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The Association of Serum Ionized Calcium and Vitamin D With Adult Cognitive Performance

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Abstract

Background—High serum calcium levels have been associated with cognitive decline in older adults. These associations have not been studied in younger adults. The possible association of vitamin D with cognitive function, independent of calcium, is unknown.

Methods—A cross-sectional study of associations of serum ionized calcium and 25-hydroxyvitamin D levels with cognitive function in younger adults (20–59 years) and older adults (60–90 years) was conducted using data from the US third National Health and Nutrition Examination Survey (NHANES III).

Results—Neither serum ionized calcium nor 25-hydroxyvitamin D was associated with cognitive function in either age group. For example, the confounder-adjusted mean difference in reaction time in young adults was 0.00 (95% confidence interval = −0.07 to 0.06) per 1 SD calcium.

Conclusion—Our results do not support an important role for calcium or vitamin D in cognitive performance in adults.

Disrupted calcium homeostasis plays a part in neurodegeneration,[1] and normalization of calcium levels in persons with hyperparathyroidism improves cognitive function.[2] Calcium ions diffuse through the blood-brain barrier, and serum calcium levels are directly related to extracellular calcium levels in the brain.[3] Vitamin D regulates calcium homeostasis,[4] and several studies have linked vitamin D to cognitive performance.[5-9]

Two prospective studies have shown that high levels of serum calcium are associated with greater cognitive decline in older adults.[10,11] No previous studies have examined the association of serum calcium with cognitive function in young adults, when reverse causality (early undetected cognitive decline resulting in changes to behavior that influence calcium levels) and survivor bias are less likely. If calcium were importantly associated with cognitive function in early life, it might provide a modifiable risk factor for preventing later cognitive decline.

We investigated the association between ionized serum calcium levels and cognitive function among the adults who participated in the third National Health and Nutrition Examination Survey (NHANES III), examining whether any association differed between

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younger adults (age, 20–59 years) and older adults (60–90 years). A previous publication using NHANES III[12] did not replicate the positive associations of vitamin D with cognitive function seen in other studies[5-9,13]; we therefore also investigated whether this was due to calcium masking the effects of 25-hydroxyvitamin D.

METHODS

NHANES III, conducted 1988–1994, is a survey of the noninstitutionalized population of the United States.[14] The data and documentation are freely available at http://www.cdc.gov/nchs/nhanes/nh3rrm.htm. In people age 20–59 years, cognitive function was assessed with 3 different tests, and the number of participants with each assessment varied. Both serum calcium levels and cognitive function test scores were available for 4314–4471 persons and both 25-hydroxyvitamin D levels and test scores for 4760–4932 persons (approximately 30% of NHANES III participants in this age group). For those age 60–90 years, these figures are 4319 and 4831, respectively (52% and 58% of older participants).

Serum calcium was analyzed with NOVA 7 analyzer (Nova Biomedical, Waltham, MA). pH-normalized calcium levels were derived by adjusting the measured ionized calcium for serum pH. 25-hydroxyvitamin D was analyzed with INCSTAR 25-OH-D I^{25} radioimmunoassay (Diasorin, Stillwater, MN).

In persons age 20–59 years, cognitive function was assessed by mean reaction time, mean of the 2 best error-corrected latencies in a symbol-digit substitution test, and the summary score from a serial-digit learning test.[15,16] For older persons, we used a combination score from both the free immediate and delayed recall. These measurements are described in more detail in the eAppendix (http://links.lww.com/EDE/A430).

The following were considered potential confounding factors due to their associations with calcium/vitamin D and cognitive function: age, sex, race/ethnicity, health status, poverty-income ratio of the household, years of education, outdoor physical activity, smoking, and alcohol use. Details of how these were measured are available on the eAppendix (http://links.lww.com/EDE/A430).

Factors that might have affected the performance in computerized cognitive tests (pretest caffeine consumption, familiarity with computer games, examiner, and test language) were included as possible covariables to improve statistical efficiency. There were considerable missing data for smoking and alcohol. In younger adults, data were available for 52% and 50% of participants for alcohol and smoking, respectively. In older adults, data were available for 29% and 57%, respectively. Therefore, these variables were not included in the main analyses, but separate sensitivity analyses were conducted to examine their effect.

Statistical analyses were conducted with Stata 11.0 (Stata Corp LP, College Station, TX). To correctly account for the sampling procedures (including clustering), the analyses were done with the svy procedure, using the sampling weights from mobile examination centers. More methodological details for this are provided in the eAppendix (http://links.lww.com/EDE/A430). We assessed the distribution of participant characteristics across quartiles of pH-normalized serum calcium and 25-hydroxyvitamin D with linear or logistic regression. Multivariable linear regression was used to examine associations of exposures with cognitive function. Serum calcium and 25-hydroxyvitamin D levels and cognitive scores were z-scored to allow the comparison between different models.

RESULTS

In participants age 20–59 years, the weighted mean (standard error) serum pH-normalized calcium was 1.24 (0.00) mmol/L (range, 0.89 to 1.95 mmol/L). Mean 25-hydroxyvitamin D level was 75.3 (1.06) nmol/L (range, 9 to 243 nmol/L). Among the older participants, mean calcium and 25-hydroxyvitamin D levels were 1.23 (0.00) mmol/L (range, 0.81 to 1.84 mmol/L) and 69.0 (0.67) nmol/L (range, 9 to 400 nmol/L), respectively. The correlation coefficient for pH-normalized calcium and 25-hydroxyvitamin D was 0.02 (95% confidence interval [CI]= −0.01 to 0.04) in the younger adults and 0.05 (0.02 to 0.07) in the older adults.

The age- and sex-adjusted characteristics across quartiles of pH-normalized calcium are shown in Tables 1 and 2. The description of these results is provided in the eAppendix (http://links.lww.com/EDE/A430). Equivalent age- and sex-adjusted characteristics across 25-hydroxyvitamin D quartiles are shown in eTables 1 and 2 (http://links.lww.com/EDE/A430).

Table 3 shows the multivariable associations of pH-normalized calcium levels and 25-hydroxyvitamin D with the cognitive test scores in both age groups. Neither pH-normalized serum calcium nor 25-hydroxyvitamin D was associated with any of the cognitive scores in either age group after adjusting for age, race/ethnicity, and sex (Model 1). Further adjustments for other possible confounders did not alter the results (Model 2). With additional mutual adjustment of associations of calcium and 25-hydroxyvitamin D for each other, the null associations remained unchanged (Model 3). The results were also unchanged when we restricted the analysis to participants with data on smoking and alcohol use, and adjustment for these did not alter the null associations (eTable 3, http://links.lww.com/EDE/A430).

DISCUSSION

We know of no previous studies that have examined the association of serum calcium with cognitive function in young adults and compare these results to similar associations in older adults. Our results in older adults are consistent with 2 previous cross-sectional analyses in this age group,[9,10] but not consistent with prospective associations relating calcium to cognitive decline.[10,11,17] Thus, our null cross-sectional findings do not necessarily rule out an association of serum calcium with cognitive decline in older age. Results may also differ among studies because of differences in the ways in which cognitive function is assessed, and in the potential confounding factors that are taken into account. Our results do suggest that between-person variation in serum calcium levels (or 25-hydroxyvitamin D levels) is not associated with cognitive function in early adulthood. In addition, we showed that the previous null association between 25-hydroxyvitamin D levels and cognitive function in the same population[12] was not masked by serum calcium levels.

The main strengths of this study are its sample size, the comparison of associations in younger and older adults, and adjustment for a wide range of potential confounders. The study population is representative of the US adult population (82% response of younger adults and 79% response of older adults who were invited to take part). Serum ionized calcium was measured instead of the total or albumin-adjusted serum calcium. The validity of total or albumin-adjusted calcium as a surrogate for the biologically-active ionized calcium has been questioned.[17,18]

The main weakness is that the study is cross-sectional, and we therefore cannot rule out an overall null effect due to the combination of a true prospective inverse association with calcium and a reverse positive association (ie, adults with higher cognitive function

engaging in more sedentary activities and consuming diets that result in higher levels of serum calcium). Because calcium and, 25-hydroxyvitamin D, together with cognitive function, were available for only 29%–32% of younger adults and 52%–58% of older adults in NHANES III, it is possible that selection bias has affected our results. However, for this selection to have resulted in the null associations we observe, in the presence of true inverse associations with calcium and positive associations with 25-hydroxyvitamin D, we would have to assume that participants with lower calcium or higher 25-hydroxyvitamin D and who were also of higher cognitive ability (or those with higher calcium or lower 25-hydroxyvitamin D, with higher cognitive ability) were more likely to not be included. Although we cannot rule this out, we think it is unlikely. Because only the noninstitutionalized population is sampled for NHANES, it has been suggested that the lack of association of vitamin D with cognition in a previous publication using these data[12] might be due to cognitive homogeneity.[8] The same criticism could be made of our results with respect to calcium. However, only a minority of the population are institutionalized because of poor cognition, particularly at younger ages, and we found no evidence that associations differed between younger and older adults. In both age groups, there was a wide range of cognitive scores, and because most people are not institutionalized these data are relevant most adults in the United States. NHANES III only has single measurements of calcium and 25-hydroxyvitamin D, which may be inadequate to reflect long-term status.[11] However, serum calcium levels are normally maintained at relatively narrow limits within individuals[19]; other studies, including those finding associations with bone phenotypes,[20-22] have used single measurements.

In summary, although some recent data suggest that even moderate hypercalcemia may be related to impaired cognitive performance, our results do not concur with those studies. These data highlight the need for much larger prospective studies on this question.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Age- and Sex-adjusted Characteristics of Young Adults (Age 20–59 Years) in NHANES III Study

Characteristic	No.	Quartiles of pH-normalized Serum Calcium Levels[a]				Test for Trend *P*
		First (0.89–1.21 mmol/L)	Second (1.22–1.24 mmol/L)	Third (1.25–1.27 mmol/L)	Fourth (1.28–1.95 mmol/L)	
Age (years)	10,435	38.2 (37.5–38.9)	37.3 (36.8–37.9)	36.4 (35.6–37.2)	35.6 (34.8–36.3)	<0.001
Education of head of household (years)	10,435	13.0 (12.6–13.3)	13.1 (12.7–13.5)	13.1 (12.7–13.5)	13.3 (12.8–13.8)	0.32
Physician's impression of health; %	14,754					0.68
Excellent	5745	28	27	26	19	
Very good	3531	30	27	24	18	
Good	3510	31	28	23	18	
Fair	1317	35	28	20	17	
Poor	220	42	22	16	21	
No data	431	31	26	21	22	
Outdoor activity during last month; %	10,237	55 (52–59)	57 (55–60)	60 (57–63)	62 (58–66)	0.03
Serum 25-hydroxyvitamin D (nmol/L)	10,425	72.0 (69.4–74.6)	75.8 (72.6–79.0)	76.1 (73.6–78.6)	77.8 (74.6–81.0)	0.003
BMI (kg/m^2)	10,425	27.4 (24.7–30.2)	37.6 (22.7–52.5)	29.4 (26.2–32.6)	26.7 (25.4–28.0)	0.34
Mean of 2 best error-corrected latencies in symbol-digit substitution test (second)	4416	2.6 (2.6–2.7)	2.6 (2.6–2.7)	2.6 (2.5–2.7)	2.6 (2.5–2.7)	0.97
Mean reaction time in simple reaction time test (millisecond)	4471	235(230–240)	232 (227–237)	234 (229–239)	237(232–242)	0.71
Total score in serial-digit learning test	4314	4.3 (3.9–4.7)	4.4(4.1–4.8)	4.2 (3.8–4.7)	4.4 (3.5–5.2)	0.67
Used Spanish in test; %	4472	5 (3–7)	4 (3–6)	3 (2–5)	3 (2–4)	0.01
Women; %	10,435	44(41–46)	46 (44–49)	53 (50–56)	56 (53–59)	<0.001
Current smoker; %	5017	64 (60–68)	64 (60–68)	60 (55–65)	63 (58–68)	0.03
No. days used alcohol during past 12 month	5048	95.7 (87.9–103.5)	93.4 (85.3–101.5)	88.2 (79.7–96.6)	97.5 (89.2–105.9)	0.74
Ethnicity; %	10,435					0.02
Non-Hispanic white	3534	28	29	26	17	
Non-Hispanic black	32,810	24	25	27	25	
Mexican-American	3134	33	30	23	14	
Other	487	32	29	22	17	
Poverty-income ratio below 1; %	10,435	11 (9–13)	12 (10–15)	12 (10–15)	15 (11–19)	0.15

[a] Data are given as mean (95% confidence interval), unless otherwise indicated. Due to rounding, some % values in do not add up to 100%.

TABLE 2

Age- and Sex-adjusted Characteristics of Old Adults (Age 60–90 Years) of the NHANES III Study

Characteristic	No.	Quartiles of pH-normalized Serum Calcium Levels[a]				Test for Trend *P*
		First (0.81–1.20 mmol/L)	Second (1.21–1.23 mmol/L)	Third (1.24–1.26 mmol/L)	Fourth (1.27–1.84 mmol/L)	
Age (years)	4319	71.4 (70.5–72.2)	70.6 (69.9–71.3)	71.0 (70.4–71.6)	70.8 (70.1–71.6)	0.41
Education of head of household (years)	4319	11.8 (11.4–12.3)	11.3 (10.9–11.8)	10.8 (10.4–11.3)	10.7 (10.3–11.1)	<0.001
Physician's impression of health; %	4319					0.94
Excellent	587	26	27	23	24	
Very good	1041	26	27	22	25	
Good	1507	25	25	23	26	
Fair	901	27	25	24	24	
Poor	167	35	24	18	23	
No data	116	29	23	26	22	
Outdoor activity during last month; %	4319	59 (53–65)	60 (55–64)	59 (55–63)	58 (53–63)	0.34
Serum 25-hydroxyvitamin D (nmol/L)	4310	66.5 (64.9–68.1)	68.8 (66.8–70.8)	72.2 (70.0–74.5)	70.2 (67.6–72.8)	0.002
BMI (kg/m^2)	4319	26.9 (26.5–27.2)	26.9 (26.5–27.4)	27.1 (26.5–27.6)	26.8 (26.4–27.3)	0.93
Combined recalled items (max 12)	4319	8.0 (7.7–8.3)	7.9 (7.7–8.2)	8.0 (7.7–8.3)	8.1 (7.8–8.3)	0.53
Women; %	4319	47 (44–51)	44 (41–48)	44 (41–47)	34 (30–38)	<0.001
Current smoker; %	2310	28 (24–33)	22 (18–27)	22 (18–28)	29 (23–35)	0.87
No. days used alcohol during past 12 months	1242	185.8 (156.3–215.3)	178.0 (138.5–217.5)	140.2 (119.1–161.2)	161.2 (131.1–191.2)	0.007
Ethnicity; %	4319					0.31
Non-Hispanic white	2540	27	26	23	24	
Non-Hispanic black	833	21	24	24	32	
Mexican-American	834	31	27	22	21	
Other	112	23	29	21	27	
Poverty-income ratio below 1; %	4319	7 (5–9)	8 (6–10)	11 (9–14)	11(8–14)	0.05

[a] Data are given as mean (95% confidence interval), unless otherwise indicated. Due to rounding, some % values in do not add up to 100%.

TABLE 3

Association of Circulating pH-normalized Calcium and 25-Hydroxyvitamin D Levels With Cognitive Test Scores (Both in z-Scores).

			Mean Difference in Test Score (SD) per 1 SD Increase in Serum Levels (95% CI)		
	No.	SD	Model 1[a]	Model 2[b]	Model 3[c]
pH-normalized serum calcium					
Age 20–59 years					
Mean reaction time[d]	4471	57.7	0.00 (−0.07 to 0.06)	−0.00 (−0.07 to 0.06)	0.00 (−0.08 to 0.07)
Best symbol-digit substitution test score[d]	4416	1.23	0.02 (−0.02 to 0.05)	0.01 (−0.02 to 0.04)	0.02 (−0.04 to 0.07)
Total serial-digit learning test score[d]	4314	5.1	0.03 (−0.02 to 0.08)	0.03 (−0.02 to 0.07)	−0.02 (−0.09 to 0.05)
Age 60–90 years					
Recalled items	4319	3.1	0.02 (−0.10 to 0.13)	0.00 (−0.03 to 0.04)	−0.02 (−0.11 to 0.06)
Serum 25-hydroxyvitamin D					
Age 20–59 years					
Mean reaction time[d]	4929	57.5	−0.03 (−0.06 to 0.01)	−0.02 (−0.05 to 0.02)	0.00 (−0.04 to 0.04)
Best symbol-digit substitution test score[d]	4869	1.22	0.00 (−0.02 to 0.02)	0.01 (−0.01 to 0.03)	0.00 (−0.03 to 0.03)
Total serial-digit learning test score[d]	4760	5.1	−0.01 (−0.04 to 0.03)	0.00 (−0.03 to 0.04)	0.01 (−0.05 to 0.06)
Age 60–90 years					
Recalled items	4831	3.1	−0.01 (−0.04 to 0.03)	−0.02 (−0.05 to 0.01)	−0.01 (−0.06 to 0.05)

[a] Model 1 is adjusted for age, race/ethnicity and sex.

[b] Model 2 is adjusted for same variables as Model 1 plus outdoor activity during past month, physician's impression of health status, BMI, and poverty-income ratio.

[c] Model 3 is adjusted for same variables as Model 2 plus mutual adjustment for 25-hydroxyvitamin D and calcium.

[d] Adjusted for language used in test, examiner, familiarity with computer games, and caffeine consumption within 3 hours.