Kidney Medicine

CKD, Brain Atrophy, and White Matter Lesion Volume: The Japan Prospective Studies Collaboration for Aging and Dementia

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Rationale & Objective: Chronic kidney disease, defined by albuminuria and/or reduced estimated glomerular filtration rate (eGFR), has been reported to be associated with brain atrophy and/or higher white matter lesion volume (WMLV), but there are few large-scale population-based studies assessing this issue. This study aimed to examine the associations between the urinary albumin-creatinine ratio (UACR) and eGFR levels and brain atrophy and WMLV in a large-scale community-dwelling older population of Japanese.

Study Design: Population-based cross-sectional study.

Setting & Participants: A total of 8,630 dementia-free community-dwelling Japanese aged greater than or equal to 65 years underwent brain magnetic resonance imaging scanning and screening examination of health status in 2016-2018.

Exposures: UACR and eGFR levels.

Outcomes: The total brain volume (TBV)-to-intracranial volume (ICV) ratio (TBV/ICV), the regional brain volume-to-TBV ratio, and the WMLV-to-ICV ratio (WMLV/ICV).

Analytical Approach: The associations of UACR and eGFR levels with the TBV/ICV, the regional brain volume-to-TBV ratio, and the WMLV/ICV were assessed by using an analysis of covariance.

Results: Higher UACR levels were significantly associated with lower TBV/ICV and higher geometric mean values of the WMLV/ICV (P for trend = 0.009 and <0.001, respectively). Lower eGFR levels were significantly associated with lower TBV/ICV, but not clearly associated with WMLV/ICV. In addition, higher UACR levels, but not lower eGFR, were significantly associated with lower temporal cortex volume-to-TBV ratio and lower hippocampal volume-to-TBV ratio.

Limitations: Cross-sectional study, misclassification of UACR or eGFR levels, generalizability to other ethnicities and younger populations, and residual confounding factors.

Conclusions: The present study demonstrated that higher UACR was associated with brain atrophy, especially in the temporal cortex and hippocampus, and with increased WMLV. These findings suggest that chronic kidney disease is involved in the progression of morphologic brain changes associated with cognitive impairment.

Visual Abstract included

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Brain atrophy is one of the morphological features of dementia.[1] Brain atrophy progresses with aging[2] and neurodegeneration,[3] but vascular risk factors, such as hypertension[4] and diabetes mellitus,[5] may also play roles in the progression of brain atrophy, possibly by contributing to small or large vessel diseases.[6,7] White matter lesions, known as a manifestation of cerebral small vessel disease,[8] are frequently observed in brain magnetic resonance imaging (MRI) of older individuals, including those with dementia. Because progressive brain atrophy and increased white matter lesions have been recognized to contribute to worsening cognitive impairment,[9,10] there is an urgent need to identify their possible risk factors.

Chronic kidney disease (CKD) is defined as albuminuria and/or reduced estimated glomerular filtration rate (eGFR). Progressed CKD is characterized by a gradual loss of microvasculature, which is thought to be related to exacerbation of small vessel disease in the kidney due to an accumulation of vascular risk factors and a reduction in the endothelial proliferative response.[11] Small vessel damage in the kidney and brain are considered to be closely related because of their anatomic and hemodynamic similarities.[12] Therefore, it can be inferred that CKD and morphologic brain changes share common pathological mechanisms.

Several cross-sectional studies have shown significant associations of higher urinary albumin-creatinine ratio (UACR) with brain atrophy and higher white matter lesion volume (WMLV),[13-17] but there were inconsistent findings on the association between lower eGFR and brain atrophy or higher WMLV.[13-19] In addition, all of these studies were evaluated in populations of less than or approximately 1,000 individuals, which may have insufficient statistical power. Furthermore, their relationship to specific brain regions has not been fully examined.

Editorial, XXX

PLAIN-LANGUAGE SUMMARY

The present study assessed the association between the urinary albumin-creatinine ratio (UACR) or estimated glomerular filtration rate (eGFR) and brain atrophy or white matter lesion volume in 8,630 dementia-free participants with brain magnetic resonance imaging data in a general Japanese older population. Higher UACR and lower eGFR levels were significantly associated with total brain atrophy, whereas higher UACR levels, but not lower eGFR, were significantly associated with higher white matter lesion volume. In addition, higher UACR levels, but not lower eGFR, were significantly associated with lower temporal cortex and hippocampal atrophy and prevalent mild cognitive impairment. The present findings suggest that chronic kidney disease is involved in the progression of morphological brain changes associated with cognitive impairment.

The Japan Prospective Studies Collaboration for Aging and Dementia (JPSC-AD) is a multisite, ongoing community-based observational study for dementia in 8 research sites of Japan, in which approximately 10,000 older participants have undergone a brain MRI examination at baseline.[20] The present study aimed to investigate the association of UACR or eGFR with brain atrophy and WMLV by using brain MRI data in a general Japanese older population.

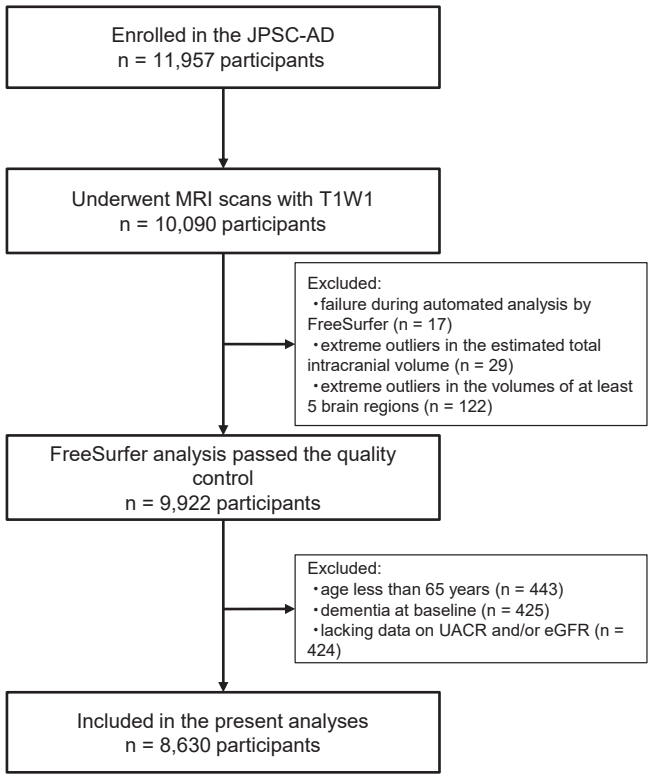

Figure 1. Selection process of the examined population. Abbreviations: eGFR, estimated glomerular filtration rate; JPSC-AD, the Japan Prospective Studies Collaboration for Aging and Dementia; MRI, magnetic resonance imaging; T1WI, T1-weighted imaging; UACR, urinary albumin-creatinine ratio.

METHODS

Study Populations

In JPSC-AD, a baseline survey was conducted in 2016-2018. A detailed description of this baseline survey has been published previously.[20] Among 11,957 participants enrolled in the JPSC-AD, 10,090 participants underwent MRI scans with 3-dimensional T1-weighted images. After the exclusion of 168 participants for whom the FreeSurfer analysis did not pass the quality control, 443 participants who were aged less than 65 years, 425 participants with dementia at baseline, and 424 participants without available data on UACR and/or eGFR, the remaining 8,630 participants were deemed eligible and included in the present study (Fig 1). This study was first approved by the Kyushu University Institutional Review Board (approval number 686-09) and then by the ethics committee of each research institute, and written informed consent was obtained from all the participants.

Brain MRI Analysis

The MRI equipment was set with T1-weighted imaging parameters according to the protocol of brain MRI for the Alzheimer Disease Neuroimaging Initiative study.[21] The segmentation and volume measurements of cortical and subcortical brain structures, including white matter lesions, and intracranial volume (ICV) were performed automatically using the FreeSurfer software (http://surfer.nmr.mgh.harvard.edu), version 5.3. The total brain volume (TBV) was calculated from brain segmentation volumes without ventricles. The cortical parcellation was performed using a Desikan-Killiany atlas.[22] All FreeSurfer automated segmentation results were checked for the presence of image defects. Specifically, the FreeSurfer estimates of each brain parameter were fitted by a linear regression model adjusting for age, squared age, and sex. When the residual of the data for an individual participant lay less than −4 standard deviation (SD) units or greater than +4 SD units from the linear regression, these data were regarded as extreme outliers. Extreme outliers in the ICV and/or the volumes of at least 5 brain regions were excluded. The raw mean value of TBV and the raw geometric mean value of WMLV were 958.18 cm^2 and 3.80 cm^2, respectively. To adjust for head size, TBV and WMLV were calculated as a percentage of ICV (ie, as the TBV-to-ICV ratio (TBV/ICV) [%] and the WMLV-to-ICV ratio (WMLV/ICV) [%]).

Because the gray matter regions of interest in the present analysis, we divided total brain into gray matter and white matter and selected from the gray matter 4 representative cerebral lobes, ie, the frontal cortex, parietal

cortex, temporal cortex, and occipital cortex, and 3 dementia-related brain regions, ie, the insular cortex, hippocampus, and amygdala, based on the findings of a previous study.[9] In addition, we also examined 5 brain regions of the temporal cortex (ie, the entorhinal cortex, parahippocampal gyrus, superior temporal gyrus, middle temporal gyrus, and inferior temporal gyrus), because a significant association between log-transformed UACR levels and the temporal cortex-to-TBV ratio was observed in the present study. In addition, as an indicator of regional brain atrophy beyond total brain atrophy, we calculated the ratio of each brain regional gray matter volume-to-TBV: ([left + right] regional brain volume/TBV) × 100 (%). The ratio of the white matter volume-to-TBV ratio was also calculated as an indicator of white matter atrophy beyond total brain atrophy.

Diagnosis of Dementia and Mild Cognitive Impairment

Dementia and mild cognitive impairment were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders, Third Revised Edition*[23] and the Petersen's criteria,[24] respectively. The detailed procedure for the diagnosis of dementia or mild cognitive impairment is described in the supplementary methods (Item S1). To standardize the accuracy in the diagnosis of dementia or mild cognitive impairment across the 8 research sites, we organized an endpoint adjudication committee consisting of expert psychiatrists or neurologists selected from each research site. If the members of the endpoint adjudication committee were in agreement regarding a diagnosis at a particular site, the diagnosis was confirmed; if not, a meeting of the endpoint adjudication committee was held, and the diagnosis was confirmed through discussion.

Measurements of UACR, eGFR, and Other Risk Factors

Detailed information on other risk factors is provided in Item S1. Urinary creatinine and albumin were measured using a turbidimetric immunoassay and the enzymatic method, respectively. The UACR was calculated by dividing urinary albumin values by urinary creatinine concentrations. Based on the Kidney Disease: Improving Global Outcomes 2021 guideline,[25] UACR was classified into 3 groups as follows: <30, 30-299, and ≥300 mg/g. Serum creatinine concentrations were measured using an enzymatic method. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation with a Japanese coefficient of 0.813.[26] eGFR was also classified into 3 groups according to the Kidney Disease: Improving Global Outcomes 2021 guideline[25] as follows: ≥60, 30-59, and <30 mL/min/1.73m^2.

Statistical Analysis

A detailed description of the statistical analysis is also given in the supplementary methods (Item S1). Briefly, WMLV/ICV and UACR were transformed using the common logarithm because of their skewed distributions. Adjusted means of TBV/ICV and geometric means of WMLV/ICV according to UACR and eGFR levels were estimated and compared using analysis of covariance. The trends in the adjusted mean values of TBV/ICV and log-transformed WMLV/ICV across the categories of UACR and eGFR were tested using a multiple regression analysis. The heterogeneity in the association within each subgroup was tested by adding a multiplicative interaction term to the relevant statistical model. In addition, the shape of associations of UACR and eGFR levels with TBV/ICV and WMLV/ICV was examined by using a restricted cubic spline model. The associations between a 1 SD increment of $\log_{10}$ (UACR) or 1 SD decrement of eGFR and the TBV/ICV, WMLV/ICV, the ratio of each regional brain volume-to-TBV, and the ratio of the white matter volume-to-TBV were examined using a multiple regression model. Regarding the multiple comparisons of the association of UACR and eGFR levels with regional brain volumes, false discovery rate correction[27] was performed to verify the multiple comparisons for which a significance level with a q-value of false discovery rate correction was defined as <0.05. We used a logistic regression analysis to calculate odds ratios and 95% confidence intervals of the association between UACR and eGFR levels and the presence of mild cognitive impairment. All statistical analyses were performed using the SAS software package version 9.4 (SAS Institute Inc). Two-sided values of P of <0.05 were considered statistically significant in all analyses.

RESULTS

The clinical characteristics of the study population according to UACR are shown in Table 1. The frequencies of male sex, low education, use of antihypertensive agents, hypertension, diabetes mellitus, electrocardiogram abnormalities, and history of stroke, the mean values of age, systolic blood pressure, diastolic blood pressure, and body mass index (BMI), and the median value of serum high-sensitivity C-reactive protein all increased significantly with higher UACR levels, whereas the frequency of alcohol intake and the mean values of serum total cholesterol and eGFR decreased significantly. Table 2 shows the clinical characteristics of the participants according to eGFR levels. The frequencies of male sex, low education, use of antihypertensive agents, hypertension, diabetes mellitus, electrocardiogram abnormalities, and history of stroke, the mean values of age and BMI, and the median values of serum high-sensitivity C-reactive protein and UACR all increased significantly with lower eGFR levels. Conversely, the frequencies of smoking habits and alcohol intake and the mean values of systolic blood pressure, diastolic blood pressure, and serum total cholesterol levels decreased significantly with lower eGFR levels.

Figure 2 presents the age- and sex-adjusted and multivariable-adjusted mean value of TBV/ICV and

Table 1. Characteristics of Participants According to UACR Levels

Variables	Total Population (n = 8,630)	UACR Levels, mg/g			*P* for Trend	Number of Missing Values
		<30 (n = 6,620)	30-299 (n = 1,707)	≥300 (n = 303)		
UACR (mg/g), median	11.2	8.2	60.9	652.0		0
eGFR (mL/min/1.73 m^2), mean (SD)	68.7 (10.9)	69.8 (9.4)	67.0 (12.2)	55.3 (19.0)	<0.001	0
Age (y), mean (SD)	73 (6)	72 (6)	75 (7)	76 (7)	<0.001	0
Male, n (%)	3,663 (42.4%)	2,750 (41.5%)	746 (43.7%)	167 (55.1%)	<0.001	0
Education ≤9 y, n (%)	2,495 (29.0%)	1,773 (26.8%)	585 (34.4%)	137 (45.4%)	<0.001	16
Systolic BP (mm Hg), mean (SD)	139.9 (18.6)	137.7 (17.9)	146.6 (19.0)	150.9 (18.8)	<0.001	1
Diastolic BP (mm Hg), mean (SD)	78.3 (11.4)	77.8 (11.1)	80.2 (12.2)	79.9 (11.4)	<0.001	1
Use of antihypertensive agents, n (%)	4,240 (49.5%)	2,898 (44.1%)	1,100 (65.1%)	242 (80.9%)	<0.001	62
Hypertension, n (%)	6,253 (72.7%)	4,471 (67.8%)	1,501 (88.1%)	281 (92.7%)	<0.001	32
Diabetes mellitus, n (%)	1,400 (16.3%)	854 (13.0%)	416 (24.4%)	130 (43.2%)	<0.001	53
Serum total cholesterol (mg/dL), mean, (SD)	207.9 (36.0)	209.1 (35.8)	204.2 (35.9)	202.1 (38.8)	<0.001	0
Body mass index (kg/m^2), mean (SD)	23.4 (3.3)	23.2 (3.2)	24.0 (3.5)	24.7 (3.8)	<0.001	6
Electrocardiogram abnormalities, n (%)	1,127 (13.1%)	735 (11.1%)	320 (18.8%)	72 (23.9%)	<0.001	28
History of stroke, n (%)	422 (4.9%)	277 (4.2%)	119 (7.0%)	26 (8.6%)	<0.001	4
Smoking habits, n (%)	706 (8.2%)	537 (8.1%)	142 (8.3%)	27 (8.9%)	0.61	28
Alcohol intake, n (%)	3,743 (43.5%)	2,910 (44.1%)	726 (42.8%)	107 (35.4%)	0.009	33
Regular exercise, n (%)	3,690 (43.3%)	2,867 (43.8%)	699 (41.7%)	124 (41.1%)	0.08	111
Serum hs-CRP (mg/L), median (IQR)	0.47 (0.23-1.00)	0.43 (0.22-0.92)	0.59 (0.27-1.25)	0.72 (0.36-1.54)	<0.001	1

Abbreviations: BP, Blood pressure; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IQR interquartile range; SD, standard deviation; UACR, urinary albumin-creatinine ratio.

Table 2. Characteristics of Participants According to eGFR Levels

Variables	eGFR Levels, mL/min/1.73 m^2			*P* for trend	Number of Missing Values
	≥60 (n = 7,160)	30-59 (n = 1,404)	<30 (n = 66)		
eGFR (mL/min/1.73 m^2), median	73.1	52.2	21.8		0
UACR (mg/g), median (IQR)	10.5 (5.8-24.2)	15.7 (6.6-50.4)	229.6 (37.3-1249.8)	<0.001	0
Age (y), mean (SD)	72 (6)	77 (7)	78 (7)	<0.001	0
Male, n (%)	2,882 (40.3%)	741 (52.8%)	40 (60.6%)	<0.001	0
Education ≤9 y, n (%)	1,946 (27.2%)	523 (37.4%)	26 (39.4%)	<0.001	16
Systolic BP (mm Hg), mean (SD)	140.2 (18.5)	138.4 (19.1)	138.6 (18.1)	0.001	1
Diastolic BP (mm Hg), mean (SD)	78.9 (11.2)	75.9 (11.8)	70.1 (11.8)	<0.001	1
Use of antihypertensive agents, n (%)	3,278 (46.1%)	901 (65.0%)	61 (93.9%)	<0.001	62
Hypertension, n (%)	5,082 (71.2%)	1,107 (79.6%)	64 (97.0%)	<0.001	32
Diabetes mellitus, n (%)	1,116 (15.7%)	266 (19.2%)	18 (27.7%)	<0.001	53
Serum total cholesterol (mg/dL), mean, (SD)	209.9 (35.7)	198.9 (35.5)	183.7 (43.5)	<0.001	0
Body mass index (kg/m^2), mean (SD)	23.3 (3.3)	23.9 (3.3)	24.3 (3.5)	<0.001	6
Electrocardiogram abnormalities, n (%)	856 (12.0%)	256 (18.3%)	15 (22.7%)	<0.001	28
History of stroke, n (%)	292 (4.1%)	123 (8.8%)	7 (10.6%)	<0.001	4
Smoking habits, n (%)	608 (8.5%)	93 (6.7%)	5 (7.6%)	0.03	28
Alcohol intake, n (%)	3,159 (44.3%)	566 (40.6%)	18 (27.3%)	<0.001	33
Regular exercise, n (%)	3,067 (43.4%)	598 (43.1%)	25 (38.5%)	0.62	111
Serum hs-CRP (mg/L), median (IQR)	0.45 (0.22-0.95)	0.60 (0.29-1.28)	0.69 (0.30-1.82)	<0.001	1

Abbreviations: BP, Blood pressure; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IQR interquartile range; SD, standard deviation; UACR, urinary albumin-creatinine ratio.

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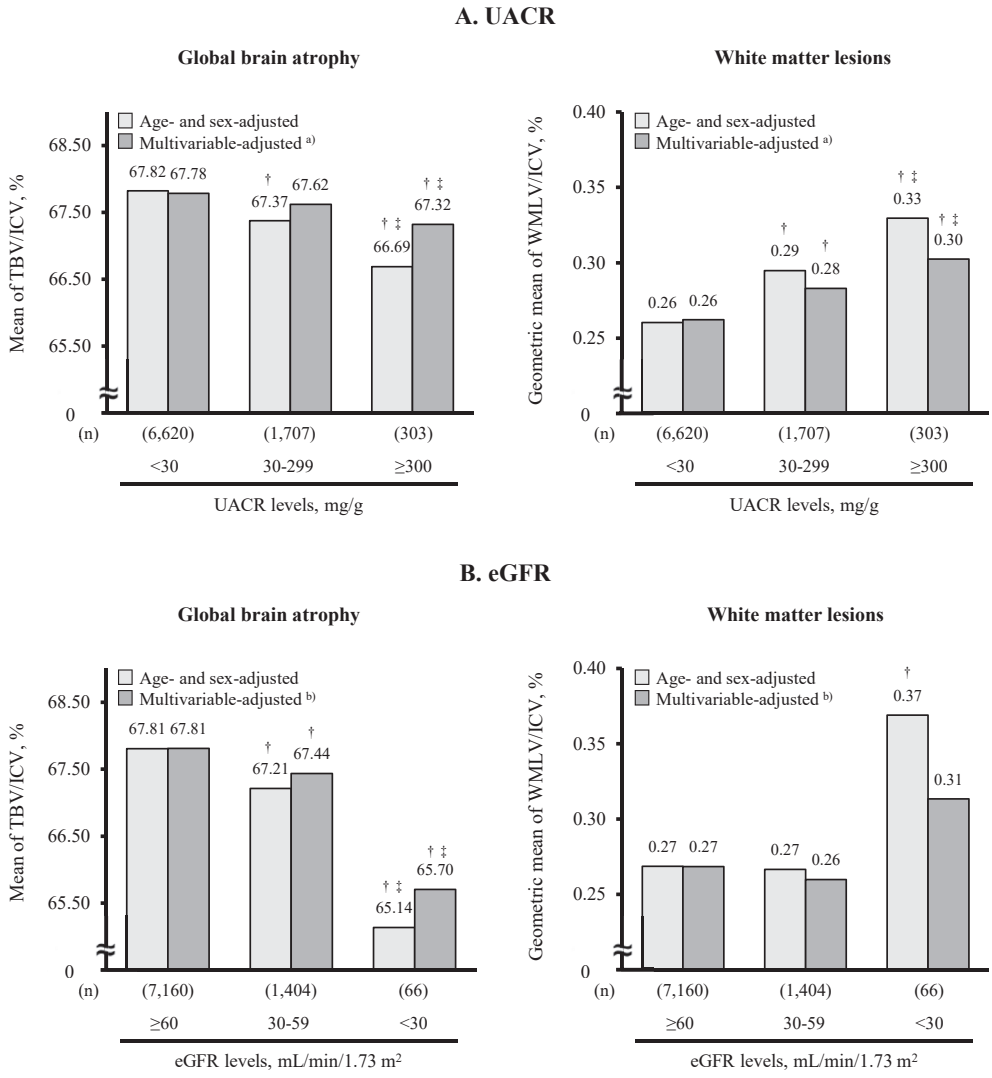

Figure 2. Age- and sex-adjusted and multivariable-adjusted mean values of the TBV-to-ICV ratios and geometric mean values of the WMLV-to-ICV ratios according to UACR (A) and eGFR (B) levels. [a]Adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, body mass index, electrocardiogram abnormalities, history of stroke, smoking habit, alcohol intake, regular exercise, serum high-sensitivity C-reactive protein (log-transformed), research site, and eGFR in the multivariable-adjusted model. [b]Adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, body mass index, electrocardiogram abnormalities, history of stroke, smoking habit, alcohol intake, regular exercise, serum high-sensitivity C-reactive protein (log-transformed), research site, and UACR (log-transformed) in the multivariable-adjusted model. † P < 0.05 versus <30.0 mg/g or ≥60 mL/min/1.73 m². ‡ P for trend <0.01. Abbreviations: eGFR, estimated glomerular filtration rate; ICV, intracranial volume; TBV, total brain volume; UACR, urinary albumin-creatinine ratio; WMLV, white matter lesion volume.

geometric mean value of WMLV/ICV according to UACR and eGFR levels. Higher UACR levels were significantly associated with a lower mean value of TBV/ICV and higher geometric mean value of WMLV/ICV after adjusting for age and sex (both P for trend <0.001; Fig 2A). These significant associations were unchanged even after adjustment for age, sex, low education, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol levels, BMI, electrocardiogram abnormalities, history of stroke, smoking habit, alcohol intake, regular exercise, serum high-sensitivity C-reactive protein, research site, and eGFR (TBV/ICV: P for trend = 0.009; WMLV/ICV: P for trend <0.001), although the difference in the multivariable-adjusted mean values of TBV/ICV between those with UACR <30 mg/g and UACR 30-299 mg/g did not reach a statistically significant level (Fig 2A and Table S1). The age- and sex-adjusted and multivariable-adjusted mean values of TBV/ICV decreased significantly with lower eGFR levels (all P for trend <0.001; Fig 2B). Compared with participants with eGFR ≥60 mL/min/1.73m^2, the multivariable-adjusted mean values of TBV/ICV decreased significantly for participants with either eGFR 30-59 mL/min/1.73m^2 or <30 mL/min/1.73m^2. On the other hand, the age- and sex-adjusted geometric mean value of WMLV/ICV increased

significantly in participants with eGFR <30 mL/min/1.73m^2 compared with those with eGFR ≥60 mL/min/1.73m^2, but there was no significant association after multivariable adjustment. These associations were unchanged even using eGFR and UACR as continuous variables (Table S1). In the subgroup analyses, there was no evidence of significant heterogeneity in the association of UACR or eGFR levels with TBV/ICV or WMLV/ICV among the subgroups of hypertension, diabetes mellitus, history of stroke, and high-sensitivity C-reactive protein, except for the association of eGFR with TBV/ICV according to diabetic status, where the magnitude of the negative association was more pronounced in individuals with diabetes (*P* for heterogeneity = 0.02) (Table S2). Because obesity and lean have been reported to be associated with CKD[28] and dementia,[29,30] we performed a sensitivity analysis in which dummy variables for BMI ≥25.0 kg/m^2 and <18.5 kg/m^2 (reference BMI 18.5-24.9 kg/m^2) were included in the relevant model, instead of BMI taken as a continuous variable. The sensitivity analysis did not yield any material differences in the findings (Table S3).

Figure 3 shows the shape of the associations of UACR and eGFR levels with TBV/ICV and WMLV/ICV, respectively, which were estimated using restricted

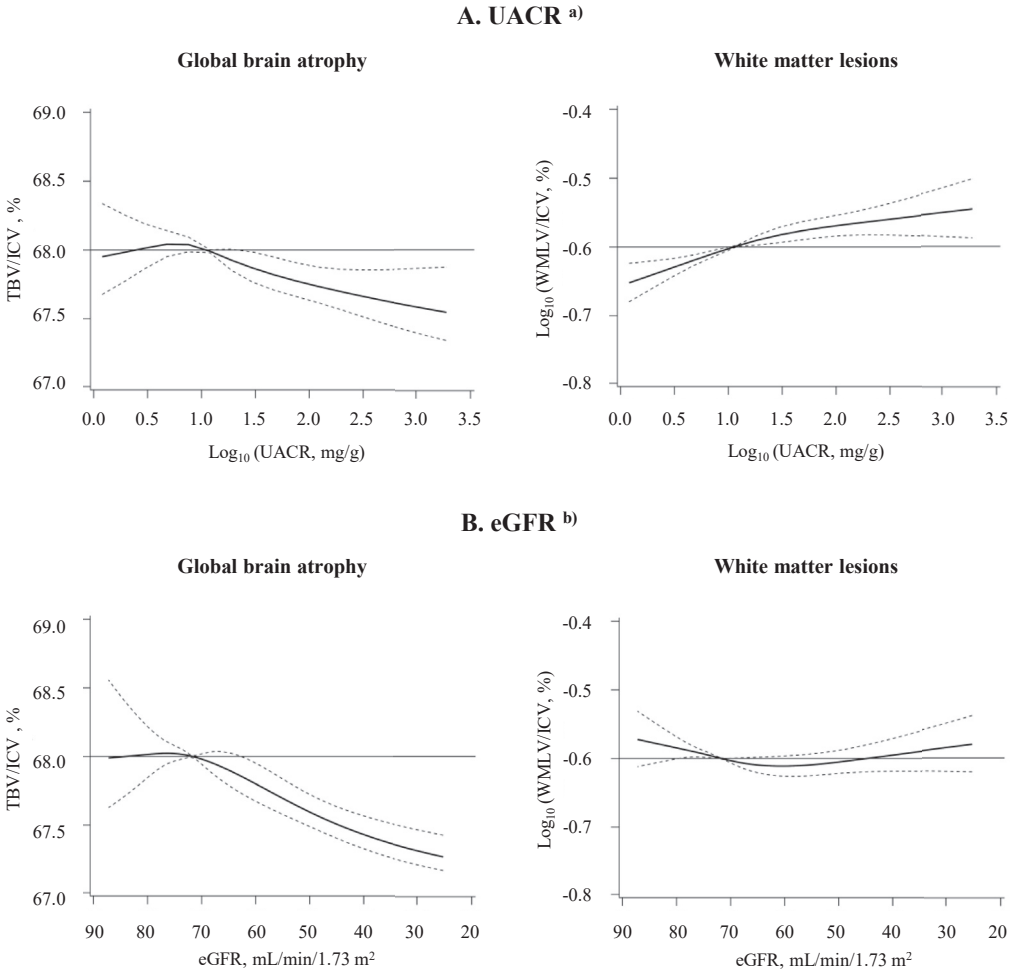

Figure 3. Restricted cubic splines for the TBV-to-ICV ratios and WMLV-to-ICV ratios according to UACR (A) and eGFR (B) levels. Solid lines represent the TBV-to-ICV ratios and WMLV-to-ICV ratios, and dashed lines represent the 95% confidence intervals of the TBV-to-ICV ratios and WMLV-to-ICV ratios. The range represents the 0.5th to the 99.5th percentile of $\log_{10}$ (UACR) and eGFR levels, respectively. A reference point was set at the 50th percentile for $\log_{10}$ (UACR) (1.05 = 11.2 mg/g at UACR) and eGFR levels (71.7 mL/min/1.73 m^2), with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles of $\log_{10}$ (UACR) (0.46, 0.88, 1.25, and 2.29) and eGFR levels (46.4, 68.4, 74.1, and 80.9 mL/min/1.73 m^2). [a]Adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, body mass index, electrocardiogram abnormalities, history of stroke, smoking habit, alcohol intake, regular exercise, serum high-sensitivity C-reactive protein (log-transformed), research site, and eGFR. [b]Adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, body mass index, electrocardiogram abnormalities, history of stroke, smoking habit, alcohol intake, regular exercise, serum high-sensitivity C-reactive protein (log-transformed), research site, and UACR (log-transformed). Abbreviations: eGFR, estimated glomerular filtration rate; ICV, intracranial volume; TBV, total brain volume; UACR, urinary albumin-creatinine ratio; WMLV, white matter lesion volume.

cubic spline analyses. The TBV/ICV tended to decrease as $\log_{10}$ (UACR) increased from around 1.0 (equivalent to UACR 10 mg/g) and as eGFR decreased from around 70 mL/min/1.73m^2. The $\log_{10}$ (WMLV/ICV) increased gradually with higher $\log_{10}$ (UACR) levels, whereas no association was found between eGFR and WMLV/ICV levels.

In addition, we investigated the associations of UACR and eGFR levels with the ratio of each regional gray matter volume-to-TBV (Table 3). In multivariable adjustment, there were significant inverse associations between $\log_{10}$ (UACR) levels and both the temporal cortex-to-TBV ratio and the hippocampus-to-TBV ratio (q-values of false discovery rate correction <0.001 and = 0.048, respectively). Subsequently, when examined by subregion of the temporal cortex, the parahippocampal gyrus-to-TBV ratio, middle temporal gyrus-to-TBV ratio, and inferior temporal gyrus-to-TBV ratio were significantly decreased with a 1 SD increase in $\log_{10}$ (UACR) (q-values of false discovery rate correction <0.001, = 0.001, and = 0.004, respectively). There was no evidence of heterogeneity between the association of UACR levels with the left and right brain volumes of each brain region (all P for heterogeneity >0.20). On the other hand, there was no significant association between eGFR levels and any of the brain regions. With regard to the association between UACR or eGFR and the white matter volume, the ratio of white matter volume-to-TBV decreased significantly with lower eGFR (the difference in the volume was −0.050 [95% confidence interval, −0.101 to 0.000] per 1 SD decrement in eGFR, P = 0.049), but not with higher UACR (the difference in the volume was 0.025 [95% confidence interval, −0.023 to 0.073] per 1 SD increment in $\log_{10}$ (UACR), P = 0.31).

Finally, we estimated the associations of UACR and eGFR levels with the presence of mild cognitive impairment. For UACR levels, higher UACR levels were associated with greater likelihood of prevalent mild cognitive impairment after adjustment for potential confounders. Meanwhile, there was no significant association between eGFR levels and the presence of mild cognitive impairment (Table 4).

DISCUSSION

The present large-scale cross-sectional study of a general population without dementia showed significant associations of higher UACR and lower eGFR levels with lower TBV/ICV. Similarly, the geometric mean values of the WMLV/ICV increased significantly with higher UACR levels. In addition, higher UACR levels were significantly associated with a lower temporal cortex-to-TBV ratio and hippocampus-to-TBV ratio, but no significant association was found between eGFR and brain regions. The present findings suggest that CKD, and especially albuminuria, is significantly associated with brain atrophy and increased white matter lesions among individuals without dementia.

In the present study, higher UACR levels were significantly associated with lower volumes of the hippocampus, parahippocampal gyrus, middle temporal gyrus, and inferior temporal gyrus, as well as TBV. A cross-sectional study of health examinations in Korea showed a significant association between higher UACR levels and lower TBV.[13] In the African American-Diabetes Heart Study MIND, the volumes of the total brain and hippocampus decreased significantly with higher UACR levels in patients with diabetes.[14] Moreover, the BRain IN Kidney Disease study reported that higher UACR levels were significantly associated with lower hippocampal and temporal cortical volume.[16] Our findings are consistent with the findings in these previous studies. In addition, the present study showed significant associations of higher UACR levels with higher WMLV/ICV. Population-based cross-sectional studies, as well as the Nutrition, Aging, and Memory in Elders Study and the Systolic Blood Pressure Intervention Trial, also showed a significant association between higher UACR levels and higher WMLV.[13,17,31,32] A similar significant association was also found in the above-mentioned clinical studies with patients with diabetes or CKD.[14-16] Because it has been reported that the hippocampus and parahippocampal gyrus are important regions for memory[33] and the middle and inferior temporal gyrus are involved in visual recognition,[34] dysfunction in these regions related to higher UACR levels may lead to cognitive decline. White matter lesions are also reported to be associated with increased risk of dementia.[10] Certainly, several clinical studies[31,32] and a population-based prospective cohort study[35] have shown that albuminuria is a significant risk factor for the presence of cognitive impairment and developing dementia. Taking these results together, it is reasonable to assume that higher UACR levels are associated with atrophy of the hippocampus and temporal cortex, higher WMLV, and subsequently, progression of cognitive impairment.

The findings regarding the association of eGFR with cognitive function, WMLV, and brain atrophy are inconsistent across the previous studies. Several epidemiologic studies failed to reveal significant associations between lower eGFR levels and risk of cognitive impairment or dementia and brain atrophy after adjusting for potential confounding factors,[35,36] but a registry-based study that enrolled 329,822 residents of Stockholm and a large-scale meta-analysis with 54,799 participants showed a significant association of lower eGFR with the development of dementia and cognitive impairment.[37,38] With regard to the association between eGFR and WHMV, several studies showed a significant association between lower eGFR levels and higher WMLV levels,[15,19] but others did not.[13,14,16,17] With regard to the association between eGFR and brain volume, a hospital-based study conducted in Japanese without neurologic disorders showed a significant association between eGFR levels and brain atrophy,[18] but clinical studies with patients with diabetes or CKD and the Rotterdam Study failed to reveal a

Table 3. Multivariable-Adjusted Differences of Regional Gray Matter Volume-to-TBV Ratios per 1 SD Increment of log_{10} (UACR) and 1 SD Decrement of eGFR

	Per 1 SD log_{10} (UACR) Increment[a]				Per 1 SD eGFR Decrement[b]			
Gray Matter Regions	**Difference in Volume[c]**	**(95% CI)**	***P* Value**	**q-Value of FDR Correction**	**Difference in Volume[c]**	**(95% CI)**	***P* Value**	**q-Value of FDR Correction**
Frontal cortex volume/TBV, %	0.0099	(−0.0093 to 0.0291)	0.31	0.38	0.0096	(−0.0106 to 0.0299)	0.35	0.60
Parietal cortex volume/TBV, %	−0.0093	(−0.0229 to 0.0042)	0.18	0.24	0.0019	(−0.0124 to 0.0162)	0.80	0.96
Temporal cortex volume/TBV, %	−0.0235	(−0.0354 to −0.0117)	<0.001	<0.001	0.0173	(0.0049 to 0.0297)	0.006	0.08
Occipital cortex volume/TBV, %	−0.0055	(−0.0127 to 0.0017)	0.13	0.20	0.0082	(0.0007 to 0.0158)	0.03	0.13
Insular cortex volume/TBV, %	0.0028	(0.0003 to 0.0053)	0.03	0.05	−0.0018	(−0.0044 to 0.0008)	0.17	0.41
Hippocampal volume/TBV, %	−0.0020	(−0.0037 to −0.0003)	0.02	0.048	0.00002	(−0.0018 to 0.0018)	0.98	0.98
Amygdala volume/TBV, %	−0.0003	(−0.0011 to 0.0005)	0.43	0.47	0.0003	(−0.0006 to 0.0011)	0.54	0.72
Subregion of temporal cortex								
Entorhinal cortex volume/TBV, %	−0.0002	(−0.0015 to 0.0010)	0.74	0.74	0.0005	(−0.0008 to 0.0018)	0.45	0.67
Parahippocampal gyrus volume/TBV, %	−0.0024	(−0.0035 to −0.0013)	<0.001	<0.001	0.0012	(0.0000 to 0.0024)	0.05	0.16
Superior temporal gyrus volume/TBV, %	−0.0038	(−0.0079 to 0.0002)	0.06	0.11	0.0026	(−0.0017 to 0.0069)	0.23	0.46
Middle temporal gyrus volume/TBV, %	−0.0086	(−0.0128 to −0.0045)	<0.001	0.001	0.0051	(0.0007 to 0.0095)	0.02	0.14
Inferior temporal gyrus volume/TBV, %	−0.0074	(−0.0118 to −0.0029)	0.001	0.004	−0.0006	(−0.0053 to 0.0041)	0.81	0.89

Note: SD was 0.6 in log_{10} (UACR) and 10.9 mL/min/1.73 m^2 in eGFR.
Abbreviations: CI, Confidence interval; eGFR, estimated glomerular filtration rate; FDR, false discovery rate; SD, standard deviation; TBV, total brain volume; UACR, urinary albumin-creatinine ratio.
[a]Values were adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, body mass index, electrocardiogram abnormalities, history of stroke, smoking habit, alcohol intake, regular exercise, serum high-sensitivity C-reactive protein (log-transformed), research site, and eGFR.
[b]Values were adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, body mass index, electrocardiogram abnormalities, history of stroke, smoking habit, alcohol intake, regular exercise, serum high-sensitivity C-reactive protein (log-transformed), research site, and UACR (log-transformed).
[c]The difference in volumes (95% CIs) represent beta coefficients (95% CIs) of the association between 1 SD increments of log_{10} (UACR) or 1 SD decrements of eGFR and each brain regional volume in the multiple regression model.

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Table 4. Age- and Sex-Adjusted and Multivariable-Adjusted Odds Ratios for Prevalent Mild Cognitive Impairment According to UACR and eGFR Levels

UACR or eGFR Levels	No. of Participants	No. of Events	Age- and Sex-Adjusted		Multivariable-Adjusted	
			Odds Ratio (95% CI)	*P* for trend	Odds Ratio (95% CI)	*P* for trend
UACR, mg/g[a]						
<30	6,620	1,019	1.00 (reference)	<0.001	1.00 (reference)	<0.001
30-299	1,707	382	1.24 (1.08-1.43)		1.27 (1.09-1.48)	
≥300	303	90	1.56 (1.19-2.05)		1.48 (1.09-2.01)	
Per 1SD $\log_{10}$ (UACR) increment	8,630	1,491	1.11 (1.05-1.17)	<0.001	1.11 (1.04-1.18)	0.003
eGFR, mL/min/1.73 m²[b]						
≥60	7,160	1,115	1.00 (reference)	0.86	1.00 (reference)	0.75
30-59	1,404	352	0.97 (0.83-1.13)		0.95 (0.81-1.12)	
<30	66	24	1.44 (0.84-2.46)		1.15 (0.64-2.07)	
Per 1 SD eGFR decrement	8,630	1,491	0.99 (0.93-1.06)	0.79	0.98 (0.91-1.05)	0.50

Note: SD was 0.6 in $\log_{10}$ (UACR) and 10.9 mL/min/1.73 m^2 in eGFR.
Abbreviations: CI, Confidence interval; eGFR, estimated glomerular filtration rate; SD, standard deviation; UACR, nrinary albumin-creatinine ratio.
[a]Adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, body mass index, electrocardiogram abnormalities, history of stroke, smoking habit, alcohol intake, regular exercise, serum high-sensitivity C-reactive protein (log-transformed), research site, and eGFR in the multivariable-adjusted model.
[b]Adjusted for age, sex, low education, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, serum total cholesterol, body mass index, electrocardiogram abnormalities, history of stroke, smoking habit, alcohol intake, regular exercise, serum high-sensitivity C-reactive protein (log-transformed), research site, and UACR (log-transformed) in the multivariable-adjusted model.

significant association between lower eGFR levels and total brain atrophy or gray matter volume.[14,16,19] Because a cross-sectional study from the Alzheimer's Disease Neuroimaging Initiative showed that lower eGFR was significantly associated with lower TBV in the unadjusted analysis, but not after adjusting for confounding factors, the authors concluded that the association between eGFR and TBV was influenced by confounding factors, such as age.[39] In the present study, on the other hand, the multivariable-adjusted mean values of TBV/ICV decreased with lower eGFR levels. Intriguingly, the present study found that there was no evidence of significant associations of eGFR levels with regional gray matter volume, WMLV, or the presence of mild cognitive impairment, whereas lower eGFR was significantly associated with lower white matter volume, which may reflect underlying comorbid conditions of cerebral vessel diseases resulting from atherosclerosis. Taken together, these results suggest that lower eGFR may not be strongly and specifically linked to regional gray atrophy, WMLV, and subsequent cognitive impairment.

The exact pathophysiologic mechanisms underlying the significant association between higher UACR and brain atrophy and WMLV are unclear, but several possible mechanisms should be discussed. Albuminuria is recognized as a marker of the accumulation of vascular risk factors, such as hypertension and diabetes. All of these are also known as risk factors for cognitive impairment or dementia,[40] and these accumulated risk factors may promote neurodegeneration and vascular damage in the brain, leading to brain atrophy and WMLV enlargement. However, in this study, the association of UACR with reduced regional brain volume and higher WMLV remained significant even after adjustment for these vascular risk factors. As another possible mechanism, systemic endothelial dysfunction may be involved in these associations. Albuminuria has been considered to be a marker of systemic endothelial dysfunction.[41] The kidney and brain have similar hemodynamic characteristics in that the small vessels branch off directly from large vessels and receive a large amount of blood flow with low vascular resistance.[12] Because these small vessels in the kidney and brain are influenced by the hemodynamics of large vessels,[12] the stiffness of vessels because of endothelial dysfunction may affect structural changes in the kidney and brain by promoting small vessel diseases.[42,43] Because the medial temporal lobe, hippocampus, and parahippocampal gyrus have been reported to be vulnerable to ischemia, these vascular damages may progress the atrophy in these areas.[44,45] In support of this hypothesis, clinical studies have shown that patients with cerebral small vessel disease, such as amyloid angiopathy, had greater brain atrophy and higher WMLV than those without.[46,47] In addition, a dysfunction of the blood–brain barrier may contribute to brain atrophy and increased WMLV. Because albuminuria has been known to be associated with reduced nitric oxide,[48] increased oxidative stress,[49] and chronic inflammation,[49] these conditions may cause extravascular leakage of serum proteins.[50]

Several limitations should be noted. First, as the present findings were derived from cross-sectional data, it is difficult to distinguish a causal association between albuminuria or reduced eGFR and regional brain atrophy, WMLV, or mild cognitive impairment. Second, because we conducted only a single measurement of UACR and eGFR levels, there may have been misclassification of UACR or eGFR levels. Third, the generalizability of our findings to other ethnicities and younger populations is limited.

Fourth, there may be residual confounding factors, such as sleep apnea and duration or severity of hypertension over time. Fifth, the associations between UACR ≥300 mg/g or eGFR <30 mL/min/1.73m^2 and each outcome may be less reliable due to the small number of participants in the respective groups.

In conclusion, the present study of general older Japanese without dementia demonstrated that higher UACR levels were significantly associated with total brain atrophy and higher WMLV. Moreover, our results suggest that higher UACR is associated with temporal cortex atrophy, hippocampal atrophy, and prevalent mild cognitive impairment. Because brain atrophy and WMLV are known morphologic changes of developing cognitive impairment,[1,8] urinary albumin may be a good biomarker for detecting high-risk individuals with brain structural changes and subsequent cognitive impairment. To validate the usefulness of UACR in clinical practice, large-scale longitudinal studies for dementia with brain MRI data are needed and anticipated.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Supplementary methods.

Table S1: Multivariable-Adjusted Mean Value of TBV/ICV and $\log_{10}$ (WMLV/ICV) According to UACR or eGFR Levels and per Every 1 SD Continuous Change in UACR or eGFR.

Table S2: Influence of a 1 SD Increment of $\log_{10}$ (UACR) or 1 SD Decrement of eGFR on the TBV-to-ICV Ratio and WMLV-to-ICV Ratio by Subgroups of Each Covariate.

Table S3: Multivariable-Adjusted Differences in the TBV-to-ICV Ratio and WMLV-to-ICV Ratio per 1 SD Increment of $\log_{10}$ (UACR) and 1 SD Decrement of eGFR in a Sensitivity Analysis Including Dummy Variables for BMI ≥25.0 kg/m^2 and <18.5 kg/m^2 (Reference BMI 18.5-24.9 kg/m^2) in the Relevant Model, Instead of BMI Taken as a Continuous Variable.

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REFERENCES

1. Frisoni GB, Fox NC, Jack CR, Scheltens P, Thompson PM. The clinical use of structural MRI in Alzheimer disease. *Nat Rev Neurol*. 2010;6(2):67-77. doi:10.1038/nrneurol.2009.215
2. Fjell AM, Walhovd KB, Fennema-Notestine C, et al. One-year brain atrophy evident in healthy aging. *J Neurosci*. 2009;29(48):15223-15231. doi:10.1523/JNEUROSCI.3252-09.2009
3. Harper L, Barkhof F, Scheltens P, Schott JM, Fox NC. An algorithmic approach to structural imaging in dementia. *J Neurol Neurosurg Psychiatry*. 2014;85(6):692-698. doi:10.1136/jnnp-2013-306285
4. Beauchet O, Celle S, Roche F, et al. Blood pressure levels and brain volume reduction: a systematic review and meta-analysis. *J Hypertens*. 2013;31(8):1502-1516. doi:10.1097/HJH.0b013e32836184b5
5. Hirabayashi N, Hata J, Furuta Y, et al. Association between diabetes and gray matter atrophy patterns in a general older Japanese population: the Hisayama Study. *Diabetes Care*. 2022;45(6):1364-1371. doi:10.2337/dc21-1911
6. Preul C, Lohmann G, Hund-Georgiadis M, Guthke T, Von Cramon DY. Morphometry demonstrates loss of cortical thickness in cerebral microangiopathy. *J Neurol*. 2005;252(4):441-447. doi:10.1007/s00415-005-0671-9
7. Jouvent E, Viswanathan A, Chabriat H. Cerebral atrophy in cerebrovascular disorders. *J Neuroimaging*. 2010;20(3):213-218. doi:10.1111/j.1552-6569.2009.00370.x
8. Pantoni L, Garcia JH. Pathogenesis of leukoaraiosis: a review. *Stroke*. 1997;28(3):652-659. doi:10.1161/01.str.28.3.652
9. Nakazawa T, Ohara T, Hirabayashi N, et al. Multiple-region grey matter atrophy as a predictor for the development of dementia in a community: the Hisayama Study. *J Neurol Neurosurg Psychiatry*. 2022;93(3):263-271. doi:10.1136/jnnp-2021-326611
10. Hu HY, Ou YN, Shen XN, et al. White matter hyperintensities and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 36 prospective studies. *Neurosci Biobehav Rev*. 2021;120:16-27. doi:10.1016/j.neubiorev.2020.11.007
11. Kang DH, Kanellis J, Hugo C, et al. Role of the microvascular endothelium in progressive renal disease. *J Am Soc Nephrol*. 2002;13(3):806-816. doi:10.1681/ASN.V133806
12. Ito S, Nagasawa T, Abe M, Mori T. Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. *Hypertens Res*. 2009;32(2):115-121. doi:10.1038/hr.2008.27
13. Cho EB, Shin HY, Park SE, et al. Albuminuria, cerebrovascular disease and cortical atrophy: among cognitively normal elderly individuals. *Sci Rep*. 2016;6:20692. doi:10.1038/srep20692
14. Sink KM, Divers J, Whitlow CT, et al. Cerebral structural changes in diabetic kidney disease: African American-Diabetes Heart Study MIND. *Diabetes Care*. 2015;38(2):206-212. doi:10.2337/dc14-1231
15. Freedman BI, Sink KM, Hugenschmidt CE, et al. Associations of early kidney disease with brain magnetic resonance imaging and cognitive function in African Americans with type 2 diabetes mellitus. *Am J Kidney Dis*. 2017;70(5):627-637. doi:10.1053/j.ajkd.2017.05.006
16. Vemuri P, Knopman DS, Jack CR, et al. Association of kidney function biomarkers with brain MRI findings: the BRINK study. *J Alzheimers Dis*. 2017;55(3):1069-1082. doi:10.3233/JAD-160834
17. Yamasaki K, Hata J, Furuta Y, et al. Association of albuminuria with white matter hyperintensities volume on brain magnetic resonance imaging in elderly Japanese - the Hisayama study. *Circ J*. 2020;84(6):935-942. doi:10.1253/circj.CJ-19-1069
18. Yakushiji Y, Nanri Y, Hirotsu T, et al. Marked cerebral atrophy is correlated with kidney dysfunction in nondisabled adults. *Hypertens Res*. 2010;33(12):1232-1237. doi:10.1038/hr.2010.171
19. Ikram MA, Vernooij MW, Hofman A, Niessen WJ, Van Der Lugt A, Breteler MMB. Kidney function is related to cerebral small vessel disease. *Stroke*. 2008;39(1):55-61. doi:10.1161/STROKEAHA.107.493494
20. Ninomiya T, Nakaji S, Maeda T, et al. Study design and baseline characteristics of a population-based prospective cohort study of dementia in Japan: the Japan Prospective Studies Collaboration for Aging and Dementia (JPSC-AD). *Environ Health Prev Med*. 2020;25(1):64. doi:10.1186/s12199-020-00903-3
21. Jack CR, Bernstein MA, Fox NC, et al. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. *J Magn Reson Imaging*. 2008;27(4):685-691. doi:10.1002/jmri.21049
22. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006;31(3):968-980. doi:10.1016/j.neuroimage.2006.01.021
23. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. American Psychiatric Association; 1987.
24. Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the quality standards subcommittee of the American Academy of Neurology. *Neurology*. 2001;56(9):1133-1142. doi:10.1212/wnl.56.9.1133
25. Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 clinical practice guideline for the management of glomerular diseases. *Kidney Int*. 2021;100(4):S1-S276. doi:10.1016/j.kint.2021.05.021
26. Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. Modification of the CKD Epidemiology Collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. *Am J Kidney Dis*. 2010;56(1):32-38. doi:10.1053/j.ajkd.2010.02.344
27. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc B*. 1995;57(1):289-300.
28. Sato Y, Fujimoto S, Konta T, et al. U-shaped association between body mass index and proteinuria in a large Japanese general population sample. *Clin Exp Nephrol*. 2014;18(1):75-86. doi:10.1007/s10157-013-0809-5
29. Ma Y, Ajnakina O, Steptoe A, Cadar D. Higher risk of dementia in English older individuals who are overweight or obese. *Int J Epidemiol*. 2020;49(4):1353-1365. doi:10.1093/ije/dyaa099
30. Yokomichi H, Kondo K, Nagamine Y, Yamagata Z, Kondo N. Dementia risk by combinations of metabolic diseases and body

mass index: Japan Gerontological Evaluation Study Cohort study. *J Diabetes Investig*. 2020;11(1):206-215. doi:10.1111/jdi.13103
31. Weiner DE, Bartolomei K, Scott T, et al. Albuminuria, cognitive functioning, and white matter hyperintensities in homebound elders. *Am J Kidney Dis*. 2009;53(3):438-447. doi:10.1053/j.ajkd.2008.08.022
32. Weiner DE, Gaussoin SA, Nord J, et al. Cognitive function and kidney disease: baseline data from the Systolic Blood Pressure Intervention Trial (SPRINT). *Am J Kidney Dis*. 2017;70(3):357-367. doi:10.1053/j.ajkd.2017.04.021
33. Lech RK, Suchan B. The medial temporal lobe: memory and beyond. *Behav Brain Res*. 2013;254:45-49. doi:10.1016/j.bbr.2013.06.009
34. Zhu Z, Gold BT, Chang CF, Wang S, Juan CH. Left middle temporal and inferior frontal regions contribute to speed of lexical decision: a TMS study. *Brain Cogn*. 2015;93:11-17. doi:10.1016/j.bandc.2014.11.002
35. Takae K, Hata J, Ohara T, et al. Albuminuria increases the risks for both Alzheimer disease and vascular dementia in community-dwelling Japanese elderly: the Hisayama study. *J Am Heart Assoc*. 2018;7(2):e006693. doi:10.1161/JAHA.117.006693
36. Gupta A, Burns JM. A single point-in-time eGFR is not associated with increased risk of dementia in the elderly. *J Am Soc Nephrol*. 2020;31(12):2965. doi:10.1681/ASN.2020081119
37. Xu H, Garcia-Ptacek S, Trevisan M, et al. Kidney function, kidney function decline, and the risk of dementia in older adults: a registry-based study. *Neurology*. 2021;96(24):e2956-e2965. doi:10.1212/WNL.0000000000012113
38. Etgen T, Chonchol M, Förstl H, Sander D. Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis. *Am J Nephrol*. 2012;35(5):474-482. doi:10.1159/000338135
39. Grasing M, Sharma P, Lepping RJ, et al. Association between the estimated glomerular filtration rate and brain atrophy in older adults. *Am J Nephrol*. 2022;53(2-3):176-181. doi:10.1159/000521892
40. Weiner DE. The cognition-kidney disease connection: lessons from population-based studies in the United States. *Am J Kidney Dis*. 2008;52(2):201-204. doi:10.1053/j.ajkd.2008.05.003
41. Garg JP, Bakris GL. Microalbuminuria: marker of vascular dysfunction, risk factor for cardiovascular disease. *Vasc Med*. 2002;7(1):35-43. doi:10.1191/1358863x02vm412ra
42. Heagerty AM, Aalkjaer C, Bund SJ, Korsgaard N, Mulvany MJ. Small artery structure in hypertension. Dual processes of remodeling and growth. *Hypertension*. 1993;21(4):391-397. doi:10.1161/01.hyp.21.4.391
43. Petrovitch H, White LR, Izmirilian G, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging study. *Neurobiol Aging*. 2000;21(1):57-62. doi:10.1016/S0197-4580(00)00106-8
44. De La Torre JC. Critically attained threshold of cerebral hypoperfusion: the CATCH hypothesis of Alzheimer's pathogenesis. *Neurobiol Aging*. 2000;21(2):331-342. doi:10.1016/S0197-4580(00)00111-1
45. Nishio K, Ihara M, Yamasaki N, et al. A mouse model characterizing features of vascular dementia with hippocampal atrophy. *Stroke*. 2010;41(6):1278-1284. doi:10.1161/STROKEAHA.110.581686
46. Fotiadis P, van Rooden S, van der Grond J, et al. Cortical atrophy in patients with cerebral amyloid angiopathy: a case-control study. *Lancet Neurol*. 2016;15(8):811-819. doi:10.1016/S1474-4422(16)30030-8
47. Gurol ME, Viswanathan A, Gidicsin C, et al. Cerebral amyloid angiopathy burden associated with leukoaraiosis: a positron emission tomography/magnetic resonance imaging study. *Ann Neurol*. 2013;73(4):529-536. doi:10.1002/ana.23830
48. Seliger SL, Longstreth WT. Lessons about brain vascular disease from another pulsating organ, the kidney. *Stroke*. 2008;39(1):5-6. doi:10.1161/STROKEAHA.107.496000
49. Freeman LR, Keller JN. Oxidative stress and cerebral endothelial cells: regulation of the blood-brain-barrier and antioxidant based interventions. *Biochim Biophys Acta*. 2012;1822(5):822-829. doi:10.1016/j.bbadis.2011.12.009
50. Knopman DS. Invited commentary: albuminuria and microvascular disease of the brain-a shared pathophysiology. *Am J Epidemiol*. 2010;171(3):287-289. doi:10.1093/aje/kwp429

Is CKD associated with brain atrophy or brain white matter lesion volume?

Kidney Medicine

Methods

Population-based cross-sectional study
Japan, 2016-2018

N = 8,630 adults aged ≥ 65 years and without dementia

Evaluation by brain MRI of:
Total brain volume **(TBV)** to intracranial volume **(ICV)** ratio
White matter lesion volume **(WMLV)** to ICV ratio

Analysis of covariance

Results

Increased urine albumin-to-creatinine ratio was associated with:

UACR → Lower **TBV/ICV** ***p=0.009** for trend; Higher **WMLV/ICV** ***p<0.001** for trend

Decreased estimated glomerular filtration rate was associated with:

eGFR → Lower **TBV/ICV** ***p<0.001** for trend; No significant association with **WMLV/ICV** after adjustment*

*After adjustment for age, sex, low education, eGFR and other clinical variables

Conclusion: Higher UACR was associated with brain atrophy, especially in the temporal cortex and hippocampus, and with increased WMLV. These findings suggest that urinary albumin may be a good biomarker for detecting high-risk individuals with brain structural changes and subsequent cognitive impairment.

Reference: Maki K, Ohara T, Hata J et al. CKD, brain atrophy, and white matter lesion volume: the Japan Prospective Studies Collaboration for Aging and Dementia. *Kidney Medicine*, 2023.

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