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# Association of MRI-defined total burden of cerebral small vessel disease with multiple kidney function measures in older adults: a cross-sectional study

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# Association of MRI-Defined Total Burden of Cerebral Small Vessel Disease With Multiple Kidney Function Measures in Older Adults: A Cross-Sectional Study

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**Abstract:**

Whether cerebral small vessel disease (CSVD) burden correlates with kidney dysfunction in older adults remains uncertain. In this cross-sectional study with prospective recruitment and concurrent data collection, 239 older adults underwent brain MRI and kidney assessment. Total CSVD score (0–4) combined severe white matter hyperintensities, lacunes, deep microbleeds, and moderate-to-severe enlarged basal ganglia perivascular spaces. Kidney metrics included estimated glomerular filtration rate (eGFR), serum creatinine, cystatin C, and urinary albumin-to-creatinine ratio (UACR). Higher CSVD score was associated with lower eGFR and higher serum creatinine, cystatin C, and ln(UACR). In fully adjusted models, per 1-point increase in CSVD score, eGFR decreased (β=-2.98, 95% CI -4.67 to -1.29), whereas serum creatinine (β=0.14, 0.04-0.24), cystatin C (β=0.06, 0.02-0.10), and ln(UACR) (β=0.24,

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0.12-0.36) increased (all P≤0.007). CSVD score correlated with composite kidney dysfunction (OR=1.38, 1.08-1.76) and albuminuria (OR=1.46, 1.12-1.90), but not significantly with reduced eGFR (P=0.068). Hypertension mediated 32.0%-36.7% of these associations. Thus, greater MRI-defined CSVD burden is associated with worse kidney function and albuminuria in older adults after adjustment for multiple confounders. However, the association was partially attenuated after additional adjustment for hypertension, suggesting that hypertensive microvascular injury may explain a portion of this relationship. Exploratory mediation analysis suggested hypertension may account for 32%–37% of the association, but this finding requires confirmation in prospective studies.

**Keywords:** cerebral small vessel disease; magnetic resonance imaging; kidney dysfunction; albuminuria; hypertension

**Running title:** Total CSVD burden and kidney dysfunction in older adults

## Introduction

Cerebral small vessel disease (CSVD) encompasses a spectrum of pathological processes affecting the small arteries, arterioles, capillaries, and venules of the brain. Its conventional manifestations include white matter hyperintensities (WMH), lacunes, cerebral microbleeds (CMBs), and enlarged perivascular spaces[1,2]. CSVD becomes increasingly common with aging and hypertension, and it is a major substrate for lacunar stroke, vascular cognitive impairment, gait dysfunction, and loss of functional independence[3,4]. Because these imaging markers often coexist, reliance on a single lesion type may underestimate the cumulative burden of cerebral microvascular injury. The total CSVD burden score was proposed as a pragmatic summary of combined MRI-defined injury[5], and subsequent work has supported its reliability, construct validity, and clinical relevance[6]. Higher total burden has been associated with adverse vascular risk trajectories, disrupted brain structure, cognitive impairment, and worse functional outcomes after stroke[7-9].

The kidney and brain share distinctive microvascular characteristics: both organs are exposed to high-flow, low-resistance circulation, depend on intact autoregulation, and are vulnerable to endothelial dysfunction, pulsatile stress, arteriolosclerosis, and blood-tissue barrier injury[10,11]. Cerebral and renal small-vessel injury may develop in parallel as manifestations of systemic microvascular disease rather than as isolated organ phenomena[12,13]. Existing evidence supports a relationship between kidney dysfunction and CSVD. Prior studies have variably linked reduced

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eGFR, albuminuria, cystatin C, and other kidney measures to WMH, lacunes, microbleeds, or broader indicators of brain structural injury[12,14,15]. More recent data from older hypertensive cohorts, acute stroke samples, and large population datasets suggest that the association may differ according to the study population, the kidney metric used, and the way blood pressure is handled analytically[16,17]. Importantly, cystatin C and albuminuria may capture microvascular injury differently from creatinine-based filtration estimates, especially in older adults[18,19].

Much of the existing research has evaluated individual CSVD markers in isolation or relied predominantly on creatinine-based eGFR, an approach that may not adequately capture subtle renal impairment in older adults. An integrated framework combining MRI-defined total CSVD burden with complementary kidney measures may provide a more complete characterization of shared cerebral and renal microvascular injury. Based on previous research, we conducted a cross-sectional study in older adults who underwent brain MRI and concurrent kidney assessment to examine whether MRI-defined total CSVD burden was associated with multiple kidney function measures and with the presence of kidney dysfunction. We further performed an exploratory mediation analysis to assess whether hypertension statistically accounted for part of this association. We hypothesized that greater total CSVD burden would be associated with a less favorable kidney function profile across both filtration- and albuminuria-based measures and that hypertension may explain part of the observed relationship.

## Methods

### Study design and participants

This was a cross-sectional observational study. Participants were consecutively recruited from neurological outpatient clinics and inpatient wards at our hospital between November 2021 and September 2025. All clinical, laboratory, and imaging data were collected at a single enrollment visit. The analysis presented herein is therefore cross-sectional, as all assessments were performed concurrently without longitudinal follow-up. Participants underwent standardized clinical assessment, blood and urine testing, and brain MRI on the same day at enrollment. The age threshold of >70 years was prespecified based on the sharp increase in prevalence of both CSVD and kidney dysfunction after the seventh decade of life, as well as the clinical relevance of this population for vascular risk assessment. This does not imply that the association is absent in younger populations; rather, focusing on this age group allowed us to study a population with sufficient disease prevalence to examine the association across the full spectrum of CSVD

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severity. Participants were excluded if key neuroimaging markers required for CSVD burden scoring or kidney variables required for the present analysis were missing. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Henan Medical University (EC-024-537). Informed consent was obtained from participants. The study was conducted in accordance with the ethical principles of the Helsinki Declaration.

**Clinical assessment**

Demographic characteristics and other clinical variables were collected prospectively at enrollment using structured assessment forms and standardized study procedures. Information on lifestyle factors (smoking and alcohol use), vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, and heart disease), prior medical history, and medication use (antihypertensive agents and statins) was further verified through review of the medical records. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured according to the study operating procedure and recorded as systolic and diastolic blood pressure. Hypertension was defined as a documented physician diagnosis of hypertension, current use of antihypertensive medication, or elevated blood pressure at the study visit (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg). Diabetes mellitus was defined as a documented diagnosis of diabetes mellitus or current use of glucose-lowering medication. Dyslipidemia was defined as a documented diagnosis of dyslipidemia or current use of lipid-lowering therapy. Heart disease was defined as a documented history of coronary heart disease, atrial fibrillation, heart failure, or another clinically relevant cardiac disorder recorded in the medical chart.

**Brain MRI and assessment of total CSVD burden**

Brain MRI was performed using a standardized clinical protocol on a Siemens 3.0T MRI scanner that included at least axial T1-weighted, T2-weighted, and fluid-attenuated inversion recovery sequences. All participants underwent brain MRI that included structural sequences for white matter lesions and lacunes together with a susceptibility-sensitive sequence for the evaluation of cerebral microbleeds. Conventional MRI markers of CSVD were assessed independently by two trained raters who were blinded to kidney measures and other laboratory results, in accordance with contemporary neuroimaging standards for CSVD research. The total CSVD burden score ranged from 0 to 4 and was constructed using the established ordinal approach that summarizes the combined presence of key MRI markers. One point was assigned for each of

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the following features: (1) severe white matter hyperintensities, defined as periventricular Fazekas grade 3 and/or deep white matter Fazekas grade 2–3; (2) presence of one or more lacunes; (3) presence of one or more deep cerebral microbleeds; and (4) moderate-to-severe enlarged perivascular spaces in the basal ganglia. For descriptive analyses, participants were categorized into four groups according to total CSVD burden (score 0, 1, 2, and ≥3). In a sensitivity analysis, the total CSVD score was recalculated using cerebral microbleeds at any location rather than restricting the microbleed component to deep locations. Inter-rater reliability was assessed on a random subset of 30 scans independently rated by both raters, who were blinded to each other's ratings and to all clinical and laboratory data. Cohen's kappa coefficients were calculated for each CSVD feature: lacunes ($\kappa = 0.82$, 95% CI: 0.68–0.96), white matter hyperintensities (weighted $\kappa = 0.79$, 95% CI: 0.65–0.93), deep cerebral microbleeds ($\kappa = 0.85$, 95% CI: 0.72–0.98), and enlarged perivascular spaces in the basal ganglia (weighted $\kappa = 0.76$, 95% CI: 0.60–0.92) (Supplementary Table S1).

**Kidney measures and outcome definitions**

Blood and urine samples were collected on the same day as the MRI. Serum creatinine was measured in the central laboratory using a standardized enzymatic assay traceable to isotope dilution mass spectrometry. Cystatin C was measured using a standardized particle-enhanced immunoturbidimetric assay calibrated to the applicable international reference material, and urinary albumin and urinary creatinine were measured using routine automated assays to calculate the urinary albumin-to-creatinine ratio (UACR, mg/g). The primary kidney filtration marker was estimated glomerular filtration rate (eGFR) derived from serum creatinine according to the equation prespecified in the study protocol. In sensitivity analyses, alternative filtration estimates based on creatinine plus cystatin C or cystatin C alone (eGFRcr-cys or eGFRcys) were also examined, reflecting current approaches to kidney function estimation in adults. The primary binary kidney outcome was composite kidney dysfunction, defined as eGFR < 60 mL/min/1.73 m² and/or UACR ≥ 30 mg/g. Reduced eGFR (eGFR < 60 mL/min/1.73 m²) and albuminuria (UACR ≥ 30 mg/g) were analyzed as secondary binary outcomes. For continuous analyses, eGFR, serum creatinine, cystatin C, and UACR were treated as dependent variables; because UACR was right-skewed, it was natural log-transformed before regression analyses.

**Statistical analysis**

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All statistical analyses and data management were performed using SPSS 26.0 for Mac (IBM Corporation, Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), and categorical variables are presented as counts and percentages. Baseline characteristics across CSVD burden categories were compared using one-way analysis of variance (ANOVA) for normally distributed continuous variables, the Kruskal–Wallis test for skewed continuous variables, and the chi-square test for categorical variables. Associations between total CSVD burden and continuous kidney measures were examined using multivariable linear regression models with CSVD burden entered as a continuous predictor (per 1-point increase). Associations between total CSVD burden and binary kidney outcomes were evaluated using logistic regression and are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Model 1 was adjusted for age and sex. Model 2 further adjusted for education, BMI, smoking, alcohol consumption, diabetes mellitus, dyslipidemia, heart disease, antihypertensive use, and statin use.

Hypertension and systolic blood pressure were not included in the primary multivariable models because they were considered biologically relevant intermediates rather than purely external confounders. Instead, they were specifically examined in exploratory mediation analyses and in sensitivity analyses designed to test the stability of the main findings under alternative adjustment strategies. Mediation analyses evaluated whether hypertension mediated the association between total CSVD burden and the three binary kidney outcomes (composite kidney dysfunction, reduced eGFR, and albuminuria). Total, direct, and indirect effects were estimated within a regression-based mediation framework, and the statistical significance of the indirect effect was determined using nonparametric bootstrap resampling (5,000 iterations). The proportion mediated was calculated as the indirect effect divided by the total effect.

Given the cross-sectional design, the mediation analyses were interpreted as exploratory rather than as definitive evidence of causality. The temporal assumptions required for formal mediation—that exposure precedes the mediator, which precedes the outcome—cannot be verified in this dataset. The rationale for examining hypertension as a mediator was based on the well-established biological framework that hypertension drives both cerebral and renal microvascular injury. We hypothesised that the CSVD-kidney association may be partially explained by hypertensive vascular injury affecting both organs, and the mediation analysis quantified the proportion of the observed statistical association attributable to this shared

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pathway. We emphasise that this is a statistical decomposition of associations, not a causal decomposition. Therefore, our mediation results should be interpreted as estimating statistical associations consistent with a mediation hypothesis, rather than as establishing causal pathways.

Additional sensitivity analyses were performed: (1) further adjustment for hypertension; (2) further adjustment for systolic blood pressure; (3) exclusion of participants with prior stroke; (4) exclusion of participants with known dementia; (5) recalculation of the total CSVD burden score using cerebral microbleeds at any location; and (6) replacement of the primary eGFR estimate with eGFRcr-cys or eGFRcys as an alternative continuous kidney outcome. To avoid model overfitting and ensure reliable estimation, the number of covariates in the fully adjusted models was limited to approximately one-tenth of the number of events for logistic regression analyses, consistent with established methodological recommendations[20]. The primary analyses (linear and logistic regression models) and the planned sensitivity analyses were pre-specified in the study protocol. The mediation analysis was pre-specified based on the biological framework that hypertension drives both cerebral and renal microvascular injury. Post-hoc analyses were conducted to further explore the robustness of the findings. All statistical tests were two-sided, and a P value <0.05 was considered statistically significant.

**Results**

The study included 239 older adults with a mean age of 73.4 ± 7.1 years, of whom 107 (44.8%) were women. According to the total CSVD burden score, 71 participants were classified as score 0, 60 as score 1, 54 as score 2, and 54 as score ≥3. Participants with greater CSVD burden were older and had progressively higher systolic blood pressure, a higher prevalence of hypertension, and more frequent use of antihypertensive medication (all P≤0.001). In contrast, sex distribution, years of education, BMI, smoking, alcohol use, diastolic blood pressure, diabetes mellitus, dyslipidemia, heart disease, and statin use did not differ significantly across CSVD categories (all P>0.05) (Table 1).

Kidney measures worsened across increasing CSVD burdens. Mean eGFR decreased stepwise from 85.4 ± 14.1 mL/min/1.73 m² in participants with a CSVD score of 0 to 72.5 ± 15.8 mL/min/1.73 m² in those with a score of ≥3 (P < 0.001). By contrast, serum creatinine, cystatin C, and UACR increased across the same categories (all P < 0.001). The prevalence of composite kidney dysfunction rose from 25.4% in the score 0 group to 59.3% in the score ≥ 3 group (P = 0.001) (Table 1).

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In linear regression analyses, a 1-point increase in total CSVD burden was associated with a lower eGFR (β = -4.82, 95% CI -6.51 to -3.13; P<0.001), higher serum creatinine (β = 0.19, 95% CI 0.10 to 0.29; P<0.001), higher cystatin C (β = 0.09, 95% CI 0.05 to 0.12; P<0.001), and higher ln(UACR) (β = 0.31, 95% CI 0.19 to 0.42; P<0.001). After adjustment for age and sex (Model 1), all four associations remained statistically significant. Further adjustment for education, BMI, smoking, alcohol consumption, diabetes mellitus, dyslipidemia, heart disease, antihypertensive use, and statin use (Model 2) only modestly attenuated the effect estimates (Table 2). In the fully adjusted model, each additional point in total CSVD burden corresponded to a 2.98 mL/min/1.73 m² lower eGFR (95% CI -4.67 to -1.29; P < 0.001), a higher serum creatinine level (β = 0.14, 95% CI 0.04 to 0.24; P = 0.007), a higher cystatin C level (β = 0.06, 95% CI 0.02 to 0.10; P = 0.003), and a higher ln(UACR) value (β = 0.24, 95% CI 0.12 to 0.36; P < 0.001).

In logistic regression analyses, higher total CSVD burden was associated with greater odds of adverse binary kidney outcomes (Table 3). In Model 1 adjusted for age and sex, each 1-point increase in total CSVD burden was associated with 52% higher odds of composite kidney dysfunction (OR = 1.52, 95% CI 1.22–1.90; P<0.001), 42% higher odds of reduced eGFR (OR = 1.42, 95% CI 1.10–1.83; P=0.007), and 58% higher odds of albuminuria (OR = 1.58, 95% CI 1.24–2.02; P<0.001). After multivariable adjustment in Model 2, the associations with composite kidney dysfunction and albuminuria remained statistically significant. Specifically, each additional point in total CSVD burden was associated with 38% higher odds of composite kidney dysfunction (OR = 1.38, 95% CI 1.08–1.76; P=0.010) and 46% higher odds of albuminuria (OR = 1.46, 95% CI 1.12–1.90; P=0.005). The association with reduced eGFR was attenuated and no longer reached statistical significance after full adjustment (OR = 1.29, 95% CI 0.98–1.69; P = 0.068).

Exploratory mediation analyses indicated that hypertension accounted for a meaningful proportion of the association between total CSVD burden and kidney outcomes (Table 4). For composite kidney dysfunction, the total effect of total CSVD burden was 0.33, of which 0.12 was mediated through hypertension. The corresponding proportion mediated was 36.2%, and the indirect effect was statistically significant (bootstrap 95% CI: 0.04 to 0.21; P = 0.004). A similar pattern was observed for the secondary kidney outcomes. For reduced eGFR, the indirect effect via hypertension was 0.08, corresponding to 32.0% of the total effect (bootstrap 95% CI 0.01 to 0.16;

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P = 0.032). For albuminuria, the indirect effect was 0.11, accounting for 36.7% of the total effect (bootstrap 95% CI 0.03 to 0.20; P = 0.008).

The sensitivity analyses summarized in Table 5 further clarified the robustness of the primary findings. When hypertension was additionally included in the regression model, the association between total CSVD burden and composite kidney dysfunction was attenuated and no longer statistically significant (OR = 1.21, 95% CI 0.93–1.57; P = 0.156). A similar attenuation was observed after further adjustment for systolic blood pressure (OR = 1.24, 95% CI 0.96–1.60; P = 0.101).

By contrast, the association between total CSVD burden and composite kidney dysfunction remained statistically significant after excluding participants with prior stroke (OR = 1.35, 95% CI 1.04–1.76; P=0.025) and after excluding those with known dementia (OR = 1.40, 95% CI 1.09–1.80; P=0.009). The findings also remained materially similar when a modified CSVD burden score based on cerebral microbleeds at any location was used (OR = 1.32, 95% CI 1.03–1.68; P = 0.027). When alternative filtration estimates based on creatinine plus cystatin C or cystatin C alone were analyzed as continuous kidney outcomes, higher total CSVD burden remained significantly associated with lower kidney filtration (β = -3.12, 95% CI -4.91 to -1.33; P < 0.001). We performed post-hoc analyses examining the association between total CSVD burden and continuous kidney outcomes after additional adjustment for hypertension and systolic blood pressure. In these models, the association with lnUACR remained statistically significant (β = 0.18, 95% CI: 0.06–0.30, P = 0.004), whereas the association with eGFR was attenuated and no longer reached statistical significance (β = -2.01, 95% CI: -4.21 to 0.19, P = 0.073). In a post-hoc analysis using a more parsimonious model including only age, sex, hypertension, and diabetes mellitus, the association between CSVD burden and composite kidney dysfunction remained statistically significant (OR = 1.42, 95% CI: 1.14–1.77, P = 0.002) (Table 5).

**Discussion**

In this cross-sectional study of 239 older adults, greater MRI-defined total CSVD burden was consistently associated with a more adverse renal profile. Prior investigations have largely relied on single kidney metrics and individual CSVD markers, we employed a validated total CSVD burden score alongside four complementary kidney measures (creatinine, cystatin C, UACR, and eGFR) to provide a more comprehensive characterization of the brain-kidney axis. This approach is particularly relevant in older adults, as cystatin C and UACR are more sensitive to early

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microvascular injury[18,19]. Our mediation analysis quantifies, for the first time in this context, that hypertension mediates 32%–37% of the association. Importantly, the robustness of our findings across multiple sensitivity analyses indicates that the observed association reflects a relationship between cerebral and renal microvascular health. Across CSVD categories, eGFR declined, whereas serum creatinine, cystatin C, UACR, and the prevalence of composite kidney dysfunction increased. In fully adjusted models, each 1-point increase in total CSVD burden corresponded to a 2.98 mL/min/1.73 m² lower eGFR, higher serum creatinine, higher cystatin C, and higher ln(UACR). Total CSVD burden was independently associated with composite kidney dysfunction and albuminuria, while the association with reduced eGFR as a dichotomized endpoint was attenuated after multivariable adjustment. Exploratory mediation analyses further suggested that roughly one-third of the CSVD-kidney association may operate through hypertension.

These findings are consistent with the view that renal dysfunction and CSVD reflect parallel manifestations of systemic small-vessel injury. Early meta-analytic work linked lower eGFR with higher odds of CSVD-related lesions[12,21], and later syntheses of cohort data extended this relationship to broader aspects of brain health[13]. Recent observational studies have strengthened the signal across diverse settings: progressive CKD has been associated with worsening WMH and CMB burden on MRI[15], kidney measures in ARIC were linked to small-vessel disease and neurodegeneration on brain MRI[14], and the Framingham Heart Study showed that albuminuria was independently associated with covert infarcts and later cognitive impairment[22]. Studies in older hypertensive adults, acute intracerebral hemorrhage, acute ischemic stroke, and the UK Biobank likewise suggest that multidimensional renal dysfunction tracks with more severe CSVD phenotypes[16,17,23,24]. The present study adds to this literature by showing that in an older clinical cohort, a conventional MRI-defined total CSVD score remains informative when renal status is characterized by multiple complementary markers rather than a single creatinine-based estimate.

The association with albuminuria remained statistically robust after full adjustment, whereas the binary reduced-eGFR endpoint did not. Albuminuria is not merely a marker of nephron loss; it also reflects glomerular endothelial injury, abnormal permeability, and diffuse microvascular dysfunction. In contrast, dichotomizing eGFR may obscure clinically relevant variation above that threshold and reduce statistical power in a modest-sized sample. The persistence of

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significant associations for continuous eGFR, cystatin C, and ln(UACR) suggests that CSVD burden tracks with renal vulnerability across a continuum, with albuminuria perhaps capturing earlier or more active microvascular injury[18,19,25]. This interpretation is in line with the current framework, which emphasizes combined consideration of filtration and albuminuria rather than reliance on eGFR thresholds alone[25].

Additional adjustment for hypertension or systolic blood pressure materially weakened the association between total CSVD burden and composite kidney dysfunction, and the bootstrap mediation analysis suggested that hypertension explained approximately 32%-37% of the total effect across kidney outcomes. This does not establish causality, but it supports the idea that hypertension is more than a nuisance covariate in the brain-kidney axis. Chronic blood pressure elevation promotes arteriolar remodeling, lipohyalinosis, impaired vasoreactivity, glomerular hypertension, and endothelial injury in both organs[3,11,26-28]. Recent research argued that CKD should be considered an active mediator in CSVD rather than a variable to be routinely adjusted away[29]. Our data are compatible with that conceptual framing: the association did not disappear entirely after mediation modeling, implying that non-hemodynamic pathways likely coexist with blood pressure-related injury.

The association between CSVD burden and composite kidney dysfunction was attenuated to non-significance after additional adjustment for hypertension, suggesting that shared hypertensive microvascular injury may largely drive this relationship. This aligns with our mediation analysis showing hypertension accounts for 32%–37% of the total effect. Notably, the association with lnUACR remained significant after hypertension adjustment, whereas the association with eGFR did not. This dissociation suggests that albuminuria may capture a component of microvascular damage relatively independent of hypertension, underscoring the value of multiple kidney measures in brain-kidney axis research. The exploratory mediation results should be interpreted with caution. The cross-sectional design cannot establish the temporal ordering required for mediation—that CSVD burden precedes hypertension, which precedes kidney dysfunction. Hypertension is conventionally viewed as an antecedent risk factor for both conditions rather than a consequence of CSVD; our model was based on the biological premise that hypertension is a shared mechanistic pathway. Additionally, our single baseline assessment of hypertension status cannot capture the dynamics of this relationship, and residual confounding from unmeasured factors such as hypertension duration, severity, and medication

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adherence may have influenced the estimates. These findings are hypothesis-generating and require confirmation in prospective cohort studies.

Several mechanisms may underlie the residual association beyond blood pressure. Endothelial dysfunction, increased vascular stiffness, chronic low-grade inflammation, oxidative stress, and barrier failure have all been implicated in CSVD pathogenesis[10,11,28]. Emerging imaging and neuropathological work suggests that blood-brain barrier disruption and perivascular clearance failure are integral components of cerebral microvascular injury[30-32], while age-related WMH progression likely reflects cumulative ischemic, inflammatory, and barrier-related damage[33]. From the renal side, recent work using multidimensional renal-related biomarkers, including blood urea nitrogen to albumin ratio, supports a broader microvascular signal rather than a purely filtration-based phenomenon[34]. Hypertension may interact with these processes and, in some settings, may contribute to CSVD through overlapping pathways involving intracranial atherosclerosis and downstream small-vessel injury[35].

The association with composite kidney dysfunction remained significant after excluding participants with prior stroke and after excluding those with known dementia, arguing against the possibility that the results were driven solely by overt cerebrovascular or degenerative disease. The results were also materially unchanged when the CMB component was broadened to any location, suggesting that the observed association was not dependent on a single operational definition of the CSVD score. The inverse association between CSVD burden and alternative filtration estimates based on creatinine plus cystatin C or cystatin C alone supports the relevance of the findings across different approaches to renal function estimation[36,37]. From a methodological standpoint, an MRI-defined total CSVD score offers a pragmatic summary of cumulative cerebral microvascular damage, while more advanced MRI methods may be reserved for mechanistic studies and longitudinal phenotyping[6,38].

This study has several limitations that should be acknowledged. First, the cross-sectional design precludes temporal or causal inference; reverse causation and bidirectional relationships remain possible. Our analytical treatment of hypertension as a mediator rather than a confounder was based on prespecified biological assumptions, but this remains a debatable analytical choice. The attenuation of the association after additional adjustment for hypertension indicates that we cannot definitively conclude that CSVD burden is independently associated with kidney dysfunction beyond hypertensive vascular injury. Therefore, our findings should be interpreted

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as demonstrating a robust association that is partially, but perhaps not entirely, mediated by hypertension, rather than as establishing full independence from shared vascular risk factors. Second, the sample was recruited from neurological outpatient clinics and inpatient wards at a single center, which may limit external generalizability and may enrich the cohort for vascular and neurological comorbidities. This selection bias is a recognized limitation of hospital-based cross-sectional studies. However, we note that the association remained significant after excluding participants with prior stroke or known dementia, suggesting that our findings are not driven solely by the most severe cerebrovascular or neurodegenerative conditions. Nevertheless, replication of our findings in community-based or population-based cohorts is essential to confirm their generalizability to the broader older adult population. Third, kidney markers, particularly UACR, were based on the available assessment rather than repeated measurements, and residual confounding from unmeasured factors such as duration and control of hypertension, arterial stiffness, inflammatory markers, diet, or medication intensity cannot be excluded. Fourth, although we performed an exploratory mediation analysis, the cross-sectional design of our study precludes any causal interpretation of the mediation results. Hypertension is conventionally regarded as a risk factor that precedes both CSVD and kidney dysfunction, and our data cannot establish the temporal sequence required for formal mediation analysis. Therefore, our mediation findings should be viewed as hypothesis-generating and in need of validation in prospective cohort studies with repeated blood pressure and kidney function measurements. Fifth, the total CSVD burden score is a semi-quantitative visual rating system that does not account for lesion volume or continuous severity gradients. Although this pragmatic approach has been widely validated against volumetric measures and demonstrates good construct validity, it may not capture subtle gradations of microvascular injury that could be detected by quantitative MRI techniques. However, the consistent results across our sensitivity analyses—including the use of alternative eGFR equations and a modified CSVD score with any-location CMBs—suggest that our findings are robust to the specific operational definition of the CSVD burden score. Sixth, although our logistic regression models for composite kidney dysfunction maintained an acceptable events-per-variable ratio (approximately 8.9), the reduced eGFR outcome had a more limited ratio (approximately 4.5), which may have reduced statistical power to detect a significant association after full adjustment. To further assess model stability, we performed an internal validation using bootstrap resampling (1,000 resamples) for the composite kidney

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dysfunction model. The optimism-corrected c-statistic was 0.71 (apparent c-statistic: 0.74), and the optimism-corrected calibration slope was 0.89, suggesting that the model is not substantially overfitted. Therefore, the non-significant association with reduced eGFR in the fully adjusted model should be interpreted with caution, as it may reflect limited power rather than a true absence of association. Seventh, although the primary analyses and planned sensitivity analyses were pre-specified, several post-hoc analyses were conducted to further explore the robustness of our findings. These post-hoc analyses should be interpreted as exploratory and hypothesis-generating. The consistency of their results with the pre-specified primary analyses provides additional reassurance regarding the robustness of our findings, but this consistency should not be overinterpreted as confirmatory evidence. Prospective multicenter studies with repeated kidney measurements, ambulatory blood pressure profiling, and quantitative MRI will be important to determine directionality and to test whether aggressive microvascular risk management can simultaneously attenuate progression in both organs. Although our study focused on older adults (>70 years), the brain-kidney axis likely operates across the adult lifespan, as early renal dysfunction and subclinical CSVD may begin decades before clinical manifestations become apparent. Future studies in midlife or younger populations are needed to determine whether similar associations are present earlier in the disease course and whether early detection of renal or cerebral microvascular injury could facilitate earlier risk stratification and intervention.

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**Conclusion**

Among older adults, greater MRI-defined total CSVD burden was associated with worse kidney function and albuminuria after adjustment for conventional confounders. However, additional adjustment for hypertension attenuated the composite kidney outcome to non-significance, suggesting that shared hypertensive vascular injury may largely explain the observed connection between the brain and kidney. Exploratory mediation analysis suggested hypertension may account for 32%–37% of the association, but this finding should be interpreted with caution given the cross-sectional design. Prospective studies with repeated blood pressure measurements are needed to further disentangle these causal pathways. In addition, our findings require validation in community-based or population-based cohorts to confirm their generalizability to the broader older adult population.

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**Author contributions**

ZS and ML contributed to the design and implementation of the research and wrote the report. JK, MS, CW, BX, LS, JP, YZ, and YY contributed to the collection of clinical data. ML, CW, and YY performed the statistical analyses. ML drew the statistical figures and tables. ZS and ML contributed to the interpretation and discussion of the results and reviewed the manuscript. All authors reviewed the manuscript and read and approved the submitted version.

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**Conflicting interests:**

All authors declare no financial or non-financial competing interests.

**Ethical statement**

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Henan Medical University (EC-024-537). Written informed consent was obtained from all participants prior to their inclusion in the study, including consent for publication of anonymized data.

**Data availability**

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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**Table 5. Sensitivity analyses for the association between total CSVD burden and kidney outcomes**

| Sensitivity analysis | Effect estimate | 95% CI | P value |
|---|---|---|---|
| Additional adjustment for hypertension | OR = 1.21 | 0.93–1.57 | 0.156 |
| Additional adjustment for systolic blood pressure | OR = 1.24 | 0.96–1.60 | 0.101 |
| Excluding participants with prior stroke | OR = 1.35 | 1.04–1.76 | 0.025 |
| Excluding participants with known dementia | OR = 1.40 | 1.09–1.80 | 0.009 |
| Modified total CSVD score using any-location CMB | OR = 1.32 | 1.03–1.68 | 0.027 |
| Using eGFRcr-cys or eGFRcys | β = -3.12 | -4.91 to -1.33 | <0.001 |
| Additional adjustment for hypertension (continuous eGFR) | β = -2.01 | -4.21 to 0.19 | 0.073 |
| Additional adjustment for hypertension (continuous lnUACR) | β = 0.18 | 0.06 to 0.30 | 0.004 |
| Parsimonious model (age, sex, hypertension, diabetes mellitus)* | OR = 1.42 | 1.14–1.77 | 0.002 |

CSVD, cerebral small vessel disease; CMB, cerebral microbleed; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio. *Outcome: composite kidney dysfunction. Adjusted for age, sex, hypertension, and diabetes mellitus.

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**Supplementary Table S1. Inter-rater agreement for individual CSVD MRI markers**

| CSVD feature | Cohen's κ (95% CI) | Interpretation* |
|---|---|---|
| Lacunes | 0.82 (0.68–0.96) | Almost perfect |
| White matter hyperintensities (Fazekas grading) | 0.79 (0.65–0.93) | Substantial |
| Deep cerebral microbleeds | 0.85 (0.72–0.98) | Almost perfect |
| Enlarged perivascular spaces (basal ganglia) | 0.76 (0.60–0.92) | Substantial |

CSVD, cerebral small vessel disease. *Interpretation according to Landis and Koch criteria: κ = 0.61–0.80 substantial agreement; κ = 0.81–1.00 almost perfect agreement. Inter-rater agreement was assessed on a random subset of 30 scans independently rated by two trained raters blinded to clinical and laboratory data.

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**Table 1. Baseline characteristics according to total CSVD burden categories**

| Characteristic | Overall (N=239) | Score 0 (n=71) | Score 1 (n=60) | Score 2 (n=54) | Score ≥3 (n=54) | *P* value |
|---|---|---|---|---|---|---|
| Age, years | 73.4 ± 7.1 | 70.2 ± 6.2 | 73.1 ± 6.8 | 75.4 ± 6.5 | 76.1 ± 7.3 | <0.001* |
| Women, n (%) | 107 (44.8) | 35 (49.3) | 28 (46.7) | 23 (42.6) | 21 (38.9) | 0.668 |
| Education, years | 10.5 ± 4.2 | 11.2 ± 4.0 | 10.8 ± 4.3 | 10.1 ± 4.1 | 9.7 ± 4.4 | 0.173 |
| Body mass index, kg/m² | 24.6 ± 3.5 | 24.2 ± 3.1 | 24.8 ± 3.6 | 24.5 ± 3.7 | 24.9 ± 3.8 | 0.614 |
| Smoking, n (%) | 48 (20.1) | 12 (16.9) | 13 (21.7) | 11 (20.4) | 12 (22.2) | 0.848 |
| Alcohol use, n (%) | 38 (15.9) | 10 (14.1) | 9 (15.0) | 9 (16.7) | 10 (18.5) | 0.919 |
| Systolic blood pressure, mmHg | 142.1 ± 19.5 | 135.2 ± 17.1 | 141.5 ± 18.8 | 145.8 ± 19.2 | 148.3 ± 21.0 | <0.001* |
| Diastolic blood pressure, mmHg | 80.4 ± 11.2 | 78.5 ± 10.4 | 80.1 ± 11.0 | 81.2 ± 11.5 | 82.5 ± 12.1 | 0.235 |
| Hypertension, n (%) | 173 (72.4) | 38 (53.5) | 43 (71.7) | 44 (81.5) | 48 (88.9) | <0.001† |
| Diabetes mellitus, n (%) | 58 (24.3) | 12 (16.9) | 15 (25.0) | 15 (27.8) | 16 (29.6) | 0.313 |
| Dyslipidemia, n (%) | 105 (43.9) | 28 (39.4) | 27 (45.0) | 25 (46.3) | 25 (46.3) | 0.821 |
| Heart disease, n (%) | 45 (18.8) | 9 (12.7) | 12 (20.0) | 11 (20.4) | 13 (24.1) | 0.378 |
| Antihypertensive use, n (%) | 148 (61.9) | 32 (45.1) | 37 (61.7) | 38 (70.4) | 41 (75.9) | 0.001† |
| Statin use, n (%) | 62 (25.9) | 16 (22.5) | 15 (25.0) | 15 (27.8) | 16 (29.6) | 0.802 |
| eGFR, mL/min/1.73 m² | 78.6 ± 16.2 | 85.4 ± 14.1 | 79.2 ± 15.3 | 75.1 ± 16.0 | 72.5 ± 15.8 | <0.001* |
| Serum creatinine, μmol/L | 81.5 ± 18.4 | 72.8 ± 14.5 | 80.1 ± 16.2 | 85.3 ± 18.8 | 88.6 ± 20.1 | <0.001* |
| Cystatin C, mg/L | 1.12 ± 0.28 | 0.96 ± 0.21 | 1.09 ± 0.25 | 1.18 ± 0.27 | 1.26 ± 0.30 | <0.001* |
| UACR, mg/g | 18.5 (9.8–45.2) | 12.4 (7.5–25.1) | 16.8 (9.2–38.5) | 22.1 (11.5–55.8) | 28.9 (14.2–72.5) | <0.001‡ |

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| | | | | | | |
|---|---|---|---|---|---|---|
| Kidney dysfunction, n (%) | 98 (41.0) | 18 (25.4) | 22 (36.7) | 26 (48.1) | 32 (59.3) | 0.001† |

CSVD, cerebral small vessel disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio. Data are presented as n (%), mean±SD, or median (IQR). CSVD, cerebral small vessel disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.*P values: One-way ANOVA for normally distributed continuous variables; †Chi-square test for categorical variables; ‡Kruskal-Wallis test for skewed continuous variables.

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**Table 2. Multivariable linear regression analyses of total CSVD burden and kidney measures**

| Outcome | Crude β (95% CI); *P* | Model 1 β (95% CI); *P* | Model 2 β (95% CI); *P* |
|---|---|---|---|
| eGFR, mL/min/1.73 m² | -4.82 (-6.51 to -3.13); <0.001 | -3.46 (-5.08 to -1.84); <0.001 | -2.98 (-4.67 to -1.29); <0.001 |
| Serum creatinine, μmol/L | 0.19 (0.10 to 0.29); <0.001 | 0.16 (0.07 to 0.26); 0.001 | 0.14 (0.04 to 0.24); 0.007 |
| Cystatin C, mg/L | 0.09 (0.05 to 0.12); <0.001 | 0.07 (0.04 to 0.11); <0.001 | 0.06 (0.02 to 0.10); 0.003 |
| ln(UACR) | 0.31 (0.19 to 0.42); <0.001 | 0.26 (0.15 to 0.38); <0.001 | 0.24 (0.12 to 0.36); <0.001 |

CSVD, cerebral small vessel disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio. Model 1 adjusted for age and sex. Model 2 adjusted for Model 1 covariates plus education, body mass index, smoking, alcohol consumption, diabetes mellitus, dyslipidemia, heart disease, antihypertensive use, and statin use. β values represent unstandardized regression coefficients per 1-point increase in total CSVD burden.

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**Table 3. Logistic regression analyses of total CSVD burden and binary kidney outcomes**

| Outcome | Model 1 OR (95% CI); P | Model 2 OR (95% CI); P |
|---|---|---|
| Kidney dysfunction (eGFR <60 and/or UACR ≥30 mg/g) | 1.52 (1.22–1.90); <0.001 | 1.38 (1.08–1.76); 0.010 |
| Reduced eGFR (eGFR <60 mL/min/1.73 m²) | 1.42 (1.10–1.83); 0.007 | 1.29 (0.98–1.69); 0.068 |
| Albuminuria (UACR ≥30 mg/g) | 1.58 (1.24–2.02); <0.001 | 1.46 (1.12–1.90); 0.005 |

CSVD, cerebral small vessel disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio. Model 1 adjusted for age and sex. Model 2 adjusted for Model 1 covariates plus education, body mass index, smoking, alcohol consumption, diabetes mellitus, dyslipidemia, heart disease, antihypertensive use, and statin use. ORs are reported per 1-point increase in total CSVD burden.

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**Table 4. Exploratory mediation analysis of hypertension in the association between total CSVD burden and kidney outcomes**

| Outcome | Total effect | Direct effect | Indirect effect via hypertension | Proportion mediated | Bootstrap 95% CI | *P* value |
|---|---|---|---|---|---|---|
| Kidney dysfunction | 0.33 | 0.21 | 0.12 | 36.2% | 0.04 to 0.21 | 0.004 |
| Reduced eGFR | 0.25 | 0.17 | 0.08 | 32.0% | 0.01 to 0.16 | 0.032 |
| Albuminuria | 0.30 | 0.19 | 0.11 | 36.7% | 0.03 to 0.20 | 0.008 |

CSVD, cerebral small vessel disease; eGFR, estimated glomerular filtration rate.

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