Research Article

Association Between Renal Function and Cognitive Ability Domains in the Einstein Aging Study: A Cross-Sectional Analysis

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Abstract

Background. The relationships between renal function and specific domains of cognitive function have rarely been explored in representative, community-based samples of older adults. We assessed the association between renal and cognitive function based on an extensive battery of neurocognitive tests.

Methods. In a sample of Einstein Aging Study participants (n = 649, age = 70+ years) we calculated estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration formula. We predefined three groups based on eGFR units of mL/min/1.73 m^2 as low (<45), medium (45–59), and high (≥60). Thirteen neurocognitive tests were subjected to principle component analysis revealing three components: a global component, an episodic memory component, and a frontal-executive component. We first examined the relationship of eGFR group to cognitive performance in each domain and then examined subtests for the domains which proved to be statistically significant.

Results. The sample (mean = 79.2, 61% = female) was distributed among eGFR categories as follows: low (n = 67), medium (n = 151), and high (n = 431). The frontal-executive domain was significantly associated with poor cognitive performance in the low eGFR group (p < .001). When we examined the neuropsychological test components for frontal-executive domain, performance was lower on two of four contributing tests (Trail Making Test Part B and the Digit Symbol Substitution test). Other domains of cognitive function were not associated with eGFR.

Conclusions. Low eGFR is associated with reduced performance on executive function. Individuals with poor renal function should be assessed for cognitive impairment. Potential mechanisms are discussed.

Key Words: Renal function—Cognition—Executive function.

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The aging process is characterized by decrements in both renal function, as measured by estimated glomerular filtration rate (eGFR), and cognitive function as measured by neuropsychological test performance (1,2). Further, decreased renal function is associated with cognitive impairment early in the course of chronic kidney disease (CKD) (38).
CKD is defined by a decreased kidney function (ie, GFR < 60 mL/min/1.73 m²) for ≥3 months, or the presence of kidney damage (ie, albuminuria), irrespective of clinical diagnosis (9). The prevalence of CKD increases strongly with age. Among individuals ≥70 years in the United States, 47% have CKD (10). In end-stage renal disease (ESRD), often defined by an eGFR < 15mL/min/1.73 m², individuals may require dialysis or transplantation (11). CKD is independently associated with mortality and ESRD across all age-groups (11).

CKD has also been independently associated with higher risk and prevalence of cognitive impairment (4,5,7,12). Cognitive impairment is a decreased functioning in ability relative to normative samples in one or more cognitive domains of function, including working and episodic memory, executive function, visuo-spatial ability, and general cognitive ability. Although most of these domains decline steadily with age, cognitive function is especially affected by disease and morbidity. Tests of global cognition such as the Mini Mental State Exam (MMSE) (13), the Modified Mini-Mental State (3MS) exam (14), and the 6-Item Screener (15) are widely used for an indicative marker of overall cognitive function. For example, the MMSE classifies normal from impaired cognitive aging using cut-off scores typically defined as: 27 ≤ 30 = normal; 19–24 = mild cognitive impairment; 10–18 = moderate cognitive impairment; ≤ 9 = severe cognitive impairment. Cognitive impairment affects most activities of daily living, including handling money, remembering to take medication, preparing meals, doing the laundry, and so on, depending on where and how severe the impairment is.

Several studies on cognition in renal function use global cognitive measures, such as the MMSE (3,12), the 3MS (4), or the Six-Item Screener (16). Several studies have used batteries of neuropsychological tests in community samples. Some of these studies show an association between CKD and executive dysfunction (5,7,17). Other associations with CKD have included poor verbal memory (5,6), poor visual spatial memory (17), poor naming, and poor category fluency (7). Such associations may identify early signs and markers of renal impairment, which in turn may have implications for general health care practice. Lastly, a few studies have focused on cognitive function in persons already afflicted with CKD or ESRD (17,18).

To our knowledge there have been no studies carried out in relatively healthy populations that explore cognitive composites based on a thorough battery of neuropsychological tests. Most studies use patient populations (5,8) and/or global tests of cognition (3,4,12) or single neuropsychological tests (5). These studies may overlook cognitive problems faced by community-dwelling elderly with renal impairment in specific domains of cognitive function. In this study, we adopted a cross-sectional design to explore the association between eGFR and specific composites of cognitive function in a relatively physically, healthy older community-dwelling sample. Strengths of our study include our large, systematically recruited, community-based sample and the broad range of neurocognitive tests summarized using principal components analysis (PCA). Based on results from earlier research (5,10,17), we hypothesized an association between decreased eGFR and executive dysfunction.

Methods

Study Population

The study sample was derived from the Einstein Aging Study (EAS), which is a longitudinal study of cognitive aging and dementia. Participants are ≥70 years, community-dwelling, English-speaking and reside in the Bronx county, New York. Participants were systematically recruited from the Health Care Financing Administration/Centers for Medicaid and Medicare Services rosters for Medicare-eligible persons who were ≥70 years between 1993 and 2004, and from New York City Board of Elections from 2004 onwards. Individuals are first mailed introductory letters about the study and then followed up by a phone call for a brief screening interview. Participants are excluded if they have visual and/or auditory impairments that interfere with neuropsychological testing, psychiatric symptomatology that interferes with test completion, and a nonambulatory status. The study protocol was approved by the local institutional review board. Written informed consent is obtained on their first clinical visit (19). There were no exclusions based on baseline cognitive status. Baseline status here is considered as the first wave for which participants have eGFR data.

Assessment of eGFR

We estimated eGFR in mL/min/1.73 m² using the Chronic Kidney Disease Epidemiology Collaboration (9). Modification of Diet in Renal Disease (Levey and coworkers (20)) formula is given by:

\[
eGFR = \frac{141 \times \text{min}(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{BW}} \times 1.018\text{[if female]} \times 1.159\text{[if black]}}{\kappa f, k}
\]

Scr is serum creatinine (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 is the minimum for Scr/κ or 1, and max is the maximum of Scr/κ or 1.

Assessment of Cognitive Function

Cognitive function was assessed using the following neuropsychological tests:

Free and Cued Selective Reminding Test

The Free and Cued Selective Reminding Test (FCSRT) (21,22) is an episodic memory test, which includes learning of 16 pictures by identifying and naming each picture. It also consists of three trials of immediate free recall, each of which is followed by cued recall in which a category cue is given to the subject to facilitate recall of the items not freely recalled. Total recall is the sum of free and cued recall; free recall (range 0–48) was used in analyses.

Wechsler Memory Scale-Revised

The Logical Memory I subtest from the Wechsler Memory Scale-Revised (WMS-R) (23) was used. This is an immediate declarative memory test (range 0–50), in which two different stories are read to the participant, and after each story the participant immediately recalls it from memory. Scores are given on the accuracy of the retelling of the story.

Wechsler Adult Intelligence Scale III

Five tests from the WAIS-III (24) were used:

Digit span

This is an index of working memory performance. In the first part (digit-span forward), the participant listens to a sequence of digits and repeats them. In the second part (digit-span backwards), the participant listens to a sequence of digits and repeats them backwards. A digit is added to the sequence after every successful trial. A point stops after two consecutive errors on a particular sequence.
This is an index of perceptual organization and measures visuospatial and abstract reasoning. It consists of a set of 14 printed geometric patterns and the participant is required to replicate the patterns using two-color blocks in a limited time period (starts off with 1 min and moves onto 2 min with task difficulty; range 0–68).

**Digit-symbol**

This is an index of processing speed. The participant copies symbols under the corresponding numbers using a key found at the top of the page. The number of symbols correctly drawn in a 120-second time period determines the score (range 0–133).

**Information**

This is also an index of verbal comprehension. The participant answers 28 questions with increasing difficulty on a broad range of general knowledge (range 0–28).

**Vocabulary**

This is an index of verbal comprehension. The participant has to verbally express the definition of 33 words. The participant can score between 0 and 2 points per word depending on how accurate the answer is (range 0–66). The test ends after six consecutive scores of 0.

**Trail Making Test**

The Trail Making Test (TMT) (25) includes two parts: A (TMTA) and B (TMTB). In TMTA the participant is given a sheet with the numbers 1–25 and the participant has to connect the numbers in sequence as quickly as possible. This test requires visual-tracking and attention. In TMTB, the participant is given a sheet with number 1–13 and letters A–M. The participant has to connect the numbers and letters in alternating sequences as quickly as possible. This task measures cognitive flexibility, visual-tracking, and good executive functioning. Both tests are timed and the score is seconds to task completion.

**Category fluency**

Category fluency (26), also known as semantic fluency, measures timed verbal fluency. The participant has 1 minute to name as many words that belong to a particular category (animals, vegetables, and fruits). The score is the total number of correctly listed items.

**The Controlled Oral Word Fluency Test**

The Controlled Oral Word Fluency Test (FAS) (27) also measures timed verbal fluency. The participant is given a letter (F, A, and S) and in 1 minute produces as many words as possible that begin with the letter. The score is the total number of correctly listed items.

**The Boston Naming Task**

The Boston Naming Task (BNT) (28) is a measure of confrontation naming. The participant has to name pictures that range from common objects to rare ones (range 0–60). Semantic and phonemic cues are given if the participant has difficulty naming any particular object; however, no score is given if the phonemic cue is used.

**Potential Confounders**

The following potential confounders were examined. Demographic confounders included age, sex, ethnicity, and total number of years of formal education. Medical confounders included hypertension, history of CVD, history of stroke, diabetes, anemia, body mass index, and prescribed nonsteroidal anti-inflammatory drugs (NSAIDS). This information was obtained via the clinical interview which included questions on medical history, medications and health behavior (19). Psychological confounders included a history of depression. This was measured using the 15-item Geriatric Depression Scale (29), with scores ≥6 indicating clinically significant depressive symptoms. Genetic confounders included apolipoprotein E allele e4, known for its association with Alzheimer’s disease (30), and cholesterylester transfer protein (CETP) with the IV or VV genotype, known for its association with longevity and in patients with hypertriglyceridemia, and coronary heart disease (31,32). These genes may mediate any associations between cognition and renal function. DNA was extracted from the whole blood or was isolated from buffy coat that had been stored at −70°C using the Puregene DNA Purification System (Gentra System, Minneapolis, Minnesota). Genotyping was performed using a Pyrosequencing PSQ HS 96A system (http://www.pyrosequencing.com).

**Statistical Analysis**

Baseline characteristics were reported using descriptive statistics. The mean ± standard deviation (SD) of continuous variables were compared using analysis of variance (ANOVA). Categorical variables are presented as percentage and the χ² test was used for comparisons.

We analyzed the raw scores of the 13 neurocognitive tests mentioned earlier using PCA to generate summary measures of cognitive domains. PCA is a data reduction technique that identifies groups of relatively homogeneous variables and transforms them into a set of linearly uncorrelated constructs. The use of the PCA in this study helped in reducing the 13 neurocognitive variables by forming robust cognitive composites. The grouping of these variables into factors was used in analyses rather than individual test scores. In this study, we conducted our PCA on a correlation matrix, which means the variables were automatically standardized, and each variable had a variance of 1. Tests were deemed to contribute to a cognitive domain provided the coefficients loaded at ≥0.45 on a component as provided by varimax rotation, which is an orthogonal method by which the variables are rotated to achieve simple and interpretable components. Regression scores generated by the PCA were used to form the cognitive composites. These scores and their SDs were all standardized. In this study, PCA was used to summarize commonality among the neuropsychological measures to identify cognitive function domains. The use of PCA provided reliable composite variables.

Although stages of CKD are defined by eGFR (Stage 1: GFR ≥90 mL/min/1.73 m²; Stage 2: eGFR 60–89 mL/min/1.73 m²; Stage 3a: 45–59 mL/min/1.73 m²; Stage 3b: 30–44 mL/min/1.73 m²; Stage 4: 15–29 mL/min/1.73 m², and Stage 5: <15 mL/min/1.73 m²), older adults with eGFR <45 mL/min are at increased risk for progression of CKD to ESRD and other adverse outcomes, whereas patients with eGFR >60 mL/min have the lowest risk (11). Therefore, we categorized our sample into eGFR ≥60, 45–59, and <45. These are well-used cuts in studies on renal function and cognition (3,4,33). We conducted unadjusted ANOVA exploring the association between eGFR in the mentioned predefined categories referred to as low (<45 mL/min/1.73 m²), moderate (45–59 mL/min/1.73 m²), and high (≥60 mL/min/1.73 m²) eGFR, and the cognitive composite outcomes of the PCA. In addition, for the cognitive domains showing an effect
of eGFR category, we conducted planned post hoc analysis of the individual tests contributing to each domain. We modeled linear hierarchical multiple regressions to determine the influence of eGFR on domain scores adjusting for covariates for those cognitive domains associated with eGFR. Only those variables that were significantly associated with eGFR in the descriptive table (ie, Table 1) were entered into the multivariate models.

Analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 22.0, SPSS Inc., Chicago, Illinois).

Results
Sample Characteristics Overall and by eGFR Category
Table 1 summarizes the sample characteristics overall and by eGFR category for the 649 eligible participants. The mean age of the sample was 79.2 years and 39% were male. Mean eGFR was 68.4 mL/min/1.73 m² overall and higher for males than females and for whites versus other racial groups. The majority of individuals (63%) had an eGFR of ≥60 mL/min/1.73 m². Individuals of 23.9% had an eGFR between 45 and 59 mL/min/1.73 m² and 13.1% had an eGFR of <45 mL/min/1.73 m². Participants with low eGFR were older (mean = 82.0, SD = 6.1), had fewer years of education (mean = 12.6, SD = 3.3), and were less likely to be white and more likely to have hypertension (prevalence = 82.0%) than individuals with moderate and high eGFR.

Principal Components Analysis of Cognitive Tests
PCA of the cognitive measures yielded three significant orthogonal components that accounted for 58.4% of the total variance. Tests were included in a component if they had coefficient loadings on components ≥0.45. The first factor included the following tests and their loadings: Vocabulary (0.813), Information (0.759) and Digit Span (0.585) from the WAIS-III, the Controlled Oral Word Fluency Test (0.673), the BNT (0.456), and Logical Memory I (0.550) from WMS-R; we named this factor as General Ability. The second factor included TMT Parts A and B (coefficient loadings = 0.812 and 0.736) and two WAIS-III subtests, the Digit Symbol Test and Block Design (coefficient loadings = 0.764 and 0.584); we named this factor as Executive Function. The final factor included the free recall score and total recall scores (coefficient loadings = 0.825 and 0.782) from the FCSRT and category fluency (coefficient loadings = 0.497). We named this factor as Episodic Memory. The component loadings of Logical Memory loaded on the General Ability component, which can be seen as a limitation; however, given that this test requires various cognitive skills, such as working memory, attention, concentration, storing and retrieving verbal information and language comprehension, it also uses a number of general ability skills. Unlike the FCSRT, which involves controlled learning, thus assuring encoding, deep semantic processing, and effective retrieval cues, Logical Memory may be a less sensitive marker of memory. In order to prevent rehearsal (working memory) and obtain long-term memory retrieval, the FCSRT also includes interference tasks of counting backwards for 20 s. Therefore, given that free and total recall from the FCSRT loaded on one component may be an indication that a more robust composite of memory was generated.

Cognitive Function
Results from the ANOVA among eGFR categories and cognitive domain Z-scores based on the PCA showed that participants with an eGFR of ≥60 mL/min/1.73 m² scored significantly lower on executive function than individuals with eGFR <45 mL/min/1.73 m² (p = .000,

Table 1. Baseline Characteristics of This Study Sample From the Einstein Aging Study According to eGFR Category (SDs and 95% CIs in brackets unless otherwise stated as % for categorical variables)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>eGFR &lt; 45</th>
<th>eGFR 45-59</th>
<th>eGFR ≥ 60</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 649</td>
<td>n = 85 (13.1)</td>
<td>n = 155 (23.9)</td>
<td>n = 409 (63.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>79.8 (5.5)</td>
<td>82.3 (6.1)</td>
<td>80.7 (5.5)</td>
<td>78.9 (5.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex, males (%)</td>
<td>253 (63.9)</td>
<td>41 (48.2)</td>
<td>62 (40.0)</td>
<td>150 (36.7)</td>
<td>.132</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>440 (67.8)</td>
<td>60 (70.6)</td>
<td>111 (71.6)</td>
<td>269 (65.8)</td>
<td>.349</td>
</tr>
<tr>
<td>Years in education</td>
<td>14.1 (3.5)</td>
<td>13.1 (3.3)</td>
<td>14.4 (3.6)</td>
<td>14.1 (3.5)</td>
<td>.015</td>
</tr>
<tr>
<td><strong>Vascular variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>415 (63.9)</td>
<td>72 (84.7)</td>
<td>115 (74.2)</td>
<td>228 (55.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>64 (9.9)</td>
<td>11 (12.9)</td>
<td>19 (12.3)</td>
<td>34 (8.3)</td>
<td>.222</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>112 (17.3)</td>
<td>19 (22.4)</td>
<td>24 (15.5)</td>
<td>69 (16.9)</td>
<td>.381</td>
</tr>
<tr>
<td>Anemia (%)</td>
<td>88 (13.6)</td>
<td>11 (12.9)</td>
<td>25 (16.1)</td>
<td>52 (12.7)</td>
<td>.563</td>
</tr>
<tr>
<td>Past smokers (%)</td>
<td>344 (53.3)</td>
<td>54 (63.5)</td>
<td>80 (51.6)</td>
<td>210 (51.9)</td>
<td>.270</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>28 (8.1)</td>
<td>6 (11.3)</td>
<td>4 (5.1)</td>
<td>18 (8.5)</td>
<td>.417</td>
</tr>
<tr>
<td>BMI</td>
<td>27.2 (4.8)</td>
<td>26.9 (4.3)</td>
<td>27.6 (4.8)</td>
<td>27.1 (4.9)</td>
<td>.524</td>
</tr>
<tr>
<td><strong>Mood</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression symptoms (%)</td>
<td>50 (8.5)</td>
<td>2 (2.6) (1.5)</td>
<td>14 (9.7) (9.9)</td>
<td>34 (9.3) (7.8)</td>
<td>.135</td>
</tr>
<tr>
<td>GDS</td>
<td>2.2 (2.1)</td>
<td>2.5 (2.2)</td>
<td>2.3 (2.3)</td>
<td>2.1 (2.1)</td>
<td>.216</td>
</tr>
<tr>
<td><strong>Genes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOEe4 carriers (%)</td>
<td>138 (24.6)</td>
<td>20 (27.0)</td>
<td>29 (21.6)</td>
<td>89 (25.3)</td>
<td>.621</td>
</tr>
<tr>
<td>CETP V carriers (%)</td>
<td>397 (68.7)</td>
<td>52 (69.3)</td>
<td>94 (67.1)</td>
<td>251 (69.1)</td>
<td>.902</td>
</tr>
</tbody>
</table>

Notes: All percentages are column percentages. APOEe4 = Apolipoprotein E allele e4; BMI = body mass index; CETP = cholesterylester transfer protein; eGFR = estimated glomerular filtration rate; NSAIDs = nonsteroidal anti-inflammatory drugs; GDS = geriatric depression scale. The Pearson’s chi-square was used for categorical variables. Bold values indicate significant results.
Similarly, those with an eGFR of 45–60 mL/min/1.73 m² also scored lower than those with an eGFR ≥ 60 mL/min/1.73 m² ($p = .023, d = 0.22$). However, there were no significant differences in general ability and episodic memory among eGFR groups.

Because the executive function composite score was significant, we ran ANOVAs by eGFR categories on the individual tests comprising this composite (Table 2). Individuals with low eGFR were significantly slower on Trails B ($p = .004, d = 0.36$) than individuals with high eGFR. They also scored significantly lower on digit symbol coding ($p = .022, d = 0.34$) than individuals with high eGFR. Individuals with low eGFR were also significantly slower on Trails B than individuals with moderate eGFR ($p = .014, d = 0.35$). Because Trails A and B are two components of one test, with Trails B being an extension of Trails A, we also tested whether Trails B remained significant once we adjusted for Trails A. Results showed that Trails B failed to remain significant after controlling for Trails A ($p = .146$).

For the hierarchal multiple linear regression, we controlled for age, sex, race, and education in Model 1 and for age, sex, race, education, and hypertension in Model 2. Results revealed that in Model 1, eGFR and demographic variables contributed significantly to the regression model ($F(5, 523) = 19.8, p < .001$) and accounted for 17.3% of the variation in executive function scores. For every mL unit increase in eGFR, the executive function composite increased by 0.10SDs ($\beta = .10, p < .05$). Older age was associated with poor executive function ($\beta = −.24, p < .001$), whereas being Caucasian was associated with high executive function ($\beta = .30, p < .001$). Lastly, for every year increase in formal education, results were associated with higher executive function ($\beta = .21, p < .001$). Introducing hypertension in the model did not explain any additional variation (Table 3).

### Table 2. PCA Mean Scores of the Individual Tests Representing Executive Function Component According to eGFR Category With Significance Values (SDs and CIs in brackets)

<table>
<thead>
<tr>
<th>Total</th>
<th>eGFR &lt; 45</th>
<th>eGFR 45–50</th>
<th>eGFR ≥ 60</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n = 649$</td>
<td>$n = 85$</td>
<td>$n = 155$</td>
</tr>
<tr>
<td>TMTA</td>
<td>59.1 (28.0, 57.0–61.3)</td>
<td>64.3 (25.9, 58.6–70.1)</td>
<td>60.9 (29.2, 56.3–65.6)</td>
</tr>
<tr>
<td>TMTB</td>
<td>138.6 (76.9, 132.3–144.9)</td>
<td>167.2 (102.6, 142.5–191.8)</td>
<td>135.2 (75.3, 122.4–147.9)</td>
</tr>
<tr>
<td>Digit symbol</td>
<td>45.2 (14.7, 44.1–46.4)</td>
<td>41.5 (12.9, 38.7–44.4)</td>
<td>44.2 (14.2, 41.9–46.5)</td>
</tr>
<tr>
<td>Block design</td>
<td>23.7 (9.2, 23.0–24.4)</td>
<td>22.9 (8.4, 21.0–24.7)</td>
<td>24.2 (8.9, 22.7–25.6)</td>
</tr>
</tbody>
</table>

Notes: PCA = principal components analysis; TMTA = Trail Making Test Part A; TMTB = Trail Making Test Part B; Sample ranges: TMTA = 20–289 s. TMTB = 36–649 s; Digit symbol coding = 0–86. Bold values indicate significant results.

### Table 3. Hierarchal Linear Regression of the Association of eGFR With Executive Function Among 649 Community-Dwelling Elderly Individuals, Adjusted for Demographics in Model 1 and for Demographics and Hypertension in Model 2

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$B$</td>
<td>$SE$</td>
<td>$\beta$</td>
<td>$B$</td>
</tr>
<tr>
<td>Constant</td>
<td>1.71</td>
<td>.68</td>
<td>.30*</td>
<td>1.81</td>
</tr>
<tr>
<td>eGFR</td>
<td>.01</td>
<td>.00</td>
<td>.30*</td>
<td>.01</td>
</tr>
<tr>
<td>Age</td>
<td>−.04</td>
<td>.01</td>
<td>−.24***</td>
<td>−.04</td>
</tr>
<tr>
<td>Sex, female</td>
<td>.13</td>
<td>.08</td>
<td>.07</td>
<td>.13</td>
</tr>
<tr>
<td>Race, white</td>
<td>.63</td>
<td>.09</td>
<td>.30***</td>
<td>.61</td>
</tr>
<tr>
<td>Education</td>
<td>.06</td>
<td>.01</td>
<td>.20***</td>
<td>.06</td>
</tr>
<tr>
<td>Hypertension</td>
<td>−.08</td>
<td>.08</td>
<td>−.04</td>
<td>−.08</td>
</tr>
</tbody>
</table>

Notes: Model 1 was adjusted for age, sex, race and education. Model 2 was adjusted for age, sex, race, education, and hypertension. $R^2$ for Model 1 = .206; $\Delta R^2$ for Model 2 = .002.

* $p < .05$, ** $p < .001$. 

### Discussion

This study demonstrated an association between low eGFR and a cognitive composite measure of executive function. This was the first study that employed the three major domains of cognitive function in aging literature (34) to explore their association with eGFR in a community-dwelling older population. Although earlier studies (5,7,17) have shown an association with tests of executive function, this was the first to show the association with the component score of executive function. In addition, low eGFR was significantly associated with reduced performance on two out of four individual cognitive tests comprising the executive domain. Moderate to large significant differences (effect sizes of 0.3 and 0.4) in measures of executive function (Digit Symbol and Trails B) between high and low eGFR, and large significant differences on just TMTB (effect size of 0.4) between moderate and low eGFR were found. However, results from this study also showed that once Trails B was adjusted for Trails A, the test did not remain significant. This suggests that the association with Trails B is not executive in nature, but rather driven by attention and psychomotor speed. Thus, the two tests, Trails B and Digit Symbol, that were significantly associated with eGFR in this study required psychomotor speed and attention. These results were also in agreement with earlier studies (5,7) which show that low eGFR scores are associated with tests of poor executive function, and that eGFR independently predicts executive function. The lack of association of eGFR category with other cognitive domains suggests some degree of specificity. This finding suggests that executive function is especially affected in poor renal function. Measures of executive function may be sensitive markers of cognitive impairment in decreased (or declining) renal function (5,7).

No significant...
associations were found between low eGFR and episodic memory and low eGFR and general ability.

More broadly, in this study we replicated well-established findings. We found that increasing age and hypertension are risk factors for decreased eGFR. The link between eGFR and executive function has several possible explanations. These processes may have a common biological substrate. For example, endothelial dysfunction occurs in early stages of renal disease, in individuals with cardiovascular risk factors, and perhaps in individuals with cognitive decline. In our study, individuals with low eGFR were older, had a higher prevalence of hypertension, and scored poorer on tests of executive function, factors that are all associated with renal disease, cardiovascular risk factors, and consequently vascular dementia. However, it is also important to note that in our study, adjustment for hypertension did not alter the association between eGFR and frontal-executive function, suggesting a shared underlying common mechanism that may be affecting both the vascular system and the brain and which might be posing parallel risk to both mechanisms. Alternatively, a general decline due to poor health and consequent physical and cognitive limitations might be taking place where decreased renal function and poor cognition may be indicators of a “diffuse” geriatric syndrome or simply markers of frailty, which is more prevalent in individuals with decreased eGFR. It may also be the case that decreased renal function may speed up cognitive and further physical decline, further contributing to the general decline that may be taking place.

Given the high prevalence rates of CKD in the United States and that CKD is becoming more and more associated with nondisease outcomes, such as functional and cognitive decline and frailty, researchers are urging future research to focus more on the impact these outcomes have on CKD progression, complications, and mortality. Furthermore, the impact microvascular and macrovascular events such as decreased eGFR and brain infarcts have on each other seem to also progress disease, with microvascular abnormalities being highly associated with executive function and consequently playing a big role in maintaining independence in later life. The consistent findings that specific cognitive functions are more vulnerable in decreased eGFR, public health implications should be considered. Our finding of an independent association between eGFR and executive dysfunction in community-dwelling elderly suggests the importance of early intervention. Tests of executive dysfunction in our study reflect difficulties with the maintenance of cognitive flexibility, compromised attention, and task switching. Clinically, Trails B and Digit Symbol in other studies have shown strong associations to AD conversion, a likely outcome in individuals with renal disease. Although episodic memory was not significantly associated with eGFR in this study, patient studies show that in more advanced CKD and ESRD, memory also becomes impaired, which may then cause compliance issues due to forgetfulness. Thus, cognitive screening and regular monitoring should take place early in the course of CKD, especially when age and hypertension are also significant factors associated with poorer outcomes in the process.

In light of these findings we strongly recommend a follow-up of these results to determine the magnitude and rapidity of change in eGFR and its association with cognitive performance over time. Longitudinal analysis will also determine (i) if the independent executive function—eGFR association holds over time, and (ii) if change in cognitive status (ie, nonimpaired to MCI or MCI to dementia) takes place in relation to eGFR.

This study had a number of strengths including comprehensive measures of cognitive function, medical and psychological variables, and demographics. This study also had a number of limitations: the participants were relatively healthy, community-dwelling older adults; this is common when studying individuals who volunteer for research, thus the findings are not reflective of patient populations. However, the study was deliberately aimed at variation in cognitive function as an outcome of eGFR. Although this was a cross-sectional study, the EAS is an ongoing study, where future opportunities are available to follow-up the sample longitudinally.

Conclusion
This cross-sectional study has shown a direct independent association between eGFR and executive function. Awareness of the ways cognition and renal function affect each other early on in potential pathological decline will help in developing effective ways to improve patient adherence and treatment options.

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Conflict of Interest
All authors declare that there are no financial, personal, or other potential conflicts of interest.

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