Vitamin D in Relation to Cognitive Impairment, Cerebrospinal Fluid Biomarkers, and Brain Volumes

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Abstract

Background. Low vitamin D status is associated with poorer cognitive function in older adults, but little is known about the potential impact on cerebrospinal fluid (CSF) biomarkers and brain volumes. The objective of this study was to examine the relations between plasma 25-hydroxyvitamin D (25(OH)D) and cognitive impairment, CSF biomarkers of Alzheimer's disease (AD), and structural brain tissue volumes.

Methods. A total of 75 patients (29 with subjective cognitive impairment, 28 with mild cognitive impairment, 18 with AD) referred to the Memory Clinic at Karolinska University Hospital, Huddinge, Sweden were recruited. Plasma 25(OH) D, CSF levels of amyloid β (Aβ1–42), total-tau, and phosphorylated tau, and brain tissue volumes have been measured. Results. After adjustment for several potential confounders, the odds ratios (95% confidence interval) for cognitive impairment were as

follows: 0.969 (0.948–0.990) per increase of 1 nmol/L of 25(OH)D and 4.19 (1.30–13.52) for 24(OH)D values less than 50 nmol/L compared with values greater than or equal to 50 nmol/L. Adjusting for CSF A β1–42 attenuated the 25(OH)D-cognition link. In a multiple linear regression analysis, higher 25(OH)D levels were related to higher concentrations of CSF A β1–42 and greater brain volumes (eg, white matter, structures belonging to medial temporal lobe). The associations between 25(OH)D and tau variables were not significant. Conclusions. This study suggests that vitamin D may be associated with cognitive status, CSF A β1–42 levels, and brain tissue volumes.

Key Words: Vitamin D, Older adults, Cognition, CSF biomarkers, MRI.

Introduction

It has been increasingly recognized that vitamin D, apart from its role in bone calcium homeostasis, plays an active role in other biologic targets such as the nervous system, the cardiovascular system, and the endocrine system (1–3). These nonclassical effects of vitamin D are not surprising because vitamin D receptors are present in many cell types including neurons (1,4). In addition, low levels of vitamin D have been linked to dementia/Alzheimer's disease (AD) and worse cognitive functioning in some but not all studies (5–9). Some biologically plausible mecha -nisms through which vitamin D may decrease the risk of dementia include the impact on the production of neurotrophic, antioxidative, and anti-inflammatory factors, protection against cardiovascular and cerebrovascular diseases, or the influence of vitamin D on amyloid phagocytosis and clearance(5). Concentrations of the 42 amino-acid form of amyloid β (Aβ1–42), total-tau (t-tau), and phosphorylated tau (p-tau181) in cerebrospinal fluid (CSF) are considered as the core CSF biomarkers for AD (10), whereas magnetic resonance imaging (MRI)-based measures are regarded as valid biomark -ers of disease state and progression (11,12). However, very few studies have so far investigated the associations of vitamin D levels in plasma with CSF biomarkers and volumetric measures of brain structures.

Vitamin D deficiency is a common condition in the elderly adults (5), and as a modifiable risk factor for dementia, it is a possible candidate for the preventive interventions.

The aim of this study was to examine the associations of plasma 25-hydroxyvitamin D (25(OH)D) levels with cognitive impairment, CSF biomarkers of AD, and brain volumes in memory clinic patients.

Methods

Study Participants

Participants included in this study were referred to the Memory Clinic at Karolinska University Hospital, Huddinge, Stockholm, Sweden, from primary care centers in the catchment area for investigation of suspected dementia. Participants were all living independently in the community (ie, they were not in need of formal care or aid from the community). A standard comprehensive protocol including clinical examination, brain imaging, electroencephalography, analyses of blood, urine, CSF, and a detailed neuropsychological evaluation was used for each individual. Diagnostic procedures have been described elsewhere (12,13). Briefly, dementia and AD were diagnosed according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Association, Fourth Edition) and NINCDS-ADRDA (the U.S. National Institute of Neurologic and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association) criteria (14). Mild cognitive impairment (MCI) patients: (i) were. not demented; (ii) had self and/or informant report of cognitive decline and impairment on objective cognitive tasks; and (iii) had preserved basic activity of daily living and minimal impairment in complex instrumental functions (15). Persons categorized as subjective cognitive impairment (SCI) had subjective cognitive complaints without objective impairment on cognitive tasks, and they represented the control group for this study. Of the participants, 29 SCI, 28 MCI, and 18 AD participants had available plasma for 25(OH)D analyses. Of these, a total of 70 participants had available data on CSF biomarkers of AD. Participants with psychiatric disorders (ie, major depression, alcohol abuse) or other conditions (ie, brain tumors, normal pressure hydrocephalus) were not considered in this study. Also, 3 participants were excluded from the tau analyses because of extremely high tau (≥1200 pg/L) levels. Out of the total 75 participants, only 28 had good-quality MRI data (9 participants with SCI, 11 participants with MCI, and 8 participants with AD). The local ethics committee at Karolinska University Hospital approved the study.

Biochemical Analyses

Plasma and CSF samples were obtained during the diagnostic workup. Plasma levels of 25(OH)D were determined using the DiaSorin immunoassay method. CSF was obtained by lumbar puncture in propylene tubes, gently mixed to avoid gradient effects, and centrifuged at 2000 g for 10 minutes. Aliquots were stored at −80°C until the biochemical analysis. Tau was determined using a sandwich enzyme-linked immnosorbent assay constructed to measure t-tau (both normal tau and hyperphosphorylated tau [p-tau181]). P-tau181 was determined using a sandwich enzyme-linked immunosorbent assay, with monoclonal antibody HT7 (recognizing all forms of tau) used as capturing antibody and biotinylated monoclonal antibody AT270 (specific to PThr181) used as a detection antibody. A β1–42 was determined using a

sandwich enzyme-linked immunosorbent assay specific for A β1–42, as previously described (12).

MRI Data Acquisition and Image Processing

MRI scanning was performed with a 1.5T Siemens Magnetom Trio. T1-weighted images were collected using a three-dimensional magnetization prepared rapid acquisition gradient-echo sequence. The imaging parameters were as follows: repetition time = 11.4 ms, time to echo = 4.4 ms, flip angle = 10º, field of view = 25 cm, matrix = 512 × 144, slice thickness = 2.5 mm, 72 continuous slices, and in place voxel dimension = 0.89 × 0.89 mm. All images were checked visually for artifacts and other brain conditions (12). Brain tissue fractions. Brain tissue fraction volumes were calculated from the high resolution T1-weighted images, using the cross-sectional version of the Structural Imaging Evaluation of Normalized Atrophy software, part of the FMRIB Software Library (FSL) (12). A specific value in cubic millimeter was obtained for total grey matter, white matter (WM), and CSF volumes. Total intracranial volume was calculated as the sum of grey matter, WM, and CSF values, and total brain volumes as the sum of grey matter and WM.

Regional brain volumes

Segmentation and labeling of brain structures were performed by Freesurfer version 4.5 (http://surfer.nmr.mgh.harvard.edu/). This procedure automatically assigns a neuroanatomical label to each voxel in an MRI volume based on probabilistic information obtained from a manually labeled training set. Results were visually examined for anatomical accuracy and edits to ensure accurate surfaces and boundaries were completed where necessary. This produced measurements of several cortical and subcortical regions of interest, including the inferior temporal gyrus, entorhinal cortex, hippocampus, thalamus, and amygdala. All measures were corrected for head size by dividing each volume to total intracranial volume.

Statistical Analysis

Sociodemographic and clinical differences among diagnostic groups were compared using the $\chi 2$ test for the proportions, analysis of variance for continuous variables with normal distributions, and nonparametric tests in case of non-normal distribution data. Results are presented as mean (standard deviation) or median (interquartile range) for continuous variables or number (%) for categorical variables.

Because of skewness, 25(OH)D values, CSF biomarkers, and brain volumes were log transformed for linear regression analyses. Additional categories for 25(OH)D status were defined according to commonly used clinical cut-offs for serum 25(OH)D: deficient

(<25 nmol/L), insufficient (25–50 nmol/L), and sufficient (>50 nmol/L) (16). Because only 4 participants had vitamin D deficiency (3 participants with MCI and 1 participant with AD), re-categorization was done to create a group of 17 participants representing suboptimal vitamin D status (<50 nmol/L) and a group of 58 participants representing sufficient vitamin D status (≥50 nmol/L).

Because cognition is actually a continuum, we tried to avoid artificially sharp distinctions between the SCI, MCI, and AD categories. These three cognitive outcomes were thus considered to have an ordinal nature (irrespective of definition, MCI is a higher degree of cognitive impairment compared with SCI, and AD is a higher degree of cognitive impairment compared with MCI), and ordinal logistic regression analysis was used to examine the relation between 25(OH)D and level of cognitive functioning and results are presented as odds ratios with 95% confidence intervals (CIs). Multiple linear regression analyses were performed to investigate associations of 25(OH)D with CSF biomarkers or volumetric measures of brain structures. Analysis were adjusted for age and sex (model 1), and then additionally for other potential confounding or mediating factors, including APOE ε4 status (absence of ε4-allele vs presence of either 1 or 2 ε4-alleles), season of blood draw, and kidney function (model 2). Because of the small sample size, only age and sex were considered in the analysis of 25(OH)D in relation to brain structures. We analyzed the data using Stata soft -ware version 12 (StataCorp, College Station, TX).

Results

The mean (standard deviation) age of the 75 study participants was 61.6 (9.1) years, 54.7% were female, and the mean (standard deviation) 25(OH)D was 67.3 (26.5) nmol/L. Median 25(OH)D concentrations did not vary significantly by season in the total population (December–February: 62.0 nmol/L; March–May: 63.5 nmol/L; June August:73.0 nmol/L; September–November: 60.0 nmol/L).

The sociodemographic and clinical characteristics of the study participants were compared according to the clinical diagnoses (Table 1). As expected, AD participants were older, had lower levels of education, and had lower Mini-Mental State Examination scores compared with SCI partici -pants. They also had decreased concentrations of A β1–42 and increased t-tau and p-tau compared with both SCI and MCI patients. In addition, the SCI participants had higher 25(OH)D concentrations compared with both MCI and AD participants. Association of 25(OH)D With Cognitive Impairment

The odds ratio for worse cognitive status for each increase of 1 nmol/L in plasma 25(OH)D was 0.980 (95% confidence interval 0.964–0.997). This association remained significant after adjusting for age and sex (model 1). Furthermore, adjusting for APOE ε4

status, season, and kidney function did not influence the results (Table 2). In this model, the odds ratio (95% confidence interval) for worse cognitive status was 4.19 (1.30–13.52) for individuals with 25(OH) D concentration less than 50 nmol/L compared with those with sufficient levels. We also conducted additional analyses controlling for CSF biomarkers of AD. In the fully adjusted model, the relation between 25(OH)D and cognitive impairment was attenuated by adjusting for CSF A β1–42: odds ratio (95% confidence interval) became: 0.976 (0.950–1.004) for 25(OH)D as a continuous variable and 2.13 (0.48–9.47) for those with suboptimal 25(OH)D levels compared with participants with sufficient levels. Adding t-tau or p-tau to the models did not change the association between 25(OH)D and cognitive impairment (Table 2).25(OH)D in Relation to CSF Biomarkers. After controlling for all study covariates, increased 25(OH)D concentrations as a continuous variable were related to higher concentrations of CSF A β1–42 (Table 3, model 2). This association was borderline significant when individuals with suboptimal 25(OH)D values were compared with sufficient values: β(SE) was −0.13 (0.07), p = .096. No significant associations between 25(OH)D and t-tau or p-tau were detected.25(OH)D and Structural Brain Tissue VolumesIncreased25(OH)D was related to lower CSF and greater WM and total brain volumes after taking age and sex into account (Table 4). Furthermore, 25(OH)D was associated with increased volumetric measures of the amygdala (β[SE]: 0.071[0.03],p = .022), thalamus (0.093[0.04], p = .032), and anterior cingulate gyrus (0.025[0.01], p = .019) and had a borderline significant association with hippocampus (0.391[0.217], p = .085) and inferior temporal gyrus (0.283[0.156], p = .086). No significant association between 25(OH)D and other brain volumetric measures were observed (data not shown).

Discussion

This study investigated plasma 25(OH)D in relation to cognitive impairment, CSF biomarkers of AD, and structural brain tissue volumes. Our results indicated that elevated plasma 25(OH)D may be associated with better cognitive status, irrespective of several potential confounders. In addition, higher 25(OH)D concentrations were associated with increased concentrations of CSF A β1–42, greater WM volume, and greater volumetric measures of several brain structures including structures of medial temporal lobe such as amygdala and hippocampus.These results are consistent with the findings from previous studies that reported a relationship between vita -min D and better cognitive performance (4–6,9,16–19) or decreased risk of dementia/AD (6–8,20). In contrast, no associations between 25(OH)D and cognition were found in the Tromso study, NHANES III survey, or the Osteoporotic Fractures in Men (MrOS) study (5,6). Possible explanations for the discrepancies are heterogeneity of study populations (ie, age, gender, target population), differences in 25(OH)D status, different inclusion of potential confounders, and

variability in cognitive measurement methods (5,6).The association between 25(OH)D and structural brain tissue volumes has been less investigated. One cross-sectional study reported a link between low 25(OH)D and MRI indicators of cerebrovascular diseases. However, in contrast with our findings, no significant association between 25(OH)D and volumetric measures of medial temporal lobe structures of the hippocampus and amygdala was observed (7).

Although the exact mechanisms behind the observed associations remain to be determined, certain hypotheses can be considered. Vitamin D may contribute to neuroprotection through its anti-ischemic, anti-inflammatory, and antioxidative properties (2,18). Experimental studies have suggested that 25(OH)D is related to the inhibition of nitric oxide synthase, upregulation of enzymes in glutathione and neurotrophin synthesis, regulation of neuronal calcium, protection of neuronal integrity, and the metabolism of numerous neurotransmitters in the central nervous system; including acetylcholine, dopamine, serotonin, and γ-aminobutyric acid (2,7). Furthermore, recent studies have suggested that vitamin D can stimulate amyloid phagocytosis and clearance (21), and the overexpression of vitamin D receptor or vitamin D treatment suppress amyloid precursor protein transcription (1). The progressive deposition of A β peptides in the brain and the formation of neurofibrillary tangles are considered the neuropathologic hallmarks of AD(10). The CSF can reflect biochemical changes that occur in the brain because it is in direct contact with the extracellular space of the brain. Therefore, AD is characterized by increased CSF levels of t-tau (reflecting intensity of neuronal and axonal degeneration), elevated CSF p-tau (reflecting tau phospho -rylation and tangle pathology), and decreased CSF A β1–42 (reflecting A β1–42 aggregation and amyloid plaque load in the brain parenchyma and hence, reduced availability of A β to diffuse into CSF) (10). Our results indicate that elevated plasma 25(OH)D is associated with increased concentration of CSF A β1–42. In addition, the association between 25(OH)D and cognitive impairment was attenuated when adjusting for CSF A β1–42, suggesting that the effect of vitamin D on cognition could be partly explained by its impact on A β1–42. Effects of vitamin D on A β clearance have been reported in recent preclinical studies; positive effects on A β degradation by macrophages (22) and on A β transport across the blood–brain barrier (23) have been demonstrated. Interestingly, one recent study did not find any significant associations between dietary intake of vitamin D and plasma A β levels. The authors concluded that the potential association of vitamin D with AD or cognition may involve pathways other than A β (24). Possible explanations for this difference are the different methods, including population characteristics, difficulties in interpreting Aβ levels in plasma compared with CSF, and vitamin D measurements (dietary intake rather than plasma concentration). Sun exposure is a larger source of vitamin D than diet, and unlike dietary intake assessment, plasma measurement is an objective measure of vitamin D, which is independent of the capacity to estimate and remember intake over a period of time. Furthermore, plasma level assessment takes into account individual

variations in metabolism, giving a reliable evaluation of the micronutrient bioavailability. Nevertheless, the impact of vitamin D on CSF A β or CSF t-tau/p-tau has previously not been investigated, and our findings need to be confirmed in larger studies.

The main strength of this study is the accurate and comprehensive clinical assessment of the participants enrolled, which included neuroimaging and CSF analyses of biomarkers incorporated in the new diagnostic criteria for AD (25). Although an association between vitamin D and cognition has been previously reported, to the best of our knowledge, no data are available about the association between 25(OH)D and CSF biomarkers of AD. Furthermore, different levels of cognitive impairment were considered, from subjective cognitive problems to fully developed dementia syndrome.

Although our findings are of potential clinical value, some limitations should be considered. This is a cross-sectional study including patients evaluated in a memory clinic, which are not representative of community-dwelling older adults in general. The small sample size limited statistical power. Furthermore, the possibility of reverse causation cannot be excluded because cognitively impaired individuals may eat poorly or may have reduced sunlight exposure or less outdoor activity, which may lead to reduced vitamin D status (26). In addition, we could not assess the role of vitamin D determinants such as physical activity, which is considered a confounder for the association between vitamin D and cognitive outcomes (5). Although adjusting for several relevant covariates that could modify our findings did not alter the results, the possibility of residual confounding cannot be excluded. The possibility of including cognitively intact subjects was limited; however, the CSF values of the SCI participants were comparable with those identified as healthy controls in a large multicenter study of older adults (27).

Finally, the proportion of poor-quality raw MRI images in the sample was relatively high. However, our restrictive image selection reduced the risk of introducing bias due to acquisition artifacts.

Taken together, our results support the hypothesis that lower 25(OH)D levels could be associated with cognitive impairment; at least partially via its association with CSF Aβ1–42, total cerebral WM volume, and several other brain structures. Due to the potential limitations, we cautiously interpret the associations revealed herein. However, our results emphasize the need for further longitudinal studies with larger samples to confirm and refine the potential beneficial role of vitamin D in individuals who are at increased risk of dementia. The deficiency of vitamin D is a common condition in the elderly adults because of limited sunlight exposure, decreased 7-dehydrocholesterol in the skin, inadequate dietary vitamin D intake, and limited physical activity. Hypovitaminosis D is easy to treat, however, few randomized controlled trials (RCTs) have so far investigated the usefulness of vitamin D in preventing cognitive impairment and dementia with mixed

results (5,6). Limitation of statistical power, study duration, and choice of target population make such studies difficult to interpret. Supplementation might be most effective in preventing cognitive impairment during a critical time window, and larger and better planned RCTs are necessary to formulate efficient guidelines for prevention (dose, treatment start and duration, target population). Recently, several large-scale RCTs of vitamin D supplementation and cognitive function in older adults have been initiated (eg, the VITAL-Cog study, NCT01669915 (28); the DIET-D study, NCT01708005 (29); and the MERE study, NCT01315704) (30). Furthermore, a phase-III RCT investigates the impact of cholecalciferol together with memantine in participants with moderate AD and hypovitaminosis D (the AD-IDEA study, NCT01409694) (31). However, in light of the scarce evidence on the role of vitamin D in AD, and the several failures of phase-III RCTs evaluating different compounds as disease-modifying treatment (32), a more refined knowledge on the biologic effects of vitamin D in AD-related pathology is needed.

Funding

This study was supported by Karolinska Institutet's Faculty funding for postgraduate students, the Swedish Research Council for Medical Research (Vetenskapsrådet), EU-FP7 project LipiDiDiet 211696, Strategic Research Program in Epidemiology (SFO) at Karolinska Institutet, Stiftelsen Solstickan, Stohnes Stiftelse, Gamla Tjänarinnor Foundation, Lindhes Foundation, Loo och Hans Ostermans stiftelse, Research Council for Health of the Academy of Finland (projects 120676, 117458, 251645), and Alzheimerfonden.

Acknowledgments

This research has made use of the SMILE medical imaging laboratory at Karolinska University Hospital, Stockholm, Sweden. We thank individuals who participated in this study.

Conflict of Interest

None declared.

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Tables

Characteristics	SCI, *N* = 29	MCI, *N* = 28	AD, *N* = 18	*p*-Value
Age (y)*	57.7 (6.1)	61.0 (9.0)	68.6 (9.6)	SCI-AD < .001; MCI-AD = .008
Sex (% ♀)	51.7	46.4	72.2	NS
Education (y)*	13.7 (3.4)	12.5 (3.7)	10.5 (3.1)	SCI-AD = .032
25(OH)D (nmol/L)†	70 (60–96)	60.5 (41.3–74.3)	60.0 (47.3–71.8)	SCI-MCA = .014; SCI-AD = .027
Season tested (%)				
December	22.2	25.0	33.3	NS
March	22.2	35.7	33.3	
June	7.4	10.7	11.1	
September	48.1	28.6	22.2	
Mini-Mental State Examination†	29 (28–30)	28 (27.3–29)	22 (19.8–26.3)	SCI-MCI = .083; SCI-AD < .001; MCI-AD < .001
APOE (% ε4+)	42.3	65.4	66.7	NS
Elevated creatinine (%)	0	10.7	6.7	NS
$A\beta_{1-42}$ (ng/L)†	861.5 (757.5–957.0)	549.5 (448.5–627.5)	450 (357.5–555.3)	SCI-MCI < .001; SCI-AD < .001; MCI-AD = .034
T-tau (ng/L)†	275 (170–320)	270 (142–409.5)	610 (376–692.5)	SCI-AD < .001; MCI-AD = .005
P-tau (ng/L)†	49.0 (37.5–58.8)	46.0 (34.0–82.0)	91.5 (62.3–122.5)	SCI-AD < .001; MCI-AD = .017
GM (cm^3)*	408.1 (9.9)	396.8 (28.2)	386.6 (20.0)	NS
WM (cm^3)*	369.1 (7.8)	362.8 (17.3)	350.8 (20.3)	SCI-AD = .082
CSF (cm^3)†	221.0 (214.2–229.4)	242.0 (212.3–259.8)	265.4 (228–291.5)	SCI-AD = .034
TBV (cm^3)†	779 (770.6–785.5)	758 (740.2–787.7)	734.6 (708.5–772.0)	SCI-AD = .034

Table 1. Characteristics of the study population

Notes: AD = Alzheimer's disease; CI = confidence interval; CSF = cerebrospinal fluid; GM = grey matter; MCI = mild cognitive impairment; NS = not significant; 25(OH)D = 25-hydroxyvitamin D; SCI = subjective cognitive impairment; TBV = total brain volume; WM = white matter.
*Mean (SD).
†Median (IQR)

	25-Hydroxyvitamin D
Model 1	0.972 (0.953–0.991)
Model 2	0.969 (0.948–0.990)
Model 2 and $A\beta_{1-42}$	0.976 (0.950–1.004)
Model 2 and t-tau	0.961 (0.936–0.987)
Model 2 and p-tau	0.965 (0.939–0.991)

Table 2. Association of Plasma 25-Hydroxyvitamin D With a Higher Degree of Cognitive Impairment

Notes: Aβ1–42 = amyloid β; p-tau = phosphorylated tau; t-tau = total-tau. Results are odds ratios (95% confidence intervals) from ordinal logistic regressions with cognitive status as dependent variable (subjective cognitive impairment, mild cognitive impairment, and Alzheimer's disease as categories ordered according to the severity of cognitive impairment); 25-Hydroxyvitamin D was analyzed as a continuous variable. Model 1: adjusted for age and sex. Model 2: additionally adjusted for APOEε4-allele, season, and kidney function.

	Model 1		Model 2	
5-Hydroxyvitamin D	β (*SE*)	*p*-Value	β (*SE*)	*p*-Value
β_{1-42} (*N* = 68)	0.23 (0.12)	.051	0.26 (0.12)	.034
-tau (*N* = 70)	0.27 (0.34)	.423	0.45 (0.36)	.213
-tau (*N* = 61)	0.09 (0.27)	.730	0.22 (0.29)	.446

Table 3. Association of Plasma 25-Hydroxyvitamin D Concentrations With Cerebrospinal Fluid Biomarkers

Notes: Aβ1–42 = amyloid β; p-tau = phosphorylated tau; t-tau = total-tau. β represents the coefficient for 25-hydroxyvitamin D analyzed as a continuous variable,
and SE represents the standard error. Model 1: adjusted for age and sex. Model 2: additionally adjusted for APOEε4-allele, season, and kidney function.

25-Hydroxyvitamin D	β (*SE*)	*p*-Value
White matter	0.126 (0.04)	.009
Grey matter	0.059 (0.08)	.447
Total brain volume	0.437 (0.19)	.031
Cerebrospinal fluid volume	−0.437 (0.19)	.031

Table 4. Association of Plasma 25-Hydroxyvitamin D Concentrations With Brain Tissue Volumes (n = 28)

Notes: β represents the age- and sex-adjusted coefficient for 25-hydroxyvtamin D analyzed as a continuous variable, and SE represents the standard error