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Serum bicarbonate concentration and cognitive function in hypertensive adults

Appendix

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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 \leq 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 \leq 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 \leq 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 \leq 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 \leq 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 \leq 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 \leq 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

