Vitamin D Status and Intakes and Their Association With Cognitive Trajectory in a Longitudinal Study of Urban Adults

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Context: Serum 25-hydroxyvitamin D [25(OH)D], and dietary and supplemental vitamin D may influence cognitive outcomes.

Objectives: Sex-, age-, and race-specific associations of vitamin D status and intake with longitudinal change in various cognitive domains were examined in a large sample of ethnically and socioeconomically diverse US urban adults.

Design: Two prospective waves of data from the Healthy Aging in Neighborhoods of Diversity across the Life Span study were used.

Participants: Adults in Baltimore, Maryland, aged 30 to 64 years at baseline (n = 1231 to 1803), were followed for a mean (± standard deviation) of 4.64 ± 0.93 years. Visit 1 occurred between 2004 and 2009; visit 2, between 2009 and 2013; there were 1.5 to 2.0 visits per participant.

Main outcome and exposure measures: Cognitive performance was assessed using 11 test scores covering domains of global cognition, attention, learning/memory, executive function, visuospatial/visuoconstruction ability, psychomotor speed, and language/verbal. Serum 25(OH)D, vitamin D intake, and use of supplements containing vitamin D were the key exposures.

Results: A consistent relationship was found between vitamin D status (overall) and supplemental intake (older women and black adults), with a slower rate of decline in the domain of verbal fluency. Higher dietary intake of vitamin D was linked to slower rate of decline in verbal memory among younger women, and a slower rate of decline in visual memory/visuoconstructive abilities among white adults. All other associations were inconsistent.

Conclusions: Vitamin D status and intakes were inversely related to domain-specific cognitive decline in US urban adults. (***J Clin Endocrinol Metab*** **103: 1654–1668, 2018)**

Cognitive impairment, a principal cause for functional disability among the elderly, can lead to dementing illness over time mainly in the forms of Alzheimer disease (AD) and vascular dementia. In fact, AD prevalence is expected to rise, reaching 100 million worldwide by 2050, with one in 85 persons potentially living with AD (1). Thus, uncovering modifiable risk factors that would prevent or delay cognitive impairment is important.

The neuroprotective effects of antioxidant nutrients (*e.g.*, vitamins E) and B vitamins (*e.g.*, folate) have been at the forefront of cognitive aging and nutritional

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Abbreviations: 25(OH)D, 25-hydroxyvitamin D; AD, Alzheimer disease; CVLT, California Verbal Learning Test; HANDLS, Healthy Aging in Neighborhoods of Diversity Across the Life Span; HEI-2010, Healthy Eating Index 2010; HS, high school; MMSE, Mini-Mental State Examination; SD, standard deviation.

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epidemiology research over the past two decades (2). Vitamin D's role in preserving cognitive function with aging has recently gained attention in epidemiological investigations (3). Its public health significance lies in the fact that vitamin D deficiency (25-hydroxyvitamin D3 [25(OH)D] <11 ng/mL [<27.5 nmol/L]) is a highly prevalent condition, particularly among the poor and among African Americans (4, 5).

Vitamin D is a steroid hormone; its primary function is to regulate body levels of calcium, phosphorus, and bone mineralization. Although sunlight exposure is its primary source through skin synthesis from 7-dehydrocholesterol, dietary and supplemental intakes of vitamin D play a key role in its overall status (3). The active form of vitamin D3, namely 1,25-dihydroxy vitamin D_3, influences many metabolic pathways through genomic and nongenomic actions that help maintain and stabilize intracellular signaling pathways involved in memory and cognitive function (3, 6, 7). The neuroprotective role of vitamin D may be mediated through vasculoprotection and preservation of neurons, partly through the expression of neurotrophins and other neurotransmitters that help protect against cognitive dysfunction, through the suppression of inflammatory cytokines (3, 5, 8). Vitamin D can also downregulate receptors in memory-relevant regions and enhance amyloid phagocytosis and clearance (8).

Serum 25(OH)D and dietary vitamin D levels were shown to influence cognitive outcomes in large epidemiological studies (9–34). This study examined associations between vitamin D status and intake with longitudinal change in various domains of cognition among a large sample of ethnically and socioeconomically diverse US urban adults. It also explored those associations systematically across sex and age groups and race. We hypothesized that vitamin D status and intake are associated with slower decline in domain-specific cognitive performance over time, but perhaps differentially by age, sex, and race.

Methods

Database

The Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study is a prospective cohort study initiated in 2004 that focuses on the cardiovascular and cognitive health of an ethnically and socioeconomically diverse urban population. Specifically, it uses area probability sampling to recruit a socioeconomically diverse sample of African American and white urban adults (30 to 64 years old) residing in 13 neighborhoods of Baltimore, Maryland (35).

Written informed consent was obtained from participants who were also provided with a protocol booklet and a video that explains study procedures. The study protocol was approved by the National Institute on Environmental Health Sciences Institutional Review Board of the National Institutes of Health. Data for the current study were derived from baseline visit 1 (during the years 2004 to 2009) and the first follow-up examination (visit 2, between 2009 and 2013). Follow-up time ranged from <1 year to ~8 years [mean ± standard deviation (SD), 4.64 ± 0.93 years].

Study sample

HANDLS initially recruited 3720 participants (phase I, visit 1). Given that only phase II had in depth data (aka Medical Research Vehicle Examination), including biochemichal indices, second 24-hour dietary recall and cognitive performance measures, 25(OH)D data were available for 1981 participants at baseline. The corresponding sample sizes for dietary and supplemental vitamin D were 2177 and 2159 participants, respectively. Complete and reliable cognitive tests at each visit varied in sample size, as well. Furthermore, the final analytic sample was determined on the basis of exposure and covariate nonmissingness at baseline and outcome nonmissingness at either visit. Supplemental Fig. 1 describes sample selection for all exposures. The final analytic sizes ranged between1231 and 1803 participants (κ = 1.5 to 1.9 observation per participant).

Cognitive assessment

Cognitive performance was assessed with seven tests yielding 11 test scores and covering seven domains (*i.e.*, global, attention, learning/memory, executive function, visuospatial/visuoconstruction ability, psychomotor speed, language/verbal): the Mini-Mental State Examination (MMSE), the California Verbal Learning Test (CVLT) immediate (List A) and CVLT-delayed free recall, digit span forward and backward tests, the Benton Visual Retention Test, animal fluency test, Brief Test of Attention, trailmaking test parts A and B, and the clock-drawing test (Supplemental Methods). All participants were judged capable of informed consent and were probed for their understanding of the protocol. Although no formal dementia diagnosis was conducted, all participants were given the MMSE as a global mental status test, which they completed successfully. We used ≥24 as the criterion for success on the MMSE, a widely accepted cutoff. In every case, low mental status performance was due to low literacy level without any sign of dementia.

Vitamin D status

Total 25(OH)D (in nanograms per milliliter) was measured using immunoassay at baseline and follow-up visits. The collected sample was ~0.8 mL of preferably fasting serum, which was refrigerated and transported to the laboratory for analysis. Visit 1 analyses were conducted at the Massachusetts General Hospital, Boston, Massachusetts (36). Visit 2 analyses were conducted by Quest Diagnostics, Chantilly, Virginia.

Dietary vitamin D

Dietary factors included in our analyses were measured at the baseline visit. Baseline 24-hour dietary recalls were obtained using the US Department of Agriculture Automated Multiple Pass Method, a computerized structured interview (37).

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Measurement aids used included measuring cups, spoons, a ruler, and an illustrated *Food Model Booklet* (38). Two recalls were administered in person by trained interviewers 4 to 10 days apart (the first during phase I and the second during phase II of visit 1). Trained nutrition professionals used Survey.Net (http://www.survey.net/), matching foods consumed with 8-digit codes from the Food and Nutrient Database for Dietary Studies, version 3.0 (39), and MyPyramid equivalents database for food groups (http://www.ars.usda.gov/SP2UserFiles/Place/80400530/pdf/mped/mped2_doc.pdf). Dietary vitamin D was among the nutrients made available by the Food and Nutrient Database for Dietary Studies, from which daily values could be estimated and expressed as micrograms per day, using the average from the two 24-hour recalls conducted at baseline.

Supplemental vitamin D

The HANDLS dietary supplement questionnaire was adapted from the 2007 National Health and Nutrition Examination Survey instrument (40). HANDLS participants provided supplement bottles during their dietary interview at the follow-up visit only (*i.e.*, visit 2). Information on over-the-counter vitamin and mineral supplements, antacids, prescription supplements, and botanicals were reported, and supplement users were asked about dose strength, dose amount consumed, length of supplement use (converted to days), frequency of use (*i.e.*, daily, monthly, seasonally, annually), and if each supplement was taken the day before their interview.

A HANDLS dietary supplement database was developed by trained nutritionists and registered dietitians. This database (https://handls.nih.gov/) consisted of four files integrated to generate daily intake of each nutrient consumed by a dietary supplement user. Vitamin D supplemental intake was ascertained for visit 1 if the daily amount (measured as international units per day) was nonzero at visit 2 and the length of time for intake was greater than or equal to the length of time (measured in days) between the two visits, per individual. Thus, the HANDLS participant was either 0: a non-vitamin D–containing supplement user at baseline or follow-up; 1: a vitamin D–containing supplement user at baseline and during follow-up; or 2: a vitamin D–containing supplement user during follow-up only. The coding of the latter exposure was reversed (*i.e.*, 0 = nonuser; 1 = follow-up user; 2 = baseline user) for the purpose of creating a summary exposure encompassing serum, diet, and supplemental vitamin D into one standardized vitamin D score.

Covariates

Covariates included in our main models were selected on the basis of their well-known association with the outcome of interest, namely, cognitive decline (41). Furthermore, their association with the exposures of interest were assessed in a separate analysis. Those included baseline age; sex; race (white *vs* African American); marital status; educational attainment [less than high school (HS); HS; more than HS]; poverty income ratio (<125% for "poor"); measured body mass index; opiate, marijuana or cocaine use (current *vs* never or former); smoking status (current *vs* never or former); and the Wide Range Achievement Test letter and word reading subtotal scores to measure literacy (Supplemental Methods). To assess depressive symptoms with focus on affective, depressed mood, the 20-item Center for Epidemiologic Studies-Depression was used. Baseline Center for Epidemiologic Studies-Depression total score was included in the analysis as a potential confounder in the association between vitamin D exposures and cognitive change or baseline performance (Supplemental Methods). The Healthy Eating Index 2010 (HEI-2010) total score, based on two 24-hour recalls administered at baseline, was used as a measure of overall dietary quality. The steps for calculating HEI-2010 are given at http://appliedresearch.cancer.gov/tools/hei/tools.html and http://handls.nih.gov/06Coll-dataDoc.html. Furthermore, season of baseline Medical Research Vehicle Examination was used as proxy for sunshine exposure and was included as covariate in all models. Finally, self-reported history of type 2 diabetes, hypertension, cardiovascular disease (*i.e.*, stroke, congestive heart failure, nonfatal myocardial infarction, or atrial fibrillation), and dyslipidemia at first visit were considered as covariates (42).

Statistical analysis

Using Stata, version 15.0 (StataCorp, College Station, TX), and accounting for sampling weights, population estimates of means and proportions were obtained. Means across stratifying variables (*e.g.*, age, sex, or race) were compared using svy:reg; the relationship between categorical variables was compared using svy:tab and design-based *F* tests. Furthermore, the relationships between vitamin D exposures, accounting for other covariates, was assessed using a series of three ordinary least square and multinomial logistic regression models, with outcomes being 25(OH)D, dietary vitamin D, and supplemental vitamin D, respectively. Importantly, mixed-effects regression models with 11 continuous cognitive test score(s) as alternative outcomes were conducted. In these models, the time variable, expressed in years elapsed between waves of data, was interacted with several covariates, including the main exposure variables, namely $VITD_{serum}$, $VITD_{diet}$ and $VITD_{suppl}$. The models assumed missingness at random, with time points ranging between ~1.5 and 2.0 visits per person (43). Predictive margins were estimated and plotted across time (years), stratifying by exposure group, from selected mixed-effects regression models, particularly those showing significant associations in the total population. When possible, this was done for the summary vitamin D exposure only.

Moderating effect of sex and age groups was tested by adding interaction terms to separate multivariable mixed-effects regressions (three- and four-way interaction terms between time, exposure, age group, and sex) and stratifying by sex and age group to examine relationships among the following groups: younger men, older men, younger women, and older women. Furthermore, moderating effects by race were also examined using a similar approach (white race and African American; Supplemental Methods), given the well-known higher prevalence of vitamin D deficiency among African Americans compared with whites and the differential rates of increases in vitamin D status recently shown by age, sex, and race groups (44). Variable time of follow-up was accounted for in the mixed-effects regression model, because annual rate of change in the outcome was of primary interest.

Moreover, selection bias may occur due to nonrandom selection of participants with complete data from the target study population. Thus, in each mixed-effect regression model, a two-stage Heckman selection process was conducted by running a probit model to compute an inverse mills ratio at the first stage (derived from the predicted probability of being selected,

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conditional on the covariates in the probit model—mainly baseline age, sex, race, poverty status, and education). At the second stage, this inverse mills ratio was entered as a covariate in the final mixed-effects regression model, as was done in a previous study (45).

In all analyses, a type I error of 0.05 was considered for main effects, whereas $P < 0.10$ was deemed significant for interaction terms (46), before correcting for multiple testing. A familywise Bonferroni procedure was used to correct for multiple testing by accounting only for cognitive tests and assuming that exposures related to separate substantive hypotheses (47). Therefore, for main effects, $P < 0.004$ (0.05/11) was considered significant. Owing to their lower statistical power compared with main effects, two-way interaction terms had their critical P values reduced to 0.009 (0.10/11), whereas three- and four-way interaction terms had their critical P value reduced to 0.05. A similar approach was adopted in two other studies (48, 49).

Results

Selected baseline and time-dependent characteristics are presented in Table 1, by age group and sex, selecting study participants with complete and reliable baseline data on MMSE scores. Key differentials by a lower education attainment and income among older participants vs young (both sexes) and among African-American vs white participants, lower literacy among African-American vs white participants, a higher prevalence of current smoking and drug use among younger men vs at least one other group, with a similar pattern were observed for African Americans compared with whites. Body mass index and HEI-2010 were both the lowest among younger men compared with other groups, and HEI-2010 indicated better dietary quality among whites compared with African Americans.

In general, younger men had the lowest prevalence of reported chronic conditions, including diabetes, hypertension, dyslipidemia, and cardiovascular disease compared with older age groups by sex. African Americans had higher prevalence of most chronic conditions, except for dyslipidemia, compared with whites. Serum 25(OH)D level was lower among African Americans who had a higher prevalence of vitamin D deficiency compared with whites, in addition to consuming a smaller amount of vitamin D in the diet. Older participants tended to have a substantial increase in serum 25(OH)D level over time compared with younger men. Older participants were more likely than younger men to be vitamin D-containing supplement users. Younger men also had the lowest prevalence of vitamin D deficiency, particularly when compared with younger women. Furthermore, examining multivariate-adjusted associations among the three vitamin D exposures (Supplemental Table 1), we found that in the subsample with complete data on all three exposures as well as baseline MMSE data (n = 923), 25(OH)D serum concentration was directly associated with baseline use of vitamin D–containing supplements. On the other hand, use of vitamin D–containing supplements during follow-up was associated with greater dietary intake of vitamin D compared with nonusers.

Table 2 lists findings that indicate persistent racial disparities in cognitive performance over the years, with poorer performance observed among African Americans. Nevertheless, only three of the 11 tests suggested a substantial cognitive decline over time in all groups combined, whereas one (MMSE total score) indicated improvement, possibly due to learning among white participants only.

In mixed-effects linear regression models (Table 3), and after correction for multiple testing, (type I error corrected to 0.009), a higher baseline serum 25(OH)D level was linked to a slower rate of decline in a test of verbal fluency (animal fluency test) overall [γ_{11}, +0.011 ($\pm$ SE, 0.003); $P = 0.001$). This relationship remained statistically significant when vitamin D exposures were combined into the summary vitamin D standardized score, as shown in Fig. 1 (per 1 SD increase, γ_{11}, + 0.17 $\pm$ 0.05; $P = 0.002$). The same exposure, however, was linked to faster rate of decline in clock-drawing test score, a test of visuospatial speed, among younger men (γ_{11}, -0.008 ± 0.002; $P = 0.001$).

Furthermore, a higher dietary intake of vitamin D (Table 4) was linked to poorer baseline performance, coupled with a slower rate of decline in verbal memory among younger women, both in terms of immediate and delayed recall (CVLT-List A and CVLT-delayed free recall). Importantly, among whites, a higher intake of vitamin D was associated with a slower rate of decline in the domain of visual memory/visuoconstructive ability (Benton Visual Retention Test score: γ_{11}, -0.044 ± 0.010; $P < 0.001$). This association was significantly stronger among whites compared with African Americans ($P < 0.05$ for three-way interaction among time, race, and exposure).

The findings of supplemental intake of vitamin D during follow-up or at baseline examined in relation to cognitive trajectory are listed in Table 5. Most notably, the use of vitamin D–containing supplements during follow-up was linked to slower rate of decline in animal fluency, particularly among older women and among African Americans. In addition, this same exposure was linked to a better baseline performance on the CVLT-List A among older men. On the other hand, it was linked to poorer performance on digit span forward and digit span backward tests among younger women, which are measures of attention and working memory.

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Table 1. Selected Baseline and Time-Dependent Study-Participant Characteristics by Age Group, Sex, and by Race for HANDLS Participants With Complete and Reliable Baseline MMSE Scores

	All[a]	Older Women (>50 Y)	Older Men (>50 Y)	Younger Women (≤50 Y)	Younger Men (≤50 Y), Referent	$P_{age\times sex}$	White Race	African American	P_{race}
% ± SE		20.9 ± 1.2	18.3 ± 1.1	33.6 ± 1.7	27.2 ± 1.6		36.4 ± 1.5	63.6 ± 1.5	
No. of participants	2574	668	511	792	603		1107	1467	
Age at baseline, y	46.9 ± 0.3	56.7 ± 0.3[b]	56.5 ± 0.3[b]	40.5 ± 0.4	40.7 ± 0.4	<0.001	46.7 ± 0.4	47.0 ± 0.4	0.52
No. of participants	2574	668	511	792	603		1107	1467	
Sex, % male	45.0 ± 1.8	—	—	—	—		46.8 ± 2.1	44.7 ± 2.4	0.52
No. of participants	2574						1107	1467	
Married, %	35.1 ± 1.7	35.4 ± 3.4	38.8 ± 3.3	29.9 ± 2.9[b]	39.1 ± 3.5	0.10	45.1 ± 2.3	29.7 ± 2.2	<0.001
No. of participants	2397	602	462	760	572		1007	1390	
Education, %									
Less than HS	4.2 ± 0.5	6.2 ± 1.4[b]	7.7 ± 1.6[b]	2.5 ± 0.6	2.4 ± 0.7	0.011	5.1 ± 0.8	3.7 ± 0.7	<0.001
HS	52.5 ± 1.7	45.4 ± 3.1	45.4 ± 3.3	55.6 ± 3.3	58.9 ± 3.4		40.2 ± 2.0	59.6 ± 2.4	
Beyond HS	38.8 ± 1.7	43.6 ± 3.3	42.8 ± 3.4	38.2 ± 3.2	33.2 ± 3.2		47.0 ± 2.2	34.1 ± 2.3	
Missing	4.5 ± 0.8	4.8 ± 1.2	4.1 ± 1.2	3.7 ± 1.5	5.6 ± 2.0		7.7 ± 1.1	2.6 ± 1.2	
No. of participants	2574	668	511	792	603		1107	1467	
Literacy (WRAT score)	43.3 ± 0.2	42.9 ± 0.4	42.2 ± 0.6	43.7 ± 0.4	43.7 ± 0.6	0.08	46.8 ± 0.3	41.2 ± 0.3	<0.001
No. of participants	2560	664	508	788	600		1103	1457	
PIR < 125%, %	19.4 ± 1.0	22.4 ± 2.2[b]	16.4 ± 1.7	22.0 ± 2.1[b]	16.0 ± 1.6	0.020	12.2 ± 0.9	23.5 ± 1.5	<0.001
No. of participants	2574	668	511	792	603		1107	1467	
Current smoking status, %									
Currently smoking	43.3 ± 1.7	31.7 ± 3.2[b]	43.1 ± 3.4	42.2 ± 3.2	53.9 ± 3.4	0.003	35.7 ± 2.0	47.8 ± 2.4	<0.001
Missing	5.0 ± 0.8	7.6 ± 2.1	4.4 ± 1.4	5.0 ± 1.6	3.3 ± 1.5		3.6 ± 2.0	5.8 ± 1.3	
No. of participants	2574	667	511	792	603		1107	1467	
Current use of illicit drugs, %									
Use, any type	48.8 ± 1.7	31.3 ± 3.2[b]	54.4 ± 3.3[b]	43.3 ± 3.3[b]	65.1 ± 3.3	<0.001	41.0 ± 2.1	53.2 ± 2.4	<0.001
Missing	7.9 ± 0.8	10.3 ± 2.2	8.8 ± 1.8	8.0 ± 1.6	5.3 ± 1.1		11.1 ± 1.3	6.1 ± 1.1	
No. of participants	2574	668	511	792	603		1107	1467	
Body mass index, kg/m^2	29.7 ± 0.3	31.7 ± 0.6[b]	28.9 ± 0.4[b]	30.7 ± 0.6[b]	27.5 ± 0.5	<0.001	29.2 ± 0.3	30.0 ± 0.4	0.14
No. of participants	2574	668	511	792	603		1107	1467	
HEI-2010 total score	43.8 ± 0.4	47.6 ± 0.9[b]	44.3 ± 0.8[b]	42.6 ± 0.7	42.2 ± 0.7	<0.001	45.2 ± 0.6	43.0 ± 0.5	0.006
No. of participants	1996	506	382	640	468		856	1140	
Depressive symptoms									
CES-D score	13.8 ± 0.4	15.1 ± 0.7[b]	12.4 ± 0.6	14.8 ± 0.8[b]	12.4 ± 0.6	0.07	13.4 ± 0.4	14.0 ± 0.5	0.44
No. of participants	2558	663	508	787	600		1100	1458	
Diabetes, %	12.7 ± 1.1	23.5 ± 2.9[b]	19.8 ± 2.8[b]	7.0 ± 1.4	7.0 ± 1.8	<0.001	10.6 ± 1.3	13.9 ± 1.5	0.10
No. of participants	2404	626	482	737	559		1032	1372	
Hypertension, %	36.9 ± 1.7	57.0 ± 3.4[b]	53.6 ± 3.6[b]	30.1 ± 3.4[b]	18.8 ± 2.7	<0.001	27.3 ± 1.9	42.1 ± 2.5	<0.001
No. of participants	2281	605	461	693	522		981	1300	
Dyslipidemia, %	23.5 ± 1.4	37.0 ± 3.0[b]	35.3 ± 3.3[b]	14.2 ± 2.3	16.7 ± 2.9	<0.001	27.8 ± 2.0	21.2 ± 1.9	0.018
No. of participants	2282	602	463	694	523		982	1300	
Cardiovascular disease,[c] %	10.9 ± 1.0	20.1 ± 2.6[b]	16.6 ± 2.7[b]	7.9 ± 1.5	4.0 ± 1.4	<0.001	8.0 ± 1.1	12.4 ± 1.4	0.010
No. of participants	2410	626	483	738	563		1035	1375	
Season (visit 1)						0.97			
Winter	24.0 ± 1.5	22.8 ± 2.7	24.9 ± 3.2	25.3 ± 3.0	22.8 ± 3.0		16.0 ± 1.8	28.7 ± 2.2	<0.001
Spring	18.7 ± 1.2	21.7 ± 2.4	17.0 ± 2.2	17.6 ± 2.1	19.0 ± 2.5		14.2 ± 1.3	21.3 ± 1.7	
Summer	21.8 ± 1.4	21.6 ± 2.6	22.1 ± 2.7	22.6 ± 2.7	20.8 ± 2.7		30.5 ± 2.0	16.8 ± 1.8	
Fall	35.4 ± 1.7	33.9 ± 3.1	36.0 ± 3.2	34.4 ± 3.2	37.4 ± 3.4		39.4 ± 2.1	33.1 ± 2.4	
No. of participants	2570	668	509	791	601		1107	1467	
25(OH)D_{base}, continuous, ng/dL	20.2 ± 0.4	20.7 ± 0.8	21.3 ± 0.9	18.9 ± 0.9	20.6 ± 0.8	0.42	28.1 ± 0.6	15.5 ± 0.4	<0.001
No. of participants	1826	479	379	539	429		797	1029	
25(OH)D_{base}, categorical, ng/dL						0.061			<0.001
<11	18.9 ± 1.7	20.0 ± 3.2	15.6 ± 3.6	24.6 ± 3.5[b]	13.7 ± 2.8		3.1 ± 0.6	28.4 ± 2.6	
≥11	81.1 ± 1.7	80.0 ± 3.2	84.4 ± 3.6	75.4 ± 3.5	86.3 ± 2.8		96.9 ± 0.1	71.6 ± 2.6	
No. of participants	1826	479	379	539	429		797	1029	
Vitamin D intake, μg/d	3.88 ± 0.15	3.28 ± 0.18[b]	4.77 ± 0.40	3.16 ± 0.21[b]	4.67 ± 0.34	0.046	4.38 ± 0.24	3.60 ± 0.18	0.009
No. of participants	1996	506	382	640	468		856	1140	
Supplemental vitamin D, %									0.009
Nonuser	61.6 ± 2.0	51.5 ± 3.7[b]	66.8 ± 3.8	59.0 ± 3.9[b]	70.6 ± 3.7	<0.001	59.7 ± 2.4	62.7 ± 2.8	
Baseline user	10.5 ± 1.2	18.1 ± 2.5	10.1 ± 2.3	5.4 ± 1.8	11.7 ± 3.0		15.3 ± 1.7	7.9 ± 1.6	
Follow-up user	27.9 ± 1.9	30.5 ± 3.7	23.2 ± 3.4	35.6 ± 3.9	17.7 ± 2.7		25.0 ± 2.2	29.4 ± 2.7	
No. of participants	1825	481	338	597	409		749	1076	

Data are reported as weighted mean ± SE of the mean or percentage ± SE of the percentage.

Abbreviations: —, no data; CES-D, Center for Epidemiologic Studies-Depression; PIR, poverty income ratio; SE, standard error; WRAT, Wide Range Achievement Test.

[a]Largest sample size was 2574.

[b]$P < 0.05$. *P* value was based on linear regression models when row variable is continuous (svy:reg) and design-based *F* test when row variable is categorical (svy:tab), comparing each of the sex and age categories to the referent category of younger men.

[c]Cardiovascular disease included self-reported stroke, congestive heart failure, nonfatal myocardial infarction, or atrial fibrillation.

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Table 2. Cognitive Performance Test Scores at Baseline (Visit 1), Follow-Up (Visit 2), and Change Between Visits, by Age Group, Sex, and Race, for HANDLS Participants With Complete and Reliable Baseline and/or Follow-Up Cognitive Scores

	All	Older Women (>50 Y)	Older Men (>50 Y)	Younger Women (≤50 Y)	Younger Men (≤50 Y)	Whites	African Americans
MMSE, total score							
Visit 1	27.9 ± 0.1	27.8 ± 0.2	27.3 ± 0.2[a]	28.1 ± 0.1	28.0 ± 0.1	28.5 ± 0.1[b]	27.5 ± 0.1
No. of participants	2,574	668	511	792	603	1107	1467
Visit 2	28.0 ± 0.1	28.0 ± 0.1	27.6 ± 0.2[a]	28.2 ± 0.1	28.2 ± 0.1	28.6 ± 0.1[b]	27.7 ± 0.1
No. of participants	1934	506	341	653	434	767	1167
P (visit 2 − visit 1)	0.07	0.47	0.29	0.46	0.41	0.047	0.21
CVLT, List A							
Visit 1	25.1 ± 0.3	25.1 ± 0.4	22.7 ± 0.4[a]	27.1 ± 0.5[a]	24.2 ± 0.6	27.0 ± 0.4[b]	24.0 ± 0.4
No. of participants	2124	548	415	660	501	885	1239
Visit 2	20.1 ± 0.3	20.0 ± 0.4	16.5 ± 0.5[a]	21.9 ± 0.5[a]	20.2 ± 0.5	22.5 ± 0.4[b]	18.7 ± 0.3
No. of participants	1976	509	358	650	459	781	1195
P (visit 2 − visit 1)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
CVLT, free delayed recall							
Visit 1	7.4 ± 0.1	7.1 ± 0.2	6.4 ± 0.2[a]	8.2 ± 0.2[a]	7.2 ± 0.3	8.4 ± 0.2[b]	6.8 ± 0.2
No. of participants	2044	529	404	636	475	853	1191
Visit 2	5.8 ± 0.1	5.7 ± 0.2	4.2 ± 0.3[a]	6.5 ± 0.3	6.0 ± 0.2	7.2 ± 0.2[b]	5.1 ± 0.2
No. of participants	1846	481	327	606	432	719	1127
P (visit 2 − visit 1)	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	<0.001
BVRT							
Visit 1	5.6 ± 0.2	6.6 ± 0.4[a]	6.1 ± 0.3[a]	5.5 ± 0.3[a]	4.5 ± 0.3	4.9 ± 0.2[b]	6.0 ± 0.2
No. of participants	2537	653	503	785	596	1095	1442
Visit 2	7.6 ± 0.2	9.1 ± 0.3[a]	8.9 ± 0.4[a]	7.3 ± 0.3[a]	6.1 ± 0.3	6.2 ± 0.2[b]	8.4 ± 0.2
No. of participants	2085	532	382	692	479	816	1269
P (visit 2 − visit 1)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Brief Test of Attention							
Visit 1	6.8 ± 0.1	6.6 ± 0.2	6.5 ± 0.2	7.0 ± 0.2	6.7 ± 0.2	7.5 ± 0.1[b]	6.3 ± 0.1
No. of participants	2147	547	436	666	498	911	1236
Visit 2	6.6 ± 0.1	6.6 ± 0.1	6.3 ± 0.2	6.8 ± 0.2	6.7 ± 0.2	7.2 ± 0.1[b]	6.3 ± 0.1
No. of participants	1907	486	347	632	442	772	1,135
P (visit 2 − visit 1)	0.38	0.90	0.38	0.28	0.81	0.027	0.96
Animal fluency							
Visit 1	19.3 ± 0.2	18.3 ± 0.3[a]	19.0 ± 0.3[a]	19.0 ± 0.4[a]	20.5 ± 0.4	21.4 ± 0.3[b]	18.1 ± 0.3
No. of participants	2577	665	520	793	599	1109	1468
Visit 2	19.5 ± 0.2	18.5 ± 0.4[a]	19.2 ± 0.4[a]	19.3 ± 0.4[a]	20.7 ± 0.6	21.7 ± 0.3[b]	18.3 ± 0.3
No. of participants	2139	548	403	696	492	839	1300
P (visit 2 − visit 1)	0.59	0.61	0.74	0.71	0.85	0.58	0.60
Digits span, forward							
Visit 1	7.4 ± 0.1	7.1 ± 0.1[a]	7.4 ± 0.2	7.6 ± 0.1	7.5 ± 0.2	8.1 ± 0.1[b]	7.1 ± 0.1
No. of participants	2524	643	505	781	595	1,081	1443
Visit 2	7.5 ± 0.1	7.0 ± 0.1[a]	7.2 ± 0.2[a]	7.7 ± 0.2	7.8 ± 0.2	8.2 ± 0.1[b]	7.1 ± 0.1
No. of participants	1971	499	372	643	457	760	1211
P (visit 2 − visit 1)	0.65	0.53	0.35	0.51	0.37	0.29	0.94
Digits span, backward							
Visit 1	5.8 ± 0.1	5.7 ± 0.1	5.6 ± 0.2	5.9 ± 0.1	5.9 ± 0.2	6.7 ± 0.1[b]	5.3 ± 0.1
No. of participants	2505	635	501	777	592	1079	1426
Visit 2	5.8 ± 0.1	5.6 ± 0.2	5.4 ± 0.2[a]	5.9 ± 0.1	6.0 ± 0.2	6.7 ± 0.1[b]	5.3 ± 0.1
No. of participants	1965	499	370	642	454	755	1,210
P (visit 2 − visit 1)	0.81	0.85	0.30	0.97	0.73	0.98	0.94
Clock-drawing test							
Visit 1	8.8 ± 0.0	8.6 ± 0.1[a]	8.9 ± 0.1	8.8 ± 0.1	8.9 ± 0.1	9.0 ± 0.0[b]	8.7 ± 0.1
No. of participants	2582	661	515	800	606	1117	1465
Visit 2	8.8 ± 0.0	8.7 ± 0.1	8.7 ± 0.1	8.8 ± 0.1	8.9 ± 0.1	9.0 ± 0.1[b]	8.6 ± 0.1
No. of participants	2104	539	386	692	487	829	1275
P (visit 2 − visit 1)	0.82	0.34	0.19	0.73	0.90	0.91	0.93
Trailmaking test, part A							
Visit 1	34.3 ± 0.6	40.8 ± 2.0[a]	38.2 ± 1.0[a]	30.3 ± 0.8	31.7 ± 0.9	29.0 ± 0.4[b]	37.5 ± 0.9
No. of participants	2466	640	476	771	579	1074	1392
Visit 2	36.5 ± 1.4	44.4 ± 5.5	41.0 ± 1.5[a]	30.9 ± 0.8	34.7 ± 2.5	29.9 ± 0.7[b]	40.0 ± 2.1
No. of participants	1874	492	339	619	424	774	1,100

(*Continued*)

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Table 2. Continued

	All	Older Women (>50 Y)	Older Men (>50 Y)	Younger Women (≤50 Y)	Younger Men (≤50 Y)	Whites	African Americans
P (visit 2 − visit 1)	0.15	0.54	0.54	0.61	0.25	0.29	0.26
Trailmaking test, part B							
Visit 1	130.2 ± 4.5	154.8 ± 8.9[a]	154.8 ± 10.3[a]	109.7 ± 6.5	120.4 ± 10.5	87.9 ± 3.4[b]	155.3 ± 6.7
No. of participants	2465	640	476	770	579	1074	1391
Visit 2	127.9 ± 5.8	136.4 ± 9.4	154.4 ± 13.9[a]	120.2 ± 10.8	114.2 ± 11.5	77.2 ± 2.3[b]	156.0 ± 8.6
No. of participants	1728	445	306	578	399	724	1004
P (visit 2 − visit 1)	0.75	0.16	0.98	0.41	0.69	0.009	0.96

Most cognitive test scores were in the direction of higher score equals better performance, except for BVRT (total errors) and trailmaking test (both parts; expressed in seconds).

Abbreviation: BVRT, Benton Visual Retention Test. See Table 1 legend for expansion of other abbreviations.

[a] $P < 0.05$ for null hypothesis of no difference in means of cognitive test scores by sex and age group within each visit (referent category: younger men). Wald test from svy:reg command.

[b] $P < 0.05$ for null hypothesis of no difference in means of cognitive test scores by race within each visit (referent category: whites). Wald test from svy:reg command.

Discussion

Key findings

The current study examined associations of vitamin D status and intakes with the cognitive trajectory among US urban adults, focusing on longitudinal change in various domains of cognition. Our analysis was stratified by age group and sex, as well as by race. Several key findings emerged. Importantly, when examining cognitive change (type I error corrected to 0.009) in relation to serum 25(OH)D level, a higher baseline serum 25(OH)D level was linked to a slower rate of decline in a test of verbal fluency (animal fluency test), overall and among men. This finding was replicated with the dietary and supplemental exposures of vitamin D at baseline, though it did not survive correction for multiple testing. Another key finding was that among whites, dietary vitamin D was associated with a slower rate of decline on a test of visual memory/visuoconstruction abilities, an association not found among African Americans, with a significant interaction by race. Equally notable is the positive association between dietary vitamin D and the rate of change in verbal memory (both immediate and delayed) among younger women. Finally, the use of supplements with vitamin D during follow-up was related to slower rate of decline in animal fluency among older women and African Americans, with some cross-sectional but inconsistent association with baseline performance in domains of verbal memory, attention, and working memory.

Previous studies: literature review

At least 14 previous cohort studies examined longitudinal relationships of vitamin D status or intake with cognitive performance over time. Of those selected studies, 11 indicated a significant finding in the hypothesized direction (9–19), whereas three were null studies (50–52). Although many of those studies had a unidimensional cognitive outcome (*e.g.*, incident AD, dementia, or global cognitive performance, impairment, or decline), their findings are notable. For instance, a large cohort study of older women aged 76 to 82 years at baseline found that the onset of non-AD dementia after a 7-year follow-up was directly related to vitamin D deficiency at baseline (11). Conversely, in the same cohort, it was found that lower baseline vitamin D intake was linked to earlier onset of AD-type dementia among older women (12). In the Nurse's Health Study (1185 women aged ≥60 years), although 25(OH)D level at baseline was associated with better cognitive function, a decade later, the study failed to find an association between baseline serum 25(OH)D level and cognitive decline over the course of 6 years (10). Moreover, another recent cohort study of German older adults (n = 572 men and women, aged ≥70 years at baseline) concluded there was a trend of a more pronounced cognitive decline with lower serum vitamin D levels, comparing the difference in performance on the Cognitive Telephone Screening Instrument [score (follow-up) − score(baseline)] across quintiles of serum 25(OH)D levels (9). Furthermore, among the more recent and larger studies (n = 6257 US women; mean age, 76.6 years), a lower baseline 25(OH)D level was associated with higher odds of cognitive impairment at baseline as well as higher odds of global cognitive decline over 4 years (17). Some of the cognitive domains that were shown to be influenced by 25(OH)D or vitamin D intake in a cohort study setting were immediate word recall (19), episodic memory (17), visual memory (18), and executive function (17).

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Table 3. Cognitive Performance Test Scores by Serum 25(OH)D Concentration, Stratified by Age Group, Sex, and Race, for HANDLS Participants With Complete and Reliable Baseline and/or Follow-Up Cognitive Scores: Mixed-Effects Regression Models

	All	Older Women (>50 Y)	Older Men (>50 Y)	Younger Women (≤50 Y)	Younger Men (≤50 Y)	Whites	African Americans
MMSE, total score							
Intercept	+26.9 ± 0.2[a]	+28.3 ± 0.4[a]	+25.7 ± 0.5[a]	+27.3 ± 0.4[a]	+26.7 ± 0.7[a]	+27.0 ± 0.3[a]	+26.4 ± 0.4[a]
Time	+0.04 ± 0.06	−0.17 ± 0.13	+0.19 ± 0.17	+0.03 ± 0.10	−0.08 ± 0.18	+0.02 ± 0.09	+0.07 ± 0.09
25(OH)D	−0.00 ± 0.01	−0.02 ± 0.01[a]	+0.04 ± 0.01[a]	+0.00 ± 0.01	−0.01 ± 0.01	+0.00 ± 0.01	+0.00 ± 0.01
25(OH)D × time	+0.000 ± 0.001	+0.004 ± 0.003	−0.008 ± 0.004	+0.002 ± 0.002	+0.000 ± 0.003	+0.000 ± 0.002	+0.000 ± 0.002
No.; κ value	1308; 1.7	341; 1.7	275; 1.6	392; 1.7	300; 1.6	567; 1.6	741; 1.7
CVLT, List A							
Intercept	+25.3 ± 0.8[a]	+26.0 ± 1.6[a]	+21.5 ± 1.6[a]	+22.6 ± 3.9[a]	+20.6 ± 2.4[a]	+25.5 ± 1.2[a]	+23.4 ± 1.1[a]
Time	−1.54 ± 0.20[a]	−1.54 ± 0.42[a]	−1.85 ± 0.39[a]	−1.27 ± 0.88	−1.13 ± 0.04	−1.49 ± 0.32[a]	−1.45 ± 0.25[a]
25(OH)D	−0.03 ± 0.02	−0.03 ± 0.03	+0.02 ± 0.04	−0.05 ± 0.04	−0.05 ± 0.04	−0.04 ± 0.03	+0.02 ± 0.03
25(OH)D × time	−0.003 ± 0.005	+0.002 ± 0.009	−0.020 ± 0.011	+0.007 ± 0.008	−0.003 ± 0.011	−0.001 ± 0.007	−0.008 ± 0.007
No.; κ value	1254; 1.6	327; 1.6	261; 1.5	382; 1.6	284; 1.6	541; 1.6	713; 1.6
CVLT, free delayed recall							
Intercept	+8.0 ± 0.4[a]	+7.6 ± 0.8[a]	+5.8 ± 0.7[a]	+8.4 ± 0.8[a]	+6.0 ± 1.2[a]	+8.3 ± 0.6[a]	+7.2 ± 0.5[a]
Time	−0.51 ± 0.09[a]	−0.56 ± 0.21[a]	−0.40 ± 0.18[a]	−0.64 ± 0.17[a]	−0.47 ± 0.35	−0.52 ± 0.15[a]	−0.55 ± 0.12[a]
25(OH)D	−0.01 ± 0.01	−0.01 ± 0.02	+0.05 ± 0.02[a,c]	−0.01 ± 0.02	−0.02 ± 0.02	−0.01 ± 0.01	+0.01 ± 0.01
25(OH)D × time	−0.000 ± 0.002	+0.001 ± 0.004	−0.011 ± 0.005[a]	+0.004 ± 0.004	+0.003 ± 0.006	−0.000 ± 0.003	−0.003 ± 0.003
No.; κ value	1231; 1.6	322; 1.6	252; 1.5	378; 1.6	279; 1.5	525; 1.5	706; 1.6
BVRT							
Intercept	+9.0 ± 0.6[a]	+8.9 ± 1.3[a]	+8.5 ± 1.3[a]	+8.3 ± 1.1[a]	+7.6 ± 1.7[a]	+8.6 ± 0.6[a]	+9.3 ± 0.9[a]
Time	+0.35 ± 0.15[a]	+0.31 ± 0.38	+0.18 ± 0.30	+0.44 ± 0.24	+0.97 ± 0.46[a]	+0.32 ± 0.20	+0.75 ± 0.21[a]
25(OH)D	−0.01 ± 0.01	+0.00 ± 0.03	−0.02 ± 0.03	−0.00 ± 0.02	−0.01 ± 0.03	+0.00 ± 0.00	−0.04 ± 0.02
25(OH)D × time	+0.002 ± 0.003	−0.002 ± 0.008	+0.005 ± 0.008	+0.001 ± 0.006	−0.003 ± 0.008	+0.002 ± 0.004	+0.004 ± 0.006
No.; κ value	1311; 1.7	340; 1.7	277; 1.6	393; 1.8	301; 1.7	568; 1.7	743; 1.7
Brief Test of Attention							
Intercept	+6.6 ± 0.3[a]	+7.2 ± 0.6[a]	+6.5 ± 0.6[a]	+6.3 ± 0.6[a]	+6.4 ± 0.9[a]	+6.8 ± 0.4[a]	+5.8 ± 0.4[a]
Time	−0.06 ± 0.07	−0.22 ± 0.15	−0.01 ± 0.15	+0.10 ± 0.13	−0.20 ± 0.27	−0.10 ± 0.11	−0.02 ± 0.10
25(OH)D	+0.00 ± 0.01	−0.01 ± 0.01	+0.02 ± 0.02	+0.00 ± 0.01	+0.01 ± 0.01	+0.00 ± 0.01	+0.01 ± 0.01
25(OH)D × time	+0.001 ± 0.002	+0.005 ± 0.003	−0.006 ± 0.004	+0.001 ± 0.003	−0.002 ± 0.004	+0.002 ± 0.002	−0.001 ± 0.003
No.; κ value	1269; 1.6	330; 1.6	266; 1.6	382; 1.7	291; 1.6	543; 1.6	726; 1.6
Animal fluency							
Intercept	+17.6 ± 0.6[a]	+16.6 ± 1.2[a]	+15.1 ± 1.3[a]	+19.3 ± 1.2[a]	+19.1 ± 2.1[a]	17.2 ± 0.9[a]	+16.8 ± 0.9[a]
Time	−0.10 ± 0.14	+0.75 ± 0.33[a]	+0.19 ± 0.31	-0.61 ± 0.24[a]	−1.16 ± 0.51[a]	+0.02 ± 0.24	−0.15 ± 0.18
25(OH)D	−0.02 ± 0.02	+0.01 ± 0.02	−0.02 ± 0.04	−0.00 ± 0.03	−0.09 ± 0.04[a]	−0.03 ± 0.02	+0.01 ± 0.02
25(OH)D × time	+0.011 ± 0.003[a,c]	+0.010 ± 0.006	+0.019 ± 0.008[a]	+0.007 ± 0.006	+0.021 ± 0.009[a]	+0.012 ± 0.005[a]	+0.012 ± 0.005[a]
No.; κ value	1317; 1.7	342; 1.7	281; 1.7	394; 1.7	300; 1.7	569; 1.7	748; 1.7
Digits span, forward							
Intercept	+6.9 ± 0.3[a]	+6.8 ± 0.5[a]	+7.1 ± 0.5[a]	+6.5 ± 0.5[a]	+8.3 ± 0.9[a]	+7.1 ± 0.4[a]	+6.3 ± 0.4[a]
Time	−0.02 ± 0.01	−0.02 ± 0.12	−0.01 ± 0.11	−0.09 ± 0.11	−0.12 ± 0.21	−0.08 ± 0.10	−0.02 ± 0.07
25(OH)D	−0.01 ± 0.01	+0.00 ± 0.01	−0.01 ± 0.01	−0.01 ± 0.01	−0.02 ± 0.02	−0.01 ± 0.01	−0.00 ± 0.01
25(OH)D × time	−0.002 ± 0.001	+0.002 ± 0.002	-0.007 ± 0.003[a]	−0.002 ± 0.002	−0.004 ± 0.004	−0.003 ± 0.002	−0.001 ± 0.002
No.; κ value	1309; 1.7	340; 1.7	276; 1.6	394; 1.7	299; 1.6	563; 1.6	746; 1.7
Digits span, backward							
Intercept	−6.2 ± 12.3	+37.1 ± 40.1	−3.3 ± 42.8	−1.38 ± 26.4	−28.4 ± 33.8	−15.4 ± 19.6	+2.00 ± 16.61
Time	+0.28 ± 2.97	−5.4 ± 11.7	−7.3 ± 11.0	+10.3 ± 6.0	+7.92 ± 7.53	+2.97 ± 4.63	−3.43 ± 4.18
25(OH)D	−0.01 ± 0.01	−0.003 ± 0.010	−0.004 ± 0.012	−0.006 ± 0.010	−0.013 ± 0.014	−0.010 ± 0.008	−0.002 ± 0.008
25(OH)D × time	−0.002 ± 0.001	−0.003 ± 0.003	−0.002 ± 0.003	−0.003 ± 0.002	−0.002 ± 0.004	−0.003 ± 0.002	−0.002 ± 0.002
No.; κ value	1312; 1.6	340; 1.6	276; 1.6	395; 1.7	301; 1.6	566; 1.6	746; 1.7
Clock-drawing test							
Intercept	+8.81 ± 0.15[a]	+8.86 ± 0.31[a]	+8.88 ± 0.31[a]	+8.83 ± 0.28[a]	+9.11 ± 0.47[a]	+9.01 ± 0.21[a]	+8.24 ± 0.23[a]
Time	−0.07 ± 0.04	−0.17 ± 0.09	−0.12 ± 0.10	−0.05 ± 0.07	−0.08 ± 0.15	−0.09 ± 0.07	−0.00 ± 0.06
25(OH)D	−0.00 ± 0.00	−0.00 ± 0.01	+0.01 ± 0.01	−0.01 ± 0.01	+0.00 ± 0.01	+0.00 ± 0.00	−0.00 ± 0.00
25(OH)D × time	+0.001 ± 0.001	+0.001 ± 0.002[b]	+0.002 ± 0.002	+0.004 ± 0.002[a,b]	−0.008 ± 0.002[a,c]	+0.001 ± 0.001	+0.002 ± 0.002
No.; κ value	1314; 1.7	340; 1.7	276; 1.6	395; 1.7	303; 1.7	570; 1.7	744; 1.7
Trailmaking test, part A							
Intercept	+31.9 ± 4.0[a]	+27.3 ± 27.1	+40.2 ± 9.8[a]	+39.0 ± 12.0[a]	+41.0 ± 12.5[a]	+23.7 ± 3.2[a]	+36.1 ± 8.2[a]
Time	+2.27 ± 1.33	+2.33 ± 9.28	+0.72 ± 3.04	−4.06 ± 3.09	+1.41 ± 4.45	+1.02 ± 0.77	2.78 ± 2.28
25(OH)D	+0.17 ± 0.09	+0.53 ± 0.25[a]	−0.05 ± 0.25	+0.07 ± 0.07	−0.13 ± 0.22	+0.03 ± 0.05	+0.26 ± 0.19
25(OH)D × time	−0.025 ± 0.032	−0.078 ± 0.086	−0.025 ± 0.082	−0.024 ± 0.017	−0.027 ± 0.077	−0.004 ± 0.012	−0.055 ± 0.058
No.; κ value	1296; 1.7	337; 1.7	265; 1.7	393; 1.7	296; 1.7	561; 1.7	735; 1.7
Trailmaking test, part B							
Intercept	+230 ± 55.7	+53.5 ± 224.9	+721.1 ± 203.8[a]	+60.0 ± 101.3	+223.7 ± 72.5[a]	+130.2 ± 81.5	+272.9 ± 41.6[a]
Time	+14.2 ± 12.7	+87.3 ± 57.3	−17.7 ± 48.7	+25.5 ± 27.3	+11.1 ± 12.3	−2.41 ± 18.30	+15.1 ± 9.1
25(OH)D	+0.28 ± 0.40	+0.14 ± 0.80	−0.47 ± 0.99	+0.66 ± 0.62	−0.73 ± 0.81	+0.35 ± 0.43	−0.19 ± 0.67

(*Continued*)

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Table 3. Continued

	All	Older Women (>50 Y)	Older Men (>50 Y)	Younger Women (≤50 Y)	Younger Men (≤50 Y)	Whites	African Americans
25(OH)D × time	−0.110 ± 0.088	+0.059 ± 0.203	−0.157 ± 0.233	−0.293 ± 0.129[a]	+0.039 ± 0.131	−0.080 ± 0.087	−0.096 ± 0.151
No.; κ value	1287; 1.6	337; 1.7	263; 1.6	391; 1.7	296; 1.7	558; 1.6	729; 1.6

Most cognitive test scores were in the direction of higher score equals better performance, except for BVRT (total errors) and the trailmaking test (both parts; expressed in seconds). 25(OH)D was centered at 20. Models were controlled for age (centered at 50 years), race, poverty status, education, marital status, literacy, current smoking status, current drug use, body mass index (centered at 30 kg/m^2), CES-D total score (centered at 15), HEI-2010 (centered at 40), self-reported diabetes, hypertension, high cholesterol level, cardiovascular disease, season, and the inverse mills ratio. All covariates were interacted with time. All inverse mills ratios were centered at zero, except for the digit span backwards test and trailmaking tests parts A and B, for which the inverse mills ratio was centered at its mean.

Abbreviations: See Table 1 and 2 legends for expansion of abbreviations.

[a] $P < 0.05$ for null hypothesis that $\gamma = 0$.

[b] $P < 0.05$ for null hypothesis of no by sex and age group, based on three- and four-way interaction terms with 25(OH)D and time.

[c] $P < 0.009$ for null hypothesis that $\gamma = 0$ for interaction between 25(OH)D and time.

[d] $P < 0.05$ for null hypothesis of no by race, based on two- and three-way interaction terms with 25(OH)D and time.

To our knowledge, at least 33 cross-sectional, retrospective, case-control and chart review studies testing this same hypothesis were conducted over a decade or so, and covering various populations of interest, with focus on older adults aged 60 to 70 years or older at baseline. However, only about 16 of those had a relatively large sample size (n > 1000), and thus had comparable statistical power to our present study (20–34, 53). Among those, 15 found direct relationships between 25(OH)D level and cognitive performance or an inverse relationship with impairment. In contrast, only one failed to detect an association (53). Although most studies included a global measure of cognitive performance, others examined specific domains of cognition. For instance, Lee *et al.* (22) showed that among middle-aged and older men, lower 25(OH)D level was specifically linked to poorer performance on the digits symbol substitution test, a measure of psychomotor speed. Among women, another smaller study of middle-aged and older adults (n = 387) suggested that low 25(OH)D level was associated with reduced spatial working memory capacity (54). Finally, other studies found this result in domains of verbal episodic memory, visual memory, short-term and working memory, semantic memory, orientation in time, executive function, attention, processing, and motor speed (26, 27, 29–34, 55).

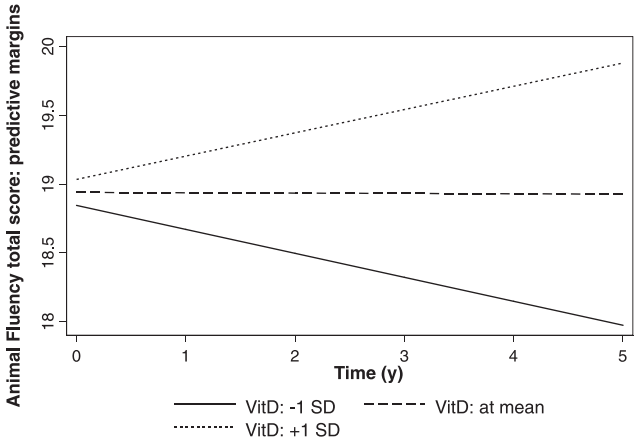

Figure 1. Predictive margins for animal fluency by standardized vitamin D score over time according to mixed-effects regression models of the total population. VitD, vitamin D.

Strengths and limitations

Our study has several notable strengths, including its large sample size that allowed stratified analyses by sex, age, and race, its longitudinal design to ascertain temporality of associations, and the use of cognitive tests that spanned many domains of cognition. Our study also controlled for potential key confounders and made use of advanced multivariable techniques, including mixed-effects regression models that considered sample selectivity. Moreover, sampling weights were considered in our descriptive analyses, whereas part of the main analysis included a summary measure for vitamin D exposure.

Nevertheless, our study findings should be interpreted in light of key limitations. First, although major potentially confounding variables were adjusted for, residual confounding cannot be ruled out. Furthermore, only two time points were available for our longitudinal analyses, which, though an improvement over cross-sectional analyses, may be limited compared with having more than three time points. Thus, our key finding of a significant relationship between higher vitamin D status or intake and cognitive decline can possibly be the result of random fluctuation in performance rather than true decline. This random fluctuation is a result of reliability in the instrument itself and may

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Table 4. Cognitive Performance Test Scores by Dietary Vitamin D Intake (Vitamin Ddiet), Stratified by Age Group, Sex, and Race, for HANDLS Participants With Complete and Reliable Baseline and/or Follow-Up Cognitive Scores: Mixed-Effects Regression Models

	All	Older Women (>50 Y)	Older Men (>50 Y)	Younger Women (≤50 Y)	Younger Men (≤50 Y)	Whites	African Americans
MMSE, total score							
Intercept	+26.9 ± 0.2[a]	+28.1 ± 0.4[a]	+26.2 ± 0.5[a]	+27.4 ± 0.3[a]	+25.6 ± 0.6[a]	+27.2 ± 0.2[a]	+26.6 ± 0.3[a]
Time	+0.06 ± 0.06	−0.08 ± 0.13	+0.15 ± 0.15	+0.02 ± 0.09	+0.22 ± 0.14	+0.04 ± 0.08	+0.04 ± 0.02
VitDdiet	+0.02 ± 0.01	−0.01 ± 0.01	+0.05 ± 0.03	+0.02 ± 0.02	+0.02 ± 0.01	−0.002 ± 0.013	+0.04 ± 0.02[a]
VitDdiet × time	−0.004 ± 0.003	−0.011 ± 0.008	−0.013 ± 0.008	−0.006 ± 0.006	+0.001 ± 0.004	−0.000 ± 0.004	-0.008 ± 0.004[a]
No.; κ value	1796; 1.6	459; 1.7	356; 1.6	568; 1.7	413; 1.6	767; 1.6	1029; 1.7
CVLT, List A							
Intercept	+24.6 ± 0.7[a]	+25.1 ± 1.5[a]	+21.6 ± 1.4[a]	+21.8 ± 2.0[a]	+21.8 ± 2.0[a]	+25.2 ± 1.0[a]	+22.2 ± 1.0[a]
Time	−1.48 ± 0.2[a]	−1.42 ± 0.38[a]	−1.90 ± 0.34[a]	−1.66 ± 0.73[a]	−0.97 ± 0.58	−1.50 ± 0.07[a]	−1.27 ± 0.22[a]
VitDdiet	−0.07 ± 0.04	+0.09 ± 0.09	−0.03 ± 0.09	−0.31 ± 0.10[a,b]	−0.00 ± 0.06	−0.11 ± 0.07	−0.04 ± 0.05
VitDdiet × time	+0.017 ± 0.009	−0.012 ± 0.024	−0.035 ± 0.020	+0.061 ± 0.021[a,c]	+0.013 ± 0.015	+0.031 ± 0.018	+0.010 ± 0.012
No.; κ value	1720; k=1.6	441; 1.6	337; 1.5	550; 1.6	392; 1.6	730; 1.5	990; 1.6
CVLT, free delayed recall							
Intercept	+7.7 ± 0.3[a]	+7.6 ± 0.8[a]	+6.3 ± 0.6[a]	+6.8 ± 1.0[a]	+6.8 ± 1.0[a]	+7.8 ± 0.5[a]	+6.8 ± 0.5[a]
Time	−0.49 ± 0.08[a]	−0.61 ± 0.18[a]	−0.54 ± 0.16[a]	−0.44 ± 0.15[a]	−0.65 ± 0.27[a]	−0.46 ± 0.13[a]	−0.51 ± 0.11[a]
VitDdiet	−0.03 ± 0.00	+0.01 ± 0.04	−0.01 ± 0.01	−0.15 ± 0.05[a,b]	+0.03 ± 0.03	−0.03 ± 0.03	−0.02 ± 0.02
VitDdiet × time	+0.011 ± 0.005[a]	+0.005 ± 0.011	+0.006 ± 0.010	+0.028 ± 0.010[a,c]	+0.002 ± 0.008	+0.011 ± 0.009	+0.010 ± 0.006
No.; κ value	1685; 1.5	435; 1.6	324; 1.5	543; 1.6	383; 1.5	709; 1.5	976; 1.6
BVRT							
Intercept	+8.6 ± 0.5[a]	+8.5 ± 1.2[a]	+8.3 ± 1.2[a]	+8.0 ± 1.0[a]	+6.8 ± 1.3[a]	+8.0 ± 0.7[a]	+9.1 ± 0.8[a]
Time	+0.42 ± 0.13[a]	+0.29 ± 0.33	+0.21 ± 0.28	+0.61 ± 0.21[a]	+0.80 ± 0.34[a]	+0.28 ± 0.17	+0.85 ± 0.18[a]
VitDdiet	−0.03 ± 0.03	−0.04 ± 0.07	−0.07 ± 0.07	+0.05 ± 0.06	−0.05 ± 0.04	+0.01 ± 0.04	−0.07 ± 0.04
VitDdiet × time	−0.008 ± 0.007	−0.022 ± 0.021	−0.018 ± 0.016	−0.020 ± 0.014	+0.007 ± 0.010	−0.044 ± 0.010[a,c,d]	+0.014 ± 0.010
No.; κ value	1800; 1.7	458; 1.7	356; 1.6	570; 1.7	416; 1.7	770; 1.7	1030; 1.7
Brief Test of Attention							
Intercept	+6.6 ± 0.3[a]	+6.9 ± 0.5[a]	+6.6 ± 0.53[a]	+6.5 ± 0.5[a]	+5.5 ± 0.7[a]	+6.7 ± 0.3[a]	+5.9 ± 0.4[a]
Time	−0.10 ± 0.06	−0.17 ± 0.14	−0.03 ± 0.15	+0.01 ± 0.11	+0.03 ± 0.19	−0.09 ± 0.09	−0.07 ± 0.09
VitDdiet	+0.01 ± 0.01	+0.01 ± 0.01	+0.02+±0.03	−0.02 ± 0.03	+0.02 ± 0.02	+0.01 ± 0.02	+0.02 ± 0.02
VitDdiet × time	+0.000 ± 0.003	+0.012 ± 0.009	−0.007 ± 0.008	+0.007 ± 0.007	+0.001 ± 0.005	+0.005 ± 0.006	−0.003 ± 0.004
No.; κ value	1730; 1.6	439; 1.6	343; 1.5	548; 1.6	400; 1.6	733; 1.6	997; 1.6
Animal fluency							
Intercept	+17.3 ± 0.6[a]	+17.3 ± 0.6[a]	+15.1 ± 1.2[a]	+18.0 ± 1.1[a]	+19.1 ± 1.7[a]	+19.1 ± 1.7[a]	+16.3 ± 0.8[a]
Time	−0.06 ± 0.12	+0.50 ± 0.26	+0.32 ± 0.27	−0.31 ± 0.22	−0.79 ± 0.38[a]	+0.08 ± 0.20	−0.14 ± 0.16
VitDdiet	+0.01 ± 0.03	+0.09 ± 0.07	−0.03 ± 0.07	+0.02 ± 0.07	−0.02 ± 0.05	+0.07 ± 0.04[d]	−0.05 ± 0.04
VitDdiet × time	+0.015 ± 0.007[a]	−0.001 ± 0.017	+0.02 ± 0.01	+0.004 ± 0.014	+0.018 ± 0.011	+0.025 ± 0.012[a]	+0.012 ± 0.008
No.; κ value	1809; 1.7	461; 1.7	363; 1.7	570; 1.7	415; 1.7	771; 1.7	1038; 1.7
Digits span, forward							
Intercept	+6.9 ± 0.2[a]	+6.9 ± 0.4[a]	+6.9 ± 0.5[a]	+6.6 ± 0.4[a]	+7.7 ± 0.7[a]	+7.0 ± 0.3[a]	+6.6 ± 0.3[a]
Time	−0.01 ± 0.05	+0.01 ± 0.10	−0.01 ± 0.11	−0.15 ± 0.10	+0.01 ± 0.16	−0.03 ± 0.09	−0.03 ± 0.06
VitDdiet	+0.01 ± 0.01	+0.03 ± 0.03	−0.01 ± 0.03	+0.01 ± 0.03	+0.01 ± 0.02	+0.00 ± 0.02	+0.01 ± 0.02
VitDdiet × time	−0.001 ± 0.003	−0.005 ± 0.007	−0.007 ± 0.006	+0.000 ± 0.007	+0.002 ± 0.004	+0.003 ± 0.05	−0.003 ± 0.003
No.; κ value	1801; 1.6	457; 1.7	357; 1.6	571; 1.7	416; 1.6	764; 1.6	1037; 1.7
Digits span, backward							
Intercept	−6.8 ± 10.1	+52.9 ± 32.2	+13.9 ± 39.4	−5.3 ± 21.9	−31.8 ± 29.2	−7.7 ± 16.3	+0.23 ± 6.30
Time	+1.06 ± 2.50	−10.2 ± 9.2	−3.9 ± 9.8	+6.0 ± 5.1	+9.6 ± 6.4	−1.3 ± 4.1	+0.53 ± 1.59
VitDdiet	+0.00 ± 0.01	+0.00 ± 0.03	+0.02 ± 0.03	−0.02 ± 0.03	+0.00 ± 0.02	−0.00 ± 0.02	+0.00 ± 0.02
VitDdiet × time	+0.004 ± 0.03	−0.004 ± 0.008	−0.011 ± 0.006	+0.008 ± 0.005[e]	+0.010 ± 0.004[a]	+0.006 ± 0.005	+0.002 ± 0.003
No.; κ value	1803; 1.6	457; 1.7	357; 1.6	572; 1.7	417; 1.6	766; 1.6	1037; 1.7
Clock-drawing test							
Intercept	+8.7 ± 0.1[a]	+9.0 ± 0.3[a]	+8.8 ± 0.3[a]	+9.0 ± 0.2[a]	+8.4 ± 0.4[a]	9.0 ± 0.2[a]	+8.3 ± 0.2[a]
Time	−0.06 ± 0.04	−0.22 ± 0.08[a]	−0.02 ± 0.02	−0.04 ± 0.07	+0.05 ± 0.11	−0.06 ± 0.06	−0.05 ± 0.05
VitDdiet	−0.00 ± 0.01	+0.01 ± 0.02	+0.02 ± 0.02	−0.00 ± 0.02	−0.01 ± 0.01	−0.01 ± 0.01	+0.01 ± 0.01
VitDdiet × time	+0.002 ± 0.002	+0.006 ± 0.005	−0.004 ± 0.005	+0.006 ± 0.004	+0.002 ± 0.003	+0.002 ± 0.003	+0.001 ± 0.003
No.; κ value	1802; 1.7	458; 1.7	354; 1.7	571; 1.7	419; 1.7	772; 1.7	1030; 1.7
Trailmaking test, part A							
Intercept	+33.3 ± 4.2[a]	−37.0 ± 20.7	+39.5 ± 8.3[a]	+38.8 ± 19.3[a]	+38.8 ± 11.3[a]	+21.4 ± 2.8[a]	+42.2 ± 7.9[a]
Time	+2.8 ± 1.3[a]	+22.9 ± 7.6[a]	+0.49 ± 2.49	−4.12 ± 5.91	+2.63 ± 3.83	+0.93 ± 0.66	+4.11 ± 2.21
VitDdiet	−0.19 ± 0.21	+0.00 ± 0.61	−0.29 ± 0.46	+0.05 ± 0.33	−0.17 ± 0.31	−0.06 ± 0.10	−0.30 ± 0.39
VitDdiet × time	+0.020 ± 0.067	−0.264 ± 0.232	+0.123 ± 0.135	+0.11 ± 0.10	+0.018 ± 0.108	+0.003 ± 0.030	+0.025 ± 0.111
No.; κ value	1780; 1.7	458; 1.7	341; 1.6	569; 1.7	409; 1.6	761; 1.7	1019; 1.7
Trailmaking test, part B							
Intercept	+180.9 ± 34.8[a]	+168.8 ± 200.0	+828.7 ± 180.0[a]	+106.7 ± 83.5[a]	+180.1 ± 60.4[a]	+102.2 ± 61.5	+269.8 ± 27.9[a]
Time	+15.6 ± 10.8	+87.6 ± 46.5	−70.9 ± 40.8	+45.5 ± 26.0	+22.8 ± 11.6[a]	+7.9 ± 16.6	+15.0 ± 7.9
VitDdiet	−0.84 ± 0.80	−2.82 ± 2.06	−0.06 ± 2.00	+3.49 ± 1.67[a]	−2.1 ± 1.0[a]	−1.08 ± 0.91	−0.62 ± 1.22

(*Continued*)

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Table 4. Continued

	All	Older Women (>50 Y)	Older Men (>50 Y)	Younger Women (≤50 Y)	Younger Men (≤50 Y)	Whites	African Americans
VitDdiet × time	+0.214 ± 0.183	+1.095 ± 0.531[a]	+0.599 ± 0.429	−0.346 ± 0.402	−0.061 ± 0.197	+0.073 ± 0.232	+0.290 ± 0.260
No.; κ value	1766; 1.6	455; 1.6	337; 1.6	565; 1.7	409; 1.6	757; 1.6	1009; 1.6

Most cognitive test scores were in the direction of higher score equals better performance, except for BVRT (total errors) and the trailmaking test (both parts; expressed in seconds). Vitamin D intake was centered at 4. Models were controlled for age (centered at 50 years), race, poverty status, education, marital status, literacy, current smoking status, current drug use, body mass index (body mass index, centered at 30 kg/m^2), CES-D total score (centered at 15), HEI-2010 (centered at 40), self-reported diabetes, hypertension, high cholesterol level, cardiovascular disease, season, and the inverse mills ratio. All covariates were interacted with time. All inverse mills ratios were centered at zero, except for the digit span backward and trailmaking tests parts A and B, for which the inverse mills ratio was centered at its mean.

Abbreviations: See Table 1 and 2 legends for expansion of abbreviations.

[a] $P < 0.05$ for null hypothesis that $\gamma = 0$.

[b] $P < 0.004$ for null hypothesis that $\gamma = 0$ for main effect vitamin D_{diet}.

[c] $P < 0.009$ for null hypothesis that $\gamma = 0$ for interaction between vitamin D_{diet} and time.

[d] $P < 0.05$ for null hypothesis of no by race, based on two- and three-way interaction terms with vitamin D_{diet} and time.

also differ across study groups. Until additional studies are done with three or more assessments on a comparable population of urban adults, this finding needs to be interpreted with caution. Furthermore, the effect size of the association between elevated 25(OH)D level and the rate of change in the domain of verbal fluency may have been large. However, in terms of absolute decline, the effect size was smaller than anticipated, possibly due to the baseline young age. Moreover, although a large battery of neuropsychological tests was available from which the cognitive domains could have been extracted using factor analysis, a prior attempt to group those individual tests into distinctive domains showed there was a lack of factorial invariance across the major variables used in the HANDLS study sampling design, including sex, race, age, and poverty status. For this reason, only individual test scores were used and interpreted in terms of their salient domain of cognitive performance. Moreover, despite our adjustment for literacy levels by including the total Wide Range Achievement Test-3 score into our models, residual confounding may persist, given the profound socioeconomic differences between whites and African Americans in this sample.

In terms of limitations due to measurement of exposure error, timing of blood sample collection may have affected the distribution of serum 25(OH)D levels, the measurement of which may have been overestimated, because the antibody also recognizes 24,25-dihydroxyvitamin D, which includes 10% to 15% of the 25(OH)D value. Furthermore, using those standard clinical tests to measure vitamin D levels, it is often found that African Americans are almost always vitamin D deficient. In fact, our previous work indicated that measured levels may not adequately reflect biological availability of vitamin D, because of genetic differences in the vitamin D binding protein among African Americans and some whites. Consequently, despite having low levels of vitamin D, some individuals with a specific genetic polymorphism in vitamin D binding protein may have adequate biologically active vitamin D (36).

Moreover, measurement errors in dietary exposures are not totally avoided by having multiple 24-hour recalls. However, for reasons listed in a previous study (56), taking the mean of two 24-hour recalls from the Automated Multiple Pass Method is considered a good estimate of typical but not long-term intake. Finally, in addition to supplemental vitamin D intake being measured only at visit 2 and extrapolated to baseline visit, estimates of vitamins and minerals contributed by dietary supplements depended mainly on the label declarations rather than analytical values. Default values were used when no information on the supplement was available.

Conclusion

In summary, our findings indicate a consistent relationship of vitamin D status (overall) and supplemental intake (older women and African Americans) with a slower rate of decline in the domain of verbal fluency. Furthermore, dietary intake of vitamin D was linked to slower rate of decline in verbal memory among younger women and a slower rate of decline in visual memory/visuoconstructive abilities among white participants. Other longitudinal and cross-sectional associations were inconsistent, at times indicating a putative adverse effect of vitamin D status and/or intake on cognitive performance. Future studies should attempt to replicate our findings in larger samples of urban adults, using a comprehensive battery of tests reduced to selected cognitive domains.

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Table 5. Cognitive Performance Test Scores by Supplemental Vitamin D Intake, Stratified by Age Group, Sex, and Race, for HANDLS Participants With Complete and Reliable Baseline and/or Follow-Up Cognitive Scores: Mixed-Effects Regression Models

	All	Older Women (>50 Y)	Older Men (>50 Y)	Younger Women (≤50 Y)	Younger Men (≤50 Y)	Whites	African Americans
MMSE, total score							
Intercept	+26.9 ± 0.2[a]	+27.6 ± 0.5[a]	27.0 ± 0.6[a]	+27.5 ± 0.4[a]	+24.5 ± 0.7[a]	+27.1 ± 0.3[a]	+26.6 ± 0.3[a]
Time	+0.06 ± 0.06	−0.02 ± 0.13	+0.04 ± 0.16	−0.01 ± 0.10	+0.33 ± 0.16[a]	+0.07 ± 0.08	+0.02 ± 0.08
Vitamin D_{sup1}[b]	−0.04 ± 0.16	+0.16 ± 0.25	+0.37 ± 0.41	−0.70 ± 0.32[a]	−0.23 ± 0.35	+0.07 ± 0.20	−0.14 ± 0.25
Vitamin D_{sup1} × time	+0.002 ± 0.041	+0.033 ± 0.071	−0.127 ± 0.103	+0.171 ± 0.086[a]	−0.003 ± 0.080	−0.016 ± 0.054	−0.000 ± 0.062
Vitamin D_{sup2}[c]	−0.01 ± 0.11	+0.45 ± 0.19[a]	+0.39 ± 0.30	−0.39 ± 0.16[a]	+0.14 ± 0.24	−0.03 ± 0.15	−0.00 ± 0.14
Vitamin D_{sup2} × time	+0.023 ± 0.026	+0.068 ± 0.050	−0.103 ± 0.076	+0.060 ± 0.041	−0.039 ± 0.057	−0.004 ± 0.039	+0.039 ± 0.035
No.; κ value	1285; 1.9	333; 1.9	245; 1.8	428; 1.9	279; 1.9	514; 1.9	771; 1.9
CVLT, List A							
Intercept	+24.9 ± 0.9[a]	+23.3 ± 1.8[a]	+23.0 ± 4.0[a]	+22.3 ± 2.8[a]	+22.2 ± 2.8[a]	+26.0 ± 1.4[a]	+22.2 ± 1.1[a]
Time	−1.5 ± 0.2[a]	−1.2 ± 0.4[a]	−1.6 ± 0.3[a]	−1.7 ± 0.8[a]	−1.13 ± 0.64	−1.52 ± 0.44[a]	−1.26 ± 0.23[a]
Vitamin D_{sup1}	−0.57 ± 0.62	−0.04 ± 1.02	−0.09 ± 1.20	−1.02 ± 1.40	−0.42 ± 1.32	−0.70 ± 0.97	+0.07 ± 0.84
Vitamin D_{sup1} × time	+0.209 ± 0.139	+0.462 ± 0.247	−0.105 ± 0.244	+0.307 ± 0.301	−0.068 ± 0.295	+0.118 ± 0.299	+0.167 ± 0.186
Vitamin D_{sup2}	+0.32 ± 0.40	−0.03 ± 0.73	+3.08 ± 0.87[a,d]	−0.43 ± 0.69	+0.66 ± 0.92	+0.98 ± 0.72	+0.13 ± 0.49
Vitamin D_{sup2} × time	+0.045 ± 0.085	+0.295 ± 0.169	−0.389 ± 0.168[a]	+0.068 ± 0.144	−0.100 ± 0.202	+0.067 ± 0.212	−0.007 ± 0.104
No.; κ value	1275; 1.7	331; 1.8	239; 1.7	427; 1.8	278; 1.8	513; 1.7	762; 1.8
CVLT, free delayed recall							
Intercept	+7.8 ± 0.4[a]	+6.6 ± 0.9[a]	+5.9 ± 0.8[a]	+8.1 ± 0.7[a]	+7.3 ± 1.3[a]	+7.9 ± 0.6[a]	+6.9 ± 0.5[a]
Time	−0.53 ± 0.09[a]	−0.49 ± 0.20[a]	−0.51 ± 0.17[a]	−0.57 ± 0.16[a]	−0.78 ± 0.29[a]	−0.49 ± 0.14[a]	−0.53 ± 0.11[a]
Vitamin D_{sup1}	+0.07 ± 0.29	+0.55 ± 0.50	−0.19 ± 0.53	+0.02 ± 0.62	+0.26 ± 0.63	+0.05 ± 0.43	+0.15 ± 0.40
Vitamin D_{sup1} × time	+0.051 ± 0.067	+0.063 ± 0.111	+0.088 ± 0.129	+0.121 ± 0.140	−0.189 ± 0.145	+0.067 ± 0.101	+0.028 ± 0.090
Vitamin D_{sup2}	+0.05 ± 0.17	+0.30 ± 0.36	+0.55 ± 0.39	−0.06 ± 0.31	−0.32 ± 0.45	+0.19 ± 0.32	+0.00 ± 0.23
Vitamin D_{sup2} × time	+0.022 ± 0.042	−0.001 ± 0.076	−0.023 ± 0.09	−0.012 ± 0.069	+0.139 ± 0.108	+0.047 ± 0.071	+0.001 ± 0.051
No.; κ value	1255; 1.7	329; 1.7	229; 1.7	422; 1.7	275; 1.7	503; 1.7	752; 1.7
BVRT							
Intercept	+8.2 ± 0.6[a]	+8.3 ± 1.4[a]	+8.2 ± 1.5[a]	+7.3 ± 1.1[a]	+7.6 ± 1.7[a]	+7.6 ± 0.9[a]	+8.0 ± 0.9[a]
Time	+0.48 ± 0.14[a]	+0.45 ± 0.34	+0.19 ± 0.31	+0.68 ± 0.22[a]	+0.69 ± 0.36[a]	+0.28 ± 0.18	+0.98 ± 0.19[a]
Vitamin D_{sup1}	+0.10 ± 0.44	+0.11 ± 0.74	+0.51 ± 1.02	−0.44 ± 0.93	−1.29 ± 0.93	+0.27 ± 0.55	+0.06 ± 0.67
Vitamin D_{sup1} × time	+0.036 ± 0.102	−0.128 ± 0.195	−0.157 ± 0.227	+0.218 ± 0.206	+0.491 ± 0.200[a]	+0.081 ± 0.123	−0.031 ± 0.153
Vitamin D_{sup2}	+0.10 ± 0.29	−0.33 ± 0.56	−0.94 ± 0.73	+0.56 ± 0.47	+0.20 ± 0.64	+0.07 ± 0.41	+0.14 ± 0.39
Vitamin D_{sup2} × time	−0.030 ± 0.043	−0.101 ± 0.137	+0.084 ± 0.150	−0.004 ± 0.096	−0.112 ± 0.138	+0.040 ± 0.087	−0.079 ± 0.090
No.; κ value	1290; 1.9	332; 1.9	244; 1.9	433; 1.9	281; 1.9	515; 1.9	775; 1.9
Brief Test of Attention							
Intercept	+6.6 ± 0.3[a]	+6.9 ± 0.6[a]	+6.6 ± 0.6[a]	+6.3 ± 0.5[a]	+6.0 ± 0.9[a]	+6.8 ± 0.4[a]	+6.0 ± 0.4[a]
Time	−0.09 ± 0.07	−0.17 ± 0.15	−0.03 ± 0.16	+0.04 ± 0.12	−0.04 ± 0.20	−0.06 ± 0.10	−0.07 ± 0.09
Vitamin D_{sup1}	+0.13 ± 0.21	+0.49 ± 0.36	−0.50 ± 0.47	+0.13 ± 0.45	+0.28 ± 0.43	+0.29 ± 0.28	−0.03 ± 0.31
Vitamin D_{sup1} × time	+0.042 ± 0.050	−0.010 ± 0.084	+0.161 ± 0.116	−0.044 ± 0.103	+0.140 ± 0.101	+0.019 ± 0.068	+0.046 ± 0.071
Vitamin D_{sup2}	−0.04 ± 0.14	+0.16 ± 0.27	−0.09 ± 0.33	−0.15 ± 0.23	−0.08 ± 0.30	−0.02 ± 0.20	−0.05 ± 0.18
Vitamin D_{sup2} × time	+0.000 ± 0.031	+0.111 ± 0.059	−0.093 ± 0.790	−0.014 ± 0.051	+0.037 ± 0.071	+0.026 ± 0.049	−0.021 ± 0.040
No.; κ value	1269; 1.8	326; 1.8	237; 1.7	427; 1.8	279; 1.8	510; 1.8	759; 1.7
Animal fluency							
Intercept	+17.6 ± 0.7[a]	+17.3 ± 1.4[a]	+13.9 ± 1.5[a]	+18.8 ± 1.3[a]	+21.7 ± 2.2[a]	+16.7 ± 1.1[a]	+17.6 ± 0.9[a]
Time	−0.16 ± 0.13	+0.33 ± 0.27	+0.37 ± 0.29	−0.35 ± 0.23	−1.04 ± 0.41[a]	+0.09 ± 0.22	−0.35 ± 0.16[a]
Vitamin D_{sup1}	+1.07 ± 0.49[a]	+1.63 ± 0.75[a]	−1.35 ± 1.06	+2.00 ± 1.03	+1.32 ± 1.15	+0.70 ± 0.70	+1.60 ± 0.67[a]
Vitamin D_{sup1} × time	+0.033 ± 0.096	+0.031 ± 0.153	+0.457 ± 0.206[a]	−0.175 ± 0.204	−0.068 ± 0.224	−0.069 ± 0.146	+0.075 ± 0.128
Vitamin D_{sup2}	−0.63 ± 0.32	−1.14 ± 0.57[a]	−0.53 ± 0.76	−0.52 ± 0.52	−0.56 ± 0.81	−0.21 ± 0.53	−0.83 ± 0.39[a]
Vitamin D_{sup2} × time	+0.106 ± 0.060	+0.318 ± 0.108[a,e]	+0.155 ± 0.141	+0.000 ± 0.100	+0.090 ± 0.156	−0.048 ± 0.104	+0.193 ± 0.073[a,e]
No.; κ value	1293; 1.9	333; 2.0	247; 1.9	432; 1.9	281; 1.9	517; 1.9	776; 1.9
Digits span, forward							
Intercept	+7.0 ± 0.3[a]	+7.1 ± 0.6[a]	+6.6 ± 0.6[a]	+6.7 ± 0.5[a]	+7.9 ± 0.8[a]	+6.8 ± 0.4[a]	+6.9 ± 0.4[a]
Time	−0.02 ± 0.06	−0.04 ± 0.11	+0.00 ± 0.12	−0.17 ± 0.10	+0.01 ± 0.16	+0.00 ± 0.10	−0.06 ± 0.07
Vitamin D_{sup1}	−0.07 ± 0.20	+0.05 ± 0.30	+0.36 ± 0.41	−0.53 ± 0.44	−0.26 ± 0.46	−0.10 ± 0.27	−0.02 ± 0.28
Vitamin D_{sup1} × time	+0.034 ± 0.041	+0.038 ± 0.069	−0.041 ± 0.088	+0.096 ± 0.091	+0.027 ± 0.059	+0.021 ± 0.062	+0.016 ± 0.054
Vitamin D_{sup2}	−0.29 ± 0.13[a]	−0.15 ± 0.23	+0.34 ± 0.30	−0.84 ± 0.22[a,d]	−0.10 ± 0.31	−0.16 ± 0.20	−0.39 ± 0.16[a]
Vitamin D_{sup2} × time	+0.286 ± 0.0253	+0.026 ± 0.046	−0.074 ± 0.060	+0.075 ± 0.045	+0.028 ± 0.059	−0.001 ± 0.045	+0.043 ± 0.030
No.; κ value	1294; 1.9	333; 1.9	247; 1.9	432; 1.8	282; 1.9	516; 1.9	778; 1.9
Digits span, backward							
Intercept	−7.7 ± 12.9	+53.4 ± 39.4	+16.1 ± 48.6	+21.9 ± 27.3	−43.7 ± 34.7	−7.2 ± 21.3	−8.15 ± 17.0
Time	+1.10 ± 2.70	−9.85 ± 9.82	+0.02 ± 10.30	+2.59 ± 5.50	+10.0 ± 6.7	−1.4 ± 4.4	+1.3 ± 3.6
Vitamin D_{sup1}	−0.06 ± 0.19	+0.25 ± 0.30	−0.48 ± 0.38	−0.36 ± 0.40	+0.19 ± 0.44	−0.16 ± 0.27	+0.05 ± 0.26
Vitamin D_{sup1} × time	−0.037 ± 0.041	−0.097 ± 0.075	+0.068 ± 0.087	−0.055 ± 0.080	+0.010 ± 0.089	−0.065 ± 0.059	−0.015 ± 0.057
Vitamin D_{sup2}	−0.22 ± 0.12	+0.17 ± 0.22	−0.09 ± 0.27	−0.58 ± 0.20[a,d]	−0.29 ± 0.30	−0.32 ± 0.20	−0.14 ± 0.15
Vitamin D_{sup2} × time	+0.017 ± 0.025	+0.011 ± 0.053	+0.019 ± 0.059	−0.004 ± 0.040	+0.035 ± 0.057	+0.010 ± 0.042	+0.019 ± 0.031
No.; κ value	1297; 1.8	333; 1.9	247; 1.9	433; 1.8	284; 1.8	518; 1.8	779; 1.8
Clock-drawing test							
Intercept	+8.8 ± 0.2[a]	+9.0 ± 0.4[a]	+9.1 ± 0.4[a]	+9.1 ± 0.3[a]	+8.9 ± 0.5[a]	+9.1 ± 0.2[a]	+8.4 ± 0.2[a]
Time	−0.08 ± 0.04[a]	-0.27 ± 0.09[a]	−0.05 ± 0.10	−0.06 ± 0.07	−0.03 ± 0.13	−0.08 ± 0.07	−0.07 ± 0.06
$VitaminD_{sup1}$	+0.26 ± 0.12[a]	+0.52 ± 0.19[a]	+0.04 ± 0.24	+0.08 ± 0.24	+0.24 ± 0.26	+0.07 ± 0.16	+0.46 ± 0.17[a]
$VitaminD_{sup1}$ × time	−0.012 ± 0.031	−0.049 ± 0.05	−0.032 ± 0.071	−0.033 ± 0.066	+0.083 ± 0.064	−0.004 ± 0.044	−0.015 ± 0.044
$VitaminD_{sup2}$	−0.07 ± 0.08	+0.18 ± 0.14	−0.27 ± 0.18	−0.15 ± 0.12	+0.05 ± 0.18	−0.17 ± 0.12	+0.02 ± 0.10

(*Continued*)

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Table 5. Continued

	All	Older Women (>50 Y)	Older Men (>50 Y)	Younger Women (≤50 Y)	Younger Men (≤50 Y)	Whites	African Americans
VitaminD$_{sup2}$ × time	+0.039 ± 0.019[a]	+0.012 ± 0.036	+0.060 ± 0.048	+0.031 ± 0.032	+0.054 ± 0.045	+0.036 ± 0.031	+0.035 ± 0.025
No.; κ value	1292; 1.9	334; —	244; 1.9	432; 1.9	282; 1.9	518; 1.9	774; 1.9
Trailmaking test, part A							
Intercept	+35.2 ± 5.3[a]	-56.9 ± 22.3[a]	+47.0 ± 10.5[a]	+59.7 ± 23.9[a]	+38.8 ± 16.2[a]	+59.7 ± 23.9[a]	+46.2 ± 9.5[a]
Time	+2.5 ± 1.4	+27.0 ± 8.4[a]	−0.64 ± 2.93	−8.02 ± 6.67	+2.71 ± 4.82	+0.54 ± 0.69	3.8 ± 2.5
Vitamin D$_{sup1}$	−5.40 ± 3.50	−3.36 ± 5.95	−1.07 ± 7.08	−6.53 ± 5.02	−6.53 ± 9.31	−1.16 ± 1.54	−8.10 ± 6.58
Vitamin D$_{sup1}$ × time	+0.199 ± 1.053	+0.633 ± 2.425	−0.417 ± 2.196	+0.085 ± 1.513	−0.974 ± 2.637	−0.153 ± 0.340	+0.521 ± 1.897
Vitamin D$_{sup2}$	−3.4 ± 2.3	−5.41 ± 4.50	−5.33 ± 5.11	−2.57 ± 2.54	−0.60 ± 6.06	+1.29 ± 1.16	−6.33 ± 3.79
Vitamin D$_{sup2}$ × time	+0.098 ± 0.649	−0.153 ± 1.763	+1.090 ± 1.429	+0.384 ± 0.729	−0.507 ± 1.831	−0.118 ± 0.244	+0.166 ± 1.055
No.; κ value	1282; 1.9	332; 1.9	240; 1.8	432; 1.9	278; 1.9	514; 1.9	768; —
Trailmaking test, part B							
Intercept	+226.4 ± 54.8[a]	+147.5 ± 220.3	+745.4 ± 212.9[a]	+107.0 ± 121.1	+316.5 ± 75.3[a]	+59.7 ± 76.5	+273.0 ± 41.7[a]
Time	+12.8 ± 11.4	+88.5 ± 47.7	−50.2 ± 42.6	+52.7 ± 27.2	−20.8 ± 23.2	+12.1 ± 17.9	+14.9 ± 8.2
Vitamin D$_{sup1}$	−3.23 ± 12.4	+15.3 ± 22.6	−20.17 ± 28.57	−10.1 ± 23.9	+6.2 ± 24.5	−0.6 ± 14.0	−5.3 ± 19.6
Vitamin D$_{sup1}$ × time	−0.714 ± 2.590	−1.454 ± 4.862	+8.58 ± 6.00	−3.019 ± 5.526	−9.377 ± 7.317	+0.392 ± 2.778	−2.557 ± 4.110
Vitamin D$_{sup2}$	+0.13 ± 8.09	−13.6 ± 17.1	−5.830 ± 20.420	+11.8 ± 12.0	−6.2 ± 15.9	+4.8 ± 10.5	−3.7 ± 11.3
Vitamin D$_{sup2}$ × time	−2.783 ± 1.608	−2.901 ± 3.517	−0.295 ± 4.114	−3.197 ± 2.616	−5.034 ± 4.926	−0.442 ± 1.961	−4.734 ± 2.303[a]
No.; κ value	1268; 1.8	329; 1.8	236; 1.8	428; 1.9	275; 1.9	510; 1.9	758; 1.8

Most cognitive test scores were in the direction of higher score equals better performance, except for BVRT (total errors) and the trailmaking test (both parts; expressed in seconds). Models were controlled for age (centered at 50 years), race, poverty status, education, marital status, literacy, current smoking status, current drug use, body mass index (centered at 30 kg/m^2), CES-D total score (centered at 15), HEI-2010 (centered at 40), self-reported diabetes, hypertension, high cholesterol level, cardiovascular disease, season, and the inverse mills ratio. All covariates were interacted with time. All inverse mills ratios were centered at zero, except for digit span backwards and the trailmaking test, parts A and B, for which the inverse mills ratio was centered at its mean.

Abbreviations: —, no data. See Table 1 and 2 legends for expansion of abbreviations.

[a] $P < 0.05$ for null hypothesis that $\gamma = 0$.

[b] Vitamin D$_{sup1}$ refers to the contrast between being a vitamin D–containing supplement user from baseline onward *vs* being nonuser of a vitamin D–containing supplement.

[c] Vitamin D$_{sup2}$ refers to the contrast between being a vitamin D–containing supplement user during follow-up only *vs* being nonuser of a vitamin D–containing supplement.

[d] $P < 0.004$ for null hypothesis that $\gamma = 0$ for main effects vitamin D$_{sup1}$ and/or vitamin D$_{sup2}$.

[e] $P < 0.009$ for null hypothesis that $\gamma = 0$ for interaction between vitamin D$_{sup1/2}$ and time.

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