Vitamin D level predicts all-cause dementia

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Abstract.
BACKGROUND: Vitamin D deficiency is common in Western societies and has been implicated in a number of health conditions including late-life dementia.
OBJECTIVE: To assess whether vitamin D level is associated with all-cause dementia in late life.
METHODS: This was a retrospective case control study using the electronic medical record of an urban medical center to obtain information on age, sex, body mass index, 25-hydroxy vitamin D (25-(OH)D) values, and presence of dementia diagnosis in patients 65 to 90 years old. We classified patients to quartiles according to vitamin D values and performed logistic regression analysis to determine associations between vitamin D quartiles and incidence of dementia diagnosis.
RESULTS: Rates of all-cause dementia decreased with increasing levels of 25-(OH)D independent of age, sex, and BMI, factors that also predicted dementia. Vitamin D levels above 38 ng/mL were associated with the lowest rate of all-cause dementia.
CONCLUSIONS: We observed dose-dependent, inverse associations of 25-hydroxy vitamin D levels with all-cause, late life dementia independent of age, sex, and BMI. There may be greater protection for supra-sufficient levels, a notion that warrants evaluation in controlled trials.

Keywords: Vitamin D, 25-(OH)D, dementia, age, sex, BMI

1. Introduction

Vitamin D is a steroid hormone essential for calcium homeostasis and bone mineralization, and insufficient vitamin D levels are implicated in a number of health conditions, among them dementia [1]. The primary natural source of vitamin D in humans is the sunlight-dependent conversion of cholesterol to vitamin D_3 (cholecalciferol) in the skin. Dietary vitamin D, mostly in the form of vitamin D_2 (ergocalciferol), can be found in food sources such as dairy products and fatty fish. Ergocalciferol and cholecalciferol are converted to calcidiol (25-hydroxycholecalciferol or 25-hydroxy vitamin D) in the liver by hydroxylation. Renal hydroxylation of 25-hydroxycholecalciferol produces the hormonally active form of vita-

min D (1,25-dihydroxycholecalciferol or calcitriol). Through cytosolic signaling, calcitriol promotes intestinal calcium absorption and bone resorption, thereby helping to maintain optimal serum parathyroid hormone levels and bone density. Severe vitamin D deficiency is a cause of osteomalacia or, if present early in life, rickets. Osteomalacia refers to bone disease as a consequence of vitamin D deficiency. Vitamin D deficiency may predispose to osteopenia and osteoporosis but these conditions often are seen in patients without deficient vitamin D status, and supplementation does not appear to improve bone mineral density in patients with osteopenia [2]. While overt clinical effects of severe vitamin D deficiency are rare in developed nations, subclinical vitamin D deficiency, often referred to as "insufficiency," is common [3], although estimates of insufficient 25-(OH)D thresholds vary. Serum 25-(OH)D levels at or below 8 to 10 ng/mL have been labeled deficient while a commonly cited threshold for insufficiency is 16 ng/mL [3]. However, there is evidence that a serum level at or below 30 ng/mL represents a stimulus for

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parathyroid hormone elevation, suggesting this level as a marker of sufficiency [4]. Among adults in the United States, the prevalence of serum 25-(OH)D less than 30 ng/mL has been estimated at 42–64% [5–7].

Recently, a substantial body of research has demonstrated the pleotropic nature of vitamin D's hormonal action as well as associations between vitamin D insufficiency and adverse neuropsychiatric outcomes. Vitamin D insufficiency has been related to increased incidence of depression [8], although supplementation studies for the treatment and prevention of depression have yielded mixed results [9–11]. Adequate levels of vitamin D also may be necessary for the maintenance of normal sleep architecture [12–14], and vitamin D supplementation has been reported to improve symptoms in chronic pain patients [15, 16].

Of particular interest is the possible link between vitamin D deficiency and cognitive impairment and dementia, given evidence that vitamin D may have neuroprotective effects [17–19] and a role in beta-amyloid plaque clearance [20, 21]. Secondary analysis of data from the Framingham Heart Study demonstrated a negative correlation between serum vitamin D values and neurocognitive performance and hippocampal volume [22]. Serum vitamin D levels below 25 ng/mL have been associated with increased risk for current cognitive impairment [23] and for future cognitive decline in older adults [24, 25]. In addition, two large studies have demonstrated increased risk of incident dementia associated with low vitamin D levels [26, 27], although other studies have not documented increased risk [28, 29]. Finally, certain polymorphisms in the vitamin D receptor gene are reportedly associated with increased risk of Alzheimer's dementia [30].

One important hypothesis that bears on dementia risk is that vitamin D is involved in the clearance of atherosclerotic plaque. This is based on associations between vitamin D deficiency and increased arterial stiffness, increased severity of atherosclerosis, and higher incidence of myocardial infarction and stroke [31–34]. Arterial disease, particularly cerebrovascular disease, has itself been established as an independent risk factor for dementia. For example, increased severity of carotid and intracranial atherosclerosis has been associated with increased prospective risk of Alzheimer's dementia [35, 36]. Recent analysis of data from the Atherosclerosis Risk in Communities Study also has shown an independent association between midlife vascular risk factors and late-life dementia [37]. These findings have implica-

tions for observed associations between low vitamin D and dementia. Because vitamin D is thought to exert anti-atherosclerotic effects, the effect of low vitamin D on dementia risk may be mediated by increased prevalence of atherosclerosis in vitamin D-deficient patients. Further, vitamin D deficiency and the presence of other vascular risk factors may produce additive contributions to dementia risk. To date, neither retrospective nor prospective studies have adequately characterized the interaction between vitamin D deficiency and vascular disease as it relates to dementia risk. Conversely, studies of vitamin D and neuropsychiatric outcomes have not provided consistent evidence of dose-response relationships or that supra-sufficient levels confer a protective effect beyond avoiding deficiency-related disease.

The goals of the present study were threefold. First, we aimed to replicate the findings of previous studies, which found an association between low serum 25-(OH)D and increased dementia risk in older adults in Western societies [26, 27]. Second, we examined the relationship between varying levels of serum vitamin D and dementia risk, in order to determine whether a dose-response relationship exists. Finally, we sought to determine whether vitamin D deficiency independently predicted dementia after adjustment for BMI, which we included as a marker of cardiometabolic risk given the evidence that elevated BMI in older adults is strongly related to hypertension [38, 39], insulin resistance [40], and inflammation [41].

2. Materials and Methods

2.1. Study design

This was a retrospective, case-control study. Study methods were reviewed by the University of Cincinnati Institutional Review Board, and the requirement for participant informed consent was waived because private health information was not obtained. Medical records of inpatients and outpatients were accessed through the University of Cincinnati Academic Health Center electronic medical record system. We included all patients with BMI and serum 25-(OH)D measurement obtained between January 1, 2012 and January 1, 2018 who were at least 65 years old at the time of assessment. When more than one vitamin D3 measurement was available, the earliest measure was included in the analysis. Individuals were excluded for a history of brain injury or post-concussive syndrome or diagnosis of any psychotic

Table 1
ICD-10 codes used to identify presence of dementia

F00.1	Dementia in Alzheimer's Disease with late onset
F00.2	Dementia in Alzheimer's Disease, atypical or mixed type
F00.9	Dementia in Alzheimer's Disease, unspecified
F01.0	Vascular dementia of acute onset
F01.1	Multi-infarct dementia
F01.2	Subcortical vascular dementia
F01.3	Mixed cortical and subcortical vascular dementia
F01.8	Other vascular dementia
F01.9	Vascular dementia, unspecified
F02.0	Dementia in Pick Disease
F02.1	Dementia in Creutzfeldt-Jakob Disease
F02.2	Dementia in Huntington Disease
F02.3	Dementia in Parkinson Disease
F02.8	Dementia in other specified diseases classified elsewhere
F03	Unspecified dementia
F04	Organic amnestic syndrome, not induced by alcohol and other psychoactive substances
G30.1	Alzheimer's Disease with late onset
G30.8	Other Alzheimer's Disease
G30.9	Alzheimer's Disease, unspecified
G31.01	Pick Disease
G31.09	Other frontotemporal dementia
G31.1	Senile degeneration of brain, not elsewhere classified
G31.81	Alpers Disease
G31.82	Leigh Disease
G31.83	Dementia with Lewy Bodies / Parkinsonism
G81.85	Corticobasal degeneration
G31.89	Other specified degenerative diseases of nervous system
G31.9	Degenerative disease of nervous system, unspecified
R54	Senility NOS

or substance use disorder. Also, individuals with a diagnosis of dementia as of January 1, 2012 were excluded.

Data from 25,847 records were included in the analysis. Dementia cases were defined as individuals with a diagnosis of dementia after January 1, 2012. We did not attempt to categorize specific dementing disorders such as Alzheimer's disease or vascular dementia because clinical diagnosis of dementia in busy medical practice often does not involve comprehensive cognitive assessment, the application of formal diagnostic criteria, or invasive biomarker studies such as cerebral spinal fluid analysis or brain biopsy. Table 1 contains a list of the ICD-10 codes used to identify dementia cases. We were not able to obtain information concerning the indication for the vitamin D test.

2.2. Statistical analysis

Logistic regression was used to assess associations between vitamin D levels and risk of dementia, while adjusting for age, sex and BMI. Age-, sex-, and BMI-adjusted odds ratios with 95% confidence intervals were computed for each quartile relative to Q3, which was chosen as the reference quartile on the basis of 25-(OH)D values [4]. Possible moderation of the vitamin D effect by each of these factors was assessed by inclusion of all possible interaction terms up to the four-way, age $\times$ sex $\times$ BMI $\times$ vitamin D interaction. We also calculated effect size estimates by converting odds ratios to Cohen's effect sizes based on the tetrachoric correlation [42].

3. Results

The characteristics of the study sample are shown in Table 2. Relative to non-demented control cases, those with dementia diagnoses included a higher percentage of males and had lower mean BMI. Cut points for quartiles were established based on the distribution of 25-(OH)D levels, and all cases were classified into one of the following: Q1:0 to 20.0 ng/mL; Q2:20.1 to 29.0 ng/mL; Q3:29.1 to 38.0 ng/mL; Q4: greater than 38.0 ng/mL. Age, sex proportions, and

Table 2

Characteristics of study sample

	Cases, n	Mean (SD) age, y	Percent male	Mean BMI (kg/m^2)
All cases	25,847	74.4 (7.9)	31.1	28.3 (6.8)
Cases without dementia	22,230	73.6 (7.2)	29.9	28.7 (6.9)
Cases with dementia	3,617	79.4 (7.9)	38.5	25.9 (6.1)
25-(OH)D Quartile 1 (0–20.0 ng/mL)	6,370	73.7 (7.4)	33.4	29.5 (7.7)
25-(OH)D Quartile 2 (20.0–29.0 ng/mL)	6,317	74.2 (7.5)	35.3	28.9 (6.8)
25-(OH)D Quartile 3 (29.0–38.0 ng/mL)	6,551	74.7 (7.6)	32.1	28.1 (6.6)
25-(OH)D Quartile 4 (>38.0 ng/mL)	6,609	75.1 (7.6)	23.8	26.7 (6.0)

Note. All 25-(OH)/D quartiles differ from each with respect to age and BMI at $p < 0.05$.

BMI differed significantly among the vitamin D quartiles at $p < 0.05$ (Table 2). BMI was inversely related to serum 25-(OH)D levels.

The unadjusted and adjusted incidence rates of dementia by vitamin D quartile and unadjusted and adjusted odds ratios comparing each quartile to the reference (quartile 3) are shown in Table 3. The incidence of dementia decreased incrementally from the lowest to the highest vitamin D quartile. All inter-quartile differences were statistically significant ($p < 0.001$) except Q2 vs Q3 ($p = 0.093$). Effect sizes estimates ranged from small to medium [43].

Serum vitamin D quartile, age, sex, and BMI all were associated with dementia at $p < 0.0001$. While age, sex, and BMI independently predicted dementia risk, none of these factors moderated the effect of vitamin D level independently or jointly, as all interactions with Vitamin D levels were not significant at $p > 0.05$.

4. Discussion

The findings demonstrate an inverse association between serum 25-(OH)D level and rate of incident dementia, and this association remained significant after adjustment for age, sex, and BMI. As expected, age, sex, and BMI also were independent predictors of dementia risk, and these latter associations also remained significant after adjustment within the logistic regression model.

Notably, the association between serum 25-(OH)D and dementia diagnosis appears exposure-dependent, as dementia risk decreased incrementally from the lowest to the highest vitamin D quartile. Further, the magnitude of this effect was not moderated by age, sex, or BMI. Although all of these factors were independently associated with dementia risk, none of them interacted significantly with vitamin D levels as predictors of dementia. The inverse, dose-dependent relationship between dementia rate and serum 25-(OH)D level has been observed previously for both all-cause dementia and Alzheimer's disease specifically [1]. In addition, a similar dose-response relationship was found in another study in which the hazard ratio for dementia was 2.25 for serum levels below 10 ng/mL and 1.53 for levels between 10 ng/mL and 20 ng/mL [26].

Although there is no controlled trial demonstrating effectiveness of vitamin D supplementation as a dementia prevention strategy, there are studies indicating that supplementation can improve cognition in older adults [44]. However, prospective supplementation trials will be essential to investigate not only the effect of vitamin D on dementia risk but also to provide information concerning differential risk with respect to deficiency, sufficiency, and suprasufficiency. As noted, in this trial we observed for the first time, that greater than sufficient vitamin D levels conferred greater protection than that associated with putatively sufficient levels, as risk for dementia in quartile 4 was significantly lower than risk in quartile 3.

Given the evidence that elevated BMI is related to insulin resistance and inflammation, factors that contribute to vascular pathology, we included BMI as a marker for cardiometabolic risk. We found an inverse association of serum 25-(OH)D with BMI, a relationship that has been observed previously [45, 46]. However, we also found that the association between vitamin D and dementia risk was not mediated by BMI, which suggested an independent neuroprotective effect of vitamin D. Further, BMI was inversely associated with dementia risk with lower BMI in patients with dementia relative to those without dementia, even after adjusting for age and sex. This finding might suggest that BMI is not a valid surrogate for vascular risk. On the other hand, it is likely that participants with dementia had already experienced weight loss related to the disease pro-

Table 3
Dementia incidence, odds ratios, and effect sizes by vitamin D quartile

Vitamin D quartile	Dementia/no dementia, n	Dementia rate	Unadjusted OR, [95% *CI*]	Adjusted OR, [95% *CI*]	d
Q1 (0–20 ng/mL)	1082 / 6370	16.95%	1.40 [1.27, 1.54]**	1.63 [1.47, 1.81]**	0.39
Q2 (20–29 ng/mL)	901 / 6317	14.26%	1.15 [1.04, 1.27]	1.21 [1.09, 1.34]	0.15
Q3 (29–38 ng/mL)	848 / 6551	12.94%	1.00 [#]	1.00 [#]	—
Q4 (>38 ng/mL)	788 / 6609	11.92%	0.91 [0.82, 1.01]**	0.86; [0.77, 0.96]**	0.12

Note: OR = odds ratio. CI = confidence interval. d = effect size. ** = $p < 0.001$. [#] = reference value.

cess at the time they received the diagnosis. Weight loss has been shown to correlate directly with dementia severity and speed of progression [47, 48]. In addition, individuals without dementia or mild cognitive impairment who experience weight loss in mid- to late-life have increased risk of future dementia [49–51], suggesting that weight loss can be a prodromal sign of dementia [52]. It has been proposed that obesity in mid-life, but not late life, is a risk factor for the development of dementia [51]. Accordingly, in some cases with prodromal or clinical dementia, BMI may cease to be a valid marker of cerebral vascular risk, owing to the effect of dementia-related weight loss.

The main strengths of this study included the large sample size, specific adjustment for potentially confounding factors, and demonstration of a dose-dependent relationship between exposure and the outcome of interest.

Among the more important limitations was the absence of information concerning the clinical indication for testing vitamin D status. It is possible that a number of patients had indications for vitamin D status testing that might influence risk for dementia, which would bias the results. Another important limitation was the unavailability of information concerning the season when levels were obtained, given that extent of sunlight exposure can alter serum 25-(OH)D levels. Further, we did not have information concerning race, another potential bias, given that skin color will alter the level of vitamin D produced with sunlight exposure. Accordingly, there may have been seasonal and race effects that was not apparent in the available dataset. However, these issues might be relatively less concerning with regard to our sample of older adults for whom outdoor activity and sunlight exposure tend to decrease while vitamin D synthesis with UVB irradiation also becomes less effective.

Another inherent study limitation has to do with the retrospective and correlational nature of our findings. It may be the case that individuals with dementia or incipient dementia maintain lifestyles with nutri-

tional patterns, extent of sunlight exposure, and other factors that will tend lower vitamin D status so that the observed associations might be influenced by behavioral factors related to dementia. Also, because our outcome of interest was all-cause dementia, we were not able to evaluate the possibility that the findings might be applicable to some dementia subtypes but not others. Limiting our analysis to specific dementia subtypes, if possible, might have strengthened our conclusions. However, dementia diagnoses such as Alzheimer's disease, vascular dementia, and others often are made on clinical grounds rather than through the application of formal diagnostic criteria. The time interval between measurement of serum vitamin D and diagnosis of dementia was not consistent. However, all laboratory measurements were obtained within six years of the diagnosis, and it has been shown that in patients who do not initiate or dose-adjust supplementation, the 5-year variability of serum vitamin D3 is approximately 2–4 ng/mL [53]. Thus, vitamin D levels were unlikely to have changed enough within the study period to influence the outcome. Further, if an individual had multiple serum vitamin D measurements, we included only the chronologically earliest value in the analysis. Our aim was to eliminate the confounding effect of physician-ordered vitamin D supplementation upon discovery of a low value. Even so, we were not able to assess directly which cases were receiving vitamin D supplementation. Finally, our study may have been statistically over-powered to detect differences in dementia rates, although an incremental effect of vitamin D level was observed, which increases the likelihood that the results reflect a true association. In addition, while the effect size estimates (Table 3) varied from small to medium, these effects can be judged to be clinically meaningful in the context of a condition with very substantial health and quality of life costs and a generally safe intervention.

Vitamin D deficiency and dementia are highly prevalent, and vitamin D deficiency is treatable with over-the-counter supplementation so that correction

of vitamin D deficiency could represent a low-cost intervention with low risk and considerable benefit. However, data from controlled trials have not yet established a basis for such a recommendation for dementia risk reduction.

In conclusion, our results support an association between vitamin D level and dementia in older adults that is likely independent of vascular risk. Our findings suggest that maintaining adequate vitamin D levels in late life can influence dementia risk, and there are indications that greater risk reduction might accrue with higher than sufficient vitamin D levels. Prospective supplementation studies are needed to confirm this association.

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Conflict of interest

The authors have no conflict of interest to report.

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