

Serum Bicarbonate Concentration and Cognitive Function in Hypertensive Adults

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Abstract

Background and objectives Cognitive function worsens as kidney function declines, but mechanisms contributing to this association are not completely understood. Metabolic acidosis, a common complication of CKD, leads to neural networks overexcitation and is involved in cerebral autoregulation. We aimed to evaluate the association between serum bicarbonate concentration as a measure of metabolic acidosis, and cognitive function in hypertensive adults with and without CKD.

Design, setting, participants, & measurements Five cognitive summary scores were measured (global cognitive function, executive function, memory, attention/concentration, and language) in 2853 participants in the Systolic BP Intervention Trial (SPRINT). Multivariable linear regression models adjusted for demographics, comorbidities, systolic BP, medications, eGFR and albuminuria evaluated the cross-sectional association between bicarbonate and cognition at SPRINT baseline. In a subset ($n=681$) who underwent brain magnetic resonance imaging, the models were adjusted for white matter hyperintensity volume, vascular reactivity, and cerebral blood flow.

Results The mean age (SD) was 68 (8.5) years. Global cognitive and executive functions were positively associated with serum bicarbonate (estimate [SEM]: 0.014 [0.006]; $P=0.01$, and 0.018 [0.006]; $P=0.003$, respectively). Each 1 mEq/L lower bicarbonate level had a similar association with global cognitive and executive function as being 4.3 and 5.4 months older, respectively. The association with global cognition persisted after magnetic resonance imaging findings adjustment (estimate [SEM]: 0.03 [0.01]; $P=0.01$). There was no association between serum bicarbonate level and memory, attention/concentration, and language.

Conclusions In a large cohort of hypertensive adults, higher serum bicarbonate levels were independently associated with better global cognitive and executive performance. (ClinicalTrials.gov: NCT01206062).

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Introduction

Acid base homeostasis is critically important, and modest fluctuations in blood pH can cause impairment in many vital functions, including neurologic performance. Hydrogen ions are important neuronal signals and are intimately involved in cerebral autoregulation (1). Acidosis has been hypothesized to be a contributing factor to the development of Alzheimer dementia (2) by making the activities between cortical pyramidal neurons and GABAergic neurons imbalanced toward overexcitation, a process similar to neural excitotoxicity (3). Additionally, hydrogen ions are a potent modulator of N-methyl-D-aspartate (NMDA)-activated currents. Low-grade chronic metabolic acidosis inhibits NMDA-activated currents, which would also result in a greater hyperexcitable state (4). However, there is limited data in both animal and human studies on the effects of chronic metabolic acidosis on cognitive function.

The kidneys play an important part in the regulation of acid base metabolism because of their ability to

secrete and excrete hydrogen ions (5). Kidney function decline is associated with impaired excretion of non-volatile acid, resulting in chronic metabolic acidosis (6). Low serum bicarbonate level, a manifestation of metabolic acidosis that often ensues with a lowering in eGFR, has multiple deleterious effects, including adverse kidney and cardiovascular outcomes and greater mortality (7–13). Although cognitive dysfunction is common in patients with CKD, the mechanisms contributing to this association are not completely understood (14–16). A graded relationship has been found between eGFR and cognition, with each 10 ml/min per 1.73 m² decline in eGFR being associated with 11% higher prevalence of cognitive impairment (14). Few studies have evaluated the risk conferred by low serum bicarbonate on cognitive function, with mixed results (17,18).

In this study, we evaluated the cross-sectional association between serum bicarbonate and measures of cognitive function in nondiabetic, hypertensive adults, with and without CKD, participating in the

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

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Systolic BP Intervention Trial (SPRINT). We hypothesize that low serum bicarbonate in CKD and non-CKD participants is independently associated with worse cognitive function.

Materials and Methods

Study Design

SPRINT is a multicenter, randomized, clinical trial (ClinicalTrials.gov: NCT01206062) that evaluated whether targeting a systolic BP <120 mm Hg will reduce cardiovascular events and mortality as compared with a systolic BP <140 mm Hg. The study design and methods have been previously published (19). Briefly, between November of 2010 and March of 2013, SPRINT recruited 9361 participants aged ≥ 50 years with hypertension at 102 clinics in the United States. Eligible participants had a systolic BP between 130 and 180 mm Hg, depending on the number of antihypertensive medications they were receiving during screening, and at least one of four cardiovascular risk factors: the presence of clinical or subclinical cardiovascular disease, an eGFR of 20–59 ml/min per 1.73 m², a Framingham 10-year risk score $\geq 15\%$, or age ≥ 75 years (19). Major exclusion criteria included diabetes mellitus, history of stroke, cardiovascular event or procedure in the prior 3 months, symptomatic heart failure in the past 6 months or left ventricular ejection fraction <35%, proteinuria >1 g/d or the equivalent as determined by spot urine measurement, polycystic kidney disease, recent immunosuppression, coexisting disease likely to affect survival, and organ transplant. A subset of 2800 participants, enriched for older SPRINT participants, was targeted to have global cognitive function measured in key specific domains of cognition at study baseline and were included in the SPRINT Memory and cognition IN Decreased hypertension (MIND) cohort. Of these, a subgroup of 677 participants completed baseline brain magnetic resonance imaging (MRI) and were included in the SPRINT MIND MRI substudy. Institutional review boards at all clinical sites approved the study protocol and all participants signed the informed consent.

Data Collection

Main Predictor. Serum bicarbonate was measured at SPRINT baseline in frozen serum samples using an enzymatic procedure with phosphoenolpyruvate carboxylase on the Modular P Chemistry analyzer at University of Minnesota Core Laboratory (interassay coefficient of variation 5.0%). Serum bicarbonate were analyzed continuously per 1 mEq/L higher level, and categorically using the following clinically relevant groups: ≤ 24 mEq/L (low), 25–28 mEq/L (reference group), and > 28 mEq/L (high). The low and high groups represent the first ($n=643$) and fourth ($n=572$) quartiles of serum bicarbonate distribution respectively, whereas the reference group represents the second and third quartiles ($n=1638$).

Outcomes. The SPRINT MIND cohort had a set of screening and extended battery cognitive tests at study baseline. Cognitive tests were administered in a private room by SPRINT administrators, all of whom had undergone detailed training on the cognitive test battery. Screening battery tests consisted of Montreal Cognitive

Assessment, Digit Symbol Substitution Tests, Logical Memory Immediate Recall, and Logical Memory Delayed Recall. Extended battery included nine tests selected to provide detailed information on multiple cognitive domains: Hopkins Verbal Learning Test Learning Trials 1–3, Hopkins Verbal Learning Test Delayed Recall, Hopkins Verbal Learning Test Delayed Recognition, Trail Making Test A, Trail Making Test B, Boston Naming Test, Rey-Osterrieth Complex Figure, Category Fluency– Animals, and Digit Span Total. The above cognitive tests were *a priori* assigned to five specific cognitive domains. Individual test results were imputed using *k* nearest neighbors for participants missing up to two test results, and set to missing for participants missing three or more tests. Individual test results were standardized using the SPRINT MIND cohort as (X–median)/interquartile range (IQR). These scores, similar to *z*-scores, were summed to develop summary cognition domain scores. The five cognitive outcomes were created for the SPRINT MIND subset and are presented in Supplemental Table 1. Higher domain scores represent better performance.

Covariates. Demographic and clinical information were obtained by questionnaires, interviews, and physical examination at baseline visit. Height, weight, and BP were recorded by trained study personnel. History of any cardiovascular disease was defined as self-report or clinical evidence of coronary artery disease, or peripheral arterial disease (19). At each study visit, participants were queried about any medication usage in the prior 30 days. All antihypertensive medications were categorized into drug classes. Smoking status was categorized as current, former, or never smokers. eGFR was calculated using the CKD Epidemiology Collaboration equation, and categorized participants as having CKD if eGFR was <60 ml/min per 1.73 m² (20). Serum creatinine concentration was measured by enzymatic procedure traceable to isotope dilution mass spectroscopy on a Roche analyzer. Urine albumin-to-creatinine ratio was calculated from a spot urine sample collected at study baseline and analyzed as a continuous variable after log transformation. Urine albumin was measured by an immunoturbidometric method on a Roche analyzer.

MRI. Brain MRI in SPRINT was performed using 3.0 T scanners and included sagittal three-dimensional fluid-attenuated inversion recovery, T2-weighted, and T1-weighted sequences with whole brain coverage, and an axial arterial spin labeling perfusion sequence (21). The University of Pennsylvania managed the MRI quality control, with each field center performing quarterly phantom scans for the evaluation of scanner stability and image distortion. MRI scanner performance across the clinical centers was stable over the duration of the study. White matter lesions were segmented to characterize brain tissue as normal or abnormal using a supervised learning-based multimodal segmentation technique (22).

Arterial spin labeling maps were transformed into cerebral blood flow (CBF) maps, with the values at each voxel in the map representing mean blood flow in ml/100 g per min (23). The CBF maps were then registered to the Jakob atlas so that mean CBF could be calculated for the whole brain and within individual regions of interest. Vascular reactivity was acquired using axial blood-oxygenation-level-dependent

Table 1. Characteristics of SPRINT MIND participants by categories of serum bicarbonate

Characteristic ^a	Total (n=2853)	Serum Bicarbonate, mEq/L		
		≤24 (n=643)	25–28 (n=1638)	>28 (n=572)
Demographics				
Age, yr (SD) ^b	68 (9)	67 (8)	69 (9)	69 (9)
Women, n (%) ^b	1053 (37)	206 (32)	604 (37)	243 (43)
Race/ethnicity, n (%)				
White	1704 (60)	388 (60)	983 (60)	333 (58)
Black	856 (30)	193 (30)	478 (29)	185 (32)
Hispanic	233 (8)	52 (8)	141 (9)	40 (7)
Other	60 (2)	10 (2)	36 (2)	14 (3)
Smoking, n (%) ^b				
Current	355 (12)	103 (16)	201 (12)	51 (9)
Former	1246 (44)	292 (45)	709 (43)	245 (43)
Never	1249 (44)	248 (39)	727 (44)	274 (48)
Body mass index, kg/m ² (SD) ^b	29.8 (5.7)	30.5 (5.7)	29.8 (5.6)	29.2 (5.8)
History of cardiovascular disease, n (%) ^b	568 (20)	154 (24)	293 (18)	121 (21)
CKD, n (%) ^b	863 (30)	256 (40)	471 (29)	136 (24)
Systolic BP, mm Hg (SD)	139 (16)	138 (16)	139 (16)	140 (17)
Laboratory data				
eGFR, ml/min per 1.73 m ² (SD) ^b	71 (20)	67 (23)	72 (19)	74 (18)
Urine albumin-to-creatinine, mg/g, median (IQR) ^b	9.7 (5.8–22.5)	10.8 (6.4–33.7)	9.4 (5.6–20.0)	9.3 (5.6–22.3)
Serum creatinine, mg/dl (SD) ^b	1.1 (0.3)	1.2 (0.4)	1.1 (0.3)	1.0 (0.3)
HDL, mg/dl (SD) ^b	53 (15)	52 (14)	54 (14)	55 (15)
LDL, mg/dl (SD)	112 (35)	111 (38)	113 (35)	111 (35)
Medication use, n (%)^b				
Diuretics ^b	1277 (45)	221 (34)	705 (43)	351 (61)
Angiotensin-converting enzyme inhibitor ^b	1058 (37)	258 (40)	613 (38)	187 (33)
Angiotensin receptor blocker	613 (22)	148 (23)	329 (20)	136 (24)
Calcium channel blocker	1024 (36)	231 (36)	597 (37)	196 (34)
β-blocker	884 (31)	206 (32)	487 (30)	191 (33)
Antiacidosis ^b	15 (0.5)	12 (2)	2 (0.1)	1 (0.2)
Aspirin	1465 (51)	325 (51)	841 (51)	299 (53)
Phosphate binders	34 (1)	9 (1)	19 (1)	6 (1)

^aThe following characteristics had missing data: smoking (n=3); body mass index (n=24); eGFR (n=9); urine albumin-to-creatinine ratio (n=139); serum creatinine (n=9); HDL (n=4); LDL (n=23); and aspirin (n=6). All other 13 covariates had no missing data.

^bStatistically significant differences were observed between the three groups of serum bicarbonate.

functional MRI (fMRI) sequence during resting and 30-second breath hold, respectively. Blood-oxygenation-level-dependent signal changes for the resting state fMRI and breath-holding task were performed with the same imaging parameters: a two-dimensional gradient-echo echo-planar imaging sequence (field of view=22 cm, matrix =64×64, slice thickness/slice spacing =3.5/0 mm, number of slices =35 covering the whole-brain, TR=2 seconds, TE=25 milliseconds, flip angle =75°, number of time points =120 for resting state fMRI and 105 for breath-holding experiments).

Statistical Analyses

Standard descriptive statistics were used to characterize the study cohort at SPRINT baseline, stratified by groups of serum bicarbonate. Continuous variables were expressed as mean (SD) or median (IQR), and compared using *t* tests or Wilcoxon rank-sum tests as appropriate. Categorical variables were expressed as proportions and compared using chi-squared tests.

Linear regression models were used to estimate the independent association between serum bicarbonate and the five cognitive function outcomes. Covariates used for adjustment in the models included age, sex, race, education, clinical network, tobacco use, history of cardiovascular

disease, systolic BP, antihypertensive medications, antiacidosis medications (sodium bicarbonate, sodium citrate, citric acid/sodium citrate), baseline eGFR, and spot urine albumin-to-creatinine ratio. Sequential multivariable models for each outcome were created on the basis of our assessment of the covariates likelihood of being a confounder in the relationship between serum bicarbonate and the five cognitive function domains. Because the test scores have been standardized to create a composite measure, their clinical relevance cannot be directly interpreted. Instead we examined the coefficients of other covariates (*i.e.*, age) and compared with the coefficients for serum bicarbonate. Secondary analyses were done to model the association between serum bicarbonate and the performance on individual cognitive tests. All models were tested for linearity of continuous variables of interest. Given the small number of missing covariate data and the large data set, imputation was not performed; participants with missing data were excluded from the multivariable analyses.

Sensitivity analyses were done to assess if the association between serum bicarbonate levels and cognitive function is modified by sex, race, educational level, CKD, albuminuria, diuretic use, or systolic BP, using an interaction between serum bicarbonate and each potential modifier. In addition,

Table 2. Performance on cognitive tests by categories of serum bicarbonate in SPRINT MIND participants

Test	Serum Bicarbonate, mEq/L			P Value
	≤24 (n=643)	25–28 (n=1638)	>28 (n=572)	
Screening battery				
Logical Memory Immediate Recall	19.3 (4.9)	19.4 (4.9)	19.2 (4.8)	0.80
Montreal Cognitive Assessment	23.3 (4.0)	23.1 (4.1)	22.6 (4.0)	0.02
Digit Symbol Coding	51.5 (14.7)	51.1 (15.0)	50.6 (15.2)	0.59
Logical Memory Delayed Recall	8.2 (3.3)	8.3 (3.4)	8.1 (3.3)	0.36
Extended battery				
Hopkins Verbal Learning Test Learning Trials 1–3	21.5 (5.0)	21.7 (5.3)	21.7 (5.1)	0.54
Trail Making Test A	43.3 (23.4)	43.8 (25.2)	42.7 (19.3)	0.65
Trail Making Test B	122.3 (72.3)	120.1 (71.0)	121.0 (70.0)	0.81
Boston Naming Test	11.9 (3.1)	11.7 (3.2)	11.6 (3.2)	0.35
Rey-Osterrieth Complex Figure	14.3 (4.5)	14.4 (4.7)	14.3 (5.0)	0.80
Category Fluency – Animals	18.1 (5.5)	17.9 (5.0)	17.6 (4.7)	0.24
Digit Span Total	16.8 (4.2)	16.9 (4.2)	16.8 (3.9)	0.57
Hopkins Verbal Learning Test Delayed Recall	5.7 (3.7)	5.6 (3.9)	5.2 (3.9)	0.04
Hopkins Verbal Learning Test Delayed Recognition	10.7 (1.7)	10.7 (1.6)	10.7 (1.7)	0.72

Values are expressed as mean (SD).

given that previous studies have suggested a U-shaped relationship between bicarbonate levels and clinical outcomes, we explored such nonlinear associations further by treating serum bicarbonate as a continuous exposure and using quadratic splines or cubic splines to model the association between serum bicarbonate and each cognitive function summary score.

In the subgroup of participants with MRI data, the models were further adjusted for the MRI findings known to be associated with worse cognitive performance. These confounders included white matter hyperintensity volume and total abnormal volume. Additionally, the models were adjusted for scanner type. Because acid base balance is intimately involved in cerebral autoregulation, the models were adjusted for vascular reactivity and CBF, measures obtained from the 30-second breath-hold fMRI. Demographic characteristics of participants in the MRI subgroup were similar to the entire study cohort.

All analyses were done using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 2853 participants underwent the extended cognitive battery testing and had available serum bicarbonate levels at SPRINT baseline; these participants were included in this analysis. The mean age (SD) was 68 (8.5) years, 1053 (37%) were women, 856 (30%) were black, and 568 (20%) had a history of cardiovascular disease. The mean (SD) bicarbonate level was 26.3 (2.6) mEq/L (median, 26 mEq/L; IQR, 25–28 mEq/L). At study entry, mean (SD) eGFR was 71 (20) (median, 73; IQR, 57–86) ml/min per 1.73 m². There were 863 (30%) participants with CKD.

Compared with participants with normal or high serum bicarbonate, participants with serum bicarbonate ≤24 mEq/L were more likely to be younger, to be men, and to have CKD or history of cardiovascular disease at study baseline. They were also more likely to be taking an angiotensin-converting enzyme inhibitor or an antacidosis medication, and less likely to be on a diuretic (Table 1).

Unadjusted comparisons of performances on individual cognitive tests by categories of serum bicarbonate are presented in Table 2. Statistically significant differences were observed across strata of serum bicarbonate for Montreal Cognitive Assessment score (mean [SD]: 23.3 [3.9], 23.1 [4.1], and 22.6 [4.0]; $P=0.02$), and Hopkins Verbal Learning Test Delayed Recall score (mean [SD]: 5.7 [3.7], 5.6 [3.9], and 5.2 [3.9]; $P=0.04$), for serum bicarbonate ≤24, 25–28, and >28 mEq/L, respectively. There were no statistically significant differences in the mean scores in other measures of cognitive function between serum bicarbonate strata (Table 2).

Association of Serum Bicarbonate with Cognitive Function

Table 3 depicts the results of multivariable linear regression models evaluating the association between serum bicarbonate as continuous variable and cognitive function scores. There was a positive linear association between serum bicarbonate and global cognitive function summary score that was consistent in hierarchical models adjusted for demographics (estimate [SEM]: 0.02 [0.005]; $P<0.01$), clinical characteristics (estimate [SEM]: 0.02 [0.006]; $P<0.01$), and eGFR and albuminuria (estimate [SEM]: 0.01 [0.006]; $P=0.01$). Similarly, there was a positive linear association between serum bicarbonate and executive function summary score that was consistent after adjustment for demographics (estimate [SEM]: 0.02 [0.006]; $P<0.01$), clinical characteristics (estimate [SEM]: 0.02 [0.006]; $P=0.004$), and eGFR and albuminuria (estimate [SEM]: 0.02 [0.006]; $P=0.002$). Each 1 mEq/L lower serum bicarbonate concentration had a similar association with global cognitive and executive function as being 4.3 and 5.4 months older, respectively (estimate [SEM] for age in the final model: -0.040 [0.002] and -0.039 [0.002], respectively). There was no statistically significant association between serum bicarbonate level and memory, attention/concentration, and language scores (Table 3). The association between serum bicarbonate and individual cognitive test results is presented in Supplemental Table 2.

Table 3. Association between continuous serum bicarbonate and summary cognitive function domains in SPRINT MIND participants

Domain	Model 1, n=2853		Model 2, n=2853		Model 3, n=2804	
	Estimate (SEM)	P Value	Estimate (SEM)	P Value	Estimate (SEM)	P Value
Global cognitive function	0.02 (0.005)	<0.01	0.02 (0.006)	<0.01	0.01 (0.006)	0.01
Executive function	0.02 (0.006)	<0.01	0.02 (0.006)	0.004	0.02 (0.006)	0.002
Memory	0.01 (0.006)	0.07	0.008 (0.006)	0.20	0.006 (0.006)	0.35
Attention/concentration	0.01 (0.006)	0.06	0.01 (0.006)	0.04	0.01 (0.006)	0.06
Language	-0.008 (0.006)	0.19	-0.009 (0.006)	0.15	-0.009 (0.006)	0.17

Model 1 adjusted for age, network, education, sex, and race. Model 2 adjusted for model 1 components as well as cardiovascular disease, systolic BP, use of diuretics, and antacidosis medications (sodium bicarbonate, sodium citrate, citric acid/sodium citrate). Model 3 adjusted for model 2 components as well as eGFR and log-transformed urine albuminuria.

In exploratory models by categories of serum bicarbonate, participants with serum bicarbonate ≤ 24 mEq/L had lower performance on global cognitive and executive function summary scores, compared with participants with serum bicarbonate 25–28 mEq/L, although these associations did not reach statistical significance (estimate [SEM]: -0.06 [0.04]; $P=0.18$, and -0.06 [0.04], $P=0.15$, respectively) (Supplemental Tables 3 and 3.1). The association between categories of serum bicarbonate and individual cognitive test results is presented in Supplemental Table 4.

Sensitivity analyses of the association between serum bicarbonate level and cognitive function scores were conducted in the following subgroups by sex, race, education, CKD status, systolic BP, albuminuria, and diuretic use. No significant interactions were observed (Supplemental Table 5).

Association of Serum Bicarbonate with Cognitive Function in the MRI Substudy

We tested the association between serum bicarbonate and cognitive function in a subgroup of 681 participants who underwent brain MRI. The positive linear association between serum bicarbonate and global cognitive function persisted after adjustment for MRI structural and functional measurements to include white matter hyperintensity volume, vascular reactivity, and CBF (estimate [SEM]: 0.03 [0.01]; $P=0.01$). There was a positive association between serum bicarbonate and executive function when

adjustments were made for demographics and traditional cardiovascular risk factors (estimate [SEM]: 0.03 [0.01]; $P=0.02$); however, these associations were attenuated and became not statistically significant after adjustments for structural brain abnormalities (estimate [SEM]: 0.02 [0.01]; $P=0.06$) as well as functional brain abnormalities (estimate [SEM]: 0.02 [0.01]; $P=0.07$) (Table 4). Characteristics of participants in the MRI subgroup are presented in Supplemental Table 6. There was no statistical significant association between serum bicarbonate level and white matter volume, CBF, and vascular reactivity (Supplemental Table 7).

Discussion

In a large cohort of hypertensive adults with and without CKD, we found a positive linear association between serum bicarbonate level and global cognitive and executive functions, independent of the degree of albuminuria, eGFR, diuretic use, or traditional cerebrovascular risk factors (age, cardiovascular disease, and BP). Each 1 mEq/L lower serum bicarbonate concentration had a similar association with global cognitive and executive function as being 4.3 and 5.4 months older, respectively. To our knowledge, this is the first study to evaluate the association between serum bicarbonate level and rigorous multiple cognitive function domain measurements in patients with and without CKD.

The relationship between serum bicarbonate and global cognitive function was maintained after adjustments for

Table 4. Association of serum bicarbonate with cognitive function domains in the SPRINT MIND MRI subgroup

Domain	Model 1, n=681		Model 2, n=681		Model 3, n=594	
	Estimate (SEM)	P Value	Estimate (SEM)	P Value	Estimate (SEM)	P Value
Global cognitive function	0.0391 (0.01)	0.001	0.0358 (0.01)	0.003	0.0328 (0.01)	0.01
Executive function	0.0304 (0.01)	0.02	0.0246 (0.01)	0.06	0.0246 (0.01)	0.07
Memory	0.0255 (0.01)	0.05	0.0256 (0.01)	0.05	0.0203 (0.01)	0.14
Attention/concentration	0.0240 (0.01)	0.07	0.0196 (0.01)	0.15	0.0164 (0.01)	0.26
Language	0.0024 (0.01)	0.86	-0.0005 (0.01)	0.97	0.0078 (0.01)	0.59

Model 1 adjusted for age, network, education, sex, race, cardiovascular disease, systolic BP, use of diuretics and antacidosis medications (sodium bicarbonate, sodium citrate, citric acid/sodium citrate), eGFR, and log-transformed urine albuminuria. Model 2 adjusted for model 1 components as well as scanner type, intracranial volume, and total abnormal volume. Model 3 adjusted for model 2 components as well as vascular reactivity and cerebral blood flow.

structural white matter abnormalities, cerebral vascular reactivity, and CBF, suggesting that chronic low levels of bicarbonate within the brain may be detrimental to neuronal function. Our models showed a trend toward a statistically significant association between serum bicarbonate and executive function in the MRI subgroup. Important to note, this was observed in a subset of SPRINT participants with available brain MRI data, so further studies on larger cohorts would be needed to assess this association. We found no association between serum bicarbonate level and memory, attention/concentration, and language domains, suggesting a potential distinct pathophysiologic process. In exploratory analyses by categories of serum bicarbonate, the lack of statistical significant association is likely explained by the loss of statistical power.

Previous studies evaluating the mechanisms of acidosis induced neuronal dysfunction described the role of impaired GABAergic neurons responsible to coordinate the activities of principal neurons and help manage well organized cognitions (24,25). A potential mechanism of acidosis leading to impaired cognition may be through overexcitation of neural networks by being a potent inhibitor of NMDA-activated currents. The possible effect of acidosis on neuronal function and not structure is also supported by the null association found between bicarbonate and structural MRI measurements. It is reasonable to assume that chronic, low degree metabolic acidosis induced by a Western diet irrespective of the level of eGFR (26) can promote neural excitotoxicity and subsequently cognitive impairment. Because pH was not available in SPRINT, it is possible that a small proportion of SPRINT participants with low bicarbonate had respiratory alkalosis. Mechanisms underlying alkalosis-induced brain dysfunction are much less understood, but they seem to be related to impairment in excitatory synaptic transmission and spike initiation in cortical GABAergic neurons (27).

A larger body of evidence describe the effect of acidosis on neurons and glia, primarily in the setting of cerebral ischemia, with most pointing toward regional lactic acidosis as a key neurotoxic insult to ischemic brain leading to direct impairment of cellular metabolism (28–31). Cognitive dysfunction, and in particular changes in processing speed, shifting between mental tasks, executive function, concentration, and attention have been long thought to be a consequence of cerebral vascular damage (32,33).

Cardiovascular disease and metabolic acidosis are common complications of CKD. Cognitive impairment is another common occurrence in CKD, and the risk of cognitive decline is dependent on the severity of CKD. The exact mechanisms of CKD promoting neuronal damage remain vaguely unknown. This study may provide a mechanistic insight into why patients with CKD have poor cognitive function. Future randomized trials with alkali supplementation should clarify if correction of metabolic acidosis in CKD will also lead to better cognitive outcomes in this population at high cardiovascular risk. The strength of the association between serum bicarbonate level and global cognitive and executive functions was relatively modest in our observational study, and should be confirmed in clinical trials testing alkali supplementation or dietary modifications to correct metabolic acidosis.

This study has several strengths, including concurrent assessment of serum bicarbonate level, kidney function, albuminuria, cognitive function tests, and brain MRI. Furthermore, a large battery of tests was used to assess cognitive function, allowing for differentiation of cognitive deficit subtypes associated with a low bicarbonate level. Also, SPRINT recruited a large sample of individuals with CKD who are more likely to have acid base abnormalities.

This study has several limitations. First, it is a cross-sectional analysis and causality cannot be inferred. Second, the acid base status assessment with a blood gas analysis was not available. Some participants might have high bicarbonate as a compensatory mechanism for respiratory acidosis, or a low bicarbonate as a compensatory response for respiratory alkalosis. Third, these analyses are on the basis of a single measurement of serum bicarbonate; whether changes in bicarbonate levels over time add incremental predictive value to the development of cognitive dysfunction will need further study. Also, using a lower category of serum bicarbonate <22 mEq/L on the basis of the current guidelines of alkali supplementation was not possible because of the small number of participants in that group. However, in exploratory analyses the same direction of the association was observed for bicarbonate ≤ 22 and 23–24 mEq/L groups when compared with 25–28 mEq/L group, for four of the five cognitive summary measures (Supplemental Table 3s). Lastly, given that many cofactors used for adjustments (age, BP, history of cardiovascular disease, *etc.*) correlate with the exposure, but they also can be a direct cause of the outcome (cognitive function), residual confounding might in part influence the study findings.

In summary, in a large cohort of hypertensive individuals at high cardiovascular risk, lower levels of serum bicarbonate were associated with worse cognitive performance. In particular, lower serum bicarbonate level was associated with reduced global cognitive function and lower performance on executive function. These findings suggest that low bicarbonate level may be detrimental to neuronal activity. Future intervention trials aimed at correcting chronic metabolic acidosis with alkali therapy are required to test a beneficial effect on the cognitive function.

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For a full list of contributors to SPRINT, please see the supplemental acknowledgment list.

Disclosures

None.

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Serum bicarbonate concentration and cognitive function in hypertensive adults

Appendix

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Supplemental Tables

Supplemental Table 1s. Tests included in the cognitive summary domains in SPRINT-MIND

Supplemental Table 2s. Association between continuous serum bicarbonate and individual tests of cognitive function in SPRINT MIND

Supplemental Table 3s. Association between categorical serum bicarbonate and cognitive function domains in SPRINT MIND

Supplemental Table 3.1s. Association between categorical serum bicarbonate (4 groups) and cognitive function domains in SPRINT MIND

Supplemental Table 4s. Association between categorical serum bicarbonate and individual tests of cognitive function in SPRINT MIND

Supplemental Table 5s. P-values for the interaction in selected subgroups in SPRINT MIND

Supplemental Table 6s. Baseline Characteristics of SPRINT MIND MRI subgroup (N=681) participants

Supplemental Table 7s. Association between serum bicarbonate levels and white matter volume, cerebral blood flow, and vascular reactivity in the SPRINT MIND MRI subgroup

Supplemental Figure

Supplemental Figure 1s. Distribution plots of serum bicarbonate (continuous exposure) and cognitive summary scores in SPRINT MIND

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Supplemental Table 1s. Tests included in the cognitive summary domains in SPRINT-MIND

Cognitive Summary Domain	Tests
Global Cognitive Function	All cognitive tests in the Screening* and Extended** battery with the exception of MoCA
Executive Function	Trail Making Test part B, Category Verbal Fluency Test - Animals, Digit Symbol Substitution, and Digit Span Backward.
Memory	Logical Memory, immediate and delayed recall, Rey-Osterrieth Complex Figure-Immediate Recall, Hopkins Verbal Learning Test Sum of Trials 1, 2 and 3, and Hopkins Verbal Learning Test Delayed Recall
Attention/Concentration	Trail Making Test Part A, Digit Span Forward, MoCA sum of attention subtests (Hand Tapping, Serial 7s, and Digits)
Language	Boston Naming, MoCA, naming subset, and MoCA, language sentence repeat task

* Screening battery tests: Montreal Cognitive Assessment (MoCA), Digit Symbol Substitution Tests, Logical Memory Immediate Recall, and Logical Memory Delayed Recall.

**Extended battery tests: Hopkins Verbal Learning Test Learning Trials 1-3, Hopkins Verbal Learning Test Delayed Recall, Hopkins Verbal Learning Test Delayed Recognition, Trail Making Test A, Trail Making Test B, Boston Naming Test, Rey-Osterrieth Complex Figure, Category Fluency – Animals and Digit Span Total.

Supplemental Table 2s. Association between continuous serum bicarbonate and individual tests of cognitive function in SPRINT MIND

	Model 1		Model 2		Model 3	
	Estimate (SE)	P-value	Estimate (SE)	P-value	Estimate (SE)	P-value
Digit Symbol (0-135)	0.18 (0.09)	0.05	0.19 (0.09)	0.05	0.20 (0.09)	0.04
Logical Memory I (0-28)	0.03 (0.03)	0.28	0.02 (0.03)	0.61	0.02 (0.03)	0.60
Logical Memory II (0-14)	0.02 (0.02)	0.35	0.01 (0.02)	0.82	0.001 (0.02)	0.98
Trail Making Test-A Time (0-300)	-0.37 (0.16)	0.02	-0.35 (0.16)	0.03	-0.35 (0.17)	0.04
Trail Making Test -B Time (0-300)	-1.44 (0.45)	0.002	-1.43 (0.47)	0.002	-1.54 (0.48)	0.001
Verbal Fluency - Animals (0-no limit)	0.01 (0.03)	0.70	0.02 (0.03)	0.62	0.01 (0.04)	0.68
Boston Naming (0-15)	0.004 (0.02)	0.82	-0.003 (0.02)	0.88	-0.002 (0.02)	0.93
Hopkins Verbal Learning Test Sum of T1-T3 (0-36)	0.08 (0.03)	0.02	0.05 (0.03)	0.12	0.05 (0.03)	0.16
Hopkins Verbal Learning Test Delayed Recall (0-12)	-0.04 (0.03)	0.09	-0.05 (0.03)	0.06	-0.06 (0.03)	0.04
Hopkins Verbal Learning Test Discrimination Index (0-12)	0.01 (0.01)	0.36	0.01 (0.01)	0.55	0.004 (0.01)	0.73
Digits Forward (0-16)	0.004 (0.02)	0.82	0.01 (0.02)	0.43	0.01 (0.02)	0.42
Digits Backward (0-16)	0.04 (0.02)	0.02	0.04 (0.02)	0.02	0.04 (0.02)	0.01
Rey-Osterrieth Complex Figure – Copy (0-24)	0.08 (0.02)	0.001	0.08 (0.02)	0.001	0.08 (0.02)	0.002
Rey-Osterrieth Complex Figure – Immediate Recall (0-24)	0.11 (0.03)	0.001	0.11 (0.03)	0.001	0.10 (0.03)	0.002
Sum of MoCA Attention Subtests: Hand Tapping, Serial 7s, Digits (0-6)	0.01 (0.01)	0.08	0.01 (0.01)	0.10	0.01 (0.01)	0.15
MoCA Naming (0-3)	-0.0002 (0.003)	0.94	-0.0004 (0.004)	0.91	-0.0003 (0.003)	0.95
MoCA Language 1: Sentence Repeat (0-2)	-0.01 (0.01)	0.01	-0.01 (0.01)	0.01	-0.01 (0.01)	0.01

Model 1 adjusted for age, network, education, sex, and race;

Model 2 adjusted for Model 1 components as well as cardiovascular disease, systolic blood pressure, use of diuretics, and anti-acidosis medications (sodium bicarbonate, sodium citrate, citric acid/sodium citrate);

Model 3 adjusted for Model 2 components as well as estimated glomerular filtration rate and log transformed urine albuminuria.

Supplemental Table 3s. Association between categorical serum bicarbonate and cognitive function domains
 (Reference: Serum Bicarbonate [25- 28mEq/L]) in SPRINT MIND

	Model 1		Model 2		Model 3	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
Global Cognitive Function						
Serum Bicarbonate \leq 24 mEq/L	-0.08 (0.04)	0.06	-0.06 (0.04)	0.18	-0.06 (0.04)	0.18
Serum Bicarbonate > 28 mEq/L	-0.0001 (0.04)		0.01 (0.04)		0.02 (0.04)	
Executive Function						
Serum Bicarbonate \leq 24 mEq/L	-0.08 (0.04)	0.11	-0.06 (0.04)	0.22	-0.06 (0.04)	0.15
Serum Bicarbonate > 28 mEq/L	-0.004 (0.04)		0.01 (0.04)		0.03 (0.04)	
Memory						
Serum Bicarbonate \leq 24 mEq/L	-0.09 (0.04)	0.08	-0.06 (0.04)	0.28	-0.05 (0.04)	0.38
Serum Bicarbonate > 28 mEq/L	-0.03 (0.04)		-0.03 (0.04)		-0.03 (0.04)	
Attention/Concentration						
Serum Bicarbonate \leq 24 mEq/L	-0.08 (0.04)	0.13	-0.07 (0.04)	0.16	-0.07 (0.04)	0.20
Serum Bicarbonate > 28 mEq/L	-0.0002 (0.04)		0.01 (0.04)		0.02 (0.04)	
Language						
Serum Bicarbonate \leq 24 mEq/L	0.04 (0.04)	0.39	0.05 (0.04)	0.32	0.04 (0.04)	0.41
Serum Bicarbonate > 28 mEq/L	-0.03 (0.04)		-0.03 (0.04)		-0.03 (0.04)	

Model 1 adjusted for age, network, education, sex, and race

Model 2 adjusted for Model 1 components as well as cardiovascular disease, systolic blood pressure, use of diuretics and anti-acidosis medications (sodium bicarbonate, sodium citrate, citric acid/sodium citrate)

Model 3 adjusted for model 2 components as well as estimated glomerular filtration rate and log transformed urine albuminuria.

Supplemental Table 3.1s. Association between categorical serum bicarbonate (4 groups) and cognitive function domains in SPRINT MIND (Reference: Serum Bicarbonate [25- 28mEq/L])

	Model 1		Model 2		Model 3	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
Global Cognitive Function						
Serum Bicarbonate \leq 22 mEq/L	-0.16 (0.06)	0.05	-0.14 (0.06)	0.09	-0.13 (0.06)	0.15
Serum Bicarbonate 23-24 mEq/L	-0.02 (0.05)		-0.005 (0.05)		-0.01 (0.05)	
Serum Bicarbonate $>$ 28 mEq/L	-0.0003 (0.04)		0.01 (0.04)		0.02 (0.04)	
Executive Function						
Serum Bicarbonate \leq 22 mEq/L	-0.17 (0.06)	0.04	-0.16 (0.06)	0.05	-0.15 (0.06)	0.05
Serum Bicarbonate 23-24 mEq/L	0.01 (0.05)		0.03 (0.05)		0.02 (0.05)	
Serum Bicarbonate $>$ 28 mEq/L	-0.003 (0.04)		0.01 (0.04)		0.03 (0.04)	
Memory						
Serum Bicarbonate \leq 22 mEq/L	-0.13 (0.06)	0.19	-0.10 (0.06)	0.40	-0.08 (0.06)	0.65
Serum Bicarbonate 23-24 mEq/L	-0.04 (0.05)		-0.02 (0.05)		-0.02 (0.05)	
Serum Bicarbonate $>$ 28 mEq/L	-0.03 (0.04)		-0.03 (0.04)		-0.03 (0.04)	
Attention/Concentration						
Serum Bicarbonate \leq 22 mEq/L	-0.13 (0.04)	0.20	-0.13 (0.07)	0.23	-0.11 (0.07)	0.33
Serum Bicarbonate 23-24 mEq/L	-0.04 (0.05)		-0.3 (0.06)		-0.04 (0.06)	
Serum Bicarbonate $>$ 28 mEq/L	-0.0002 (0.04)		0.01 (0.04)		0.02 (0.04)	
Language						
Serum Bicarbonate \leq 22 mEq/L	0.04 (0.07)	0.81	0.04 (0.07)	0.78	0.04 (0.07)	0.84
Serum Bicarbonate 23-24 mEq/L	0.01 (0.06)		0.02 (0.06)		0.009 (0.06)	
Serum Bicarbonate $>$ 28 mEq/L	-0.03 (0.04)		-0.03 (0.04)		-0.03 (0.04)	

Model 1 adjusted for age, network, education, sex, and race

Model 2 adjusted for Model 1 components as well as cardiovascular disease, systolic blood pressure, use of diuretics and anti-acidosis medications (sodium bicarbonate, sodium citrate, citric acid/sodium citrate)

Model 3 adjusted for model 2 components as well as estimated glomerular filtration rate and log transformed urine albuminuria.

Supplemental Table 4s. Association between categorical serum bicarbonate and individual tests of cognitive function in SPRINT MIND (Reference: Serum Bicarbonate [25- 28mEq/L])

Component	Model 1		Model 2		Model 3	
	Estimate (SE)	P-value	Estimate (SE)	P-value	Estimate (SE)	P-value
Digit Symbol (0-135)						
Serum Bicarbonate ≤ 24 mEq/L	-0.62 (0.59)	0.54	-0.37 (0.60)	0.69	-0.36 (0.60)	0.55
Serum Bicarbonate > 28 mEq/L	0.07 (0.62)		0.26 (0.62)		0.47 (0.62)	
Logical Memory I (0-28)						
Serum Bicarbonate ≤ 24 mEq/L	-0.25 (0.20)	0.45	-0.12 (0.20)	0.82	-0.13 (0.21)	0.80
Serum Bicarbonate > 28 mEq/L	-0.08 (0.21)		-0.06 (0.21)		-0.05 (0.21)	
Logical Memory II (0-14)						
Serum Bicarbonate ≤ 24 mEq/L	-0.23 (0.14)	0.19	-0.14 (0.14)	0.33	-0.13 (0.14)	0.35
Serum Bicarbonate > 28 mEq/L	-0.17 (0.15)		-0.20 (0.15)		-0.20 (0.15)	
Trail Making Test-A Time (0-300)						
Serum Bicarbonate ≤ 24 mEq/L	0.82 (1.02)	0.10	0.68 (1.04)	0.17	0.65 (1.06)	0.15
Serum Bicarbonate > 28 mEq/L	-1.79 (1.06)		-1.66 (1.08)		-1.80 (1.09)	
Trail Making Test -B Time (0-300)						
Serum Bicarbonate ≤ 24 mEq/L	6.48 (2.94)	0.04	5.50 (2.97)	0.05	5.81 (3.01)	0.04
Serum Bicarbonate > 28 mEq/L	-2.15 (3.06)		-3.32 (3.09)		-3.73 (3.12)	
Verbal Fluency - Animals (0-no limit)						
Serum Bicarbonate ≤ 24 mEq/L	-0.08 (0.22)	0.90	-0.05 (0.22)	0.97	-0.01 (0.23)	0.99
Serum Bicarbonate > 28 mEq/L	-0.09 (0.23)		-0.05 (0.23)		0.004 (0.23)	
Boston Naming (0-15)						
Serum Bicarbonate ≤ 24 mEq/L	0.06 (0.12)	0.84	0.10 (0.13)	0.75	0.08 (0.13)	0.81
Serum Bicarbonate > 28 mEq/L	0.06 (0.13)		0.03 (0.13)		0.06 (0.13)	

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Component	Model 1		Model 2		Model 3	
	Estimate (SE)	P-value	Estimate (SE)	P-value	Estimate (SE)	P-value
Hopkins Verbal Learning Test Sum of T1-T3 (0-36)						
Serum Bicarbonate \leq 24 mEq/L	-0.50 (0.22)	0.06	-0.35 (0.22)	0.25	-0.32 (0.22)	0.31
Serum Bicarbonate $>$ 28 mEq/L	0.003 (0.22)		0.02 (0.23)		0.04 (0.23)	
Hopkins Verbal Learning Test Delayed Recall (0-12)						
Serum Bicarbonate \leq 24 mEq/L	-0.05 (0.17)	0.08	0.01 (0.17)	0.08	0.01 (0.17)	0.08
Serum Bicarbonate $>$ 28 mEq/L	-0.39 (0.18)		-0.39 (0.18)		-0.40 (0.18)	
Hopkins Verbal Learning Test Discrimination Index (0-12)						
Serum Bicarbonate \leq 24 mEq/L	-0.12 (0.08)	0.23	-0.10 (0.08)	0.36	-0.10 (0.08)	0.40
Serum Bicarbonate $>$ 28 mEq/L	0.01 (0.08)		0.01 (0.08)		0.0001 (0.08)	
Digits Forward (0-16)						
Serum Bicarbonate \leq 24 mEq/L	-0.14 (0.11)	0.45	-0.16 (0.11)	0.34	-0.16 (0.11)	0.35
Serum Bicarbonate $>$ 28 mEq/L	-0.06 (0.11)		-0.01 (0.12)		-0.01 (0.12)	
Digits Backward (0-16)						
Serum Bicarbonate \leq 24 mEq/L	-0.19 (0.10)	0.15	-0.18 (0.10)	0.18	-0.19 (0.10)	0.14
Serum Bicarbonate $>$ 28 mEq/L	-0.02 (0.10)		0.01 (0.11)		0.03 (0.11)	
Rey-Osterrieth Complex Figure -COPY (0-24)						
Serum Bicarbonate \leq 24 mEq/L	-0.25 (0.15)	0.06	-0.25 (0.15)	0.06	-0.22 (0.16)	0.08
Serum Bicarbonate $>$ 28 mEq/L	0.19 (0.16)		0.21 (0.16)		0.22 (0.16)	
Rey-Osterrieth Complex Figure -Immediate Recall (0-24)						
Serum Bicarbonate \leq 24 mEq/L	-0.43 (0.20)	0.04	-0.42 (0.20)	0.05	-0.36 (0.21)	0.09
Serum Bicarbonate $>$ 28 mEq/L	0.15 (0.21)		0.18 (0.21)		0.19 (0.21)	
Sum of MoCA Attention Subtests: Hand Tapping, Serial 7s, Digits (0-6)						
Serum Bicarbonate \leq 24 mEq/L	-0.10 (0.05)	0.15	-0.09 (0.05)	0.21	-0.08 (0.05)	0.32
Serum Bicarbonate $>$ 28 mEq/L	-0.02 (0.05)		-0.02 (0.05)		-0.01 (0.05)	
MoCA Naming (0-3)						
Serum Bicarbonate \leq 24 mEq/L	0.01 (0.02)	0.89	0.01 (0.02)	0.85	0.01 (0.02)	0.93
Serum Bicarbonate $>$ 28 mEq/L	-0.01 (0.02)		-0.01 (0.02)		-0.004 (0.02)	

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Component	Model 1		Model 2		Model 3	
	Estimate (SE)	P-value	Estimate (SE)	P-value	Estimate (SE)	P-value
MoCA Language 1: Sentence Repeat (0-2)						
Serum Bicarbonate \leq 24 mEq/L	0.04 (0.03)	0.08	0.04 (0.03)	0.09	0.03 (0.03)	0.13
Serum Bicarbonate $>$ 28 mEq/L	-0.05 (0.03)		-0.05 (0.03)		-0.05 (0.03)	

Model 1 adjusted for age, network, education, sex, and race;

Model 2 adjusted for Model 1 components as well as cardiovascular disease, systolic blood pressure, use of diuretics, and anti-acidosis medications (sodium bicarbonate, sodium citrate, citric acid/sodium citrate);

Model 3 adjusted for Model 2 components as well as estimated glomerular filtration rate and log transformed urine albuminuria.

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Supplemental Table 5s. P-values for the interaction in selected subgroups in SPRINT MIND

	P-values for interaction for selected variable X serum bicarbonate level						
	Sex	Race	Education	CKD Status	SBP	UACR	Diuretic Use
Global Cognitive Function	0.53	0.21	0.09	0.61	0.42	0.72	0.74
Executive Function	0.39	0.16	0.26	0.61	0.58	0.99	0.53
Memory	0.86	0.87	0.30	0.36	0.31	0.31	0.83
Attention/Concentration	0.99	0.07	0.01	0.43	0.85	0.47	0.28
Language	0.81	0.47	0.08	0.32	0.26	0.67	0.89

CKD = Chronic Kidney Disease; SBP= Systolic Blood Pressure; UACR= Urine Albumin/Creatinine Ratio

Supplemental Table 6s. Baseline Characteristics of SPRINT MIND MRI subgroup (N=681) participants

	Mean (SD) or N (%)
Age, years (SD)	68 (8.3)
Women, n (%)	272 (40)
Race/Ethnicity, n (%)	
Black	219 (32)
Hispanic	30 (4)
Other	11 (2)
White	421 (62)
Estimated glomerular filtration rate, mL/min/1.73m ² (SD)	72 (19.9)
Urine albumin/creatinine, mg/g, (SD)	59.9 (356.8)
Systolic blood pressure, mmHg (SD)	138 (16.5)
Serum bicarbonate, mEq/L (SD)	26.4 (2.5)

Supplemental Table 7s. Association between serum bicarbonate levels and white matter volume, cerebral blood flow, and vascular reactivity in the in SPRINT MIND MRI subgroup

	Model 1		Model 2		Model 3	
	Estimate (SE)	p-value	Estimate (SE)	p-value	Estimate (SE)	p-value
White matter volume	-0.002 (0.02)	0.92	-0.005 (0.02)	0.79	-0.0005 (0.02)	0.97
Cerebral blood flow	0.04 (0.20)	0.83	0.09 (0.21)	0.68	0.30 (0.22)	0.17
Vascular reactivity	-0.005 (0.007)	0.50	-0.006 (0.007)	0.39	-0.007 (0.007)	0.34

Model 1 adjusted for scanner type, Intracranial Volume (ICV), age, network, education, sex, and race

Model 2 adjusted for Model 1 components as well as cardiovascular disease, systolic blood pressure, use of diuretics, and anti-acidosis medications (sodium bicarbonate, sodium citrate, citric acid/sodium citrate)

Model 3 adjusted for Model 2 components as well as estimated glomerular filtration rate and log transformed urine albumin

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Supplemental Figure 1s. Distribution plots of serum bicarbonate (continuous exposure) and cognitive summary scores in SPRINT MIND

