HHS Public Access

Author manuscript

Nutr Neurosci. Author manuscript; available in PMC 2021 September 01.

Published in final edited form as:

Nutr Neurosci. 2020 September ; 23(9): 688–695. doi:10.1080/1028415X.2018.1545291.

Serum vitamin D and cognition in a cohort of Boston-area Puerto Ricans.

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Abstract

BACKGROUND: Vitamin D has been suggested as a protective factor for cognitive health, however results of prior studies have been mixed. To examine whether serum 25(OH)D concentration is related to cognition and cognitive decline in a study of Boston Area Puerto Ricans.

METHODS: We examined the association between serum 25(OH)D, cognitive function and cognitive decline in a longitudinal study of 967 Boston Area Puerto Rican adults.

RESULTS: In analyses adjusted for potential confounders, participants in the bottom quintile of 25(OH)D had similar cognitive function at baseline, as measured by a global cognitive score (mean difference: 0.09 (95% CI: −0.02, 0.19; p-trend: 0.18), and similar 2-year rates of cognitive decline (mean difference: −0.01 (95% CI: −0.09, 0.07), p-trend: 0.61) as those in the top 25(OH)D quintile. No significant associations were observed between baseline serum 25(OH)D

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Disclosure of Interest
The authors report no conflicts of interst.

concentration and 2-year change in individual cognitive test scores or change in executive function or memory domains.

CONCLUSIONS: We observed no significant association between serum 25(OH)D and cognition in this cohort of Boston Area Puerto Ricans.

Keywords

epidemiology; nutrition; minority; aging; 25(OH)D; cognition; cohort; biomarker

INTRODUCTION

Background/rationale:

Vitamin D is a fat-soluble vitamin that has been implicated as a protective factor in a wide range of chronic diseases, including multiple sclerosis (1, 2), cancer (3, 4), and cardiovascular disease (5–7). It has well-known anti-inflammatory and antioxidant properties (8, 9). Vitamin D receptors are located in brain regions that are key for cognitive function (10, 11). It has, thus, been suggested that Vitamin D may play an important role in cognitive aging and the maintenance of healthy cognition(12).

The principal source of Vitamin D is its synthesis in the skin via sunlight exposure (13). Dietary sources of Vitamin D include fatty fish, meats, fish liver oils, eggs, dairy and vitamin-fortified products(14–16). Serum 25(OH)D is the accepted biomarker of Vitamin D status in humans and is commonly used in epidemiological studies of Vitamin D(14). Although debated, generally accepted cutoffs for serum 25(OH)D are: 1) sufficient (≥30 nmol/L), 2) insufficient (<30 nmol/L but >20 nmol/L) and 3) deficient (<20 nmol/L). More than 40% of the US population is estimated to be deficient in Vitamin D, and the deficiency disproportionally impacts minority populations(17).

A number of cross-sectional and longitudinal studies have examined the association between 25(OHD) and cognition. Several cross-sectional studies have reported lower cognition among participants with low 25(OH)D, compared to those with sufficient concentration (18–21). Longitudinal studies of 25(OH)D and cognitive decline have produced mixed results (22–28).

Mainland US Puerto Ricans represent a significant portion of the US Hispanic population. This population suffers from well-documented health disparities (29) and has been shown to have high rates of chronic disease including depression, type 2 diabetes, heart disease and cognitive impairment (30–33). Thus, identification of modifiable risk factors for cognitive function and decline is key to improving the long-term cognitive health of this at-risk population.

Objectives:

In this study, we investigated whether serum 25(OH)D concentration was related to cognitive function and 2-year cognitive decline in a longitudinal study of Boston Area Puerto Ricans.

METHODS

Study Design, Setting and Participants.

The study design and methodology are described in previous publications (34–38). This study was approved by the Institutional Review Board at the university where the study was conducted. All study participants provided written informed consent. Briefly, 1499 participants in the Boston Puerto Rican Study were 45–75 years old at baseline. Participants were interviewed in their home by bilingual interviewers in English and Spanish, and information was collected on their demographic factors, current health conditions and and health behaviors. During the baseline visits, the interviewers also collected anthropometric and blood-pressure measurements, and administered a food-frequency questionnaire. The interviewers provided instructions on fasting and returned to draw fasting blood samples soon after the interview. The interviewers were trained and performed cognitive testing on the participants at study baseline and after two years of follow-up. Our analysis was restricted to 967 study participants with complete cognitive data at baseline and at the 2-year follow-up, as well complete data on serum 25(OH)D.

Variabes, data sources and measurenment:

Serum vitamin D measurement.—Serum vitamin D was measured in fasting blood samples obtained at baseline as 25(OH)D, by extraction followed by 25I radioimmunoassay Packard COBRA II Gamma Counter (DiaSorin Inc., Stillwater, MN 55082). These measurements had intra and inter-assay coefficients of variation of 10.8% and 9.4% respectively. In our study sample, serum vitamin D ranged from 10 nmol/L to 120 nmol/L with a mean of 43.8 nmol/L.

Outcomes.—A trained research assistant administered a cognitive testing battery in either English (2%) or Spanish (98%) to all eligible study participants (36). The battery of cognitive tests consisted of the following: 1) Mini-Mental State Examination (MMSE, a test of general cognition) (39); a 16-word list learning test (40) that included 2) word-list learning (sum of words recalled over 5 attempts), 3) recognition 4) percentage retention (number of words recalled after a delay as a proportion of the number of correct responses on the fifth learning trial); 5) digit span forward and backward (a test of working memory) (40); 6) the Stroop test (40); 7) verbal fluency (naming as many words as possible starting with a given letter) (40); 8) clock drawing (41); and 9) figure copying (42) (a test of executive function). The full battery of tests was administered at baseline and at the 2-year follow-up. In our data analysis, we used a baseline global cognitive and 2-year global cognitive change scores as our outcomes. The baseline global cognitive score was calculated as the mean of the z-scores of baseline values of the following cognitive tests: MMSE, word list learning, recognition, percentage retention, Stroop, letter fluency, digit span forward and backward, clock drawing, and weighted figure copying. The 2-year global cognitive change score was calculated as the mean of the z-scores of the changes between baseline and year 2 in each of the aforementioned individual tests. Derivation of both the baseline global cognitive score and the 2-year global cognitive change score are described in detail in previous publications (37).

Furthermore, we used principal-components analysis (PCA) with varimax rotation (37) to quantify the relationship between serum 25(OH)D and two major cognitive function factors: 1) executive function, and 2) memory. We performed PCA on baseline cognitive data, resulting in two principal components with eigenvalues >1. Based on the loadings for the individual baseline test scores on the two principal components, specific individual components were designated as contributing to the cognitive domains of executive function and memory. By definition, each PCA-derived composite score had a mean of 0 and a standard deviation of 1. Composite scores were also computed for year-two follow-up testing data using the means, standard deviations, and scoring coefficients from the baseline PCA. Difference scores between the follow-up and baseline observations were calculated for each domain, and descriptive statistics were obtained for these difference scores. For each cognitive domain, a "decline" was defined as a drop in score ≥ one standard deviation from the group-mean difference score.

Covariates.—Information collected at baseline included age, years of education, physical activity, smoking status, alcohol intake and other demographic variables. Body Mass Index (BMI, in kg/m^2) was computed from body weight and height as measured during the interview by trained field workers. A physical activity score, a variation of the Framingham physical activity index, a weighted 24-h score of typical daily activity, based on hours spent doing heavy, moderate, light, or sedentary activity was computed and used as a covariate(43) The field workers also measured blood pressure at three time points during the study. Study participants with mean systolic blood pressure ≥ 140 mm Hg and/or a mean diastolic blood pressure ≥ 90 mm Hg were classified as having hypertension. A certified phlebotomist drew fasting (12-h) blood samples in the home of the study participants on a day following the interview. Participants with fasting plasma glucose > 7.0 nmol/L or those who reported taking medications for diabetes (insulin or oral medicines) were considered as having type 2 diabetes (44). The TaqMan single nucleotide polymorphism genotyping assay (Applied Biosystems) was used to assess APOE genotype, with a success rate of 95%.

Statistical methods: R version 3.3.1 was used for all statistical analyses. Compared to participants who were excluded due to missing data on exposure and outcome, included participants were older (mean age 58.1 vs 56.4, $p<0.001$), had higher serum 25(OH)D (mean 43.8 nmol/L vs 35.5 nmol/L; $p<0.001$), higher baseline MMSE score (mean 23.9 vs 20.01; $p<0.001$), and a higher proportion of women (73.1% vs. 59.2%; $p < 0.001$).

Primary analyses were conducted using quintiles of baseline 25(OH)D concentration. In the analyses of executive and memory domains, we used tertiles of baseline 25(OH)D because of the low number of participants who met the criteria for significant (>1 standard deviation) decline in those domains. We performed additional sensitivity analyses with serum 25(OH)D in three categories: sufficient ($c_{25(OH)D}$ >=30 nmol/L), insufficient (20 nmol/L <= $c_{25(OH)D}$ < 30 nmol/L) and deficient ($c_{25(OH)D}$ < 20 nmol/L). The results of these analyses are presented in the supplementary tables. We used multivariable linear regression and calculated the adjusted mean differences and 95% confidence intervals (95% CI) in cognitive decline across quintiles of 25(OH)D. We adjusted our multivariate models for age in years, sex, season of blood collection, physical activity (physical activity (PA) score <30,

PA score 30–40, PA score 40–50, PA score >=50), education (<5th grade, 5–8th grade, 9–12 grade, some college or college degree, some graduate school), diabetes (yes/no), smoking (never/past/current), alcohol use (never/past current), hypertension (yes/no), BMI (normal weight/overweight/obese), multivitamin supplement use (yes/no), CRP, and APOE (presence of APOE 4). Linear trends were tested for significance with a linear variable representing the median of the quintiles. We used the missing indicator method to account for missingness in model covariates.

The goal of our primary analyses was to assess the association between serum 25(OH)D and a global cognitive decline score. In addition, we examined associations of baseline serum 25(OH)D with baseline values as well as 2-year change in each individual test score including MMSE, world list learning, recognition, percentage retention, Stroop, letter fluency, digit span forward and backward, clock drawing, and weighted figure copying).

We adjusted all multivariable models for age in years, season of blood collection, sex, education (less than 5th grade/5th-8th grade/9th-12th grade/some college or bachelor's degree/at least some graduate school), diabetes, smoking (never/past/current), alcohol use (never/past/current), c-reactive protein (CRP, < 3 vs. higher), hypertension (yes/no), body mass index (BMI), multivitamin supplement use, and APOE (presence of APOE 4). Longitudinal models of 2-year cognitive change were additionally adjusted for the appropriate baseline cognitive score.

Because Vitamin D supplements may have been prescribed to participants with severely low 25(OH)D levels, and may confound the association between serum 25(OH)D levels and cognition, we conducted sensitivity analyses adjusting for initiation of supplement use between baseline and year 2. We also conducted sensitivity analyses restricted to participants a) who did not initiate vitamin D supplement use between baseline and year 2 (N = 840) and b) who never reported vitamin D supplement use at baseline or year 2 (N = 744). We performed additional sensitivity analyses adding a measure of average skin melanin to our models, as well as adjusting for depression using baseline values of the Center for Epidemiologic Studies Depression Scale.

Finally, we assessed effect modification due to the association between serum 25(OH)D and cognitive decline by age, sex, smoking or BMI. Effect modification was evaluated by including multiplicative terms of these variables with the cognitive decline variable in the regression models. We performed these interaction analyses for our primary analyses - the global cognitive decline models.

RESULTS

This sample of Puerto Rican adults tended to have low education, and high prevalence of diabetes, hypertension and obesity (Table 1). Participants in the higher quintiles of serum 25(OH)D were older (p-trend 0.03), had lower prevalence of current smoking (p-trend 0.03), higher physical activity (p-trend: 0.02) and had lower prevalence of high CRP (p-trend 0.07). Baseline BMI, MMSE score, sex distribution, % past smoker, education level, current or

past alcohol use, and prevalence of diabetes or hypertension did not differ significantly across vitamin D quintiles.

After adjusting for potential confounders, including age in years, sex, season of blood collection, physical activity, education, diabetes smoking, alcohol use, hypertension, BMI, multivitamin supplement use, CRP, and APOE4, serum 25(OH)D was not associated with global cognitive function at baseline (Table 2, Model 2). The mean difference in global cognition, comparing participants in the bottom to those in the top quintile of 25(OH)D, was 0.09 (95% CI: −0.02, 0.19; p-trend: 0.17) Likewise, in a longitudinal model adjusted for covariates, baseline 25(OH)D was not significantly associated with 2-year cognitive change. The mean difference in 2-year global cognitive decline, comparing participants in the bottom to those in the top quintile of 25(OH)D, was −0.01 (95% CI: −0.09, 0.07), p-trend: 0.64) (Table 3, Model 2). Results of sensitivity analyses treating 25(OH)D in categories of deficient, insufficient and sufficient, were similar to the main analyses (Supplementary Tables S2 and S3).

In multivariable adjusted cross-sectional analyses of individual cognitive tests, baseline serum 25(OH)D was inversely related to performance on the Stroop test (p-trend: 0.02) but not on any of the other tests. In longitudinal analyses, higher 25(OH)D concentration was related to better performance on the test of figure copying (p-trend: 0.02), but not any other tests. Results of analyses of individual cognitive tests are presented in supplemental tables S4 and S5.

We did not observe significant associations between baseline 25(OH)D and either the executive function or memory domains. Comparing the lowest to the highest tertile of baseline serum 25(OH)D, the odds of decline were 1.16 (95% CI: 0.50, 2.71; p-trend: 0.58) for 2-year change in executive function and 1.09 (95% CI: 0.62, 1.92; p-trend: 0.81) for memory (Table 4). Results for executive and memory domains were similar in linear models (Supplemental Table S1), as well as in cross-setional analyses.

Results of sensitivity analyses adjusting for initiation of vitamin D supplement use between baseline and year 2 of the study, and for average skin melanin, did not differ significantly from our main results. Furthermore, the results of analyses restricted to participants who a) did not initiate vitamin D supplements (N = 840) or b) never reported vitamin D supplement use (N = 744) did not differ from our main results. Results adjusted for baseline depression symptomology (CESD scale) were not materially different from the main results.

We did not observe significant interactions with smoking, BMI, sex, or baseline MMSE score (all p-interaction > 0.1). In analyses restricted to participants 50 years of age or younger, the mean difference in 2-year cognitive declie comparing participants in the top vs. bottom quintile of 25(OH)D was 0.095 (p-trend: 0.25).

DISCUSSION

Key Results:

In the population of Boston Area Puerto Rican adults considered in this study, we observed no significant association between serum 25(OH)D and cognition or cognitive decline over 2 years of follow-up.

Interpretation:

Epidemiological evidence on the association between serum 25(OH)D and cognition has been mixed. A number of cross-sectional studies have shown lower performance on tests of cognition in persons with low 25(OH)D concentration, compared to those with sufficient concentration (18–21, 45–52). However, cross-sectional studies may be subject to reverse causation. Longitudinal studies and randomized control trials are more suited to support a potential causal association between 25(OH)D and coginitive impairment. Several longitudinal studies have observed an association between lower serum 25(OH)D and faster rates of cognitive decline(21, 28, 53, 54). Llewellyn et al. (53) found that elderly participants with low 25(OH)D had an increased risk of cognitive decline over 6 years. In a longitudinal cohort of 6247 community-dwelling older women, Slinin et al. (54) reported higher odds of global cognitive decline over 4 years (OR = 1.31 (95% CI: 1.04–1.64) among women with deficient 25(OH)D (54). Matchar et al. (28) followed a community-based longitudinal cohort of 1202 cognitively intact elderly adults in China for 2 years and found a doubling in the odds of cognitive decline and a tripling in the odds of incident cognitive impairment (MMSE score <18) among participants in the lowest compared to the highest quartile of serum 25(OH)D. In a study of 1639 participants who underwent cognitive testing via telephone, Breitling et al. (27) reported twice the odds of 2-year decline in COGTEL scores in women, and a weaker association in men. In the Progetto Veneto Anziani (Pro.V.A.) cohort that followed 1,927 elderly cognitively intact participants at baseline, deficient baseline 25(OH)D was associated with a 30% increase in the risk of cognitive dysfunction over 4.4 years (55).

Despite the above findings of a significant association between serum 25(OH)D and cognition, a number of other studies detected no such association. Chan et al. (56), found no significant association between baseline 25(OH)D and cognition in cross-sectional analyses among 939 community-dwelling Chinese men aged over 65. Slinin et al. (26) reported no association between serum 25(OH)D and either baseline cognitive function or incident cognitive decline in a study of 1604 elderly men enrolled in the Osteoporotic Fractures in Men Study. In another cohort study of community-living elderly men, Olsson et al. (25) also showed no significant association between baseline Vitamin D status, including plasma 25(OH)D, and dementia or cognitive impairment over 18 years.

Prior studies of 25(OH)D and cognition have varied with regards to exposure (dietary vs serum 25(OH)D, outcome (cognitive tests used) assessment, as well as study design and duration. Cross-sectional studies are particularly subject to reverse causation, because poor cognitive status could lead to poor nutrition, lower physical activity and lower sunlight exposure, and thus low serum 25(OH)D.

Strengths and limitations:

Our study has several strengths, particularly a longitudinal design, thorough assessment of exposure, covariates and outcome. The study benefited from extensive and repeated assessments of cognition, including a variety of validated instruments. The study also benefited from careful assessment of potential confounders, including dietary factors, and comorbidities, at baseline. This allowed us to adjust our analyses for these potential confounders and also to examine the potential for effect modification. The use of serum 25(OH)D, a widely used and accepted biomarker of Vitamin D status is also a strength of our study, as 25(OH)D provides a reliable estimate of a person's Vitamin D status and has been used extensively is studies of vitamin D and chronic disease (14).

Generalizability:

This study focused on a unique and underserved population of community dwelling American Puerto Ricans, which allowed us to contribute much-needed evidence of the potential association between serum 25(OH)D and cognition relevant to this group, which suffers from many health disparities(29). However, because of the unique population used, our findings might not be entirely generalizable to other populations. The significance of the finding is relevant to Hispanics and Puerto Ricans residing within the US. According to the US census, Hispanics are the fastest-growing population in the US, and are expected to become the majority in the US by 2045. Puerto Ricans are the 2nd most prevalent Hispanic group in the US, after Mexican Americans.

The relatively short two-year follow-up interval between cognitive testing may have limited our ability to detect an association between 25(OH)D and cognitive change. Because vitamin D status is dependent on sun exposure, it may vary across the year. We did not have a measure for sun exposure, but adjusted our results for season of blood collection. Furthermore, although we adjusted for a wide range of potential confounders, we cannot exclude confounding by other non-measured factors and residual confounding.

In summary, the results of our study do not support the hypothesis that higher serum 25(OH)D may improve cognition and impact 2-year cognitive change in Puerto Ricans living in Massachusetts. However, larger studies with longer follow-up in a variety of populations is needed to better understand the role of Vitamin D in cognition and cognition change.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Esther Carver for assistance with this manuscript.

Funding

This work was supported by the National Institutes of Health under Grant P01 AG023394 and Grant P50 HL105185. Natalia Palacios receives funding from the National Institutes of Health under Grant R01 NS097723.

Biographical Notes:

Natalia Palacios is an Assistant Professor in the Department of Public Health at the University of Massachussets, Lowell. Her research focuses on the epidemiology of neurolgoical disease, including Parkinson's Disease, ALS and cognitive decline. She is interested in the role of diet, lifestyle factors and biomarkers in these conditions, particularly the gut microbiome. Is currently PI of an NIND R01 investigating the assocaition between the gut microbiome and Parkinson Disease within the Nurses Health Study and Health Professionals Follow-up Study cohorts.

Tammy Scott is an Assistant Professor at the Friedman School of Nutrition Science and Policy, as well as the Tufts University School of Medicine Department of Psychiatry. Her research is focused on the impact of nutrition on aging and cognition, mood and quality of life. She has extensive experience in conducting human studies, and is the neurocognition expert in multiple NIH- and foundation-funded clinical trials and observational studies. She is affiliated with the Tufts Clinical and Translational Science Institute (CTSI) as part of the Biostatistics, Epidemiology, and Research Design (BERD) Center. Scott has served for over twelve years on the Tufts Health Sciences Campus Institutional Review Board, and is on the editorial advisory board for the Tufts Health and Nutrition Letter.

Neha Sahasrabudhe is a doctoral student in Public Health at the Univeristy of Massacnussets, Lowell. Her doctoral thesis focuses on dietary and lifestyle factors and risk of chronic disease within the Boston Area Puerto Rican Study. She holds a Masters degree in mathematics from the University of Massachussets, Lowell.

Xiang Gao is an Associate Professor in the Department of Nutritional Sciences, College of Health and Human Development, Pennsylvania State University. Dr Gao's research interests include nutritional Epidemiology, sleep disorders, neurological diseases, aging, global health and stress. Data from several large international ongoing prospective cohorts have been used, in which approximately ~500,000 men and women have been followed regarding their lifestyles and health conditions. These cohorts include the Nurses' Health Study, the Health Professionals Follow-up Study, the Cancer Prevention Study II Nutrition Cohort, and the Kailuan Cohort.

Katherine Tucker is Professor of Nutritional Epidemiology and Director of the Center for Population Health at UMass Lowell. She is Editor-in Chief of Advanced in Nutrition, an international review journal. Dr. Tucker has contributed to more than 3000 articles in scientific journals. Her research focuses on dietary intake and risk of chronic diseae, including osteoporosis, cognitive decline, obesity, metabolic syndrome, and heart disease, and on dietary methodology. She is PI of the Boston Puerto Rican Health Study, a longitudinal study on the roles and interactions of stress, social support, diet, and health behavior and genetic predisposition in relation to health disparities in Puerto Rican adults.

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Table 1.

Baseline characteristics of the 967 study participants with complete data on serum 25(OH)D and complete cognitive data at baseline and 2-year follow-up.

	Baseline Serum Vitamin D Quintile					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**p-trend**
	n = 150	**n = 213**	**n = 219**	**n = 179**	**n = 206**	
Serum 25(OH)D (range)	21.2	31.5	41.5	51.1	68.4	
nmol/L	(10–25)	(27–35)	(38–45)	(48–55)	(58–120)	
Age (mean), years[a]	55.6	56.0	56.4	56.8	57.1	0.03
BMI (mean), kg/m^2	32.6	32.2	31.8	31.4	31.0	0.63
MMSE score (mean)	24.1	24.0	23.9	23.8	23.7	0.21
Women %[b]	74.7	74.0	73.3	72.5	71.8	0.53
Past smoker %	29.4	30.2	30.9	31.8	32.6	0.51
Current smoker %	27.4	24.8	22.3	20.0	17.9	0.03
Physical activity score (mean)	31.4	31.6	31.8	32.0	32.2	0.02
Less then high school education %	41.7	41.0	40.3	39.5	38.8	0.37
Current alcohol use %	44.1	43.9	43.7	43.6	43.4	0.96
Past alcohol use %	28.9	28.5	28.2	27.8	27.4	0.63
Diabetes %	36.9	36.1	35.4	34.7	33.9	0.39
High CRP (≥3 mg/dL) %	61.5	59.3	57.0	54.7	52.4	0.07
Hypertension %	71.7	70.3	68.9	67.5	66.1	0.72

All values adjusted for age and sex.

[a] adjusted for sex

[b] adjusted for age

Table 2.

Cross-sectional associaitons between baseline serum 25(OH)D and baseline global cognitive function.[a]

		Baseline Serum 25(OH)D Quintile					
		Q1	**Q2**	**Q3**	**Q4**	**Q5**	**p-trend**
		n = 150	**n = 213**	**n = 219**	**n = 179**	**n = 206**	
Global Cognitive Score	**Model 1**[b]	0.06 (−0.06, 0.17)	0.03 (−0.08, 0.13)	0.001 (−0.10, 0.10)	0.05 (−0.06, 0.16)	Ref	0.26
	Model 2[c]	0.09 (−0.02, 0.19)	0.06 (−0.03, 0.16)	0.07 (−0.02, 0.17)	0.08 (−0.02, 0.18)	Ref	0.18

[a]The baseline global cognitive score was calculated as the mean of the z-scores of baseline values of the following cognitive tests: MMSE, word list learning, recognition, percentage retention, Stroop, letter fluency, digit span forward and backward, clock drawing, and weighted figure copying.

[b]Multivariate model adjusted for age and sex and season of blood collection.

[c]multivariable model, adjusted for age in years, sex, season of blood collection, physical activity (physical activity (PA) score <30, PA score 30–40, PA score 40–50, PA score >=50), education (<5th grade, 5–8th grade, 9–12 grade, some college or college degree, some graduate school), diabetes (yes/no), smoking (never/past/current), alcohol use (never/past current), hypertension (yes/no), BMI (normal weight/overweight/obese), multivitamin supplement use (yes/no), CRP, and APOE (presence of APOE 4).

Table 3.

Mean difference (95% CI) in cognitive decline during the 2 - year follow-up of Boston Puerto Rican Health Study participants according to quintiles of baseline serum 25(OH)D.

		Baseline Serum 25(OH)D Quintile					
Global Cognitive Score		**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**p-trend**
		n = 150	**n = 213**	**n = 219**	**n = 179**	**n = 206**	
	Model 1[b]	−0.01 (−0.09, 0.07)	−0.03 (−0.10, 0.04)	−0.01 (−0.09, 0.06)	−0.02 (−0.09, 0.06)	Ref	0.66
	Model 2[c]	−0.01 (−0.09, 0.07)	−0.01 (−0.08, 0.06)	0.01 (−0.06, 0.08)	−0.0008 (−0.07, 0.08)	Ref	0.61

[a]The 2-year global cognitive change score was calculated as the mean of the z-scores of the changes between baseline and year 2 of MMSE, word list learning, recognition, percentage retention, Stroop, letter fluency, digit span forward and backward, clock drawing, and weighted figure copying.

[b]Multivariate model adjusted for age, sex, season of blood collection and baseline score

[c]multivariable model, adjusted for age in years, sex, season of blood collection, physical activity (physical activity (PA) score <30, PA score 30–40, PA score 40–50, PA score >=50), education (<5th grade, 5–8th grade, 9–12 grade, some college or college degree, some graduate school), diabetes (yes/no), smoking (never/past/current), alcohol use (never/past current), hypertension (yes/no), BMI (normal weight/overweight/obese), multivitamin supplement use (yes/no), CRP, and APOE (presence of APOE 4).

Table 4.

Association between tertiles of serum 25(OH)D and change in executive function and memory domains, as odds of >=1SD decline.

		Baseline Serum 25(OH)D Tertile			
		Tertile 1	**Tertile 2**	**Tertile 3**	**p-trend**
Executive Function Component Score Decline (>=1SD)					
OR (95% CI)	Crude[a]	1.16 (0.50, 2.69)	1.46 (0.67, 3.25)	REF	0.62
OR (95% CI)	Multiv[b]	1.16 (0.50, 2.71)	1.81 (0.67, 3.25)	REF	0.58
Memory Component Score Decline (>=1SD)					
OR (95% CI)	Crude[a]	1.07 (0.63, 1.80)	0.87 (0.52, 1.48)	REF	0.73
OR (95% CI)	Multiv[b]	1.09 (0.62, 1.92)	0.83 (0.47, 1.45)	REF	0.81

[a] adjusted for age, sex and baseline score

[b] multivariable model, adjusted for age in years, sex, season of blood collection, physical activity (physical activity (PA) score <30, PA score 30–40, PA score 40–50, PA score >=50), education (<5th grade, 5–8th grade, 9–12 grade, some college or college degree, some graduate school), diabetes (yes/no), smoking (never/past/current), alcohol use (never/past current), hypertension (yes/no), BMI (normal weight/overweight/obese), multivitamin supplement use (yes/no), CRP, and APOE (presence of APOE 4).