The relationship of kidney tubule biomarkers with brain imaging in CKD patients in SPRINT

**Key Points:**

*Urine biomarker concentrations reflecting kidney tubule injury and dysfunction were not associated with brain MRI measures.

*Higher eGFR was associated with lower total brain cerebral blood flow.

*The first evaluation of the relationship of kidney tubule biomarkers with brain imaging by MRI in CKD patients.

**Abstract:**

Previously published data were used for this study., Garimella PS, Lee AK, Ambrosius WT, et al. Markers of kidney tubule function and risk of cardiovascular disease events and mortality in the SPRINT trial. Eur Heart J. 2019;40(42):3486-3493.

**Funding:** HHS | NIH | National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): Lindsay M. Miller, SF32DK127590-02; HHS | NIH | National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): Joachim H. Ix, K24DK10427; HHS | NIH | National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): Michael G. Shlipak, Joachim H. Ix, RO1DK098234; HHS | NIH | National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): Manjula Kurella Tamura, R01 DK092241

**Author Contributions:** Lindsay Miller: Conceptualization; Formal analysis; Funding acquisition; Writing - original draft; Writing - review and editing Manjula Kurella Tamura: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Resources; Writing - original draft; Writing - review and editing Nicholas Pajewski: Conceptualization; Writing - original draft; Writing - review and editing Dena Rifkin: Conceptualization; Writing - review and editing Daniel Weiner: Conceptualization; Writing - review and editing Maria Marquine: Writing - review and editing Michael Shlipak: Conceptualization; Writing - review and editing Joachim Ix: Conceptualization; Supervision; Writing - original draft; Writing - review and editing

**Data Sharing Statement:** Previously published data were used for this study., Garimella PS, Lee AK, Ambrosius WT, et al. Markers of kidney tubule function and risk of cardiovascular disease events and mortality in the SPRINT trial. Eur Heart J. 2019;40(42):3486-3493.

Copyright 2021 by American Society of Nephrology.
Nasrallah IM, Pajewski NM, Auchus AP, et al. Association of intensive vs standard blood pressure control with cerebral white matter lesions. Jama. 2019;322(6):524-534.

Data cannot be shared: SPRINT data requires a sponsor and paper proposal.

Clinical Trials Registration:

Registration Number:

Registration Date:

The information on this cover page is based on the most recent submission data from the authors. It may vary from the final published article. Any fields remaining blank are not applicable for this manuscript.
The relationship of kidney tubule biomarkers with brain imaging in CKD patients in SPRINT

Lindsay M. Miller¹; Manjula Kurella Tamura²; Nicholas M. Pajewski³; Dena Rifkin¹,⁴; Daniel Weiner⁵; Maria Marquine⁶; Michael G. Shlipak⁷; Joachim H. Ix¹,⁴

1. Division of Nephrology-Hypertension, University of California San Diego, San Diego, CA, USA
2. Department of Medicine-Nephrology, Stanford University, and Palo Alto Veterans Affairs Health Care System, Palo Alto, CA, USA
3. Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC, USA
4. Veterans Affairs San Diego Healthcare System, San Diego, CA, USA
5. Department of Medicine, Nephrology, Tufts Medical Center, Boston, MA, USA
6. Department of Medicine and Psychiatry, University of California San Diego, San Diego, CA, USA
7. School of Medicine, University of California San Francisco, San Francisco, CA, USA

Corresponding Author: Lindsay M. Miller, PhD; Location: Veterans Medical Research Foundation, Room 117B, Building 13, 3350 La Jolla Village Dr #151A, San Diego, CA 92161; Email: Lmmiller@health.ucsd.edu
Chronic kidney disease (CKD) is associated with stroke and small vessel brain disease, likely reflecting ischemic injury from impaired cerebral blood flow (CBF) regulation.\textsuperscript{1,2} However, estimated glomerular filtration rate (eGFR) and urine albumin to creatinine ratio (UACR) primarily quantify glomerular function and injury. A prior report from the Systolic Blood Pressure Intervention Trial (SPRINT) described that lower eGFR was associated with higher CBF, but not with white matter hyperintensities.\textsuperscript{3} Conversely, higher UACR was associated with white matter hyperintensities, but not CBF, suggesting that different mechanisms may contribute to each.

Biomarkers of kidney tubular function provide noninvasive measurements of kidney tubule health, offering insights beyond eGFR and UACR. Kidney tubules are critical for numerous functional processes to maintain homeostasis, and tubule atrophy and fibrosis are detectable even with normal eGFR levels. Urine tubule biomarkers are prognostic for subsequent loss of kidney function and cardiovascular disease (CVD) beyond eGFR and UACR.\textsuperscript{4,5} Prior studies suggest that vascular damage to the kidney tubules may lead to fibrosis, which may have similar pathology as cerebral vascular injury.\textsuperscript{6} Because both the kidney and brain are two organs that regulate organ perfusion independent of systemic blood pressure, we hypothesized that biomarkers reflecting kidney injury and dysfunction may associate with brain perfusion and ischemia.

Among SPRINT participants with CKD, markers of kidney injury and dysfunction have been associated with different domains of cognitive function.\textsuperscript{7} However, evaluating the association between measures of cerebrovascular disease that may precede subsequent cognitive decline may provide insights into the mechanisms that underlie the kidney-brain axis. Using a subgroup of SPRINT participants with CKD, we evaluated the cross-sectional association of kidney tubular biomarkers with total brain CBF, total brain volume (TBV), and abnormal white matter lesions (WML).

The trial design and outcomes are described elsewhere.\textsuperscript{8} Of the 9361 randomized participants, an ancillary study measured 8 kidney tubule health biomarkers (Table 1) among 2,514 individuals with eGFR below 60 mL/min/1.73m\textsuperscript{2} at the baseline study visit.\textsuperscript{9} Among these 2,514, 211 individuals participated in a brain magnetic resonance imaging (MRI) sub study at baseline.\textsuperscript{10} All
participants provided written informed consent, and Institutional Review Boards of all participating institutions approved the study.

Each urine biomarker was transformed on the log$_2$ scale. We evaluated their associations with total brain CBF, TBV, and WMls using linear regression adjusted for urine creatinine to account for urine concentration, type of MRI scanner, intracranial volume, age, sex, race (black vs. white/other), years of education, body mass index (BMI), history of CVD, systolic and diastolic blood pressure, use of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARBs), eGFR and urine albumin. We also provide the associations of eGFR and urine albumin with the MRI measures separately for the purposes of comparisons of strengths of association.

The mean age was 72.3 (± 9.0) years and 56% were women. Other participant characteristics and median concentrations of biomarkers can be found in Table 1. We found no association between urine tubule biomarkers with any of the MRI measures. Generally, higher concentrations of biomarkers were associated with lower total brain CBF and smaller total brain volume (Table 2). Higher eGFR was associated with a lower total brain CBF, but not TBV or abnormal WMls. Urine albumin was not associated with any of the 3 brain MRI outcomes.

In our study of 211 SPRINT participants with CKD, we found that urine biomarker concentrations reflecting kidney tubule injury and dysfunction were not associated with brain MRI measures at baseline. Similar to what has been found previously in SPRINT, we found that higher eGFR was associated with lower total brain CBF. While, to our knowledge, this is the first evaluation of the relationship of kidney tubule biomarkers with brain imaging by MRI in CKD patients, the study has important limitations. First, lack of statistically significant associations may be due to limited statistical power. Consistent with this, while we observed the association of higher eGFR with lower TBV consistent with prior findings in the larger SPRINT sample, we failed to observe associations of urine albumin with abnormal WMV. However, we can conclude that any association of kidney tubule dysfunction markers with these brain MRI findings is likely modest in strength, and weaker than with eGFR. The study is also cross-sectional, precluding evaluation of temporality.

In conclusion, among hypertensive individuals with CKD, concentrations of kidney tubule biomarkers were not associated with neuroimaging markers of cerebrovascular disease. However, given prior findings that these same biomarkers were independently associated with different domains of cognitive function and the limited sample size available here, future studies are warranted to evaluate these biomarkers in larger study samples and over time to clarify mechanisms and identify temporal patterns that may relate kidney function and cognitive decline.
Disclosures: J. Ix reports the following: Consultancy Agreements: Sanifit, Bayer, Ardelyx, AstraZeneca, Jnana; Research Funding: Baxter International; and Scientific Advisor or Membership: AlphaYoung. M. Tamura reports the following: Honoraria: American Federation for Aging Research; and Scientific Advisor or Membership: CJASN Editorial Board, Clin-Star Advisory Board, Beeson External Advisory Committee. M. Marquine reports the following: Research Funding: NIH. N. Pajewski reports the following: Ownership Interest: Eyenovia; Ocufenire Pharma; and Scientific Advisor or Membership: Journal of the American Geriatrics Society. D. Rifkin reports the following: Scientific Advisor or Membership: AJKD Editorial Board (feature editor), ABIM Nephrology Exam Committee; and Other Interests/Relationships: Co-investigator, US site; EMPA-KIDNEY study (pending). M. Shlipak reports the following: Consultancy Agreements: Cricket Health, Intercept Pharmaceuticals, University of Washington-Cardiovascular Health Study, Veterans Medical; Research Funding: Bayer Pharmaceuticals; Honoraria: Bayer, AstraZeneca, Boeringer Ingelheim; Scientific Advisor or Membership: American Journal of Kidney Disease, Journal of the American Society of Nephrology, Circulation; and Other Interests/Relationships: Board Member, Northern California Institute for Research and Education. D. Weiner reports the following: Consultancy Agreements: Participated in Medical Advisory Boards for Janssen Biopharmaceuticals (2019), Akebia (2020, 2021), Cara Therapeutics (2020), and Tricida (2019). Honoraria for Akebia were paid to DCI.; Research Funding: All compensation paid to Tufts MC: Dialysis Clinic, Inc (site PI for trials contracted with DCI including Ardelyx (ongoing) and Cara Therapeutics (completed)); Janssen Biopharmaceuticals (site PI, completed 2019); AstraZeneca (site PI, completed 2020); Goldfinch Bio (site PI, ongoing); CSL Behring (site PI, ongoing); Honoraria: National Kidney Foundation for editorial positions at Kidney Medicine and AJKD; Elsevier for royalties from the NKPs Primer on Kidney Diseases; Scientific Advisor or Membership: Co Editor-in-Chief, NKF Primer on Kidney Diseases, 8th Edition; Editor-in-Chief, Kidney Medicine; Medical Director of Clinical Research, Dialysis Clinic Inc; Member, ASN Quality and Policy Committees and ASN representative to KCP; Scientific Advisory Board, National Kidney Foundation; and Other Interests/Relationships: Chair, adjudications committee, VALOR Trial (George Institute, CRO, sponsored by Tricida); Member, Data Monitoring Committee, "Feasibility of Hemodialysis with GARNET? in Chronic Hemodialysis Patients with a Bloodstream Infection" Trial (Avania CRO). The remaining author has nothing to disclose.

Funding: Dr. Lindsay Miller was supported by a Ruth L. Kirschstein National Research Service Award from the National Institute of Diabetes and Digestive Kidney Diseases (NIDDK; 5F32DK127590-02). Dr. Joachim H. Ix was supported by mid-career mentoring award from the NIDDK (K24DK110427). The ancillary study measurements and data analysis were supported by an R01 award from the NIDDK to Drs. Ix and Shlipak (R01DK098234). Dr. Nicholas Pajewski was supported by R01AG055606, and the Alzheimer’s Association. Dr. Kurella Tamura is supported by R01 DK092241 from NIDDK.

Acknowledgments: The Systolic Blood Pressure Intervention Trial was funded by the National Institutes of Health (including the National Heart, Lung, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the National Institute of Neurological Disorders and Stroke) under contracts HHSN268200900040C, HHSN268200900046C, HHSN268200900047C, HHSN268200900048C, and HHSN268200900049C and interagency agreement A-HL-13-002-001. It was also supported in part with resources and use of facilities through the Department of Veterans Affairs. Azilsartan
and chlorthalidone (combined with azilsartan) were provided by Takeda Pharmaceuticals International Inc. Additional support was provided through the following National Center for Advancing Translational Sciences clinical and translational science awards: UL1TR000439 (awarded to Case Western Reserve University); UL1RR025755 (Ohio State University); UL1RR024134 and UL1TR000003 (University of Pennsylvania); UL1RR025771 (Boston University); UL1TR000093 (Stanford University); UL1RR025752, UL1TR000073, and UL1TR001064 (Tufts University); UL1TR000050 (University of Illinois); UL1TR000005 (University of Pittsburgh); 9U54TR000017-06 (University of Texas Southwestern Medical Center); UL1TR000105-05 (University of Utah); UL1 TR000445 (Vanderbilt University); UL1TR000075 (George Washington University); UL1 TR000002 (University of California, Davis); UL1 TR000064 (University of Florida); and UL1TR000433 (University of Michigan); and by National Institute of General Medical Sciences, Centers of Biomedical Research Excellence award NIGMS P30GM103337 (awarded to Tulane University).

Author Contributions: Lindsay Miller: Conceptualization; Formal analysis; Funding acquisition; Writing - original draft; Writing - review and editing. Manjula Kurella Tamura: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Resources; Writing - original draft; Writing - review and editing. Nicholas Pajewski: Conceptualization; Writing - original draft; Writing - review and editing. Dena Rifkin: Conceptualization; Writing - review and editing. Daniel Weiner: Conceptualization; Writing - review and editing. Maria Marquine: Writing - review and editing. Michael Shlipak: Conceptualization; Writing - review and editing. Joachim Ix: Conceptualization; Supervision; Writing - original draft; Writing - review and editing.

Data Sharing Statement: Previously published data were used for this study: Garimella PS, Lee AK, Ambrosius WT, et al. Markers of kidney tubule function and risk of cardiovascular disease events and mortality in the SPRINT trial. Eur Heart J. 2019;40(42):3486-3493. doi:10.1093/eurheartj/ehz392

Nasrallah IM, Pajewski NM, Auchus AP, et al. Association of intensive vs standard blood pressure control with cerebral white matter lesions. Jama. 2019;322(6):524-534.

Data cannot be shared: SPRINT data requires a sponsor and paper proposal.
References

1. Ikram MA, Vernooij MW, Hofman A, Niessen WJ, van der Lugt A, Breteler MM. Kidney function is related to cerebral small vessel disease. Stroke. 2008;39(1):55-61.

2. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. J Appl Physiol (1985). 2008;105(5):1652-1660. doi:10.1152/japplphysiol.90549.2008

3. Tamura MK, Pajewski NM, Bryan RN, et al. Chronic kidney disease, cerebral blood flow, and white matter volume in hypertensive adults. Neurology. 2016;86(13):1208-1216. doi:10.1212/WNL.0000000000002527

4. Nath KA. Tubulointerstitial changes as a major determinant in the progression of renal damage. American Journal of Kidney Diseases. 1992;20(1):1-17.

5. Howie AJ, Ferreira MAS, Adu D. Prognostic value of simple measurement of chronic damage in renal biopsy specimens. Nephrology Dialysis Transplantation. 2001;16(6):1163-1169.

6. Basile DP, Anderson MD, Sutton TA. Pathophysiology of Acute Kidney Injury. Compr Physiol. 2012;2(2):1303-1353. doi:10.1002/cphy.c110041

7. Weiner DE, Gaussoin SA, Nord J, et al. Cognitive function and kidney disease: baseline data from the Systolic Blood Pressure Intervention Trial (SPRINT). American Journal of Kidney Diseases. 2017;70(3):357-367.

8. Group SR. A randomized trial of intensive versus standard blood-pressure control. New England Journal of Medicine. 2015;373(22):2103-2116.

9. Garimella PS, Lee AK, Ambrosius WT, et al. Markers of kidney tubule function and risk of cardiovascular disease events and mortality in the SPRINT trial. Eur Heart J. 2019;40(42):3486-3493. doi:10.1093/eurheartj/ehz392

10. Nasrallah IM, Pajewski NM, Auchus AP, et al. Association of intensive vs standard blood pressure control with cerebral white matter lesions. Jama. 2019;322(6):524-534.
Table 1. Characteristics of Participants (n=211)

| Characteristics                                | Mean (SD) or N (%) |
|------------------------------------------------|--------------------|
| Age, y                                         | 72.3 (9.0)         |
| Female Sex                                     | 118 (56%)          |
| Black Race                                     | 46 (22%)           |
| Education, y                                   | 7.8 (2.4)          |
| Body Mass Index, kg/m²                         | 29.6 (5.5)         |
| History of CVD                                 | 24 (11%)           |
| Systolic BP, mmHg                              | 139.8 (17.4)       |
| Diastolic BP, mmHg                             | 75.2 (12.4)        |
| Use of Angiotensin II Receptor Blockers        | 57 (27%)           |
| Use of ACE inhibitors                          | 74 (35%)           |
| eGFR, mL/min/1.73m2                            | 45.9 (10.4)        |
| Scanner                                        |                    |
| 3T GE MR750W                                   | 14 (7%)            |
| 3T Philips Achieva 3.2                         | 69 (33%)           |
| 3T Siemens Skyra VD11B                        | 19 (9%)            |
| 3T Siemens Tim Trio VB17                      | 45 (21%)           |
| 3T Siemens Verio VB17                         | 64 (30%)           |
| Outcomes                                       |                    |
| Total Brain Volume, cm³                        | 1110.6 (115.3)     |
| Total Brain CBF, mL/100 mg/min                 | 38.3 (12.3)        |
| Abnormal WML Volume, cm³                       | 2.3 (1.0)          |
| Urine Biomarkers                               |                    |
| IL18, pg/mL                                    | 30.6 (16.4, 57.1)  |
| KIM-1, pg/mL                                   | 848.0 (388.2, 1596.3) |
| NGAL, ng/mL                                    | 27.6 (14.7, 59.2)  |
| YKL40, pg/mL                                   | 9.10 (7.7, 10.3)   |
| MCP-1, pg/mL                                   | 180.7 (89.6, 329.1) |
| A1M, mg/g                                      | 13.4 (7.1, 24.95)  |
| B2M, ng/mL                                     | 104.2 (38.8, 333.5) |
| Umod, ng/mL                                    | 6.5 (4.3, 9.9)     |
| Urine albumin, mg/g                            | 17 (8, 52)         |

Abbreviations: IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; MCP-1, monocyte chemoattractant protein-1; B2M, β2-microglobulin; A1M, α1-microglobulin; Umod, uromodulin.
Table 2. Cross-sectional Association between Biomarkers of Kidney Tubule Function and Injury [per 2-fold higher] with MRI Measures of Brain Function

| Biomarker                  | Total Brain CBF (mL/100 mg/min) | Total Brain Volume (cm³) | Abnormal WML (cm³) | β coefficient (95% CI) |
|----------------------------|----------------------------------|--------------------------|--------------------|------------------------|
| Log₂ IL18, pg/mL           | -0.28 (-1.46, 0.90)              | -2.06 (-7.42, 3.29)      | -0.06 (-0.16, 0.03) |
| Log₂ KIM-1, pg/mL          | 0.39 (-0.59, 1.37)               | -2.79 (-7.23, 1.65)      | -0.02 (-0.10, 0.06)  |
| Log₂ NGAL, ng/mL           | -0.20 (-1.25, 0.84)              | -2.97 (-7.71, 1.77)      | 0.03 (-0.06, 0.12)   |
| Log₂ YKL40, pg/mL          | -0.06 (-0.84, 0.72)              | -3.16 (-6.68, 0.36)      | 0.01 (-0.06, 0.07)   |
| Log₂ MCP-1, pg/mL          | -0.03 (-1.15, 1.09)              | -3.49 (-8.56, 1.57)      | -0.01 (-0.10, 0.09)  |
| Log₂ A1M, mg/g             | 0.61 (-0.86, 2.08)               | -0.57 (-7.26, 6.12)      | -0.01 (-0.14, 0.11)  |
| Log₂ B2M, ng/mL            | -0.19 (-0.79, 0.42)              | 0.34 (-2.41, 3.10)       | 0.01 (-0.04, 0.06)   |
| Log₂ Umod, ng/mL           | 1.40 (-0.23, 3.04)               | 0.91 (-6.59, 8.40)       | 0.06 (-0.08, 0.19)   |
| eGFR, mL/min/1.73m²        | **-0.28 (-0.43, -0.14)***        | 0.45 (-0.19, 1.09)       | -0.01 (-0.02, 0.05)  |
| Log₂ Urine Albumin, mg/g   | -0.01 (-0.01, 0.01)              | 0.02 (-0.01, 0.05)       | 0.0002 (-0.0004, 0.001) |

Values are given as β coefficient (continuous analysis). Values in parentheses are 95% CI.

***P<0.001

Abbreviations: IL-18, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin; MCP-1, monocyte chemoattractant protein-1; YKL40, chitinase-3-like protein; B2M, β2-microglobulin; A1M, α1-microglobulin; Umod, uromodulin; eGFR, estimated glomerular filtration rate

Models adjusted for urine creatinine, type of MRI scanner, intracranial volume, age, sex, race (black vs. white/other), years of education, BMI, history of CVD, systolic and diastolic BP, use of ARB or ACE, eGFR and urine albumin (except for models with eGFR and urine albumin as predictors)