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Association between vitamin D deficiency and cognitive function in the elderly Korean population

A Korean frailty and aging cohort study

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Abstract

It is well known that vitamin D (VitD) plays an important role in bone and calcium metabolism in the human body. VitD has additional roles in the body including modulation of cell growth, neurogenesis, neuroprotection, detoxification, immune function, and reduction of inflammation. Recent studies reveal insufficiency of VitD as a risk factor for cognitive decline or dementia. VitD has a role in normal brain function; insufficiency of VitD may lead to decreased memory and cognitive function.

Using 2 years of baseline data from Korean frailty and aging cohort study, 2990 subjects (1415 men and 1575 women) were recruited. A short form of Korean version of the consortium to establish a registry for Alzheimer disease (CERAD-K), an assessment of cognitive status in patients with dementia was used. Among CERAD-K tests, we included word list memory/recall/recognition, digit span (forward, backward), trail making test (TMT) A, and mini-mental state examination in the Korean version of the CERAD assessment packet (MMSE-KC). Serum samples were collected and 25-hydroxyvitamin D (25(OH)D) was measured. Serum 25(OH)D concentrations were classified into clinically relevant categories as: deficient (<10 nmol/L), insufficient (10–30 nmol/L), and sufficient (≥30 nmol/L).

The mean age of participants was 76.5 ± 3.9 years, and 52.7% were women. Among 2990 participants, 119 (4.0%) were classified as 25(OH)D deficient and 2253 (75.3%) as insufficient. Only 618 (20.7%) participants were sufficient for 25(OH)D. Among them performance in MMSE-KC, TMT A, and digit span tests was better in sufficient, insufficient, and deficient groups, which was statistically significant ($P < .05$). However, in multivariable regression analysis after adjusting for age, sex, body mass index, education, center, seasonality, physical activity, and alcohol use, association between 25(OH)D and cognitive function was not statistically significant.

Although, when comparing VitD levels, there were differences in cognitive tests among the groups, fully adjusted analysis did not show any association. This result suggests that cognition was not affected by VitD levels alone but also population and sociological variables. In a fully adjusted model, there was no statistically significant association between VitD and cognitive function in the elderly Koreans in logistic regression analysis.

Abbreviations: 25(OH)D = 25-hydroxyvitamin D, CERAD-K = Korean version of the consortium to establish a registry for Alzheimer disease, KFACS = Korean frailty and aging cohort study, MMSE-KC = Mini-Mental State Examination in the Korean version of the CERAD assessment packet, TMT = trail making test, VitD = vitamin D.

Keywords: cognitive function, geriatrics, vitamin D

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1. Introduction

In the human body, it has been well established that vitamin D (VitD) plays an important role in bone and calcium metabolism. Also, several studies have associated insufficiency of VitD with chronic diseases such as diabetes, metabolic disorders, cardiovascular diseases, autoimmune diseases, and even some malignancies. VitD has other roles in the body including modulation of cell growth, neurogenesis, neuroprotection, detoxification, immune function, and reduction of inflammation.[1] In recent studies, insufficiency of VitD was linked with cognitive decline or dementia. Although there are a few hypotheses, the relationship between serum VitD concentration and cognitive function was not clear. A range of neuroprotective (eg, increased phagocytosis of amyloid-beta peptide, regulation of neurotrophins and calcium homeostasis, anti-inflammatory, and antioxidant action) mechanisms have been identified suggesting VitD may play a substantial role in preventing dementia.[2,3] Because no large double-blind randomized-control trials were investigating whether VitD supplementation can prevent dementia, further study needed. There is a need for study. In the normal brain, the mechanism of neuroprotection by VitD is mostly via the VitD receptor, which is a nuclear receptor that combines with the retinoid X receptor to regulate gene transcription.[4] Because VitD has a neuroprotective function, the insufficiency of VitD may lead to decreased memory and cognitive function. VitD receptors are located in the human cortex and hippocampus, which are crucial areas for cognitive functioning, and an absence or malfunction has been associated with neurodegenerative dementia such as Alzheimer disease (AD). Indeed, in elderly patients with AD, VitD deficiency is very common with an incidence of 70% to 90%.[5]

The incidence of cognitive decline is increasing rapidly due to an increase in the elderly Korean population. According to the nationwide Korean Eldery Survey, cognitive decline measured using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K) in the elderly aged over 65, estimated that cognitive decline occurred in 24.1% and overall dementia in 8.1%. It is expected that the number of dementia patients will double every 20 years until 2050 in Korea.[6] Prolonged life expectancy and growing elderly population require active medical intervention to prevent cognitive decline. Therefore, it is valuable to find modifiable factors that are associated with cognitive decline. One of these factors is VitD. Although there are several studies examining the association between VitD and cognitive decline in Korea, the evidence from these studies is not consistent and the number of participants were relatively small.

The purpose of this study was to investigate the relationship between serum VitD level and global cognitive function in elderly Koreans using baseline data from the Korean frailty and aging cohort study (KFACS) (a nationwide cohort study since 2016). We hypothesize that there is a positive correlation between VitD levels and cognitive decline. We studied the multivariable-adjusted association between VitD level and cognitive decline using data from KFACS.

2. Methods

2.1. Data and study population

We used data from KFACS to investigate the relationship between VitD level and cognitive function in community-dwelling individuals aged 70 years or older. Among the 3014 participants, 24 elderly participants who were diagnosed with dementia, with severe cognitive impairment and who could not answer a questionnaire or who did not give informed consent, were excluded. The aim of KFACS is to identify the risk factors and preventive measures for the adverse consequences of frail community-dwelling elderly. KFACS is a multicenter, longitudinal study, with the baseline survey conducted in 2016 to 2017. Sex and age-stratified community residents aged 70 to 84 years from urban and rural regions nationwide were eligible for participation in the study.[7] A total of 2990 participants (1415 men and 1575 women) were recruited in this survey. Participants were recruited from 10 nationwide multi-centers. In medical institutions including 8 hospitals and 2 public health centers, participants were individually interviewed along with clinical examination, and blood tests. KFACS protocol was approved by the Institutional Review Board (IRB) of the Clinical Research Ethics Committee of the Kyung Hee University Medical Center, and all subjects provided written informed consent (IRB number: 2015-12-103).

2.2. Cognitive function

The cognitive function was assessed using the Korean version of the CERAD-K, an assessment of cognitive status in patients with dementia. CERAD-K is a neuropsychological assessment that consists of 8 tests such as Verbal Fluency, Modified Boston Naming, Mini-Mental State Examination, Word List Memory, Constructional Praxis, Word List Recall, Word List Recognition, and Constructional Praxis Recall.[8] Among the 8 tests, we included Word list memory/recall/recognition, digit span (forward, backward), trail making test (TMT) A, and MMSE in the Korean version of the CERAD assessment packet (MMSE-KC) for evaluating cognitive function. MMSE-KC consists of 5 domains: direction (10 points), memory (6 points), attention (5 points), language ability (6 points), comprehension, and judgment (3 points). The total score is 30, with lower scores reflecting a poor cognitive function.[8] Word List Memory test is an immediate recall test for new information. Every 2 seconds, participants read 10 commonly used words and instantly recall as many words as possible for 90 seconds. The total score is considered as 30. Word List Recall test evaluates the short-term memory wherein the participant recalls 10 words from the Word List Memory task after 15 minutes. Similar to the Word List Memory task, participants are given 90 seconds, and the total score is 10. In the Word List Recognition test, subjects have to distinguish between 10 words presented in the Word List Memory test and a new set of 10 words for recognition ability. The total score is considered as ten.[9] The Digit Span test was used to test working memory and attention-concentration. Respondents were asked to recall numbers forwards (range 3–9) and backwards (range 2–8).[10] The TMT is a neuropsychological test of visual attention, sequential processing, motor speed, and task switching. Processing speed was assessed using trail making test A (TMT-A), the subject was asked to list numbers from 1 to 25 in an ascending order. The maximum time given to complete the test was 300 seconds. Longer time to complete the TMT-A test indicates poor performance.[9] Frontal assessment battery (FAB) is a brief tool of bedside test for assess the screening of frontal dysexecutive syndrome and Alzheimer dementia affecting both cognitive and executive function. The FAB consists of 6 domains: conceptualization (similarities task), mental flexibility (lexical fluency), programming (Luria motor

tests), sensitivity to interference (conflicting instructions task), inhibitory control (go-no-go task), and environmental autonomy (an evaluation of prehension behavior). The total score is up to 18 points, the higher, the better.[11]

2.3. Serum 25-hydroxyvitamin D (25(OH)D) measurement

Serum 25(OH)D used to analyze VitD levels in the body. Serum samples were collected during the visit. 25(OH)D was measured with Architect 25-OH D vitamin kit (Abbott Diagnostics, Lake Forest, IL). Serum 25(OH)D concentrations were divided into clinically relevant categories as deficient (<10 ng/mL, same as 25 nmol/L), insufficient (10–30 ng/mL, same as 25–75 nmol/L), and sufficient (≥30 ng/mL, same as 75 nmol/L).[12]

2.4. Statistical analysis

The demographic characteristics of the participants were analyzed by Chi-square test for categorical variables and Kruskal–Wallis test of variance for continuous variables. Kruskal–Wallis test was used for estimating the relationships between 25(OH)D level and cognitive function. The results are presented as mean ± standard deviation or number (%) according to the characteristics of the variables. Univariable and multivariable analysis was performed using logistic regression odds ratios (ORs) with corresponding 95% confidence intervals (CIs). We analyzed individually across 25(OH)D level groups by separate logistic regression models. In generalized linear models, we were used to examining the association trend between serum 25(OH)D level and cognitive function. Cognitive functions analyzed as dependent variables depend on 25(OH)D level groups. In the case of multiple correlations between cognitive function and other potential cofounders, all analyses were adjusted for age, sex, education, location of residence, baseline cognitive function, season tested, alcohol use, current smoker, depression, body mass index, marriage, annual income, presence of osteoarthritis, and cardiovascular disease. The collected data were analyzed using SPSS 23.0 (IBM, Inc., Chicago, IL) software and *P*-value <.05 was considered significant.

3. Results

The baseline characteristics of KFACS participants included in the analysis of cognitive function are presented in Table 1. Out of a total of 3014 participants, 2990 were included in the current study. Of the 2990 participants, 119 (4.0%) were classified to 25 (OH)D deficient and 2253 (75.3%) were considered as having 25 (OH)D insufficiency. Only 618 (20.7%) were shown to have sufficient levels of 25(OH)D. Among the demographic characteristics of the participants, body mass index (BMI), sex, education, marriage, income, and alcohol use were significantly related to

Table 1

Baseline characteristics of 2990 participants in KFACS based on serum 25(OH)D level.

	25 (OH)Vit.D (ng/mL)			
Characteristic	**Deficiency (<10, n=119)**	**Insufficiency (10–30, n=2253)**	**Sufficiency (>30, n=618)**	***P*-value**
Age, mean (SD)	76.6 (4.1)	76.4 (3.9)	76.7 (3.7)	.119
BMI, mean (SD)	24.9 (3.1)	24.5 (3.0)	24 (2.9)	***.002****
Sex (%)				
Male	29 (2.0)	1064 (75.1)	323 (22.9)	***<.001****
Female	90 (5.7)	1189 (75.4)	297 (18.8)	
Season tested, n (%)				
Mar–May	16 (11.0)	107 (73.8)	22 (15.2)	***<.001****
Jun–Aug	77 (4.9)	1179 (75.6)	303 (19.4)	
Sep–Nov	16 (1.9)	640 (77.0)	176 (21.1)	
Dec–Feb	10 (2.1)	337 (72.3)	119 (25.5)	
Education (%)				
Educated less than 6 yr	74 (5.1)	1116 (77.3)	254 (17.6)	***<.001****
Educated over than 7 yr	45 (2.9)	1137 (73.5)	364 (23.5)	
Marriage (%)				
Married	63 (3.2)	1491 (74.6)	445 (22.2)	***<.001****
Bereavement, Separation, Divorce, Single	56 (5.7)	760 (76.8)	174 (17.5)	
Income (%)				
More than 3 million won per month	19 (3.88)	346 (70.6)	125 (25.5)	***<.001****
1–3 million won per month	27 (2.5)	801 (74.7)	244 (22.8)	
Less than 1 million won per month	68 (5.5)	957 (76.9)	219 (17.6)	
Residency (%)				
Urban	93 (4.3)	1577 (75.5)	421 (20.2)	.0904
Rural	26 (2.8)	676 (75.2)	197 (22.0)	
Current smoker (%)	8 (4.6)	133 (76.9)	32 (18.5)	.708
Alcohol use (%)	41 (2.8)	1127 (75.7)	321 (21.5)	***.002****
Osteoarthritis (%)	37 (4.9)	564 (74.1)	160 (21.0)	.335
Cardiovascular Disease (%)	85 (4.0)	1572 (74.2)	463 (21.8)	.058
Diabetes mellitus (%)	24 (3.6)	495 (74.7)	144 (21.7)	.701
Depression (%)	2 (2.3%)	60 (69.0)	25 (28.7)	.15

25 (OH)D = 25-hydroxyvitamin D, BMI = body mass index, KFACS = Korean frailty and aging cohort study.

* *P*-value for Chi-square test for categorical variables and Kruskal–Wallis test analysis of variance for continuous variables.

Table 2

Analysis of cognitive function in 2990 KFACS participants based on serum 25 (OH)D level.

	25 (OH)Vit.D (ng/mL)				
	Total (n = 2990)	Deficiency (<10, n = 119)	Insufficiency (10–30, n = 2253)	Sufficiency (>30, n = 618)	*P*-value
MMSE KC	25.5 ± 3.3	25.0 ± 3.2	25.4 ± 3.4	25.8 ± 3.1	***.012*** *
Wordlist: memory	16.6 ± 4.3	17.1 ± 4.3	16.5 ± 4.4	16.7 ± 4.2	.286
Wordlist: recall	77.0 ± 24.4	75.8 ± 21.9	76.9 ± 25.0	77.8 ± 22.4	.624
Wordlist: recognition	8.5 ± 24.4	8.6 ± 1.9	8.5 ± 1.9	8.5 ± 1.8	.651
TMT-A	84.7 ± 63.7	104.2 ± 78.0	85.7 ± 63.9	77.4 ± 59.0	***<.001*** *
Digit span	10.5 ± 3.8	9.6 ± 3.8	10.4 ± 3.8	10.9 ± 3.7	***<.001*** *
FAB	13.3 ± 3.1	13.0 ± 3.1	13.3 ± 3.1	13.5 ± 2.9	.243

25 (OH)D = 25-hydroxyvitamin D, BMI = body mass index, FAB = frontal assessment battery, KFACS = Korean frailty and aging cohort study, MMSE-KC = MMSE in the Korean version of the CERAD assessment packet, TMT = trail making test.

* *P*-value for Kruskal–Wallis test analysis of variance for continuous variables.

the level of VitD. Compared to women, men were more likely to be in the VitD sufficient group. Those who had lower serum 25 (OH)D were more likely to have a higher BMI, were tested between December and February, less educated, not married, and less income.

Table 2 represents the analysis of cognitive function in the KFACS participants with respect to serum 25(OH)D level. In the Kruskal–Wallis test analysis performance in the MMSE-KC, TMT test, and digit span tests was better in sufficient, insufficient group and deficiency group in that order, which were statistically significant.

In a unadjusted logistic regression model, participants with 25 (OH)D sufficiency were more likely to have a better cognitive function as seen in the MMSE-KC, TMT test, and digit span test (Table 3). However, these associations were attenuated and were not statistically significant following adjustment for age, sex, education, season tested, current smoking status, body mass index, family income, and alcohol consumption. In a fully adjusted logistic regression model, there was no association between 25(OH)D level and cognitive function (Table 3).

A similar pattern of associations was observed when we analyzed with a unadjusted generalized linear model. Significant positive linear trends were found between 25(OH)D and cognitive function tested by MMSE-KC, TMT test, as well as digit span (Table 4). However, these associations were attenuated and were not statistically significant after full adjustment (Table 4).

4. Discussion

There are a number of studies on the relationship between VitD and cognitive function, and many have demonstrated a positive correlation between them. In a cross-sectional study of 3325 elderly Americans aged 65 and older, Llewellyn et al associated VitD levels with cognitive functions such as MMSE, East Boston Memory test and Weschler Adult Intelligence scale. In this study, using adjusted multivariate logistic model, increased OR of cognitive impairment was seen in participants with VitD deficiency.[13] A recent prospective study of 318 older adults found a significant annual decline in verbal memory (immediate and delayed word list recall) in those moderately and severely deficient in serum VitD (12 to <20 and <12 ng/mL, respectively) compared to those sufficient (20 ng/mL) over a mean of 4.8 years.[14] In a meta-analysis of 8 studies, when 2749 participants were categorized based on the level of VitD as 20 ng/mL, participants with a high VitD concentration had high mean MMSE scores. (OR = 1.2 CI: 0.5–1.9).[15] Although tests to evaluate memory and performance vary from study to study, MMSE was used as a tool for assessing global cognition and these tests showed an association with VitD deficiency. In another

Table 3

Logistic regression analysis of cognitive functions in 2990 KFACS participants based on serum 25 (OH)D level.

	25 (OH)Vit.D (ng/mL)								
		Unadjusted model				Fully adjusted model			
	Deficiency (<10)	Insufficiency (10–30)		Sufficiency (>30)		Insufficiency (10–30)		Sufficiency (>30)	
Dependent variables	(Reference)	OR (CI)	*P*-value	OR (CI)	*P*-value	OR (CI)	*P*-value	OR (CI)	*P*-value
MMSE KC	1	1.03 (0.98–1.09)	.256	1.07 (1.02–1.13)	***.025***	0.99 (0.89–1.09)	.811	0.99 (0.89–1.11)	.910
Wordlist: memory	1	0.97 (0.93–1.01)	.126	0.98 (0.93–1.03)	.369	1.01 (0.93–1.09)	.853	0.99 (0.91–1.07)	.741
Wordlist: recall	1	1.00 (0.99–1.01)	.821	1.00 (0.99–1.01)	.538	1.01 (0.99–1.02)	.423	1.00 (0.99–1.02)	.572
Wordlist: recognition	1	0.99 (0.89–1.09)	.806	0.97 (0.87–1.08)	.617	1.17 (1.02–1.35)	.030	1.11 (0.96–1.29)	.181
TMT-A	1	1.00 (0.99–1.00)	***.006*** *	0.99 (0.99–1.00)	***<.001*** *	1.00 (1.00–1.01)	.952	1.00 (0.99–1.01)	.762
Digit span	1	1.06 (1.00–1.11)	***.033*** *	1.09 (1.03–1.15)	***<.001*** *	1.05 (0.95–1.17)	.309	1.09 (0.98–1.21)	.108
FAB	1	1.03 (0.98–1.10)	.269	1.06 (0.99–1.12)	.095	1.04 (0.92–1.17)	.531	0.99 (0.87–1.11)	.825

25 (OH)D = 25-hydroxyvitamin D, BMI = body mass index, CI = confidence interval, FAB = frontal assessment battery, KFACS = Korean frailty and aging cohort study, MMSE-KC = MMSE in the Korean version of the CERAD assessment packet, OR = odds ratio, TMT = trail making test.

* Unless otherwise indicated. Data are reported as relative risk (95% confidence interval). All analyses have been adjusted for age, sex, education, residence of location, baseline cognitive function, season tested, alcohol use, current smoker, depression, body mass index, marriage, annual income, presence of osteoarthritis, and cardiovascular disease.

Table 4

Generalized linear model analysis of cognitive functions in 2990 KFACS participants based on serum 25 (OH)D level.

		25 (OH)Vit.D (ng/mL)							
		Unadjusted model				Fully adjusted model			
		Insufficiency (10–30)		Sufficiency (>30)		Insufficiency (10–30)		Sufficiency (>30)	
Variables	Deficiency (<10)	B estimate (CI)	*P*-value	B estimate (CI)	*P* value	B estimate (CI)	*P*-value	B estimate (CI)	*P* value
Model A: MMSE KC	Reference	0.36 (−0.25 to 0.98)	.249	0.73 (0.07 to 1.39)	***.031***	−0.11 (−0.96 to 0.73)	.788	−0.07 (−0.96 to 0.81)	.866
Model B: Wordlist: memory	Reference	−0.63 (−1.44 to 0.17)	.125	−0.39 (−1.25 to 0.47)	.374	0.04 (−1.013 to 1.21)	.947	−0.28 (−1.51 to 0.94)	.652
Model C: Wordlist: recall	Reference	0.51 (−3.94 to 4.97)	.820	1.47 (−3.26 to 6.22)	.542	2.46 (−4.33 to 9.26)	.477	1.76 (−5.37 to 8.89)	.629
Model D: Wordlist: recognition	Reference	−0.04 (−0.40 to 0.31)	.807	−0.09 (−0.47 to 0.27)	.612	0.59 (0.05 to 1.13)	***.031***	0.41 (−0.15 to 0.98)	.150
Model E: TMT-A	Reference	−17.2 (−29.0 to −5.46)	***.004***[*]	−25.2 (−37.8 to −12.7)	***<.001***[*]	−1.74 (−16.8 to 13.3)	.812	−3.26 (−19.1 to 12.5)	.686
Model F: Digit span	Reference	0.77 (0.06 to 1.48)	***.034***[*]	1.21 (0.45 to 1.97)	***.002***[*]	0.45 (−0.51 to 1.41)	.361	0.79 (−0.21 to 1.80)	.123
Model G: FAB	Reference	0.32 (−0.24 to 0.89)	.266	0.51 (−0.09 to 1.11)	.098	0.9 (−0.55 to 0.94)	.613	−0.11 (−0.90 to 0.67)	.772

25(OH)D = 25-hydroxyvitamin D, BMI = body mass index, CI = confidence interval, FAB = frontal assessment battery, KFACS = Korean frailty and aging cohort study, MMSE-KC = MMSE in the Korean version of the CERAD assessment packet, OR = odds ratio, TMT = trail making test.

[*] Unless otherwise indicated. Data are reported as relative risk (95% confidence interval). All analyses have been adjusted for age, sex, education, location of residence, baseline cognitive function, season tested, alcohol use, current smoker, depression, body mass index, marriage, annual income, presence of osteoarthritis, and cardiovascular disease.

nationwide prospective Korean Longitudinal Study on Health and Aging study with 405 participants, 145 subjects with severe VitD deficiency defined as <10 ng/mL, and baseline MMSE scores of less than 27 were also independently associated with the development of mild cognitive impairment.[16]

However, some of these results are conflicting. In a prospective cohort of VitD and cognitive function using MMSE, among 1182 elderly Swedish men (mean age: 71 years), after a maximum of 18 years of follow-up, 250 men developed all-cause dementia, and an additional 80 men showed a decline in the cognitive function. In an adjusted model of Cox and logistic regression, there was no association between the baseline VitD status and the incidence of dementia or cognitive impairment during the follow-up period.[17] In another prospective cohort study of 1604 men for the association of VitD with cognitive function follow-up for an average of 4.6 years with MMSE and TMT-B in a model adjusted for age, season, and site showed that participants with lower VitD levels had a higher cognitive impairment, but the test for trend did not reach statistical significance.[18] Although the 2 studies mentioned above included only men, our study included both men and women, and the baseline statistical differences between the 2 groups were corrected by variable adjustment. A 2 population prospective cohort study with a 5-year follow up of 1291 participants from the US and 915 participants from the Dutch, for visual memory by Benton visual retention test and verbal memory by Rey auditory verbal learning test was carried out. Based on the study, they suggest an association between severe VitD deficiency and a decline in the visual memory but no decline in verbal memory.[19] Previous studies showed no correlation between VitD and cognitive function in males and visual memory. There is also a theoretical basis for explaining the conflicting results. A previous meta-analysis by Chen et al[20] reported that VitD supplementation reduced CRP levels, but the meta-analysis included only RCTs targeting younger population with acute inflammation as defined by CRP levels >10 mg/L. The meta-analysis by the University of Florida reported that VitD had no significant effect on IL-6 and CRP levels.[21] Additionally, 2 other systemic reviews[22,23] concluded that evidence of a relationship between VitD supplementation and inflammatory biomarkers are still weak in human studies. In other words, there was no evidence that VitD can reduce CRP or IL-6, a known important indicator for potential functional declines with aging. In this study, we analyzed a variety of cognitive functions, including global cognitive function, memory, performance scale in a larger population.

The risk factors of cognitive impairment are multifactorial such as age,[24] gender, education period,[25] annual income,[26] alcohol use,[27] smoking,[28] depression,[29] obesity, and cardiovascular disease.[30] Therefore, multiple assessments should also be undertaken to assess the cause of decline in cognitive function. We also found that several factors in the baseline characteristics are related to VitD deficiency. These results indicate that the VitD level, as well as cognitive function, is affected by various factors. In addition to participants' health status social-economic state was also related to the VitD level. This result is similar to previous studies with VitD. This study showed a correlation between cognitive function and VitD when the variables were not adjusted, but the fully adjusted model between the 2 was not statistically significant. Since there are many causes for cognitive dysfunction and VitD deficiency, the correlation between the 2 was not significant in this study.

This is the first large, population-based study of over two thousand elderly participants to investigate the link between VitD and cognitive function in Korea. In KFACS, VitD deficiency was not significantly associated with a decline in cognitive function compared to VitD sufficiency. Our findings are contrary to a vast majority of current findings. There could be several explanations for this discrepancy. First, the level of VitD is relatively low in the elderly Korean population compared to other populations. In the United States, the VitD sufficiency group was 37.5% of the total elderly population,[13] whereas only 20% was sufficient in this cohort study. Even though it is a lower VitD level compared to other studies, but it was still higher compared to previous Korean studies. In the previous Korea National Health and Nutrition Examination Surveys study, from 2008 to 2014 the VitD level of 7196 elderly people over 65 years was 20.1 ng/ml in females and 18.3 ng/ml in males, which is lower than our results.[31] In addition, there is no definite consensus on cut-off for sufficient level of VitD. According to several studies and experts, a value higher than 30 ng/mL is considered as sufficient levels of VitD. This is the cut-off value where parathyroid hormone levels begin to level off at their nadir, and the optimal level for intestinal

calcium transport in calcium metabolism.[12] There is an ongoing debate regarding the cutoffs for VitD deficiency and the optimum value for physical and mental health without a global consensus. Therefore, considering the same cut-off value of the VitD level as other studies may not be applicable to Korea. Further studies are needed set a new level of VitD that is sufficient for preventing cognitive impairment.

There are some limitations to this study. First, this is a cross-sectional study of vitamin levels and cognitive function in patients. However, as mentioned earlier, since vitamin levels and cognition are affected by various confounding factors, it is necessary to study the change of cognitive function affected by a change in VitD level through a prospective study or randomized controlled trials. Second, participants were not investigated for intake of VitD supplement. VitD is widely used for prevention and treatment of osteopenia and osteoporosis; therefore, many postmenopausal women or older men may take VitD as an supplement. However, in this study we did not investigate supplement intake. Third, since the cohort study excluded patients with dementia or those who did not fully understand the questionnaire, this study did not consider the relationship between VitD and dementia. Besides, there is a possibility that the participant did not perform optimally due to mood changes or fatigue caused by several tests during 1 visit.

The strength of this study is that it statistically controls potential confounding demographic characteristics, including socioeconomic status, clinical comorbidity, and past medical history. The tool for assessing cognitive impairment included neurological tests that could test different cognitive domains. KFACS is a multicenter, longitudinal, and a large population cohort study. In this study, there is no association between VitD and cognitive function when controlling for confounders that may affect the VitD level or cognitive function. Although these results are not consistent with the previous studies, this is a large population study, and the data contains various demographic information and cognitive scales, so our result is meaningful in understanding the relationship between VitD and cognition.

5. Conclusion

In this study, MMSE-KC, TMT test, and digit span tests were better in the high VitD level populations, which was statistically significant. However, when we adjusted all of these variables, it resulted in no direct correlation between VitD deficiency and cognitive impairment. Although our study does not indicate that VitD is a direct risk factor to cognitive decline, VitD could be a covariable factor.

Further prospective or randomized control study is necessary to evaluate the change in cognitive function according to changes in VitD level.

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