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Associations of Hyponatremia with Cognition Function and All-Cause Mortality: Post Hoc Analysis of the Systolic BP Intervention Trial

Amara Sarwal,[1] Robert E. Boucher,[1] Nikita Abraham,[1] Ravinder Singh,[1] Xiangyang Ye,[1] Farahnaz A. Moghaddam,[1] Sydney E. Hartsell,[1] Guo Wei,[1] and Srinivasan Beddhu[1,2]

Key Points

- Incident hyponatremia is associated with probable dementia.
- Incident hyponatremia does not seem to be associated with mild cognitive impairment or death.

Abstract

Background Acute neurologic effects of severe hyponatremia are well-known. However, the long-term association of hyponatremia with cognitive impairment is unclear.

Methods In this *post hoc* analysis of the Systolic Blood Pressure Intervention Trial, we examined whether incident hyponatremia is a risk factor of mild cognitive impairment (MCI) or probable dementia (PD). In those with baseline serum sodium level ≥130 mmol/L, we defined incident hyponatremia in the first 6 months as a Systolic Blood Pressure Intervention Trial safety alert for serum sodium level <130 mmol/L from randomization to the 6-month visit. In multivariate Cox regression models adjusted for baseline cognitive function and other variables, we related incident hyponatremia in the first 6 months with subsequent MCI or PD in 8540 participants with cognitive outcomes data and with all-cause mortality (ACM) in 9135 participants with mortality data.

Results Incident hyponatremia in the first 6 months was noted in 116 participants (1.4%). Older age, female sex, non-Black race, lower body mass index, and randomization to intensive systolic BP control were associated with incident hyponatremia. Compared with those without hyponatremia, those with incident hyponatremia had higher risk of PD (2.1 versus 0.9 events/100 person-years; hazard ratio [HR], 3.08; 95% confidence interval [CI], 1.48 to 6.41) but not MCI (3.1 versus 3.6 events/100 person-years; HR, 0.95; 95% CI, 0.54 to 1.68) and the composite of MCI/PD (5.0 versus 4.2 events/100 person-years; HR, 1.28; 95% CI, 0.82 to 2.0). There were no significant differences in ACM (HR, 1.84; 95% CI, 0.90 to 3.73).

Conclusions Biologic plausibility for the association of incident hyponatremia with PD but not MCI or death is unclear. The association of incident hyponatremia with PD could reflect a chance finding or noncausal biologic association or causal relationship.

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Introduction

Hyponatremia is a common electrolyte disorder that has been associated with chronic comorbidities, such as congestive heart failure or liver disease, as well as certain medication use, such as thiazide diuretics. Symptomatic hyponatremia can manifest in numerous ways, such as with nausea, muscle cramping, weakness, or fatigue. Acute neurologic effects of severe hyponatremia, such as confusion, lethargy, seizure, coma, and death, are also well-recognized.[1–3] However, it is unclear whether hyponatremia has long-term effects on cognitive function.

There was a retrospective cohort study that used claims data and found that compared with controls, patients with hyponatremia had a higher risk of subsequent dementia.[4] Because dementia takes several years to manifest, most of the previous prospective studies evaluating hyponatremia and cognitive impairment were cross-sectional examining the associations of serum sodium levels with screening cognitive

[1]Division of Nephrology & Hypertension, University of Utah School of Medicine, Salt Lake City, Utah
[2]Medical Service, Veterans Affairs Salt Lake City Health Care System, Salt Lake City, Utah

Correspondence: Dr. Srinivasan Beddhu, Division of Nephrology, University of Utah, 421 Wakara Way, Suite 360, Salt Lake City, UT 84108. Email: Srinivasan.beddhu@hsc.utah.edu

function tests, such as Montreal Cognitive Assessment (MoCA).[5–8] There are conflicting data on the associations of serum sodium levels with probable dementia (PD).[4,9]

Mild cognitive impairment (MCI) is considered to be a clinical state between normal cognitive aging and dementia.[10] In other words, just as CKD is considered an intermediate clinical state between normal kidney function and end stage kidney disease, MCI is a state between normal aging and dementia. To our knowledge, there is a paucity of data on the associations of hyponatremia with the risk of MCI.

Therefore, we examined the longitudinal associations of incident hyponatremia with carefully collected and adjudicated cognitive outcomes of MCI or PD using the data from the Systolic Blood Pressure Intervention Trial (SPRINT).[11,12]

Methods

Overview of SPRINT and SPRINT—Memory and Cognition in Decreased Hypertension

SPRINT was a randomized, controlled, open-label trial that compared the effects of intensive systolic BP control (systolic BP goal <120 mm Hg) versus standard systolic BP control (systolic BP goal <140 mm Hg) on cardiovascular disease (CVD) events and all-cause mortality (ACM). There were 9361 participants aged 50 years or older with baseline systolic BP 130–180 mm Hg randomized between November 2010 and March 2013. Exclusion criteria included history of diabetes mellitus, stroke, secondary cause of hypertension, significant proteinuria, a recent CVD event in the previous 3 months, left ventricular ejection fraction <35%, residence in a nursing home, history of dementia, or recent substance use.[13] Trained study coordinators conducted study visits using a standardized study protocol.[11] To reach the randomly assigned systolic BP goals, the study investigators followed a standardized BP protocol. Medication classes that were encouraged included first-line antihypertensives of angiotensinogen-converting enzyme inhibitors (ACEis)/aldosterone receptor blockers (ARBs), dihydropyridine calcium channel blockers (CCBs), and thiazide diuretics, although other antihypertensives were allowed.[11–13] The SPRINT primary outcome was a CVD composite of first occurrence of nonfatal myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, or mortality due to CVD. ACM was a predefined key secondary end point.

In the SPRINT—Memory and Cognition in Decreased Hypertension (SPRINT-MIND), a substudy of SPRINT, the effects of intensive systolic BP control on cognitive function outcomes of MCI and PD were examined in 8563 SPRINT participants with nonmissing cognitive function data.[11–13] Cognitive status was ascertained using a three-step process, details of which have been previously published.[13] In brief, all participants underwent cognitive screening at baseline, 24 months, and 48 months or at closeout visit. The screening tests included the MoCA, Digit Symbol Coding test, and Logical Memory test. Participants who scored below predefined thresholds for race and level of education underwent further testing with Functional Activities Questionnaire. If participants scored >0 on the Functional Activities Questionnaire or scored <1 on the five-point Delayed Recall subtest of the MoCA, they underwent further testing using an extended cognitive battery that measured attention/concentration, verbal and nonverbal memory, language, and executive functions. If a participant died before the follow-up assessment, the Dementia Questionnaire for that participant was completed with the help of a prespecified contact. An expert adjudication panel that included neurologists, neuropsychologists, geriatricians, and geropsychologists reviewed the cognitive test scores, proxy functional status reports, and other data collected during the study and classified participants into one of three primary categories: no cognitive impairment, MCI, or PD. Additional details of the SPRINT-MIND study and cognitive function adjudication are provided in the supplement (Supplemental Figure 1 and SPRINT-MIND protocol chapter).

The trial was designed to assess cognition at baseline, 2 years, 4 years, and study closeout (if it was >1 year from the previous assessment). The BP intervention was stopped early in August 2015 because of its significant benefit on CVD events, which was before many of the cognitive assessments that would have been performed at the 4-year mark. Participants' BP management was returned to their primary care providers after August 2015. A final cognitive assessment was conducted between 2017 and 2018.

Current Analysis Study Cohort

In this *post hoc* secondary analysis, of the 9361 randomized SPRINT participants, we included 9323 SPRINT participants with baseline serum sodium ≥130 mmol/L and nonmissing baseline through 6-month serum sodium values (Figure 1) to relate the association of incident hyponatremia with ACM because some of those with missing cognitive status data died before the follow-up cognitive function assessment was performed. We excluded those with baseline hyponatremia. Of the 9135 participants included in ACM analysis, 8540 were included in the SPRINT-MIND substudy with nonmissing cognitive status data. We used this cohort of 8540 participants for current analyses relating incident hyponatremia with cognitive function outcomes.

This study is institutional review board exempt because we used a limited access public dataset.

Definition of Incident Hyponatremia

During the trial, serum chemistry profile, including serum sodium, was measured at the SPRINT central laboratory at baseline/randomization, monthly for the first 3 months, every 6 months from month 6, and as needed at the discretion of the site investigator. The SPRINT coordinating center sent a clinical safety alert to the site investigator if the serum sodium level was <130 mmol/L. In the 9323 participants included with baseline serum sodium level ≥130 mmol/L, we defined incident hyponatremia in the first 6 months as a SPRINT safety alert for serum sodium level <130 mmol/L from randomization to the 6-month SPRINT visit. We used a 6-month cutoff to define incident hyponatremia to allow longer follow-up duration for the outcomes to occur.

Definitions of Cognitive Outcomes for Current Analysis

Per SPRINT protocol, MCI was defined as time to the occurrence of the first of two consecutive occurrences of MCI (amnestic or nonamnestic). However, this definition

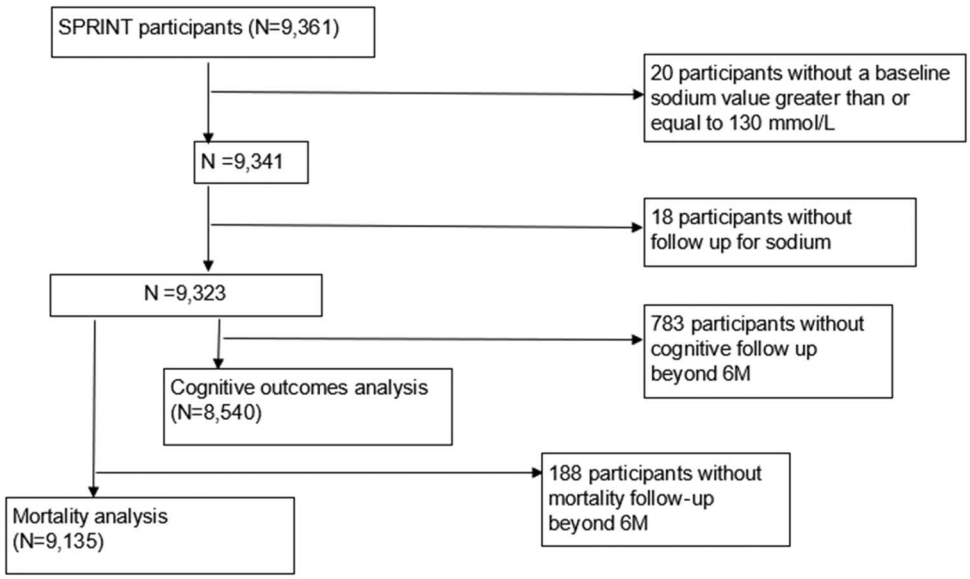

Figure 1. Flowchart of participants. SPRINT, Systolic Blood Pressure Intervention Trial.

conditions the analysis on surviving to next scheduled cognitive assessment and having the next assessment performed. To address this concern, we defined MCI for the current analysis as time to protocol-defined MCI or time to the first occurrence of MCI with the second confirmation missing because the assessment was not performed or the participant died before the second confirmation assessment, as depicted in Supplemental Figure 2. We used the SPRINT-adjudicated PD outcome for this analysis.

The primary outcome in this analysis was time to the occurrence of cognitive impairment, measured by either MCI or PD. Because amnestic MCI has consistently been associated with increased risk of progression to dementia, we also conducted a sensitivity analysis of time to a single occurrence of amnestic MCI/PD.[14]

Statistical Methods

Baseline characteristics, 6-month serum sodium levels, and antihypertensive medication use in the first 6 months were compared between those with and without hyponatremia using *t* tests, chi-squared tests, or Wilcoxon rank-sum tests. These comparisons were repeated in the larger ACM cohort. Logistic regression models were used to relate the incidence of hyponatremia by 6 months with baseline factors (age, female sex, Black race, intensive systolic BP group, body mass index [BMI], smoking status, Framingham risk score, CVD, congestive heart failure, systolic BP, diastolic BP, serum sodium level, and eGFR) as well as the use of thiazide diuretics, loop diuretics, ACEis/ARBs, CCBs, and the maximum number of antihypertensive medications in the first 6 months.

In a multivariate Cox regression model, we related incident hyponatremia in the first 6 months with time to a subsequent MCI event adjusted for the baseline factors (age, female sex, Black race, intensive systolic BP group, BMI, smoking status, Framingham risk score, CVD, congestive heart failure, systolic BP, diastolic BP, serum sodium level, eGFR, and MoCA score), 6-month factors (systolic BP, diastolic BP, and eGFR), as well as the use of thiazide diuretics, loop diuretics, ACEis/ARBs, CCBs, and the maximum number of antihypertensive medications in the first 6 months. In the Cox models, time 0 was defined as the 6-month visit with serum sodium measurement. Time at risk for participants was started after the 6-month visit, with censoring at death, loss to follow-up, or end of the study.

We used similar Cox regression models to relate incident hyponatremia in the first 6 months with time to a composite of MCI alone, MCI/PD, PD alone, and ACM alone. Additional Cox regression models were applied with a cubic spline term for 6-month serum sodium level or change in serum sodium level from baseline to 6 months with time to subsequent MCI alone, MCI/PD, PD alone, and ACM alone. Fine–Gray model was used to assess competing risk of death and cognitive outcomes (Supplemental Figure 3).

Results

Of the 8540 participants included in the cognitive outcomes analysis, 116 (1.4%) developed incident hyponatremia in the first 6 months. Incident hyponatremia in the first 6 months was more common in the intensive than the standard systolic BP arm (1.8% versus 0.9%, $P < 0.001$). The mean serum sodium level at the time of incident hyponatremia diagnosis was 127±2 mmol/L. Compared with those without incident hyponatremia, those with incident hyponatremia had lower baseline (140±2 versus 136±3 mmol/L, $P < 0.001$) and 6-month (140±2 versus 133±5 mmol/L, $P < 0.001$) serum sodium levels. In general, participants with incident hyponatremia were older, more likely to be women, less likely to be Black, and had a lower BMI (Table 1). Compared with those without incident hyponatremia, those with incident hyponatremia in the first 6 months had a higher proportion of thiazide diuretic, ACEi/ARB, and CCB use during this period (Table 2). In the ACM cohort of 9135 participants, there were 126 hyponatremia events (1.4%) in the first 6 months

Table 1. Clinical characteristics of participants with and without hyponatremia in the first 6 months (*N*=8540)

Participant Characteristics	Without Hyponatremia (*n*=8424)	With Hyponatremia (*n*=116)
Age, yr[a]	68±9	72±9
Female, *n* (%)[b]	2946 (35)	56 (49)
Black, *n* (%)[a]	2635 (31)	11 (9)
Randomized to the intensive systolic BP arm, *n* (%)[a]	4190 (50)	78 (68)
Baseline systolic BP, mm Hg[a]	139±15	149±19
Baseline diastolic BP, mm Hg	78±12	78±13
6-mo systolic BP, mm Hg[b]	128±15	131±17
6-mo diastolic BP, mm Hg[a]	72±11	69±11
CVD, *n* (%)	1683 (20)	19 (17)
Stroke, *n* (%)	43 (1)	1 (1)
Congestive heart failure, *n* (%)	281 (3)	5 (4)
CKD, *n* (%)	2349 (28)	27 (23)
BMI, kg/m^2[a]	29.9±5.7	27.5±5.9
Baseline eGFR by MDRD, ml/min per 1.73 m^2[b]	72±20	76±23
6-mo eGFR by MDRD, ml/min per 1.73 m^2[b]	72±21	77±23
Urine albumin-to-creatinine ratio, mg/g	9 (6–21)	15 (8–29)
Baseline serum sodium concentration, mmol/L[a]	140±2	136±3
6-mo serum sodium concentration, mmol/L[a]	140±2	133±5
Baseline MoCA score	23±4	24±4

CVD, cardiovascular disease; BMI, body mass index; MoCA, Montreal Cognitive Assessment.
[a]$P < 0.001$.
[b]$P < 0.05$.

after randomization. Overall, the differences between those with and without hyponatremia in the ACM cohort were similar to that observed in the cognitive function cohort (Supplemental Table 1).

In a multivariable logistic regression model (Table 3), older age, randomization to the intensive systolic BP group, higher baseline systolic BP, and use of ACEis/ARBs in the first 6 months after randomization were significantly associated with higher risk of hyponatremia in the first 6 months, whereas thiazide diuretics versus no diuretics in the first 6 months had a clinically relevant, but statistically nonsignificant, higher risk of hyponatremia. On the other hand, Black race and higher baseline serum sodium levels were associated with lower risk of hyponatremia. The results were largely similar when analyses were repeated in the ACM cohort (*N*=9135) (Supplemental Table 2).

Associations of Incident Hyponatremia in the First 6 Months with Subsequent Cognitive Outcomes

There were 641 SPRINT protocol-defined MCI events over a total of 39,505 years of follow-up. For this analysis, there were 1254 MCI events over 35,098 total years of follow-up. There were 324 PD events over 36,622 years of follow-up and 1485 MCI/PD events over 35,033 years of follow-up.

The subsequent incidence of MCI in those with hyponatremia versus those without hyponatremia in the first 6 months was 3.1 versus 3.6 events per 100 person-years of follow-up (Figure 2). In a multivariable Cox regression model with adjustment for baseline factors (as described in methods) and the use of thiazide diuretics, loop diuretics, ACEis/ARBs, CCBs, and the maximum number of antihypertensive medications in the first 6 months, incident hyponatremia within the first 6 months was not associated

Table 2. Antihypertensive use of participants with and without hyponatremia from baseline to 6 months (*N*=8540)

Antihypertensives	Without Hyponatremia in the First 6 mo (*n*=8424)		With Hyponatremia in the First 6 mo (*n*=116)	
	Baseline	0–6 mo	Baseline	0–6 mo
Total diuretic use, %	47	74	47	86
Thiazide diuretic use, %	40	67	41	79
Loop or potassium-sparing diuretic use, %	7	7	5	7
ACEi/ARB use, %	58	79	67	92
CCB use, %	35	55	34	70
Total no. of antihypertensives	1.9±1.1	2.1±1.1	2.7±1.1	3.1±1.0

ACEi, angiotensinogen-converting enzyme inhibitor; ARB, aldosterone receptor blocker; CCB, calcium channel blocker.

Table 3. Predictors of incident hyponatremia in the first 6 months (*N*=8540)

Predictors	Odds Ratio (95% CI)
Each SD[a] higher baseline age	1.43 (1.05 to 1.94)
Female sex	1.05 (0.59 to 1.90)
Black race	0.32 (0.15 to 0.62)
Baseline CVD	0.58 (0.33 to 1.04)
Baseline congestive heart failure	1.47 (0.50 to 4.29)
Each SD[a] higher BMI	0.94 (0.74 to 1.19)
Randomization to the intensive BP control group	1.77 (1.13 to 2.79)
Each SD[a] higher baseline serum sodium	0.28 (0.24 to 0.33)
Each SD[a] higher baseline systolic BP	1.73 (1.33 to 2.25)
Each SD[a] higher diastolic BP	0.95 (0.72 to 1.25)
Each SD[a] higher baseline eGFR	1.16 (0.94 to 1.44)
First 6 mo—thiazide diuretic use (versus none)	1.79 (0.93 to 3.43)
First 6 mo—loop diuretic use (versus none)	1.13 (0.37 to 3.41)
First 6 mo—ACEi/ARB use	2.55 (1.14 to 5.74)
First 6 mo—CCB use	1.65 (0.99 to 2.74)
First 6 mo—each additional antihypertensive used	1.11 (0.85 to 1.46)

CI, confidence interval; CVD, cardiovascular disease; BMI, body mass index; ACEi, angiotensinogen-converting enzyme inhibitor; ARB, aldosterone receptor blocker; CCB, calcium channel blocker.
[a]SD for age 9.3 years, body mass index 5.8 kg/m^2, serum sodium 2.4 mmol/L, systolic BP 15.5 mm Hg, diastolic BP 11.8 mm Hg, and baseline eGFR 20.4 ml/min per 1.73 m^2.

with subsequent MCI (hazard ratio [HR], 0.95; 95% confidence interval [CI], 0.54 to 1.68). However, the subsequent incidence of PD (Figure 2) was higher in those with hyponatremia in the first 6 months (2.1 events versus 0.9 events per 100 person-years, 314 events over 36,155 years of follow-up versus ten events over 467 years of follow-up, respectively) with a HR of 3.08 (95% CI, 1.48 to 6.41). For the composite of MCI/PD (Figure 2), there was no significant difference between those with and without hyponatremia (HR, 1.28; 95% CI, 0.82 to 2.02). In the Fine–Gray model that accounted for competing risk of death, the results were largely similar to those of the main models (PD subdistribution HR [SHR], 2.40; 95% CI, 1.19 to 4.87; MCI SHR, 0.84; 95% CI, 0.50 to 1.42; and MCI/PD SHR, 1.15; 95% CI, 0.76 to 1.74).

Associations of Hyponatremia in the First 6 Months with ACM

In the 9135 participants included for ACM analyses, there were 469 deaths over 30,522 total years of follow-up. ACM (2.9 versus 1.5 per 100 person-years) was higher in those with hyponatremia compared with those without hyponatremia in the first 6 months; however, this was not statistically significant (HR, 1.84; 95% CI, 0.90 to 3.73) in a multivariate Cox regression model adjusted for variables listed above (Figure 2).

Associations of 6-month serum sodium and delta serum sodium (6-month serum sodium minus baseline serum sodium) levels as continuous variables with subsequent cognitive outcomes and ACM: In spline regression analyses, using the 6-month serum sodium value of 140 mmol/L as the reference, there was no evidence that lower serum levels were associated with higher risk of subsequent MCI, MCI/PD composite, or ACM (Figure 3, A, B, and D), whereas there seemed to be a higher risk of PD (Figure 3C). The results were similar for spline regression analyses relating 6-month delta serum sodium to above outcomes (Figure 4, A–D).

Intensive systolic BP control treatment effects on cognitive outcomes and ACM across the range of 6-month serum sodium levels and 6-month delta sodium levels: There was no evidence that the effects of intensive systolic BP control on cognitive outcomes or ACM were deleterious at lower 6-month serum sodium or delta sodium levels (Supplemental Figures 4 and 5, A–D).

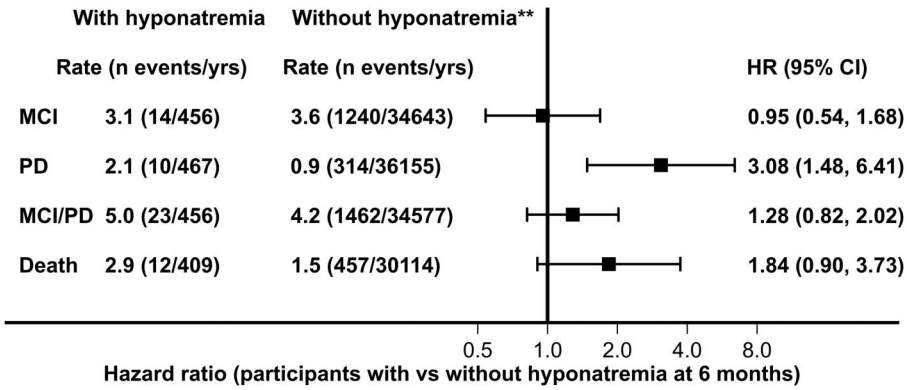

Figure 2. Associations of incident hyponatremia in the first 6 months with subsequent cognitive outcomes and ACM. Models adjusted for baseline age; female sex; Black race; intensive systolic BP group; BMI; smoking status; CVD; congestive heart failure; systolic and diastolic BPs; eGFR at baseline; Framingham risk score; baseline serum sodium level; baseline MoCA score; 6-month systolic BP; 6-month diastolic BP; 6-month eGFR; maximum number of antihypertensive medications within the first 6 months; as well as diuretic, ACEi, ARB, and CCB use. ACEi, angiotensinogen-converting enzyme inhibitor; ACM, all-cause mortality; ARB, aldosterone receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; PD, probable dementia.

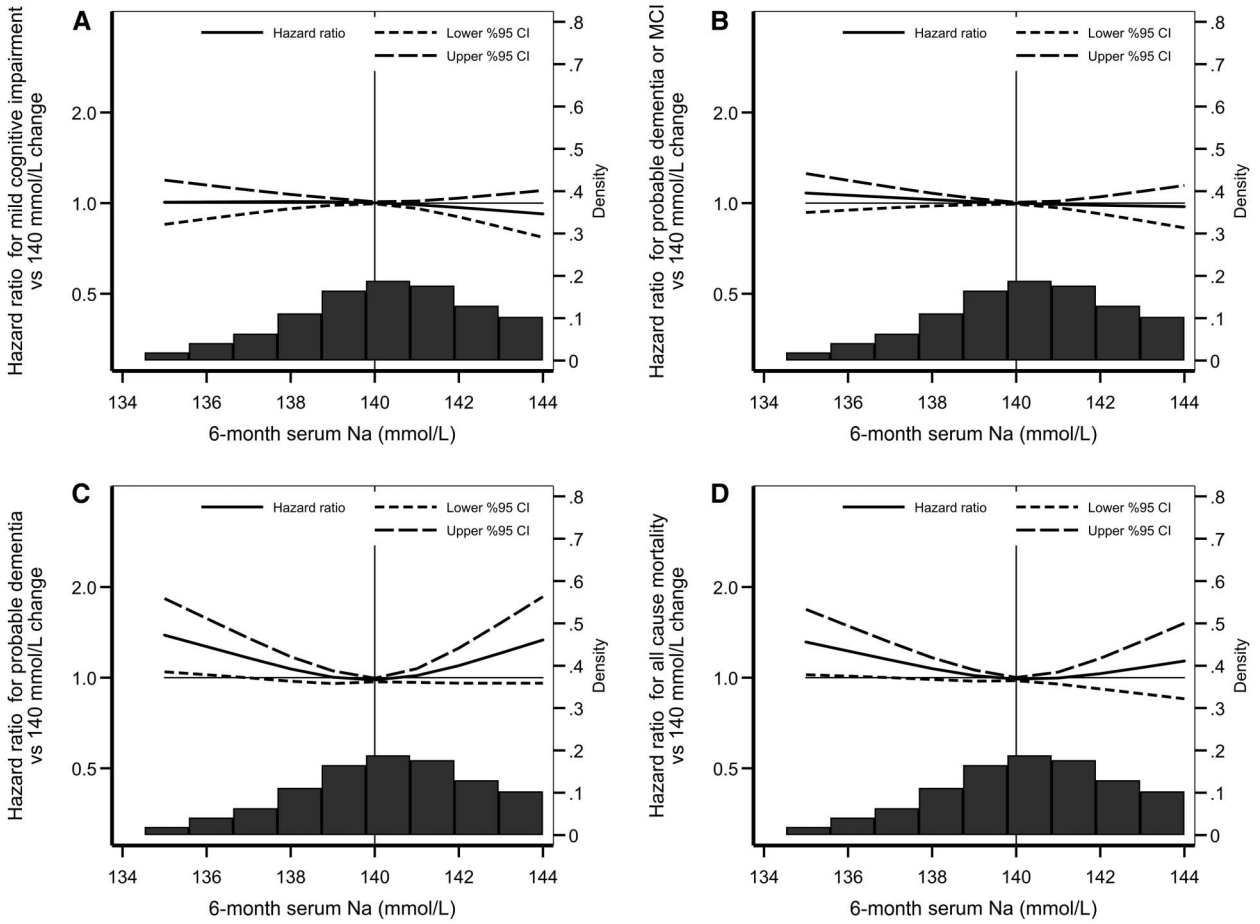

Figure 3. Spline regression models relating 6-month serum sodium levels to subsequent cognitive outcomes and ACM. (A) Relating 6-month serum sodium level to subsequent MCI. (B) Relating 6-month serum sodium level to subsequent MCI/PD. (C) Relating 6-month serum sodium level to subsequent PD. (D) Relating 6-month serum sodium level to subsequent ACM models adjusted for baseline factors (age, female sex, Black race, intensive systolic BP group, BMI, smoking status, Framingham risk score, CVD, congestive heart failure, systolic BP, diastolic BP, serum sodium level, eGFR, and MoCA score), 6-month factors (systolic BP, diastolic BP, and eGFR), as well as the use of thiazide diuretics, loop diuretics, ACEis/ARBs, CCBs, and the maximum number of antihypertensive medications in the first 6 months. ACEi, angiotensinogen-converting enzyme inhibitor; ACM, all-cause mortality; ARB, aldosterone receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; CVD, cardiovascular disease; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; PD, probable dementia.

Sensitivity Analyses

Event rates for alternate definitions for MCI are summarized in Supplemental Table 3. Using alternate definitions for MCI, incident hyponatremia in the first 6 months was not associated with the risk of subsequent amnestic MCI (HR, 0.97; 95% CI, 0.56 to 1.67), amnestic MCI/PD (HR, 1.29; 95% CI, 0.84 to 1.99), protocol MCI (HR, 0.62; 95% CI, 0.25 to 1.52), and protocol MCI/PD (HR, 1.24; 95% CI, 0.71 to 2.14).

Discussion

Previously, it was reported that a serum sodium level of 130 mmol/L occurred in 3.8% of participants in the intensive treatment arm and 2.1% in the standard treatment arm over the total duration of SPRINT.[11] In this *post hoc* analysis of SPRINT, we observed that incident hyponatremia defined as serum sodium concentrations <130 mmol/L in the first 6 months after randomization was not uncommon, with an overall incidence of 1.4%. It was nearly twice as common in the intensive systolic BP arm compared with the standard systolic BP arm (1.8% versus 0.9%, $P < 0.001$). We did not observe an association of incident hyponatremia in the first 6 months with subsequent occurrence of MCI or ACM; however, it was associated with higher risk of PD.

Serum sodium is the predominant driver of serum osmolality. Because both hypo- and hyperosmolar states affect brain volume, serum osmolality is tightly regulated. Mechanisms of brain adaptation include water flow into the cerebrospinal fluid and systemic circulation from the brain as well as movement of intracellular electrolytes to the extracellular compartment.[15] Because it has been thought that the brain cannot lose more than 18% of its total ion content, continued hyponatremia will likely lead to edema of the brain.[15] Common acute neurologic symptoms of hyponatremia include confusion and lethargy, whereas most severe manifestations include seizure, coma, brain herniation, and death. Hence, it is biologically plausible that hyponatremia might have long-term neurologic effects.

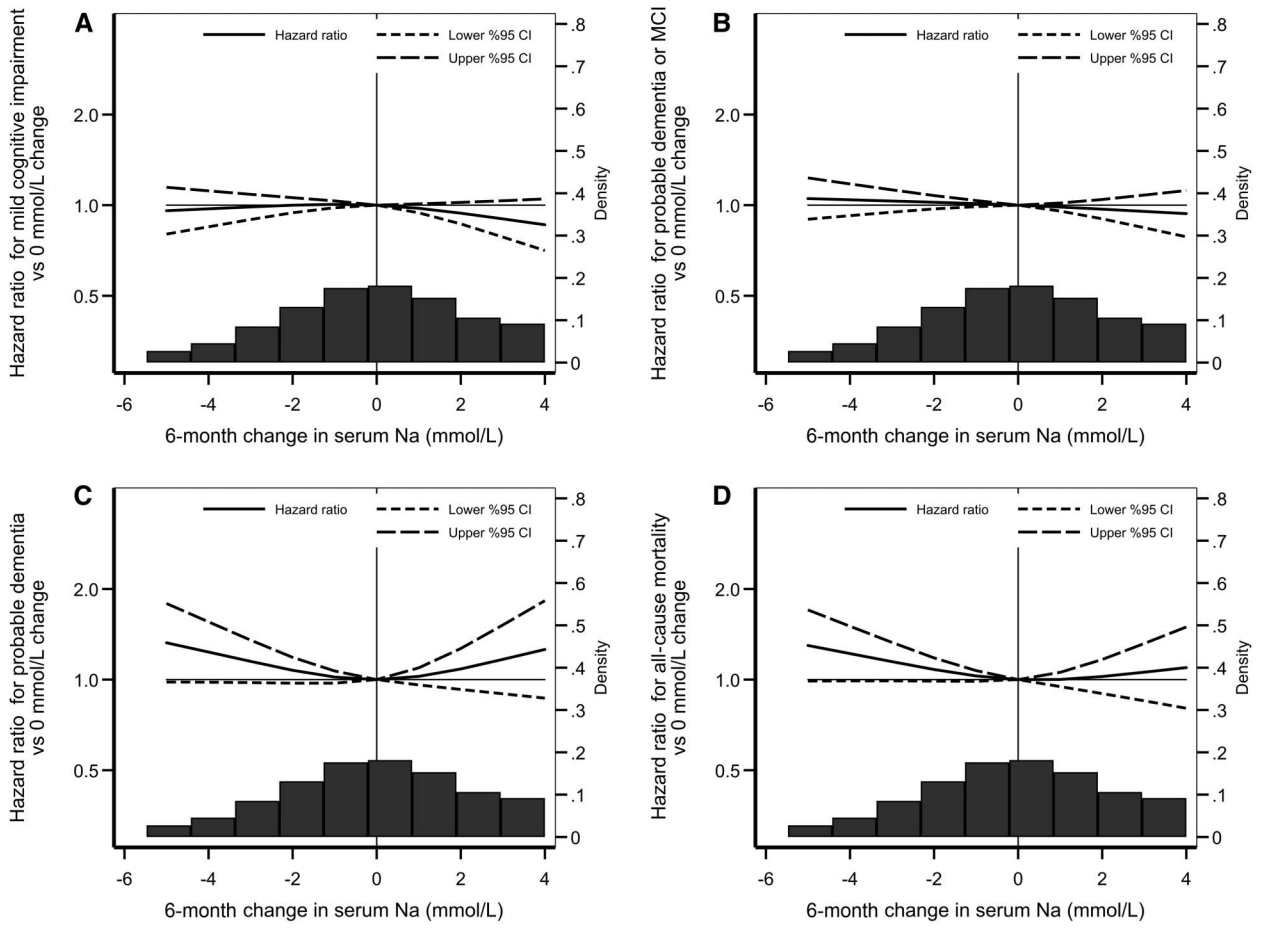

Figure 4. Spline regression models relating 6-month change in serum sodium levels to subsequent cognitive outcomes and ACM. (A) Relating 6-month change in serum sodium level to subsequent MCI. (B) Relating 6-month change in serum sodium level to subsequent MCI/PD. (C) Relating 6-month change in serum sodium level to subsequent PD. (D) Relating 6-month change in serum sodium level to subsequent ACM. Models adjusted for baseline factors (age, female sex, Black race, intensive systolic BP group, BMI, smoking status, Framingham risk score, CVD, congestive heart failure, systolic BP, diastolic BP, serum sodium level, eGFR, and MoCA score), 6-month factors (systolic BP, diastolic BP, and eGFR), as well as the use of thiazide diuretics, loop diuretics, ACEis/ARBs, CCBs, and the maximum number of antihypertensive medications in the first 6 months. ACEi, angiotensinogen-converting enzyme inhibitor; ACM, all-cause mortality; ARB, aldosterone receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; CVD, cardiovascular disease; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; PD, probable dementia.

In a cross-sectional study of patients seen in an emergency department, patients with chronic asymptomatic hyponatremia compared with patients with normal serum sodium levels had attention and gait impairments.[16] In another cross-sectional study of 476 patients receiving peritoneal dialysis, hyponatremia, defined as mean serum sodium level ≤135 mmol/L taken over the preceding 3 months, was associated with lower Modified Mini-Mental State Examination scores, longer completion time of trials A and B, and executive dysfunction.[6] In a cross-sectional study of 3282 community-dwelling adults with a mean age of 66.8±7.8 years, compared with those with a serum sodium level of 130 mmol/L, those with a serum sodium level of 135 mmol/L had approximately 5% higher cognitive function scores.[17] In addition, in a cross-sectional study conducted in a sample of the National Health and Nutrition Examination Survey participants, hyponatremia was associated with lower memory and executive functioning scores.[18] Further cross-sectional analyses of hyponatremia and cognition have been published[19]; however, the concern is that reverse causality can lead to the observed associations. In a longitudinal, population-based cohort of older men, lower baseline serum sodium levels were associated with greater decline in cognitive function scores.[20]

The reported associations of serum sodium levels with PD are also controversial. Indeed, as noted above, International Classification of Diseases-9 diagnoses of hyponatremia was associated with subsequent International Classification of Diseases-9 diagnoses of dementia in a retrospective cohort study that used claims data.[4] In a recently published analysis of the Rotterdam Study, an ongoing prospective population-based cohort study that was started in 1990, serum sodium collected between 1997 and 2008 was compared with cognitive outcomes.[9] That study found no significant associations of low serum

sodium levels with risk of dementia despite follow-up until 2018.

In this analysis, we examined the longitudinal associations of incident hyponatremia with adjudicated MCI and PD in a hypertensive population. Contrary to our hypothesis, we did not observe an association between incident hyponatremia and MCI, a clinical state between normal cognitive aging and dementia.[10] Of note, the results remained consistent with sensitivity analyses with protocol-defined MCI as well as amnestic MCI alone. Nonetheless, we observed an association of incident hyponatremia with the risk of PD. The biologic plausibility for the association of incident hyponatremia with PD but not MCI is unclear because one would expect that mild hyponatremia would be more likely associated with MCI rather than PD. Indeed, there was a nearly four-fold higher incidence of MCI (1254 events in 35,204 years of follow-up) than PD (324 events in 36,728 years of follow-up) in this cohort. Therefore, it is unclear whether the association of incident hyponatremia with PD is a causal relationship. The other possibilities include a chance observation or that incident hyponatremia might be a marker of those at higher risk of PD.

As shown in Table 1, older age, female sex, non-Black race, lower BMI, and randomization to intensive systolic BP control were associated with incident hyponatremia. However, in a multivariate logistic regression model, older age and randomization to intensive systolic BP control were independently associated with higher risk and higher baseline serum sodium level. Black race was associated with a lower risk of incident hyponatremia. It is conceivable that lowering of systolic BP and a resultant decrease in eGFR leads to increased antidiuretic hormone levels with a consequent decrease in the serum sodium level.

The strengths of the current analyses include the use of carefully collected data in a large randomized controlled trial. Serum sodium levels were measured in all SPRINT participants at scheduled intervals in the central laboratory. Cognitive outcomes were carefully collected and adjudicated in SPRINT. The limitations include *post hoc*, postrandomization analysis; the relatively fewer number of incident hyponatremia events in the first 6 months; and the relatively shorter duration of follow-up. It is possible that a larger number of patients with incident hyponatremia with a much longer duration of follow-up might have uncovered an association of incident hyponatremia with MCI or ACM. However, even with the fewer number of patients with hyponatremia, we still noted an association with PD. It is conceivable that there might be a potential differential accuracy of diagnosis of MCI versus PD. However, as noted in the sensitivity analyses, we considered several alternate definitions of MCI and noted similar lack of associations of incident hyponatremia with MCI.

In conclusion, incident hyponatremia is relatively common with intensive systolic BP lowering. While incident hyponatremia in the first 6 months was not associated with subsequent MCI or ACM, it was still associated with higher risk of subsequent PD. This association might not be causal; rather, incident hyponatremia might be a marker of those at higher risk of PD.

Disclosures

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Author Contributions

Conceptualization: Srinivasan Beddhu, Amara Sarwal.
Data curation: Srinivasan Beddhu, Robert E. Boucher, Ravinder Singh, Guo Wei, Xiangyang Ye.
Formal analysis: Srinivasan Beddhu, Robert E. Boucher, Amara Sarwal.
Funding acquisition: Srinivasan Beddhu.
Investigation: Srinivasan Beddhu, Amara Sarwal.
Methodology: Srinivasan Beddhu, Robert E. Boucher, Amara Sarwal.
Project administration: Srinivasan Beddhu.
Resources: Srinivasan Beddhu.
Software: Srinivasan Beddhu, Robert E. Boucher.
Supervision: Srinivasan Beddhu.
Validation: Srinivasan Beddhu, Amara Sarwal, Robert Boucher.
Visualization: Srinivasan Beddhu, Amara Sarwal.
Writing – original draft: Srinivasan Beddhu, Amara Sarwal.
Writing – review & editing: Nikita Abraham, Srinivasan Beddhu, Robert E. Boucher, Sydney E. Hartsell, Farahnaz A. Moghaddam, Ravinder Singh, Guo Wei, Xiangyang Ye, Amara Sarwal.

Data Sharing Statement

Previously published data were used for this study.[21]

Supplemental Materials

This article contains the following supplemental material online at http://links.lww.com/KN9/A391.

Supplemental Methods. SPRINT-MIND chapter from the SPRINT protocol.

Supplemental Table 1. Clinical characteristics of participants with and without hyponatremia in the first 6 months in the all-cause mortality cohort (N=9135).

Supplemental Table 2. Predictors of hyponatremia in the first 6 months after randomization in the all-cause mortality cohort (N=9135).

Supplemental Table 3. Event rates by alternate definitions of MCI in those with and without incident hyponatremia in the first 6 months.

Supplemental Figure 1. Overview of the SPRINT-MIND study.

Supplemental Figure 2. Pictorial depiction of mild cognitive impairment definition.

Supplemental Figure 3. Fine–Gray model assessing competing risk of death.

Supplemental Figure 4. Spline regression models relating treatment effect across 6-month serum sodium levels to subsequent cognitive outcomes and all-cause mortality. (A) Hazard ratio for treatment effect across 6-month serum sodium level related to MCI. (B) Hazard ratio for treatment effect across 6-month serum sodium level related to PD/MCI. (C) Hazard ratio for treatment effect across 6-month serum sodium level related to PD. (D) Hazard ratio for treatment effect across 6-month serum sodium level related to ACM.

Supplemental Figure 5. Spline regression models relating treatment effect across 6-month change in serum sodium levels to subsequent cognitive outcomes and all-cause mortality. (A) Hazard ratio for treatment effect across 6-month change in serum sodium level related to MCI. (B) Hazard ratio for treatment effect across 6-month change in serum sodium level related to MCI/PD. (C) Hazard ratio for treatment effect across 6-month change in serum sodium level related to PD. (D) Hazard ratio for treatment effect across 6-month change in serum sodium level related to ACM.

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