Chronic Kidney Disease and Cognitive Impairment in the Elderly: The Health, Aging, and Body Composition Study

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Previous studies suggest a link between chronic kidney disease (CKD) and cognitive impairment. Whether the longitudinal course of cognitive impairment differs among people with or without CKD is unknown. Data collected in 3034 elderly individuals who participated in the Health, Aging, and Body Composition study were analyzed. Cognitive function was assessed with the Modified Mini-Mental State Exam (3MS) at baseline and then 2 and 4 yr after baseline. Cognitive impairment was defined as a 3MS score <80 or a decline in 3MS >5 points after 2 or 4 yr of follow-up among participants with baseline 3MS scores ≥80. Participants with CKD, defined as an estimated GFR (eGFR) <60 ml/min per 1.73 m², were further divided into two eGFR strata. Unadjusted mean baseline 3MS scores and mean declines in 3MS scores over 4 yr were significantly more pronounced for participants with lower baseline eGFR. More advanced stages of CKD were associated with an increased risk for cognitive impairment: Odds ratio (OR) 1.32 (95% confidence interval [CI] 1.03 to 1.69) and OR 2.43 (95% CI, 1.38 to 4.29) for eGFR 45 to 59 ml/min per 1.73 m² and <45 ml/min per 1.73 m², respectively, adjusted for case mix, baseline 3MS scores and other potential confounders. CKD is associated with an increased risk for cognitive impairment in the elderly that cannot be fully explained by other well-established risk factors. Studies aimed at understanding the mechanism(s) responsible for cognitive impairment in CKD and efforts to interrupt this decline are warranted.

The prevalence of cognitive impairment and dementia in ESRD is more than double that of the general population (1–3). However, the reasons for this high rate remain uncertain. Specifically, it is not known whether cognitive impairment is mediated by the direct effects of uremia, per se, or is attributable to a high prevalence of predisposing risk factors among individuals with ESRD and side effects of the hemodialysis treatment. Recent studies suggest that chronic kidney disease (CKD) may also be a risk factor for cognitive impairment (4–6). Many of the factors that have been proposed as mediators of cognitive impairment in ESRD, such as anemia and inflammation, may be present in individuals with earlier stages of CKD (7,8).

CKD has been associated with an increased risk for dementia in elderly individuals (4) and with poorer performance on tests of global cognitive function, executive function, language, and memory (5,6). However, previous studies were conducted in mostly white populations and did not explore several hypothesized mediators of impairment, such as anemia and inflammation. Moreover, no studies have examined the association between CKD and performance on serial cognitive function tests, and only one study stratified analyses by the severity of CKD (6). The goals of this study were to determine the strength of the association between CKD and cognitive function in a biracial cohort of community-dwelling elderly and to explore potential mediators of cognitive impairment and whether these extinguish or otherwise modify the association between CKD and cognitive impairment. We hypothesized that CKD would be associated with cognitive impairment in cross-sectional and longitudinal analyses and that the association would be “dose (severity)-dependent” and independent of established risk factors for cognitive impairment, such as age, low educational attainment, diabetes, hypertension, and other cardiovascular disease risk factors.

Materials and Methods

Participants

The Health, Aging, and Body Composition (Health ABC) study is a prospective cohort study designed to evaluate the effects of aging on
body composition and functional status in 3075 community-dwelling elderly individuals. Cognitive function is a secondary outcome. Health ABC participants were recruited between April 1997 and June 1998 from a sample of white and black Medicare-eligible adults in the Memphis, TN, and Pittsburgh, PA, vicinities; the University of California San Francisco served as the project’s data coordinating center. The study was initiated and supported by the Laboratory of Epidemiology, Demography, and Biometry of the National Institute on Aging. Exclusion criteria included (1) difficulties in activities of daily living, walking one quarter of a mile, or climbing 10 steps; (2) life-threatening illness; (3) difficulty communicating with the interviewer; or (4) intention of moving from the vicinity in the subsequent 3 yr. There were no exclusion criteria on the basis of the presence of kidney disease. The Institutional Review Boards at all clinical sites and the University of California San Francisco approved the study protocol and analysis plan, respectively, and all participants signed informed consent.

Cognitive Function Testing and Definition of Outcomes
Trained personnel administered the Modified Mini-Mental State Exam (3MS) to study participants at baseline and then 2 and 4 yr after baseline. The 3MS is a test of global cognitive function with components for concentration, orientation, language, praxis, and memory. Scores on the 3MS range from 0 to 100, with higher scores denoting better cognitive function. 3MS scores <80 are highly sensitive and specific for the diagnosis of dementia (9). The 3MS is considered more sensitive than the traditional 30-point Mini-Mental State Exam, especially for mild cognitive change, and is increasingly being used in epidemiologic studies of aging and cognition (10,11). For cross-sectional analyses, we defined cognitive impairment as a baseline 3MS <80. For longitudinal analyses, we defined cognitive impairment as a 3MS score <80 or a decline in 3MS >5 points at 2 or 4 yr of follow-up among participants with baseline 3MS scores ≥80. These criteria have been previously used in longitudinal studies of cognitive function (10,12). Because mean scores on the 3MS vary by education and blacks in the Health ABC cohort had fewer years of education, we explored whether definitions of impairment on the basis of race or educational attainment changed the associations of interest. For these analyses, we used a 3MS cutpoint of <75 for individuals with less than a high school education and a 3MS cutpoint of <80 for individuals with a high school education.

Estimation of Kidney Function
Blood samples for measurement of serum creatinine and other laboratory parameters were obtained at baseline after an overnight fast. Serum creatinine was measured on frozen serum at a central laboratory using the Kodak Ektachem 700 Analyzer (Rochester, NY), which uses a colorimetric assay. We estimated the GFR (eGFR) for each participant using the Modification of Diet in Renal Disease (MDRD) formula incorporating baseline age, gender, race, and serum creatinine concentration (13). CKD was defined as an eGFR <60 ml/min per 1.73 m². To assess for threshold effects, we stratified participants with CKD into two eGFR strata: eGFR 45 to 59 ml/min per 1.73 m² and eGFR <45 ml/min per 1.73 m². To determine whether our results were significantly changed by the method used to estimate kidney function, we also used the Cockcroft-Gault estimated creatinine clearance (eCrCl) formula (14). Because age is an important predictor of cognitive function and age is also a component of the MDRD and Cockcroft-Gault formulas, we also conducted companion analyses stratifying participants by gender-specific serum creatinine cutoffs rather than eGFR or eCrCl.

Covariates
We selected variables from the Health ABC database that are known or hypothesized to be associated with cognitive function, CKD, or both. Demographic characteristics, chronic health conditions, medication use, education level, income, and lifestyle factors were ascertained by questionnaire for all Health ABC participants at enrollment. Diabetes was defined as a fasting plasma glucose level >126 mg/dl, self-report of diabetes, or the use of medications for diabetes. Baseline cardiovascular conditions, including coronary artery disease, cerebrovascular disease, and heart failure, were determined on the basis of self-report and the use of selected medications, using disease algorithms similar to those used in the Cardiovascular Health Study (15). With the exception of hematocrit concentration, which was measured 2 yr after the baseline visit, all laboratory values were measured at baseline. For longitudinal analyses, we also included cardiovascular events, defined as hospitalization for stroke, heart failure, myocardial infarction, or angina.

Analytic Cohort
Serum creatinine was unavailable in 28 (0.9%) participants, and scores on the 3MS were unavailable for 44 (1.4%) participants, yielding an analytic cohort of 3034 (98.7%). Baseline demographic and clinical factors among the 41 Health ABC participants who had missing serum creatinine and/or 3MS scores did not differ significantly from the 3034 in the analytic cohort (data not shown).

Statistical Analyses
Continuous variables were expressed as mean ± SD and compared using ANOVA or the Kruskal-Wallis test. Categorical variables were expressed as a percentage and compared using the chi² test. We compared mean baseline and 4-yr change scores across strata of eGFR using mixed models accounting for correlation among individual participants. We used logistic regression analysis to examine the risk for cognitive impairment as a function of baseline eGFR. First we conducted unadjusted analyses exploring the relation between eGFR in predefined strata and the outcome of interest. Next, we adjusted for baseline 3MS scores and case mix: age, race, gender, and education. After the initial multivariable models were fit, we manually added selected explanatory variables to evaluate for residual confounding, predefined as a change of 10% or more in the parameter estimates for eGFR strata. The following covariates were examined as potential modifiers of the relation between eGFR and cognitive impairment: chronic health conditions including diabetes; medications including aspirin, statins, and class of antihypertensive; baseline systolic and diastolic BP; baseline measurements of lipids, C-reactive protein, and IL-6; hematocrit concentration (measured 2 yr after baseline); and incident cardiovascular events. Variables that were not normally distributed (C-reactive protein and IL-6) were analyzed in tertiles rather than as continuous measurements. The change in model fit was explored by using linear or higher order terms for eGFR rather than eGFR strata. We tested for effect modification with multiplicative interaction terms for eGFR and selected covariates. We considered two-sided P < 0.05 statistically significant. Analyses were conducted using SAS 8.2 (SAS Institute, Cary, NC).

Results
Participant characteristics stratified by eGFR are shown in Table 1. The mean age of all participants was 74 ± 3 yr (range 68 to 80 yr). Forty-two percent were black, and 52% were female. Compared with participants without CKD, those with CKD were older, more likely to be black, and less likely to have graduated high school (P < 0.05 for all). As expected, there was
a higher prevalence of diabetes and cardiovascular disease in those with CKD, as well as significant differences in several anthropometric and laboratory measures across the three groups. Baseline cognitive function was poorer and the decline in cognitive function over 4 yr was greater for those with a lower eGFR. Unadjusted baseline 3MS scores were 89.8 ± 0.2, 90.5 ± 0.4, and 86.9 ± 0.8 for participants with an eGFR ≥60, 45 to 59, and <45 ml/min per 1.73 m², respectively (P < 0.0001). These differences persisted after adjusting for case mix (Figure 1). Four-year change scores on the 3MS also differed significantly by eGFR. The decline in 3MS scores was almost 2 points greater among participants with an eGFR <45 ml/min per 1.73 m² versus those with an eGFR ≥60 ml/min per 1.73 m² after accounting for case mix (Figure 2). In cross-sectional analyses, CKD was associated with an increased risk for cognitive impairment at baseline (3MS <80). For example, in unadjusted analyses, participants with an eGFR <45 ml/min per 1.73 m² had almost a two-fold higher risk of cognitive impairment at baseline (odds ratio [OR] 1.91; 95% confidence interval [CI], 1.17 to 3.12) compared with those with an eGFR ≥60 ml/min per 1.73 m². The association between an eGFR <45 ml/min per 1.73 m² and baseline impairment was not statistically significant after adjustment for case mix (OR 1.64; 95% CI, 0.94 to 2.87).

### Table 1. Baseline characteristics of Health ABC participants

<table>
<thead>
<tr>
<th>Baseline eGFR (ml/min per 1.73 m²)</th>
<th>eGFR ≥60 (n = 2381)</th>
<th>eGFR 45 to 59 (n = 534)</th>
<th>eGFR &lt;45 (n = 119)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>73.5 ± 2.9</td>
<td>73.9 ± 2.8</td>
<td>74.3 ± 2.9</td>
<td>0.0002</td>
</tr>
<tr>
<td>Female (%)</td>
<td>51%</td>
<td>56%</td>
<td>52%</td>
<td>0.09</td>
</tr>
<tr>
<td>Black (%)</td>
<td>44%</td>
<td>27%</td>
<td>50%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High school graduate (%)</td>
<td>74%</td>
<td>79%</td>
<td>71%</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>24%</td>
<td>24%</td>
<td>39%</td>
<td>0.002</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>2%</td>
<td>5%</td>
<td>13%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cerebrovascular disease (%)</td>
<td>7%</td>
<td>10%</td>
<td>15%</td>
<td>0.002</td>
</tr>
<tr>
<td>Physical activity (kcal/wk)</td>
<td>85 ± 71</td>
<td>79 ± 64</td>
<td>60 ± 58</td>
<td>0.0003</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.2 ± 4.9</td>
<td>27.5 ± 4.7</td>
<td>27.4 ± 6.0</td>
<td>0.53</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>136 ± 21</td>
<td>136 ± 22</td>
<td>142 ± 24</td>
<td>0.003</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>72 ± 12</td>
<td>71 ± 12</td>
<td>73 ± 13</td>
<td>0.08</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.0 ± 0.2</td>
<td>1.2 ± 0.2</td>
<td>2.2 ± 1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>202 ± 38</td>
<td>203 ± 40</td>
<td>208 ± 48</td>
<td>0.33</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>121 ± 34</td>
<td>122 ± 36</td>
<td>124 ± 41</td>
<td>0.80</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>54 ± 17</td>
<td>53 ± 16</td>
<td>51 ± 17</td>
<td>0.07</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>2.8 ± 4.2</td>
<td>3.1 ± 4.2</td>
<td>6.9 ± 11.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>2.3 ± 1.9</td>
<td>2.5 ± 2.0</td>
<td>3.8 ± 2.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hematocrit (%)b</td>
<td>40.8 ± 3.8</td>
<td>40.1 ± 4.2</td>
<td>38.2 ± 4.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Health ABC, Health, Aging, and Body Composition; eGFR, estimated GFR.

*bMeasured 2 yr after baseline.

![Figure 1. Adjusted baseline Modified Mini-Mental State Exam (3MS) scores by estimated GFR (eGFR). Note: Scores adjusted for age, race, gender, and education. P < 0.01 for trend.](image1)

![Figure 2. Adjusted 4-yr change in 3MS scores by eGFR. Note: Scores adjusted for age, race, gender, and education. *P < 0.01 for comparison with eGFR ≥60 ml/min per 1.73 m² and eGFR 45 to 59 ml/min per 1.73 m².](image2)
Of the 3034 participants with baseline serum creatinine and cognitive function measurements, 305 had baseline cognitive impairment and were excluded from the longitudinal analyses. Among the remaining participants, 154 died and an additional 169 had no repeat cognitive function testing during the 4 yr of follow-up. Compared with participants who received follow-up cognitive function testing, those with missing data were older, more likely to be black, less likely to have graduated high school, and more likely to have baseline cerebrovascular disease and lower 3MS scores. Those with missing data also had a slightly lower baseline eGFR (73 versus 71 ml/min per 1.73 m²; P = 0.04).

Of the remaining 2406 participants, 872 (36%) developed cognitive impairment during follow-up: 315 (13%) had a decline in 3MS >5 points, 299 (12%) had a 3MS <80, and 258 (11%) met both criteria for impairment. There was a significant, graded risk for cognitive impairment associated with the severity of CKD, even after accounting for baseline 3MS scores and case mix (Table 2). To determine whether this relationship was influenced by the cut point used to define impairment, we conducted similar analyses using education-specific 3MS cut points. The association between kidney function and cognitive impairment was unchanged with this alternate definition: OR 1.32 (95% CI, 1.05 to 1.65) and OR 2.72 (95% CI, 1.64 to 4.49) for eGFR 45 to 60 and <45 ml/min per 1.73 m², respectively.

To examine whether the associations were uniform throughout the age range, we evaluated the OR for cognitive impairment in participants below and above the median age (73 yr). The OR for cognitive impairment in analyses stratified by age and adjusted for case mix were similar: Below the median age, OR 1.62 (95% CI, 1.17 to 2.25) and OR 2.38 (95% CI, 1.10 to 5.11), and for those above the median age, OR 1.10 (95% CI, 0.80 to 1.51) and OR 3.36 (95% CI, 1.69 to 6.70) among participants with an eGFR 45 to 60 and <45 ml/min per 1.73 m², respectively. When we used eCrCl rather than eGFR to estimate kidney function, the results were not different (Table 2). We also examined the relation between cognitive impairment and kidney function using gender-specific serum creatinine cutoffs. We chose cutoffs that represented the top 10% and top 1% of serum creatinine values for each gender: For men, ≤1.4 mg/dl, 1.5 to 1.9 mg/dl, ≥2.0 mg/dl; and for women, ≤1.2 mg/dl, 1.3 to 1.7 mg/dl, and ≥1.8 mg/dl. Compared with those with a “normal” serum creatinine value, those in the top 10% had an OR for cognitive impairment of 1.53 (95% CI, 1.05 to 2.24), and those in the top 1% had an OR of 3.15 (95% CI, 1.28 to 7.75) after adjustment for case mix.

We explored these associations by fitting additional models with potential mediators of cognitive impairment. Adjustment for a number of clinical factors and laboratory measures, including baseline cardiovascular disease, diabetes, BP, and incident stroke, did not extinguish the significant, increased risk for cognitive impairment associated with CKD (Table 3). Inclusion of baseline lipids, C-reactive protein, and IL-6 levels or hematocrit concentration modestly attenuated the relation between cognitive impairment and kidney function for participants with an eGFR <45 ml/min per 1.73 m² but did not change the significant effect estimate for those with an eGFR 45 to 59 ml/min per 1.73 m². There was a significant, graded risk for cognitive impairment among participants with CKD even after controlling for all of these factors: eGFR 45 to 59 ml/min per 1.73 m² (OR 1.32; 95% CI, 1.03 to 1.69) and eGFR <45 ml/min per 1.73 m² (OR 2.86; 95% CI, 1.38 to 4.29). CKD accounted for approximately 10% of the risk for impairment explained by the final multivariable model. Among modifiable risk factors for cognitive impairment included in the final multivariable model, the contribution of CKD was second only to that of education and roughly equivalent to the contribution of incident stroke.

**Discussion**

Few studies have examined the risks for dementia and cognitive impairment among people with CKD. Seliger et al. (4) reported an elevated risk for incident dementia in elderly individuals who had CKD and participated in the Cardiovascular Health Cognition Study. Kidney function was analyzed as a continuous variable using the inverse of serum creatinine or as a dichotomous variable using gender-specific serum creatinine cutoffs. In this study, an elevated serum creatinine concentration was associated with a 37% increased risk for incident dementia. We have published two cross-sectional studies that have described an association between CKD and cognitive impairment. In a single-center study of 160 individuals, study patients with CKD, defined as an estimated GFR <60 ml/min per 1.73 m², had significantly poorer performance on tests of executive function and verbal memory compared with published norms (5). Among those with CKD, eGFR was inversely related to performance on tests of global cognitive function and verbal memory. In another study of 1015 women who partici-

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**Table 2. Odds ratios and 95% confidence intervals for cognitive impairment at follow-up by baseline eGFR (ml/min per 1.73 m²)**

<table>
<thead>
<tr>
<th>eGFR ≥ 60 (n = 1911)</th>
<th>eGFR 45 to 59 (n = 426)</th>
<th>eGFR &lt; 45 (n = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.00</td>
<td>1.14 (0.92 to 1.41)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.00</td>
<td>1.31 (1.04 to 1.65)</td>
</tr>
</tbody>
</table>

*a* The corresponding adjusted odds ratios for estimated creatinine clearance (eCrCl) 45 to 59 and eCrCl < 45 ml/min per 1.73 m² are 1.32 (1.08 to 1.60) and 2.04 (1.50 to 2.77), respectively.

*b* Model adjusted for age, race, gender, education, and baseline Modified Mini-Mental State Exam (3MS).
cognitive impairment, as did the group with an eGFR almost one fifth of the study cohort, had an increased risk for ml/min per 1.73 m². Because there is a high prevalence of CKD respective.

In the current study, those with an eGFR of 45 to 59 ml/min per 1.73 m², because the association between eGFR and cognitive impair-

ment is not limited to those with advanced CKD. In the current severity of CKD, suggesting a causal relation between CKD and over, we show that the change in cognitive function over time residual effects of age, race, and other key confounders. More-

tia. In this study, adjustment for incident stroke only modestly disease may explain the association between CKD and demen-

attenuated the elevated risk for cognitive impairment for par-

ticipants with an eGFR 45 ml/min per 1.73 m², suggesting that factors other than the severity of cerebrovascular disease are involved in the patho-

genesis of cognitive impairment in CKD.

The mechanisms that might contribute to cognitive impair-

ment in CKD remain unclear. Individuals with CKD have an increased prevalence of cardiovascular disease risk factors associated with cognitive impairment in the general population (17–19) and a higher prevalence of established cardiovascular disease. The results shown here suggest that the relation between CKD and cognitive impairment is independent of these factors, as well as other factors that are jointly implicated in cardiovascular disease and dementia, including proxies of inflammation and atherosclerosis. Individuals with CKD have an increased risk for stroke (20), an established risk factor for cognitive impairment and dementia in the general population (21). In previous studies, CKD and ESRD were more strongly associated with vascular dementia than Alzheimer’s dementia (1,4), suggesting that an increased burden of cerebrovascular disease may explain the association between CKD and demen-

tia. In this study, adjustment for incident stroke only modestly attenuated the elevated risk for cognitive impairment for participants with an eGFR <45 ml/min per 1.73 m² and did not change the effect estimates for those with an eGFR 45 to 60 ml/min per 1.73 m², suggesting that factors other than the severity of cerebrovascular disease are involved in the pathogenesis of cognitive impairment in CKD.

CKD is associated with a number of other factors that have been proposed as mediators of cognitive impairment, including anemia, increased levels of inflammatory cytokines, oxidative stress, and alterations in lipid and homocysteine metabolism. For example, anemia is thought to be a key mediator of cognitive impairment in people with ESRD (22,23) and more recently has been associated with cognitive impairment in elderly individuals without known kidney disease (24). Inflammatory mechanisms have been implicated in the pathogenesis of vas-

Table 3. Odds ratios and 95% confidence intervals for cognitive impairment at follow-up among individuals with an eGFR <60 ml/min per 1.73 m², adjusted for clinical and laboratory variables

<table>
<thead>
<tr>
<th>Model</th>
<th>eGFR 45 to 59</th>
<th>eGFR &lt;45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted for case mix and baseline 3MS</td>
<td>1.31</td>
<td>2.86</td>
</tr>
<tr>
<td>Adjusted for case mix, baseline 3MS, and cardiovascular disease</td>
<td>1.30</td>
<td>2.80</td>
</tr>
<tr>
<td>Adjusted for case mix, baseline 3MS, and diabetes</td>
<td>1.30</td>
<td>2.76</td>
</tr>
<tr>
<td>Adjusted for case mix, baseline 3MS, and baseline blood pressure</td>
<td>1.31</td>
<td>2.85</td>
</tr>
<tr>
<td>Adjusted for case mix, baseline 3MS, and incident stroke</td>
<td>1.32</td>
<td>2.80</td>
</tr>
<tr>
<td>Adjusted for case mix, baseline 3MS, and baseline lipids</td>
<td>1.34</td>
<td>2.77</td>
</tr>
<tr>
<td>Adjusted for case mix, baseline 3MS, and baseline inflammatory markers</td>
<td>1.28</td>
<td>2.69</td>
</tr>
<tr>
<td>Adjusted for case mix, baseline 3MS, and hematocrit concentration</td>
<td>1.29</td>
<td>2.64</td>
</tr>
<tr>
<td>Full model</td>
<td>1.32</td>
<td>2.43</td>
</tr>
</tbody>
</table>

*aCase mix: age, race, gender, and education.
*bBaseline coronary artery disease, cerebrovascular disease, and heart failure.
*cLDL, HDL, and total cholesterol concentration.
*dC-reactive protein and IL-6 concentration.
*eHematocrit concentration measured 2 yr after baseline.
*fFull model adjusted for case mix, baseline 3MS, baseline cardiovascular disease, diabetes, BP, lipids, inflammatory markers, hematocrit concentration, and incident stroke. LR $\chi^2$ for full model $= 219.6$, $P < 0.0001$. The corresponding adjusted odds ratios for eCrCl 45 to 59 and eCrCl < 45 ml/min per 1.73 m² are 1.44 (95% CI, 1.17 to 1.78) and 2.03 (95% CI, 1.46 to 2.83), respectively.

pated in the Heart Estrogen/Progestin Replacement Study, eGFR was significantly associated with performance on tests of global cognitive function, executive function, language, and memory (6). Women with an eGFR <30 ml/min per 1.73 m² had a five-fold greater odds of cognitive impairment compared with women with an eGFR ≥60 ml/min per 1.73 m², independent of age, race, and other potential confounders. This study demonstrates that CKD, defined as an eGFR <60 ml/min per 1.73 m², is associated with an increased risk for cognitive impairment in a large cohort of community-dwelling elderly individuals. These associations were independent of the residual effects of age, race, and other key confounders. Moreover, we show that the change in cognitive function over time and the risk for cognitive impairment vary directly with the severity of CKD, suggesting a causal relation between CKD and cognitive impairment. Furthermore, these results are important because the association between eGFR and cognitive impairment is not limited to those with advanced CKD. In the current study, those with an eGFR of 45 to 59 ml/min per 1.73 m², almost one fifth of the study cohort, had an increased risk for cognitive impairment, as did the group with an eGFR <45 ml/min per 1.73 m². Because there is a high prevalence of CKD in the population (16), the attributable risk of CKD as a contributory factor to cognitive decline is large.

The mechanisms that might contribute to cognitive impairment in CKD remain unclear. Individuals with CKD have an increased prevalence of cardiovascular disease risk factors associated with cognitive impairment in the general population (17–19) and a higher prevalence of established cardiovascular disease. The results shown here suggest that the relation between CKD and cognitive impairment is independent of these factors, as well as other factors that are jointly implicated in cardiovascular disease and dementia, including proxies of inflammation and atherosclerosis. Individuals with CKD have an increased risk for stroke (20), an established risk factor for cognitive impairment and dementia in the general population (21). In previous studies, CKD and ESRD were more strongly associated with vascular dementia than Alzheimer’s dementia (1,4), suggesting that an increased burden of cerebrovascular disease may explain the association between CKD and dementia. In this study, adjustment for incident stroke only modestly attenuated the elevated risk for cognitive impairment for participants with an eGFR <45 ml/min per 1.73 m² and did not change the effect estimates for those with an eGFR 45 to 60 ml/min per 1.73 m², suggesting that factors other than the severity of cerebrovascular disease are involved in the pathogenesis of cognitive impairment in CKD.

CKD is associated with a number of other factors that have been proposed as mediators of cognitive impairment, including anemia, increased levels of inflammatory cytokines, oxidative stress, and alterations in lipid and homocysteine metabolism. For example, anemia is thought to be a key mediator of cognitive impairment in people with ESRD (22,23) and more recently has been associated with cognitive impairment in elderly individuals without known kidney disease (24). Inflammatory mechanisms have been implicated in the pathogenesis of vas-
cular and Alzheimer’s dementia. Elevated levels of inflammatory cytokines have been demonstrated in neuropathology specimens from patients with dementia (25) and have been prospectively associated with cognitive decline (12). Serum lipid levels have also been linked with cognitive impairment (26). Adjustment for these factors, individually or in aggregate, did not account for the significantly increased risk for impairment that we found associated with CKD. We could not evaluate the contribution of other proposed causative factors, such as elevated levels of homocysteine and oxidative stress (27,28).

We did not examine the consequences of cognitive impairment in the current study; however, studies in the general population suggest that the presence of cognitive impairment or dementia predicts death and disability in elderly individuals (29–31). Although similar longitudinal studies are lacking in the CKD and ESRD populations, there is some evidence that cognitive impairment is associated with poor outcomes among hemodialysis patients as well (3). Thus, identifying cognitive impairment among individuals with CKD may facilitate preventive strategies to reduce the burden of cognitive impairment and dementia among elderly individuals with CKD and ESRD. Moreover, it is plausible that cognitive impairment could adversely affect several aspects of patient care, including adherence to therapy and dialysis planning. Our results show that the risk for cognitive impairment is increased across the spectrum of CKD, well before individuals develop ESRD, but is especially pronounced for those with an eGFR <45 ml/min per 1.73 m². Therefore, clinicians should consider the potential consequences of cognitive impairment in their elderly patients with CKD and target screening strategies toward those with advanced CKD or those who possess other risk factors for dementia.

This study has several limitations. The optimal method for estimating kidney function among the elderly is uncertain. When we used eCrCl or gender-specific serum creatinine cut-offs rather than MDRD eGFR, the results were unchanged, suggesting that the findings presented here are robust. We had only one measure of serum creatinine and other laboratory variables. Serial measurements of serum creatinine (and, thus, eGFR) may have strengthened the link between CKD and cognitive function and provided more precise adjustment for confounding factors. As with other longitudinal studies of the elderly, attrition as a result of death or follow-up loss may influence the study results. However, the loss of individuals with more baseline impairment and lower kidney function would be expected to bias our study results toward the null. Although we attempted to adjust for a number of potential confounding factors, residual confounding as a result of misclassification of known covariates or from unmeasured variables may still exist. Thus, it remains unresolved whether CKD is truly causally implicated or simply a marker for other factors associated with cognitive impairment. Finally, because Health ABC participants were ambulatory elderly individuals living in the community, we may have underestimated the burden of CKD-associated cognitive impairment, which may be more prominent among institutionalized individuals.

In summary, we found a significantly increased risk for cognitive impairment associated with CKD in a large, biracial cohort of community-dwelling elderly individuals. The risk for impairment varied by the severity of CKD, such that those with a lower eGFR had a greater risk for cognitive impairment but was present even in those with milder levels of CKD. These results were not explained by several established risk factors for cognitive impairment in the general population. Our findings serve to underscore the significant risk for impairment associated with CKD. In light of the rapidly growing population of elderly individuals with CKD and ESRD, further prospective studies are needed to determine the natural history and consequences of cognitive decline in individuals with CKD, as well as the optimal methods for detection, prevention, and therapy.

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