Serum Sodium and Cognition in Older Community-Dwelling Men

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Abstract

Background and objectives Mild hyponatremia is a common finding in older adults; however, the association of lower serum sodium with cognition in older adults is currently unknown. We determined whether lower normal serum sodium is associated with cognitive impairment and risk of cognitive decline in community-dwelling older men.

Design, setting, participants, & measurements Five thousand four hundred thirty-five community-dwelling men aged ≥65 years who participated in Osteoporotic Fractures in Men, a cohort study with a median follow-up for cognitive function of 4.6 years, were included in this analysis. Multivariable logistic regression was used to examine the association between baseline fasting serum sodium levels and the odds of prevalent cognitive impairment (cross-sectional analysis; modified Mini-Mental Status [3MS] score <1.5 SD [<84] below or Trail Making Test Part B time >1.5 SD above the mean [>223 seconds]) and cognitive decline (prospective analysis [*n*=3611]; decrease in follow-up 3MS score or increase in Trails B time >1.5 SD of the mean score/time change [>9 or >67 seconds]).

Results Participants were aged 74±6 years with a fasting mean serum sodium level of 141±3 mmol/L. Fifteen percent (*n*=274), 12% (*n*=225), and 13% (*n*=242) had prevalent cognitive impairment in tertiles 1, 2, and 3, respectively. After adjustment, lower serum sodium was associated with prevalent cognitive impairment (tertile 1 [126–140 mmol/L] versus tertile 2 [141–142 mmol/L], odds ratio [OR], 1.30; 95% confidence interval [95% CI], 1.06 to 1.61). Fourteen percent (*n*=159), 10% (*n*=125), and 13% (*n*=159) had cognitive decline in tertiles 1, 2, and 3, respectively. Lower serum sodium was also associated with cognitive decline (tertile 1 versus tertile 2, OR, 1.37; 95% CI, 1.06 to 1.77). Tertile 3 (143–153 mmol/L) was additionally associated with cognitive decline. Results were similar in sensitivity analyses according to clinical cut-offs and by quartiles.

Conclusions In community-dwelling older men, serum sodium between 126–140, and 126–140 or 143–153 mmol/L, are independently associated with prevalent cognitive impairment and cognitive decline, respectively.

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Introduction

Subtle impairments in cognition are common with aging, even in the absence of clinically apparent dementia (1). In particular, conceptual reasoning, memory, processing speed, attention, and working memory, as well as some executive functions, decline with aging (1,2). Older adults with mild cognitive impairment are more likely to experience cognitive decline over time and to progress to dementia or Alzheimer's disease (3–5).

Hyponatremia is also a common but generally mild condition in older adults, with an increasing prevalence with advancing age (6–8). It is less common and usually milder in community-dwelling adults compared with hospitalized older adults (6). Although mild hyponatremia was once thought to be asymptomatic, recent studies suggested it is linked to attention deficits, gait disturbances, and risk of falls in patients admitted to the emergency department (9,10). Additionally, mild hyponatremia has been associated with risk of fracture, cardiovascular events, and mortality in community-dwelling adults (11–14).

Cognitive impairment and neurologic disturbances can occur with severe hyponatremia, particularly with large or rapid decreases in serum sodium levels (15–17). However, the association between lower serum sodium and impaired cognition in older adults is currently uncertain. We hypothesized that lower normal serum sodium would be associated with prevalent cognitive impairment and the risk of cognitive decline over time in asymptomatic, community-dwelling older men.

Materials and Methods

Study Design

The study methods of the Osteoporotic Fractures in Men (MrOS) study have been described previously (18).

Briefly, 5994 men 65 years of age or older were recruited from six geographic areas: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monongahela Valley near Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California, between March of 2000 and April of 2002 (19). To be eligible, participants had to be able to walk unassisted, be free from bilateral hip replacement, and be able to provide self-reported data; they had to reside near a clinical site for the study duration, be free from medical conditions that (in the judgment of the investigator) would result in imminent death, and be able to provide informed consent. Among 5994 individuals who participated in baseline testing, 461 were missing laboratory data. Of the remaining 5533, 25 were excluded due to missing data for serum sodium, any cognitive testing (*i.e.*, missing both modified Mini-Mental Status [3MS] examination score and Trail Making Test Part B [Trails B] time), and/or covariates (described below). An additional 73 participants were missing data for baseline cognitive impairment (*i.e.*, missing 3MS score or Trails B time and not meeting the criteria for cognitive impairment for the opposite test), leaving 5435 participants to be included in the prevalent analyses. Participants were included in the analysis if they met criteria for cognitive impairment for one test (*i.e.*, 3MS or Trails B time, with data for the opposite test missing). This decision was made because if criteria were met for cognitive impairment for one test, classification would not change regardless of performance on the opposite test; however, if criteria were not met for cognitive impairment for one test, it was not possible to classify a person as unimpaired without having information from the opposite test.

Of the 5435 participants, 3647 who did not have cognitive impairment at baseline (741 had baseline cognitive impairment) both attended in the follow-up visit (between January of 2005 and December of 2006) and had measurement of cognitive function, thus were considered for analysis of cognitive decline. Of the 3647, 36 were excluded due to missing data for cognitive impairment (*i.e.*, missing 3MS score or Trails B time and not meeting the criteria for cognitive impairment for the opposite test), and the remaining 3611 were included in the cognitive decline analyses. All participants provided written informed consent, and this study was approved by the investigational review boards at the participating centers in adherence with the Declaration of Helsinki.

Study Variables

Serum sodium was measured in fasting baseline samples stored at −70°C and thawed for analysis at a central laboratory (Oregon Veterans Administration Clinical Laboratory, Portland, OR) using a Roche COBAS Integra 800 automated analyzer (Roche Diagnostics Corp., Indianapolis, IN). The analyzer was calibrated daily and the interassay coefficient of variation for serum sodium was 2.5% (20).

Cognitive function was evaluated at baseline (2000–2002) and follow-up (in 2005) by both the 3MS examination (21) and Trails B time (22). Cognitive impairment was defined as described previously (23–25). Cognitive impairment at baseline (prevalent analyses) was defined as a 3MS score <1.5 SD below the mean (<84) or Trails B time >1.5 SD above the mean (>223 seconds), on the basis of previously established criteria (23–25). Cognitive impairment at follow-up (cognitive decline analyses) was defined as a decrease in 3MS score or increase in Trails B time >1.5 SD of the mean change in completion score (>9) or time (>67 seconds), respectively.

Confounders related to serum sodium and cognitive impairment, all measured at baseline, were selected *a priori* as potential covariates, and all were measured at baseline. Baseline questionnaires and interviews were administered by trained and certified clinical staff. Race/ethnicity, education, smoking status, and alcohol intake were determined by self-report. Education was classified into five categories (high school or less, some college, college, some graduate school, and graduate school). Smoking was defined as current, former, or never. Alcohol intake was characterized as a dichotomous variable according to whether 12 or more drinks had been consumed in the past 12 months, on the basis of overall low intake in the MrOS cohort (18). Body-mass index was calculated using body weight measured using a balance beam or digital scale and height measured with a Harpenden stadiometer. Physical activity was measured using the Physical Activity Scale for the Elderly questionnaire (26).

Creatinine was measured using fasting baseline serum samples stored at −70°C and thawed for analysis at a central laboratory (Oregon Veterans Administration Clinical Laboratory, Portland, OR), using an enzymatic method calibrated with materials assayed by isotope-dilution mass spectrometry and an interassay coefficient of variation of 5.3% (27). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (28). Analysis of serum glucose was performed using a hexokinase method at the University of Washington using previously unthawed, fasted samples stored at −70°C. The interassay coefficient of variation on the basis of blind duplicates was <3% (29). Serum glucose was measured as ancillary study and was missing in n=141 and n=81 in the cross-sectional and longitudinal analyses, respectively. History of diabetes, hypertension, stroke, chronic obstructive pulmonary disease, or cardiovascular disease (defined as history of myocardial infarction, angina, or heart failure) was determined by self-report of diagnosis by a doctor or other health care provider. Health-related quality of life was evaluated using a modified Medical Outcomes Study 12-Item Short Form Mental Health Composite Score, with a modification classifying health status according to five categories (excellent, good, fair, poor, or very poor) (30). Participants were asked to bring all of the medications they had taken in the past 30 days to the clinical center for data collection. All medications recorded by the clinics were entered into an electronic medications inventory (San Francisco Coordinating Center, San Francisco, CA). Each medication was matched to its ingredient(s) on the basis of the Iowa Drug Information Service Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA) (31). BP was measured in rested, seated participants.

Statistical Analyses

The association of serum sodium with prevalent cognitive impairment and cognitive decline was assessed using

logistic regression models. Serum sodium levels were evaluated by tertile, using tertile 2 predefined in the analysis to serve as the reference group due to being a mid-normal value, and on the basis of previous studies demonstrating an adverse association of both higher and lower serum sodium levels with clinical outcomes (11–13). It was determined *a priori* to use serum sodium tertiles to better explore the relation between the exposure and outcomes variables in a nonbiased way. We also examined serum sodium as a continuous predictor variable (per unit decrease).

The initial model was unadjusted, then multivariable adjusted models were performed to include age, race/ethnicity, and education (model 1); model 1 plus smoking status, alcohol intake, body-mass index, and physical activity (model 2); model 2 plus eGFR, cardiovascular disease, diabetes, hypertension, stroke, and chronic obstructive pulmonary disease (model 3); and model 3 plus quality-of-life measures and serum glucose level (model 4). Thiazide diuretic use was missing for n=211 and n=150 for the prevalent cognitive impairment and cognitive decline analyses, respectively, but was added to model 4 for those not missing as an additional sensitivity analysis. Loop diuretics and selective serotonin reuptake inhibitors were also considered for inclusion as covariates, but were omitted due to the low percentage of participants using each in the MrOS study (32,33). Additionally, heart failure was considered for inclusion as a covariate, but was omitted because only 5% of participants had prevalent heart failure.

As secondary analyses, linear regression was used to assess the association of baseline serum sodium level with baseline 3MS score and baseline Trails B time, as well as the longitudinal association of baseline serum sodium level with change in 3MS score and change in Trails B time. To improve the distributional properties of the outcome variables in these models, 3MS score and Trails B time were transformed as follows: log([110−3MS score]^{½}) and log(Trails B time), respectively. We also performed robust regression analysis considering potential outliers and leverages to justify the use of the linear regression models.

Other sensitivity analyses were performed categorizing serum sodium level on the basis of clinical cut-offs (hyponatremia: <136 mmol/L; normonatremia: 136–145 mmol/L; and hypernatremia: >145 mmol/L), and also by quartiles and more resolute categories of serum sodium level (<136, 136–138, 139–140, 141–142, 143–144, and ≥145 mmol/L). Finally, additional sensitivity analyses were run excluding those with serum sodium <136 mmol/L and excluding those using thiazide diuretics. We also examined death before last observed date of follow-up cognitive testing as a potential competing risk of cognitive decline, as determined by state death certificates (18).

Measures of cognitive function and covariates at baseline were summarized by serum sodium tertiles (as well as by clinical cut-offs and quartiles) and presented as mean (SD) for continuous variables and n (%) for categoric variables. Comparisons across tertiles (as well as across categories according to clinical cut-offs and quartiles) were made using a chi-squared test for categoric data and ANOVA for continuous variables.

Two-tailed values of $P<0.05$ were considered statistically significant for all analyses. All statistical analyses were performed using SAS version 9.4.

Results

Participant Characteristics at Baseline for Prevalent Cognitive Impairment (Cross-Sectional) Analyses

Five thousand four hundred thirty-five men who participated in the MrOS study were included in the prevalent cognitive impairment analyses. Among these participants, the mean±SD age was 74±6 years and 91% (n=4939) were white. The mean fasting serum sodium level was 141±3 mmol/L. The mean 3MS examination score was 93±6 and the mean Trails B time was 135±59 seconds. Individuals with lower serum sodium levels were less likely to be white, more likely to smoke, more likely to drink alcohol, had a higher serum glucose level, were more likely to have diabetes and hypertension, and were more likely to use thiazide diuretics. Baseline Trails B time was also slower in those with lower serum sodium levels (Table 1).

Relation between Serum Sodium and Prevalent Cognitive Impairment (Cross-Sectional Results)

The prevalence of cognitive impairment was 15% (n=274), 12% (n=225), and 13% (n=242) for tertile 1 (126–140 mmol/L), tertile 2 (141–142 mmol/L), and tertile 3 (143–153 mmol/L), respectively (P=0.05). The number of participants meeting criteria for prevalent cognitive impairment on the basis of 3MS score, Trails B time, or both was 243, 352, and 146, respectively. In both unadjusted and adjusted analyses, lower serum sodium level (tertile 1) was associated with increased odds of prevalent cognitive impairment compared with the reference group (tertile 2) (Table 2). In continuous analyses, lower serum sodium was also associated with greater odds of cognitive impairment. Additional adjustment for thiazide diuretic did not significantly attenuate this association (tertile 1 odds ratio (OR), 1.22 [95% confidence interval (95% CI), 0.97 to 1.55] compared with the reference group).

Participant Characteristics at Baseline for Cognitive Decline (Longitudinal) Analyses

Three thousand six hundred eleven men were included in the cognitive decline analyses, with a mean follow-up interval of 4.6±0.3 years. Among these participants, the mean±SD age was 72±5 years and 93% (n=3364) were white. The mean fasting serum sodium level was 142±3 mmol/L. The mean baseline 3MS score was 95±4 and the mean baseline Trails B test time was 115±38 seconds, with no significant differences by tertiles of serum sodium level. Individuals with lower serum sodium levels were less likely to be white, had a higher serum glucose level, were more likely to have diabetes and hypertension, and were more likely to use thiazide diuretics (Table 3).

Relation between Serum Sodium and Cognitive Decline (Longitudinal Results)

The incidence of cognitive decline was 14% (n=159), 10% (n=125), and 13.0% (n=159) for tertile 1, tertile 2, and tertile 3, respectively (P=0.03). The number of participants

Table 1. Baseline characteristics of study participants for prevalent cognitive impairment (cross-sectional) analysis by tertiles of baseline serum sodium levels

Variable	Tertile 1 (126–140 mmol/L) (*n*=1814)	Tertile 2 (141–142 mmol/L) (*n*=1818)	Tertile 3 (143–153 mmol/L) (*n*=1803)
Age, yr	74±6	74±6	74±6
Race (% white)[a]	89	92	92
Education			
High school or less	23	24	27
Some college	24	23	22
College	18	18	18
Some graduate school	11	11	11
Graduate school	25	24	23
Smoking[a]			
Never smoker	36	38	38
Current smoker	5	3	3
Former smoker	59	59	59
Alcohol intake, ≥12 drinks in past 12 mo[a]	68	64	63
BMI category			
Underweight	0.2	0.1	0.1
Normal weight	28	27	26
Overweight	51	50	52
Obese	21	23	22
Physical activity score	146±70	147±67	148±68
CKD-EPI eGFR, ml/min per 1.73 m^2	76±16	75±15	75±15
Serum glucose, mg/dl[a]	109±29	105±23	103±18
CVD	24	24	23
Diabetes[a]	14	10	9
Hypertension[a]	48	40	42
Stroke	6	5	6
COPD	11	10	11
Excellent or good health status	85	84	86
SF-12 MCS score	55.6±7.1	55.7±6.8	55.4±6.9
Thiazide diuretic use[a]	17	11	10
3MS score	93±6	93±6	93±6
Trails B, time, s[a]	138±62	133±57	134±58
Serum sodium, mmol/L[a]	139±2 139; (138, 140)	142±1; 142 (141, 142)	144±1; 144 (143, 145)

Data are mean±SD, median (interquartile range), or %. Serum glucose is missing for *n*=141, thiazide diuretic use is missing for *n*=211, and Trails B time is missing for *n*=53. *P* values are comparisons across tertiles made using a chi-squared test for categoric data and ANOVA for continuous variables. BMI, body-mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; SF-12 MCS score, Medical Outcomes Study 12-Item Short Form Mental Health Composite Score (health-related quality of life); 3MS, modified Mini-Mental Status examination; Trails B, Trail Making Test Part B.
[a]$P<0.05$ across tertiles by chi-squared test for categoric data and ANOVA for continuous variables.

meeting criteria for cognitive decline on the basis of 3MS score, Trails B time, or both was 261, 235, and 53, respectively. In both unadjusted and fully adjusted analyses, lower serum sodium level (tertile 1; 126–140 mmol/L) was associated with increased odds of cognitive decline compared with the reference group (tertile 2; 141–142 mmol/L) (Table 4). This association was only slightly attenuated after further adjustment for thiazide diuretic use (tertile 1 OR, 1.33 [95% CI, 0.99 to 1.77] compared with the reference group).

Secondary Analyses

There was no cross-sectional association between baseline serum sodium level and 3MS score in either tertile or continuous analyses (Supplemental Table 1). However, lower serum sodium was cross-sectionally associated with slower Trails B time in all models (Supplemental Table 2; model 4: β-estimate=2.83 [95% CI, 0.44 to 5.23]$\times 10^{-2}$ for tertile 1 versus tertile 2 [Trails B time was log-transformed]). Baseline serum sodium level was not significantly associated with either change in 3MS score at follow-up or change in Trails B time at follow-up (longitudinal analysis; Supplemental Tables 3 and 4).

Sensitivity Analyses

Using clinical cut-offs, 100 participants were classified as hyponatremic (serum sodium level <136 mmol/L), 5120 as normonatremic (serum sodium level 136–145 mmol/L), and 215 as hypernatremic (serum sodium level >145 mmol/L) at baseline for prevalent cognitive impairment (cross-sectional) analyses. Consistent with the tertile analysis, there were increased odds of cognitive impairment (model 4, OR, 2.35 [95% CI, 1.40 to 3.94]) in the hyponatremic group compared with the normonatremic group (Supplemental Table 5). There was no significant difference in the odds of cognitive decline (longitudinal analysis) in the hyponatremic group; however, only 52 individuals were hyponatremic at baseline in the cognitive decline analysis (Supplemental Table 6).

Table 2. Associations (odds ratio [95% confidence interval]) between tertiles of serum sodium levels and prevalent cognitive impairment by logistic regression models (cross-sectional analysis)

Model	Tertile 1 (126–140 mmol/L) (*n*=1814)	Tertile 2 (141–142 mmol/L) (*n*=1818)	Tertile 3 (143–153 mmol/L) (*n*=1803)	Continuous (per 5 mmol/L lower serum sodium)
Unadjusted	1.26 (1.04 to 1.52)	Ref	1.10 (0.90 to 1.33)	1.19 (1.02 to 1.37)
Model 1	1.31 (1.07 to 1.61)	Ref	1.11 (0.90 to 1.36)	1.24 (1.06 to 1.45)
Model 2	1.32 (1.08 to 1.62)	Ref	1.11 (0.90 to 1.37)	1.25 (1.07 to 1.47)
Model 3	1.30 (1.05 to 1.59)	Ref	1.10 (0.90 to 1.36)	1.24 (1.05 to 1.45)
Model 4	1.30 (1.06 to 1.61)	Ref	1.09 (0.88 to 1.34)	1.24 (1.05 to 1.46)

The prevalence of cognitive impairment was 15% (*n*=274), 12% (*n*=225), and 13% (*n*=242) for tertile 1, tertile 2, and tertile 3. Model 1: adjusted for age, race/ethnicity, and education. Model 2: adjusted for model 1, smoking, alcohol intake, body-mass index category, and physical activity. Model 3: model 2+eGFR (Chronic Kidney Disease Epidemiology Collaboration equation), and history of cardiovascular disease, diabetes, hypertension, stroke, and chronic obstructive pulmonary disease. Model 4: model 3+quality-of-life measures and serum glucose level. Serum glucose level is missing in *n*=141.

Additional sensitivity analyses were performed with classification according to quartiles of baseline serum sodium level. Again, the lowest quartile of serum sodium level (126–139 mmol/L) was associated with increased odds of prevalent cognitive impairment (cross-sectional analysis; model 4, OR, 1.45 [1.14, 1.84]) compared with the reference group (quartile 2; 140–141 mmol/L) (Supplemental Table 7). Results were similar for cognitive decline (longitudinal analysis; quartile 1 model 4, OR, 1.31 [0.98, 1.76] versus quartile 2) (Supplemental Table 8). We additionally performed cross-sectional (Supplemental Table 9) and longitudinal analyses (Supplemental Table 10) examining more resolute categories of serum sodium level (<136, 136–138, 139–140, 141–142, 143–144, and ≥145 mmol/L), indicating increased odds of prevalent cognitive impairment in the two lowest categories and increased odds of cognitive decline in the 136–138, 143–144, and >145 mmol/L categories in the fully adjusted model. Sensitivity analyses excluding those with a serum sodium level <136 mmol/L (Supplemental Tables 11 and 12) and excluding those using thiazide diuretics (not shown) did not appreciatively alter the association of baseline serum sodium level with prevalent cognitive impairment or cognitive decline (cross-sectional and longitudinal analysis). Additionally, in sensitivity analyses excluding those with heart failure, results were nearly identical for both the cross-sectional and longitudinal analysis (not shown).

Finally, we examined the potential competing risk of death before cognitive decline. A total of 809 participants reached the composite end point of either cognitive decline (*n*=443) or death (*n*=366) without cognitive decline who did not have cognitive impairment at baseline. In the fully adjusted model (model 4), the association of serum sodium with this composite end point (OR, 1.24 [95% CI, 1.01 to 1.52] tertile 1 [126–140 mmol/L] compared with tertile 2 [141–142 mmol/L]) was slightly attenuated compared with the association of serum sodium with cognitive decline (Table 4), but remained statistically significant.

Discussion

We have observed that serum sodium between 126 and 140 mmol/L is associated with both prevalent cognitive impairment and cognitive decline in community-dwelling older men. The association appears to have been contributed to, at least for prevalent cognitive impairment, primarily by the Trails B test rather than 3MS score. To our knowledge, our findings are the first to demonstrate an independent association between lower serum sodium and cognitive decline in generally healthy, community-dwelling older men.

The association between mild hyponatremia or lower normal serum sodium and cognition in community-dwelling individuals has not been well characterized previously. However, our results are consistent with initial analyses related to this association. A brief early report also demonstrated reduced cognitive function in older adults with serum sodium levels <135 mmol/L using an audio recorded cognitive screening tool (34). Similarly, after adjustment, 129 elderly patients with mild-to-moderate hyponatremia (118–131 mmol/L) performed worse on the mini-mental status examination compared with those with normal serum sodium (35). In a rather small case-control study, 16 patients admitted to the emergency department with mild hyponatremia (126±5 mmol/L) and a syndrome of inappropriate antidiuretic hormone secretion had impaired performance on attention tests, which was improved after correction of hyponatremia (9). Additionally, mild hyponatremia has been shown to associate with cognitive decline in patients receiving chronic hemodialysis (36) and peritoneal dialysis (37). Of note, a phase 3b pilot trial in 57 middle-aged and older adults with chronic hyponatremia (serum sodium <135 mmol/L) found no change in neurocognitive function with tolvaptan compared with placebo treatment, with the exception of improved psychomotor speed (38). The present results provide the first evidence that lower serum sodium is associated with both prevalent cognitive impairment and cognitive decline in generally healthy, community-dwelling older men.

Recent studies demonstrate that mild hyponatremia is also associated with gait disturbances, risk of falls, and risk of bone fractures, as well as cardiovascular events and mortality (9–13). Our results extend these previous findings that lower serum sodium appears unlikely to be truly asymptomatic, because serum sodium between 126 and 140 mmol/L was associated with cognitive impairment and

Table 3. Baseline characteristics of study participants for cognitive decline (longitudinal) analysis by tertiles of baseline serum sodium levels

Variable	Tertile 1 (126–140 mmol/L) (*n*=1175)	Tertile 2 (141–142 mmol/L) (*n*=1214)	Tertile 3 (143–153 mmol/L) (*n*=1222)
Age, yr	72±5	72±5	73±5
Race (% white)[a]	92	93	95
Education			
High school or less	18	19	21
Some college	23	23	22
College	19	19	20
Some graduate school	12	13	12
Graduate school	28	26	26
Smoking			
Never smoker	38	39	40
Current smoker	4	2	3
Former smoker	58	39	58
Alcohol, ≥12 drinks in past 12 mo	71	68	68
BMI category			
Underweight	0.2	0.1	0.1
Normal weight	28	26	24
Overweight	50	51	55
Obese	21	23	21
Physical activity score	155±69	153±66	152±66
CKD-EPI eGFR, ml/min per 1.73 m^2	77±14	76±14	76±14
Serum glucose, mg/dl[a]	107±28	105±22	103±18
CVD	20	20	20
Diabetes[a]	11	9	7
Hypertension[a]	44	38	40
Stroke	4	4	4
COPD	9	10	10
Excellent or good health status	89	91	89
SF-12 MCS score	56.1±6.6	56.2±6.2	56.2±5.9
Thiazide diuretic use[a]	14	11	10
3MS score	95±4	95±4	95±3
Trails B time, s	116±39	115±38	115±36
Serum sodium, mmol/L[a]	139±2; 139 (138, 140)	142±1; 142 (141, 142)	144±1; 144 (143, 145)

Data are mean±SD, median (interquartile range), or %. Serum glucose is missing in *n*=81, thiazide diuretic use is missing for *n*=150, and change in Trails B time is missing for *n*=28. *P* values are comparisons across tertiles made using a chi-squared test for categoric data and ANOVA for continuous variables. BMI, body-mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; SF-12 MCS score, Medical Outcomes Study 12-Item Short Form Mental Health Composite Score (health-related quality of life); 3MS, modified Mini-Mental Status examination; Trails B, Trail Making Test Part B.

[a]$P<0.05$ across tertiles by chi-squared test for categoric data and ANOVA for continuous variables.

cognitive decline. The lowest tertile (tertile 1) in this analysis, which was independently associated with both prevalent cognitive impairment and cognitive decline, included a range of serum sodium levels from 126 to 140 mmol/L, with a mean level of 139±2 mmol/L (prevalent analysis). In sensitivity analyses with hyponatremia defined as a clinical cut-off of <136 mmol/L, only 100 and 52 participants in the prevalent cognitive impairment and cognitive decline analyses, respectively, had clinical hyponatremia. Thus, the majority of the individuals in tertile 1 (94% and 96% for prevalent cognitive impairment and cognitive decline analyses, respectively) had very mild hyponatremia above this clinical cut-off, or even the lower end of normonatremia. Furthermore, exclusion of individuals with serum sodium levels <136 mmol/L did not appreciatively change the observed associations, and these associations were also evident in the more resolute category of serum sodium level of 136–138 mmol/L. Thus, the degree of hyponatremia in this group was quite mild or at the lower end of normal, and may likely be overlooked in many clinical practice settings.

In linear regression analysis, lower serum sodium level was strongly associated with slower Trails B time in the baseline analysis, with no significant association with 3MS score. The Trail Making Part B test measures visuospatial scanning and tracking ability, as well as response shifting, a component of executive function (2,39). However, the Trail Making Part A test was not administered in MrOS, which limits the interpretation of the Trails B results. In the absence of part A of the Trails test, generalized psychomotor slowing of processing can mask additional impairments that could potentially be observed in the executive components of Trails B, without specific deficiencies in response shifting (39). In contrast, the 3MS score is considered a measure of global cognitive function, including orientation, attention, immediate and short-term recall, and language (21). Thus, the association of lower serum sodium with cognitive impairment may be

Table 4. Associations (odds ratio [95% confidence interval]) between tertiles of serum sodium levels with cognitive decline by logistic regression models (longitudinal analysis)

Variable	Tertile 1 (126–140 mmol/L) (*n*=1175)	Tertile 2 (141–142 mmol/L) (*n*=1214)	Tertile 3 (143–153 mmol/L) (*n*=1222)	Continuous (per 5 mmol/L lower serum sodium)
Unadjusted	1.36 (1.06 to 1.75)	Ref	1.30 (1.02 to 1.67)	1.01 (0.83 to 1.24)
Model 1	1.37 (1.06 to 1.77)	Ref	1.32 (1.03 to 1.70)	0.99 (0.81 to 1.22)
Model 2	1.38 (1.07 to 1.78)	Ref	1.33 (1.03 to 1.71)	1.00 (0.82 to 1.22)
Model 3	1.37 (1.06 to 1.77)	Ref	1.33 (1.03 to 1.71)	0.99 (0.81 to 1.21)
Model 4	1.37 (1.06 to 1.77)	Ref	1.32 (1.03 to 1.71)	0.97 (0.79 to 1.19)

The incidence of cognitive decline was 14% (*n*=159), 10% (*n*=125), and 13.0% (*n*=159) for tertile 1, tertile 2, and tertile 3. Model 1: adjusted for age, race/ethnicity, and education. Model 2: adjusted for model 1, smoking, alcohol intake, body-mass index category, and physical activity. Model 3: model 2+eGFR (Chronic Kidney Disease Epidemiology Collaboration equation), and history of cardiovascular disease, diabetes, hypertension, stroke, and chronic obstructive pulmonary disease. Model 4: model 3+quality of life and serum glucose level. Serum glucose is missing in *n*=81.

contributed to primarily by the association of lower sodium with an aspect of executive function.

Mechanistically, hyponatremia may contribute to cognitive impairment *via* astrocyte swelling in response to hypotonicity. This induces release of osmolytes, some of which act as excitatory neurotransmitters (such as glutamate) in order to regulate brain volume, which may contribute to neuronal abnormalities or injury (17,40). However, this mechanism is likely applicable in the setting of acute rather than chronic hyponatremia. Of note, in a recent rodent model of hyponatremia induced by inappropriate secretion of antidiuretic hormone, there was cognitive impairment in a novel object recognition test. This appeared to be mediated by elevated extracellular glutamate concentration in the hippocampus and decreased uptake by the astrocytes, suggesting impaired long-term potentiation as a contributing mechanism (41). Similarly, stable chronic hyponatremia <135 mmol/L also caused impaired memory in another rodent model, which was corrected by normalization of plasma sodium concentrations (42).

Lower serum sodium has also been associated with other adverse outcomes longitudinally, including mortality (7,12–14) and major cardiovascular events (12,13). One possible explanation linking lower serum sodium with cognitive decline is that lowering extracellular sodium increases markers of oxidative stress *in vitro* and *in vivo* (43), and chronic hyponatremia is also associated with numerous manifestations of senescence in rodents (44). Indeed, oxidative stress is a causal factor in brain senescence, which contributes to cognitive decline (45).

Notably, we also found an association of high serum sodium (tertile 3) with cognitive decline in the fully adjusted model. Although this was not an *a priori* aim of this analysis, this finding is consistent with limited available literature. Hypernatremia may reflect inadequate access to water or an impaired thirst mechanism (46), and dehydration is associated with cognitive impairment (47). Additionally, high dietary sodium has been previously associated with a greater decline in cognitive function in older adults (48), and high dietary sodium may induce a small but clinically significant rise in serum sodium levels (49,50). This observation also suggests that the association of serum sodium level may have a U- or J-shape association with cognitive function.

There are several limitations to this study. Because of the design of the MrOS study, this analysis excluded women. Prior studies in severe acute hyponatremia suggest women are at higher risk of neurologic consequences. Thus, whether lower serum sodium is associated with cognitive impairment in older women is uncertain and requires future study. The relation between serum sodium and cognitive impairment is associative and not causal, and there may be residual confounding, such that lower serum sodium may be a marker of underlying pathophysiology, not an independent risk factor (51,52). Serum sodium levels were only available at baseline and were not repeated over the course of the MrOS study, thus an analysis of time-varying serum sodium levels was not possible. Approximately one-third of participants were not followed longitudinally, which also introduces survivor bias. When death was added as a composite end point the observed association of serum sodium with cognitive decline was only slightly attenuated; however, information was not available regarding other events that may have occurred between visits to contribute to cognitive decline. Additionally, many of the covariates were determined from self-report, which may have resulted in errors in characterization of potential confounders such as comorbid conditions. Important strengths of our study include a large sample size and the availability of data on a large number of important covariates. Additionally, data were available for analysis of both prevalent cognitive impairment and cognitive decline. Finally, results were very similar across all adjusted models and when comparing the main tertile analysis to sensitivity analyses according to clinical cut-offs, quartiles, and more resolute categories of serum sodium levels.

In conclusion, serum sodium between 126 and 140 mmol/L is associated with both prevalent cognitive impairment and cognitive decline in community-dwelling older men. Future research is needed to determine if these associations are similar in the general aging population, as both mild cognitive impairment and lower serum sodium are common occurrences with aging. Additional research is also needed to discern the mechanisms by which lower

serum sodium is associated with cognitive impairment and decline. Lower serum sodium is likely to be unnoticed in contemporary clinical practice. Future studies should determine whether correction of lower serum sodium may influence cognition in older adults.

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Disclosures

K.Y. serves on the data safety monitoring board for Takeda Pharmaceuticals Inc. and a National Institutes of Health–sponsored study. She provides consultancy for Novartis and Pfizer and is on the Beeson Scientific Advisory Board. E.S.O. provides consultancy for Merck and receives research funding from Merck and Lily. M.C. provides consultancy for Vifor and receives research funding from Otsuka.

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