Title

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Permalink

https://escholarship.org/uc/item/7xq6x6cw

Journal

American Journal of Epidemiology, 180(1)

ISSN

0002-9262

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Publication Date

2014-07-01

DOI

10.1093/aje/kwu102

Peer reviewed

Original Contribution

Kidney Function and Cognitive Health in Older Adults: The Cardiovascular Health Study

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Recent evidence has demonstrated the importance of kidney function in healthy aging. We examined the association between kidney function and change in cognitive function in 3,907 participants in the Cardiovascular Health Study who were recruited from 4 US communities and studied from 1992 to 1999. Kidney function was measured by cystatin C–based estimated glomerular filtration rate (eGFR$_{cys}$). Cognitive function was assessed using the Modified Mini-Mental State Examination and the Digit Symbol Substitution Test, which were administered up to 7 times during annual visits. There was an association between eGFR$_{cys}$ and change in cognitive function after adjustment for confounders; persons with an eGFR$_{cys}$ of less than 60 mL/minute/1.73 m^2 had a 0.64 (95% confidence interval: 0.51, 0.77) points/year faster decline in Modified Mini-Mental State Examination score and a 0.42 (95% confidence interval: 0.28, 0.56) points/year faster decline in Digit Symbol Substitution Test score compared with persons with an eGFR$_{cys}$ of 90 or more mL/minute/1.73 m^2. Additional adjustment for intermediate cardiovascular events modestly affected these associations. Participants with an eGFR$_{cys}$ of less than 60 mL/minute/1.73 m^2 had fewer cognitive impairment–free life-years on average compared with those with eGFR$_{cys}$ of 90 or more mL/minute/1.73 m^2, independent of confounders and mediating cardiovascular events (mean difference = −0.44, 95% confidence interval: −0.62, −0.26). Older adults with lower kidney function are at higher risk of worsening cognitive function.

aging; chronic kidney disease; cognitive function; congestive heart failure; myocardial infarction; prospective study; stroke; successful aging

Recent evidence has demonstrated the importance of kidney function in healthy aging (1). Reduced kidney function is associated with cardiovascular outcomes, frailty, and other adverse health outcomes (2–5). There is evidence from cross-sectional studies that poor kidney function is associated with cognitive impairment (6, 7), as well as evidence from longitudinal studies that poor kidney function is associated with declines in cognitive function (8–17). Cognitive impairment is a disability that has severely limiting effects on quality of life and life expectancy, and it precedes the onset of dementia (18). Previous studies have used many different measures of cognitive function, some over several waves of follow-up (8, 9, 16); however, the majority of studies used serum creatinine

as the marker of kidney function (6–15). Creatinine measurements can be limited in the setting of aging because of the dual influence of kidney function and muscle mass on serum creatinine concentrations; persons with low muscle mass may have normal or low concentrations of creatinine despite the presence of reduced kidney function. Cystatin C is an alternative measure of kidney function that is not associated with muscle mass and may be a more accurate measure in the elderly population (19, 20).

Few studies have used cystatin C to evaluate the association between kidney function and cognitive outcomes. One study in the Health, Aging, and Body Composition cohort found a significant association between serum concentrations

of cystatin C and cognitive function in elderly participants (21). A publication from the Cardiovascular Health Study (CHS) showed an association between cystatin C and an outcome described as "successful aging," which was defined as remaining free of 3 major classes of disease (i.e., incident cancer, cardiovascular disease, and chronic obstructive pulmonary disease) and without a persistent physical disability or cognitive impairment (1). Another report from the Uppsala Longitudinal Study found an association between cystatin C and Alzheimer's disease in a cohort of elderly men (22).

A recent review of studies investigating the association between kidney function and cognitive function recognized the need for more studies using multiple tests of cognitive function and measures of cognition that are relevant to patients (16). The current study extends the prior literature by evaluating associations of estimated glomerular filtration rate measured by cystatin C and cognitive function measured by 2 different test batteries over 6 years of follow-up in the CHS. In addition, we explored intermediate clinical cardiovascular events as potential mediating factors. Finally, although kidney function and cognitive function are both associated with an increased risk of death, prior analyses have not accounted for this competing risk. By evaluating kidney function with an outcome of cognitive impairment–free life-years (CIFLYs), we more thoroughly describe this association using an outcome that 1) is meaningful to older adults and 2) accounts for the dual impact of kidney dysfunction on cognitive impairment and death. We hypothesized that baseline cystatin C–based kidney function would be associated with a decline in cognitive function and CIFLYs, and that these associations would be mediated by clinical cardiovascular disease.

METHODS

Study population

The Cardiovascular Health Study (CHS) is a community-based study of adults aged 65 years and older at baseline. The primary aim of the CHS is to evaluate risk factors for the development and progression of cardiovascular disease in the elderly (23). The study recruited persons from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania, in 1989–1990. Black participants were actively recruited during a supplemental enrollment process of the CHS during 1992–1993; they comprise 15% of CHS participants. The eligibility criteria were as follows: 1) age 65 years or older; 2) not institutionalized; 3) expected to remain in the current community for 3 years or longer; 4) not undergoing active treatment for cancer; and 5) provided informed consent without requiring a proxy respondent. The 1992–1993 visit is used as the baseline for the present study in order to have the same baseline year for the initial and supplemental cohorts.

Participants completed study visits at enrollment and annually through 1998–1999. During these visits, researchers conducted interviews and physical examinations, administered health questionnaires, and collected blood specimens. Hospital discharge summaries and *International Classification of Diseases, Ninth Revision*, codes were collected for all

hospitalizations during the follow-up period. The study was approved by institutional review boards at each site, and informed consent was obtained from all participants.

Cognitive function

Cognitive function was measured annually during in-person visits from 1990 to 1999 using the Modified Mini-Mental State (3MS) Examination and the Digit Symbol Substitution Test (DSST). The 3MS Examination is a measure of global cognition with possible scores ranging from 0 to 100, and the DSST is a measure of executive cognitive abilities and processing speed with scores ranging from 0 to 90 (24, 25). There was substantial missingness for both 3MS Examination and DSST scores in this study. Of 25,920 potential person-visits, 15% were missing 3MS Examination scores, and 19% were missing DSST scores. Beginning in 1996, participants who did not attend the in-person visit were contacted by telephone and asked to complete the Telephone Interview for Cognitive Status, a brief interview designed to identify cognitive impairment in patients with Alzheimer's disease. The Telephone Interview for Cognitive Status was used to impute missing 3MS Examination data by using the method of Arnold et al. (26). Additionally, missing 3MS Examination values were imputed by carrying nonmissing values from previous years forward 1 year and nonmissing values from later years backward 1 year. After these imputations, only 5% of the person-visits were missing 3MS Examination scores. We did not impute DSST scores because there was no CHS-validated conversion of the Telephone Interview for Cognitive Status to the DSST. We considered 3MS Examination score to be the primary outcome of interest because of the missingness in the DSST scores and because the 3MS Examination is more commonly used in epidemiologic and clinical studies. Incident cognitive impairment was defined as a score of less than 80 on the 3MS Examination during 2 consecutive visits, a score of less than 80 on the 3MS Examination and then a missing score on the next visit, or missing 3MS Examination scores for 4 consecutive years (i.e., 2 consecutive missing values after the imputation procedure described above) (27). We created the following new outcome as an additional analysis: CIFLYs, which is the time a person remains alive and free of cognitive impairment. This measure counts the number of years a person remains alive and not cognitively impaired and ranges from 0 to 6 years.

Kidney function

Kidney function was measured by serum cystatin C, a measure that may better estimate glomerular filtration rate in the elderly than serum creatinine (19, 20). Assays were performed in serum specimens obtained from fasting participants. Specimens had been stored at −70°C. Serum cystatin C was measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring, Inc., Deerfield, Illinois) with a nephelometer (BN II, Dade Behring, Inc.) (28). The assay remained stable, with no change in the values measured, over 5 cycles of freezing and thawing. The assay range was 0.195–7.330 mg/L. The interassay coefficient of

variation ranged from 2.3% to 3.1%, and the intraassay coefficient of variation ranged from 2.0% to 2.8%. Cystatin C–based estimated glomerular filtration rate (eGFR$_{cys}$) was calculated on the basis of the Chronic Kidney Disease Epidemiology Collaboration equation ($133 \times$ (serum cystatin C / $0.8)^{-0.499} \times 0.996 \times$ age ($\times 0.932$ if female) for serum cystatin C ≥ 0.8 mg/L; $133 \times$ (serum cystatin C / $0.8)^{-1.328} \times 0.996 \times$ age ($\times 0.932$ if female) for serum cystatin C <0.8 mg/L) (29). Prior research has demonstrated that serum creatinine–based estimated glomerular filtration rate (eGFR$_{creatinine}$) misclassifies some older adults with low creatinine concentrations as having normal kidney function (19). Because of this, we chose eGFR$_{cys}$ as the measure of kidney function.

Other measures

Age, sex, race, smoking status, and educational level were determined by self-reports at baseline. Hypertension was assessed at baseline using self-reports, as well as information on medication use and blood pressure. Blood pressure and diabetes were assessed annually. Diabetes was defined as a fasting glucose level greater than 125 mg/dL or the use of insulin or hypoglycemic medications, and borderline diabetes was defined as a fasting glucose level between 100 and 125 mg/dL. Height and weight were measured annually by standard protocol, and body mass index was calculated as weight (kg)/height (m)^2. Existence of depressive symptoms was classified as a score of at least 16 on the Center for Epidemiologic Studies Depression Scale (short-form), a self-reported measure of depressive symptoms experienced during the previous week. Methods of measurement for apolipoprotein E (APOE) alleles have been published elsewhere (27). C-reactive protein was measured by immunoassay. Cardiovascular events (i.e., myocardial infarction, stroke, and congestive heart failure) were adjudicated annually by a CHS outcome-assessment committee using standardized criteria including medical records and participant interviews (30). Deaths were identified by a review of obituaries, medical records, death certificates, and the Centers for Medicare and Medicaid Services health care utilization database for hospitalizations, as well as from household contacts; we achieved 100% complete follow-up for ascertainment of death status.

Statistical methods

We restricted our study population to those with cystatin C measured at the 1992–1993 visit ($n = 4,734$), and we excluded 827 participants who had a prior history of myocardial infarction, stroke, or congestive heart failure, for a total sample size of 3,907. Participants with a prior history of clinical cardiovascular disease were excluded to enable us to examine these events as mediating variables between kidney function and cognitive function. Kidney function was classified as eGFR$_{cys}$ of less than 60, 60–89.9, or ≥ 90 mL/minute/1.73 m^2, and the baseline characteristics of persons were summarized across these groups. Using linear regression models, we examined the cross-sectional association of eGFR$_{cys}$ and 3MS Examination and DSST scores, with and without adjustment for potential confounders (i.e., age, sex, race, education, smoking, body mass index, diabetes, hyper- tension, C-reactive protein,

depressive symptoms, and APOE genotype). We next examined the longitudinal association by using linear mixed models with 3MS Examination and DSST scores as the outcomes, adjusted first for follow-up year only, and then adjusted for the potential confounders listed above. Models with the hypothesized mediators of myocardial infarction, stroke, and congestive heart failure were also examined to measure the mediating effect of these interim events on the association of interest. These hypothesized mediators were time-dependent, and mediation was evaluated on the basis of the change in the magnitude of the association of interest with and without the hypothesized mediators. The association between eGFR$_{cys}$ and CIFLYs was investigated through unadjusted and adjusted linear regression models. The association between eGFR$_{cys}$ and life-years of follow-up was also investigated through the same models.

Several sensitivity analyses were performed. We conducted an analysis that included persons with prevalent cardiovascular disease, as well as one that included time-dependent hypertension status to account for the potential bidirectional relationship between kidney function and blood pressure. An analysis examined the association between eGFR$_{cys}$ and 3MS Examination score without any 3MS Examination score imputation. We performed another analysis using eGFR$_{creatinine}$ as the predictor of interest to examine the difference between using eGFR$_{cys}$ and eGFR$_{creatinine}$. The impact of missingness of 3MS Examination score was investigated using stabilized inverse probability of censoring weights (31). We modeled the probability of censoring by using pooled logistic regression models; candidate variables were the same as the list of potential confounders above, as well as kidney function and lagged 3MS Examination score. The censoring models were fit with the deletion/substitution/addition algorithm to identify the best fit prediction model (32). Standard errors were estimated using a bootstrap procedure based on 1,000 replicates.

All analyses were conducted using R software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In the remainder of the article, the unit of measurement for eGFR$_{cys}$ and eGFR$_{creatine}$, mL/minute/1.73 m^2, has been omitted for brevity. Of the 3,907 participants in our sample, 778 (20%) had eGFR$_{cys}$ of less than 60; 2,415 (62%) had eGFR$_{cys}$ of 60–89.9; and 714 (18%) had eGFR$_{cys}$ of 90 or more (Table 1). On average, participants with higher eGFR$_{cys}$ tended to be younger, were more likely to be female, and were more likely to self-report nonwhite race. The participants with higher eGFR$_{cys}$ also tended to have a higher level of education, were more likely to have never smoked, had lower body mass index values and systolic blood pressure, and had higher diastolic blood pressure. Additionally, participants with higher eGFR$_{cys}$ were less likely to have hypertension, had lower average C-reactive protein levels, were more likely to have depressive symptoms, were more likely to be carriers of the APOE 4 allele, and had higher average scores on the 3MS Examination and DSST. The average length of follow-up was 5.3 years.

At baseline, eGFR$_{cys}$ was associated with 3MS Examination score; persons with eGFR$_{cys}$ of less than 60 had lower 3MS Examination scores compared with participants with eGFR$_{cys}$ of 90 or more. This cross-sectional association no

Table 1. Baseline Characteristics of Participants Stratified by Baseline Kidney Function Measured by eGFR$_{cys}$, Cardiovascular Health Study, 1992–1993

Characteristic	Subjects With eGFR$_{cys}$ <60[a] (n = 778)			Subjects With eGFR$_{cys}$ 60–89.9[a] (n = 2,415)			Subjects With eGFR$_{cys}$ ≥90[a,b] (n = 714)		
	Mean (SD)[c]	No.	%[c]	Mean (SD)[c]	No.	%[c]	Mean (SD)	No.	%
Age, years	77.5 (5.9)***			74.3 (4.7)***			72.7 (4.2)		
Female sex		437	56.2***		1,451	60.1***		506	70.9
Nonwhite race		104	13.4***		374	15.5***		214	30.0
Education									
Less than high school		236	30.4**		587	24.3		171	24.0
High school or GED		217	27.9		713	29.6		190	26.7
Some college or vocational school		252	32.4		837	34.7		258	36.2
Graduate or professional school		72	9.3*		274	11.4		93	13.1
Smoking									
Never		363	46.7		1,155	47.9		345	48.6
Former		316	40.6		990	41.0		278	40.4
Current		99	12.7		268	11.1		78	11.1
Body mass index[d]	27.6 (5.0)***			26.6 (4.6)***			25.7 (4.2)		
Systolic blood pressure, mm Hg	138.9 (22.5)***			135.8 (20.8)			135.0 (20.0)		
Diastolic blood pressure, mm Hg	70.8 (11.3)**			71.7 (11.1)			72.3 (11.2)		
Diabetes									
Diagnosed		123	16.1		287	12.0**		115	16.3
Borderline		98	12.8		230	9.6		70	9.9
No diabetes		542	71.0		1,867	78.3*		521	73.8
Self-reported hypertension		390	50.2***		908	37.6		244	34.2
C-reactive protein, mg/L	7.3 (13.6)***			4.9 (8.4)*			4.1 (7.2)		
Depressive symptoms (CES-D score ≥16)		37	4.8		99	4.1		25	3.5
APOE 4 allele carrier		159	22.5*		567	25.5		186	28.5
3MS Examination score	88.8 (10.5)***			91.0 (8.9)			91.0 (9.1)		
DSST score	35.8 (14.0)***			40.2 (13.3)			41.3 (13.9)		
Cognitive impairment (3MS Examination score <80)		104	13.4**		196	8.1		64	9.0

Abbreviations: APOE, apolipoprotein E; CES-D, Center for Epidemiologic Studies Depression Scale; DSST, Digit Symbol Substitution Test; eGFR$_{cys}$, cystatin C–based estimated glomerular filtration rate; GED, General Education Development; 3MS, Modified Mini-Mental State.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

[a] eGFR$_{cys}$ is measured in mL/minute/1.73 m^2.

[b] eGFR$_{cys}$ ≥90 mL/min/1.73 m^2 was considered the reference group.

[c] P values based on pairwise χ^2 tests for categorical variables and Student's t tests for continuous variables.

[d] Weight (kg)/height (m)^2.

longer reached statistical significance after adjustment for confounders (Table 2). Additionally, there were no statistically significant differences in mean 3MS Examination score for those with eGFR$_{cys}$ of 90 or more compared with those with eGFR$_{cys}$ of 60–89.9. The results were similar when we examined DSST score as the outcome. There was a statistically significant cross-sectional association between eGFR$_{cys}$ and DSST score at baseline; unlike the results for 3MS Examination scores, the association among persons with eGFR$_{cys}$ of less than 60 compared with those with eGFR$_{cys}$ of 90 or more remained significant despite adjustment for confounders.

There was a highly significant association between baseline eGFR$_{cys}$ and longitudinal change in 3MS Examination score over the 6 years of follow-up, and this association persisted even after adjustment for confounders and hypothesized mediators. Both those with eGFR$_{cys}$ of less than 60 and those with eGFR$_{cys}$ of 60–89.9 had significantly faster declines in 3MS Examination scores compared with those with eGFR$_{cys}$ of 90 or more over the study period (Table 3). Participants with lower eGFR$_{cys}$ had a steeper decline in predicted 3MS Examination score over time (Figure 1). There was a longitudinal association between eGFR$_{cys}$ and DSST score (Table 3); there was a steeper decrease in DSST score over the study period among participants with lower eGFR$_{cys}$ compared to those with higher eGFR$_{cys}$, even after adjustment for potential confounders and hypothesized mediators.

Table 2. Cross-Sectional Association of Kidney Function With Mean Difference[a] in Cognitive Function at Baseline, Cardiovascular Health Study, 1992–1993

Cognitive Function Test, by Model	Subjects With eGFR$_{cys}$ 60–89.9[b]		Subjects With eGFR$_{cys}$ <60[b]	
	Mean Difference	95% CI	Mean Difference	95% CI
3MS Examination				
Model 1[c]	0.03	−0.75, 0.80	−2.15***	−3.09, −1.21
Model 2[d]	−0.31	−0.98, 0.36	−0.78	−1.65, 0.09
DSST				
Model 1[c]	−1.10	−2.24, 0.05	−5.51***	−6.92, −4.11
Model 2[d]	−0.72	−1.71, 0.26	−1.63*	−2.90, −0.36

Abbreviations: CI, confidence interval; DSST, Digit Symbol Substitution Test; eGFR$_{cys}$, cystatin C–based estimated glomerular filtration rate; 3MS, Modified Mini-Mental State.

* $P < 0.05$; *** $P < 0.001$.
[a] Reference group is subjects with eGFR$_{cys}$ of ≥90.
[b] eGFR$_{cys}$ is measured in mL/minute/1.73 m^2.
[c] Unadjusted model.
[d] Adjusted for the following confounders: eGFR$_{cys}$, age, sex, race, education, smoking, body mass index (weight (kg)/height (m)^2), diabetes, history of hypertension, C-reactive protein, apolipoprotein E genotype, and depression symptoms.

Higher eGFR$_{cys}$ was associated with life-years of follow-up, and this association remained after adjustment for confounders and hypothesized mediators (Table 4). Participants with eGFR$_{cys}$ of less than 60 had a lower average number of life-years compared to those with eGFR$_{cys}$ of 90 or more (mean difference = −0.35, 95% confidence interval (CI): −0.47, −0.23). Participants with eGFR$_{cys}$ of less than 60 also had fewer CIFLYs compared to those with eGFR$_{cys}$ of 90 or more (mean change in CIFLYs = −0.44, 95% CI: −0.62, −0.26). The association between eGFR$_{cys}$ and CIFLYs was of greater magnitude compared to the association with life-years for all comparisons; in the fully adjusted models, the estimate for CIFLYs was 26% greater (−0.44 vs. −0.35) than the estimate for life-years (Table 4).

A sensitivity analysis that included participants with a history of prevalent clinical cardiovascular disease had similar results compared with the main analysis (fully adjusted estimates for mean change in 3MS Examination score per year were −0.17 (95% CI: −0.27, −0.06) for those with eGFR$_{cys}$ of 60–89.9 vs. those with eGFR$_{cys}$ of ≥90 and −0.58 (95% CI: −0.70, −0.45) for those with eGFR$_{cys}$ of <60 vs. those with eGFR$_{cys}$ of ≥90).

Another sensitivity analysis that included time-dependent hypertension status instead of hypertension status at baseline found similar results (mean changes in 3MS Examination

Table 3. Longitudinal Association of Kidney Function With Mean Annual Change in Cognitive Function[a], Cardiovascular Health Study, 1992–1999

Cognitive Function Test, by Model	Subjects With eGFR$_{cys}$ 60–89.9[b]		Subjects With eGFR$_{cys}$ <60[b]	
	Mean Difference Per Year	95% CI	Mean Difference Per Year	95% CI
3MS Examination				
Model 1[c]	−0.21***	−0.31, −0.10	−0.74***	−0.87, −0.61
Model 2[d]	−0.17**	−0.28, −0.07	−0.64***	−0.77, −0.51
Model 3[e]	−0.17**	−0.27, −0.07	−0.62***	−0.75, −0.49
Model 4[f]	−0.15**	−0.25, −0.04	−0.53***	−0.67, −0.40
DSST				
Model 1[c]	−0.17**	−0.27, −0.07	−0.42***	−0.55, −0.28
Model 2[d]	−0.18**	−0.28, −0.07	−0.42***	−0.56, −0.28
Model 3[e]	−0.15**	−0.25, −0.05	−0.37***	−0.50, −0.23
Model 4[f]	−0.16**	−0.27, −0.06	−0.37***	−0.51, −0.24

Abbreviations: CI, confidence interval; DSST, Digit Symbol Substitution Test; eGFR$_{cys}$, cystatin C–based estimated glomerular filtration rate; 3MS, Modified Mini-Mental State.

** $P < 0.01$; *** $P < 0.001$.
[a] Reference group is subjects with eGFR$_{cys}$ of ≥90.
[b] eGFR$_{cys}$ is measured in mL/minute/1.73 m^2.
[c] Basic model: eGFR$_{cys}$ × year.
[d] Adjusted for the following confounders: eGFR$_{cys}$ × year, age, sex, race, education, smoking, body mass index (weight (kg)/height (m)^2), diabetes, history of hypertension, C-reactive protein, apolipoprotein E genotype, and depression symptoms.
[e] Adjusted for the following hypothesized mediators: eGFR$_{cys}$ × year, myocardial infarction, stroke, and congestive heart failure.
[f] Adjusted for the following confounders and hypothesized mediators: eGFR$_{cys}$ × year, age, sex, race, education, smoking, body mass index, diabetes, history of hypertension, C-reactive protein, apolipoprotein E genotype, depression symptoms, myocardial infarction, stroke, and congestive heart failure.
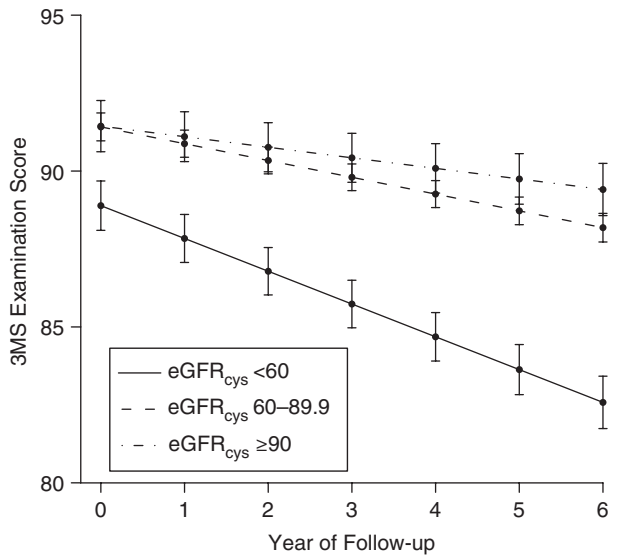
Figure 1. Baseline cystatin C–based estimated glomerular filtration rate ($eGFR_{cys}$) and predicted Modified Mini-Mental State (3MS) Examination score, Cardiovascular Health Study, 1992–1999. $eGFR_{cys}$ is measured as mL/minute/1.73 m^2. Bars, 95% confidence intervals.

Table 4. Kidney Function, Life-Years, and Cognitive Impairment–Free Life-Years Over 6 Years of Follow-up[a], Cardiovascular Health Study, 1992–1999

Life-Year Outcome, by Model	Subjects With $eGFR_{cys}$ 60–89.9[b]		Subjects With $eGFR_{cys}$ <60[b]	
	Mean Difference	95% CI	Mean Difference	95% CI
Life-years				
Model 1[c]	−0.08	−0.16, 0.01	−0.53***	−0.63, −0.43
Model 2[d]	−0.02	−0.11, 0.07	−0.36***	−0.48, −0.24
Model 3[e]	−0.06	−0.15, 0.02	−0.49***	−0.60, −0.39
Model 4[f]	−0.01	−0.11, 0.08	−0.35***	−0.47, −0.23
CIFLYs				
Model 1[c]	−0.08	−0.22, 0.07	−0.81***	−0.99, −0.64
Model 2[d]	−0.07	−0.21, 0.08	−0.48***	−0.66, −0.30
Model 3[e]	−0.04	−0.19, 0.10	−0.70***	−0.88, −0.52
Model 4[f]	−0.04	−0.20, 0.08	−0.44***	−0.62, −0.26

Abbreviations: CI, confidence interval; CIFLY, cognitive impairment–free life year; $eGFR_{cys}$, cystatin C–based estimated glomerular filtration rate.

*** $P < 0.001$.

[a] Reference group is subjects with $eGFR_{cys}$ of ≥90.

[b] $eGFR_{cys}$ is measured in mL/minute/1.73 m^2.

[c] Unadjusted model.

[d] Adjusted for the following confounders: $eGFR_{cys}$, age, sex, race, education, smoking, body mass index (weight (kg)/height (m)^2), diabetes, history of hypertension, C-reactive protein, apolipoprotein E genotype, and depression symptoms.

[e] Adjusted for the following hypothesized mediators: $eGFR_{cys}$, myocardial infarction, stroke, and congestive heart failure.

[f] Adjusted for the following confounders and hypothesized mediators: $eGFR_{cys}$, age, sex, race, education, smoking, body mass index, diabetes, history of hypertension, C-reactive protein, apolipoprotein E genotype, depression symptoms, myocardial infarction, stroke, and congestive heart failure.

score per year were −0.13 (95% CI: −0.23, −0.03) for those with $eGFR_{cys}$ of 60–89.9 vs. those with $eGFR_{cys}$ ≥90 and −0.52 (95% CI: −0.65, −0.39) for those with $eGFR_{cys}$ <60 vs. those with $eGFR_{cys}$ ≥90). A sensitivity analysis that examined the association between $eGFR_{cys}$ and 3MS Examination score without imputation found similar results (mean changes in 3MS Examination score per year of −0.14 (95% CI: −0.25, −0.04) for those with $eGFR_{cys}$ of 60–89.9 vs. those with $eGFR_{cys}$ ≥90 and −0.55 (95% CI: −0.68, −0.42) for those with $eGFR_{cys}$ <60 vs. those with $eGFR_{cys}$ ≥90). We found a strong correlation between $eGFR_{cys}$ and $eGFR_{creatinine}$ in our study population (Pearson's correlation coefficient = 0.69). A sensitivity analysis using $eGFR_{creatinine}$ failed to find a statistically significant difference in average decrease in 3MS Examination score per year between participants with eGFR of 60–89.9 versus those with eGFR ≥90 (mean change in 3MS Examination score per year = −0.05, 95% CI: −0.08, 0.18); however, it remained statistically significant when comparing those with $eGFR_{creatinine}$ of less than 60 versus those with $eGFR_{creatinine}$ of 90 or more (mean change in 3MS Examination score per year = −0.33, 95% CI: −0.48, −0.18). Finally, a sensitivity analysis was performed to examine the impact of the remaining 3MS Examination score missingness. Using the deletion/substitution/addition algorithm, we estimated the missing function as the following:

$$\log \left[\frac{p(\text{not missing 3 MS Examination score})}{1 - p(\text{not missing 3 MS Examination score})} \right]$$
$$= 0.506 - 0.457 \times \text{cystatin C} + 1.166 \times \text{heart failure}$$
$$+ 0.037 \times \text{prior 3 MS Examination score}.$$

Using the inverse probability of censoring weights, we found that the longitudinal association was similar and remained significant in the fully adjusted model (mean changes in 3MS Examination score per year were −0.17 (95% CI: −0.30, −0.05) for those with $eGFR_{cys}$ of 60–89.9 vs. those with $eGFR_{cys}$ ≥90 and −0.58 (95% CI: −0.77, −0.39) for those with $eGFR_{cys}$ <60 vs. those with $eGFR_{cys}$ ≥90).

DISCUSSION

In a community-dwelling sample of older adults, cystatin C–based kidney function was associated with both the level and change in cognitive function over 6 years of follow-up. The longitudinal association was robust to adjustment for confounders and hypothesized mediators, including demographic characteristics, risk factors, and incident cardiovascular disease and heart failure events; participants with worse baseline kidney function had a steeper decline in predicted cognitive function over the study period. Reduced kidney function was also associated with fewer CIFLYs.

Our findings are consistent with those of prior studies that found an association between kidney function and cognitive

function. Several studies have found an association between eGFR$_{creatinine}$ and incident cognitive impairment or dementia (12, 14, 33); however, other studies have reported conflicting results (10, 15, 34). A study from the Rush Memory and Aging Project, which investigated the association between eGFR$_{creatinine}$ and decline in cognitive function, found a statistically significant association over 5 years of follow-up (8). Similarly, another study found that change in eGFR$_{creatinine}$ was significantly associated with change in cognitive function over 5 years (9). Both of these studies found this association across multiple domains of cognitive function, including global cognition, working memory, and abstract reasoning, and they found that this association persisted despite controlling for cardiovascular risk factors and events, similar to the results of our study. However, unlike our study, these studies used serum creatinine levels to estimate kidney function. We found that using eGFR$_{creatinine}$ as the predictor of interest instead of eGFR$_{cys}$ decreased the effect size of the association and failed to demonstrate a difference in cognitive decline between persons with eGFR$_{creatinine}$ of 60–89.9 and those with eGFR$_{creatinine}$ of 90 or more.

One study that used cystatin C to estimate kidney function found that, among participants in the Health, Aging, and Body Composition cohort, a population of well-functioning older adults (including both black and white subjects), those with higher cystatin C at baseline had a greater likelihood of developing cognitive impairment over the 7-year study period (for persons with cystatin C >1.25 mg/L vs. persons with cystatin C <1.0 mg/L, odds ratio = 1.92, 95% CI: 1.37, 2.69) (21). Our study confirmed the association between cystatin C–based kidney function in a community-based cohort and demonstrated that this association was robust against adjustment for intermediate cardiovascular events. Additionally, the present study accounted for the impact of kidney function on death and found that persons with eGFR$_{cys}$ of less than 60 had an average of 0.44 fewer years of cognitively intact life compared with persons with eGFR$_{cys}$ of 90 or more over 6 years, even after accounting for potential confounders and mediating events. We did not find a statistically significant difference in life-years or CIFLYs for persons with eGFR$_{cys}$ of 60–89.9, a group that has been described as having "preclinical kidney disease" (3), compared with persons with eGFR$_{cys}$ of 90 or more.

It has been previously suggested that the mechanisms underlying the association between kidney function and cognitive function may be inflammation and increasing cardiovascular events resulting from chronic kidney disease (35). Our study demonstrates that the association between cystatin C–based kidney function and cognitive function is independent of inflammation, measured by C-reactive protein, as well as intermediate cardiovascular events, including myocardial infarction, stroke, and congestive heart failure. It is possible that changes in brain function due to subclinical or unmeasured ischemic disease may mediate the association between kidney function and cognitive function. Additionally, kidney function is an excellent indicator of vascular aging, reflecting a lifetime of exposure to hypertension, diabetes, and other vascular stressors. It is possible that the association is not caused directly by kidney function, but rather that kidney function is a marker for vascular aging, which is inversely related to cognitive function in older adults.

There are several limitations to this study. First, the mechanism for this association is still unclear; therefore, a causal link between kidney function and cognitive function in older adults is difficult to establish. Second, there was a limited length of follow-up, which may have decreased our ability to describe this association. Third, we did not have a direct measure of glomerular filtration rate; this measure is invasive, time-consuming, and difficult to obtain in a large-scale study of older adults. Finally, lack of data on urinary albumin may be a limitation because some evidence suggests it may be more strongly associated with stroke and abnormalities detected by magnetic resonance imaging (36).

In summary, kidney function is associated with change in cognitive function over time in older adults. This indicates that people with reduced kidney function are at higher risk for declines in cognitive health. Earlier interventions for people with declining kidney function may help preserve cognitive function and deter its devastating effects on quality of life and independence.

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