CKD Associates with Cognitive Decline

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ABSTRACT
Cognitive impairment and chronic kidney disease (CKD) will become increasingly prevalent in the aging US population. Although evidence exists that CKD is a risk factor for cognitive decline, longitudinal studies are limited and largely have excluded ethnically diverse populations. The Northern Manhattan Study includes a population-based, prospective, stroke-free cohort. We assessed global cognitive function annually using the modified Telephone Interview for Cognitive Status (TICS-m) and estimated kidney function using Cockcroft–Gault creatinine clearance (CCl), Modification of Diet in Renal Disease estimated GFR (eGFR), and serum creatinine (sCr). We examined the association between CKD and change in TICS-m scores over time, adjusting for sociodemographic and vascular risk factors. Of 2172 subjects (mean age 71.5 yr, mean follow-up 2.9 yr), 59% were Hispanic, 20% were black, and 63% were women. Participants with a CCl < 60 ml/min and those with a CCl between 60 and 90 ml/min performed significantly worse on the TICS-m over time than those with a CCl > 90 ml/min, adjusting for potential confounders. Our results were similar when we used eGFR or sCr to estimate kidney function. In conclusion, decreased kidney function associates with greater cognitive decline, even in those with mild CKD. Kidney disease may represent a novel mechanism leading to cognitive impairment and a target for early intervention.

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pants with an elevated risk of dementia and cardiovascular disease.\textsuperscript{12,13}

**RESULTS**

The Northern Manhattan Study (NOMAS) includes a prospective cohort with 3298 participants at baseline, and complete data for estimates of kidney and cognitive function were available for 3029 participants. Of these, 857 participants had either died or suffered strokes before their first modified Telephone Interview for Cognitive Status (TICS-m), leaving 2172 participants for this analysis. Compared with those not included (n = 1126), participants in the current sample were younger (mean age 66 versus 75 yr, P < 0.0001) and more likely to be Hispanic (59\% versus 39\%, P < 0.001) and have Medicaid (46\% versus 40\%, P = 0.01). The sample was also healthier, with a lower baseline creatinine (mean 0.9 \textmu g/dl, P < 0.0001), lower total homocysteine (tHcy; 2.2 versus 2.4 nmol/L, P < 0.0001), and lower prevalences of hypertension (72\% versus 77\%, P = 0.01), diabetes (19\% versus 27\%, P < 0.0001), cardiac disease (21\% versus 31\%, P < 0.0001), smoking (16\% versus 19\%, P = 0.03), and alcohol abstention (64\% versus 74\%, P < 0.0001).

Baseline characteristics of this sample are shown in Table 1, grouped by both creatinine clearance (CCl) and eGFR levels. Only three participants would be considered to have ESRD defined by a CCl (n = 2) or eGFR (n = 1) of <15 ml/min (0.1\%). Those with worse kidney function tended to be older, female, non-Hispanic, and more educated. A higher proportion of these participants also had cardiac disease and elevated tHcy, but a lower proportion had diabetes. A significantly higher proportion of subjects with low eGFR had hypertension but not when CCl was used as the metric for kidney disease.

Table 2 shows coefficients for (1) the annual change in TICS-m scores for each measure of kidney function (Table 2, unadjusted), (2) further adjusted for sociodemographic variables (Model 1), and (3) further adjusted for vascular risk factors (Model 2). In our fully adjusted model, participants with a baseline CCl <60 ml/min declined by an average of 0.4 points per year in their TICS-m scores compared with those with a CCl >90 ml/min (P < 0.001), whereas those with a CCl between 60 and 90 ml/min declined by an average of 0.2 points per year (P < 0.001; Table 2). The results for eGFR were similar.

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics</th>
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<tbody>
<tr>
<td>Creatinine clearance</td>
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<tr>
<td>&lt;60 ml/min</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Women</td>
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<tr>
<td>Completed high school</td>
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<tr>
<td>Medicaid</td>
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<tr>
<td>Race</td>
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<td>White</td>
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<td>Black</td>
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<tr>
<td>Hispanic</td>
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<tr>
<td>Other</td>
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<tr>
<td>Medical history</td>
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<tr>
<td>Cardiac disease</td>
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<td>Hypertension</td>
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<td>Systolic blood pressure, mmHg (SD)</td>
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<td>Diastolic blood pressure, mmHg (SD)</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Total homocysteine (&lt;8.4 \mu mol/L)</td>
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<tr>
<td>8.4–12 \mu mol/L</td>
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<tr>
<td>&gt;12 \mu mol/L</td>
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<tr>
<td>Moderate alcohol consumption</td>
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<td>Smoking status</td>
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<tr>
<td>Former smoker</td>
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<tr>
<td>Current smoker</td>
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<td>Baseline TICS-m score (SD)</td>
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</table>

TICS-m, modified Telephone Interview for Cognitive Status.
creatinine (sCr), TICS-m scores declined an average of 0.04 points per year. Thus, in our 60 to 90 ml/min CCl and eGFR scores is not linear, and this approximation is most valid close to the mean age (71 yr).

To put these parameter estimates in perspective, we examined systolic and diastolic BP continuously using linear and quadratic terms. This did not alter our findings regarding the association between cognition and kidney function (data not shown). Anemia can also have a negative impact on cognition, but adjusting for hematocrit did not affect our results. Finally, we investigated the use of certain medications that are known to be psychoactive (antidepressants, benzodiazepines, β-blockers, and antipsychotics) and found that inclusion of these variables in our models did not change our results and there was no interaction between use of these medications and kidney function.

DISCUSSION

In this prospective cohort study in a multiethnic stroke-free population, we found that CKD was associated with cognitive decline and that this relationship extended to those with mildly reduced eGFR or CCl.

These results add to the growing body of literature identifying an association between kidney disease and cognition. Several studies have shown an elevated risk of dementia in patients with ESRD. Longitudinal studies on mild to moderate CKD have included an analysis of the CHS, that found that an elevated sCr carried a 37% increased risk of incident dementia. In the Health, Aging, and Body Composition Study, those with an eGFR <60 ml/min had a worse baseline modified Mini-Mental Status Examination score and had higher rates of cognitive impairment over 2 to 4 yr of follow-up. Furthermore, the odds of cognitive decline were higher in those with eGFR <45 ml/min, as compared with those with eGFR between 45 and 60 ml/min. Our study demonstrates a dose-response relationship with cognitive decline that begins with even milder impairments in kidney function (CCI or eGFR between 60 and 90 ml/min).

The longitudinal nature of this study and the dose-response relationship observed strengthen the premise that CKD is an independent risk factor for cognitive decline. A variety of potential mechanisms support this hypothesis. Most likely, CKD, through its adverse effects on the cerebral vasculature, potentiates vascular cognitive impairment (VCI). We have shown previously that a CCI between 15 and 60 ml/min is independently associated with a 43% increase in stroke and greater white matter disease, both of which are risk factors for dementia and VCI. In this study, subjects were stroke-free at baseline, and we censored TICS-m scores if they occurred after an incident stroke. Thus, if kidney disease caused cognitive decline, then it must have been through subclinical vascular damage or a nonvascular mechanism.

Another biologically plausible mechanism involves inflammation, which is often greater in a CKD population. For
example, total homocysteine is inversely related to kidney function, and it also may contribute to cognitive impairment. Although we adjusted for serum tHcy, we did not account for other inflammatory markers that could mediate cognitive decline, such as IL-6. In recent years, basic and clinical research has supported a causal role for inflammation, endothelial dysfunction, and oxidative stress in the development of vascular disease. These derangements are all characteristic of CKD and further support the kidney’s hypothesized role in VCI and Alzheimer’s disease, where the same processes may be at work. Ours is not a dementia study, nor do we have data on its subtypes. However, limited data hint at a greater role for CKD in the development of vascular dementia over Alzheimer’s disease, although more research is needed to clarify these relationships.

Another possible mediator is anemia, which is usually found at more advanced stages of CKD and also is associated with dementia. In fact, the reversal of anemia has been associated with an improvement in cognitive function. However, adjusting for hematocrit did not alter our results for any measure of kidney function, indicating that the underlying mechanisms related to CKD in this sample are independent of anemia.

This study has several limitations. First, we relied only on one sCr measurement per subject and did not have repeat measurements to assess change in kidney function. Second, we lacked urine samples to identify participants with albuminuria as their only manifestation of CKD, and this is relevant because albuminuria has been associated with cognitive decline. Third, the Modification of Diet in Renal Disease (MDRD) and Cockcroft–Gault formulas are less accurate when the true GFR is >60 ml/min. Although more accurate formulas to estimate function are under development and validation and biomarkers such as cystatin C show promise, none is currently in clinical use. To minimize misclassification in those with GFR >60 ml/min, we used both formulas in addition to the sCr to estimate kidney function. We employed this approach to demonstrate the consistency of our results across methods of estimating kidney function and for internal validation. Also, this sample may have been biased due to an inherent survivor effect as participants were healthier than those not included at baseline, and the TICS-m was not administered to subjects until several years into the study. However, this most likely would have reduced the apparent effect of kidney function on cognition. Finally, unmeasured confounding, stemming from insufficient data on the length of exposure to vascular risk factors such as hypertension or diabetes mellitus or on the severity of underlying vascular disease, are limitations.

Despite these limitations, there are several strengths to this study. First, this was a longitudinal study with repeated assessments of cognition supporting a causal role of CKD in cognitive decline. Second, because there is no consensus on the preferred method of estimating kidney function in Hispanics, we used three different estimations of kidney function, which were all in agreement. Third, we assessed cognition using the TICS-m, a tool that is not constrained by ceiling effects and has been used in other large studies where in-person examination is not practical. Fourth, NOMAS is a population-based multiethnic cohort that allows some generalization to blacks and Hispanics and an urban US population.

In conclusion, we found that CKD is linearly associated with cognitive decline in a multiethnic urban population, adjusting for multiple risk factors. This relationship existed for those with mildly reduced kidney function and may be attenuated in Hispanics compared with whites. Our study adds to the growing evidence that kidney disease is a risk factor for cognitive decline and provides a potential novel target for intervention to lower the risk of dementia in those also at risk of CKD. Future studies are needed to address the mechanism by which CKD might affect cognition, the cognitive domains specifically affected, differential effects of race–ethnicity and age on this association, and the effects of interventions to slow CKD-related cognitive dysfunction.

**CONCISE METHODS**

**Cohort**

The NOMAS is a population-based, prospective cohort of 3298 subjects recruited from northern Manhattan between 1993 and 2001. The details of enrollment have been described elsewhere. Briefly, community participants were eligible if they met the following conditions: (1) no history of stroke, (2) age greater than or equal to 40 yr, and (3) residence in a household with a telephone for at least 3 mo in northern Manhattan. The TICS-m, a global test of cognition, was added to our annual follow-up assessment beginning in 2001 and administered yearly.

**Baseline Evaluation and Follow-Up**

Trained bilingual research assistants and study physicians collected demographic, medical, and laboratory data at enrollment using standardized data collection techniques and risk factor questions based on the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System. Subjects were contacted annually via telephone starting in 1998 to gather information regarding illnesses, hospitalizations, vital status, and cardiovascular events.

**Estimation of Kidney Function**

Baseline kidney function was estimated using sCr, CCI using the Cockcroft–Gault formula, and eGFR using the MDRD formula:

\[
CCI = (140 - \text{age}) \times \left(\frac{\text{weight in kg}}{(\text{serum creatinine} \times 72)}\right) \\
\times (0.85 \text{ for women})
\]

\[
eGFR = 186.3 \times (\text{serum creatinine}^{-1.134}) \\
\times (\text{age}^{-0.203}) \times (0.742 \text{ for women}) \times (1.21 \text{ for blacks})
\]

Serum creatinine was treated as a continuous variable. Furthermore, CCI and eGFR were trichotomized as follows: <60 ml/min, 60
to 90 ml/min, and >90 ml/min (reference). Serum creatinine was measured by the kinetic Jaffe reaction. We did not include participants in this analysis if they were missing data to estimate any of the three measures of kidney function \((n = 82, 2.5\%)\).

**Cognitive Assessment**

As a global measure, the TICS-m was designed to assess a variety of cognitive domains, including attention, language, calculation, and immediate recall of ten words.\(^4,4\) The TICS-m includes a delayed recall of the ten words and has been validated in clinical and research settings.\(^4,4,4\) Only 187 participants did not have TICS-m evaluations (5.6%). Incomplete TICS-m tests were not analyzed, because the total score is not valid.

**Other Covariate Measures**

Established risk factors for cognitive impairment and kidney function were selected as covariates for multivariable analysis. Race–ethnicity was based on self-identification. Educational status was dichotomized based on whether or not high school had been completed. Insurance status was dichotomized to Medicaid \textit{versus} not. Diabetes was defined based on the subject’s self-reported history, usage of hypoglycemic medications, or fasting blood sugar \(\geq 126\) mg/dl. A history of hypertension included BP \(\geq 140/90\) mmHg (based on an average of two measurements with a mercury sphygmomanometer), the patient’s self-reported history of hypertension, or antihypertensive medication use. Moderate alcohol usage was defined as current drinking between one drink per month and two drinks per day at baseline. Smoking status was categorized as never smoked, current smoker (within the last year), or former smoker. Past cardiac disease included any history of angina, myocardial infarction, congestive heart failure, coronary artery disease, atrial fibrillation, or valvular heart disease. Serum total homocysteine was measured using methods licensed for commercial use and was log-transformed to a normal distribution.\(^49\)

**Statistical Analysis**

Sample characteristics were assessed in relation to CKD by comparing means and proportions using ANOVA or \(\chi^2\) tests as appropriate. We used mixed effects models to evaluate whether the change in TICS-m score over time was dependent on kidney function. To evaluate this, we included an interaction term between levels of kidney function and time between TICS-m examinations. We examined separately each estimate of kidney function (CCl, eGFR, and sCr) and adjusted for potential confounders, including age, gender, race–ethnicity, education, insurance status, hypertension, diabetes, alcohol consumption, smoking status, history of cardiac disease, and serum levels of tHcy. We censored TICS-m scores occurring after incident strokes, because stroke increases the risk for cognitive impairment and dementia.\(^20,50\)

Anemia and certain medications can cause cognitive dysfunction, and both are seen commonly in CKD, so we carried out secondary analyses adjusting for baseline hematocrit and psychoactive medication use. Analyses were conducted with SAS 9.1.3 software (Cary, NC).

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**DISCLOSURES**

None.

**REFERENCES**


