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ORIGINAL ARTICLE
Epidemiology

Association of Albuminuria With White Matter Hyperintensities Volume on Brain Magnetic Resonance Imaging in Elderly Japanese

— The Hisayama Study —

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Background: Both chronic kidney disease and brain white matter hyperintensities (WMH) are known to be risk factors of dementia and mortality.

Methods and Results: In 2012, 1,214 community-dwelling Japanese subjects aged ≥65 years underwent brain magnetic resonance imaging (MRI) scans and a comprehensive health examination. This study investigated associations of the urinary albumin : creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR) with the WMH volume to intracranial volume (WMHV : ICV) ratio, and the association of the combination of UACR and the WMHV : ICV ratio with cognitive decline and mortality risk. The geometric mean of the WMHV : ICV ratio was 0.223% in the entire study population, and increased significantly with higher UACR levels after adjusting for potential confounding factors (0.213% for normoalbuminuria, 0.248% for microalbuminuria, and 0.332% for macroalbuminuria; P_{trend}=0.01). In contrast, there was no clear association between eGFR and the WMHV : ICV ratio. Compared with subjects with normoalbuminuria and a smaller WMHV : ICV ratio (<0.257% [median]), subjects with albuminuria and a larger WMHV : ICV ratio (≥0.257%) had higher probabilities of cognitive decline at baseline and all-cause death during the follow-up.

Conclusions: This study suggests that subjects with albuminuria have a greater risk of WMH enlargement and that the combination of albuminuria and WMH enlargement increases the risk of cognitive decline and all-cause mortality in an elderly Japanese population.

Key Words: Albuminuria; Cognitive decline; General population; Mortality; White matter hyperintensities

Albuminuria and reduced estimated glomerular filtration rate (eGFR) are components of chronic kidney disease (CKD), and both have been acknowledged as risk factors for stroke, dementia, and death.[1–6] The major causes of CKD include small vessel diseases in the kidney due to glomerular endothelium dysfunction.[7] Conversely, white matter hyperintensities (WMH) in the brain are a type of cerebral small vessel disease often observed on T_2-weighted or fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) among the elderly and have been reported to be associated with an increased risk of the development of stroke, dementia, and death.[8–10] Disorders of the small blood vessels in the kidney and brain are considered to be closely linked because of their anatomical and hemodynamic similarities.[11] In this regard, it is inferred that albuminuria and brain WMH have common pathological mechanisms.

Several cross-sectional observational studies conducted in Western countries have reported that elevated urinary albumin levels are significantly associated with larger WMH volumes, which were measured quantitatively by automatic techniques.[12–15] Only 1 study has used automatic quantitative evaluation of WMH in Asian populations with different genetic and lifestyle backgrounds.[16] Moreover, several epidemiological studies have examined the association of albuminuria with WMH enlargement in general Asian populations.[17–21] However, in these studies the extent of WMH was evaluated by semiquantitative methods, such

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as the Fazekas scale,[22] which tended to be subjective and less sensitive in discrimination than the automated volumetric technique of WMH.[23,24] In addition, no studies have investigated the association of the combination of albuminuria and WMH enlargement with clinical outcomes, such as cognitive decline and all-cause mortality.

The aims of the present study were to investigate the association of urinary albumin or eGFR with WMH enlargement using an automated volumetric technique, and to examine the association of the combination of albuminuria and WMH enlargement with clinical outcomes, such as cognitive decline and all-cause mortality, using cross-sectional and prospective data from a general Japanese elderly population.

Methods

Study Population

The Hisayama Study was established in 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan. In this town, elderly residents have been examined for comprehensive screening surveys of cognitive function and activities of daily living every 5–7 years since 1985.[25–27] In 2012, 1,906 residents aged ≥65 years (93.6% of the town's total population in this age group) participated in the screening survey, and 1,342 (70.4%) underwent brain MRI.[27] One subject who refused to participate in the study was excluded, as were another 36 without sufficient MRI data for the evaluation of WMH volume, 90 without available urinary and/or blood samples, and 1 without electrocardiogram (ECG) records. The remaining 1,214 subjects (533 men, 681 women) were eligible for the present study.

Measurements of Urinary Albumin : Creatinine Ratio (UACR) and eGFR

Spot urine samples were obtained at the health examination. Urinary creatinine and albumin were measured using the turbidimetric immunoassay method and the UACR was calculated by dividing urinary albumin values by urinary creatinine concentrations. The UACR was categorized using the cut-off points from the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[28] as follows: normoalbuminuria, UACR <30.0 mg/g; microalbuminuria, UACR 30.0–299.9 mg/g; and macroalbuminuria, UACR ≥300.0 mg/g. In addition, normoalbuminuria was further divided into tertiles as follows: low-normal (≤7.3 mg/g), medium-normal (7.4–12.8 mg/g), and high-normal (12.9–29.9 mg/g). Serum creatinine concentrations were measured using an enzymatic method. eGFR was calculated using the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation with a Japanese coefficient of 0.813, as reported previously.[2,29] eGFR was classified into 3 groups according to the KDIGO 2012 guideline[28] as follows: ≥60, 30–59, and <30 mL/min/1.73 m^2.

Assessment of WMH Enlargement on Brain MRI

The brains of the participants were scanned using a 1.5-Tesla MRI scanner (Intera Pulsar; Philips Medical Systems, Best, Netherlands) with a multichannel head coil, as described previously.[27] We collected 3-dimensional T_1-weighted images, conventional T_1- and T_2-weighted images, FLAIR images, T_2*-weighted images, and magnetic resonance angiography of the brain. WMH lesions on T_1-weighted and FLAIR images were segmented using the Lesion Segmentation Toolbox (LST) for SPM12.[30] We first tried to identify the optimal threshold of signal intensity (κ value) to determine WMH lesions using a subsample of 128 subjects (~10%) randomly selected from the study population. For all subjects in this subsample, WMH volumes were measured automatically using the LST with various thresholds of signal intensity (ranging from 0.05 to 1.00, at intervals of 0.05). In addition, 2 trained stroke neurologists independently measured WMH volumes for all subjects in the subsample manually using the FLAIR images. Finally, by comparing the WMH volumes measured by LST to those measured by the neurologists (taken as the average of 2 measurements), we determined that the optimum threshold of signal intensity to identify WMH lesions in this study was 0.15. Under this condition, the inter-rater concordance of WMH volumes measured by LST and the neurologists was the highest (inter-class correlation coefficient=0.75). Accordingly, WMH volumes measured by LST with 0.15 as a threshold of intensity were used for all participants in the main analysis. The intracranial volume (ICV) was calculated as the sum of the gray matter volume, white matter volume, and cerebrospinal fluid volume. Automatic measurements of gray matter volume, white matter volume, and cerebrospinal fluid volume of the brain were made using VBM8 Toolbox, version 435 (University of Jena, Jena, Germany; http://dbm.neuro.uni-jena.de/vbm/) in SPM8 running in MATLAB (MathWorks, Natick, MA, USA), as described previously.[27] In the present study, the ratio of WMH volume to ICV volume (WMHV : ICV; %) was used as an indicator of WMH enlargement.[31,32] Larger and smaller WMHV : ICV ratios were defined as those ≥0.257% (median) and <0.257%, respectively: the median value of the WMHV : ICV ratio was used to divide patients into 2 groups with minimal arbitrariness, because there has been no consensus on an appropriate cut-off value for elderly populations.

Assessment of Cognitive Function

The Mini-Mental State Examination (MMSE)[33] was administered to all participants at the baseline comprehensive screening surveys. The MMSE was performed face to face in a quiet room by a trained clinical psychologist and checked by an expert psychiatrist and a stroke physician in the study team. Cognitive decline was defined as an MMSE score <24 points.[33]

Follow-up Surveys for Mortality

The subjects were followed-up prospectively from the date of baseline examination to 30 November 2016 or until death (median 4.3 years; interquartile range [IQR] 4.3–4.4 years). As described previously,[34] health information was collected annually by health examination and by letter or telephone for subjects who did not undergo the health examination or who had moved away from the town. In addition, information about death was collected through a daily monitoring system established by a study team consisting of local physicians and members of the town's Health and Welfare Office. During the follow-up period, 77 subjects died, and there were no subjects who could not be traced or contacted.

Covariates

In the baseline examination, a self-administered question-

Table 1. Age- and Sex-Adjusted Baseline Characteristics of Participants According to UACR or eGFR Levels

	UACR levels				eGFR levels (mL/min/1.73 m²)			
	Normoalbuminuria (n=908)	Microalbuminuria (n=263)	Macroalbuminuria (n=43)	P_{trend}	≥60 (n=844)	30–59 (n=354)	<30 (n=16)	P_{trend}
Age (years)[A]	74±0.2	76±0.4	75±1.0	<0.001	72±0.2	77±0.4	81±2.7	<0.001
Women (%)[B]	56.9	55.3	44.1	0.17	65.4	52.5	34.3	<0.001
Hypertension (%)	66.7	80.5	97.6	<0.001	64.4	70.4	74.7	0.11
SBP (mmHg)	132±0.6	140±1.1	152±2.7	<0.001	134±0.7	132±1.2	129±8.1	0.20
DBP (mmHg)	75±0.3	79±0.6	83±1.6	<0.001	76±0.4	75±0.7	70±4.7	0.15
Antihypertensive agents (%)	49.9	67.6	92.9	<0.001	45.2	57.1	75.2	0.002
Diabetes (%)	17.3	35.2	59.4	<0.001	19.9	19.6	38.0	0.86
Hypercholesterolemia (%)	53.9	58.8	81.1	0.001	55.1	60.2	52.8	0.26
Total cholesterol (mg/dL)[C]	200±1.1	192±2.1	200±5.1	0.02	202±1.4	200±2.2	169±15.0	0.28
Lipid-lowering agents (%)	32.4	41.1	57.2	<0.001	30.4	36.6	41.6	0.10
BMI (kg/m²)	22.8±0.1	23.8±0.2	24.2±0.5	<0.001	23.0±0.1	23.3±0.2	21.9±1.5	0.30
ECG abnormalities (%)	13.6	22.7	25.2	<0.001	13.2	11.1	0.0	0.28
Current alcohol intake (%)	39.4	39.1	45.2	0.71	37.4	36.0	37.2	0.75
Current smoking (%)	5.7	5.4	6.9	0.89	5.9	1.9	34.1	0.04
Regular exercise (%)	19.8	17.6	16.2	0.35	18.4	24.7	23.2	0.06
eGFR (mL/min/1.73 m²)	64.8±0.6	63.1±0.6	52.7±0.6	<0.001	70.1±0.2	52.6±0.4	25.0±2.4	<0.001
eGFR <60 mL/min/1.73 m² (%)	25.7	32.2	54.4	<0.001				
UACR (mg/g)	9.6 (9.3–10.0)	63.5 (59.3–68.1)	590.0 (498.6–698.1)	<0.001	15.0 (13.7–16.4)	15.9 (13.8–18.4)	42.5 (16.2–111.3)	0.005

Values are shown as the mean±SD or as percentages, except for urinary albumin:creatinine ratio (UACR), which is given as the geometric mean (95% confidence interval [CI]) because of the skewed distribution. Normoalbuminuria was defined as UACR <30.0 mg/g, microalbuminuria was defined as UACR 30.0–299.9 mg/g, and macroalbuminuria was defined as UACR ≥300.0 mg/g. [A]Adjusted for sex. [B]Adjusted for age. [C]To convert cholesterol in mg/dL to mmol/L, multiply values by 0.0259. BMI, body mass index; DBP, diastolic blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

naire concerning the current use of antihypertensive agents, insulin, oral glucose-lowering agents, and lipid-lowering medication, smoking habits, alcohol intake, and physical activity was completed by each participant and checked by trained interviewers. Smoking habits and alcohol intake were categorized as current use or no current use. Regular exercise was defined as engaging in sports 3 or more times a week during leisure time. Blood pressure was measured 3 times after the subject had rested for at least 5 min in the sitting position using an automated sphygmomanometer (BP-203 RVIIIB; Omron Healthcare, Kyoto, Japan). The mean of the 3 measurements was used for the present analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and/or current treatment with antihypertensive agents. Diabetes was defined as fasting plasma glucose ≥126 mg/dL, 2-h 75-g oral glucose post-load or casual glucose levels ≥200 mg/dL, and/or current use of oral glucose-lowering agents or insulin. Serum total cholesterol (TC) levels were measured enzymatically. Hypercholesterolemia was defined as serum TC ≥220 mg/dL or current use of lipid-lowering medication. Body height and weight were measured in light clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). ECG abnormalities were defined as left ventricular hypertrophy (Minnesota Code 3-1), ST depression (4-1, 2, 3), or atrial fibrillation (8-3).

Statistical Analysis

The means and frequencies of risk factors across UACR or eGFR levels were compared by linear or logistic regression analysis, respectively. The WMHV:ICV ratio was natural log (ln) transformed because its distribution was skewed. For 2 participants who had no WMH (WMHV:ICV ratio=0%), their WMHV values were substituted by the next smallest value (0.0021 mL) before the calculation of ln-transformed WMHV:ICV ratios. Age- and sex-adjusted or multivariable-adjusted geometric means of WMHV:ICV ratios with 95% confidence intervals (CIs) according to UACR or eGFR levels were estimated and compared using analysis of covariance (ANCOVA). In the multivariable-adjusted model, age, sex, and some potential confounders (hypertension, diabetes, hypercholesterolemia, BMI, ECG abnormalities, smoking habits, alcohol intake, and regular exercise), and either eGFR or log-transformed UACR were included. A sensitivity analysis was performed after excluding participants with cognitive decline at baseline. The heterogeneity in the association of UACR levels with the WMHV:ICV ratio between subgroups was tested by adding a multiplicative interaction term in the relevant

Table 2. Geometric Mean (95% CIs) of the WMHV : ICV Ratio According to UACR or eGFR Levels

	No. subjects	Age- and sex-adjusted		Multivariable-adjusted	
		Geometric mean (95% CI) of the WMHV : ICV ratio (%)	P-value	Geometric mean (95% CI) of the WMHV : ICV ratio (%)	P-value
UACR levels[A]					
Normoalbuminuria (UACR <30.0 mg/g)	908	0.209 (0.193–0.228)	Ref.	0.213 (0.195–0.231)	Ref.
Microalbuminuria (UACR 30.0–299.9 mg/g)	263	0.258 (0.221–0.301)	0.04	0.248 (0.212–0.291)	0.17
Macroalbuminuria (UACR ≥300.0 mg/g)	43	0.357 (0.244–0.523)	0.01	0.332 (0.223–0.493)	0.06
P_{trend}			<0.001		0.01
eGFR levels[B]					
≥60 mL/min/1.73 m^2	844	0.222 (0.203–0.242)	Ref.	0.223 (0.204–0.243)	Ref.
30–59 mL/min/1.73 m^2	354	0.225 (0.196–0.259)	0.97	0.224 (0.195–0.258)	0.99
<30 mL/min/1.73 m^2	16	0.272 (0.145–0.511)	0.78	0.242 (0.129–0.456)	0.96
P_{trend}			0.67		0.85

[A]Adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, BMI, ECG abnormalities, smoking habit, alcohol intake, regular exercise, and eGFR in the multivariable-adjusted model. [B]Adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, BMI, ECG abnormalities, smoking habit, alcohol intake, regular exercise, and log-transformed UACR in the multivariable-adjusted model. ICV, intracranial volume; WMHV, white matter hyperintensities volume. Other abbreviations as in Table 1.

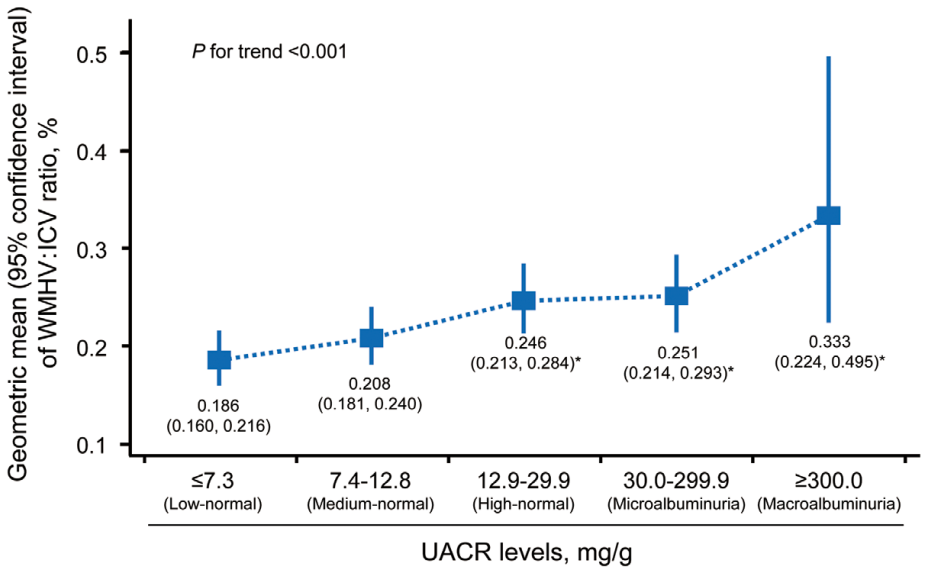

Figure 1. Multivariable-adjusted geometric means of the white matter hyperintensities volume to intracranial volume (WMHV : ICV) ratio according to the tertiles of the urinary albumin : creatinine ratio (UACR) in subjects with normoalbuminuria (low-normal, medium-normal, and high-normal) as well as in subjects with microalbuminuria and macroalbuminuria. Data show the geometric mean (95% confidence intervals) of the WMHV : ICV ratio at each UACR level. Values were adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, body mass index, electrocardiogram abnormalities, smoking habit, alcohol intake, regular exercise, and estimated glomerular filtration rate. *P<0.05 compared with the low-normal group.

statistical model. Logistic regression analysis was used to estimate odds ratios (ORs) with 95% CIs for the cognitive decline at baseline. A Cox proportional hazards model was used to estimate hazard ratios (HRs) with 95% CIs for the development of all-cause death during follow-up. The interaction of UACR and the WMHV : ICV ratio in the association with cognitive decline or all-cause death was assessed by adding an interaction term in the relevant statistical models.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Two-tailed P<0.05 was considered significant in all analyses.

Ethical Considerations

This study was approved by the Kyushu University Institutional Review Board for Clinical Research (Reference no. 2019-499) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Table 3. Association of the Combination of Albuminuria and WMHV : ICV Ratio With Cognitive Decline (Mini-Mental State Examination Score <24)

	No. subjects	No. events	Age- and sex-adjusted		Multivariable-adjusted	
			Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
UACR levels						
Normoalbuminuria (UACR <30.0 mg/g)	908	89	1.00	Ref.	1.00	Ref.
Albuminuria (UACR ≥30.0 mg/g)	306	48	1.39 (0.94–2.06)	0.10	1.42 (0.93–2.16)	0.10
WMHV : ICV ratio						
Smaller (<0.257%)	607	38	1.00	Ref.	1.00	Ref.
Larger (≥0.257%)	607	99	1.88 (1.23–2.87)	0.004	1.86 (1.21–2.86)	0.005
Combination of UACR levels and WMHV : ICV ratio						
Normoalbuminuria with smaller WMHV : ICV ratio	488	28	1.00	Ref.	1.00	Ref.
Normoalbuminuria with larger WMHV : ICV ratio	420	61	1.86 (1.13–3.05)	0.01	1.89 (1.15–3.12)	0.01
Albuminuria with smaller WMHV : ICV ratio	119	10	1.37 (0.64–2.93)	0.42	1.50 (0.69–3.25)	0.31
Albuminuria with larger WMHV : ICV ratio	187	38	2.44 (1.39–4.27)	0.002	2.48 (1.38–4.47)	0.002
$P_{interaction}$				0.93		0.78

Adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, BMI, ECG abnormalities, smoking habit, alcohol intake, regular exercise, and eGFR in the multivariable model. Abbreviations as in Tables 1,2.

Results

Baseline Characteristics of the Study Population

Of all 1,214 subjects, 681 (56.1%) were women and the mean (±SD) age was 74.3±6.6 years. The frequency of microalbuminuria, macroalbuminuria, and reduced eGFR (defined as eGFR <60 mL/min/1.73 m^2) was 21.7% (n=263), 3.5% (n=43), and 30.5% (n=370), respectively. The age- and sex-adjusted clinical characteristics of the study subjects by UACR and eGFR levels are listed in **Table 1**. The mean age and the proportion of hypertension, diabetes, hypercholesterolemia, obesity, ECG abnormalities, and reduced eGFR increased significantly with higher UACR. Similar associations were observed when the normoalbuminuria group was further categorized into 3 tertile categories (**Supplementary Table 1**). With regard to eGFR levels, the proportion of subjects who used antihypertensive agents, the proportion of current smokers, the mean age, and the geometric mean of UACR all increased significantly with lower eGFR, whereas subjects with lower eGFR were significantly less likely to be female (**Table 1**).

Association of UACR or eGFR With WMHV : ICV Ratio

Associations between UACR or eGFR and the WMHV : ICV ratio are given in **Table 2**. The age- and sex-adjusted geometric mean value of the WMHV : ICV ratio increased significantly with higher UACR (normoalbuminuria: 0.209%; microalbuminuria: 0.258%; macroalbuminuria: 0.357%; P_{trend}<0.001). Compared with the normoalbuminuria group as a reference group, the microalbuminuria and macroalbuminuria groups had a significantly larger WMHV : ICV ratio. A similar association was observed even after adjusting for potential confounding factors (normoalbuminuria: 0.213%; microalbuminuria: 0.248%; macroalbuminuria: 0.332%; P_{trend}=0.01), and sensitivity analysis after excluding 137 participants with cognitive decline also showed a significant association (normoalbuminuria: 0.193%; microalbuminuria: 0.229%; macroalbuminuria: 0.279%; P_{trend}=0.03 [multivariable-adjusted]). To investigate whether elevated UACR levels within the normal range were associated with WMH enlargement, the normoalbuminuria group was further divided into tertiles, as shown in **Figure 1**. The high-normal group, as well as the microalbuminuria and macroalbuminuria groups, had significantly higher WMHV : ICV ratios than the low-normal group. A similar association was observed after exclusion of participants with cognitive decline (data not shown). In contrast, no clear association was observed between eGFR levels and the WMHV : ICV ratio in either age- and sex-adjusted or multivariable-adjusted models (**Table 2**).

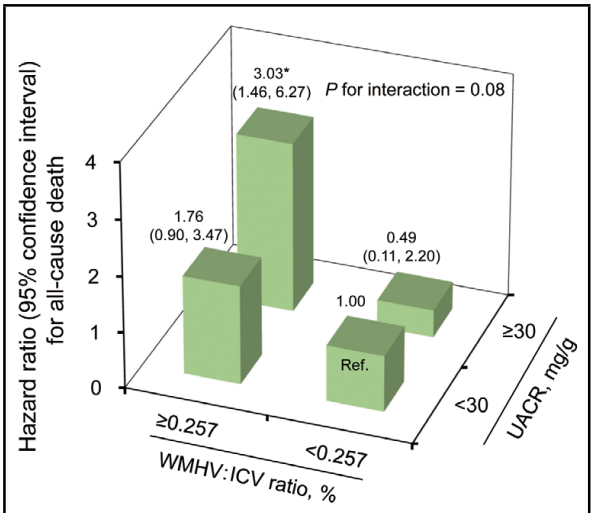

Figure 2. Association of the combination of albuminuria and the white matter hyperintensities volume to intracranial volume (WMHV : ICV) ratio with all-cause death. Data are shown as hazard ratios with 95% confidence intervals. Values were adjusted for age, sex, hypertension, diabetes, hypercholesterolemia, body mass index, electrocardiogram abnormalities, smoking habit, alcohol intake, and regular exercise. *P<0.05 compared with the reference (Ref.) group (urinary albumin : creatinine ratio [UACR] <30 mg/g and WMHV : ICV ratio <0.257%).

The association between UACR levels and WMHV : ICV ratio was analyzed among subgroups of subjects with

major cardiovascular risk factors. As indicated in **Supplementary Table 2**, there was no evidence of heterogeneity in the association between UACR and the WMHV : ICV ratio among the subgroups stratified by age, sex, hypertension, diabetes, or current smoking ($P_{heterogeneity}>0.4$ for all).

Association of UACR Levels or WMHV : ICV Ratio With Cognitive Decline

Next, the cross-sectional association of UACR levels or WMHV : ICV ratio with cognitive decline at baseline was investigated (**Table 3**). A larger WMHV : ICV ratio (≥0.257% [median]) was significantly associated with a higher probability of cognitive decline (multivariable-adjusted OR 1.86; 95% CI 1.21–2.86; P=0.005), whereas the association between albuminuria (UACR ≥30.0 mg/g) and cognitive decline did not reach statistical significance (multivariable-adjusted OR 1.42; 95% CI 0.93–2.16; P=0.10). We then analyzed the association of the combination of albuminuria and larger WMHV with cognitive decline. Subjects with albuminuria and a larger WMHV : ICV ratio had a significantly greater probability of cognitive decline than those with normoalbuminuria and a smaller WMHV : ICV ratio (multivariable-adjusted OR 2.48; 95% CI 1.38–4.47; P=0.002). There was no evidence of an interaction between UACR levels and the WMHV : ICV ratio on cognitive decline ($P_{interaction}=0.78$).

Association of UACR Levels or WMHV : ICV Ratio With the Risk of Mortality

Finally, the association of UACR levels or WMHV : ICV ratio with the risk of all-cause mortality was investigated using prospective longitudinal data with a median follow-up of 4.3 years. Subjects with a larger WMHV : ICV ratio had a significantly higher risk of all-cause mortality than those with a smaller WMHV : ICV ratio (multivariable-adjusted HR 2.46; 95% CI 1.35–4.48; P=0.003), but the association between albuminuria and the risk of all-cause mortality failed to reach statistical significance (multivariable-adjusted HR 1.50; 95% CI 0.92–2.46; P=0.11). As shown in **Figure 2**, the multivariable-adjusted HR for all-cause death was significantly higher in subjects with albuminuria and a larger WMHV : ICV ratio than in those with normoalbuminuria and a smaller WMHV : ICV ratio (HR 3.03; 95% CI 1.46–6.27; P=0.003). We found no significant interaction between UACR levels and the WMHV : ICV ratio on all-cause death ($P_{interaction}=0.08$).

Discussion

In the present study we demonstrated that the WMHV : ICV ratio increased significantly with higher UACR levels, even among subjects whose UACR was within the normal range. This association remained unchanged after adjusting for potential confounding factors and after excluding the subjects with cognitive decline. Conversely, we did not observe a clear association between reduced eGFR and the WMHV : ICV ratio. In addition, the combination of albuminuria and a larger WMHV : ICV ratio increased the probability of cognitive decline at baseline and the risk of all-cause mortality during follow-up.

Previous epidemiological studies have shown that elevated urinary albumin is associated with larger WMHV,[12–16] which is consistent with the findings of the present study. This study showed that increased urinary albumin, within the normal range, was significantly associated with larger WMHV in a general elderly population. In support of this finding, the Heart Outcomes Prevention Evaluation Study demonstrated that UACR, even within the normal range, was associated with increased risk for cardiovascular events.[35] The results of the present and that previous study suggest that urinary albumin, even within the normal range, may be a useful early marker for cardiovascular and cerebral small vessel diseases. Conversely, we found no evidence of a clear association between reduced eGFR and the WMHV : ICV ratio. The Genetics of Microangiopathic Brain Injury Study also failed to show a clear association between eGFR and WMHV.[12] In contrast, several previous studies showed that worse kidney function is associated with a larger WMHV.[15,16,36,37] The reason for the discrepancy among studies is unclear, but may be due to differences in the distribution of age and other background characteristics (e.g., older population and a small number of participants with advanced kidney dysfunction in the present study), as well as the genetic background of the study participants. The association between eGFR and WMH enlargement should be reviewed in other large-scale population studies or meta-analyses.

There are several possible mechanisms that could explain the association between albuminuria and WMH. First, albuminuria may be a marker for the accumulation of other conventional risk factors for WMH, such as hypertension and diabetes. However, the association between albuminuria and WMHV remained significant even after adjustment for these risk factors, indicating that mechanisms other than the accumulation of conventional risk factors may exist. Second, albuminuria may be a marker for endothelial dysfunction in the kidney. The kidney and brain are hemodynamically similar in that their small blood vessels diverge directly from large vessels, and thus they are continuously perfused with large amounts of blood with low vascular resistance.[38,39] Therefore, these organs are vulnerable to vascular endothelial damage when exposed to high arterial pressure under common vascular risk factors.[11] Vascular endothelial dysfunction induces a reduction in endothelial nitric oxide synthesis, an increase in oxidative stress, and activation of inflammation. These effects, in turn, can lead to serum protein leaks due to hypervascular permeability in glomerular endothelial cells and disorders of the blood-brain barrier, thereby promoting albuminuria and cerebral small vessel diseases such as WMH.[40–43]

In the present study, increased UACR was associated with WMH enlargement even in the sensitivity analysis after exclusion of participants with cognitive decline, suggesting that WMH enlargement may occur before the development of cognitive decline among subjects with albuminuria. In addition, we demonstrated that the combination of albuminuria and larger WMHV was associated with an increased probability of cognitive decline in the cross-sectional analysis and a higher risk of all-cause death during the median 4.3 years of follow-up. The presence of both albuminuria and increased WMHV implies the severity of vascular endothelial dysfunction and the progression of damage to multiple systemic organs, resulting in higher risks of cognitive decline and mortality.

The present study has several limitations that need to be considered. First, levels of UACR, eGFR, WMHV : ICV ratio and cognitive function were evaluated at the baseline examination in 2012. Because the associations among these

variables were assessed by means of a cross-sectional design, we could not definitively establish causality among them. Second, only a single measurement of UACR or eGFR was performed at the baseline examination. This may have resulted in the misclassification of participants into different categories of UACR or eGFR. Such misclassification would weaken the association observed in the present study, biasing the results towards the null hypothesis. Therefore, the association reported in the present study may be underestimated. Third, although the multivariable model included a comprehensive set of confounding factors, a few residual confounders were not considered, such as endothelial dysfunction, oxidative stress, and inflammation. Fourth, although the participation rate of the present study was fairly high, approximately one-third of the residents were not included. The individuals who did not participate in this study were likely to be older and to have more unhealthy backgrounds than those taking part in the study. Therefore, we may have underestimated the association in the present study. Finally, because the participants in this study were limited to elderly Japanese, the results may not be generalizable to other races or younger populations.

Conclusions

In a population of general Japanese elderly, we demonstrated that elevated urinary albumin, even within the normal range, was associated with a larger WMHV. Moreover, our data suggest that the combination of albuminuria and WMH enlargement additively increases the risks of cognitive decline and all-cause mortality. Because WMH is known to be a risk factor for symptomatic stroke, dementia, and death, the measurement of urinary albumin may be useful for detecting subjects at high risk for small vessel disease in the brain and for establishing a preventive strategy against the future development of stroke, dementia, and death, as well as end-stage kidney failure. Further prospective studies are needed to characterize the association between albuminuria and WMH.

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Data Availability

The deidentified participant data will not be shared.

Disclosures

T.K. is a member of *Circulation Journal*' Editorial Team. The other authors report no potential conflicts of interest.

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Supplementary Files

Please find supplementary file(s);
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