Moderate chronic kidney disease is associated with reduced cognitive performance in midlife women

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Several studies have shown that general and specific cognitive dysfunction may be present during the early stages of chronic kidney disease. These studies, however, were conducted in elderly patients with comorbid conditions and used a limited battery of cognitive tests. Here we determined whether 40- to 54-year-old women in a population-based cohort in Taiwan with moderate chronic kidney disease have reduced cognitive performance. In total, 64 women with moderate chronic kidney disease (estimated glomerular filtration rate (eGFR) stage 3) were randomly matched by age and education with 192 control individuals with eGFR stage 2 or better. All patients underwent the Rey Auditory-Verbal Learning Test, visual memory, verbal fluency, Trail Making Test, digit spans, and Hospital Anxiety and Depression Scale neuropsychological tests. Women with moderate chronic kidney disease had significantly worse performance in delayed recalls and backward digit span than controls. Mixed effects modeling showed that women with moderate chronic kidney disease had reduced cognitive performance after controlling for body mass index, menopausal status, and psychosocial distress. Thus, in a population-based sample, we found that midlife women have reduced cognitive performance associated with early-stage chronic kidney disease. If confirmed, routine cognition evaluation of patients with mild chronic kidney disease may help identify this problem earlier because mild cognitive impairment can convert to dementia.

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KEYWORDS: chronic kidney disease; cognitive function; midlife; women

Chronic kidney disease (CKD) is a worldwide public health problem. The prevalence of CKD, which was approximately 11% in both the United States and Taiwan, has increased dramatically during recent decades and may rise even further in the future. The association between end-stage renal disease and cognitive impairment has long been well recognized. Because CKD is considered treatable and preventable during its early stages, recent studies have focused on patients with less advanced CKD. In one of these studies, moderate renal impairment, which is defined by elevated serum creatinine, was found to be associated with an increased risk of dementia. Other studies have suggested that general cognitive dysfunction or specific cognitive impairments are already present during the early stages of CKD. However, most of these studies were conducted in elderly cohorts or in patients with comorbid conditions. The only exception was a recent study based on the Third National Health and Nutrition Examination Survey, which showed an association of moderate CKD with reduced cognitive performance in a cohort of 20- to 59-year-old adults. Nevertheless, this study was constrained by a limited battery of cognitive tests.

Previous research suggested that either vascular cognitive impairment or mixed vascular cognitive impairment and Alzheimer’s disease appear to be more common in hemodialysis patients than Alzheimer’s disease alone. Therefore, the pathophysiology of cognitive impairment in aging dialysis patients was considered an accelerated model of vascular dementia. The most common impaired cognitive domains in patients with advanced CKD were memory and executive function. However, it is unclear which specific cognitive domains are involved during the early stage of CKD.

Here, we conducted a study of cognitive function in subjects with CKD in a population-based cohort of midlife women. Our goals were to determine whether subjects with CKD have cognitive deficits compared to their healthy counterparts and whether these cognitive deficits are of the same type as those previously reported by other studies. We hypothesized that reduced cognitive performance, especially executive dysfunction and memory impairment, were associated with CKD even in the early stage.
RESULTS
Study population
Of the 1622 subjects initially contacted, 88 (5.4%) refused to participate, 37 (2.3%) missed the evaluation due to losing their mail or moving, 9 (0.5%) were excluded because they had severe mental retardation, psychosis, or severe hearing or visual impairments, and 465 (28.7%) were excluded because of incomplete data. After these exclusions, a total of 1023 women (63%) completed the study. The participants were slightly younger than the nonparticipants in age (45.3 ± 3.9 vs 46.0 ± 4.2 years, P < 0.001). The demographics, health-related characteristics, and kidney function of all participants are presented in Table 1. Sixty-three women (6.2%) had a history of cardiovascular disease, including myocardial infarction, coronary disease, heart failure, angina pectoris, and arrhythmia. No subject reported having had a stroke. The mean estimated glomerular filtration rate (eGFR) was 82.6 ± 16.6 ml/min per 1.73 m², and 64 women (6.3%) had moderate CKD (eGFR: 30–59 ml/min per 1.73 m²). None of the subjects had severe CKD (eGFR < 30 ml/min per 1.73 m²). Twenty participants reported having had a renal disease previously. Only 3 women among the 64 moderate CKD subjects (4.7%) were aware that they had CKD.

Sixty-four participants with moderate CKD were matched by their age and education group to 192 women without CKD. Compared with the sampled subjects (N = 256), the excluded participants (N = 767) were younger (44.6 ± 3.6 vs 47.5 ± 4.0 years, P < 0.001) and had more years of education (6.8 ± 4.7 vs 5.1 ± 4.5 years, P < 0.001). The women with moderate CKD exhibited lower eGFR values (54.2 ± 6.8 vs 82.4 ± 13.2, P < 0.001), higher BUN levels (17.9 ± 7.6 vs 15.0 ± 3.8, P < 0.001), higher creatinine levels (1.0 ± 0.5 vs 0.8 ± 0.1, P = 0.002), higher Hospital Anxiety and Depression Scale (HADS) scores (8.8 ± 5.6 vs 7.2 ± 5.5, P = 0.04), and lower body mass index (BMI) values (20.5 ± 2.2 vs 24.9 ± 3.5, P < 0.001) than the matched controls (Table 1). The two groups had no differences in mean age, years of education, or the proportions of individuals with diabetes mellitus, hypertension, systolic blood pressure, serum total cholesterol, serum total triglycerides, postmenopausal status, and lifestyle variables.

Results of neuropsychological tests
Table 2 shows the cognitive performance results of the women with moderate CKD and their matched controls. In comparison with their matched controls, the women with moderate CKD had worse performances in the Rey Auditory-Verbal Learning Test (RAVLT) delayed recall and backward digit span tests.

Table 1 | Characteristics of study subjects sorted by eGFR category

<table>
<thead>
<tr>
<th>eGFR (ml/min per 1.73 m²)</th>
<th>Total (n=1023)</th>
<th>≥60, n=192</th>
<th>30–59, n=64</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.3 ± 3.9</td>
<td>47.5 ± 4.0</td>
<td>47.6 ± 4.1</td>
<td>0.87</td>
</tr>
<tr>
<td>Education (years)</td>
<td>6.4 ± 4.7</td>
<td>5.1 ± 4.5</td>
<td>6.5 ± 4.7</td>
<td>0.99</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>82.6 ± 16.6</td>
<td>82.4 ± 13.2</td>
<td>54.2 ± 6.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1 ± 3.6</td>
<td>24.9 ± 3.5</td>
<td>20.5 ± 2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HADS score</td>
<td>7.9 ± 5.5</td>
<td>7.2 ± 5.5</td>
<td>8.8 ± 5.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Postmenopause (%)</td>
<td>21.6%</td>
<td>31.3%</td>
<td>35.9%</td>
<td>0.49</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>5.2%</td>
<td>5.7%</td>
<td>4.7%</td>
<td>0.75</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>8.1%</td>
<td>9.9%</td>
<td>6.3%</td>
<td>0.38</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>123.0 ± 16.4</td>
<td>123.1 ± 15.1</td>
<td>120.9 ± 17.6</td>
<td>0.34</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77.8 ± 10.3</td>
<td>77.6 ± 9.0</td>
<td>76.2 ± 8.9</td>
<td>0.31</td>
</tr>
<tr>
<td>BUN</td>
<td>14.7 ± 3.9</td>
<td>15.0 ± 3.8</td>
<td>17.9 ± 7.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.1</td>
<td>1.0 ± 0.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum total cholesterol (mmol/l)</td>
<td>192.6 ± 36.6</td>
<td>197.9 ± 37.7</td>
<td>199.8 ± 38.2</td>
<td>0.72</td>
</tr>
<tr>
<td>Serum total triglyceride (mmol/l)</td>
<td>100.0 ± 72.8</td>
<td>105.2 ± 65.3</td>
<td>109.8 ± 147.2</td>
<td>0.74</td>
</tr>
<tr>
<td>Smoke habit (%)</td>
<td>1.0%</td>
<td>1.0%</td>
<td>1.6%</td>
<td>0.74</td>
</tr>
<tr>
<td>Alcohol habit (%)</td>
<td>10.5%</td>
<td>9.9%</td>
<td>7.8%</td>
<td>0.62</td>
</tr>
<tr>
<td>Cardiovascular disease (%)</td>
<td>6.2%</td>
<td>6.8%</td>
<td>7.8%</td>
<td>0.79</td>
</tr>
<tr>
<td>Exercise (%)</td>
<td>47.2%</td>
<td>42.2%</td>
<td>43.8%</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HADS, Hospital Anxiety and Depression Scale.

Table 2 | Performance in neuropsychological tests of subjects with CKD and control subjects

<table>
<thead>
<tr>
<th>eGFR (ml/min per 1.73 m²)</th>
<th>≥60 (n=192)</th>
<th>30–59 (n=64)</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVLT delayed recall</td>
<td>11.3 ± 2.5</td>
<td>10.1 ± 2.7</td>
<td>0.001</td>
</tr>
<tr>
<td>RAVLT learning score</td>
<td>47.9 ± 9.5</td>
<td>49.5 ± 9.6</td>
<td>0.23</td>
</tr>
<tr>
<td>RAVLT recognition score</td>
<td>13.9 ± 1.5</td>
<td>14.0 ± 1.6</td>
<td>0.54</td>
</tr>
<tr>
<td>Continuous recognition paradigm of Kimura Category verbal fluency: animal</td>
<td>14.8 ± 4.0</td>
<td>14.1 ± 4.4</td>
<td>0.23</td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>69.3 ± 36.8</td>
<td>81.6 ± 56.6</td>
<td>0.16</td>
</tr>
<tr>
<td>Trail Making Test B</td>
<td>119.1 ± 56.0</td>
<td>124.8 ± 75.2</td>
<td>0.99</td>
</tr>
<tr>
<td>Forward digit span</td>
<td>9.7 ± 2.8</td>
<td>9.6 ± 2.9</td>
<td>0.84</td>
</tr>
<tr>
<td>Backward digit span</td>
<td>4.9 ± 2.5</td>
<td>3.0 ± 2.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RAVLT, Rey Auditory-Verbal Learning Test.

*Bold type indicates P < 0.01.
The HADS score was associated with performance in forward digit span according to the Spearman’s correlation analysis \((r = 0.09, P = 0.007)\); however, it was not associated with the other cognitive measures. Postmenopausal subjects displayed reduced cognitive performance in the RAVLT delayed recall \((10.4 \pm 2.9\) vs \(11.3 \pm 2.4, P = 0.01,\) Mann–Whitney U-test), forward digit span \((9.1 \pm 2.9\) vs \(10.0 \pm 2.8, P = 0.03,\) Mann–Whitney U-test), and backward digit span \((3.9 \pm 2.4\) vs \(4.9 \pm 2.6, P = 0.02,\) Mann–Whitney U-test) tests compared to premenopausal subjects. No relationship was observed between the BMI values and the cognitive test results.

A linear mixed effects model was carried out for each cognitive domain to assess the significance of the effect of moderate CKD diagnosis while matching for age and years of education. The random effects variance estimates are nonsignificant in each model. The results were significant for the RAVLT delay recall (estimated mean \pm standard error: moderate CKD group \(10.1 \pm 0.3\) vs matched control \(11.3 \pm 0.2, P = 0.001)\), and backward digit span (estimated mean \pm standard error: moderate CKD group \(2.8 \pm 0.3\) vs matched control \(4.9 \pm 0.2, P < 0.001)\) domains and nonsignificant for the other neuropsychological tests. We again observed significant relationships between moderate CKD and cognitive performances as measured by the backward digit span test \((P < 0.001)\) and the RAVLT delayed recall \((P < 0.001)\) after adjusting for BMI values, HADS scores, and postmenopausal status covariates.

Otherwise, serum creatinine was associated with poor performances in Trail Making Test A (\(\beta\) coefficients \(= 0.26, R^2 = 0.25, P < 0.001\)), forward digit span (\(\beta\) coefficients \(= -0.17, R^2 = 0.22, P = 0.003\)), and backward digit span (\(\beta\) coefficients \(= -0.18, R^2 = 0.27, P = 0.002\)) after adjusting for age, years of education, BMI values, HADS scores, and postmenopausal status covariates.

**DISCUSSION**

We examined a cohort of midlife women in Taiwan with moderate CKD. The vast majority of the women had not been previously diagnosed with CKD. We observed that subjects with moderate CKD performed worse on the neuropsychological tests than did age- and education-matched controls without CKD. The cognitive deficits were most apparent in the domains of memory, attention, and frontal executive function. The results of our study showed that women with moderate CKD had deficits in attention and working memory, indicated by lower scores in the backward digit span test, which is considered a sensitive measure of frontal-executive cognitive changes.\(^{15}\) We also showed that women with moderate CKD manifested poor performance in verbal memory tasks as indicated by lower RAVLT delayed recall scores. However, the subjects with moderate CKD performed similar to controls in the RAVLT learning and recognition tests, which measure nonexecutive retrieval functions. The findings suggest that the poor performance on verbal memory tasks in subjects with moderate CKD may be caused by deficiencies in executive processes that support memory retrieval.\(^{16}\) The results using serum creatinine as a continuous independent variable suggest that women with moderate CKD had poorer performance in attention, visual tracking, and working memory, the involved cognitive domains are similar to the finding using eGFR as independent variable. The neuropsychological profiles of women with moderate CKD in this study are similar to the profiles of patients with vascular cognitive impairment.\(^{17}\) In studies of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, who are generally young and therefore less likely to have concomitant pathological changes associated with Alzheimer’s disease, impairments in working memory and executive function have been observed during the very early phase of the disease before transient ischemic attacks or strokes.\(^{18}\) This pattern of impairment has been suggested to represent the core of the cognitive syndrome associated with small-vessel subcortical ischemic diseases.\(^{19,20}\) Our findings support the theory that ischemic cerebrovascular disease and the underlying vascular pathology may have a role in the cognitive impairments of patients with CKD.\(^{21}\)

Most previous research on cognition and the risk of dementia in patients with mild to moderate CKD had been performed in elderly subjects. Furthermore, there have been inconsistencies across these studies in terms of the specific cognitive impairments that were associated with CKD.\(^{9,21}\) Although one study found that executive function, psychomotor skills, language, and attention were impaired in postmenopausal, elderly women with CKD,\(^{10}\) another study reported that visual recognition, visual memory, attention, visual processing speed, and psychomotor performance were negatively affected by CKD.\(^{11}\) A study of relatively healthy adults, aged 20–59 years, showed that patients with moderate CKD performed poorly in visual attention and visual recall tasks, as assessed by the Symbol Digit Substitution Test and the Serial Digit Learning Test, respectively.\(^{12}\) The results of our study show that women with moderate CKD perform poorly in verbal and working memory and executive function tasks, which had not been previously assessed in individuals of this age group.

Menopausal transition in midlife can be related to decreases in some types of cognitive performance in women.\(^{22}\) In this study, adjusting for menopausal status did not affect the significance of the association between moderate CKD and reduced cognitive performance. Prior studies have found that a significant proportion of end-stage renal disease and CKD patients suffer from depression,\(^{23}\) which may influence their cognitive performance.\(^{24}\) In our study, the level of mood symptoms was higher in women with moderate CKD than in the matched controls. Notwithstanding, adjusting for the level of anxiety and depressive symptoms measured by the HADS did not appreciably change the association between moderate CKD and reduced cognitive performance. In addition, our study observed no
significant associations between cognitive performance and BMI values despite the fact that women with moderate CKD had lower BMI values than the controls.

The prevalence of moderate CKD in our cohort was 6.3%, which is similar to the percentage reported for women in a large prospective cohort that had a representative sample of adults in Taiwan (6.4%). Furthermore, the low levels of awareness (4.7%) of CKD status observed in our study were consistent with a prior study in Taiwan that reported a high prevalence and low awareness of CKD.25

The strength of the present data is that it studies a cohort from a homogenous community, which allows us to assess a group of subjects with early CKD that were not biased by medical treatment. The neuropsychological tests in our study assessed the five major cognitive domains commonly used to define mild cognitive impairment: memory, attention, language, visual-spatial, and executive function.26 There are some potential limitations to our study. First, the cause of the moderate CKD could not be determined by this cross-sectional study. Herbal medicines or medications to treat glomerulonephritis may be possible causes of CKD in our sample. However, because we did not collect data regarding medication usage, we could not ascertain whether they caused CKD. Second, although we tried to adjust for most known confounders, we could not control for all possible confounding factors such as proteinuria, anemia, and inflammation. Finally, all of our CKD subjects were Taiwanese, midlife women, who presented the disease in a moderate degree, which limits the generalizability of our findings to other ethnic groups, men, and elderly women.

In summary, moderate CKD was significantly associated with poorer cognitive performance in verbal memory, attention, working memory, and executive function in a population-based sample of women aged 40–54 years. These findings suggested that cognitive dysfunction could develop in the early stage of CKD even among midlife adults without dominant medical comorbidities. Because mild cognitive impairment may convert to dementia,26 physicians who take care of people with CKD should consider evaluating their cognition routinely to identify this problem earlier.

SUBJECTS AND METHODS

Study populations

The Kinmen Women-Health Investigation cohort is a community-based study of midlife women in Taiwan that has previously been described in detail.14 Kinmen is an outlying island of Taiwan with Han Chinese inhabitants. According to the registration record and data collected during visits by research assistants, 1622 women aged 40–54 years were invited to participate in the study, who lived in the two selected rural townships (Kin-Hu and Kin-Cheng). A note regarding the study was published in local newspapers. Approximately 1 week after the release of the announcement, all targeted women were contacted by mail in an attempt to enroll the eligible women. If a subject did not visit after three phone calls, a research assistant would visit the subject's home. The institutional review board of the Taipei Veterans General Hospital approved the study protocol.

Procedure

All subjects completed self-administered questionnaires in the presence of trained interviewers to collect personal information, including sociodemographic data, medical histories, lifestyle factors, menopausal statuses, and mental health conditions. The interviewers assisted subjects who were illiterate or who did not understand questions. Serum creatinine and blood urea nitrogen levels were measured from serum at a single central laboratory using standard methods. Blood pressure, body weight, and height were also measured. The BMI was calculated as the body weight divided by the body height squared (kg/m²) for each subject. A 45-min battery of neuropsychological tests was performed within 2 months of the blood test.

Creatinine assay and definition of CKD

Plasma creatinine (normal reference value 0.5–0.9 mg/dl (44–80 μmol/l) in women) was measured using Jaffe’s kinetic method with a sample blank on a Hitachi 717 automatic analyzer (Boehringer Mannheim, Hitachi, Tokyo, Japan) and human Creatinine Liquicolor. The method was calibrated using the calibration for automatic systems, identification number 759350 (Roche Diagnostics, Mannheim, Germany), with reference creatinine concentrations (usually 3.62 mg/dl (319 μmol/l)) that were determined using gas chromatography–mass spectrometry. The assayed chemistry control (Lyphochek; Bio-Rad, Irvine, CA, USA) was used for quality control to monitor the precision of the laboratory testing procedures.

Because serum creatinine levels showed poor correspondence to GFR in a prior Taiwanese study2 and may lead to underdiagnoses of CKD,27 we used the abbreviated equation from the Modification of Diet in Renal Disease Study to estimate GFR (186 × serum creatinine⁻¹.154 × age−0.203 × 0.742, where serum creatinine is measured in mg/dl).28 The application of the abbreviated Modification of Diet in Renal Disease Study equation has been verified in Chinese populations with CKD.29 CKD categorizations were performed using the National Kidney Foundation, USA (K-DOQI) guidelines.6 Moderate CKD, or CKD stage 3, was defined by an eGFR value between 30 and 59 ml/min per 1.73 m².

Neuropsychological battery

Rey Auditory-Verbal Learning Test. The RAVLT is a measure of verbal learning and memory.30 Three kinds of raw scores are used to score the test. The learning score sums the number of correct words that are immediately recalled across the five learning trials, the delay recall score is the total number of words reported correctly during the delayed recall, and the recognition score is the total number of words correctly recognized. The delayed recall score was used as an index of verbal memory with executive load, whereas the
learning and recognition scores were considered to reflect nonexecutive retrieval processes.30

**Forward and backward digit span subtest of the Wechsler Adult Intelligence Scale-Revised.** The digit span subtest of the Wechsler Adult Intelligence Scale-Revised comprises two different tests in which the patient is required to repeat digits in forward (forward digit span) and reverse (backward digit span) order. The forward digit span test is related to attention and concentration, whereas the backward digit span test is a measure of attention and working memory.31

**Continuous recognition paradigm of Kimura.** The continuous recognition paradigm of Kimura involves the sequential presentation of 70 nonsense figures.32 Four figures are repeated seven times within the test. The subject is instructed to answer ‘yes’ or ‘no’ as to whether a figure has been seen previously or not. The raw score is the number of correctly recognized repeated figures. The continuous recognition paradigm of Kimura is a measure of visual recognition and memory.

**Trail Making Test, parts A and B.** This Trail Making Test involves connecting numbers (part A) or numbers alternating with letters (part B) on a sheet of paper.33 The score is the time to complete the task, measured in seconds. Part A evaluates processing speed, part B tests executive function, and both parts A and B evaluate visual-spatial scanning. The higher the score is, the lower the performance was.

**Verbal fluency.** In the verbal fluency test, the subject names as many animals as possible in 1 min.34 The raw score is the number of different animals correctly named with one point for each correct response. This test measures language and executive function.

**Questionnaire about the demographics, lifestyle, and other health factors**

Women who had not menstruated within the previous 12 months were categorized as postmenopausal. Regular daily smoking, weekly alcohol drinking, and weekly exercise were recorded as lifestyle factors. We measured the degree of psychological distress using the HADS, which was developed for and validated in nonpsychiatric medical patients. Items in the survey relating to mood disorders and physical illnesses were eliminated.35 In this scale, high scores indicated poor mental health.

The women also reported if they had any of the following diseases: stroke, myocardial infarction, coronary disease, heart failure, angina pectoris, arrhythmia, or hypertension. Awareness of chronic renal disease was defined as having moderate CKD and self-reporting having chronic renal disease.

**Statistical analysis**

All statistical analyses were carried out using SPSS for Windows version 15.0 (SPSS, Chicago, IL, USA). Demographics and other health-related variables were compared between the moderate CKD and those without using t-tests or χ²-tests, as appropriate. All results are presented as the mean ± standard deviation (s.d.), unless otherwise noted. Correlation analyses were performed using Spearman’s correlations. The prevalence of CKD and the performance in cognitive tests can be affected by age and educational levels.3,36,37 To control these confounding factors, we used a matched sample study. Women without CKD were defined as control subjects. The individuals in the control group were matched to cases by age (within 1 year) and years of education (within 1 year). To reduce the measurement error of the dependent variables, we randomly assigned three controls to each woman with moderate CKD. The total number of our selected control group was 192.

In the first step of data analysis, the means and standard deviations of group performance on each neuropsychological measure were calculated and compared by Mann–Whitney U-test. In the second step, mixed effects models were used to quantify associations between each neuropsychological measure (continuous outcomes) and case/control status. The mixed effects model accounts for the correlation that exists between the matched participants. To understand whether differences in each cognitive function domain could be attributed to differences between cases and controls, we adjusted final models for potential confounding variables. To avoid the eGFR might be a proxy for age, we also used serum creatinine as a continuous variable to analyze its relationship to cognitive function. To balance the type I and type II errors in multiple comparisons, we defined a significant P-value as being <0.01.

**DISCLOSURE**

All the authors declared no competing interests.

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