Albuminuria, cognition, and MRI biomarkers of cerebrovascular disease in American Indians of the Zuni Pueblo

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ABSTRACT

Background: Elevated urine albumin to creatinine ratio (UACR) is associated with cerebrovascular disease and cognitive impairment in older adults, though few studies have evaluated these relationships in midlife. This is particularly important to assess in American Indian populations, which are disproportionately impacted by diabetes and kidney disease. Additionally, evidence suggests that biomarkers may perform differently in underrepresented groups, thus, it is crucial to validate biomarkers in this unique population.

Methods: Twenty-five participants from the Zuni Pueblo underwent neuropsychological assessment and an MRI that included fluid attenuated inversion recovery (FLAIR) and diffusion imaging to calculate recently developed MRI markers of cerebrovascular small vessel disease (Peak width of Skeletonized Mean Diffusivity (PSMD), mean free-water fraction (mFW), white matter hyperintensity (WMH)).

Results: Regression analyses indicated no significant associations between UACR, MRI biomarkers and cognitive outcomes. Analyses of covariance indicated that the Zuni Indian cohort exhibited reduced white matter damage relative to an existing cohort of older adults with vascular cognitive impairment when accounting for age, sex, and education. Slower processing speed was associated with greater white matter disease across all measures examined.

Conclusions: Our pilot study validated the use of MRI biomarkers of cerebrovascular disease in this unique cohort of American Indians.

1. Introduction

Albuminuria is a common complication of diabetes and a leading cause of end-stage renal disease. [1] Elevated levels of urine albumin to creatinine ratio (UACR), an indicator of albuminuria, is also associated with cognitive decline and increased risk of cognitive impairment and dementia, [2] even in the context of normal estimated glomerular filtration rate (eGFR). [3] It may also serve as a risk marker of renal endothelial dysfunction and cerebrovascular disease in older adults, which has led some to suggest that cerebrovascular disease is one mechanism by which elevated UACR leads to cognitive impairment. As most studies evaluate the associations between UACR, cerebrovascular disease, and cognitive impairment in older adults, and evidence suggests elevated UACR in midlife is associated with increased dementia incidence, [4] there is a crucial need to determine if these relationships are present in midlife. This is important to evaluate within the American Indian population and the Zuni Indians of New Mexico, as they are disproportionately impacted by kidney disease and albuminuria. [5] [6] Additionally, because biomarkers are typically evaluated in predominantly non-Hispanic white populations and evidence suggests that underrepresented groups may be more adversely impacted by pathological processes [7–9], there is a need to determine if we see similar associations in this unique population. Taken together, we aim to determine whether albuminuria is associated with MRI biomarkers of early cerebrovascular disease and worse cognitive functioning in midlife, at-risk group.

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Older adults with albuminuria have, on average, a 35% increased risk of cognitive impairment or dementia, whereas the associations between low eGFR and cognitive outcomes are mixed. [10,11] It is hypothesized that albuminuria leads to cognitive impairment and an increased risk of dementia via shared risk factors (e.g., hypertension, cardiovascular disease, type 2 diabetes mellitus) [12] that result in systemic damage of both the kidney and brain vasculature. [13] UACR may be a marker of systemic endothelial dysfunction [14] and when elevated, it is recommended that cardiovascular risk factors are managed aggressively. Prior studies have largely examined albuminuria in the context of lower kidney function, [15–17] and indicate that UACR and eGFR are independent risk factors for cerebrovascular events. [18,19] Recent meta-analyses indicate that albuminuria is more strongly associated with vascular dementia and cognitive performance in domains primarily affected by microvascular disease. [20]

Cerebrovascular related dysfunction that can be evaluated with MRI, including the quantification of white matter hyperintensities (WMH), lacunar infarcts, and microbleeds. [13] Prior work has demonstrated that UACR, but not eGFR, is associated with WMH and cortical atrophy in older adults. [21–23] Cerebrovascular small vessel disease is responsible for vascular cognitive impairment and dementia (VCID) and may also play a potential role in the development of Alzheimer’s disease. [24] Recently, the MarkVCID consortium has developed biomarkers to detect cerebrovascular related brain changes. [25] The current study leverages two of these metrics that have been developed to detect white matter changes before the development of overt WMH, the most commonly examined MRI indicator of cerebrovascular small vessel disease. The first, Peak width of Skeletonized Mean Diffusivity (PSMD) [26] captures variation in the white matter microstructure within the major white matter fiber tracts. The second, mean free-water fraction (mFW) captures variation across the white matter. To facilitate comparison with prior studies, we also examine the volume of WMH. Notably, the relationships between these recently developed MRI biomarkers of early cerebrovascular related disease have not been examined with respect to measures of albuminuria (UACR).

Prior work suggests that because biomarkers, typically developed in predominantly non-Hispanic white populations, may perform differently in underrepresented groups [7]. Though highly reliable and valid [26,27], these metrics have not been validated in American Indians. Typical approaches to validating these metrics include evaluating the associations between the measures and processing speed. Therefore, a secondary aim of our study is to evaluate the association between biomarkers and cognition in the Zuni population.

The current study addresses these gaps in the literature and has two primary aims. The first evaluates whether albuminuria is associated with lower white matter integrity and worse cognitive outcomes in a mid-life, at risk cohort. We also compare this cohort to a convenience sample of older adults with varying degrees of cognitive impairment. The second evaluates the associations between MRI biomarkers and cognitive outcomes as a means to validate these measures within this unique population.

2. Materials and methods

2.1. Participants

This study was approved by the University of New Mexico Health Sciences Center Human Research Review Committee. The research team also gained approval from the Zuni tribal council for this research prior to funding. We adhered to the Declaration of Helsinki and all participants provided written consent and received monetary compensation as appreciation for sharing their time and expertise. Potential study participants were recruited using two methods. First, Zuni Community Health Representatives (CHRs) used the Zuni Health Initiative (ZHI) project’s clinical database for American Indian Chronic Renal Insufficiency Cohort (AI-CRIC). Second, individuals were recruited through visits by CHRs through Zuni households, presentations at tribal health programs and at the health care center, distribution of flyers at local businesses and the civic center, and through other health programs. The inclusion/exclusion criteria for this ancillary study included the following: Between the ages of 25 and 80 years of age, people living with diabetes for longer than five years, HbA1c > 7.0% or FPG 126 mg/dL or random glucose >200 mg/dL, and microalbuminuria. Exclusion criteria included: active infection /Inflammation (AIDS, active hepatitis B), malignancy, history of chronic inflammatory disease (e.g. lupus, rheumatoid arthritis), severe malnutrition (serum albumin < 2.5 mg/dL and BMI <18), pregnancy, liver dysfunction, severe congestive heart failure, on experimental drug protocols, exclusion for MRI (pacemakers, metal implants, claustrophobia, etc.), self-reported history of stroke, seizures, traumatic brain injury, or other major brain illness, current antipsychotic or antiepileptic medications, severe visual or hearing impairment that would interfere with completion of the neuropsychological test battery, cognitive impairment or current incarceration.

An additional cohort of participants from the University of New Mexico collected as part of our NIH funded studies examining cerebrovascular disease and cognition in older adults with and without dementia was used as a comparison sample. In our prior studies, diagnoses were made via consensus that included a team of neurologists and focused on characterizing patients based on the degree of cognitive impairment (normal cognition or cognitive impairment, which included mild cognitive impairment and dementia) and etiological factors driving cognitive impairment (e.g. Alzheimer’s disease, cerebrovascular disease). We used this convenience cohort to evaluate whether there were significant group differences in MRI biomarkers between the Zuni cohort and individuals who were: cognitively normal (CN), exhibited cerebrovascular small vessel disease type of VCID, or exhibited evidence of cognitive impairment, but minimal ischemic cerebrovascular disease (non-VCID). CN patients exhibited no cognitive impairment. For further detail on this cohort, please refer to. [28]

2.2. Kidney function assessment

Similar to our prior publications [29] serum and urine creatinine values were measured by an enzymatic method, and eGFR was computed using the Chronic Kidney Disease Epidemiology Collaboration equation. [30] Urine albumin was measured by nephelometric immunoassay, and all concentrations were above the detection limit of the assay (5.0 mg/L).

2.3. Neuropsychological assessment

Participants underwent neuropsychological assessment including the Version 3 of the Alzheimer’s Disease Centers’ Neuropsychological Test Battery in the Uniform Data Set [31] in addition to the Hopkins Verbal Learning Test – Revised. [32] Our primary measures included: general cognitive ability (Montreal Cognitive Assessment; MoCA), processing speed (Trails A), executive (Trails B), and memory (Craft Story delay) measures.

2.4. Neuroimaging

The MRI data was collected on a Siemens 3 T PRISMA scanner. The imaging protocol closely followed the Alzheimer’s disease neuroimaging initiative (ADNI) protocol with a) T1-weighted MPRAGE (1x1x1 mm), b) Fluid-attenuated inversion recovery (FLAIR) (1x1x1.2 mm), c) a diffusion sequence (2x2x2 mm) with 127 volumes, with a 3-shell gradient table consisting of b = 0, 500, 1000, and 2000 s/mm2. A multi-echo T2-star was also collected to look for microbleeds but was not used in this analysis. We measured two indices of white matter damage, PSMD and mFW, each calculated from the diffusion images. Diffusion data was processed following methods detailed elsewhere using publicly available scripts to obtain measures of PSMD. [26] mFW and volume of
WMH were also calculated and averaged across the white matter following the MarkVCID methods (www.Markvcid.org). Volumetric hippocampal volumes were completed using FreeSurfer image analysis suite. Higher PSMD, mFW, and WMH are all indicators of greater white matter damage.

### 2.5. Statistical analyses

Descriptive statistics were calculated to summarize patient characteristics. Medians and interquartile ranges (IQR) were calculated for continuous variables and were compared across groups by the Kruskal-Wallis test. Frequencies and percentages were calculated for categorical variables and were compared with the χ² test.

We conducted a multiple linear regression for each cognitive variable as the dependent variables (MoCA, Trails A, Trails B, and Craft Story delay) with the mean arterial pressure (MAP), kidney function metrics (UACR, eGFR), and imaging metric (PSMD, mFW, WMH, hippocampal volume) as predictors in separate models, adjusting for age, sex, and total brain volume. Skewed data was transformed using logarithmic transformations.

To evaluate whether the Zuni cohort exhibited greater white matter disease relative to our existing cohorts, we compared white matter metrics in the Zuni cohort relative to the CN, VCID, non-VCID existing cohort. We conducted Analyses of Covariance (ANCOVAs) to evaluate group differences in our white matter metrics (PSMD, mFW, WMH) between the Zuni, CN, non-VCID, and VCID cohorts accounting for age, sex and education as covariates. Analyses were performed in R (v4.1.0 [33]).

### 3. Results

#### 3.1. Participant characteristics

Twenty-five participants were enrolled in the Zuni cohort. One participant was removed from subsequent analyses due to the presence of an incidental finding that suggested a prior moderate to severe traumatic brain injury. Table 1 displays the characteristics of the participants split by the presence of albuminuria at the time of assessment (UACR ≥30). With the exception of one individual (eGFR = 40), eGFR values indicated all participants were within stage 1–2 of kidney disease. Participants with albuminuria exhibited a greater prevalence of self-reported hypertension and significantly higher diastolic blood pressure.

A convenience sample of older adults with varying degrees of cognitive impairment and cerebrovascular disease was used to evaluate whether the Zuni cohort exhibited a degree of white matter damage similar to these cohorts. As this was a convenience comparison group, there were significant group differences in age and education (Zuni participants were significantly younger and had less education), which were included as a covariate in subsequent analyses (Table 2).

#### 3.2. Associations between kidney metrics, imaging metrics, and cognitive outcomes

Multiple linear regression models are summarized in Table 3. Notably, MAP, UACR, and eGFR were not significantly associated with any of the cognitive outcomes examined. Results indicated that hippocampal volume was associated with general cognitive ability (MoCA), but this association was not significant when controlling for age, sex, and total brain volume. An overview of white matter imaging metrics is provided in Box 1. Both measures of white matter integrity, PSMD and mFW, were associated with processing speed (Trails A response time). Specifically, greater PSMD was associated with slower response times (s). Greater mFW was similarly associated with slower response times (s; Fig. 1).

### Table 1

Clinical characteristics of the Zuni sample.

| Characteristics          | UACR ≥30 | UACR <30 | Total | P     |
|--------------------------|----------|----------|-------|-------|
|                         | (N = 14) | (N = 10) |       |       |
| Male (%)                 | 6 (43%)  | 3 (30%)  | 9 (38%) | 0.831 |
| Age (years)              | 49 [46; 58] | 54 [48; 57] | 51 [47; 58] | 0.537 |
| Education (years)        | 12 [12; 14] | 12 [11; 12] | 12 [12; 14] | 0.111 |
| BMI                      | 33 [27; 44] | 32 [27; 42] | 32 [27; 43] | 0.931 |
| Systolic BP              | 129 [122; 139] | 126 [120; 137] | 129 [121; 138] | 0.446 |
| Diastolic BP             | 86 [78; 87] | 76 [71; 80] | 81 [74; 87] | 0.017 |
| Total Brain Volume (mm³) | 893,779 [861,969;1,021,997] | 848,477 [797,027;917,928] | 874,910 [844,893;948,574] | 0.108 |
| Age Diagnosed Diabetes   | 33 [23; 40] | 39 [30; 45] | 34 [25; 40] | 0.276 |
| Hypertension (%)         | 11 [85%] | 4 [20%] | 13 [57%] | 0.007 |
| UACR                     | 246 [65; 740] | 4 [10; 14] | 41 [10; 342] | <0.001 |
| eGFR                     | 71 [64; 74] | 98 [84; 116] | 75 [69; 98] | <0.001 |
| AIC                      | 11 [10; 13] | 8 [6; 12] | 10 [8; 12] | 0.128 |
| log10(PSMDex10⁶)          | 0.271 [0.258;0.331] | 0.318 [0.238;0.428] | 0.281 [0.248;0.366] | 0.585 |
| log10(mFWx10⁶)           | 1.260 [1.226;1.304] | 1.277 [1.205;1.400] | 1.264 [1.225;1.319] | 0.437 |
| Hippocampal volume (mm³) | 7289 [6474;8047] | 6763 [5926;6961] | 6960 [6343;7840] | 0.122 |
| MoCA (total)             | 27 [24; 28] | 24 [21; 26] | 26 [22; 28] | 0.140 |
| Trails A (s)             | 26 [25; 34] | 38 [25; 48] | 28 [25; 40] | 0.207 |
| Trails B (s)             | 86 [63; 115] | 120 [101; 174] | 98 [66; 126] | 0.096 |
| Craft Story Delay        | 16 [14; 20] | 14 [11; 20] | 16 [11; 20] | 0.481 |

Note: Values are Median or n (%). IQR bounds [Q1; Q3] are 25th and 75th percentiles. P-values reported from the Kruskal-Wallis test for continuous data and from the chi-square test with continuity correction for categorical data.
Table 3

| MoCA* | MAP | 0.006 | 0.31 | 0.306 | 0.297 |
|-------|-----|-------|-----|--------|------|
|       | UACR* | -0.035 | 0.18 | -0.016 | 0.551 |
|       | eGFR | 0.004 | -0.070 | 0.033 | 0.294 |
|       | PSMD | 0.003 | 0.003 | 0.003 | 0.003 |
|       | UACR* | 0.838 | 0.29 | 0.872 | 0.384 |
|       | WF | 1.130 | -0.735 | 0.222 | 0.636 |
|       | WMH | 0.018 | 0.81 | 0.121 | 0.197 |
|       | PSMD | -0.140 | 0.175 | 0.546 | 5.179 |
| Hippocampal Volume | -1.445e-4 | 0.041 | -3.27e-5 | 0.794 |
| Trails A* | MAP | 0.002 | 0.56 | 0.002 | 0.468 |
|       | UACR* | -0.011 | 0.34 | -0.005 | 0.688 |
|       | eGFR | 1.917-4 | 0.89 | 5.175-4 | 0.710 |
|       | PSMD | 1.024 | 0.001 | 0.328 | 1.855 |
|       | WF | 1.192 | 0.000 | 0.400 | 2.057 |
|       | WMH | 0.052 | 0.122 | 0.092 | 0.012 |
| Hippocampal Volume | -5.9875 | 0.059 | -4.432e-5 | 0.422 |
| Trails B* | MAP | 0.002 | 0.69 | 0.002 | 0.639 |
|       | UACR* | -0.007 | 0.001 | -0.006 | 0.010 |
|       | eGFR | -0.022 | 0.18 | -0.013 | 0.443 |
|       | PSMD | 3.245e-4 | 0.87 | 5.601e-4 | 0.783 |
|       | WF | 0.946 | -0.010 | 0.05 | 0.191 |
|       | WMH | 1.108 | 0.05 | 0.087 | 0.229 |
| Hippocampal Volume | -1.266e-4 | 0.003 | -1.935e-4 | 0.009 |
| Craft Story Delay | MAP | -0.168 | 0.18 | -0.179 | 0.058 |
|       | UACR* | -0.024 | 0.364 | 0.006 | 0.637 |
|       | eGFR | 0.023 | 0.705 | 1.123 | 0.850 |
|       | PSMD | 3.046 | 2.00 | 2.995 | 0.002 |
| Hippocampal Volume | 0.004 | 0.004 | 0.004 | 0.061 |

Note: *variables transformed prior to analysis; bold indicates significant p < 0.05; MoCA = Montreal Cognitive Assessment; MAP = mean arterial pressure; UACR = urine albumin to creatinine ratio; eGFR = estimated glomerular filtration rate; PSMD = Peak width of Skeletonized Mean Diffusivity; mFW = mean free-water fraction.

3.3. White matter damage in the Zuni cohort

A visual example of the WMH is shown in Fig. 2. A Zuni participant with low white matter damage is presented alongside a Zuni participant with the highest white matter damage in the cohort. Statistical analyses demonstrated that after adjusting for age, sex, and education, there was a statistically significant difference across all white matter metrics (Fig. 3; PSMD: $F_{(166,3)} = 117.978, p < 0.001$; mFW: $F_{(163,3)} = 57.505, p < 0.001$). Post hoc analysis were performed with a Bonferroni adjustment. The average PSMD was statistically lower in the Zuni cohort (0.299 ± 0.086) relative to all groups (CN: 0.468 ± 0.086, Non-VCID: 0.564 ± 0.092, VCID: 0.717 ± 0.130, p < 0.001). The average mFW was statistically lower in the Zuni cohorts (1.271 ± 0.074) relative to VCID (1.509 ± 0.097, p < 0.001), but not Non-VCID (1.403 ± 0.085 p = 0.015) and CN (1.326 ± 0.069, p = 0.953). Lastly, average WMH volumes were statistically lower in the Zuni cohort (2.512 ± 0.924) relative to Non-VCID (3.774 ± 0.659, p < 0.001) and VCID (4.425 ± 0.373, p < 0.001), but not CN (3.185 ± 0.658, p = 0.456).

4. Discussion

The current study examined the relationship between UACR, MRI biomarkers of cerebrovascular small vessel disease (PSMD, mFW, WMH), and cognitive functioning in a cohort of Zuni Indians diagnosed with diabetes and albuminuria. The Zuni sample included individuals both with and without albuminuria at the time of the study (Table 1). Individuals with current albuminuria exhibited both increased frequency of hypertension diagnoses and significantly higher diastolic blood pressure. In contrast to our hypotheses, UACR was not associated with MRI markers of cerebrovascular small vessel disease or cognitive outcomes in this mid-life, at risk population. While we did not have a control cohort for these individuals, we were able to compare the white matter metrics in the Zuni cohort relative to older adults with no cognitive impairment (CN) and individuals with cognitive impairment with (VCID) and without (non-VCID) evidence of cerebrovascular small vessel disease, accounting for age, sex, and education. These results indicated that the Zuni cohort had either lower or similar white matter damage to CN older adults and consistently reduced white matter damage relative to VCID and non-VCID. Additionally, we observed significant associations between the MRI markers and cognitive outcomes, consistent with those observed in predominantly non-Hispanic white samples. Specifically, similar measures of white matter integrity, PSMD and mFW, were associated with processing speed performances, consistent with prior work. [26,34] These results validate the use of these metrics within this unique population.

Given the prior literature and associations between albuminuria and cerebrovascular small vessel disease, we hypothesized an association between UACR and with recently developed MRI biomarkers of cerebrovascular small vessel disease that can capture early changes in the white matter before the development of overt WMH. Given the Zuni population is disproportionally impacted by diabetes and kidney disease, [35] may experience robust associations between albuminuria and cognitive functioning. Due to limited sample size, we were unable to evaluate whether the association between albuminuria and cognition would be present in only older individuals in our sample. Much of the prior work reporting associations between UACR, cerebrovascular disease, and cognitive decline was also conducted in chronic kidney disease patients. [36] Our cohort was primarily within Stage 1 or 2 of kidney disease, suggesting that more severe kidney dysfunction in conjunction with
Box 1
Overview of imaging metrics.

| Imaging measure                                    | Quantification                                                                 | Interpretation                                                                 |
|---------------------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Volume of white matter hyperintensities (WMH)     | Automated quantification of the volume of white matter hyperintensities is obtained from FLAIR image. | White matter hyperintensities are white matter lesions that are hyperintense on FLAIR. Larger volumes are associated with cognitive impairment. Increased PSMD is considered an indication of early white matter degeneration that possibly precedes development of WMH. |
| Peak width of Skeletonized Mean Diffusivity (PSMD) | Automated quantification of white matter microstructure within major white matter fiber tracts obtained from diffusion images. | Increased PSMD is considered an indication of early white matter degeneration that possibly precedes development of WMH. |
| Mean free-water fraction (mFW)                    | Automated quantification of white matter microstructure across the white matter obtained from diffusion images. | Increased mFW is considered an indication of early white matter degeneration that possibly precedes development of WMH. |

Fig. 1. Associations between imaging metrics and cognitive outcomes. A) Increased peak width of skeletonized mean diffusivity (PSMD) was associated with slower response times on Trails A. B) Increased mean free-water fraction (mFW) was associated with slower response times on Trails A. C) Larger hippocampal volumes were associated with better performance on Trails B.

Fig. 2. Example FLAIR images from exemplar participants. Prior examinations primarily focus on either qualitative or quantitative evaluation of white matter hyperintensities. A Zuni participant with no white matter damage is compared and a Zuni participant with the highest white matter damage in the cohort and a VCID participant with high white matter damage.
albuminuria may be necessary to impact cognition in midlife.

In addition to examining associations between kidney and MRI cerebrovascular disease metrics within the Zuni cohort, we also evaluated whether the Zuni cohort exhibited reduced white matter damage relative to older adults with and without cognitive impairment/cerebrovascular disease. Overall, our results indicated that the Zuni Indian cohort exhibited reduced white matter damage relative to an existing cohort of older adults with vascular cognitive impairment when accounting for age, sex, and education. Depending on the metric examined, the Zuni cohort exhibited either significantly reduced (PSMD) or no difference (mFW and WMH) in the white matter biomarkers relative to CN older adults when accounting for age, sex, and education. Without demographic correction, it is clear that the Zuni cohort exhibited significantly reduced white matter damage, suggesting that the lack of differences is driven by demographic factors (e.g. differences in age are driving potential differences). Without a demographically matched cohort, it is challenging to interpret these findings. However, it is clear the Zuni cohort exhibits significantly reduced white matter damage relative to older adults with VCID.

There is an enormous need to develop and validate biomarkers for VCID across diverse populations. American Indians are underrepresented in AD and VCID research, resulting in limited information regarding the clinical utility of these biomarkers within American Indian populations. Further, increasing evidence suggests that underrepresented groups may be more vulnerable or resilient to the effects of neuropathology based on numerous factors. American Indians are disproportionately impacted by dementia risk factors and experience a greater incidence of dementia [37], highlighting a need to understand the complex relationships between sociocultural factors, biological factors, and cognitive outcomes in this population. The current study is taking the first step to validate the use of the MarkVCID biomarkers within this unique population by demonstrating consistent associations between MRI biomarkers and cognitive outcomes associated with cerebrovascular small vessel disease. Future work is necessary to expand this and evaluate the impact of multiple domains of influence on health outcomes, consistent with National Institute of Aging [38] and National Institute of Minority Health and Health Disparities [39] frameworks.

The current study was intended as a pilot study that requires future validation in larger cohorts. While we saw minimal evidence that the associations between UACR and outcomes would be significant in larger sample sizes, it is important to consider that the current study is based on a small sample that spans a large age range. Additionally, the comparison cohort was used to determine if the severity of white matter damage was similar to that observed in older adults, though there are limitations when comparing groups that significantly differ in age that we may not be accounting for in our statistical models. Future studies that include a cohort of Zuni Indians matched on age, sex, and education would be helpful to further evaluate these relationships.

Taken together, we examined whether the degree of albuminuria in a Zuni Indian population is associated with cognition and cerebrovascular small vessel disease. We did not find associations between UACR and cognition in this middle-aged sample. We observed significant associations between cerebrovascular MRI biomarkers and cognitive outcomes. The latter validates the use of these measures within this population. Future research is necessary to understand at what age and disease severity does albuminuria lead to white matter damage and correspondingly worse cognitive outcomes. Longitudinal assessment would be helpful to evaluate whether albuminuria is associated with cognitive decline over time in this population.

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**CRediT authorship contribution statement**

Sephira G. Ryman: Methodology, Formal analysis, Writing – original draft. Arvind Caprihan: Methodology, Software. Gary Rosenberg: Conceptualization, Writing – review & editing. Jillian Prestopnik: Project administration, Supervision, Investigation. Michele Quam: Investigation, Writing – review & editing. Donica Ghahtae: Investigation, Writing – review & editing. Vernon S. Pankratz: Formal analysis. Thomas Faber: Conceptualization, Writing – review & editing. Mark Unruh: Resources, Writing – review & editing. Vallab Shah: Conceptualization, Funding acquisition, Writing – review & editing.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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