Albuminuria and Cerebral Small Vessel Disease: A Systematic Review and Meta-Analysis

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OBJECTIVES: To determine whether albuminuria, a marker of systemic endothelial dysfunction, is associated with cerebral small vessel disease (SVD).

DESIGN: Systematic review following the Meta-analyses Of Observational Studies in Epidemiology guidelines; independent reviewers searched Pubmed/Medline and Scopus, data were extracted, studies were evaluated on quality, and random-effects models were implemented for meta-analysis.

SETTING: Observational studies quantifying an association between albuminuria and cerebral SVD.

PARTICIPANTS: Adults.

MEASUREMENTS: Magnetic resonance imaging–defined markers of cerebral SVD; white matter hyperintensities (WMHs), lacunar infarcts (LIs), cerebral microbleeds (CMBs), and enlarged perivascular spaces (EPVSs).

RESULTS: Of 31 eligible studies comprising 23,056 participants identified, 27 were included in quantitative synthesis. Most of the studies were cross-sectional and of varying quality. On meta-analysis, albuminuria was associated with greater risk of WMHs (odds ratio (OR) = 1.70, 95% confidence interval (CI) = 1.43–2.01; 13,548 subjects, 2,665 cases; I^2 = 44%), LIs (OR = 1.86, 95% CI = 1.49–2.31; 12,857 subjects, 998 cases; I^2 = 27%), CMBs (OR = 1.78, 95% CI = 1.30–2.43; 7,645 subjects; 748 cases; I^2 = 39%), and EPVSs in the basal ganglia (OR = 1.78, 95% CI = 1.02–3.09; 1,388 subjects, 399 cases; I^2 = 37%) and centrum semiovale (OR = 3.27, 95% CI = 1.49–7.20; 1,146 subjects, 460 cases; I^2 = 66%). Sensitivity analyses for high-quality and general population studies, but also studies controlling for cardiovascular disease risk factors and renal function, confirmed the findings and resolved the moderate heterogeneity and publication bias that were evident in the overall analyses.

CONCLUSION: Albuminuria is independently associated with cerebral SVD, indicating shared microvascular pathology in the kidney and the brain. The results suggest that peripheral systemic microvascular disease biomarkers could be useful in the evaluation of brain microvascular damage. **J Am Geriatr Soc 2018.**

Key words: albuminuria; proteinuria; kidney disease; cerebral small vessel disease; stroke

Widespread vascular injury in the brain and the ensuing effect on structural and functional connectivity are main contributors to neurocognitive dysfunction.[1] Cerebral small vessel disease (SVD) is responsible for more than 20% of strokes, which are the major contributor to vascular dementia and a potential pathogenetic mechanism to Alzheimer's disease.[2,3] Investigation of cerebral SVD is possible by observing its effects on the brain parenchyma using magnetic resonance imaging (MRI), including white matter hyperintensities (WMHs), lacunar infarcts (LIs), cerebral microbleeds (CMBs), and enlarged perivascular spaces (EPVSs).[3]

Because of the unity of the vasculature, SVD is considered a systemic disorder,[4] and microcirculatory damage in other organs could accompany its occurrence in the brain. The kidney and the brain have similar hemodynamic properties, with low resistance and high circulatory flow.[5] Chronic kidney disease (CKD) has been associated with cerebral SVD and cognitive decline,[6,7] but in advanced disease stages, factors related to impaired clearance could be the main contributors and confound the association between CKD and SVD.[8]

Albuminuria is an early marker of kidney disease, corresponding to a subclinical time-point when the estimated glomerular filtration rate (eGFR) may have not yet been affected.[9,10] Albuminuria has been associated with coronary artery disease, stroke, and cardiovascular

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mortality.[11,12] Pathophysiologically, it arises due to glomerular capillary leak, primarily caused by kidney microangiopathy,[13] and has been proposed as a sensitive biomarker of systemic endothelial dysfunction.[13]

In a previous meta-analysis, we showed that albuminuria is associated with risk of dementia and cognitive decline.[14] We hypothesized that this is the result of concurrent SVD pathology in the kidney and the brain,[14] and there is evidence of an association between albuminuria and SVD neuroimaging markers, although it is mainly derived from small studies in heterogeneous populations.[15–18] We sought to explore the aforementioned hypothesis in a comprehensive systematic review of published literature.

METHODS

This systematic review, based on a predefined protocol, follows the Meta-analysis of Observational Studies in Epidemiology[19] guidelines (Table S1).

Study Selection

Two reviewers screened Medline through PubMed and Scopus from their inception through April 25, 2017, using specific search strategies (Methods S1). No restrictions on language or publication year were applied. Reference lists of eligible studies and relevant reviews were additionally hand-searched. In cases of disagreement between reviewers, a consensus was reached; the two reviewers re-evaluated and justified their selection, and if the disagreement persisted, a team consensus was reached in which, based on the predefined selection criteria, all authors agreed on the eligibility of the article. Eligible articles were evaluated for overlap based on geographical setting, study period, sample size, and outcome. Authors of studies not quantifying the association of interest but providing necessary information were contacted for appropriate analyses.

Cohort, case-control, and cross-sectional studies quantifying an association between albuminuria and neuroimaging markers of cerebral SVD were considered eligible. Case series, case reports, and in vitro and animal studies were excluded, as were studies including solely children or adolescents.

The exposure variable of interest was albuminuria and defined by albumin-to-creatinine ratio (ACR) or 24-hour urinary albumin excretion. Cut-offs of ≥30 mg/g for ACR or ≥30 mg/24 h for 24-hour urinary albumin excretion determined presence of albuminuria.[20] However, studies using sex-specific albuminuria definitions (ACR≥17 mg/g for men and ≥25 mg/g for women)[20] or even lower cut-off points were also included. Some studies assessed proteinuria according to positive dipstick measurements or 24-hour urinary protein excretion. Because this method is highly correlated with urine ACR but has lower diagnostic accuracy,[21] following a nonexclusion policy and in accordance with previous large consortia meta-analyses,[11,22] we also included these studies. Subsequent sensitivity analyses according to method of albuminuria assessment were undertaken to avoid potential misinterpretation of findings due to assessment bias. Studies assessing albumin excretion or ACR as continuous variables were eligible for the systematic review but were excluded from quantitative synthesis.

The SVD neuroimaging markers WMHs, LIs, CMBs, and EPVS were considered as outcomes.[3] We further aimed to explore cerebral superficial siderosis (CSS), but no relevant studies were identified. Only studies assessing SVD using MRI were considered for eligibility. Studies on WMHs were included if they provided a dichotomous definition based on validated scoring systems or continuous measures of WMH volume. Studies assessing total cerebral SVD burden were also considered for eligibility.

Data Abstraction and Quality Assessment

Two blinded observers extracted information on publication details, study sample characteristics (age, sex, body mass index, diabetes mellitus, hypertension, cardiovascular disease (CVD), CKD, eGFR, cholesterol levels, smoking status), albuminuria assessment, and SVD outcomes in a prepiloted spreadsheet. Effect estimates and their 95% confidence intervals (CIs) derived from the highest adjusted analysis of the effect of albuminuria on cerebral SVD were extracted. In cases of missing data, the authors were contacted.

Because the vast majority of studies were cross-sectional, the modified Newcastle-Ottawa Scale subscale for cross-sectional studies was used for quality assessment.[23,24] For sample representativeness, population-based studies and studies of community-dwelling individuals with diabetes mellitus or hypertension were considered to be truly or somewhat representative of the target population and were awarded 1 point; no point was awarded to studies of individuals with acute stroke and in cases of highly selected populations such as volunteers or nurses. A sample size of at least 200 and a nonrespondent proportion of 20% or less were required to receive 1 point in the respective categories. For exposure assessment, 2 points were given to studies actively measuring albuminuria, 1 point to studies on proteinuria, and no points in cases of nonactive assessments. On comparability items, adjustment for demographic factors (age, sex), CVD risk factors (diabetes mellitus, hypertension, coronary artery disease, stroke), and renal function parameters (eGFR, CKD) were each given 1 point. Lastly, outcome assessment using active MRI evaluation of all participants was given with 2 points, whereas 1 point was given for medical follow-up without MRI evaluation to all participants; registry-based assessment of outcome did not receive points. Two reviewers blindly conducted quality assessment.

Statistical Analysis

Odds ratios (ORs) and their 95% CIs from individual studies assessing the association between albuminuria, as a dichotomous variable, and WMHs, LIs, CMBs, or EPVSs were pooled using random-effect models. For studies assessing the effect of albuminuria on WMH volume, standardized mean differences were calculated or estimated,[25] and ORs were subsequently derived.[26]

Heterogeneity was assessed using the I^2 estimation and the Cochran Q statistic. I^2 values in the ranges of 30% to 50% were considered indicative of moderate heterogeneity, 51% to 75% large heterogeneity, and greater than 75%r very large heterogeneity.[27] Subgroup analyses were

conducted according to study design, albuminuria assessment, study population, confounding adjustment, and quality score. The effect of specific confounders was evaluated using metaregression analysis. Publication bias was quantified using the Egger test (significance level at $P < .10$), and funnel plots were designed. Stata version 13.0 (Stata Corp., College Station, TX) was used for the analyses.

RESULTS

Search Results

The study selection process is presented in Figure 1. The search strategy yielded 1,507 articles (after removal of duplicates), and 8 articles were derived from additional hand searching. After titles and abstracts were screened, the full texts of 54 publications were evaluated. Thirty-five studies were considered eligible, but 4 were excluded because of overlap, resulting in 31 unique studies for inclusion in the systematic review, 27 of which provided appropriate quantitative data to be included in the meta-analysis. A list of eligible studies is provided as Supplementary References.

Study Characteristics

Table S2 summarizes the characteristics of the 31 eligible studies. Most were cross-sectional, with only 4 having a cohort design. Eleven were population-based, and 20 were patient-based. Seven recruited individuals from the general community, whereas 1 study included community-dwelling individuals with low income and restricted functionality. Two studies recruited subjects with at least 2 siblings with type 2 diabetes mellitus or essential hypertension, and another study included individuals with CKD in addition to healthy controls. Patient-based studies included individuals with hypertension, diabetes mellitus, and first-ever acute stroke. The eligible studies included 23,056 participants.

Albuminuria was assessed using ACR in 22 studies, urinary albumin or protein excretion levels in 5 studies, and protein dipstick in 4 studies. Different cut-offs were used to define albuminuria, with some studies conducting continuous analyses according to ACR levels. Presence of SVD was actively evaluated using MRI in all studies except a longitudinal study that assessed incidence of LIs during medical follow-up. After excluding overlapping studies, 21 unique studies assessed presence of WMHs or volume of WMH lesions in the brain. LIs were assessed in 13 studies; 10 defined the outcome as 1 or more Lis and 1 study as more than 3 lacunae, and 2 studies examined silent brain infarcts reported to be mainly attributed to LIs. Eleven studies evaluated the presence of CMBs; some considered exclusively deep brain and infratentorial locations, whereas others also included lobar CMBs. Advanced EPVSs were assessed in 5 studies, defined as more than 10 in the basal ganglia, the centrum semiovale, or the entire brain.

Quality Assessment

Variable quality was recorded across the included studies (total score range 4–10; Table S3). Nine studies scored fewer than 7 points, 12 scored 7 to 8 points, and 10 scored 9 to 10 points. Several studies lost points because of lack of representativeness of the recruited sample and because of the high proportion or nondescription of nonrespondents. Although most studies adjusted the results for demographic variables, only 21 studies controlled for CVD risk factors and 13 for renal function. On the positive side, only 6 studies had an inadequate sample size, and the majority of studies scored the maximum with regard to assessment of exposure and outcome.

Albuminuria in Association with SVDs: Meta-Analysis

When pooling effect estimates, albuminuria was associated with greater odds of having WMHs (OR = 1.70, 95% CI = 1.43–2.01; 18 studies; 13,548 subjects; Figure 2A), although moderate heterogeneity was noted ($I^2 = 44\%$, $P = .03$). This association persisted when WMHs were assessed as a dichotomous outcome (OR = 1.77, 95% CI = 1.46–2.14%; 14 studies; 12,229 subjects; 2,665 cases; $I^2 = 43\%$, $P = .04$) or continuously as WMH volume (Cohen *d*: 0.22; 95% CI = 0.01–0.42; 4 studies; 1,319 subjects; $I^2 = 48\%$, $P = .13$) (Figure S1). Greater odds of LIs (OR = 1.86, 95% CI = 1.49–2.31; 12 studies; 12,857 subjects; 998 cases; $I^2 = 27\%$, $P = .18$) (Figure 2B) and CMBs (OR = 1.78, 95% CI = 1.30–2.43; 8 studies; 7,645 subjects; 748 cases; $I^2 = 39\%$, $P = .12$; Figure 2C) were also found. After stratification according to CMB location, albuminuria was associated with deep brain (OR = 1.78, 95% CI = 1.18–2.70; 3 studies; 4,286 subjects; 197 cases; $I^2 = 10\%$, $P = .34$) but not lobar (OR = 0.92, 95% CI = 0.55–1.93; 4 studies; 3,311 subjects; 325 cases; $I^2 = 0\%$, $P = .72$) CMBs (Figure S2). Albuminuria was significantly associated with advanced EPVSs in the basal ganglia (OR = 1.78, 95% CI = 1.02–3.09; 2 studies; 1,388 subjects, 399 cases) and centrum semiovale (OR = 3.27, 95% CI = 1.49–7.20; 1,146 subjects, 460 cases) (Figure 2D).

The former associations persisted in sensitivity analyses according to study design, study population, albuminuria assessment, and quality score (Table 1). All associations also remained statistically significant between studies after adjusting for age, sex, CVD risk factors, and renal function. When studies referring to the general population were pooled, heterogeneity was resolved in the WMH and LI analyses while effect estimates retained their statistical significance.

Metaregression and Publication Bias Analyses

Metaregression analysis for WMHs and LIs did not identify any significant effect of major confounders (age, sex, hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, stroke, body mass index, eGFR, smoking status, total, low-density lipoprotein and high-density lipoprotein cholesterol levels, mean systolic and diastolic blood pressure) on the reported associations. Presence of publication bias assessed using the Egger test was documented for the overall WMH ($P = .005$) and LI ($P = .03$) analyses. After restricting analyses to studies of the highest quality, publication bias was no longer significant (Egger $P = .27$ for WMH; $P = .12$ for LI). Funnel plots are presented in Figure S3.

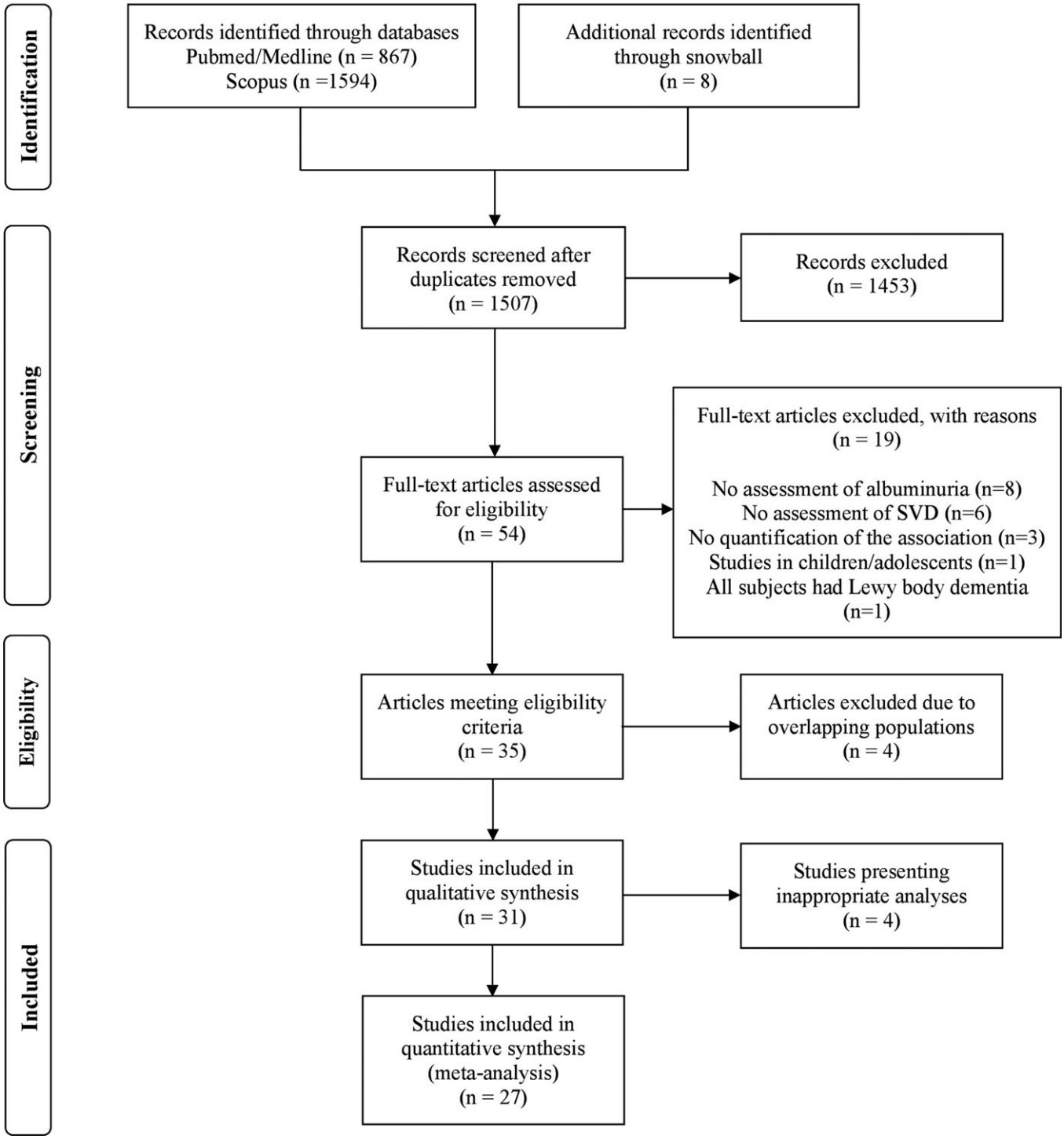

Figure 1. Flowchart on selection of eligible studies. Successive steps followed for identification of eligible studies from database search to meta-analysis.

Albuminuria in Association with SVD: Results of Studies Not Included in Meta-analysis

Four studies presented results in alternative analyses not fitting our quantitative synthesis, although the results were consistent with the meta-analysis. In particular, the Brain in Kidney Disease study[28] evaluated 240 subjects with CKD and controls and reported that a 10% increment in ACR was independently associated with an increase of 0.24% in WMH volume, but no association with CMBs was documented. A cross-sectional study of 568 individuals with hypertension without a history of stroke found that 1 SD increase in ACR was associated with higher odds for deep and infratentorial CMBs (OR = 2.03, 95% CI = 1.41–4.31), but no association was found for lobar CMBs.[29] A population-based study[30] found an association between baseline ACR and WMH volume after 7 years (β = 0.039, P = .05) and a stronger association when ACR

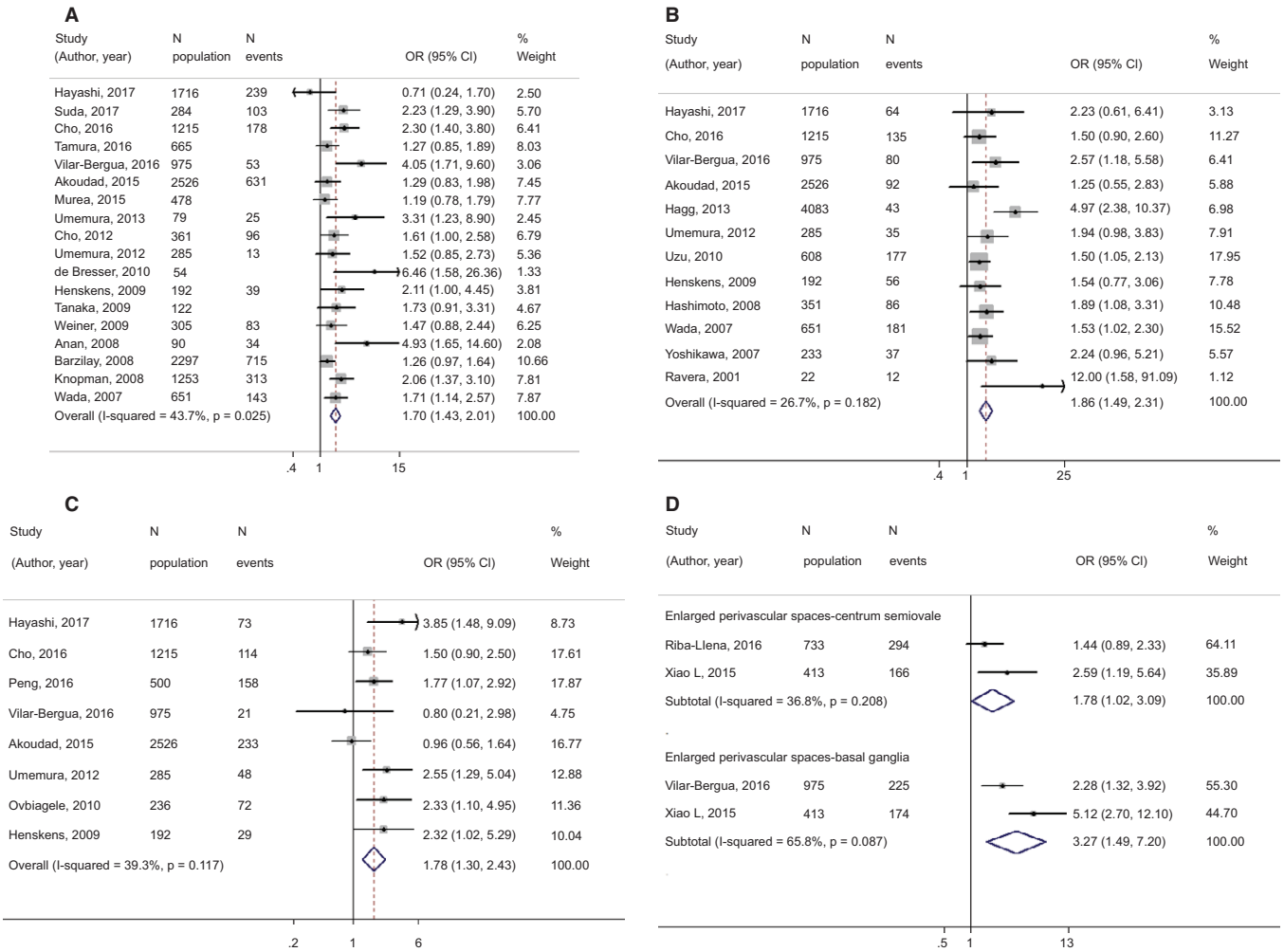

Figure 2. Association between albuminuria and (A) white matter hyperintensities, (B) lacunar infarcts, (C) cerebral microbleeds, and (D) enlarged perivascular spaces. The data markers correspond to odds ratios (ORs) for individual studies; shaded boxes around data markers reflect the statistical weight of the study; error bars indicate 95% confidence intervals (CIs); diamonds indicate pooled-effect estimates with 95% CIs.

and WMH were concurrently assessed ($\beta = 0.073$, $P < .001$). An analysis of the total burden of cerebral SVD (WMHs, LIs, CMBs, EPVSs) in 210 individuals with acute stroke found greater burden in subjects with proteinuria (OR = 2.15, 95% CI = 1.16–3.98).[31]

DISCUSSION

In this meta-analysis, albuminuria was associated with MRI markers of cerebral SVD, including WMHs, LIs, CMBs, and EPVSs. Despite moderate heterogeneity and statistically detectable publication bias, when sensitivity analyses were restricted to population-based studies with the lowest risk of bias, these associations did not lose their statistical significance. The metaregression analyses did not reveal any significant confounder that might mediate the reported associations, although a lack of cohort studies evaluating the longitudinal risk of cerebral SVD in individuals with albuminuria was also documented.

SVD is considered a generalized disorder of the microvasculature affecting different end organs with anatomical and hemodynamic similarities. Because the kidney and the brain are both exposed to high circulatory flow with low resistance, common pathogenetic processes and risk factors, such as aging and high arterial pressure, could lead to similar microvascular injury in both organs.[32] Endothelial dysfunction could lead to glomerular leakage of protein in the kidney and disruption of blood-brain barrier integrity in cerebral capillaries,[33,34] which has been suggested as the underlying cause of the observed neuroimaging parenchymal changes in SVD.[35] Therefore, SVD in one organ could indicate similar changes in the other.

Although it has been suggested that cerebral SVD should be treated as a unique disease,[3,33] the majority of studies included in this review examined specific biomarkers, precluding a meta-analysis for a combined SVD outcome, although the pooled effect estimates for the 3 main outcomes (WMHs, LIs, CMBs) were of similar size (ORs between 1.70 and 1.86). For CMBs, the effect was evident only when they were located in the deep brain and not in strictly lobar locations. This is expected, because SVD is mainly located in the perforating arterioles supplying deep brain structures,[33] whereas strictly lobar CMBs could indicate other underlying causes—mainly cerebral amyloid angiopathy.[36]

Table 1. Sensitivity and Subgroup Analyses for Association Between Albuminuria and Risk of White Matter Hyperintensities, Lacunar Infarcts, and Cerebral Microbleeds

Sensitivity and Subgroup Analyses (Albuminuria vs no Albuminuria)	White Matter Hyperintensities			Lacunar Infarcts			Cerebral Microbleeds		
	k	OR (95% CI)	Heterogeneity, I^2, P-Value	k	OR (95% CI)	Heterogeneity, I^2, P-Value	k	OR (95% CI)	Heterogeneity, I^2, P-Value
Overall analysis	18	1.70 (1.43–2.01)	44%, .03	12	1.86 (1.49–2.31)	27%, .18	8	1.78 (1.30–2.43)	39%, .12
Study design									
Cross-sectional and case-control studies	18	1.70 (1.43–2.01)	44%, .03	11	1.68 (1.40–2.01)	0%, .71	8	1.78 (1.30–2.43)	39%, .12
Prospective studies	0	—	—	1	4.97 (2.38–10.37)	—	0	—	—
Study population									
General population	8	1.48 (1.22–1.80)	37%, .14	5	1.59 (1.23–2.06)	0%, .90	3	1.62 (0.83–3.14)	70%, .04
Individuals with hypertension	4	1.81 (1.16–2.83)	52%, .10	4	2.14 (1.33–3.46)	24%, .27	3	2.06 (1.19–3.56)	17%, .30
Individuals with diabetes	4	3.09 (1.69–5.65)	35%, .20	3	2.44 (1.15–5.16)	76%, .02	0	—	—
Individuals with clinically overt stroke	1	1.84 (1.29–2.64)	0%, .38	0	—	—	2	1.92 (1.27–2.92)	0%, .55
Exposure assessment									
Urinary albumin-to-creatinine ratio/24-h urinary albumin excretion	17	1.73 (1.46–2.04)	42%, .04	11	1.86 (1.49–2.31)	33%, .14	5	1.52 (1.01–2.29)	42%, .14
Dipstick (proteinuria)	1	0.71 (0.24–1.70)	—	1	2.23 (0.61–6.41)	—	3	2.20 (1.47–3.31)	10%, .33
Level of adjustment									
Age, sex	9	1.73 (1.31–2.29)	62%, .007	8	1.96 (1.47–2.60)	31%, .18	5	1.54 (1.02–2.31)	44%, .13
Cardiovascular disease risk factors[a]	9	1.75 (1.32–2.31)	63%, .006	7	1.95 (1.42–2.68)	40%, .12	4	1.35 (0.89–2.02)	31%, .23
Renal function	6	1.67 (1.17–2.34)	66%, .01	4	1.85 (1.33–2.58)	0%, .71	3	1.68 (1.02–2.78)	29%, .24
All of the above	6	1.67 (1.17–2.34)	66%, .01	4	1.85 (1.33–2.58)	0%, .71	2	1.38 (0.86–2.23)	0%, .39
Study quality, Newcastle-Ottawa Scale score									
9–10	8	1.62 (1.31–2.00)	47%, .07	5	1.65 (1.28–2.11)	0%, .70	3	1.18 (0.82–1.68)	0%, .42
7–8	3	1.50 (0.86–2.62)	51%, .13	5	2.23 (1.42–3.50)	53%, .08	4	2.26 (1.62–3.14)	0%, .50
<7	7	2.04 (1.39–2.99)	51%, .06	2	3.41 (0.48–24.26)	72%, .06	1	2.32 (1.02–5.29)	—

Heterogeneity *P*-values derived from Cochran Q test.

[a]Blood pressure, diabetes mellitus, cholesterol level, body mass index, history of cardiovascular disease.

k = number of study arms; OR = odds ratio; CI = confidence interval.

It is challenging to disentangle the potentially confounding effects of comorbidities, particularly CKD, diabetes mellitus, and hypertension. Anemia, hypertension, hyperparathyroidism, acidosis, hyperhomocysteinemia, chronic inflammation, uremic toxins accumulation, and atherogenic effects that could directly or indirectly affect the brain microvasculature accompany CKD.[37,38] In individuals with diabetes mellitus, microvascular damage is a complication, and microalbuminuria is used as a marker of renal insult,[39] and cerebral SVD is more common than in the general population.[40] Similarly, both organs are common targets of hypertension, with microvascular complications constituting the first subclinical stage of damage,[41] although our results indicate that the observed associations are at least partially independent of these comorbidities, because they were evident even in population-based studies controlling for these confounders. The potentially plausible explanations are not mutually exclusive but could act concurrently.

In our recent meta-analysis, we showed that albuminuria was associated with greater risk of dementia and cognitive decline in the general population cross-sectionally and longitudinally.[14] When classifying according to subtype, the effect size was stronger for vascular dementia, but the odds remained high for Alzheimer's disease. In addition, albuminuria was associated with deficits in cognitive domains primarily affected in vascular dementia. Given the correlation between albuminuria and generalized endothelial dysfunction[13] and the relationship between cerebral SVD and cognitive decline,[42] vascular dementia,[2] and Alzheimer's disease,[43] the results (highlighting an independent association between albuminuria and cerebral SVD) of the current meta-analysis lend support to the hypothesis that cerebral SVD may partially mediate the association between albuminuria and dementia.

Our results should be interpreted in the context of methodological considerations. There was moderate heterogeneity in the major analyses for WMHs and CMBs, which could be attributed to specific between-study differences. First, only 11 studies were conducted in a population-based context, and excluding patient-based studies of individuals with hypertension, diabetes mellitus, or stroke, resolved the heterogeneity. Second, with regard to exposure assessment, some studies examined proteinuria using dipstick, which has a diagnostic accuracy highly correlated with but lower than that of ACR;[21] once more, sensitivity analyses did not modify the reported associations. Third, there was considerable variability in SVD definitions, mainly regarding WMHs, with some studies examining only high-grade WMHs determined using different scoring systems and others examining WMH volume; regardless of the method of assessment, the results of meta-analysis were the same. Fourth, there was variability in the MRI protocols and strength of MRI scanners in the studies evaluating CMBs.

In addition to heterogeneity, different statistical approaches did not allow us to include all of the eligible studies in the quantitative synthesis, but given the similar findings in the excluded studies, selection bias appears to be unlikely. In addition, statistically detectable publication bias was found in the main analyses for WMHs and LIs; as expected, this was probably because of the small, patient-based studies with high risk of bias, because the sensitivity analysis for high-quality studies confirmed the robustness of the findings diminishing publication bias. As identified according to the risk-of-bias assessment, many studies did not control for confounders, but once more, sensitivity analysis for studies sufficiently addressing the major confounders confirmed our findings. An additional drawback of the included studies was that they did not assess the effect of prospective albuminuria remission or progression on risk and progression of cerebral SVD. Previous randomized controlled trials have shown that angiotensin axis blockade with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers leads to microalbuminuria remission and subsequently to better renal and cardiovascular outcomes in individuals with hypertension and diabetes mellitus,[44,45] but its effect on cerebrovascular health and cognition has not been examined. Last and most important, the lack of prospectively designed studies in the general population evaluating the association between albuminuria and incident SVD remains the major methodological shortcoming of the published literature.

In conclusion, this meta-analysis supports an independent association between albuminuria and SVD in the brain as assessed using different neuroimaging markers. Current evidence indicates that shared microvascular pathology in the kidney and the brain is the main contributing mechanism, possibly suggesting that brain microvasculature damage could be evaluated via peripheral systemic microvascular disease biomarkers. Thus, that cerebral SVD mediates the previously described association between albuminuria and dementia supports our initial hypothesis. Prospective population-based studies are required to evaluate the longitudinal association between albuminuria and cerebral SVD progression.

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Conflict of Interest: The authors have no conflicts.

Author Contributions: MG: Study concept and design, acquisition of data, data analysis, interpretation of data, drafting first version of manuscript. DC: Acquisition of data, data analysis, drafting first version of manuscript. GT: Study concept and design, interpretation of data, critical revision of manuscript for intellectual content. EP: Study concept and design, interpretation of data, revision of manuscript for intellectual content. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Supplementary References. Complete reference list of eligible studies included in this systematic review.

Methods S1. Detailed search strategy used for Pubmed and Medline for identification of eligible studies for this systematic review.

Table S1. Meta-analysis of Observational Studies in Epidemiology guidelines checklist for authors.

Table S2. Characteristics of eligible studies included in qualitative synthesis.

Table S3. Evaluation of the quality of included studies based on the Newcastle-Ottawa scale.

Figure S1. Association of albuminuria with white matter hyperintensities, when assessed as (A) a dichotomous outcome or (B) continuously as WMH volume.

Figure S2. Association of albuminuria with cerebral microbleeds (CMBs) by their location in the brain (lobar and deep brain).

Figure S3. Funnel plots depicting publication bias in meta-analyses for the association of albuminuria with (A) white matter hyperintensities (WMHs), (B) lacunar infarcts (LIs), and cerebral microbleeds (CMBs).