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Low 25-Hydroxyvitamin D Concentrations and Risk of Incident Cognitive Impairment in Black and White Older Adults: The Health ABC Study

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Abstract

Using data from the Health, Aging, and Body Composition study, we examined whether low 25-hydroxyvitamin D (25[OH]D) concentrations were associated with prevalent or incident cognitive impairment. Serum 25(OH)D concentrations were measured in 2,786 older adults and categorized as <20 ng/mL, 20 to <30 ng/mL, or ≥30 ng/mL. Cognitive impairment was defined as a score >1.5

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Conflict of interest

DKH reports that he has received funds/grants for this work. The other authors report no conflicts of interest in this work.

Disclosure statement

KMS is currently a full time employee of Genentech. All work in this manuscript was completed while she was employed by Wake Forest School of Medicine.

Author contribution

Kilpatrick contributed to conceptualization, interpretation of data, and drafting manuscript. Houston, Sink involved in the conceptualization, design, interpretation of data, and critical revision of manuscript. Lovato contributed to designing, statistical analysis, interpretation of data, and critical revision of manuscript. All authors contributed in the critical review of manuscript. All authors approved the final version.

standard deviations below race and education specific means on either digit symbol substitution test or modified mini-mental state test. Logistic regression determined the odds of cognitive impairment at baseline and year 5 by 25(OH)D category. 25(OH)D concentrations were <30 ng/mL in 57.3% of whites and 84.6% of blacks. After excluding participants with baseline cognitive impairment (n = 340), 13% of whites and 13% of blacks developed cognitive impairment by year 5. In whites, 25(OH)D concentrations <30 ng/mL were not associated with prevalent or incident cognitive impairment. Black participants with 25(OH)D concentrations <20 ng/mL had a higher odds of prevalent, but not incident cognitive impairment (OR (95% CI): 2.05 (1.08–3.91), p = 0.03) compared to participants with 25(OH)D concentrations ≥30 ng/mL. Low 25(OH)D concentrations were associated with twofold higher odds of prevalent cognitive impairment in blacks.

Keywords

Cognitive impairment; vitamin D

Introduction

Recent evidence indicating vitamin D may play an important role in cognition has created significant interest in determining the clinical association between 25-hydroxyvitamin D (25[OH]D) concentrations and cognitive impairment. The vitamin D receptor and associated activating enzymes have been demonstrated to be co-located in the brain in areas which are known to play a role in cognition, including the hippocampus and cerebral cortex. These areas appear to be highly susceptible to degeneration during illness and aging and, it has been hypothesized, vitamin D may play a neuroprotective effect through antioxidant mechanisms, upregulating neuronal proteins, and decreasing inflammation from vascular events.[1] Furthermore, several recent studies have shown specific cognitive domains may be impacted by low 25(OH)D concentrations, including executive function[2] and visual memory.[3–6] Because cognitive impairment is a major cause of morbidity in the aging population, establishing a firm link between cognitive impairment and low 25(OH)D concentrations could, in theory, offer another treatment or preventative modality.

In the past few years, many researchers have evaluated the association between 25(OH)D concentrations and cognition, and, although results are conflicting, several observational studies have indicated a positive association between low 25(OH)D concentrations and cognitive impairment.[7–15] Recently several systematic reviews and meta-analyses have provided additional data to support this finding.[16–19] The authors are, however, cautious about drawing conclusions without data from intervention trials. In addition, methodological differences, the inability to exclude reverse causality, and the inclusion of relatively homogenous participant populations are significant limitations of these observational studies.[20]

A recent meta-analysis by van der Schaft included the only six prospective studies published to that point and each consisted of geographically localized, single gender, racially homogenous populations,[18] limiting the generalizability of results, particularly for the black

population who have substantially lower 25(OH)D concentrations than whites,[21,22] and higher risk of dementia.[23]

Using data from the Health aging and body composition (Health ABC) study, we previously showed that global cognitive function as measured by the modified mini-mental state test (3MS) was associated with 25(OH)D concentrations <30 ng/mL and cognitive decline was greater over time,[24] but we did not examine the association with cognitive impairment, a more clinically pertinent outcome. In our previous study, the mean decline in 3MS score among patients with deficient 25(OH)D concentrations was found to be statistically significant, but the average change in mean score was only −0.7 and it remains unclear if this change correlates with clinically meaningful cognitive impairment. In this study, we aimed to determine whether low 25 (OH)D concentrations were associated with an increased risk of developing cognitive impairment in the same study population using a clinically relevant cut point to define cognitive impairment. Participants in this study are unique in that they comprise a large cohort of racially diverse, well-functioning older adults living in two different communities within the United States.

Methods

Study participants

Health aging and body composition enrolled 3,075 community-dwelling, well-functioning participants aged 70–79 years old from Pittsburgh, Pennsylvania, and Memphis, Tennessee recruited between April 1997 and June 1998. Eligibility criteria included: 1) self-report of no difficulty walking one-fourth of a mile, climbing up 10 steps, or performing activities of daily living; 2) absence of life-threatening illness; 3) plan to remain in the geographic area for at least 3 years; and 4) no current enrollment in lifestyle intervention trials. Health ABC was approved by institutional review boards of the participating sites. All participants signed informed consent. Serum 25(OH)D concentrations were obtained in 2,786 participants at year 2, and these participants comprise the population used for these analyses.

Predictor

Serum 25(OH)D concentrations were obtained at year 2 of the study, when the dietary assessment was performed.[25] 25(OH)D concentrations were measured using a radioimmunoassay (DiaSorin, Stillwater, MN). The interassay coefficient of variation was 6.8%. 25(OH)D was categorized as <20, 20–<30, and ≥30 ng/mL based on recently recommended cut-points from the Endocrine Society.[26]

Outcome measures

Cognitive tests, including the modified mental state test (3MS)[27] and Digit symbol substitution test (DSST),[28] were administered at years 1 and 5. The DSST requires participants to match digit and symbol pairs in a time limited trial which measures speed of processing and working memory, components of executive function. The 3MS is a 100-point expanded version of the mini-mental status exam and measures global cognition. Cognitive impairment was defined as performance worse than 1.5 standard deviations (SD) below sample derived race and education specific means on either test. We chose −1.5 SD as our

cut-point because it is commonly used clinically and neuropsychologically, and is considered to be consistent with at least mild cognitive impairment.[29]

Covariates

Demographic data included age, sex, highest educational level completed (entered into multivariable models as a continuous variable, number of years), study site, and season in which 25(OH)D concentrations were measured (September–November, December–February, March–May, and June–August). Alcohol (current, former, never), smoking status (current, former, never), and walking time (minutes walked per week) comprised the lifestyle habits. Medical comorbidities included prevalent diabetes and cardiovascular disease (defined as a history of myocardial infarction or cerebrovascular accident) using algorithms based on self-report, clinical assessments, and medication use at baseline; kidney disease (glomerular filtration rate <60 mL/min); depressive symptoms as measured by the center for epidemiologic studies depression scale[30]; and body mass index from measured weight and height (weight [kg]/height $[m]^2$). Dietary supplement and medication use was determined by reviewing all medications and supplements brought to each clinic visit by the participant. Dietary supplements with ≥4 vitamin or mineral ingredients were considered multivitamins. Vitamin D-containing supplements were defined as those containing vitamin D and ≤2 additional ingredients.

Statistical analysis

Analyses of 25(OH)D concentrations and cognition were conducted using SAS statistical software version 9.2 (SAS Institute, Inc., Cary, NC). Differences in the frequencies and means of covariates by 25(OH)D concentrations were examined using chi-square tests for categorical variables and one-way ANOVA for continuous variables. Multivariate logistic regression models were adjusted for factors that may confound the association between 25 (OH)D concentrations and cognitive impairment, including demographic information, lifestyle habits, and medical comorbidities. Results are presented stratified by race. *P*-values reflect test for trend.

Results

Participant characteristics by race are described in Table 1. Briefly, in the combined sample, participants were of similar age across 25(OH)D subgroups and there was no significant difference in 25(OH)D concentrations between study sites. Those who had low 25(OH)D concentration (<20 ng/mL) (32.9%) were more likely to be female, have ≥12 years of education and less likely to be white. They were also more likely use tobacco products, less likely to take supplements and less likely to be physically active. Participants with low 25(OH)D concentrations were more likely to have diabetes and cardiovascular disease and be obese.

At baseline, 198 (11.8%) whites and 142 (13.1%) blacks met our definition of cognitive impairment, and 57.3% of whites and 84.6% of blacks had 25 (OH)D concentrations <30 ng/mL. Unadjusted and adjusted odds ratios for prevalent cognitive impairment by race and vitamin D status are shown in Table 2. There was no association between 25(OH)D

concentrations and cognitive impairment at baseline in white participants. Among black participants, however, both the unadjusted and adjusted odds of cognitive impairment was approximately twofold higher in participants with 25(OH)D concentrations <20 ng/mL compared to participants with 25(OH)D concentrations ≥30 ng/mL.

After excluding those with prevalent cognitive impairment at baseline (n = 340; 198 whites and 142 blacks) and those lacking follow-up cognitive assessments at year 5 (n = 403; 202 whites and 201 blacks), 176 (13.8%) white participants and 99 (13.3%) black participants developed incident cognitive impairment on either or both the DSST and 3MS by year 5. Participants who lacked follow-up cognitive assessments were older, had lower education, were more likely to be men, black, current smokers, and had lower baseline 3MS and DSST scores. There was no association between vitamin D status at year 2 and odds of developing cognitive impairment in either whites or blacks at year 5 (Table 3).

Discussion

Vitamin D status was not associated with baseline or incident cognitive impairment in whites. However, low 25(OH)D concentration was associated with prevalent, but not incident, cognitive impairment in blacks. This is one of only a few studies[31,32] to include large numbers of black participants and to demonstrate a difference in association between cognition and 25(OH)D concentrations by race. The results of similar studies in predominantly white participants to date have been mixed, with five longitudinal studies indicating a positive association[8,11,13,14,33] and two studies observing no association.[32,34]

The majority of studies published to date have included small numbers of black participants and only two, to our knowledge, stratified results by race.[31,32] In a small, cross sectional study (n = 60), a positive association between low 25(OH)D concentrations (<20 ng/mL) and cognitive impairment was discovered among black participants, but not among white participants,[31] consistent with our finding of an association between low vitamin D and prevalent cognitive impairment in blacks, but not whites. However, two recently published longitudinal studies did not suggest an association between race and cognitive impairment. Using data from the ARIC Brain MRI Study, which included nearly 50% black participants, Schneider et al. found 25(OH) D concentrations <20 ng/mL were not associated with increased risk of developing cognitive impairment or hospitalization for dementia in whites or blacks.[32] Miller et al., found that while lower 25(OH)D concentrations were associated with cognitive decline in a multiethnic cohort, the study sample was too small to examine interactions between race, vitamin D status, and cognitive impairment.[15]

Due to higher melanin levels in the skin, blacks can have 25(OH)D concentrations up to 50% lower than white counterparts.[21,35] Hence, this population may be more susceptible to cognitive impairment related to low 25(OHD) concentrations. Because of the discrepancy in 25(OH)D concentrations, others have suggested the definition of low 25(OH)D concentration may need to be race-specific.[36,37] A recent study indicated a difference in vitamin D binding proteins between blacks and whites may account for discrepancies in 25(OH)D concentrations and actual bioavailable 25(OH)D may be comparable between races.[38] Additional information will be needed not only to determine whether there is an

association between low 25(OH)D concentrations and cognition in blacks, but to also determine an accurate definition of a low 25(OH)D concentration in this racial group.

The large, multisite design, and racially diverse population of the Health ABC study has allowed us to contribute to the evolving discussion about the association between low 25(OH)D concentrations and cognitive impairment. Few studies demonstrating a null association (among white participants) have been published to date. This was identified as a limitation to drawing firm conclusions about the association between low 25(OH)D concentrations and cognition in the recently published meta-analyses and systematic review.[16–19] In addition, we have contributed to an area of needed study: further evaluation of the association between low 25(OH)D concentrations and cognition in the black population. The majority of prior studies have included predominantly white participants, and our data suggest there may be a racial difference in this potential association.

Discrepancies between our results (no association between vitamin D status and incident cognitive impairment) and those of some other longitudinal analyses may be in the way we defined cognitive impairment and in the fact that our cognitive battery was limited. We aimed to define clinically relevant cognitive impairment using a composite of two common tests of cognition, the 3MS and DSST. And although other longitudinal studies have assessed cognitive decline, the clinical relevance of this change is uncertain. For example, two studies which showed an association between vitamin D deficiency and cognitive impairment used a cut off of >3 point decrease on MMSE to define impairment.[11,14] While this cut off accurately represents decline, it may not represent impairment in cognition since a change from 30 to 27, for example, may not represent “impaired” cognition. While Slinin et al. used a cut off of >1.5 SD below the sample mean to define cognitive impairment at baseline in the 2012 Study of Osteoporotic Fractures, they defined cognitive decline during the follow up period as a >1 SD change from baseline.[8] We used >1.5 SD below the mean to define cognitive impairment both at baseline and at year 5 and capture clinically relevant changes in cognition.

Several recent studies have evaluated the association of vitamin D deficiency and cognitive impairment using a clinical diagnosis of dementia with mixed results.[13,32,33] Littlejohns et al. found a positive association between all cause dementia among older adults with vitamin D deficiency (defined as < 20 ng/mL)[13] and Annweiler et al. described an association between 25(OH)D concentrations <10 ng/mL and causes of dementia other than Alzheimer’s disease.[33] Based on the data available in the Health ABC study, we were not able to asses a clinical diagnosis of dementia.

There are some additional methodological considerations when interpreting the results of this study. For example, we categorized the lowest vitamin D group as having 25(OH)D concentrations <20 ng/mL. Several studies demonstrating a positive association between low 25(OH)D concentrations and cognitive impairment used <10 ng/mL as the cut off for vitamin D deficiency.[7–12] However, only 4% of Health ABC participants had 25(OH)D concentrations <10 ng/mL. In addition, although cognitive tests were administered longitudinally, 25(OH)D concentrations were measured only at year 2 and baseline cognitive testing and 25(OH)D measurement occurred 1 year apart. Although these measurements

were not performed concurrently, prior work suggests that serum 25(OH)D concentrations at a single time point are a useful biomarker of vitamin D status over a 5-year period[39] and our methodology is similar to other longitudinal studies.[8,11,34] Another potential limitation is that the operational definition of cognitive impairment does not include a full clinical assessment and may not have been sensitive enough to pick up subtle deficits and changes, particularly since we did not have a broad representation of cognitive domains including the absence of a visual memory task which has recently been found by several investigators to be associated with vitamin D levels.[3–6] However, we defined cognitive impairment as 1.5 SD below race and education specific means on two commonly used measures (3MS and DSST) to identify clinically meaningful changes in cognition since Health ABC does not have adjudicated mild cognitive impairment or dementia outcomes. Finally, differential loss to follow up of cognitively impaired participants could bias results. As noted in the results, 403 participants did not complete follow-up cognitive testing and they were more likely to have lower cognitive performance at baseline. Thus, as in many observational studies of cognitive outcomes, we may have missed an association between low vitamin D levels and incident cognitive impairment because those who are becoming cognitively impaired are less likely to return for repeat cognitive testing.

In conclusion, although no association between low 25(OH)D concentrations and incident cognitive impairment was found in this cohort of well-functioning older adults, an association with prevalent cognitive impairment was found in blacks. This warrants further investigation with other cohorts of black participants.

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Take away points

1. Prevalent cognitive impairment may be associated with low 25(OH)D concentrations in black participants.
2. Vitamin D status was not associated with baseline or incident cognitive impairment in whites.
3. Additional studies are needed to further evaluate the effect of low 25(OH)D concentrations on cognitive impairment in different racial and ethnic groups.

Table 1

Participant characteristics by vitamin D status: Health ABC study; numbers represent mean (standard deviation) or %.

	White (*n* = 1,681)				Black (n = 1,096)			
	<20ng/mL	**20 to <30 ng/mL**	**≥30 ng/mL**	***P*-value**	**<20 ng/mL**	**20 to <30 ng/mL**	**≥30 ng/mL**	***P*-value**
N (%)	319 (19.0)	643 (38.3)	719 (42.8)		591 (53.9)	336 (30.7)	169 (15.4)	
Demographics								
Age, years	73.8 (2.8)	73.9 (2.9)	73.6 (2.8)	0.18	73.5 (2.9)	73.3 (2.8)	73.5 (2.8)	0.72
Female	52.4	45.6	46.7	0.13	58.7	56.6	52.1	0.30
Education level				0.22				0.19
<12 years	13.2	11.7	11.0		43.8	43.5	37.3	
12 years	37.3	34.2	31.6		31.6	28.3	29.6	
>12 years	49.5	54.1	57.4		24.5	28.3	33.1	
Memphis site	52.0	52.1	51.6	0.98	46.0	51.2	50.3	0.27
Health status and related behaviors								
Alcohol intake at least 1/week	37.4	37.9	38.0	0.06	16.3	14.9	18.6	0.38
Current smoker	9.1	5.8	4.9	0.06	17.6	11.3	16.7	0.13
BMI (kg/m^2)				<0.001				<0.001
<25	27.6	33.4	43.1		24.2	25.6	31.4	
25–30	45.8	47.0	44.2		34.5	43.2	47.9	
30+	26.7	19.6	12.7		41.3	31.3	20.7	
Minutes walked/week				0.001				0.49
0	45.0	34.8	31.9		51.4	50.6	46.4	
0,1–150	31.1	32.0	32.9		29.4	28.0	28.0	
150+	23.9	33.1	35.2		19.2	21.4	25.6	
REALM score	63.9 (5.2)	63.8 (4.9)	63.8 (4.9)	0.98	54.1 (15.9)	56.0 (14.5)	53.8 (17.8)	0.23
CES-D score	5.1 (5.6)	4.4 (5.1)	4.6 (5.6)	0.18	4.7 (5.2)	4.5 (4.7)	4.5 (5.2)	0.73
eGFR <60mL/min/1.73 m^2	26.1	20.6	27.6	0.01	15.9	18.4	12.4	0.22
Type 2 diabetes	13.8	10.6	9.2	0.08	22.2	19.1	18.3	0.38
Previous CVD	29.8	24.3	20.5	0.004	24.7	22.3	24.9	0.69
Multivitamin use	17.7	40.5	56.6	<0.001	11.3	31.2	53.0	<0.001
Calcium supplement use	12.9	26.3	35.8	<0.001	4.9	14.3	25.0	<0.001

	White (*n* = 1,681)				Black (n = 1,096)			
	<20ng/mL	**20 to <30 ng/mL**	**≥30 ng/mL**	***P*-value**	**<20 ng/mL**	**20 to <30 ng/mL**	**≥30 ng/mL**	***P*-value**
Vitamin D supplement use	4.7	12.3	18.4	<0.001	1.7	7.2	16.7	<0.001
			Cognitive performance					
3MS Score (0–100) % impaired[a]	92.6 (5.6)	93.3 (5.4)	93.1 (6.0)	0.21	85.5 (9.7)	86.9 (10.1)	87.4 (8.6)	0.02
	8.8	6.2	7.7	0.32	9.0	7.1	4.1	0.10
DSST (0–133) % impaired[a]	39.9 (11.5)	40.9 (11.5)	42.3 (12.2)	0.005	26.9 (14.3)	27.8 (14.5)	29.8 (14.6)	0.07
	5.3	6.2	5.8	0.86	7.1	6.9	5.9	0.86

[a]Impaired defined as performance >1.5 SD worse than the mean for race and education.

BMI, body mass index; CES-D, center for epidemiologic studies depression scale; REALM, rapid estimate of adult literacy in medicine; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease (defined as a history of myocardial infarction or cerebrovascular accident; 3MSE, modified mini mental state test; DSST, digit symbol substitution test.

Table 2

Odds (95% confidence interval) of prevalent cognitive impairment by race and vitamin D status: Health ABC study.

		25(OH)D Category			
		<20 ng/mL	**20 to <30 ng/mL**	**≥30 ng/mL**	***P*-value for trend**
White (*n* = 1,681)	Unadjusted	0.94 (0.62–1.41)	0.89 (0.64–1.24)	Ref	0.76
	Adjusted[a]	0.88 (0.56–1.37)	0.84 (0.59–1.21)	Ref	0.56
Black (*n* = 1,096)	Unadjusted	1.80 (1.01–3.20)	1.41 (0.75–2.63)	Ref	0.05
	Adjusted[a]	2.05 (1.08–3.91)	1.71 (0.86–3.40)	Ref	0.03

[a]Adjusted confounders: age, sex, study site, season, BMI category (<25, 25–<30, ≥30 kg/m^2), walking time (0, >0 – <150, ≥150 min/week), highest educational level completed, depressive symptoms as measured by the center for epidemiologic studies depression scale, kidney disease (eGFR <60 mL/min/1.73 m^2), diabetes, cardiovascular disease (defined as a history of myocardial infarction or cerebrovascular accident), alcohol consumption (current, former, never), and smoking (current, former, never).

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Table 3

Odds (95% confidence interval) of incident cognitive impairment by race and vitamin D status: Health ABC study.

		25(OH)D category			
		<20 ng/mL	**20 to <30 ng/mL**	**≥30 ng/mL**	***P*-value for trend**
White (*n* = 1,276)	Unadjusted	1.02 (0.65–1.61)	1.17 (0.83–1.67)	Ref	0.93
	Adjusted[a]	1.02 (0.62–1.67)	1.12 (0.77–1.64)	Ref	0.95
Black (*n* = 742)	Unadjusted	1.01 (0.55–2.06)	1.17 (0.77–1.64)	Ref	0.97
	Adjusted[a]	1.06 (0.55–2.06)	1.27 (0.63–2.53)	Ref	0.86

[a]Adjusted confounders: age, sex, study site, season, BMI category (<25, 25–<30, ≥30 kg/m^2), walking time category (0,>0 to <150, ≥150 min/week), highest educational level completed, depressive symptoms as measured by the center for epidemiologic studies depression scale, kidney disease (eGFR <60 mL/min/1.73 m^2), diabetes, cardiovascular disease (defined as a history of myocardial infarction or cerebrovascular accident), alcohol consumption (current, former, never), and smoking (current, former, never).

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