Serum Sodium in Relation to Various Domains of Cognitive Function in the Elderly US Population

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Abstract

Background:

Recent evidence suggests that sodium imbalances may be associated with cognitive impairment; however, the association between specific domains of cognition remains unclear. This study examines the association between serum sodium levels and immediate and delayed verbal memory as measured by the CERAD Word Learning Test (CERAD WLT), executive function as measured by the Animal Fluency test (AFT), and sustained attention, working memory, and processing speed as measured by the Digit Symbol Substitution test (DSST) in the elderly population of the US aged 60 and older who participated in the 2011–2014 National Health and Nutrition Examination Surveys (n=2,700).

Methods:

Cognitive function tests were performed by trained interviewers and sodium levels were measured using indirect ion selective electrode methodology.

Results:

After adjusting for all covariates, CERAD WLT scores showed significant positive associations with sodium levels (Immediate recall (IR) $\beta = 0.11$ (SE = 0.04, p-value 0.018); Delayed recall (DR) $\beta = 0.07$ (SE = 0.03, p-value 0.009)). Compared to individuals with normal sodium levels, individuals with hyponatremia were significantly associated with lower CERAD WLT-DR ($\beta = -0.71$, SE = 0.23, p-value 0.005) and AFT scores ($\beta = -1.58$, SE = 0.68, p-value 0.027), and showed a borderline significant relationship with lower CERAD WLT-DR scores ($\beta = -1.11$, SE = 0.56, p-value 0.057). Individuals with hypernatremia did not show any significant relationships with cognitive test scores, compared to those with normal sodium levels.

Conclusions:

Our cross-sectional study showed that lower sodium levels were associated with cognitive change, especially regarding memory and executive function.

1. Background

Sodium is one of the major extra-cellular fluid electrolytes, which is important in maintaining extracellular fluid volume and potentials across cell membranes (1, 2). Imbalances in sodium concentrations have been known to manifest as headaches, confusion, nausea, and restlessness, while rapid changes in sodium concentrations result in acute neurologic symptoms such as seizures and impaired mental status (2, 3). Hyponatremia is commonly defined as serum sodium concentrations less than 136 mmol/L and is prevalent in the elderly due to impaired water-excretory capacity associated with normal aging (4). Most cases of hyponatremia are mild and relatively asymptomatic; however, recent evidence suggests that hyponatremia may be associated with gait disturbances, falls, and cognitive impairment (5–9).

Only a few studies have addressed the relationship between serum sodium levels and cognitive function; however, the definition of cognitive function appears to vary among studies. In addition, studies only examine single domains of cognitive function, or assess multiple domains grouped as a single variable. Previous studies addressing the relationship between serum sodium levels and cognitive function have assessed cognitive function using a combination of attention tests (Visual Vigilance, Working Memory or Digit Span, Go/No Go, Intermodal Comparison, Divided Attention, Phasic Alert tests) (7), the Audio Recorded Cognitive Screening (ARCS) tool (8), a combination of the modified Mini-Mental Status Exam (MMSE) and the Trail Making Test (9), and a combination of the Mini Mental State Examination and Clock Completion Test (5). In addition, most previous studies are limited to specific populations (i.e. men or single hospital settings) (5, 7, 9).

Cognitive change is part of the normal process of aging (10). In contrast to cognitive domains such as language, some cognitive abilities such as memory, executive function, and processing speed decline over time, and the rate of decline varies among individuals (10, 11). Cognitive performance is usually categorized in terms of domains of functioning (i.e. executive functioning, processing speed), and these domains are linked to specific areas of the brain (12, 13). In order to differentiate between the various types of conditions causing cognitive impairment, specific subdomains are assessed separately (13). As a result, it is of importance to determine the specific domains of cognitive function associated with serum sodium levels. Our study aims to assess the relationship between serum sodium levels and various domains of cognitive function including, memory, executive function, and processing speed using the CERAD Word Learning Test (CERAD WLT), Animal Fluency test (AFT), and the Digit Symbol Substitution test (DSST) in the elderly population of the US aged 60 and older.

2. Methods

2.1. Study population

Data on serum sodium levels and cognitive test scores were obtained from the 2011–2012 and 2013–2014 National Health and Nutrition Examination Surveys (NHANES), a representative survey of the non-institutionalized population in the US (14). A total of 19,931 individuals were included from both cycles, and the CERAD WLT-IR was conducted in 3,131 individuals. Among these subjects, serum sodium levels were measured in 2,946 individuals, and 2,700 individuals had data for all covariates.

2.2 Cognitive Tests

The NHANES cognitive functioning questionnaire included the CERAD WLT, AFT, and DSST. The CERAD WLT evaluates immediate and delayed verbal memory. The test is composed of three consecutive learning trials, followed by a delayed recall test. Each learning trial is followed by an immediate recall test. In the learning trials, participants were presented with 10 words. Immediately following the learning trial, participants were instructed to recall as many words as possible. The number of words correctly recalled was recorded as the score for each learning trial, with a maximum possible score of 10. This process was repeated three times, and the final score for the CERAD WLT-IR was recorded as the sum of scores from the three trials. The delayed recall test was conducted after conducting the AFT and DSST (approximately 8–10 minutes after starting the CERAD WLT). Participants were asked to recall as many words as possible, and scores were recorded as a number out of 10. The AFT assesses executive function. Participants were instructed to name as many animals as possible in one minute, and the number of animals named was recorded as the score. Individuals who did not pass the practice test, naming three articles of clothing, did not participate in the AFT. The DSST examines sustained attention, working memory, and processing speed. The test consists of a paper form that has a legend at the top in which 9 numbers are matched with 9 symbols. Participants are given 133 numbers and are asked to copy the corresponding symbol presented in the legend. The total number of correct matches copied within 2 minutes is recorded as the score out of 133 (15, 16).

2.3 Measurements of Serum Sodium Levels

Blood samples were collected by a phlebotomist at the NHANES Mobile Examination Centers (17, 18). Specimens were stored at appropriate refrigerated conditions (2–8 degrees Celsius) before being shipped to the Collaborative Laboratory Services, Ottumwa, Iowa for analysis. Sodium levels were measured using the DxC800 system using indirect ion selective electrode methodology. The DxC800 measures sodium levels using the voltage created by sodium ion exchange (19, 20).

2.4 Other Variables of Interest

Covariates were obtained from the NHANES 2011–2014 and included sex (male or female), age, ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), annual family income (less than $20,000 or $20,000 or more), education (less than high school, high school graduate, or more than high school), marital status (married, never married, widowed, divorced, separated, or living with partner), smoking status (never, former smokers, or current smoker), alcohol consumption (yes or no), physical activity (yes or no), body mass index (BMI) (underweight (< 18.5 kg/m2), normal weight (18.5–24.9 kg/m2), overweight (25.0–29.9 kg/m2), or obese (> 30 kg/m2)), glomerular filtration rate (GFR) (ml/min per 1.73 m^2), and serum glucose levels (mg/dL). GFR was calculate using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI eGFR) (21).

2.5 Statistical Analysis

Serum sodium levels were analyzed as both continuous and categorical variables by hyponatremia, normonatremia, and hypernatremia status. Pearson's correlation coefficients among cognitive test scores and serum sodium levels were calculated. Linear regression analysis was performed to determine the relationship between serum sodium levels and cognitive test scores, and provided beta coefficients and standard errors (SE) for cognitive test scores among individuals with hyponatremia and hypernatremia compared to those with the normal serum sodium levels as the reference group. The adjusted linear regression model 1 was adjusted for all potential confounders including age, sex, race, income, education, marital status, smoking history, alcohol consumption, physical activity, BMI, and GFR. The adjusted model 2 was additionally adjusted for serum glucose levels.

To account for the complex sampling design, weighted estimates of the population parameters. Analyses were performed with the PROC SURVEY procedures of SAS 9.4 statistical analysis package (SAS Institute, Cary, NC, USA). The statistical significance was set at $\alpha = 0.05$.

3. Results

The characteristics of the study population with data for CERAD WLT-IR (n = 2,700) are shown in Table 1. The mean age of participants was 69.6 (± 6.8) years (range: 60–80), and women represented 51.5% of the overall sample. Most participants were non-Hispanic white (48.7%), not impoverished (74.4%), had an education beyond high school (50.7%), and married (55.0%). A majority of the participants were overweight (35.3%) or obese (37.9%). Mean CKD-EPI eGFR was 73.5 (± 19.8) ml/min per 1.73 m^2 and mean serum glucose was 112.8 (± 43.3) mg/dL.

Table 1
Characteristics of the study population

Characteristics	Mean ± SD or N(%)
No of participants	2700
Sex	
Male	1310 (48.5%)
Female	1390 (51.5%)
Age at interview (year)	69.6 ± 6.8
Ethnicity	
Non-Hispanic white	1316 (48.7%)
Non-Hispanic black	615 (22.8%)
Hispanic	514 (19.0%)
Others	255 (9.4%)
Annual Family Income	
Less than $20,000	692 (25.6%)
$20,000 and over	2008 (74.4%)
Education	
Less than high school	696 (25.8%)
High school graduate	634 (23.5%)
More than high school	1370 (50.7%)
Marital status	
Married	1484 (55.0%)
Never married	152 (5.6%)
Widowed/divorced/separated	1064 (39.4%)
Smoking history	
Never smoked	352 (13.0%)

[a] Response to the question: "In any one year, have you had at least 12 drinks of any type of alcoholic beverage?"

[b] Response to the question: "In a typical week do you do any moderate-intensity sports, fitness, or recreational activities that cause a small increase in breathing or heart rate such as brisk walking, bicycling, swimming, or volleyball for at least 10 minutes continuously?"

Characteristics	Mean ± SD or N(%)
Ex-Smoker	1015 (37.6%)
Current Smoker	1333 (49.4%)
Alcohol consumption[a]	
Yes	1832 (67.9%)
No	868 (32.1%)
Physical Activity[b]	
Yes	1055 (39.1%)
No	1645 (60.9%)
BMI (kg/m^2)	
Underweight (< 18.5)	38 (1.4%)
Normal weight (18.5–24.9)	685 (25.4%)
Overweight (25.0-29.9)	953 (35.3%)
Obesity (> 30)	1024 (37.9%)
CKD-EPI eGFR, ml/min per 1.73 m^2	73.5 ± 19.8
Serum glucose, mg/dL	112.8 ± 43.3

[a] Response to the question: "In any one year, have you had at least 12 drinks of any type of alcoholic beverage?"

[b] Response to the question: "In a typical week do you do any moderate-intensity sports, fitness, or recreational activities that cause a small increase in breathing or heart rate such as brisk walking, bicycling, swimming, or volleyball for at least 10 minutes continuously?"

Table 2 shows the distribution of participants among cognitive function tests, and the means and Pearson correlation coefficients among sodium levels and cognitive test scores. The average sodium level was 139.7 (± 2.5) mmol/L, and the mean scores for the CERAD WLT-IR, CERAD WLT-DR, AFT, and DSST were 18.7 (± 4.9), 5.9 (± 2.4), 16.6 (± 5.5), and 46.4 (± 17.2) respectively. Sodium showed positive correlations with the test scores, and all correlations were significant excluding the relationship between sodium and AFT scores. Statistically significant ($p < 0.05$) positive correlation coefficients were observed between all cognitive test scores.

Table 2
Means and Pearson correlation coefficients among sodium levels and cognitive test scores in the study population

	n	Mean ± SD	Pearson’s correlation coefficients (p-value)				
			Sodium, mmol/L	CERAD WLT		AFT score	DSST score
				IR score	DR score		
Sodium, mmol/L		139.7 ± 2.5	1.00				
CERAD WLT-IR score	2700	18.7 ± 4.9	0.09 (< 0.001)	1.00			
CERAD WLT-DR score	2697	5.9 ± 2.4	0.08 (< 0.001)	0.73 < 0.001)	1.00		
AFT score	2686	16.6 ± 5.5	0.03 (0.093)	0.39 (< 0.001)	0.35 (< 0.001)	1.00	
DSST score	2619	46.4 ± 17.2	0.06 (0.002)	0.47 (< 0.001)	0.45 (< 0.001)	0.50 (< 0.001)	1.00

Table 3 shows the results of linear regression analyses between serum sodium levels and cognitive test scores. CERAD WLT-IR and CERAD WLT-DR showed significant positive associations with sodium levels in all models (CERAD WLT-IR: unadjusted model: 0.12 (SE = 0.04, p-value 0.007), model 1: 0.12 (SE = 0.04, p-value 0.009), model 2: 0.11 (SE = 0.04, p-value 0.018); CERAD WLT-DR: unadjusted model: 0.07 (SE = 0.02, p-value 0.003), model 1: 0.08 (SE = 0.02, p-value 0.004), model 2: 0.07 (SE = 0.03, p-value 0.009)). Beta coefficients for the associations between AFT and DSST scores, and sodium levels showed positive associations with varying significance. In the unadjusted model DSST scores showed a borderline significant association with sodium levels (beta = 0.24, SE = 0.14, p-value 0.099) and AFT scores showed a borderline significant association with sodium levels in model 1 (beta = 0.07, SE = 0.04, p-value 0.080). All other associations were not significant.

Table 3
Associations between serum sodium levels and cognitive test scores by linear regression models

Model	Cerad immediate recall (n = 2700)		Cerad delayed recall (n = 2697)		AFT (n = 2686)		DSST (n = 2619)	
	Beta ± SE	P	Beta ± SE	P	Beta ± SE	P	Beta ± SE	P
Unadjusted	0.12 ± 0.04	0.007	0.07 ± 0.02	0.003	0.07 ± 0.04	0.147	0.24 ± 0.14	0.099
Model 1[a]	0.12 ± 0.04	0.009	0.08 ± 0.02	0.004	0.07 ± 0.04	0.080	0.21 ± 0.13	0.114
Model 2[b]	0.11 ± 0.04	0.018	0.07 ± 0.03	0.009	0.06 ± 0.04	0.148	0.16 ± 0.13	0.229

[a] Adjusted for age, marital status, ethnicity, smoking status, alcohol consumption, physical activity, income, obesity, education GFR

[b] Adjusted for model 1 + serum glucose levels

Table 4 shows the associations between serum sodium levels and cognitive test scores by hyponatremia and hypernatremia status. Compared to individuals with normal sodium levels, individuals with hyponatremia were significantly associated with lower cognitive test scores in the unadjusted model (CERAD WLT-IR beta = -1.91, SE = 0.60, p-value 0.003; CERAD WLT-DR beta = -1.08, SE = 0.25, p-value < 0.001; AFT beta = -2.65, SE = 0.66, p-value < 0.001; DSST beta = -6.87, SE = 2.57, p-value 0.012). In Model 1, individuals with hyponatremia were significantly associated with lower CERAD WLT-IR (beta = -1.20, SE = 0.56, p-value 0.038), CERAD WLT-DR (beta = -0.78, SE = 0.23, p-value 0.002), and AFT scores (beta = -1.68, SE = 0.73, p-value 0.028), compared to individuals with normal sodium levels. In Model 2, individuals with hyponatremia were significantly associated with lower CERAD WLT-DR (beta = -0.71, SE = 0.23, p-value 0.005) and AFT scores (beta = -1.58, SE = 0.68, p-value 0.027), and showed a borderline significant relationship with lower CERAD WLT-DR scores (beta = -1.11, SE = 0.56, p-value 0.057). In contrast, individuals with hypernatremia did not show any significant relationships with cognitive test scores, compared to those with normal sodium levels.

Table 4
Linear regression analysis of serum sodium levels and cognitive test scores by hyponatremia and hypernatremia status

Test type	Model	Hyponatremia (< 135 mmol/L)		Normal (135–145 mmol/L)		Hypernatremia (> 145 mmol/L)	
		Beta ± SE	**P**	**Beta ± SE**	**P**	**Beta ± SE**	**P**
CERAD WLT-IR	n	93		2599		9	
	Unadjusted	-1.91 ± 0.60	0.003	Reference		3.31 ± 2.34	0.167
	Model 1[a]	-1.20 ± 0.56	0.038	Reference		2.88 ± 2.05	0.170
	Model 2[b]	-1.11 ± 0.56	0.057	Reference		2.96 ± 2.09	0.166
CERAD WLT-DR	n	93		2596		9	
	Unadjusted	-1.08 ± 0.25	< 0.001	Reference		1.12 ± 0.92	0.233
	Model 1[a]	-0.78 ± 0.23	0.002	Reference		0.98 ± 0.82	0.241
	Model 2[b]	-0.71 ± 0.23	0.005	Reference		1.04 ± 0.84	0.227
AFT	n	93		2584		10	
	Unadjusted	-2.65 ± 0.66	< 0.001	Reference		-2.31 ± 2.68	0.395
	Model 1[a]	-1.68 ± 0.73	0.028	Reference		-2.61 ± 1.90	0.178
	Model 2[b]	-1.58 ± 0.68	0.027	Reference		-2.53 ± 1.95	0.203
DSST	n	87		2524		9	
	Unadjusted	-6.87 ± 2.57	0.012	Reference		4.21 ± 7.10	0.557
	Model 1[a]	-3.25 ± 2.25	0.159	Reference		2.54 ± 4.61	0.585

[a] Adjusted for age, marital status, ethnicity, smoking status, alcohol consumption, physical activity, income, obesity, education GFR

[b] Adjusted for model 1 + serum glucose levels

	Model 2[b]	-2.77 ± 2.25	0.228	Reference	3.00 ± 4.89	0.543

[a] Adjusted for age, marital status, ethnicity, smoking status, alcohol consumption, physical activity, income, obesity, education GFR

[b] Adjusted for model 1 + serum glucose levels

4. Discussion

In a cross-sectional study of United States women sampled from the 2010–2011 and 2013–2014 NHANES, serum sodium levels were positively associated with cognitive test scores in the elderly. Serum sodium levels were positively associated with CERAD WLT scores, which assess the memory sub-domain. Compared to individuals with normal sodium levels, individuals with serum sodium levels below 135 mmol/L showed lower CERAD WLT (memory sub-domain) and AFT (executive function) scores. The relationship between hyponatremia status and the DSST, which assesses processing speed, sustained attention, and working memory scores, was no longer significant after adjustment. In short, serum sodium levels were significantly associated with the memory sub-domain assessed by the CERAD WLT and executive function assessed by the AFT, but not with processing speed, sustained attention, and working memory evaluated by the DSST.

In line with the results of our study, previous studies have reported an association between low sodium levels and cognitive function; however, these studies have only examined single domains of cognitive function (i.e. attention), or have assessed multiple domains grouped as a single variable. A case-control study performed in a general hospital in Brussels reported that individuals with low serum sodium levels (n = 122, range: 115–132 mmol/L, mean ± standard deviation [SD] = 126 ± 5 mmol/L) were associated with a higher odds of falling (odds ratio [OR] = 67.43, 95% confidence interval [CI] = 7.48–607.42) and significantly slower mean response times in the attention tests (difference: 58 milliseconds, P < .001) compared to individuals with normal sodium levels (n = 244, mean ± SD = 139 ± 2 mmol/L) (7). Eight different visual and auditory attention tests were included in the battery of attentional tests (7). A cross-sectional study from the Hunter Community Study, a population-based prospective cohort study in Australia revealed that subjects with serum sodium levels equal to 130 mmol/L showed lower ARCS tool scores compared to individuals with serum sodium levels equal to 135 mmol/L (8). The ARCS scores is a vague tool which reflects a wide range of cognitive domains (22). A recent study from the Osteoporotic Fractures in Men study, revealed that men with sodium levels of 126–140 mmol/L were associated with a 1.30 odds (95% CI = 1.06–1.61) of cognitive impairment, compared to individuals with sodium levels of 141–142 mmol/L. In this study, cognitive impairment was defined as a modified Mini-Mental Status score less than 84 or a Trail Making Test Part B time greater than 233 seconds (9). In addition, a study conducted in 150 patients aged 70 years and older from the University Hospital Cologne, showed that resolution of hyponatremia (< 130 mmol/L) by > 5 mmol/L was significantly associated with an increase in MMSE scores (ΔMMSE: 1.8 ± 3.0 vs. 0.7 ± 1.9; p = 0.002) (23). Reversibility has also been reported in previous animal studies mentioned below (24, 25).

The mechanisms behind this association is unclear; however, abnormalities in brain osmolyte levels such as glutamate may play a role (6, 24, 25). In chronic hyponatremia, brain cells export osmolytes such as glutamate, which may influence memory (26, 27). An animal study showed that sustained low levels of serum sodium concentrations caused reversible cognitive impairment measured by a novel object recognition test and contextual fear conditioning tests (25). In vivo analysis of brain samples from chronic hyponatremic rats in this study revealed elevated extracellular glutamate concentrations in the hippocampus and decreased glutamate uptake by astrocyte cultures (25, 28). In addition, another study in rats proposed brain cell swelling as another explanation. In this study, rats with chronic hyponatremia, which showed reversible memory impairments assessed using the passive avoidance test, also showed brain swelling (24). However, the reason why lower serum sodium levels are associated with memory sub-domain and executive function, in contrast to sustained attention, working memory, and processing speed, is unknown, and further studies are recommended to clarify the mechanism behind such association.

Our study has examined the relationship between serum sodium levels and various cognitive domains in a nation-wide population of US adults. Nevertheless, our study has several limitations. Firstly, due to the cross-sectional nature of the study, any casual or temporal relationships cannot be assessed. Moreover, due to the cross-sectional nature of the NHANES data, we were unable to differentiate between acute and chronic hyponatremia. Despite this fact, it is more likely that the sodium status of most participants reflect chronic levels as acute changes in sodium levels are known to cause neurologic symptoms (i.e. seizures and altered mental status) as a result of cerebral edema (3). Thirdly, the relationship between cognitive test scores and serum sodium levels may not necessarily be linear. Resultantly, our results may not be generalized to populations with different sodium levels. Fourthly, although we have considered basic sociodemographic variables, GFR, and serum glucose levels as covariates, previous studies have also included disease history and quality-of-life measures (7, 9). Therefore, we cannot completely eliminate the possibility of residual confounding. Fifthly, the range of cognitive test scores performed by the NHANES remains limited, and further studies evaluating the relationship between other domains of cognitive function and serum sodium levels are recommended.

5. Conclusions

In conclusion, lower sodium levels were associated with cognitive change, especially regarding memory and executive function in a population based study of US adults aged 60 and over, pointing to hyponatremia as a risk factor of cognitive impairment. When evaluating memory and executive function in the elderly, serum sodium levels should be taken into account, as they may cause reversible changes in cognitive function. In addition, further studies should be conducted in order to elucidate the mechanism behind such relationships.

6. Abbreviations

CERAD Word Learning Test (CERAD WLT), Immediate recall (IR), Delayed recall (DR), Digit Symbol Substitution test (DSST), Animal Fluency test (AFT), National Health and Nutrition Examination Surveys (NHANES), body mass index (BMI), glomerular filtration rate (GFR), Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI eGFR), standard errors (SE), odds ratio (OR), standard deviation (SD), confidence interval (CI), Audio Recorded Cognitive Screening (ARCS), mini-mental state examination (MMSE)

Declarations

Ethics approval and consent to participate

The present study was exempt from formal ethics review as a secondary analysis of existing NHANES public data under the US Health & Human Services (HHS) regulations at 45 CFR 46.101(b). The NHANES surveys were approved by the US National Center for Healthcare Statistics (NCHS) Research Ethics Review Board (ERB), and the NCHS IRB/ERB protocol number for NHANES 2011-2014 was a continuation of #2011-17. Participants gave written informed consent before the home interview and health exams.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are available on the NHANES website, https://www.cdc.gov/nchs/nhanes/index.htm.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SHL, JYM, BK, SWH, JHH, and KBM made substantial contributions to the conception and design of the work. SHL, JYM, and KBM analyzed and interpreted the data. BK, SWH, and JHH have contributed to drafting and substantively revising the work. All authors read and approved the final manuscript.

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