answered “yes” for either of the two questions.

Statistical analysis

Means were calculated for continuous variables and percentages were calculated for categorical variables. The mean values of plasma 25(OH)D_3 and potential confounding factors categorized by cognitive function were evaluated using the unpaired Student’s t test for continuous variables and chi-square test for categorical variables. The odds ratios (OR) and 95% confidence intervals for CI (MMSE cutoff score of <18) were estimated according to quartiles of plasma 25(OH)D_3 levels and one standard deviation (SD) decrement of plasma 25(OH)D_3 levels (19.6 nmol/L) with logistic regression models. Adjustments were made for age, gender, education (number of years), BMI (kg/m^2), systolic and diastolic blood pressure (mmHg), estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2), plasma glucose (nmol/L), plasma triglyceride (mmol/L), total cholesterol (mmol/L), current smoker (yes or no), current drinker (yes or no), outdoor activities (yes or no), ADLs (at least one ADL limitation), depression (yes, no, or not able to answer/no response), and study sites.

Sensitivity analysis was performed using educational level to adjust MMSE scores[30]. We examined potential bias in estimating the cognition status of participants with a single cutoff of MMSE<18. The results were similar to those in our model using unadjusted MMSE scores (data not shown).

A test for linear trend across the plasma 25(OH)D_3 levels was conducted by assigning median values of plasma 25(OH)D_3 for each quartile. The statistical significance of the interactions for gender and age was tested using cross-product terms for gender and age with plasma 25(OH)D_3 levels. All statistical tests were two-tailed, and values of $p<0.05$ were

regarded as statistically significant. The SAS statistical package version 9.2 (Statistical Analysis System Inc., Cary, NC) was used for analysis.

RESULTS

Out of 2378 participants, 2004 individuals (936 men and 1,068 women) with plasma $25(OH)D_3$ measurements and MMSE responses were included in our analysis. Those without vitamin D measurements and missing MMSE responses were older (89.8 (±13.0) versus 84.9 (±12.7)), had fewer years of education (1.5 (±2.7) versus 2.0 (±3.2)), and were more likely to be women (64.7% versus 53.3%), compared to those without missing data ($p < 0.001$ for all).

Table 1 shows the descriptive statistics of subjects who were cognitively intact compared to those who were cognitively impaired. Those who were cognitively impaired were more likely to be older and female in comparison to those who were cognitively intact. The mean value of $25(OH)D_3$, number of years of education, BMI, eGFR, triglycerides, and total cholesterol for subjects who were cognitively impaired were significantly lower than for cognitively intact subjects. Smoking, drinking, and outdoor activities were more common in cognitively intact participants. The prevalence of at least one ADL limitation was higher in cognitively impaired subjects compared to cognitively intact subjects.

Table 2 shows the odds ratios and 95% confidence intervals from our logistic regressions. There was a reverse association between plasma $25(OH)D_3$ levels and CI. After adjusting for independent covariates, these positive relationships remained statistically significant. The multivariable adjusted odds ratio for lowest versus highest plasma vitamin D quartiles was 2.15 (1.05–4.41) for CI, and the multivariable odds ratio associated with 1-SD decrement of plasma vitamin D was 1.32 (1.00–1.74) for CI. The association between plasma $25(OH)D_3$ levels and CI did not vary significantly between men and women (p for interaction=0.74), between the 60 to 79 years and the 80 years and above age groups (p=0.52) (data not shown).

DISCUSSION

We found that low vitamin D levels were associated with increased odds of CI in a Chinese population, and that this association remained unchanged even after adjusting for covariates. We observed no gender differences. This is the largest study in Asia to include men and women. Our population also included the oldest old to provide a comprehensive look at the effects of vitamin D on cognition in the elderly across a wide variety of age groups.

Van Schoor and Lips[23] found that vitamin D levels vary greatly across the world. The common threshold for adequate vitamin D levels is 50nmol/L, while others argue that a range of 75–100 nmol/L is the appropriate range for optimal health. Compared to other countries, Asia has lower levels of vitamin D, dipping down to 12–13nmol/L in adolescent Chinese girls in winter[23]. In North America, the National Health and Nutrition Examination Survey reported a mean of 49.8nmol/L in adults in 2005–2006[10]. In our study, the mean vitamin D level for our population was 43.1nmol/L. This was lower compared to means in other studies. For example, Okunoet al[20] reported a mean of 57.1nmol/L in a sample of

older Japanese adults. Van der Schaftet al[10] detailed mean vitamin D levels from other studies, which were higher than ours: 44.7 - 69.0 nmol/L. The lower levels of vitamin D reported in our study and in others on Asian populations highlight the importance of studying vitamin D from a global perspective.

In our analysis, we found that decreased vitamin D levels were associated with higher adjusted odds (OR=2.15) of CI in both men and women. This was comparable to other studies which have also used a version of the MMSE. For example, Slinin et al[18] reported that participants with vitamin D levels less than 31.8nmol/L were more likely to have CI (OR=1.60). Llewellyn et al found the same odds ratio in their Italian sample for those with vitamin D levels less than 25nmol/L[7].

We used the cutoff of MMSE<18 in our analysis without adjusting for education level because 78% of our sample either did not answer the education question in the questionnaire or had less than three years of education. The mean number of years of education was two, highlighting the general lack of education. The sensitivity analysis we performed showed that even after MMSE scores were adjusted for education level[30], the odds ratios and confidence intervals were not substantially different.

People with CI, greater number of ADL limitations, depression and advanced age could have limited sunlight exposure as a result of living in nursing homes or being confined indoors, leading to lower vitamin D levels. However, even after adjusting for these potential confounders, our odds ratio of 2.15 was statistically significant, emphasizing the robustness of the association between vitamin D and odds of CI.

Other studies had different findings. Wilkinset al[21] reported no difference in MMSE scores across different vitamin D groups (they reported a negative association using the Short Blessed Test), and Okuno et al[20] only found a negative association in men in his Japanese sample. The gender interaction term in our study was not significant, suggesting no gender difference in our sample in the association between vitamin D and risk of CI. The variety of instruments used to measure cognitive assessment and differing definitions of vitamin D deficiencies are limitations in the existing research on vitamin D and cognition, as pointed out by Etgenet al[9].

One of our study's limitations was the possibility of reverse causality. To the extent possible, we accounted for such effects by adjusting for outdoor activities. In the absence of a compelling instrumental variable, this limitation is inherent in cross-sectional studies. Using data from the 2014 wave of the CLHLS, we will attempt to clarify the temporal relationships between low vitamin D levels and CI.

Another limitation was that vitamin D levels were obtained in the summer when vitamin D levels are probably at their peak. This likely led to an overestimation of average vitamin D levels. However, unless there was an interaction between vitamin D and seasons, this would not have led to a bias in favor of an association between vitamin D and CI, but rather would have increased the confidence interval for the OR. We also did not have information on use of vitamin D supplements. Since 87% of our subjects reported not taking any supplements

(no additional information on specific nature of supplements), it was unlikely that use of vitamin D supplements would explain the association.

Several issues deserve attention beyond causal direction and time. One is the clarification of a gender effect; while previous studies[1, 12, 20] highlighted gender differences in the relationship between vitamin D levels and cognition, the gender interaction term in our study was insignificant. The follow up study will provide a larger sample and additional power to discern any gender effect. A second issue is why Asians have lower vitamin D levels compared to other populations. Finally, even if the relationship between vitamin D and CI is causal, it will be crucial to understand potentially modifiable factors, in addition to or instead of vitamin D supplements, which could reduce the likelihood of CI.

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Table 1

Descriptive Statistics

	Total sample (n=2004)	Cognitively intact (n=1639)	Cognitively impaired (n=365)
Plasma vitamin D_3 (nmol/L), mean (±SD)	43.1 (± 19.6)	45.6 (± 19.6)	31.9 (± 15.3)‡
Age (years), mean(±SD)	84.9 (± 12.7)	82.1 (± 12.0)	97.3 (± 7.0)‡
Female, %	53.3	47.7	78.4‡
Education (years), mean(±SD)	2.0 (± 3.2)	2.4 (± 3.4)	0.4 (± 1.4)‡
BMI (kg/m^2), mean (±SD)	21.3 (± 4.38)	21.6 (± 4.4)	19.9 (± 4.1)‡
Systolic blood pressure (mmHg), mean (±SD)	139.6 (± 23.1)	139.7 (± 22.8)	138.9 (± 24.6)
Diastolic blood pressure (mmHg), mean (±SD)	80.5 (±12.1)	80.6 (± 11.7)	80.3 (± 13.7)
eGRR ($mL/min/1.73\ m^2$), mean (±SD)	78.2 (± 25.1)	78.9 (± 25.0)	75.4 (± 25.5)*
Triglyceride (mmol/L), mean (±SD)	1.00 (± 0.65)	1.03 (± 0.68)	0.89 (± 0.45)‡
Total cholesterol (mmol/L), mean (±SD)	4.32 (± 0.99)	4.35 (± 0.98)	4.15 (± 1.01)†
Fasting glucose (nmol/L), mean (±SD)	4.64 (± 2.13)	4.62 (± 2.18)	4.69 (± 1.89)
Current smoker, %	17.7	20.3	6.0‡
Current drinker, %	16	17.9	7.4‡
At least one ADL limitation, %	17.2	9.4	52.1‡
Outdoor activities, %	54.8	61.3	25.8‡
Depression, %	7.0	7.1	6.9

Data are shown as mean (±SD), frequency as a number (%).

Differences between groups were assessed by t-test and chi square test.

*p<0.05;

†p<0.01;

‡p<0.001

Cognitive impairment is defined as MMSE score <18.

Table 2

Odds ratios (95% confidence interval) of CI by quartiles of plasma vitamin D_3 (25(OH) D) levels of cognitively intact subjects

	Quartiles of plasma vitamin D_3 (25(OH)D), nmol/L					
	1 (high)	**2**	**3**	**4 (low)**	***P* for linear trend**	**1 SD decrement of plasma vitamin D_3**
Plasma vitamin D_3						
Median, nmol/L	66.8	49.3	37.1	24.1		
Range, nmol/L	57.0–208.7	43.0–57.0	31.6–43.0	5.7–31.6		
Cognitively impaired	27	39	75	224		
Cognitively intact	409	410	410	410		
Unadjusted OR	1.00	1.44(0.87–2.40)	2.78(1.75–4.40)‡	8.32(5.45–12.7)‡	<0.001	2.79(2.36–3.30)‡
Adjusted[a] OR	1.00	1.21(0.55–2.66)	1.22(0.57–2.62)	2.15(1.05–4.41)*	0.05	1.32(1.00–1.74)*

[a] Adjusted for age, gender, education, BMI, systolic and diastolic blood pressure, eGFR, plasma glucose, plasma triglyceride, total cholesterol, current smoking, current drinking, outdoor activities, ADL limitations, depression, and study sites.

* p<0.05;

† p<0.01;

‡ p<0.001