Vitamin D Levels and the Risk of Cognitive Decline in Chinese Elderly People: the Chinese Longitudinal Healthy Longevity Survey

David B. Matchar¹,2, Choy-Lye Chei¹,3, Zhao-Xue Yin⁴, Victoria Koh¹, Bibhas Chakraborty⁵, Xiao-Ming Shi⁴, and Yi Zeng⁶,⁷

¹Health Services and Systems Research, Duke-NUS Medical School, Singapore. ²Department of Medicine, Duke University School of Medicine, Durham, North Carolina. ³Department of Public Health Medicines, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan. ⁴Division of Non-Communicable Disease Control and Community Health, Chinese Center for Disease Control and Prevention, Beijing, China. ⁵Centre for Quantitative Medicine, Duke-NUS Medical School, Singapore. ⁶Center for the Study of Aging and Human Development and the Geriatric Division of School of Medicine, Duke University, Durham, North Carolina. ⁷Center for Healthy Aging and Development Studies, National School of Development, Peking University, Beijing, China.

Address correspondence to David B. Matchar, MD, Health Services and Systems Research, Duke-NUS Medical School, 8 College Road Singapore 169857. E-mail: david.matchar@duke-nus.edu.sg.

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Abstract

Background: Vitamin D has a neuroprotective function, potentially important for the prevention of cognitive decline. Prospective studies from Western countries support an association between lower vitamin D level and future cognitive decline in elderly people. No prospective study has examined this association in Asia.

Methods: This community-based cohort study of elderly people in China follows 1,202 cognitively intact adults aged ≥60 years for a mean duration of 2 years. Plasma vitamin D level was measured at the baseline. Cognitive state of participants was assessed using the Mini-Mental State Examination (MMSE). Cognitive impairment was defined as an MMSE score <18. Cognitive decline was defined as ≥3 points decline from baseline. Multivariable logistic regression models were used to examine the association between quartiles of vitamin D levels with cognitive decline and incidence of cognitive impairment.

Results: Participants with low vitamin D level had an increased risk of cognitive decline. Compared with the highest quartile of vitamin D levels, the multivariable odds ratios (ORs; 95% confidence interval) for cognitive decline were 2.1 (1.3–3.4) for the second highest quartile, 2.2 (1.4–3.6) for the third highest quartile, and 2.0 (1.2–3.3) for the lowest quartile. The multivariable ORs of incident cognitive impairment for the second highest, third highest, and lowest versus highest quartiles of vitamin D levels were 1.9 (0.9–4.1), 2.6 (1.2–5.6), and 3.2 (1.5–6.6), respectively.

Conclusions: This first follow-up study of elderly people, including the oldest-old, in Asia shows that low vitamin D levels were associated with increased risk of subsequent cognitive decline and impairment.

Keywords: Chinese elderly people—Cognitive decline—Cognitive impairment—Follow-up study—Vitamin D

Vitamin D is a secosteroid hormone necessary for maintaining good musculoskeletal health; its deficiency is associated with increased risks of cardiovascular and neurodegenerative diseases (1,2). Vitamin D is primarily synthesized in the skin upon exposure to sunlight; smaller amounts are obtained through dietary intake. More recently, enzymes responsible for the synthesis of its active form have been found to be distributed throughout the human brain (3). These enzymes facilitate on-site calcium homeostasis, immunomodulation, antioxidative mechanisms, and beta-amyloid clearance by vitamin D, thereby conferring a protective effect on the central nervous system.
system \(^{(4,5)}\). This growing body of evidence suggests that vitamin D has a neuroprotective function that is potentially important for the prevention of cognitive decline. Although the importance of vitamin D cannot be disregarded, there is still no consensus on its optimal level. This is especially pertinent in the elderly people, the oldest-old in particular, as cutaneous synthesis of vitamin D decreases with age \(^{(6)}\). Moreover, their impaired mobility and limited outdoor activities can further exacerbate vitamin D deficiency. As the oldest-old are the most rapidly growing segment of the elderly population \(^{(7)}\), vitamin D’s association with cognitive decline in the oldest-old may have important public health implications for long-term care facility planning and health care expenditures.

Cross-sectional studies have generally found a positive association between vitamin D status and cognitive performance in older adults \(^{(8,9)}\). Recent prospective studies from United States and Europe support an association between diminished vitamin D status and future cognitive decline \(^{(10–13)}\). Since cutaneous synthesis is the main source of vitamin D, there exists great variability in vitamin D levels across populations due to differences in latitude, seasons, and race/ethnicity, such as level of skin pigmentation \(^{(14)}\). Yet no prospective study has been conducted in elderly Asian populations.

Therefore, we conducted, to the best of our knowledge, the first large, longitudinal, community-based study of Chinese elderly adults in longevity areas of the Chinese Longitudinal Healthy Longevity Survey to investigate the association between vitamin D level and cognitive decline in elderly adults. These longevity areas with exceptionally high densities of centenarians provide an opportunity to explore this association in the oldest-old. Given the evidence of vitamin D’s neuroprotective effect, we hypothesized that low levels of its major circulating form, \(25(\text{OH})\text{D}_3\), is associated with subsequent cognitive decline and cognitive impairment in the oldest-old.

Methods

Subjects

Chinese Longitudinal Healthy Longevity Survey is an ongoing longitudinal survey established in 1998. Baseline and follow-up surveys were conducted in half of the counties and cities in the selected 22 provinces in 1998, 2000, 2002, 2005, 2008–2009, 2011–2012, and 2014. Details of this survey have been described elsewhere \(^{(15)}\). In 2012, a biomarker substudy 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, Yongtu County of Guangxi Autonomous Area, Sanshui District of Guangdong Province, Chengmai County of Hainan Province, and Rudong County of Jiangsu Province. A total of 2,378 subjects aged ≥60 years participated in the baseline study. Follow-up assessments were conducted in 2014 (mean follow-up = 2.0±0.2 years). For the purposes of the present study, subjects with missing baseline vitamin D levels \((n = 134)\), Mini-Mental State Examination (MMSE) score \((n = 211)\), or cholesterol levels \((n = 4)\), or baseline MMSE score <18 \((n = 296)\), or self-reported dementia \((n = 9)\) were excluded. Of the remaining 1,724 subjects, 216 died during follow-up and 281 were lost to follow-up. Twenty-five subjects without MMSE scores at follow-up were also excluded. The final sample consisted of 1,202 subjects. Compared with the final sample, excluded subjects \((n = 1,176)\) were older (mean age ± standard deviation [SD] 91.1±12.0 vs. 80.3±11.3 years), had lower MMSE scores \((16.7±11.7 vs. 27.9±2.8)\), and lower plasma \(25(\text{OH})\text{D}_3\) levels \((38.8±18.9 vs. 45.1±19.5; p < .0001 for all comparisons; see Supplementary Table 1)\).

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 \(^{(16)}\), which is widely used to assess cognitive status. It 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. Cognitive decline was defined as a decline of MMSE score ≥3 points at follow-up \(^{(10)}\). As previously described, we used a cutoff of <18 to categorize subjects as cognitively impaired \(^{(17)}\).

Plasma \(25(\text{OH})\text{D}_3\) concentration

Fasting venous blood was collected in heparin anticoagulant vacuum tubes and centrifuged at 20°C, 2,500 rpm for 10 min. The plasma was isolated and frozen at −20°C, shipped on wet ice to the central laboratory at Capital Medical University in Beijing, then stored at −80°C until analysis.

Plasma \(25(\text{OH})\text{D}_3\) was measured using an enzyme-linked immunosassay by Immunodiagnostic Systems Limited (IDS Ltd, Boldon, UK). The inter-assay and intra-assay coefficients of variation were <10% and <8%, respectively.

Determination of independent covariates (see Supplementary Material, for details)

Statistical analysis

Means and percentages were calculated by quartiles of \(25(\text{OH})\text{D}_3\) levels for continuous variables and categorical variables, respectively. Differences in baseline characteristics across quartiles of \(25(\text{OH})\text{D}_3\) levels were compared using \(\chi^2\) test for categorical variables, analysis of variance for continuous variables with normal distribution, and the Kruskal–Wallis test for variables with skewed distribution.

We used general linear models to examine the changes in MMSE score over the follow-up in each \(25(\text{OH})\text{D}_3\) quartile. Adjusted mean changes in MMSE score were obtained for each \(25(\text{OH})\text{D}_3\) quartile.

The odds ratios (ORs), along with their 95% confidence intervals (CIs), for reduction of ≥3 MMSE points from baseline and transition to an MMSE score <18 were estimated according to quartiles of plasma \(25(\text{OH})\text{D}_3\) levels and 1 SD decrement of plasma \(25(\text{OH})\text{D}_3\) levels (19.5 mmol/L) with logistic regression models. Adjustments were made for age, gender, education (yes or no), abdominal obesity (yes or no), baseline MMSE score, hypertension (yes or no), type 2 diabetes (yes or no), estimated glomerular filtration rate, total cholesterol (mmol/L), current smoker (yes or no), current drinker (yes or no), blood collection season (March–May, June–August, and September–November) \(^{(18)}\), activities of daily living (at least one activity of daily living limitation), depression (yes, no, or not able to answer/no response), and rural (yes or no) \(^{(18)}\). A test for linear trend across plasma \(25(\text{OH})\text{D}_3\) levels was conducted by assigning median values of plasma \(25(\text{OH})\text{D}_3\) for each quartile. We used multivariable-adjusted penalized smoothing spline plots to examine possible \(25(\text{OH})\text{D}_3\) threshold levels for cognitive decline and cognitive impairment.

All statistical tests were two-tailed, and values of \(p < 0.05\) were regarded as statistically significant. The SAS statistical package version 9.3 (Statistical Analysis System Inc., Cary, NC) was used for analysis except for the spline plots, which were fitted in R version 3.1.1 \(^{(19)}\).
Results

The majority of the participants (82.4%) in this study resided in rural areas. The mean age of the total study population was 80.3±11.3 years and 47.1% were female participants.

Subjects’ basic characteristics by quartiles of 25(OH)D₃ levels are shown in Table 1. Participants with lower plasma 25(OH)D₃ levels were more likely to be older, female participants, have abdominal obesity, hypertension and less education than those with higher levels. Smoking and alcohol use were more common in those with higher 25(OH)D₃ levels. The mean MMSE score was significantly lower, whereas mean eGFR was significantly higher in those with lower 25(OH)D₃ levels. Prevalence of at least one activity of daily living limitation was higher in participants with lower 25(OH)D₃ levels compared with those with higher levels.

The decline in adjusted mean MMSE score between survey waves was greater in participants in the lowest (−3.05), third (−2.73), and second (−2.37) quartiles of 25(OH)D₃ levels than the highest quartiles (−1.44; see Supplementary Figure 1).

Table 2 shows the ORs and 95% CI of cognitive decline by quartiles of baseline 25(OH)D₃ levels and to baseline 25(OH)D₃ levels 1 SD below the mean. Participants with lower 25(OH)D₃ levels had a higher risk of a decrease of ≥3 MMSE points over the 2-year follow-up compared with those with higher levels. The multivariable ORs (95% CI) of cognitive decline were 2.02 (1.24–3.28), 2.07 (1.26–3.41), and 1.83 (1.10–2.05) for the second, third, and lowest quartiles, respectively. The multivariable OR associated with 1 SD decrement of 25(OH)D₃ levels was 1.35 (1.10–1.66) for cognitive decline.

The odds of developing cognitive impairment increased with lower baseline 25(OH)D₃ levels; this relationship remained statistically significant after adjustment for age, sex, education, baseline MMSE score, depression, outdoor activities, activities of daily living limitations, and other potential confounders (Table 2). The multivariable ORs of transitioning from a baseline MMSE score ≥18 to <18 was statistically significantly higher for the third and lowest versus the highest quartiles of 25(OH)D₃ levels: 2.41 (1.12–5.19) and 2.89 (1.36–6.14), respectively. The multivariable OR associated with 1 SD decrement of 25(OH)D₃ levels was 1.59 (1.17–2.17) for cognitive impairment. The association between 25(OH)D₃ levels and incidence of cognitive impairment did not vary between men and women (p for interaction = 0.96) and between groups aged 60–79 years and ≥80 years (p = 0.64; data not shown).

In the multivariable-adjusted spline smoothing plots, the risk of cognitive decline reduced when the vitamin D level is above the threshold of 50 nmol/L. The risk of cognitive impairment increased with decreasing 25(OH)D₃ levels, however no threshold effect was observed (Figure 1).

Discussion

We observed that low 25(OH)D₃ levels, reflective of vitamin D status, were associated with subsequent cognitive decline and cognitive impairment in a large elderly population including the oldest-old. This represents the first longitudinal study of the relationship between vitamin D status and cognition in Asian men and women, and this temporal association strengthens the hypothesis of a causal association.

Our findings were consistent with previous cohort studies showing that vitamin D status predicts cognitive decline. A meta-analysis of eight studies found a significant association between vitamin D status and cognition using the MMSE assessment (20). Another meta-analysis of five cross-sectional and two longitudinal studies also found that low levels of vitamin D were significantly associated with a higher risk of cognitive impairment (21). A recent study of 2,777 community-dwelling elderly people in the United States found

Table 1. Baseline Characteristics of Subjects by Quartiles of Plasma Vitamin D₃ Levels

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n=1202)</th>
<th>1 (high) (n = 300)</th>
<th>2 (n = 301)</th>
<th>3 (n = 301)</th>
<th>4 (low) (n = 300)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma 25(OH)D₃ (nmol/L), mean (±SD)</td>
<td>45.1±19.1</td>
<td>70.7±17.2</td>
<td>48.9±3.7</td>
<td>36.6±5.1</td>
<td>24.3±5.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age (years), mean (±SD)</td>
<td>80.3±11.3</td>
<td>77.9±10.7</td>
<td>79.2±10.4</td>
<td>80.5±10.9</td>
<td>83.5±12.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Female, %</td>
<td>47.1</td>
<td>31.0</td>
<td>44.9</td>
<td>49.8</td>
<td>62.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Education (≥1 year), % (n = 1,194)</td>
<td>47.9</td>
<td>59.0</td>
<td>49.5</td>
<td>47.7</td>
<td>35.5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Waist circumference (cm), mean (±SD), (n = 1,183)</td>
<td>81.4±11.0</td>
<td>80.7±12.3</td>
<td>81.3±9.7</td>
<td>82.8±11.4</td>
<td>80.9±10.6</td>
<td>.10</td>
</tr>
<tr>
<td>Abdominal obesity, % (n = 1,183)</td>
<td>44.4</td>
<td>43.7</td>
<td>43.2</td>
<td>50.8</td>
<td>46.0</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Season of blood collection, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>March–May</td>
<td>24.8</td>
<td>16.0</td>
<td>18.6</td>
<td>25.9</td>
<td>38.7</td>
<td></td>
</tr>
<tr>
<td>June–August</td>
<td>70.0</td>
<td>69.0</td>
<td>76.7</td>
<td>73.4</td>
<td>60.7</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>September–November</td>
<td>5.2</td>
<td>15.0</td>
<td>4.7</td>
<td>0.7</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>62.8</td>
<td>56.0</td>
<td>60.8</td>
<td>68.4</td>
<td>66.0</td>
<td>.01</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>7.2</td>
<td>5.3</td>
<td>9.0</td>
<td>7.0</td>
<td>7.7</td>
<td>.38</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²), mean (±SD)</td>
<td>80.9±24.8</td>
<td>78.0±22.8</td>
<td>81.4±23.6</td>
<td>80.5±24.5</td>
<td>83.5±25.8</td>
<td>.05</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L), mean (±SD)</td>
<td>4.37±0.95</td>
<td>4.38±0.87</td>
<td>4.39±0.92</td>
<td>4.37±1.04</td>
<td>4.34±0.98</td>
<td>.90</td>
</tr>
<tr>
<td>Current smoker, % (n = 1,191)</td>
<td>21.7</td>
<td>29.9</td>
<td>25</td>
<td>17.8</td>
<td>14.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Current drinker, % (n = 1,196)</td>
<td>18.7</td>
<td>27.5</td>
<td>20.4</td>
<td>16.7</td>
<td>13.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>MMSE score, mean (±SD)</td>
<td>27.9±2.8</td>
<td>28.5±2.3</td>
<td>28.3±2.4</td>
<td>27.8±2.7</td>
<td>26.9±3.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>At least one ADL limitation, % (n = 1,167)</td>
<td>6.3</td>
<td>3.7</td>
<td>3.1</td>
<td>5.2</td>
<td>13.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Depression, %</td>
<td>6.2</td>
<td>4.3</td>
<td>5.3</td>
<td>4.3</td>
<td>11.0</td>
<td>.01</td>
</tr>
<tr>
<td>Rural, %</td>
<td>82.4</td>
<td>88.0</td>
<td>83.1</td>
<td>77.1</td>
<td>81.3</td>
<td>.01</td>
</tr>
</tbody>
</table>

Note: Data are shown as mean ± SD, frequency as percentage (%). 25(OH)D₃ = 25-hydroxyvitamin D₃, ADL = activity of daily living, eGFR = estimated glomerular filtration rate, MMSE = Mini-Mental State Examination.

*p for differences by quartiles vitamin D levels.
Table 2. Odds Ratios (95% Confidence Interval) of Cognitive Decline and Cognitive Impairment in Cognitively Intact Subjects at Baseline by Quartiles of Plasma Vitamin D₃ Levels

<table>
<thead>
<tr>
<th>Quartiles of plasma 25(OH)D₃, nmol/L</th>
<th>1 (high)</th>
<th>2</th>
<th>3</th>
<th>4 (low)</th>
<th>p for linear trend</th>
<th>1 SD decrement of plasma vitamin D₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma vitamin D₃</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, nmol/L</td>
<td>66.4</td>
<td>48.9</td>
<td>36.6</td>
<td>25.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, nmol/L</td>
<td>56.2–208.7</td>
<td>42.4–56.1</td>
<td>31.5–42.4</td>
<td>6.5–31.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number at risk</td>
<td>300</td>
<td>301</td>
<td>301</td>
<td>300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive decline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cases at follow-up (n)</td>
<td>41</td>
<td>72</td>
<td>77</td>
<td>96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted OR</td>
<td>1.00</td>
<td>1.99(1.30–3.03)</td>
<td>2.17(1.43–3.30)</td>
<td>2.97(1.98–4.48)</td>
<td>&lt;.0001</td>
<td>2.60(1.36–1.88)</td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>1.00</td>
<td>2.02(1.24–3.28)</td>
<td>2.07(1.26–3.41)</td>
<td>1.83(1.10–3.05)</td>
<td>.0206</td>
<td>1.35(1.10–1.66)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive impaired at follow-up (n)</td>
<td>13</td>
<td>23</td>
<td>35</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted OR</td>
<td>1.00</td>
<td>1.83(0.91–3.68)</td>
<td>2.91(1.50–5.61)</td>
<td>5.75(3.09–10.7)</td>
<td>&lt;.0001</td>
<td>2.17(1.69–2.79)</td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>1.00</td>
<td>1.77(0.81–3.86)</td>
<td>2.41(1.12–5.19)</td>
<td>2.89(1.36–6.14)</td>
<td>.0040</td>
<td>1.59(1.17–2.17)</td>
</tr>
</tbody>
</table>

Note: 25(OH)D₃, 25-hydroxyvitamin D₃.

*Adjusted for age, gender, education (yes/no), baseline MMSE score, abdominal obesity (yes/no), hypertension (yes/no), diabetes (yes/no), eGFR, total cholesterol, current smoker (yes/no), current drinker (yes/no), season, ADL limitations (at least one limitation), depression (yes/no), and rural (yes/no).

†p < .05; ‡p < .01; §p < .001.

Figure 1. Multivariable-adjusted smoothing spline plots showing log-odd ratios of cognitive decline and cognitive impairment by 25(OH)D₃ levels. Model adjusted for age, gender, education, body mass index, season, current smoker, current drinker, and depression.

The observation of temporal association between 25(OH)D₃ levels and subsequent cognitive function supports the notion that vitamin D has a clinically important neuroprotective effect. A wide variety of mechanisms for this effect has been proposed and is supported by animal studies. Vitamin D has been found to modulate neuronal calcium homeostasis, cerebral process of detoxification, immunomodulation, and beta-amyloid clearance. Calcitriol (1,25-(OH)₂D₃), the active metabolite form of vitamin D₃, downregulates L-type sensitive calcium channel in the hippocampus, which can protect neurons against excitotoxic insults (28). It can also stimulate the expression of calcium binding proteins such as parvalbumin, calbindin-D₉k, and calbindin-D₂₈k (29,30). Moreover, calcitriol attenuates the production of nitric oxide through inhibiting the expression of inducible nitric oxide synthase in the spinal cord and brain (31). High nitric oxide levels are thought to play a role in inflammatory disorders, neurodegenerative disorders, and neurotoxicity (32). Calcitriol can control brain detoxification processes by upregulating γ-glutamyl transpeptidase activity and exerting a neuroprotective effect during brain damage (33). It is also an immunosuppressor and may be neuroprotective by inhibiting autoimmune damage to nervous system (4,33). Vitamin D may reduce the accumulation of Aβ42 peptide in stimulating the innate immune system, specifically the phagocytosis and clearance of beta-amyloid peptide by macrophages (34).

Despite animal and epidemiological evidence, the notion that vitamin D is both causally related and clinically important in cognitive
function is not established. Although we identified a temporal association and adjusted for characteristics that induced both low 25(OH)D3 levels and were associated with cognitive impairment (e.g., outdoor exposure), there may have been unmeasured confounders. One promising epidemiological approach to the problem of confounding, Mendelian randomization, has not resolved this potential problem. A recent study indicated that single nucleotide polymorphisms related to serum vitamin D status did not predict cognitive function (35). However, single nucleotide polymorphisms associated with the vitamin D receptor gene (Apal, rs7975232) was found to be significantly associated with word recall and digit–symbol coding tests (35), which strengthen the findings that vitamin D receptor polymorphisms are associated with Alzheimer's disease (36).

Compelling evidence for a causal association from randomized trials has yet to resolve this clinically important issue. In the Women's Health Initiative Calcium and Vitamin D Trial, 4,143 women aged 65 years were randomized to either receive calcium 1,000 mg and vitamin D3 400 IU or placebo. During the mean follow-up of 7.8 years, no association was found between treatment and the incidence of probable dementia, incidence of mild cognitive impairment, or cognitive function (37). One explanation for lack of an effect was the joint administration of vitamin D with calcium; increased serum calcium has been associated with increased risk of cognitive decline in elderly people and increased intake of calcium may mask the neuroprotective effect of vitamin D (38). A randomized trial of high-dose versus low-dose vitamin D3 in Alzheimer's disease patients found no benefit (additional 6,000 IU per day to ongoing low-dose vitamin D3, 1,000 IU daily for 8 weeks) on cognitive function. Although serum 25(OH)D3 levels increased in the intervention group, the increase may not have been sufficient to benefit cognitive function (39). Another clinical trial that examined the effect of vitamin D levels (30,000 IU vitamin D3 3 times per week over 4 weeks) in nursing home residents with low vitamin D status observed no effect of vitamin D supplementation on cognitive function. This may be attributed to shorter treatment duration and smaller sample size (40).

In the current study, “we found that there may be a threshold effect for risk of cognitive decline but not for risk of cognitive impairment. Lack of evidence of threshold effect for cognitive impairment is at variance with a previous study” (18) where the risk of developing all-cause dementia and Alzheimer’s disease increased markedly below concentrations of 25(OH)D3 levels around 50 nmol/L. The lack of evidence of threshold in the current study may be due to the relatively shorter follow-up time (2.0 years vs. to 5.6 years) and smaller sample size (1,202 subjects vs. 1,658 subjects) compared with the previous study.

As noted, one limitation of our study is that some confounding factors related to cognitive decline and vitamin D intake such as apolipoprotein E genotype, diet, direct sun exposure, and supplements intake were unadjusted for. Thus, we could not examine an effect modification by apolipoprotein E allele. However, a recent prospective study reported that the association between low vitamin D levels and decline of cognitive function domains remained significant even after controlling for apolipoprotein E allele and other potential confounders (12). Further studies are required to confirm the potential effect of vitamin D status on cognitive decline in the presence and absence of apolipoprotein E allele. We report our findings based on cohort specific vitamin D quartiles in order to maximize the power to identify categorical effects. To facilitate comparisons with studies based on common clinical cut points, we include Supplementary Table 2, which uses cut points comparable to previous research for both cognitive decline and CI.

Our included subjects were younger, had better functional abilities and healthier lifestyle behaviors compared with those excluded from the analysis. Although we cannot exclude the possibility of this participation bias attenuating our results, it would unlikely lead to a bias in favor of an association between vitamin D and cognitive decline, as these subjects also had higher 25(OH)D3 level and MMSE scores at baseline. Further, it was unlikely that vitamin D supplementation would explain the association in this study, as 87% of the participants reported no use of vitamin supplements. Moreover, Chinese Longitudinal Healthy Longevity Survey oversampled the oldest-old in China, and 25(OH)D3 level in the present study is relatively lower among younger or Western populations (17). Our findings must be interpreted in this light.

The strengths of the present study were its prospective design, large numbers of participants were followed up, and the collection of plasma blood samples during the surveys. These allowed us to investigate the association between vitamin D status and risk of cognitive decline in cognitively intact participants over time and to adjust for important potential confounding variables. Furthermore, we assessed the cognitive function of studied subjects at baseline and adjusted for baseline MMSE score in our model, reducing the possible influence of low baseline 25(OH)D3 levels on cognitive decline.

In conclusion, our longitudinal study indicates that low 25(OH)D3 levels are associated with subsequent cognitive decline and cognitive impairment. Despite the lack of conclusive results from intervention studies, the weight of this and other epidemiological studies reinforce the importance of more intensive investigation on the effects of vitamin D supplements on cognitive decline. Further, it points to the need to fully explain the association between vitamin D and cognitive function so that we may identify an effective intervention to stem the rapidly increasing prevalence of cognitive decline associated with an aging population.

Supplementary Material
Please visit the article online at http://gerontologist.oxfordjournals.org/ to view supplementary material.

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Conflict of Interest
The authors have no conflict of interest to declare.
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