



Low serum 25-hydroxyvitamin D increases cognitive impairment in elderly people

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Abstract

It has been reported that many elderly people have low serum levels of 25-hydroxyvitamin D [25(OH)D] and that serum 25(OH)D levels may have a relationship with cognitive function. The aim of this study was to examine the relationship between serum 25(OH)D levels and cognitive function in a Japanese population. This cross-sectional study was performed as a part of the Project in Sado for Total Health (PROST). The PROST study evaluated cognitive state and serum vitamin D level from June 2011 to November 2013 for 740 patients (431 men and 309 women). The Mini-Mental State Examination-Japanese version (MMSE-J) and serum 25(OH)D level measurements were used as assessment tools. Cognitive impairment was defined using MMSE-J ≤ 23 as a cutoff. Multiple logistic regression analyses were performed to calculate the odds ratios (ORs) for low MMSE-J scores. The average subject age was 68.1 years, the average MMSE-J score was 25.9, and the average 25(OH)D level was 24.6 ng/mL. Significant ORs for cognitive impairment were observed for both high age and low serum 25(OH)D. The adjusted OR for the lowest versus highest serum 25(OH)D quartiles was 2.70 (95% confidence interval 1.38–5.28, $P=0.0110$). Low serum 25(OH)D levels were independently associated with a higher prevalence of cognitive impairment.

Keywords Cognitive impairment · 25-Hydroxyvitamin D · Cross-sectional study · Mini-Mental State Examination-Japanese Version (MMSE-J)

Introduction

The population of Japan is rapidly aging, with an especially steep curve relative to the rest of the world. In our advanced-age society, dementia is one of the main reasons for nursing care, and the prevention of dementia is an important problem. Furthermore, it has been reported that serum

25-hydroxyvitamin D [25(OH)D] levels are greatly reduced in elderly people.

The vitamin D receptor (VDR) is required for normal function in various tissues and systems, including the immune, musculoskeletal, nervous, and cardiovascular systems. Lack of vitamin D is associated with diverse clinical pathologies [1]. We reported previously that vitamin

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D insufficiency or deficiency may occur in patients with osteoporotic fractures [2, 3]. In that study, the relationship of dementia prevalence with 25(OH)D levels indicated a tendency for 25(OH)D levels to decrease as dementia progressed [2].

Several studies have reported on the relationship between cognitive impairment and low serum 25(OH)D levels [4–6], but further studies in additional countries and with different ethnic groups are necessary. In Japan, only a few large cross-sectional studies have examined the relationship between cognitive impairment and serum 25(OH)D, and the findings have not been consistent.

The aim of this cross-sectional study was to examine the relationship between cognitive function and serum 25(OH)D levels in a hospital-based Japanese population. If low serum 25(OH)D levels are associated with cognitive impairment, this would suggest that vitamin D deficiency is a risk factor for cognitive impairment.

Materials and methods

Study site

This study was carried out in Sado City, Japan, which is located on Sado Island, where all residents live in the city. Sado Island is situated north of the main Japanese island of Honshu and is located in Niigata Prefecture on the Sea of Japan, at latitude 37°48′N–38°20′N and longitude 138°12′E–138°34′E. Sado Island has an area of 855 km², and a population of 61,820 (29,576 male and 32,244 female) as of July 1, 2011, of which 22,778 (9210 men and 13,568 women) (36.9%) were 65 years old or older. The working population is 22% in primary, 19% in secondary, and 59% in tertiary industries [7]. Access to the island is only possible by sea.

Subjects

A registry referred to as the Project in Sado for Total Health (PROST) was initiated in June 2008 in conjunction with the Center for Inter-Organ Communication Research, Niigata University Graduate School of Medicine and Dental Sciences, and included patients aged 20 years and older who visited Sado General Hospital. Details regarding PROST have been described elsewhere [8–10].

The assessment of cognitive state using the Mini-Mental State Examination-Japanese Version (MMSE-J) began in PROST in June 2011. Measurement of serum 25(OH)D levels of the registrants was carried out until November 2013. A total of 912 people (527 men and 385 women) participated in PROST from June 2011 to November 2013. These participants were included for the current study. Of the 912

participants, 127 were excluded due to lack of agreement to undergo the MMSE-J examination, and 45 were excluded due to lack of 25(OH)D measurements at the time of enrollment. The remaining 740 participants were the subjects of this study.

Measurements

Data were collected for age, sex, body height, and weight (body mass index: BMI).

Cognitive function was assessed using the MMSE-J, which is widely used for that purpose in Japan. MMSE-J scores range from 0 to 30, with lower scores indicating greater cognitive impairment. The MMSE-J assesses participants' orientation, memory, attention, backward repetition, language, and written and visual construction. Cognitive impairment was defined as an MMSE-J score of ≤ 23 . Its reliability and validity are well documented [11]. The MMSE-J was administered by interview.

Blood samples were collected at the time of enrollment in PROST. Serum 25(OH)D levels were measured throughout the year by a double-antibody radioimmunoassay (RIA2) using a kit supplied by DiaSorin (Stillwater, MN, USA). The detection limit was 6 ng/mL. According to the guidelines presented recently by the Japan Endocrine Society and the Japanese Bone Metabolism Society [12], vitamin D sufficiency is judged as a level greater than or equal to 30 ng/mL, and serum 25(OH)D levels less than or equal to 30 ng/mL are considered insufficient. More specifically, (a) serum 25(OH)D levels between 20 and 30 ng/mL are classified as insufficiency, and (b) serum 25(OH)D levels less than or equal to 20 ng/mL are classified as deficiency.

Intact serum parathyroid hormone (PTH) was measured with an electrochemiluminescence immunoassay (ECLIA) (Roche Diagnostics, Basel, Switzerland), in which intact-PTH molecules are detected. The detection limit was 4 pg/mL. The normal range is 10–65 pg/mL.

Demographic characteristics (including age and sex), stroke and diabetes and hypertension history, and information on lifestyle were obtained by interview. Current height and weight were measured at the time of enrollment in PROST. Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m²). Physical activity levels were estimated by calculating time spent walking (h/day). For smoking, participants were classified as non-smokers, past smokers, or current smokers.

Statistical analysis

Comparisons between the two groups were performed using the Mann–Whitney *U* test and Chi-square test, and correlations were examined using Spearman's rank correlation test. Simple and multiple logistic regression analyses were

performed to calculate the odds ratios (ORs) for scores on the MMSE-J ≤ 23 . For analysis, 25(OH)D levels and intact-PTH levels were divided into quartiles, and BMI was divided into quintiles. We evaluated potential predictors adjusting for covariates, including age, sex, BMI, history of stroke and diabetes and hypertension, smoking, time spent walking, and taking active vitamin D agents. The analyses were performed using SAS statistical package (Release 9.4, Cary, NC, USA). A P value < 0.05 was considered statistically significant.

Informed consent

Written informed consent was obtained from all participants included in the study.

Results

The characteristics of the patients in the study are shown in Table 1. The average age was 68.1 years. The average MMSE-J score was 25.9. The average 25(OH)D level was 24.6 ng/mL. The level was significantly lower in women than in men ($P < 0.01$). The fraction of patients with 25(OH)D < 20 ng/mL was 29.1%, split into 17.9% for men and 44.7% for women. The fraction with vitamin D insufficiency ($20 \text{ ng/mL} \leq 25(\text{OH})\text{D level} < 30 \text{ ng/mL}$) was 43.6%.

Correlations between the MMSE-J score and the 25(OH)D levels were examined. The MMSE-J score correlated positively with 25(OH)D level ($r = 0.098$, $P < 0.01$). Separate analyses of the male and female subjects found that the MMSE-J score correlated positively with the 25(OH)D level for both ($r = 0.098$, $P < 0.05$ for men, $r = 0.136$, $P < 0.05$ for women). On the other hand, there was no significant correlation between age and 25(OH)D level ($r = 0.011$, $P = 0.775$).

Figure 1 shows the average serum 25(OH)D levels stratified by age. The peak serum levels occurred in the age range 50–70 years. The average level of serum 25(OH)D was lower in subjects less than 50 years old and more than 90 years old.

Findings related to the MMSE-J category are shown in Table 2. The group with MMSE-J ≤ 23 included 186 subjects (25.1%) whose average age was significantly higher ($P < 0.001$) than that in the MMSE-J > 23 group. In addition, the 25(OH)D levels were significantly lower ($P < 0.01$), and the intact-PTH level was significantly higher ($P < 0.01$), in the MMSE-J ≤ 23 group than in the MMSE-J > 23 group.

A multiple logistic regression analysis was performed to determine the independent factors associated with cognitive impairment (MMSE-J ≤ 23) (Table 3). Significant ORs were observed for age, 25(OH)D level, and intact-PTH. The adjusted OR for the lowest versus the highest serum 25(OH)D quartiles was 2.62 (95% confidence interval C 1.53–4.47, $P = 0.0008$). The adjusted OR for the highest versus the lowest serum intact-PTH was 1.82 (95% CI 1.14–2.91, $P = 0.0018$). The association between BMI quintile and cognitive impairment was U-shaped.

As there have been reports that dialysis has an influence on cognitive function, we conducted an analysis excluding patients being treated with dialysis [10, 13–15]. As it is known that several other clinical factors affect cognitive function, the analysis was adjusted for BMI, history of stroke, diabetes mellitus, hypertension, smoking, taking active vitamin D agents, and time spent walking (Table 4). Significant ORs were observed for the age and 25(OH)D variables, similar to those found in the total analysis. The adjusted OR for the lowest versus highest serum 25(OH)D quartiles was 2.70 (95% CI 1.38–5.28, $P = 0.0110$). The association between intact-PTH quartile and cognitive function was not significant.

Furthermore, to eliminate the effects of aging as much as possible, we conducted a sub-analysis that was limited

Table 1 Characteristics of the subjects (means or numbers) stratified by sex

	Mean \pm SD (range) or number (%)			P value
	Total ($N = 740$)	Men ($N = 431$)	Women ($N = 309$)	
Age (years)	68.1 \pm 11.6 (27–94)	67.6 \pm 11.7 (27–91)	68.8 \pm 11.4 (31–94)	0.2593
MMSE-J score	25.9 \pm 3.7 (10–30)	25.8 \pm 3.6 (10–30)	26.1 \pm 3.8 (10–30)	0.0612
(Max 30 points)	27.0 (median)	27.0 (median)	27.0 (median)	
MMSE-J ≤ 23	186 (25.1%)	108 (25.1%)	78 (25.2%)	0.9544
25(OH)D (ng/mL)	24.6 \pm 9.0 (6–64)	26.6 \pm 8.9 (6–64)	21.9 \pm 8.4	< 0.0001
25(OH)D < 20 (ng/mL)	215 (29.1%)	77 (17.9%)	138 (44.7%)	< 0.0001
iPTH (pg/mL)	52.0 \pm 61.3 (5–1030)	52.5 \pm 64.9 (10–1030)	51.4 \pm 56.1 (5–430)	0.6461
BMI (kg/m ²)	23.9 \pm 4.0 (14.8–46.5)	24.2 \pm 3.5 (16.0–41.4)	23.5 \pm 4.6 (14.8–46.5)	0.0002
	9 missing values	4 missing values	5 missing values	

Comparisons between the sexes were performed using the Mann–Whitney U test or Chi-square test

MMSE-J Mini-Mental State Examination-Japanese Version, BMI body mass index, 25(OH)D 25-hydroxyvitamin D level, iPTH intact parathyroid hormone level

Fig. 1 Average serum 25(OH)D level for each age range (bars are \pm SD). The peak is from age 50–70 years

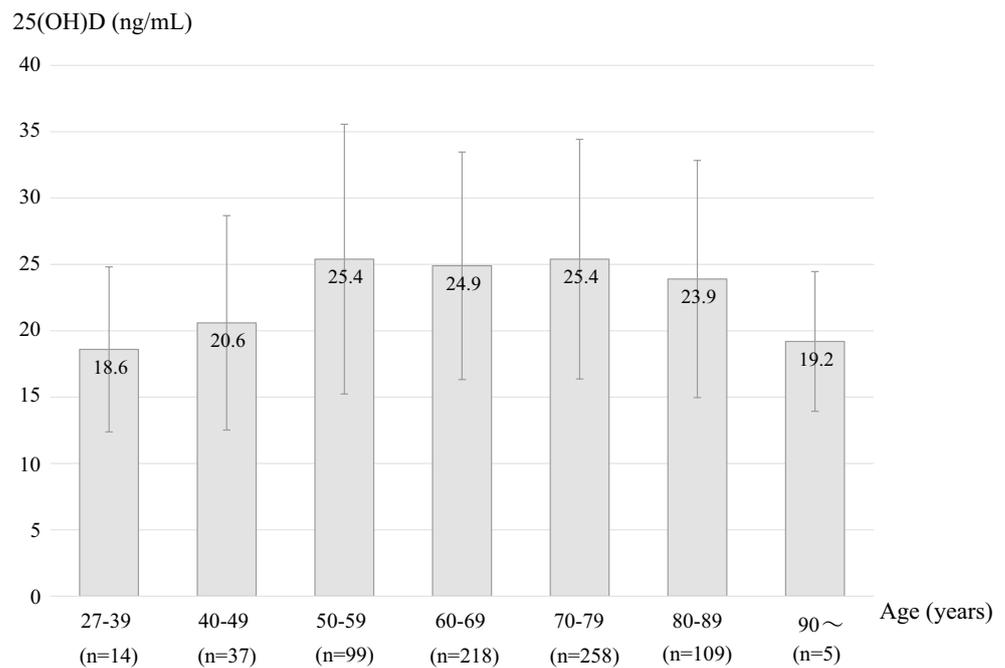


Table 2 Characteristics of subjects according to MMSE-J category

Variables	MMSE-J \leq 23 (N=186)	MMSE-J > 23 (N=554)	P value
Age (years)	74.6 \pm 9.1	65.9 \pm 11.5	<0.0001
Sex (male)	108 (25.1%)	323 (25.1%)	0.9544
25(OH)D (ng/mL)	23.1 \pm 8.8	25.2 \pm 9.0	0.0048
iPTH (pg/mL)	59.0 \pm 55.5	49.7 \pm 63.1	0.0012
BMI (kg/m ²)	23.5 \pm 3.8	24.0 \pm 4.0	0.1880
	5 missing values	4 missing values	

Comparisons between the two groups were performed using the Mann–Whitney *U* test or Chi-square test
25(OH)D 25-hydroxyvitamin D level, iPTH intact parathyroid hormone level, BMI body mass index

to subjects 60–89 years old (Table 5). Significant ORs were still observed for the age and 25(OH)D variables, similar to those found in the total age analysis. The adjusted OR for the lowest versus highest serum 25(OH)D quartiles was 2.82 (95% CI 1.43–5.58).

Discussion

Based on the multiple regression analyses, a low level of serum 25(OH)D was an independent factor associated with MMSE-J \leq 23 for both men and women. Our study is the largest study including both men and women to examine cognitive function and serum 25(OH)D levels in Japan. Furthermore, in a subgroup analysis excluding dialysis patients and adjusted for age, sex, BMI, history of stroke, diabetes and hypertension, smoking, time spent walking, and consumption of active vitamin D, the 25(OH)D level remained as an independent factor associated with cognitive

impairment. The adjusted OR for the lowest versus the highest plasma vitamin D quartiles was 2.70. A similar result was obtained in the sub-analysis limited to subjects 60–89 years old. The adjusted OR for the lowest versus the highest plasma vitamin D quartiles was 2.82.

Chei et al. [4] reported a similar result in China using a cutoff of MMSE < 18 (N=2004). They reported that the adjusted OR for the lowest versus the highest plasma vitamin D quartiles was 2.15. In the current study, the adjusted OR was slightly higher than theirs, though the cut-off MMSE point was also higher than theirs.

There have been several previous reports that are compatible with these results. Balion et al. [5] found in a meta-analysis that low serum vitamin D concentrations were a risk factor for both cognitive impairment and Alzheimer's disease. Matchar et al. [16] reported in their longitudinal survey that compared with the highest quartile of serum vitamin D levels, the OR for cognitive decline was about 2 for the other quartiles. This suggests that low levels of 25(OH)D may not

Table 3 Odds ratios for cognitive impairment based on each variable ($N=740$)

Predictor variables	Subjects, N	Cognitive impairment, N (prevalence, %)	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)
Sex			$P=0.9544$	$P=0.6708$
Male	309	78 (25.2)	1 (ref.)	1 (ref.)
Female	431	108 (25.1)	0.99 (0.71–1.39)	1.08 (0.76–1.55)
Age (years)			P for trend < 0.0001	P for trend < 0.0001
< 60	150	8 (5.3)	1 (ref.)	1 (ref.)
60–69	218	39 (17.9)	3.87 (1.75–8.54)	3.94 (1.78–8.71)
70–79	258	84 (32.6)	8.57 (4.01–18.29)	8.57 (4.01–18.29)
≥ 80	114	55 (48.3)	16.55 (7.42–36.87)	16.51 (7.40–36.83)
BMI (kg/m ²)			P for trend = 0.1125	P for trend = 0.6354
First Q (< 20.6)	156	50 (32.1)	1.62 (0.97–2.70)	1.81 (1.04–3.15)
Second Q (20.6–22.6)	145	35 (24.1)	1.09 (0.63–1.88)	1.18 (0.67–2.10)
Third Q (22.7–24.3)	146	33 (22.6)	1 (ref.)	1 (ref.)
Fourth Q (24.4–26.4)	146	32 (21.9)	0.96 (0.55–1.67)	1.07 (0.59–1.93)
Fifth Q (≥ 26.5)	147	36 (21.8)	1.11 (0.65–1.91)	1.53 (0.86–2.75)
25(OH)D (ng/mL)			P for trend = 0.0019	P for trend = 0.0006
First Q (< 18)	155	56 (36.1)	2.03 (1.27–3.24)	2.81 (1.63–4.84)
Second Q (18–23)	185	46 (24.9)	1.19 (0.74–1.91)	1.11 (0.66–1.87)
Third Q (24–29)	198	40 (20.2)	0.91 (0.56–1.47)	0.88 (0.53–1.45)
Fourth Q (≥ 30)	202	44 (21.8)	1 (ref.)	1 (ref.)
iPTH (pg/mL)			P for trend = 0.0019	P for trend = 0.0026
First Q (< 27)	172	38 (22.1)	1 (ref.)	1 (ref.)
Second Q (27–34)	189	34 (18.0)	0.77 (0.46–1.30)	0.81 (0.47–1.42)
Third Q (35–49)	191	50 (26.2)	1.25 (0.77–2.03)	1.15 (0.69–1.91)
Fourth Q (≥ 50)	188	64 (34.0)	1.82 (1.14–2.91)	1.93 (1.17–3.19)

Simple and multiple logistic regression analyses were performed to calculate the odds ratios (ORs) for scores on the MMSE- $J \leq 23$

CI confidence interval, BMI body mass index, 25(OH)D 25-hydroxyvitamin D level, iPTH intact parathyroid hormone level

^aAdjusted for age and sex (except for the variables sex and age); sex was adjusted for age, and age was adjusted for sex

only associate with cognitive impairment but may also be a risk factor for cognitive decline.

On the other hand, Okuno et al. [17] found a negative association only in men, in 316 community-dwelling elderly people aged 65 years or older in Japan. They found no association in women, but suggested that this was caused by a lack of participation by women with cognitive impairment. We have reported that mean 25(OH)D levels tended to decrease as the degree of dementia progressed ($P < 0.05$) [2]. In the current study, we obtained results that are consistent with this previous study.

There have been many studies of neurobiological mechanisms that could explain the association between vitamin D and cognitive function. Brewer et al. [18] reported direct neuroprotective actions of 1,25-dihydroxyvitamin D₃ at relatively low concentrations and selective downregulation of L-type voltage-sensitive Ca²⁺ channel expression in hippocampal neurons of rats. Kalueff et al. [19] reported that vitamin D acts as an important neurosteroid hormone in the brain. Karakis et al. [20] reported that low 25(OH)D

concentrations were associated with a smaller hippocampal volume and poorer neuropsychological function in the Framingham Heart Study. We suggest that our results are compatible with these studies of vitamin D function in the central nervous system.

In our study, the average 25(OH)D level was significantly lower in women than in men (Table 1). Suzuki et al. [21] reported similar results, and suggested that the reasons for this sex difference may be general inactivity and lower intake of vitamin D from daily food in elderly Japanese women than in men. In addition, we suggest that women are more likely to avoid sun exposure than men.

Vitamin D deficiency (25(OH)D < 20 ng/mL) occurred in 29.1% of our subjects, including 17.9% of men and 44.7% of women. Vitamin D insufficiency (20 ≤ 25(OH)D < 30 ng/mL) occurred in 43.6%. If the total number of patients with insufficiency and deficiency are added together, then a total of 72.7% of our participants are classified as being in a non-sufficient state.

Table 4 Odds ratios for cognitive impairment based on each variable, excluding patients with dialysis ($N=644$)

Predictor variables	Subjects, n	Cognitive impairment, N (prevalence, %)	Unadjusted OR (95% CI)	Adjusted ^a OR (95% CI)
Sex			$P=0.5148$	$P=0.1327$
Female	271	67 (24.7)	1 (ref.)	1 (ref.)
Male	373	84 (22.5)	0.89 (0.61–1.28)	0.68 (0.4–1.12)
Age (years)			P for trend < 0.0001	P for trend < 0.0001
< 60	127	5 (3.9)	1 (ref.)	1 (ref.)
60–69	181	26 (14.4)	4.09 (1.53–11.0)	5.34 (1.88–15.14)
70–79	233	71 (30.5)	10.69 (4.19–27.28)	10.53 (3.94–28.16)
≥ 80	103	49 (47.6)	22.14 (8.36–58.66)	25.78 (8.33–79.82)
25(OH)D (ng/mL)			P for trend = 0.0012	P for trend = 0.0110
First Q (< 19)	145	45 (31.0)	2.41 (1.39–4.16)	2.70 (1.38–5.28)
Second Q (19–24)	171	44 (25.7)	1.85 (1.08–3.18)	1.44 (0.79–2.64)
Third Q (25–30)	163	36 (22.1)	1.52 (0.87–2.65)	1.28 (0.70–2.37)
Fourth Q (≥ 31)	165	26 (15.8)	1 (ref.)	1 (ref.)
iPTH (pg/mL)			P for trend = 0.0566	P for trend = 0.2834
First Q (< 26)	151	34 (22.5)	1 (ref.)	1 (ref.)
Second Q (26–32)	162	28 (17.3)	0.72 (0.41–1.26)	0.78 (0.42–1.43)
Third Q (33–42)	161	39 (24.2)	1.10 (0.65–1.86)	0.85 (0.48–1.54)
Fourth Q (≥ 43)	170	50 (29.4)	1.43 (0.87–2.38)	1.27 (0.71–2.19)

Simple and multiple logistic regression analyses were performed to calculate the odds ratios (ORs) for scores on the MMSE-J ≤ 23

CI confidence interval, BMI body mass index, 25(OH)D 25-hydroxyvitamin D level, iPTH intact parathyroid hormone level

^aAdjusted for age, sex, BMI, history of stroke and diabetes and hypertension, smoking, time spent walking, and taking active vitamin D agents (except for the variables sex and age). The values for sex are adjusted for age and the values for age are adjusted for sex

There was no significant correlation between age and 25(OH)D levels. The average level of serum 25(OH)D was low in the subjects less than 50 years old and more than 90 years old (Fig. 1). This reason for this is unclear, but it was considered that MMSE-J was particularly associated with 25(OH)D levels in the elderly.

We have previously reported low levels of vitamin D in hip fracture patients and in spine fracture patients [2, 3]. Furthermore, there are other reports that show an association between elevated C-reactive protein concentration due to chronic inflammation and lower cognitive function in elderly people [9, 22]. Therefore, we suggest that, in elderly people, low 25(OH)D levels caused by reduced physical activity and decreased sun exposure lead to fragility-related fractures and cognitive impairment. Furthermore, the lack of adequate nutrition in the elderly may contribute to the functional decline of internal organs due to chronic inflammation and may thus cause fractures and cognitive impairment, leading to a further decrease in serum 25(OH)D levels. Therefore,

it is possible that these factors are mutually associated. To examine this hypothesis, a longitudinal study is necessary for a multifactorial analysis of causality.

This study has several limitations. First, our subjects were hospital-based patients who had various health problems, so they may not represent the general population of the same age group. Second, we did not assess the subjects for education level, an important factor associated with cognitive impairment [23]. Third, although vitamin D supplementation might affect serum 25(OH)D levels, we did not obtain information about whether the subjects were taking vitamin D supplements.

In the current study, we found that low serum 25(OH)D levels were independently associated with a higher prevalence of cognitive impairment. Since non-sufficiency of vitamin D is highly prevalent in Japan, we suggest the importance of supplementation for individuals who have low levels of serum 25(OH)D.

Table 5 Odds ratios for cognitive impairment based on each variable, excluding patients with dialysis (60–89 years old, $N=517$)

Predictor variables	Subjects, N	Cognitive impairment, N (prevalence, %)	Model 1 Adjusted ^a OR (95% CI)	Model 2 Adjusted ^b OR (95% CI)
Sex			$P=0.9720$	$P=0.193$
Female	217	61 (28.1)	1 (ref.)	1 (ref.)
Male	295	81 (27.5)	1.01 (0.67–1.51)	0.66 (0.39–1.13)
Age (years)			P for trend < 0.0001	P for trend < 0.0001
60–69	181	26 (14.4)	1 (ref.)	1 (ref.)
70–79	233	71 (30.5)	2.61 (1.58–4.31)	2.84 (1.68–4.81)
80–89	98	45 (45.9)	5.07 (2.85–9.02)	5.5 (2.82–10.73)
25(OH)D (ng/mL)			P for trend = 0.0028	P for trend = 0.0091
First Q (< 19.5)	128	49 (38.3)	3.01 (1.59–5.70)	2.82 (1.43–5.58)
Second Q (19.5–24)	113	33 (29.2)	1.50 (0.81–2.83)	1.43 (0.75–2.75)
Third Q (25–30)	137	35 (25.6)	1.48 (0.81–2.70)	1.2 (0.6–2.38)
Fourth Q (≥ 31)	134	25 (18.7)	1 (ref.)	1 (ref.)
iPTH (pg/mL)			P for trend = 0.1088	P for trend = 0.1397
First Q (< 26)	114	31 (27.2)	1 (ref.)	1 (ref.)
Second Q (26–32)	124	25 (20.2)	0.73 (0.39–1.35)	0.74 (0.39–1.42)
Third Q (33–43)	141	38 (27.0)	0.94 (0.53–1.67)	0.79 (0.42–1.48)
Fourth Q (≥ 44)	133	48 (36.1)	1.46 (0.84–2.55)	1.38 (0.74–2.57)

Multiple logistic regression analyses were performed to calculate the odds ratios (ORs) for scores on the MMSE-J ≤ 23

CI confidence interval, BMI body mass index, 25(OH)D 25-hydroxyvitamin D level, iPTH intact parathyroid hormone level

^aAdjusted for age and sex (except for the variables sex and age). The values for sex were adjusted for age and the values for age were adjusted for sex

^bAdjusted for age, sex, BMI, history of stroke and diabetes and hypertension, smoking, time spent walking, and taking active vitamin D agents (except for the variables sex and age). The values for sex are adjusted for age and the values for age are adjusted for sex

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest All authors have no conflicts of interest to declare.

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