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Authors

Wilson, Valerie K
Houston, Denise K
Kilpatrick, Laurel
et al.

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Relationship Between 25-Hydroxyvitamin D and Cognitive Function in Older Adults: The Health ABC Study

Valerie K. Wilson, MD[1], **Denise K. Houston, PhD**[1], **Laurel Kilpatrick, MD**[2], **James Lovato, MS**[3], **Kristine Yaffe, MD**[4], **Jane A. Cauley, DrPH**[5], **Tamara B. Harris, MD, MS**[6], **Eleanor M. Simonsick, PhD**[7], **Hilsa N. Ayonayon, PhD**[8], **Stephen B. Kritchevsky, PhD**[1], **Kaycee M. Sink, MD, MAS**[1], and **for the Health ABC study**

[1]Department of Internal Medicine, Wake Forest School of Medicine, Winston Salem, NC

[2]Department of Internal Medicine, University of Alabama at Birmingham, Birmingham, AL

[3]Department of Biostatistics, Wake Forest School of Medicine, Winston Salem, NC

[4]Departments of Psychiatry, Neurology and Epidemiology and Biostatistics, University of California at San Francisco, San Francisco, CA

[5]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA

[6]Intramural Research Program, National Institute on Aging, Bethesda, MD

[7]Clinical Research Branch, National Institute on Aging, Baltimore, MD

[8]Department of Epidemiology & Biostatistics, University of California at San Francisco, San Francisco, CA

Abstract

Objectives—To examine the relationship between 25-hydroxyvitamin D (25(OH)D) levels and cognitive performance over time in older adults in the Health, Aging, and Body Composition (Health ABC) study.

Design—Prospective cohort study

Setting—Community-dwelling participants in Pittsburgh, PA, and Memphis, TN

Participants—2,777 well-functioning adults aged 70–79 at baseline with serum 25(OH)D measured at the 12 month follow-up visit and cognitive function measured at baseline and 4-year follow-up visit.

Corresponding Author: Valerie K. Wilson, MD, Sticht Center on Aging, Medical Center Blvd, Winston-Salem, NC 27157, Office number: 336-713-8250, Fax number: 336-713-8252, vwilson@wakehealth.edu. **Alternate Corresponding Author:** Kaycee M. Sink, MD, MAS, kmsink@wakehealth.edu.

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Measurements—Vitamin D status was categorized as 25(OH)D levels <20 ng/mL, 20 - <30 ng/mL, or ≥ 30ng/mL. Cognition was measured using the Modified Mini-Mental State Exam (3MS) and Digit Symbol Substitution Test (DSST). Linear regression models adjusting for multiple covariates, including age, education, sex, race, site, season, physical activity, and comorbidities were used in the analysis.

Results—Sixty-eight percent of participants had 25(OH)D levels<30 ng/mL. Lower 25(OH)D levels were associated with lower baseline cognitive scores on the 3MS (adjusted means (95% CI): 89.9 (89.4–90.4), 90.8 (90.4–91.3), and 90.6 (90.2–91.1) for <20, 20-<30, and ≥30ng/mL, respectively; p trend =0.02) and the DSST (35.2 (34.5–36.0), 35.9 (35.2–36.6), and 37.0 (36.3–37.8), p trend =0.01). Participants with low 25(OH)D levels had greater declines in 3MS scores over 4 years than those with higher levels (LS mean change (95% CI): −1.0 (−1.5 to −0.6), −0.8 (−1.2 to −0.3), and −0.2 (−0.7 to 0.2) for <20, 20-<30, and ≥30ng/mL, respectively; p=0.05). There was no significant difference in DSST decline by 25(OH)D level.

Conclusion—Low 25(OH)D levels were associated with worse global cognitive function and greater decline over time as measured by the 3MS. Intervention trials are needed to determine if vitamin D supplementation can reduce cognitive decline.

Keywords

Vitamin D; cognition; cognitive function; memory

INTRODUCTION

Low 25-hydroxyvitamin D (25(OH)D) is a common problem affecting older adults.[1] Low 25(OH)D levels have been correlated with cardiovascular disease, various autoimmune diseases, diabetes, malignancy, falls, fractures, and depression.[2] Increasing data suggest that vitamin D may also have a role in cognition. Vitamin D receptors (VDR) were found in the brains of experimental animals over twenty years ago[3] including the rat hippocampus, an area crucial for memory development.[4] Vitamin D has also been found to promote neuronal growth in vitro in rat brains.[5] VDRs have subsequently been confirmed to exist in human brains and these VDRs have been found to exist in a similar distribution as that found in rodent brains.[6] A decreased number of VDR mRNA in areas of the hippocampus and a higher frequency of VDR polymorphisms have been associated with Alzheimer's disease in comparison with age-matched controls.[7;8] Vitamin D may also have a neuronal protective effect by enhancing antioxidant pathways in areas of the brain responsible for cognition.[9]

Despite its biological plausibility, a relationship between 25(OH)D levels and cognition has not been established clinically. Recent meta-analyses that primarily included cross-sectional studies concluded that low 25(OH)D is associated with cognitive impairment.[10;11] A recent systematic review evaluating both cross-sectional and prospective data concluded that low 25(OH)D was associated with worse cognitive outcomes.[12] However, only three of the five previously published prospective studies with 25(OH)D levels demonstrated a higher risk of cognitive decline over time in participants with low 25(OH)D levels,[13–15] while the other two prospective studies did not observe an association between 25(OH)D levels and cognition.[16;17] Some reasons for conflicting results in the vitamin D-cognition relationship

include a variety of different tools being utilized to measure cognition across studies and differing definitions of vitamin D insufficiency or deficiency. In addition, there may be differences in the cognitive domain affected by vitamin D status. For example, Buell and colleagues found that higher 25(OH) D levels (>20 ng/mL) were associated with better performance on tests of executive function, but not memory.[18] The purpose of this study was to examine the relationship between 25(OH)D levels and cognitive performance at baseline and cognitive decline over 4 years in the Health, Aging and Body Composition Study (Health ABC), a large cohort of well-functioning older adults.

METHODS

Study Population

The Health ABC cohort consists of 3075 Medicare-eligible, white and black, well-functioning, community-dwelling older adults who were aged 70–79 when they were recruited between April 1997 and June 1998 from Pittsburgh, PA and Memphis, TN. At the time of enrollment, they reported no difficulty walking ¼ mile, climbing 10 stairs or performing activities of daily living, and were free of known life-threatening illnesses. Serum 25(OH)D levels were measured at the 12-month follow-up visit to coincide with detailed dietary assessments made at that time. Cognitive testing was done at baseline and at the 4-year follow-up exam. For this analysis, participants were excluded if they did not have 25(OH)D measured at the 12-month follow-up visit (n=282), or were missing education (n=7) or cognitive scores (n=9) at baseline. The final baseline analysis sample included 2,777 participants. For the longitudinal analyses, participants were excluded if they were missing one of the cognitive measures at the 4-year follow-up visit (n=543). The final longitudinal analysis sample consisted of 2234 individuals. The Institutional Review Boards at both clinical sites and the coordinating center approved the study and all participants signed written informed consents.

Vitamin D status

Blood samples were obtained after an overnight fast and stored at −70°C until the time of analysis. Serum levels of 25(OH)D were measured using a 2-step radioimmunoassay (25-hydroxyvitamin D 1251 RIA kit, DiaSorin, Stillwater, Minnesota).The inter-assay coefficient of variation was 6.78% for log-transformed values.

Cognitive Measures

Global cognitive function was measured using the Modified Mini-Mental State examination (3MS), which is an extended, 100-point, version of the Mini-Mental StateExam.[19] The 3MS has good reliability and validity and assesses orientation, concentration, recall, language, visuospatial function, and verbal fluency.[19]

The Digit Symbol Substitution Test (DSST) is a timed test in which participants must transcribe symbols matched to numbers using a legend. The score represents the number of correct items completed in 90 seconds. It is a well validated measure that assesses processing speed, executive function, and working memory.[20]

Covariates

Variables that could confound the relationship between 25(OH)D levels and cognitive function were examined including age, race, sex, education, field site (Memphis versus Pittsburgh), season in which blood was drawn, body mass index (BMI), alcohol consumption, smoking status, physical activity, and use of calcium, multivitamins, or vitamin D supplements. Physical activity was based on the reported time spent walking for exercise or other walking (e.g., for transportation) over the past seven days. Comorbidities examined included: impaired renal function defined as an estimated glomerular filtration rate (eGFR) < 60mL/min, depressive symptoms measured by the Center for Epidemiologic Studies Depression Scale (CES-D), the presence of diabetes, and cardiovascular disease defined as prior coronary heart disease or cerebrovascular disease.

Statistical Analysis

Analyses of 25(OH)D levels and cognition were conducted using SAS statistical software version 9.2 (SAS Institute, Inc., Cary, NC). Serum 25(OH)D levels were categorized as <20, 20-<30, and ≥30 ng/mL, common cut-points used to define vitamin D deficiency, insufficiency and sufficiency, respectively.[21] Differences in the frequencies and means of covariates by 25(OH) D levels were examined using chi-square tests for categorical variables and one-way ANOVA for continuous variables. Multiple linear regression models were used to examine the associations between 25(OH) D levels and cognition at baseline and over 4-years of follow-up. Model 1 was adjusted for education only. Model 2 was adjusted for education, age, sex, race, site, season, BMI, alcohol consumption, smoking status, physical activity and the medical comorbidities described above. To examine the association between baseline 25(OH)D levels and change in cognitive scores, the difference between cognitive scores at the 4-year follow-up and baseline visits were modeled directly, adjusting for baseline cognitive scores. Least square means and 95% confidence intervals are presented. Wald type p-values are presented.

RESULTS

The mean age of the study population (n=2777) was 73.6 years, 48.8% were women, and 39.5% were black. In this population of community dwelling older adults, 32.9% of participants had 25(OH)D levels<20 ng/mL and 35.5% had levels 20-<30 ng/mL. The baseline characteristics of the study population are listed in Table 1. As would be expected, low 25(OH)D levels were associated with female sex, black race, obesity, and fewer minutes walking for physical activity in the past week. Low 25(OH)D levels were also associated with prevalent diabetes, cardiovascular disease, greater alcohol consumption, and current smoking. Higher 25(OH)D levels were associated with vitamin D supplement use, calcium supplement use, multivitamin use, normal renal function, and higher level of education. Participants excluded from the cross-sectional analysis (n = 298, 9.7%) because of missing 25(OH)D levels, education, or cognitive scores were more likely to be male, black, have higher scores on the CES-D, and have less than a high school education (p<0.05).

At baseline, low 25(OH)D levels were associated with lower global cognitive function as measured by the 3MS (Table 2). Participants who were vitamin D deficient scored lower on

the 3MS than those who were vitamin D sufficient (p= 0.02 in fully adjusted model). Low 25(OH)D levels were also associated with lower cognitive scores on the DSST at baseline (Table 2). Participants with sufficient vitamin D levels had more correct answers in 90 seconds than the deficient participants (p=0.01 in fully adjusted model). In analyses that examined prevalent cardiovascular disease and diabetes as potential mediators of the relationship between25(OH)D and cognitive function, the results were similar after further adjustment for prevalent cardiovascular disease and diabetes (data not shown).

Two thousand and two hundred and thirty four participants with cognitive tests at the 4-year follow-up exam were included in the longitudinal analyses. Participants excluded from the longitudinal analyses (n = 543, 19.6%) were more likely to have lower 25(OH)D levels and 3MS and DSST scores at baseline (p <0.001). They also were less educated, less likely to be using vitamin supplements, and were more likely to have diabetes, kidney disease, and cardiovascular disease. In this analysis, low 25(OH)D levels were associated with a greater decline in cognitive function over time as measured by the 3MS and DSST in minimally adjusted models (Table 3). However, after adjusting for potential confounders, vitamin D deficiency was associated with greater 3MS decline only (p=0.05); where the mean decline in 3MS score was greater over 4years of follow-up for participants deficient in vitamin D at baseline compared with those who were sufficient (p= 0.05). Low 25(OH)D levels were not associated with a decline in DSST scores over time in fully adjusted models (p=0.22).Additionally, similar declines in 3MS (−1.5 (−2.0 to −1.1), −1.0 (−1.4 to −0.6), and −0.7 (−1.1 to −0.3), p=0.05) and DSST scores (−3.4 (−4.1 to −2.6), −2.7 (−3.4 to −2.1) and −2.4 (−3.0 to −1.7), p=0.21) over time by 25(OH)D category(<20, 20-<30, and ≥30 ng/mL, respectively) were observed after excluding participants with low 3MS scores (<80) at baseline (n=262). Prevalent cardiovascular disease and diabetes were examined as potential mediators of the relationship between 25(OH)D and decline in cognitive function; however, the results were similar after further adjustment for cardiovascular disease and diabetes (data not shown).

A race interaction was added to all fully adjusted models to see if there were differences in the associations between 25(OH)D levels and cognitive scores based on race. There was not a significant 25(OH)D by race interaction for baseline or change in both cognitive scores in fully adjusted models.3MS and DSST scores were lower in blacks; however, the effect of 25(OH)D was similar in both race groups.

DISCUSSION

In this large, well-functioning, community-dwelling population of older adults, low 25(OH)D levels were cross-sectionally associated with lower cognitive scores as measured by the 3MS and DSST. Vitamin D deficiency was also associated with a greater decline in global cognitive function over 4years of follow-up as measured by the 3MS. A difference in decline in DSST scores over time was not seen in fully adjusted models.

Our results add to a growing body of literature suggesting a relationship exists between 25(OH)D levels and decline in cognitive function. In the InCHIANTI study of adults aged 65 and older followed over six years, low 25(OH)D levels (<10 ng/mL) were associated

with cognitive decline as measured by the MMSE and Trails Making Test B (TMT-B).[15] Slinin et al also found an association between low 25(OH)D levels (<10 ng/mL) and decline in MMSE over 4 years, but not with TMT-B, in women in the Study of Osteoporotic Fractures.[13] However, low 25(OH)D levels were not associated with cognitive decline as measured by the 3MS or TMT-B in the Osteoporotic Fractures in Men (MrOS) Study with an average follow up of 4.6 years.[17] Breitling et al. also did not observe a significant association between low 25(OH)D levels and worse cognitive function at 5-year follow-up; however, this study lacked measures of baseline cognitive function.[16]

Controversy still exists regarding which domains of cognition are influenced more by vitamin D. Buell et al found that low 25(OH)D levels were associated with worse scores in executive functioning, attention, and processing speed, but not in memory in a cohort of older patients receiving home health services.[18] Similarly, analyses from the NHANES III study also concluded that attention was affected, while memory appeared to not be adversely affected by vitamin D deficiency.[22] Prospectively, Slinin et al did not find an association with low vitamin D levels and a decline in executive functioning over time, as measured by TMT-B.[13] Llewellyn et al found an association with cognitive decline over time in global cognitive function, as assessed by the MMSE, and executive function as assessed by TMT-B, but not processing speed, as assessed by TMT-A.[15] Our results indicate that low 25(OH)D levels are associated with global cognitive function, attention, working memory, and speed of processing at baseline and global cognitive decline over time. However, Health ABC did not conduct an extensive battery of cognitive tests; thus, we were unable to examine potential associations between 25(OH)D levels and different cognitive domains.

It has been historically difficult to evaluate the cognitive literature as a whole concerning vitamin D and cognition because of the many potential confounders, different categories used to define vitamin D status, and different tests used for measuring cognition. Strengths of our study include the large, bi-ethnic, extensively characterized population allowing us to adjust for many potential confounders such as season, physical activity, and multiple medical comorbidities. In addition, we had repeated measures of two commonly used tests of cognition assessing multiple cognitive domains, including global function, executive function, and processing speed.

Several methodological considerations should be pointed out in the interpretation of our results. While we did show a longitudinal relationship between 25(OH)D levels and cognitive performance, the observational nature of this study limits causal inference in the association between 25(OH)D and cognitive function. Though we had extensive covariates in the models, there may be unknown confounders that weren't included in our analysis that could explain the associations we found. There is also the possibility of reverse causality in that those with lower cognitive function at baseline may have decreased their outdoor activity resulting in lower 25(OH)D levels. However, few participants (n=262, 9.4%)had low 3MS scores (defined as <80) at baseline. Furthermore, the longitudinal results were similar after excluding participants with low baseline 3MS scores.

Another potential limitation is that 25(OH)D levels were only measured once, at the 12 month follow-up, and not contemporaneously with the initial cognitive testing. However,

evidence from other studies show that year-to-year 25(OH)D levels are highly correlated.[23] Furthermore, participants who lacked cognitive data at the 4-year follow-up exam were more likely to have lower 25(OH)D levels and 3MS and DSST scores, which would likely attenuate the observed results. The clinical implications of these findings are still uncertain. A0.7 point difference in 3MS scores and 0.8 point greater decrease in 3MS scores over time are modest. However, the effect of being vitamin D deficient was equivalent to being over 3.6 years older cognitively at baseline as measured by the 3MS, which may indeed be clinically relevant. The Health ABC cohort was selected to include well-functioning residents from two US communities at baseline which may limit the generalizability of the findings to those with relatively high cognitive function at baseline.

Vitamin D deficiency and cognitive impairment are both prevalent conditions in older adults and this study contributes to the mounting data suggesting a relationship between 25(OH)D levels and cognition exists. The public health impact of a potential causative link is large. Data from the Women's Health Initiative Calcium and Vitamin D Trial and Memory Study examining calcium and vitamin D supplementation on cognitive outcomes found no benefit in cognition in participants who were randomized to calcium (1000 mg) and vitamin D (400 IU) compared to placebo.[24] However, this population was not vitamin D deficient overall at baseline, had few incident cases of cognitive impairment, and was given a low dose of vitamin D_3, which could have negatively impacted the results. Clinical trials to determine whether vitamin D supplementation can prevent cognitive decline and definitively establish a causal relationship between low 25(OH)D levels and cognitive impairment are needed to make well-supported recommendations. Further research is also indicated to evaluate whether specific cognitive domains are especially sensitive to low 25(OH)D levels.

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Table 1

Baseline Characteristics of the Health ABC Cohort by Vitamin D Status

	25-Hydroxyvitamin D Level			
	<20 ng/mL	**20-<30 ng/mL**	**≥30ng/mL**	**P-value**
N (%)	910 (32.8)	979 (35.3)	888 (31.9)	
Mean age, yrs	73.6 (2.9)	73.7 (2.9)	73.6 (2.8)	0.63
Female, %	56.5	49.3	47.8	<0.001
White race, %	35.1	65.7	81.0	< 0.001
BMI category,%:				< 0.001
< 25 kg/m^2	25.4	30.8	40.9	
25 – <30 kg/m^2	38.5	45.7	44.9	
30+ kg/m^2	36.2	23.6	14.2	
Physical Activity (minutes walking/week),%:				< 0.001
0 minutes	49.1	40.3	34.7	
1 – <150 minutes	30.0	30.6	32.0	
150 + minutes	20.9	29.1	33.3	
Education Level,%:				< 0.001
< 12th grade	33.1	22.6	16.0	
High school graduate	33.6	32.2	31.2	
Some secondary	33.3	45.3	52.8	
Depressive Symptoms (CES-D) score	4.9 (5.3)	4.4 (5.0)	4.6 (5.5)	0.21
eGFR< 60 mL/min, %	19.5	19.9	24.7	0.01
Prevalent Type 2 Diabetes, %	19.2	13.5	10.9	< 0.001
Prevalent CVD, %	26.5	23.6	21.3	0.03
Alcohol Intake : % at least 1/week	23.7	30.0	34.3	< 0.001
Current Smoker, %	14.6	7.7	7.1	< 0.001
Memphis Site, %	48.1	51.8	51.4	0.23
Multivitamin use, %	13.6	37.3	56.0	< 0.001
Calcium Supplement use, %	7.7	22.2	33.8	< 0.001
Vitamin D Supplement use, %	2.8	10.5	18.1	< 0.001

P-values based on chi-square tests for categorical variables and one-way ANOVA for continuous variables.

BMI=Body mass index, CES-D=Center for Epidemiologic Studies Depression Scale(0–60),eGFR= estimated glomerular filtration rate, CVD=Cardiovascular disease defined as prior heart attack or stroke.

Table 2

Mean 3MS and DSST scores at baseline by vitamin D status (Least Square Means and 95% Confidence Intervals)

	25-hydroxyvitamin D Level			
	< 20 ng/mL	**20-<30 ng/mL**	**≥ 30 ng/mL**	**p-value**
3MS(0–100)				
Model 1[a]	88.9 (88.4 to 89.4)	91.0 (90.5 to 91.4)	91.2 (90.8 to 91.7)	< 0.001
Model 2[b]	89.9 (89.4 to 90.4)	90.8 (90.4 to 91.3)	90.6 (90.2 to 91.1)	0.02
DSST(0–133)				
Model 1[c]	33.1 (32.3 to 33.9)	36.2 (35.4 to 36.9)	38.5 (37.7 to 39.3)	<0.001
Model 2[d]	35.2 (34.5 to 36.0)	35.9 (35.2 to 36.6)	37.0 (36.3 to 37.8)	0.01

Model 1: adjusted for education only. Model 2: fully adjusted model including education, age, sex, race, site, season, kidney disease (eGFR <60), CES-D score, alcohol consumption, smoking, BMI, and physical activity.

Wald type p-values are presented.

[a] n=2776

[b] n=2708

[c] n=2748

[d] n=2680

Table 3

Change in 3MSE and DSST scores from baseline to the 4-year follow-up exam by vitamin D status (Least square mean change and 95% Confidence Intervals)

	25-hydroxyvitamin D Level			
	< 20 ng/mL	**20-<30 ng/mL**	**≥ 30 ng/mL**	**p-value**
3MS(0–100)				
Model 1[a]	−1.3 (−1.8 to −0.9)	−0.6 (−1.0 to −0.2)	0.2 (−0.2 to 0.6)	< 0.001
Model 2[b]	−1.0 (−1.5 to −0.6)	−0.8 (−1.2 to −0.3)	−0.2 (−0.7 to 0.2)	0.05
DSST(0–133)				
Model 1[c]	−3.3 (−4.0 to −2.6)	−2.5 (−3.1 to −1.9)	−1.9 (−2.6 to −1.3)	0.02
Model 2[d]	−3.1 (−3.8 to −2.4)	−2.7 (−3.3 to −2.1)	−2.2 (−2.9 to −1.5)	0.22

Model 1: adjusted for education only. Model 2: fully adjusted model including education, baseline cognitive scores, age, sex, race, site, season, kidney disease (eGFR <60), CES-D score, alcohol consumption, smoking, BMI, and physical activity.

Wald type p-values are presented.

[a] n=2225

[b] n=2207

[c] n=2225

[d] n=2175