Effect of Kidney Dysfunction on Cerebral Cortical Thinning in Elderly Population

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Chronic kidney disease has been linked to cognitive impairment and morphological brain change. However, less is known about the impact of kidney functions on cerebral cortical thickness. This study investigated the relationship between kidney functions and global or lobar cerebral cortical thickness (CTh) in 259 non-demented elderly persons. Forty-three participants (16.7%) had kidney dysfunction, which was defined as either a glomerular filtration rate (GFR) of <60 ml/min/1.73 m² or presence of proteinuria. Kidney dysfunction was associated with lower global (β = −0.05, 95% CI = −0.08 to −0.01) as well as frontal, parietal, temporal, occipital, and insular lobar CTh. In the stratified analysis, the associations were more pronounced in women, APOEε4 non-carriers, and participants with a lower cognitive score. Besides, kidney dysfunction significantly increased the risk of cortical thinning, defined as being the lowest CTh tertile, in the insular lobe (adjusted odds ratio = 2.74, 95% CI = 1.31 – 5.74).

Our results suggested that kidney dysfunction should be closely monitored and managed in elderly population to prevent neurodegeneration.
dementia are both common diseases in the elderly, and CKD has been proposed as an independent risk factor for cognitive impairment\(^a\). A population-based study had demonstrated that cognitive impairment is common not only in hemodialysis patients, but also in the less severe stages of CKD\(^b\). CKD was also linked to subclinical brain MRI abnormalities, such as cerebral small vessel disease, white matter hyperintensities, or global brain atrophy.\(^c\)\(^d\)\(^e\)\(^f\)\(^g\)\(^h\)\(^i\)\(^j\)\(^k\)\(^l\)\(^m\)\(^n\)\(^o\)\(^p\)\(^q\)\(^r\)\(^s\)\(^t\)\(^u\)\(^v\)\(^w\)\(^x\)\(^y\)\(^z\) However, less is known about the relationship between kidney functions and cortical thickness of the brain, especially in a nondisabled elderly population. Therefore, the present study aimed to investigate the potential impact of kidney dysfunctions on cerebral cortical thickness in a group of independently living older persons. This study further explored whether age, gender, APOE\(\epsilon\)4 status and cognitive function affect the association between kidney function and cerebral cortical thickness.

**Methods**

**Study Population.** This is a cross-sectional study from a prospective cohort study (2011-present). Participants aged 65 years or older were recruited from the annual Elderly Health Checkup (EHC) at National Taiwan University Hospital (NTUH) from 2011 to 2013, and all participants underwent a brain MRI examination, except those with contraindications (e.g., implantation of a cardiac pacemaker, defibrillators or other electronic devices, received intracranial metal coils, or claustrophobia). A total of 397 participants who underwent a brain MRI examination were recruited. To clarify the cross-sectional relationship between kidney function and structural brain change, the MRI examination had to be performed within 6 months of specimen collection, along with questionnaire administration, and other clinical examinations \((n = 263)\). As the study aimed to investigate the brain structural change among elderly people without known destructive or degenerative neurological diseases, we excluded those with a history of stroke \((n = 3)\) or using medication for Alzheimer’s disease (AD, \(n = 1)\). After exclusion, 259 participants were included for statistical analysis. Informed consent was obtained from each participant before administration of questionnaires, performing clinical assessments, and collection of biological specimen at NTUH. The research plan, informed consent, questionnaires, and application forms were approved by the Institutional Review Board at NTUH. All methods were carried out in accordance with the approved guidelines and regulations.

**Acquisition of MRI.** Brain MRI was performed using a single 1.5-T scanner with high-resolution T1-weighted volumetric MRI scans. All MRI images were processed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu). The FreeSurfer image analysis suite can perform surface extraction, cortical parcellations and thickness computation\(^i\). The cortical thickness (CTh) of each participant was derived from a surface-based pipeline consisting of several stages, including but not limited to the following: image registration via affine transformation to Montreal Neurological Institute atlas, correction of intensity inhomogeneities, removal of skull using a deformable template model, classification of voxels into white matter and non-white matter based on intensity, tessellation of gray-white matter boundaries, automated correction of topological defects, and surface reconstruction to delineate the gray matter-cerebrospinal fluid and gray matter-white matter borders. Ultimately, cortical thickness was obtained at each vertex by computing the shortest distance between the above two surfaces (gray matter-cerebrospinal fluid and gray-white matter). In the FreeSurfer analysis suite, there were 34 predefined regions of interest in each cerebral hemisphere\(^i\). Cortical thickness (CTh) was expressed in micrometers as global (whole brain) average and lobar (left and right thickness averaged for frontal, parietal, temporal and occipital lobes) average. The method of cortical thickness measurements has been validated with histological data\(^i\) and manual measurements\(^i\), and has been used in several previous studies\(^i\)\(^j\)\(^k\)\(^l\)\(^m\)\(^n\)\(^o\)\(^p\)\(^q\)\(^r\)\(^s\)\(^t\)\(^u\)\(^v\)\(^w\)\(^x\)\(^y\)\(^z\). Further, total intracranial volume was quantified by automatic segmentation with the FreeSurfer analysis suite. White matter lesions, defined as areas in cerebral white matter that appear abnormally hypointense on T1-weighted or hyperintense on T2-weighted images, were semi-quantitatively graded according to an age-related white matter change rating scale \((score 0–3, \text{with a higher score representing more severe lesions})\) by an experienced neuroradiologist who was unaware of the study population\(^i\)\(^j\)\(^k\)\(^l\)\(^m\)\(^n\)\(^o\)\(^p\)\(^q\)\(^r\)\(^s\)\(^t\)\(^u\)\(^v\)\(^w\)\(^x\)\(^y\)\(^z\). Lacunes were defined as small lesions \((\leq 15 \text{mm in diameter})\) with a low signal on T1-weighted and high signal on T2-weighted images. The presence or absence of lacunes was recorded. In addition to the use of continuous CTh variable for analysis, CTh was further organized into tertiles to identify potential susceptible population from a public health perspective. Cerebral cortical thinning was defined as the lowest tertile (T1), while normal CTh was defined as the remaining tertiles (T2\(\text{ }\)T3).

**Kidney function.** To estimate kidney function parameters, the serum creatinine level was obtained from a blood test, and glomerular filtration rate \((\text{GFR})\) was calculated using the Chronic Kidney Disease Epidemiology Collaboration \((\text{CKD-EPI})\) equation\(^i\): 

\[
GFR = 141 \times \min \left( \frac{\text{Scr}}{\kappa}, 1 \right)^{\alpha} \times \max \left( \frac{\text{Scr}}{\kappa}, 1 \right)^{-1.209} \times 0.993^{0.911} \times 1.018 \text{ (if female)}
\]

In this equation, Scr is serum creatinine \((\text{mg/DL})\), \(\kappa\) is 0.7 for females and 0.9 for males, \(\alpha\) is \(-0.329\) for females and \(-0.411\) for males, min indicates the minimum of \(\text{Scr}/\kappa\) or 1, and max indicates the maximum of \(\text{Scr}/\kappa\) or 1. This equation was more accurate, less biased, and better for precision than the traditionally used Modification of Diet in Renal Disease Study \((\text{MDRD})\) equation\(^i\). Urine was also collected from each participant for urinalysis. The level of urinary protein was examined using a urine dipstick and was classified into absence \((\text{dipstick reading 0 or +})\) or presence \((1+\text{ or } 2+\text{ or } 3+)\) of proteinuria, with \(1+\) approximately corresponding to a proteinuria level of 30 mg/DL, which is the cut-off value for microalbuminuria\(^i\)\(^j\)\(^k\)\(^l\). In this study, ‘kidney dysfunction’ was defined if a participant had either a GFR < 60 ml/min/1.73 m\(^2\) or presence \((\geq 1+)\) of proteinuria.
Covariates. A set of relevant covariates was obtained during the study period (2011–2013). Demographic data included age, gender, body mass index (BMI), years of education, and history of smoking. Medical comorbidities such as hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome, or depressive symptoms were documented based on self-report by the participants, available medical records or laboratory data. Laboratory data from blood specimens included total cholesterol, triglycerides, glucose, and APOE4 status. Cognitive function was evaluated by a trained assistant using the Taiwan version of Montreal Cognitive Assessment (MoCA-T)24, which is a brief test that evaluates several cognitive domains, including visuospatial, executive function, language, verbal memory, attention, and orientation. The MoCA-T scores range from 0 to 30. Participants with MoCA-T score of less than 24 would be classified as having cognitive impairment24. In addition, participants were surveyed using the self-report Center for Epidemiologic Studies Depression (CES-D) scale to assess symptoms of depression, with 20-item score that ranged from 0 to 60. Participants with scores 16 or higher on CES-D scale would be assigned as presence of depressive symptoms25.

Statistical analysis. To examine differences in characteristics between participants with or without kidney dysfunction, a Chi-square test was used for categorical variables, and Student’s t test or Mann-Whitney U-test were used for continuous variables. Correlation between GFR and CTh (global and lobar) was evaluated by Spearman’s rank sum test, and a partial correlation model (represented as $\rho$) was applied after adjustment of age, gender, years of education, MoCA-T score, and APOE4 status.

To explore whether the level of GFR or presence of kidney dysfunction were related to global and lobar CTh, multivariable linear regression models were applied. Because one single GFR unit was relatively small, it was expressed as every 10 ml/min/1.73 m$^2$ increase in the regression models. In model 1, important covariates including age, gender, years of education, MoCA-T score, and APOE4 status were added to test whether kidney dysfunction related to cortical thinning was independent of cerebral small vessel disease and vascular risk factors. A logistic regression model was used to estimate adjusted odds ratio (aOR) and 95% confidence intervals (CI) with cortical thinning versus normal CTh for GFR values or kidney dysfunction, respectively. The adjusted covariates were the same as the linear regression models described above. False discovery rate correction was used to correct for inflated type I error because of multiple comparisons. An additional stratified analysis was performed based on age groups (65–74 vs ≥75 years old), gender, cognitive status (MoCA-T < 24 vs MoCA-T ≥ 24), and APOE4 status (carriers vs non-carriers). All analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary, NC, USA). All statistical tests were two-sided, and $P$ values of $<0.05$ were considered significant.

Results

Characteristics of study population. A total of 259 participants (mean age 73.0 ± 5.2 years old, male 45.6%) from an elderly health checkup program who underwent a comprehensive baseline data collection and brain MRI study were included for analysis. The mean global thickness of the participants was 2.24 ± 0.12 mm. Thirty-five participants had a GFR of <60 ml/min/1.73 m$^2$, thirteen had presence of proteinuria, and a total of 43 participants were classified as having kidney dysfunction. For those with kidney dysfunction, they were generally older, were less educated, had a lower MoCA-T score, had more severe white matter lesions, had thinner global and most of the lobar CTh except the limbic lobe (Table 1). The GFR values were positively correlated with the global and year CTh in an unadjusted model (Spearman’s $\rho$ = 0.06, respectively). If using the linear regression model 1, GFR had a significant impact on global CTh in those 24 participants with kidney dysfunction, with 20-item score that ranged from 0 to 60. Participants with scores 16 or higher on CES-D scale would be assigned as presence of depressive symptoms25.

Association between kidney function (GFR or kidney dysfunction) and cortical thinning. No significant association was observed between GFR and global or lobar cortical thinning in the logistic regression models (Table 3), except the borderline finding in the frontal lobe (aOR = 2.74, 95% CI = 1.31–5.74, $P=0.01$; Table 3). However, the effect did not exist for global or other lobar cortical thinning.

Stratified analyses by important potential confounders. No significant interaction existed between kidney dysfunction and age, gender, cognitive or APOE4 status for global CTh ($P_{interaction}=0.98$, 0.08, 0.54, and 0.06, respectively). If using the linear regression model 1, GFR had a significant impact on global CTh in those participants with cognitive impairment (MoCA-T < 24) ($\beta=0.02$, 95% CI = 0.002–0.04; Table 4). In contrast, kidney dysfunction was independently associated with lower global CTh in subgroups of younger age (aged 65–74 years-old, $\beta=-0.05$, 95% CI = −0.10 to −0.01), female ($\beta=-0.09$, 95% CI = −0.15 to −0.04), and APOE4 carriers.
equivalent to 20.5 years of aging, while the impact on APOE also proteinuria, a potent marker for early kidney damage, compared to their use of blood markers such as GFR, between the two studies that should be emphasized. First, we included not only the glomerular filtration rate but association and sensory-motor areas. Our findings paralleled their results, however, there were several differences association between GFR and total gray matter volume in 434 non-disabled elderly persons10. GFR for more than 3 months23. As our study had a cross-sectional design, we were unable to diagnose partic-

Table 1. Characteristics of the study participants according to the status of kidney dysfunction. Data are presented as mean ± standard deviation. *Depressive symptomsae defined as scores 16 or higher on Center for Epidemiologic Studies Depression (CES-D) Scale, a self-report scale to assess symptoms of depression with 20-item score ranged from 0 to 60. **P values were obtained from Student’s t tests (normally-distributed continuous variables), Mann-Whitney U tests (non-normally distributed continuous variables), and Chi-square tests (categorical variables) for comparing participants with or without kidney dysfunction.

Discussion
The present study demonstrated that decreased kidney function was associated with cerebral cortical thinning in an independently living elderly population. The association was more salient and consistent when combining the results indicated that patients in the lowest GFR quartile had a significantly thinner cortex than those in the middle-aged and elder adults28. They found that kidney function was related to cortical thickness in widespread association and sensory-motor areas. Our findings paralleled their results, however, there were several differences between the two studies that should be emphasized. First, we included not only the glomerular filtration rate but also proteinuria, a potent marker for early kidney damage, compared to their use of blood markers such as GFR,
Table 2. Association between kidney function and CTh by multiple linear regression models. *Kidney dysfunction is defined as either GFR < 60 ml/min/1.73 m² or presence (≥1+) of proteinuria. aModel 1 was adjusted for age, gender, education years, APOE ε4 carrier status, MoCA-T score, and intracranial volume; Model 2 was additionally adjusted for degree of white matter lesion, lacunes, hypertension, diabetes mellitus, body mass index, and smoking. False discovery rate q value < 0.05. Numbers in bold indicated significant findings (before correction for multiple comparisons).

| Cortical thinning | GFR (every 10 ml/min/1.73 m²) | Kidney Dysfunction* |
|-------------------|-------------------------------|---------------------|
|                   | aOR (95% CI)b | P value | aOR (95% CI)b | P value |
| Global            | 0.91 (0.73–1.14) | 0.42     | 1.82 (0.85–3.91) | 0.13 |
| Frontal lobe      | 0.79 (0.63–0.99) | 0.04     | 1.83 (0.84–3.98) | 0.13 |
| Temporal lobe     | 0.92 (0.74–1.13) | 0.41     | 1.57 (0.74–3.33) | 0.24 |
| Parietal lobe     | 0.95 (0.76–1.18) | 0.63     | 1.33 (0.62–2.87) | 0.47 |
| Occipital lobe    | 0.96 (0.78–1.19) | 0.71     | 1.96 (0.93–4.16) | 0.08 |
| Limbic lobe       | 0.93 (0.76–1.16) | 0.54     | 0.84 (0.39–1.82) | 0.66 |
| Insular lobe      | 0.86 (0.70–1.05) | 0.14     | 2.74 (1.31–5.74) | 0.01 |

Table 3. Association of kidney function and cortical thinning (lower tertile of global or lobar CTh) by logistic regression models. *Kidney dysfunction is defined as either GFR < 60 ml/min/1.73 m² or presence (≥1+) of proteinuria. aThe model was adjusted for age, gender, education years, APOE ε4 carrier status, MoCA-T score, and intracranial volume. False discovery rate q value was 0.056. Numbers in bold indicated significant findings.

creatinine, and BUN to represent kidney function. Besides, their study employed the surface-based general linear model analysis which incorporated covariate once a time, while we applied a multivariable linear regression to embrace all potential confounders. In doing so, common confounding factors, such as age, sex, educational level, APOE ε4 carrier status, and cognitive function could be incorporated into the model, in order to examine these associations in a more comprehensive method. In summary, both studies addressed an important viewpoint that kidney function was closely related to brain morphology even among healthy individuals.

The reasons that kidney dysfunction had a negative effect on the cortical thickness were probably multifactorial (Fig. 1). It had been observed that systemic catabolism of amyloid beta was largely performed by kidney or liver in mice29. In both probable AD patients and normal controls, the serum creatinine level was significantly correlated with plasma amyloid beta (either Aβ 40 or Aβ 42)22. Consequently, the accumulation of Aβ in the body and its downstream neurodegeneration was still the main hypothetical model for the pathophysiological process in AD23. Therefore, reduced kidney function could lead to impaired peripheral excretion and an abnormal accumulation of circulating Aβ, ultimately resulting in cortical thinning.

Another explanation might be related to a background atherosclerotic state and cerebrovascular dysregulation. Many studies have found that CKD independently contributed to subclinical brain lesions on MRI, such as silent brain infarcts, lacunes, white matter hyperintensities, or cerebral microbleeds. 26, 31–33. These were mainly lesions of cerebral small vessel disease and could lead to brain atrophy and cortical thinning26. In our study, the independent association between GFR and cortical thickness was attenuated after adjustment of white matter lesions, lacunes, and other vascular risk factors (model 2), but the association persisted between kidney dysfunction and cortical thickness. These results implied that both an excretion abnormality (GFR per se) and endovascular dysfunction (proteinuria) were associated with cortical thinning, and the underlying pathophysiological process may be independent of cerebral small vessel disease.

Yet another mechanism may contribute to the chronic inflammatory state that exists in patients with CKD27. It has been shown that inflammation could mediate the relationship between metabolic syndrome and cortical thinning. Additional work to explore the contribution of inflammatory markers in the kidney dysfunction related cortical thinning is worthy of investigation.

One interesting finding was that kidney dysfunction was associated with profound cortical thinning in the insular lobe. Although the function of the insula was not fully understood, it was usually linked to emotional process, autonomic function and interoception26, 40. Abnormal changes in insular cortical thickness have been
found in patients with chronic musculoskeletal pain, abdominal pain, migraine or smoking addiction. In patients with mild AD, depression and anxiety symptoms were found to be associated with thinning of the insular cortex. We did not find a significant correlation between insular cortical thickness and depressive symptoms scores (based on Center for Epidemiological Studies Depression scale) in our study population. Possible factors contributing to the kidney-dysfunction related insular thinning included circulating toxin, accumulation of $A_\beta$, or oxidative stress brought by endothelial dysfunction.

Several demographic factors have been found to be associated with changes in cortical thickness. Increasing age was generally associated with less cortical thickness. In our subgroup analysis, we found that kidney dysfunction was significantly related to a lower global CTh, while the old-old group (≥75 years-old) also demonstrated a non-significant relationship. Hence, increasing age did not seem to have an important effect on kidney-dysfunction related cortical thinning. However, close monitoring of kidney function during earlier lifespan was important since the accumulation of $A_\beta$ could start from middle age.

Secondly, women tended to have a greater cortical thickness than their age-matched counterpart, and our results were in line with these findings (women vs men: $+ 47.7 \mu m$, 95% CI = 21.4–74.1 $\mu m$ in age-adjusted global cortical thickness). Interestingly, we found that kidney dysfunction had more prominent effects on global CTh in women (equivalent to an aging effect of 20.5 years). Whether this was because men had more competing risk factors such as oxidative stress brought by endothelial dysfunction.

Generally, $APOE_4$ carriers, even those with normal cognition, had lower cortical thickness. We found that $APOE_4$ status demonstrated a border-line modification effect ($P_{interaction} = 0.06$) on the association between kidney dysfunction and global CTh, and $APOE_4$ non-carriers were more likely to be affected by kidney dysfunction. A recent study that demonstrated the association between kidney function factor and CTh did not find $APOE_4$ status being an effect modifier. However, their finding was in fact concordant with ours that the negative impact of kidney function on the CTh was more prominent among $APOE_4$ non-carriers. The results suggested that kidney function should be carefully assessed and monitored in $APOE_4$ non-carriers who have a risky factor of neurodegeneration, or women were more susceptible to kidney dysfunction, is worthy of further exploration.

Table 4. Association of kidney function and global CTh by multiple linear regression models, stratification by important factors. *Kidney dysfunction is defined as either GFR < 60 ml/min/1.73 m$^2$ or presence (≥1 + ) of proteinuria. The models were routinely adjusted for factors including age, gender, education years, $APOE_4$ carrier status, MoCA-T score, and intracranial volume, except the factors used for stratifications. Numbers in bold indicated significant findings.

| Subgroup | N  | GFR (every 10 ml/min/1.73 m$^2$) | Kidney Dysfunction* |
|----------|----|---------------------------------|---------------------|
| Age      |    | $\beta$ (95% CI)$^a$ | $P$ value | $\beta$ (95% CI)$^a$ | $P$ value |
| ≥75      | 84 | 0.02 (−0.003, 0.04) | 0.09 | −0.08 (−0.13, 0.007) | 0.08 |
| <75      | 175| 0.01 (−0.002, 0.02) | 0.10 | −0.05 (−0.10, −0.007) | 0.02 |
| Gender   |    |                                |                    |                                |        |
| Male     | 118| 0.007 (−0.008, 0.02) | 0.37 | −0.02 (−0.07, 0.03) | 0.51 |
| Female   | 141| 0.02 (−0.0001, 0.03) | 0.05 | −0.09 (−0.15, −0.04) | 0.002 |
| $APOE_4$ |    |                                |                    |                                |        |
| Carrier  | 42 | 0.01 (−0.02, 0.04) | 0.42 | 0.005 (−0.10, 0.11) | 0.92 |
| Non-carrier | 215 | 0.01 (−0.001, 0.02) | 0.09 | −0.06 (−0.10, −0.02) | 0.01 |
| MoCA−T   |    |                                |                    |                                |        |
| ≥24      | 213| 0.006 (−0.006, 0.02) | 0.32 | −0.04 (−0.08, 0.007) | 0.19 |
| <24      | 46 | 0.02 (0.002, 0.04) | 0.03 | −0.07 (−0.15, 0.006) | 0.07 |

Figure 1. Postulated mechanism of kidney dysfunction in relation to cortical thinning.
measurement of the urinary albumin-to-creatinine ratio to determine the degree of albuminuria. That said, a dipstick test result of less than 1+ usually had a high negative predictive value with a minimal risk of missed diagnosis of microalbuminuria4. Additional study to explore a possible linear relationship between the level of albuminuria and CTh is desirable. Third, we did not use a commonly used case-control method to compare differences in regional CTh, as we studied a relatively homogeneous group of participants without any known neurodegenerative diseases or significant medical illness. Moreover, we focused on a potential preclinical association between kidney function changes and CTh. We did not perform the surface-based analysis to generate maps of regional differences by the Freesurfer suite like some researchers did28, since we applied a multivariable linear regression approach to embrace all potential confounders into one model. Lastly, this study was conducted among Taiwanese elderly adults, who were mainly Han Chinese, so it was limited to generalize our study results to other racial or ethnic groups.

In summary, our findings suggest that kidney dysfunction is associated with cerebral cortical thinning in community-dwelling, non-demented elderly population. Further prospective study is warranted to evaluate whether interventions to protect kidney function or to reduce proteinuria could effectively slow the progression of cerebral cortical thinning. Thus, the critical role of kidney function can be better elucidated in the process of neurodegeneration.

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Author Contributions

C.H.C. conceived this work, analyzed the data, wrote the manuscript, and had primary responsibility for final content. P.H.T. and Y.C.C. analyzed the data and wrote the manuscript. J.H.C., Y.C.C. and M.J.C. designed the study and recruited the study participants. Y.C.C. assessed the neuro-imaging and served as the consultant of neuro-radiology. C.J.Y. served as the consultant of nephrology. T.E.C. and M.J.C. served as the consultant of neurology. S.C.T. and S.J.Y. conducted the medical examinations. All authors discussed the results and commented on the manuscript.

Additional Information

Competing Interests: The authors declare that they have no competing interests.

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