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# Cognitive impairment and hippocampal atrophy in chronic kidney disease

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**Background:** Cognition impairment is well known in patients with chronic kidney disease (CKD). The relationship between brain structure and cognitive performance in CKD patients is still under investigation. The study aimed to quantitatively assess the relationship between brain structure and cognitive performance in patients with CKD.
**Methods:** We recruited 39 patients with CKD and 39 age- and sex-matched control participants from a tertiary medical center. All participants underwent 3-T MRI scan neuropsychological assessments, and renal function tests. FreeSurfer software was used for imaging processing and analysis, including measurement of cortical thickness and gray matter (GM) and white matter volumes.
**Results:** Compared with control subjects (73.1±7.5 years old), patients with CKD (76.4±8.4 years old) had significantly lower scores on the Mini-Mental State Examination, and forward digit span test ($P<.01$). Patients with CKD had smaller cerebral GM volume, hippocampus, and decreased cortical thickness ($P<.01$) relative to the control group. Estimated glomerular filtration rate (eGFR) was correlated with cognitive performance, cortical thickness, GM volume, and hippocampal volume ($P<.001$). Linear regression analysis revealed that eGFR and GM volume were independently negatively associated with cognitive performance ($P<.001$), while eGFR and age were negatively associated with cortical thinning and GM volume after controlling for confounding factors.
**Conclusions:** This study demonstrated that impaired kidney function is associated not only with poor cognitive performance, but also with small cerebral GM volume and reduced cortical thickness.

KEYWORDS
cardiovascular disease, chronic kidney disease, cognition, cortical thickness, gray matter volume, Hippocampus, magnetic resonance imaging

## 1 | INTRODUCTION

Chronic kidney disease (CKD) is a major health issue worldwide due to its progressive course and the risk of adverse outcomes. Cognitive impairment has long been recognized in patients with end-stage renal disease (ESRD). The prevalence of cognitive impairment in persons with kidney failure is approximately 30%-60%,[1-3] more than twice that found in an age-matched general population.[4] Our previous study demonstrated that middle-aged women with moderate CKD had significantly worse cognitive performance in delayed recalls and backward digit span tests than did control subjects.[5] Other studies have also suggested that general cognitive dysfunction or specific cognitive impairments are already present in early stages of CKD.[6,7]

About one-third of middle-aged patients with CKD were found to have silent cerebral white matter (WM) lesions associated closely with vascular nephropathy.[8] Some studies showed that more white matter

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hyperintensity (WMH) were noted in the brains of patients with CKD[9] and a study conducted in Japan using indirect semiquantitative measurement determined that the estimated glomerular filtration rate (eGFR) was strongly associated with cerebral atrophy.[10] Little is known about the relationships between cognitive performance and brain structure features, as characterized by detailed quantitative evaluation, in patients with CKD. Thus, the aims of this study were to analyze the correlation between brain structure and cognitive dysfunction by quantitative measurement of gray matter (GM), WM parameters, and the cognitive performance in patients with CKD.

## 2 | METHODS

### 2.1 | Participants

We recruited patients with CKD and age- and sex-matched control participants from the nephrology and general outpatient clinics, respectively, of Taipei Veterans General Hospital (TVGH). The control subjects are those patients, or their spouses, who visit the clinics without memory complaints and with normal renal function. All patients with CKD have independent activities of daily living despite of various cognitive performances. Among these patients with CKD, two patients had stage 2 (mild), 18 patients had stage 3 (moderate), 11 patients had stage 4 (severe), and eight patients had stage 5 (kidney failure) CKD. We classified subjects according to eGFR, determined using the abbreviated Modification of Diet in Renal Disease (MDRD) formula[11]:

$$eGFR = 186 \times (\text{serum creatinine [mg/dL]}^{-1.154}) \times \text{age}^{(-0.203)} \times (0.742 \text{ for women}).$$

Chronic kidney disease was categorized according to the criteria of the U.S. National Kidney Foundation Kidney Disease Outcomes Quality Initiative.[12] Staging was based on the presence of kidney damage and level of kidney function, defined by eGFR. Kidney damage was defined as pathologic abnormalities or markers of damage, including abnormalities detected by blood or urine test (e.g., hematuria, proteinuria, or pyuria) or imaging studies (e.g., renal cyst or collecting system abnormality), for more than 3 months. Stage 1 was defined as eGFR>90, stage 2 (mild function reduction) as eGFR of 60-89 mL/min/1.73 $m^2$, stage 3 (moderate reduction) as eGFR of 30-59 mL/min/1.73 $m^2$, stage 4 (severe reduction) as eGFR of 15-29 mL/min/1.73 $m^2$), and stage 5 (kidney failure) as eGFR<15 mL/min/1.73 $m^2$.

Exclusion criteria were current dialysis therapy, including peritoneal dialysis and hemodialysis; pregnancy or breastfeeding; history of chemotherapy or radiation therapy for any cancer; psychiatric disorder; hearing or visual disability that could affect cognitive tests; clinical evidence of prior stroke; and prior diagnosis of dementia and abnormal activity of daily function.

### 2.2 | Data collection and assessments

We recorded demographic and medical history data for each participant and measured blood pressure, body weight, and height. The body mass index (BMI) was calculated as body weight divided by body height squared (kg/$m^2$). All study participants underwent neuropsychological testing and brain magnetic resonance imaging (MRI). Blood samples were collected for the laboratory measurement of serum creatinine level, eGFR, and lipid profile.

#### 2.2.1 | Neuropsychological tests

The following tests were administered:

a. Mini-Mental State Examination (MMSE)[13]: This 11-item questionnaire, which evaluates subjects' memory, orientation, attention, calculation, and language, was used to screen for cognitive impairment. The highest possible score is 30 points, and lower scores reflect poorer cognition.
b. Forward and backward digit span subtests of the Wechsler Adult Intelligence Scale-Revised[14]: These tests require the participant to repeat digits in forward and reverse orders, respectively. The forward digit span test was used to evaluate attention and concentration, and the backward digit span test was used to evaluate attention and working memory.
c. Verbal fluency test[15]: This test requires the subject to name as many animals as possible in 1 minute. The score is the number of different animals correctly named (one point for each correct response). This test can be used to evaluate language and executive function.

#### 2.2.2 | MRI data acquisition

Brain MRI series were performed using a 3T MRI scanner (Discovery 750; General Electric, Milwaukee, PA, USA) with a $T_1$-weighted pulse sequence. Imaging parameters were repetition time/echo time/inversion time ([TR/TE/TI])=2530/3.49/1100 ms, flip angle=7°, partition thickness=1.33 mm, image matrix=256×256, 128 partitions, and field of view=21×21 cm. A fluid attenuation inversion recovery (FLAIR) turbo spin-echo sequence was also performed using the following parameters: TR/TE/TI=6000/127.7/1864 ms, slice thickness=1 mm, image matrix=256×256, 180 slices, and field of view=26×26 cm.

#### 2.2.3 | Image processing

Structural $T_1$ MRI reconstruction was performed used FreeSurfer, version 5.1.0, which is a set of software tools for the study of neuroanatomy from brain MRI data.[16-18] In the cortical surface stream, the tools construct models of the boundary between WM and GM, as well as the pial surface boundary between GM and cerebrospinal fluid (CSF). The GM/WM boundary was further processed to yield two triangulated mesh models with optimally 10242 vertices for each hemispheres.[19-21] This cortical surface model was then used to facilitate visualization after "inflation".[19,20]

After reconstruction of these surfaces, an array of anatomical measures was generated, including cortical thickness, surface area, cortex curvature, surface normal direction at each point on the cortex, and volumes of major subcortical and ventricular structures. Procedures for the measurement of cortical thickness have been previously

**TABLE 1** Demographic and clinical characteristics of the study population

| | CKD (n=39) | Control (n=39) | *P* |
|---|---|---|---|
| Sex (male) | 31 (79.4%) | 32 (82.5%) | .78 |
| Age (years) | 76.4±8.4 (54-85) | 73.1±7.5 (61-85) | .07 |
| Education (years) | 10.9±4.9 (0-16) | 12.9±4.5 (0-16) | .07 |
| Body mass index | 24.6±3.0 | 24.0±2.7 | .52 |
| Diabetes mellitus | 29 (74.4%) | 8 (20.1%) | .008 |
| Hypertension | 34 (85.0%) | 24 (61.5%) | .02 |
| Dyslipidemia | 24 (60.0%) | 15 (38.5%) | .035 |
| Serum creatinine (mg/dL) | 2.50±1.50 | 0.93±0.16 | <.001 |
| eGFR (mL/min/1.73 $m^2$) | 35.0±17.3 | 79.3±13.4 | <.001 |
| Mini-Mental Status Examination | 25.0±4.2 | 28.4±1.4 | <.001 |

Data are presented as n (%), mean±standard deviation, or mean±standard deviation (range). CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

validated with histological analysis[22] and manual processing.[23,24] In addition, FreeSurfer defined a cortical surfaced-based atlas based on average folding patterns mapped to a sphere. Surfaces from individuals were aligned with this atlas with a high-dimensional nonlinear registration algorithm. The registration is based on aligning the cortical folding patterns and so directly aligns the anatomy instead of image intensities. The spherical atlas naturally forms a coordinate system in which point-to-point correspondence between subjects can be achieved. This coordinate system can then be used to morph between an individual subject and standard brain template and to create group maps (similar to how Talairach space is used for volumetric measurements[17]). Moreover, an array of non-cortical structures, including the hippocampus, amygdala, lateral ventricles, and thalamus, was also automatically labeled. The total intracranial volume is used to normalize volumes by simple division.

White matter hyperintensity was defined as hyperintense changes on intermediate-intensity FLAIR and $T_2$-weighted images with no corresponding $T_1$ abnormality. WMH volumes were determined using FLAIR images and by automated WM lesion segmentation, the Lesion Segmentation Toolbox[25]; it was an extension toolbox of Statistical Parametric Mapping (SPM8), which is written in MATLAB (MathWorks, Natick, MA, USA). Previous study had showed good validity for determining WMH volume compared with subjective WM lesion rating scale.[26]

### 2.3 | Statistical analysis

All statistical analyses were carried out using SPSS (IBM SPSS statistics, version 22.0, Armonk, NY, USA). Demographic and other health-related variables were compared between the moderate to severe CKD and control groups using *t* tests or chi-square tests, respectively. All results are presented as means±standard deviation, unless otherwise noted. Moreover, the brain volumetric measurements were corrected for age and neuropsychological tests were corrected for age and education by multiple linear regression. The *t*-statistics and associated *P* values were used in testing whether a given coefficient in regression equation is significantly different from zero. To test the hypothesis that CKD diagnosis was associated with neuropsychological test performance (outcome variable), Pearson correlation analyses and multivariate regression analyses adjusted for potential confounding variables, which were eGFR, age, education, diabetes, hypertensions, and hyperlipidemia, were performed. To balance type I and type II errors in multiple comparisons, we defined a significance level of $P<.01$. Statistical maps of the difference in cortical thickness were thresholded at a false discovery rate (FDR) of 0.05.[27]

## 3 | RESULTS

### 3.1 | Characteristics of the study population

In total, 39 (31M/8F) patients with CKD (mean age, 76.4±8.4 [range, 54-85] years) and 39 (32M/7F) subjects with normal renal function (mean age, 73.1±7.5 [range, 61-85] years) participated in this study. No difference in age, sex, education level, or BMI was observed between groups. Table 1 displays demographic and medical characteristics of the study sample.

Estimated glomerular filtration rate values were lower among patients with CKD than among control subjects (35.0±17.3 vs 79.3±13.4, $P<.001$). The rates of diabetes and dyslipidemia were higher among patients with CKD than among control subjects ($P<.01$).

### 3.2 | Results of neuropsychological testing

Table 2 shows neuropsychological test results. Compared with the control group, patients with CKD had significantly lower scores on the MMSE (28.4±1.4 vs 25.0±4.2) and forward digit span test (11.0±2.1 vs 9.1±2.2; both corrected $P<.01$). No difference in the backward digit span test and verbal fluency was observed between groups after correcting for age and education by multiple linear regression model (Table 3).

### 3.3 | Hippocampus, gray matter volume, and cortical thickness

Brain morphometric values are presented in Table 2. The effect of CKD status on brain volume after corrected for age by multiple linear

**TABLE 2** Neuropsychological test scores and white matter and gray matter parameters

| | CKD (n=39) | Control (n=39) | *P* |
|---|---|---|---|
| Verbal fluency | 11.7±3.2 | 10.8±3.1 | .04 |
| Forward digit span | 9.1±2.2 | 11.0±2.1 | .03 |
| Backward digit span | 5.8±2.6 | 7.0±2.1 | .35 |
| WMH volume ($mm^3$) | 18.8±19.0 | 12.0±15.1 | .09 |
| Gray matter volume ($10^4$ $mm^3$) | 45.1±4.3 | 48.1±3.6 | .004 |
| White matter volume ($10^4$ $mm^3$) | 34.7±5.4 | 38.1±4.4 | .007 |
| Hippocampus ($10^3$ $mm^3$) | 6.7±0.8 | 7.5±0.8 | <.001 |
| Total intracranial volume ($10^4$ $mm^3$)* | 146.0±17.4 | 149.9±14.3 | .29 |
| Cortical thickness (mm) | 2.49±0.15 | 2.59±0.12 | <.001** |

CKD, chronic kidney disease; WMH, white matter hyperintensity.
*Estimated total intracranial volume.
**Corrected *P* using FDR=0.05.

regression is shown in Table 3. Detailed regression analyses are listed in Table S1. Cerebral GM, WM, and hippocampus volumes were smaller in patients with CKD than in control subjects by 6.2%, 8.9% and 10.7%, respectively (*P*<.01) (Figure 1). There is no significant difference in WMH volume between two groups. Average cortical thickness was lower among patients with CKD than among control subjects (2.49±0.15 vs 2.59±0.12 mm, *P*=.003). Using an FDR of 0.05, we found that 2.7% and 3.5% of brain surface vertices in the right and left hemispheres (n=10 242 each), respectively, were smaller in the CKD group than in the control group. Figure 2 shows the main differences in cortical thickness between groups. There are in the bilateral occipito-temporal medial lingual gyri, left frontal pole, bilateral superior temporal sulci, left calcarine sulci, left inferior temporal sulcus, right superior circular insula, and right parieto-occipital sulcus (Table S2).

### 3.4 | Correlation analysis of renal function, cognition, and brain measurement

Estimated glomerular filtration rate was moderately correlated with MMSE score, cortical thickness, and GM and hippocampal volumes (*r*=.48, .43, .35, and .37, respectively; all *P*<.001), but not with WM or WMH volume (*r*=.27 and −.07, respectively; *P*=.02 and *P*=.58) (Figure 3). In addition, MMSE score was correlated with GM and hippocampal volumes (*r*=.42 and .31, respectively; both *P*<.001).

A multiple linear regression model was created for each neuropsychological test to assess the significance of the effects of moderate to severe CKD diagnosis and brain morphometric measurement. GM volume, hippocampal volume, and cortical thickness were set as dependent variables while independent variables were eGFR, age, years of education, diabetes, hypertension, and dyslipidemia. Table 4 showed

**TABLE 3** Estimates of multiple linear regression models with neuropsychological test scores and brain volume parameters as dependent variables and age, education, and CKD as independent variables, showing effects by standardized coefficients (beta value)

| | Variables control in the models | | |
|---|---|---|---|
| Dependent variable | Age | CKD[a] | Education |
| MMSE | −0.03 | −0.42** | 0.25 |
| Verbal fluency | −0.37* | 0.24 | 0.18 |
| Forward digit span | −0.11 | −0.35* | 0.15 |
| Backward digit span | −0.21 | −0.10 | −0.41** |
| WMH volume | 0.19 | 0.15 | |
| Gray matter volume | −0.19 | −0.32* | |
| White matter volume | −0.12 | −0.31* | |
| Hippocampus volume | −0.30* | −0.38** | |
| Total intracranial volume | 0.09 | −0.14 | |
| Cortical thickness | −0.28* | −0.33* | |

CKD, chronic kidney disease; MMSE, Mini-Mental State Examination; WMH, white matter hyperintensity; CKD[a], 0=normal control, 1=CKD.
**P*<0.01.
***P*<0.0001.

eGFR and age significantly predicted hippocampal volume, cortical thickness, and GM volume (*P*<.01).

## 4 | DISCUSSION

In this study, we found that eGFR was moderately correlated with cognitive function, cortical thickness, and GM volume. Study participants with reduced kidney function, had impaired cognitive performance, less cortical thickness, and smaller hippocampal volume and GM volume than did subjects with normal renal function. In further regression analysis, we found that renal function and age were major contributing factors for cortical thickness, GM, and hippocampal volume after controlling for confounding factors.

A few studies have reported brain atrophy and WMH burden in patients with CKD or renal failure.[9,10,28-31] A meta-analysis of numerous structural and functional neuroimaging studies that examined children and adults with CKD identified several clear trends, including cerebral atrophy, WMH, cerebral infarction, microbleeding, and cerebral blood flow pattern with affective disorders.[31] In the retrospective population-based Rotterdam Scan Study, subjects with low eGFR had smaller brain and deep WM volumes and more WMH.[30] No close relationship was found between eGFR and GM or WM volume, which is not fully consistent with our results.[30] The demographic characteristics of participants in the Rotterdam Scan Study differed from those of our study subjects, such as lower percentage of diabetes and hypertension, and the higher ratio of male patients to female patients than those in our study population. Nevertheless, the Rotterdam Scan Study lacked neuropsychological assessment, which precluded correlation of brain measurements with cognitive

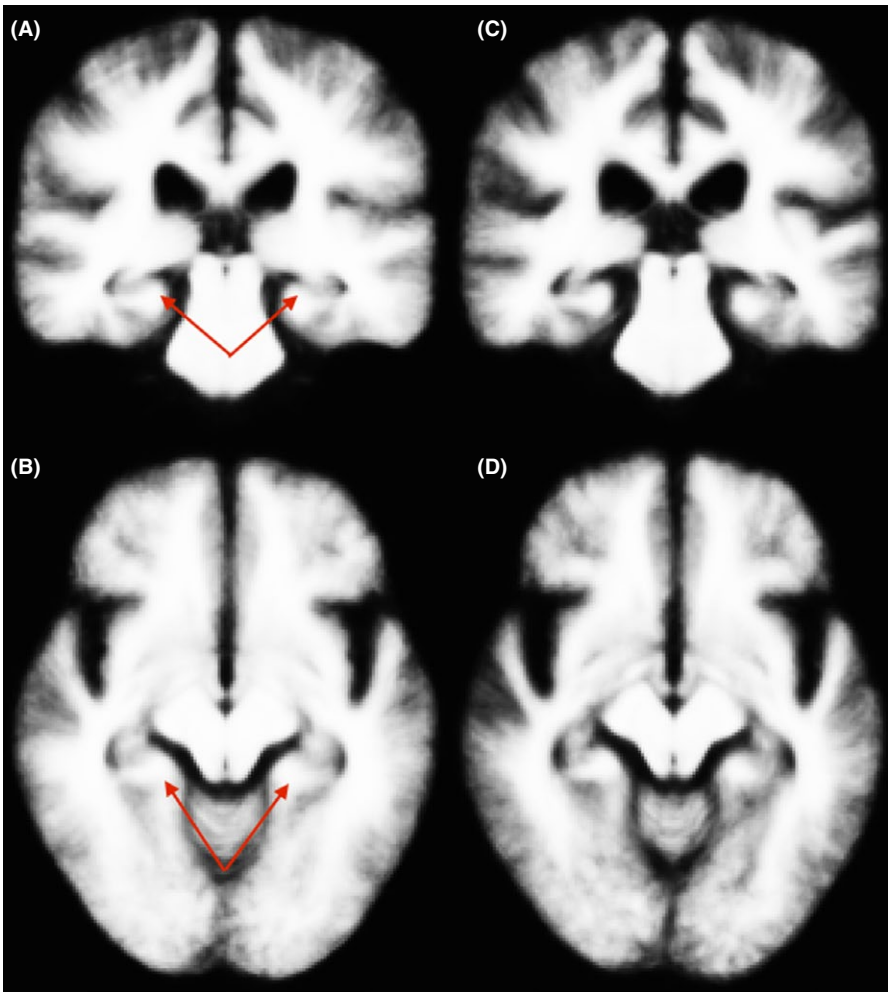


**FIGURE 1** The average brain volume image of control subjects is shown on A (coronal view) and B (axial view), whereas the brain average volume image of patients with chronic kidney disease (CKD) is shown on C and D. Red arrow indicates the hippocampus which is located according to Talairach coordinates. Dilated ventricle and perisylvian space and reduced hippocampal volume are noted in CKD group

performance. Most previous imaging analyses were focused on grading of WMH and detection of ischemic infarction, which were based on qualitative visual rating, rather than objective quantitative measurement. However, little about quantitative measurement of brain structure in patients with CKD was reported. Furthermore, our study quantitatively showed the GM, WM, and hippocampus volumes decreased by 6.2%, 8.9%, and 10.7%, respectively, in patients with CKD compared with control subjects. The hippocampal volume seems to be more affected by eGFR and age than global GM and WM volume.

We observed significant cortical thinning in bilateral superior temporal sulci and medial lingual gyri in these patients with CKD, while the patients with CKD showed lower global cognition scores and poorer performance in working memory (forward digit span) than control group. Cortical thinning has been associated with cardiovascular risk factors, such as hypertension and diabetes, in patients with mild cognitive impairment or dementia.[32] However, eGFR and age were independently related to GM volume and cortical thickness in analyses controlling for the vascular component in our study. The CKD group also showed a significant reduction in hippocampal volume. Hippocampal atrophy has been shown to be an effective marker differentiating people with normal and impaired cognition, regardless of WMH and lacunar infarcts.[33] Thus, renal function seems to be an independent factor affecting cortical atrophy and thinning *via* an uncertain mechanism rather than cerebrovascular risk factors. Nevertheless, the difference in WMH between patients with CKD and control subjects did not reach significant level in this study. This result may be explained by the more frequent occurrence of WMH in patients with advanced CKD and those receiving hemodialysis, whereas about half of patients in our study had moderate CKD.

In line with previous studies,[2,5,34] the present study showed that patients with CKD had poorer global cognitive function, executive function, verbal, and working memory than control subjects. A recent meta-analysis found that cross-sectional and longitudinal studies have demonstrated a significantly increased risk of cognitive impairment in patients with CKD.[35] Furthermore, another longitudinal cohort study conducted in Japan found that CKD is independently associated with the risk of dementia in patients with vascular components.[36] These results are consistent with the hypothesis of a connection between renal impairment and dementia risk.

The close relationship between cardiovascular risk factors and small vessel dementia is well established.[37] Recently, CKD was shown to be related to neurological disorders and this brain-renal connection is thought to involve small vessel disease in the kidney and brain, based on hemodynamic similarities.[38] The main pathologic vascular feature of CKD, albuminuria, implied impaired kidney vascular integrity, which might be

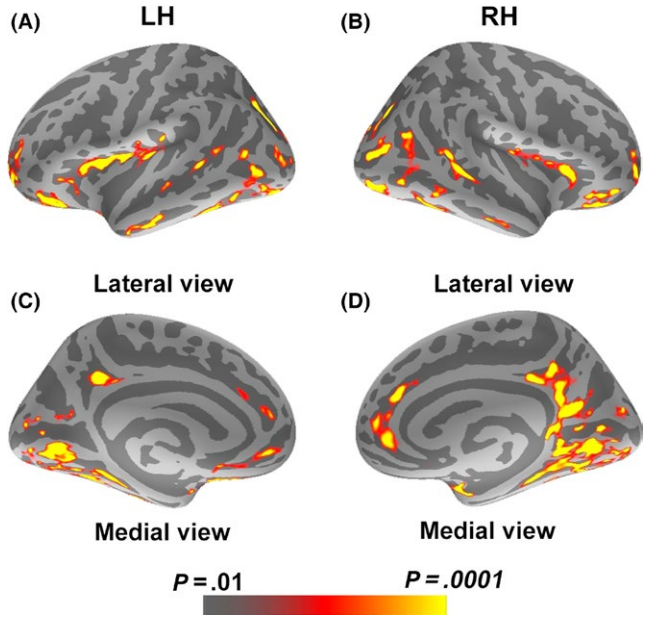


**FIGURE 2** Maps identifying regions of lesser cortical thickness (highlighted) in patients with chronic kidney disease relative to control subjects. Main affected regions were the lateral temporal, orbital frontal, and occipital lobes. (A,C) lateral and medial sides of the left hemisphere, respectively; (B,D) lateral and medial sides of the right hemisphere, respectively. Scale for false discovery rate(FDR) *P* values is .01-.0001. LH, left hemisphere; RH, right hemisphere

found in other organs with similar vascular bed. Recent study showed lower eGFR is independently associated with lower cerebral blood flow. The impaired cerebral autoregulation, which may be related to hypoperfusion, was thought to increased risk of dementia.[39] Furthermore, it has been suggested that various toxins have been involved in the pathogenesis of cognitive impairment in uremic patients.[40] Oxidative radicals, elevated serum homocysteine level, and inflammation have also been related to cognitive impairment in dialysis patients. These factors were thought to lead to vascular endothelial dysfunction and thus aggravate the atherosclerosis and risk of dementia.[41] These studies implied the impaired renal function, as measured by decreased eGFR, with alterations in water and electrolytes balance, accumulation of vasoactive species, and chronic inflammation is related to cerebral small vessel disease, independent of cardiovascular risk factors.[30] These findings are consistent with our study results, which impaired eGFR is correlated with reduced GM volume and global cognitive performance, independent of other cardiovascular disease. In contrast, some study showed that mild CKD was associated with an increased risk of Alzheimer disease (AD).[36] The longitudinal BRain IN Kidney disease study found smaller GM volume in ROIs associated with both AD (tempo-parietal areas) and VCI (frontal lobes), worse cognition function than patients without CKD.[42,43] Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) reported both Alzheimer type and vascular pathology were found in most elder sample with cognitive decline by necropsy.[44] Thus, the possibilities of mixed AD and VCI in CKD group should be taken in to account.

The strengths of this study include the examination of patients with moderate CKD and the use of automated MRI analysis, which allowed us to accurately quantify cortical thinning and GM and WM atrophy and to investigate subcortical WM lesions. We clearly demonstrated associations between CKD and cognitive performance, cortical GM volume, cortical thickness, and eGFR. To our knowledge, this study is the first to report on cognitive impairment in patients with CKD based on comprehensive quantitative measurement of brain structure and renal function.

This study has some limitations. First, diabetes was more prevalent among patients with CKD than among control subjects, reflecting a similar difference in the Taiwanese population (the prevalence of diabetes is about 15% in individuals with and 4% in those without CKD).[45] To eliminate the effect of this difference, we used a multiple linear regression model adjusted for age, education, diabetes, and other comorbidities. Second, patients were recruited from a tertiary medical center, rather than a community-based hospital, which may have led to selection bias. Third, smoking is indeed a major cardiovascular factor. Although the prevalence of smoking in adults in Taiwan is getting lower, from 24% in 2004 to 14.4% in 2013,[46] it might have some bias because we did not control this risk factor. Forth, present study does not include CSF markers and PET isotope study, and the possibilities of prodrome of AD in CKD group cannot be excluded. Finally, although cortical thickness, GM volume, and MMSE score were lower in the CKD group than in control subjects in the present study, cause-effect relationships between renal function, brain morphometric features and cognitive performance remain uncertain because of the cross-sectional study design and lack of longitudinal data.

In conclusion, the results of this study show that impaired kidney function is independently related to cerebral hippocampal volume, GM volume, cortical thickness, and cognitive performance after adjusting for confounding vascular risk factors. The mechanism of cognitive impairment in patients with CKD may not only be related to small vessel disease but also involved the neurodegenerative process. Our results further emphasize the importance of identifying those with subclinical CKD, in whom impaired renal function might play a crucial role in cognitive decline and brain morphometric changes. These patients might benefit from early and appropriate therapy. Clinicians' monitoring of cognitive performance in patients with CKD using brain structure surveys is important. However, more studies are needed to investigate the extent to which any intervention can be beneficial.

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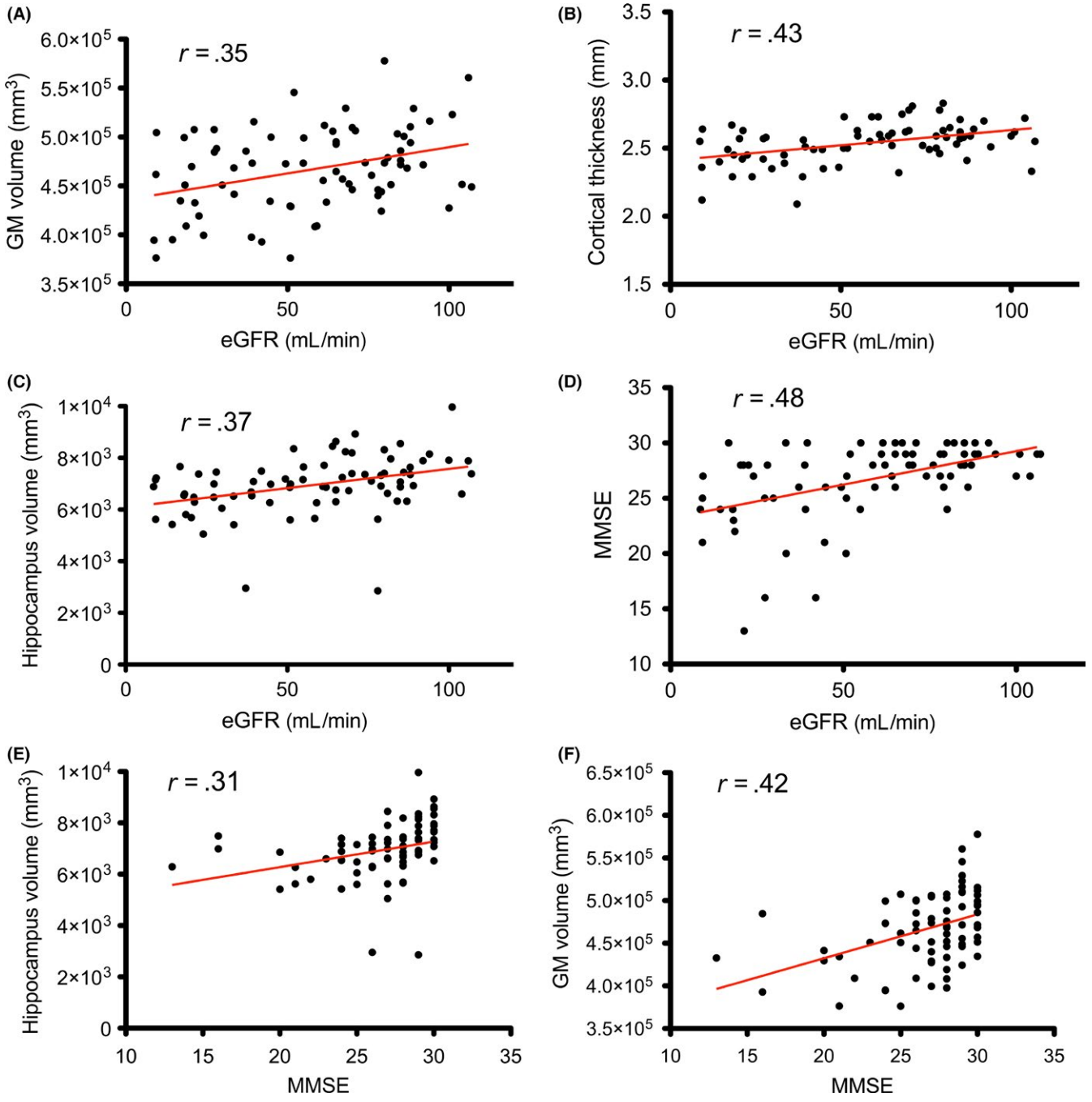


**FIGURE 3** Correlations among estimated glomerular filtration rate (eGFR), gray matter volume, and MMSE score eGFR was correlated with brain structure measurement and cognitive performance. (A-D) while cognition was correlated with global and hippocampal volume(E,F). *r*=correlation coefficient. MMSE, Mini-Mental State Examination; eGFR, estimated glomerular filtration rate (mL/min/1.73 $m^2$)

**TABLE 4** Results of multiple linear regression analyzing renal function and age as predictors of brain structure

| | eGFR (standardized coefficient) | Age (standardized coefficient) | Adjusted $R^2$ | *P* |
|---|---|---|---|---|
| Hippocampal volume | 0.41 | −0.35 | 0.30 | .001 |
| Cortical thickness | 0.36 | −0.33 | 0.25 | <.001 |
| Gray matter volume | 0.32 | −0.22 | 0.15 | .001 |

Data are $R^2$=coefficient of determination. eGFR, estimated glomerular filtration rate.

## AUTHOR CONTRIBUTIONS

Chun-Yuan Chang performed drafting/revising the manuscript, analysis and interpretation of data, statistical analysis, and image processing. Chih-Ching Lin revised the manuscript and performed study concept and design, acquisition of data, and study supervision. Chia-Fen Tsai revised the manuscript, and performed study concept and design, and acquisition of data. Wu-Chang Yang revised the manuscript and performed study concept and design, acquisition of data, and study supervision. Shuu-Jiun Wang revised the manuscript, performed study concept and design, study supervision, and obtained funding. Fa-Hsuan Lin revised the manuscript and carried out analysis and interpretation of data, image software support, and study supervision. Jong-Ling Fuh revised the manuscript, performed study concept and design, analysis and interpretation of data, statistical analysis, study supervision, and obtained funding.

## CONFLICT OF INTEREST

C-Y Chang and W-C Yang have no disclosure. C-F Tsai has received research support from the Taipei Veterans General Hospital. S.-J. Wang has served on the advisory boards of Allergan, Eli Lilly Taiwan, and DaiiSankyo. He has received speaking honoraria from local companies (Taiwan branches of MSD, Elli Lilly, and GSK). He has received research grants from the Taiwan National Science Council, Taipei Veterans General Hospital, Taiwan Headache Society, and Norvatis Taiwan branch. C-C Lin and J.-L. Fuh have received research support from the Taiwan National Science Council and Taipei Veterans General Hospital. Fa-Hsuan Lin has received research support from the Taiwan National Science Council.

## ETHICAL STANDARD

All the participants have the informed consent signed. The study was conducted in accordance with the Declaration of Helsinki Criteria and was approved by the Institutional Review Board of the Taipei Veterans General Hospital.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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