Vitamin D Levels and Cognition in Elderly Adults in China

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OBJECTIVES: To evaluate the association between vitamin D level and cognitive impairment in individuals aged 60 and older.

DESIGN: Cross-sectional cohort study.

SETTING: Chinese Longitudinal Healthy Longevity Survey, a community-based cohort study in areas in China where the density of centenarians is exceptionally high.

PARTICIPANTS: Individuals with mean age of 84.9 ± 12.7 (N = 2,004).

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

RESULTS: The cross-sectional association between quartiles of plasma vitamin D level and cognitive impairment (MMSE score <18) was modeled using logistic regressions. Plasma vitamin D levels were lower in individuals with cognitive impairment (31.9 ± 15.3 nmol/L) than in those without (45.6 ± 19.6 nmol/L). There was a reverse association between plasma vitamin D and cognitive impairment. After adjusting for age, sex, chronic conditions, smoking and drinking habits, outdoor activities, depression, and activity of daily living limitations, the association remained significant. The multivariable-adjusted odds ratio for lowest versus highest vitamin D levels was 2.15 (95% confidence interval (CI) = 1.05–4.41) for cognitive impairment, and the multivariable odds ratio associated with a 1-standard deviation decrement in plasma vitamin D was 1.32 (95% CI = 1.00–1.74) for cognitive impairment.

CONCLUSION: Low plasma vitamin D levels were associated with greater odds of cognitive impairment. Further prospective studies in Asian populations are needed to examine the causal direction of this association. **J Am Geriatr Soc 62:2125–2129, 2014.**

Key words: vitamin D; cognition; elderly; oldest old; China

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Approximately 14% of the world has inadequate 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 vitamin D levels lead to a higher risk of mortality, fractures, and chronic disease in elderly adults.[2,3] Vitamin D deficiency also increases the probability of stroke, diabetes mellitus, 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 in elderly adults may have significant implications for geriatric care and long-term care facility planning.

Cross-sectional and longitudinal studies of older adults from the United States and Europe have generally found that low serum vitamin D levels are associated with greater odds of cognitive impairment.[1,7,9–17] Single-sex studies report that, in women, a negative relationship exists between vitamin D levels and cognitive impairment.[11,13,18] Another study[19] found no such association in a sample of older Chinese men. In samples with men and women, the results are mixed.[12,20]

In addition to sex, the type of cognitive assessment used in studies affects the relationship between vitamin D levels and cognitive performance. One study[21] highlighted that, although its 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 cognitive impairment, Mini-Mental State Examination

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(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 are associated with different sunlight exposure (skin pigmentation, sunscreen use, latitude, seasons), age, obesity, and presence of chronic diseases.[22] A previous study found significant regional differences in vitamin D levels around 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. Vitamin D levels were analyzed in older Chinese men in Hong Kong, and it was found that, although vitamin D levels were inversely related to depression, they were not associated with cognitive impairment.[19] A study of elderly Japanese men observed that those with low vitamin D levels had lower MMSE scores.[20]

The current study addresses the dearth of evidence on vitamin D levels and cognitive impairment in Asian populations. Data from the 2012 wave in the Chinese Longitudinal Healthy Longevity Survey (CLHLS), a community-based study in areas in China where the density of centenarians is exceptionally high, were used. Using the MMSE to assess cognitive impairment, it was hypothesized that, consistent with evidence of vitamin D's neuroprotective effect, participants with lower vitamin D levels would have greater odds of cognitive impairment.

METHODS

Subjects

The 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 substudy of the 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.

Individuals aged 60 and older (N = 2,378) were recruited in the biomarker substudy. 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 orientation, memory, attention, calculation, language, and written and visual construction. As previously described, a score of less than 18 was used 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 centrifuged at 20°C, 2,500 revolutions per minute for 10 minutes. The plasma was isolated and frozen at −20°C, shipped on wet ice to the central laboratory at Capital Medical University in Beijing, and 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 demographic characteristics (age, sex, education), lifestyle (smoking, 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). Trained medical personnel measured blood pressure measurements and performed phlebotomy. Fasting plasma glucose and plasma creatinine was measured using an automatic biochemistry analyzer (7180; Hitachi, Tokyo, Japan) using commercially available diagnostic kits (Roche Diagnostic, Mannheim, Germany). Estimated glomerular filtration rate (eGFR) was determined using the Modification of Diet in Renal Disease (MDRD) equation: eGFR (mL/min per 1.73 m^2) = $186 \times (\text{creatinine}/88.4)^{-1.154} \times (\text{age})^{-0.203} \times$ (0.742 if female).[29] Depression was determined using two questions: In the last 12 months, have you felt sad, blue or depressed for 2 weeks or more? In the last 12 months, have you lost interest in things such as hobbies, work, or activities that usually give you pleasure? Subjects were determined to have depressive symptoms if they answered yes to either of the questions.

Statistical Analysis

Means were calculated for continuous variables and percentages for categorical variables. The mean values of plasma 25(OH)D_3 and potential confounding factors categorized according to cognitive function were evaluated using the unpaired Student *t* test for continuous variables and chi-square test for categorical variables. Odds ratios (OR) and 95% confidence intervals (CIs) for cognitive impairment (MMSE score <18) were estimated according to quartile of plasma 25(OH)D_3 levels and a 1–standard deviation (SD) decrement of plasma 25(OH)D_3 level (19.6 nmol/L) using logistic regression models. Adjustments were made for age, sex, education (years), BMI, systolic and diastolic blood pressure (mmHg), eGFR, 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 (≥1 ADL limitations), depression (yes, no, not able to answer or no response), and study site.

Sensitivity analysis was performed using educational level to adjust MMSE scores.[30] Potential bias in estimating the cognition of participants was examined using a MMSE score of less than 18. The results were similar to those in the model using unadjusted MMSE scores (data not shown).

A test for linear trend across 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 sex and age was tested using cross-product terms for sex and age with plasma 25(OH)D_3 levels. All statistical tests were two-tailed, and $P < .05$ was regarded as statistically significant. SAS version 9.2 (SAS Institute, Inc., Cary, NC) was used for analysis.

RESULTS

Of 2,378 participants, 2004 (936 men, 1,068 women) with plasma 25(OH)D_3 measurements and MMSE responses were included in the analysis. Those without vitamin D measurements and missing MMSE responses were older (89.8 ± 13.0 vs 84.9 ± 12.7), had fewer years of education (1.5 ± 2.7 vs 2.0 ± 3.2), and were more likely to be female (64.7% vs 53.3%) than those without missing data ($P < .001$ for all).

Table 1 compares the characteristics of cognitively intact subjects with those of cognitively impaired subjects. Those who were cognitively impaired were more likely to be older and female than those who were cognitively intact. Mean 25(OH)D_3 level, years of education, BMI, eGFR, triglycerides, and total cholesterol were significantly lower for cognitively impaired subjects than for cognitively intact subjects. Smoking, drinking, and outdoor activities were more common in cognitively intact participants. The prevalence of one or more ADL limitations was higher in cognitively impaired subjects than in those who were cognitively intact.

Table 1. Descriptive Statistics

Variable	Total Sample, N = 2,004	Cognitively Intact, n = 1,639	Cognitively Impaired, n = 365[a]
Plasma vitamin D_3, nmol/L, mean ± SD	43.1 ± 19.6	45.6 ± 19.6	31.9 ± 15.3[d]
Age, mean ± SD	84.9 ± 12.7	82.1 ± 12.0	97.3 ± 7.0[d]
Female, %	53.3	47.7	78.4[d]
Education, years, mean ± SD	2.0 ± 3.2	2.4 ± 3.4	0.4 ± 1.4[d]
Body mass index, kg/m^2, mean ± SD	21.3 ± 4.38	21.6 ± 4.4	19.9 ± 4.1[d]
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
Estimated glomerular filtration rate, mL/min per 1.73 m^2, mean ± SD	78.2 ± 25.1	78.9 ± 25.0	75.4 ± 25.5[b]
Triglycerides, mmol/L, mean ± SD	1.00 ± 0.65	1.03 ± 0.68	0.89 ± 0.45[d]
Total cholesterol, mmol/L, mean ± SD	4.32 ± 0.99	4.35 ± 0.98	4.15 ± 1.01[c]
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[d]
Current drinker, %	16.0	17.9	7.4[d]
≥1 activity of daily living limitations, %	17.2	9.4	52.1[d]
Outdoor activities, %	54.8	61.3	25.8[d]
Depression, %	7.0	7.1	6.9

Differences between groups were assessed using the *t*-test and chi-square test.
[a]Mini-Mental State Examination score <18.
$P <$ [b].05, [c].01, [d].001.
SD = standard deviation.

Table 2. Cognitive Impairment According to Quartile of Plasma Vitamin D_3 Level of Cognitively Intact Subjects

Variable	Quartile 1 (high)	Quartile 2	Quartile 3	Quartile 4 (low)	*P* for Linear Trend	1 Standard Deviation Decrement of Plasma Vitamin D_3
Plasma vitamin D_3, nmol/L, median (range)	66.8 (57.0–208.7)	49.3 (43.0–57.0)	37.1 (31.6–43.0)	24.1 (5.7–31.6)		
Cognitively impaired, n	27	39	75	224		
Cognitively intact, n	409	410	410	410		
Unadjusted OR (95% CI)	1.00	1.44 (0.87–2.40)	2.78 (1.75–4.40)[c]	8.32 (5.45–12.7)[c]	<.001	2.79 (2.36–3.30)[c]
Adjusted OR (95% CI)[a]	1.00	1.21 (0.55–2.66)	1.22 (0.57–2.62)	2.15 (1.05–4.41)[b]	.05	1.32 (1.00–1.74)[b]

[a]Adjusted for age, sex, education, body mass index, systolic and diastolic blood pressure, estimated glomerular filtration rate, plasma glucose, plasma triglyceride, total cholesterol, current smoking, current drinking, outdoor activities, activity of daily living limitations, depression, and study sites.
$P <$ [b].05, [c].001.
OR = odds ratio; CI = confidence interval.

Table 2 shows the ORs and 95% CIs from the logistic regressions. There was a reverse association between plasma 25(OH)D_3 level and cognitive impairment. After adjusting for independent covariates, these positive relationships remained statistically significant. The multivariable adjusted OR for lowest versus highest plasma vitamin D quartiles was 2.15 (95% CI = 1.05–4.41) for cognitive impairment, and the multivariable odds ratio associated with 1 – SD decrement of plasma vitamin D was 1.32 (95% CI = 1.00–1.74) for cognitive impairment. The association between plasma 25(OH)D_3 level and cognitive impairment did not vary significantly between men and women (P for interaction = .74) or between participants aged 60 to 79 and those aged 80 and older (P = .52) (data not shown).

DISCUSSION

Low vitamin D levels were associated with greater odds of cognitive impairment in a Chinese population, and this association remained unchanged after adjusting for covariates. No sex differences were found. This is the largest study in Asia to include men and women. The population also included the oldest old to provide a comprehensive look at the effects of vitamin D on cognition in elderly adults of a wide variety of ages.

A previous study[23] found that vitamin D levels vary greatly around the world. A common threshold for adequate vitamin D level is 50 nmol/L (2.5 nmol/L = 1ng/mL), whereas others argue that a range of 75 to 100 nmol/L is the appropriate range for optimal health.[23] Asians have lower vitamin D levels than individuals from other areas—as low as 12 to 13 nmol/L in adolescent Chinese girls in winter.[23] In North America, the National Health and Nutrition Examination Survey reported a mean of 49.8 nmol/L in adults in 2005–06.[10] In the current study, the mean vitamin D level was 43.1 nmol/L, which is lower than means in other studies. For example, one study[20] reported a mean of 57.1 nmol/L in a sample of older Japanese adults, and another study[10] detailed mean vitamin D levels from other studies that were higher than those in the current study (44.7–69.0 nmol/L). The lower vitamin D levels reported in the current study and in others on Asian populations highlight the importance of studying vitamin D from a global perspective.

The current analysis found that low vitamin D levels were associated with higher adjusted odds (OR = 2.15) of cognitive impairment in men and women. This was comparable with the findings of other studies that also used a version of the MMSE. For example, one study[18] reported that participants with vitamin D levels of less than 31.8 nmol/L were more likely to have cognitive impairment (OR = 1.60). Another study found the same OR in their Italian sample for participants with vitamin D levels of less than 25 nmol/L.[7]

A MMSE score of less than 18 was used in the current analysis without adjusting for education level because 78% of the sample did not answer the education question in the questionnaire or had less than 3 years of education. The mean number of years of education was 2, highlighting the general lack of education. The sensitivity analysis performed showed that, even after MMSE scores were adjusted for education level,[30] the ORs and CIs were not substantially different.

People with cognitive impairment, more ADL limitations, and depression and of older age could have limited sunlight exposure as a result of living in nursing homes or being confined indoors, leading to lower vitamin D levels, but even after adjusting for these potential confounders, the OR of 2.15 was statistically significant, emphasizing the robustness of the association between vitamin D and odds of cognitive impairment.

Other studies had different findings. One study[21] reported no difference in MMSE scores in different vitamin D groups (reporting a negative association using the Short Blessed Test), and another[20] found a negative association only in men in a Japanese sample. The sex interaction term in the current study was not significant, suggesting no sex difference in the sample in the association between vitamin D and cognitive impairment. 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 previously.[9]

One of the study's limitations was the possibility of reverse causality. To the extent possible, such effects were accounted for 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, an attempt will be made to clarify the temporal relationships between low vitamin D level and cognitive impairment.

Another limitation was that vitamin D levels were obtained in the summer when they are probably at their peak. It is likely that this led to an overestimation of average vitamin D levels, but 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 cognitive impairment but rather would have increased the CI for the OR. There was also no information on use of vitamin D supplements. Because 87% of the 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 questions deserve attention beyond causal direction and time. One is the clarification of a sex effect; although previous studies[1,12,20] highlighted sex differences in the relationship between vitamin D level and cognition, the sex interaction term in the current study was insignificant. The follow-up study will provide a larger sample and additional power to discern any sex effect. A second question is why Asians have lower vitamin D levels than other populations. Finally, even if the relationship between vitamin D and cognitive impairment is causal, it will be crucial to understand potentially modifiable factors, in addition to or instead of vitamin D supplements, that could reduce the likelihood of cognitive impairment.

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Author Contributions: Chei, Matchar: study design and concept. Chei, Raman: data analysis and interpreation. Chei, Raman, Yin, Shi, Zeng, Matchar: drafting and revision of manuscript. All authors read and approved the final manuscript.

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