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

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ABBREVIATIONS:

Cardiovascular Health Study (CHS)

Confidence interval (CI)

Modified Mini-Mental State Exam (3MS)

Digital Symbol Substitution Test (DSST)

Cognitive Impairment-Free Life-Years (CIFLY)

Cystatin C-Based Estimated Glomerular Filtration Rate ($eGFR_{cys}$)

Creatinine-Based Estimated Glomerular Filtration Rate ($eGFR_{creatinine}$)

Serum Cystatin C (Scys)

Health, Aging, and Body Composition cohort (Health ABC)

ABSTRACT

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, recruited from 4 U.S. communities, and studied from 1992 - 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 Exam and the Digit Symbol Substitution Test 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 $eGFR_{cys} < 60$ ml/min/1.73m^2 had a 0.64 (95% confidence interval: 0.51, 0.77) point/year faster decline in Modified Mini-Mental State Exam score and a 0.42 (95% confidence interval: 0.28, 0.56) point/year faster decline in Digit Symbol Substitution Test score compared with persons with $eGFR_{cys} \geq 90$ ml/min/1.73m^2. Additional adjustment for intermediate cardiovascular events modestly impacted these associations. Participants with $eGFR_{cys} < 60$ ml/min/1.73m^2 had fewer cognitive impairment-free life-years on average compared with those with $eGFR_{cys} \geq 90$ ml/min/1.73m^2, independent of confounders and mediating cardiovascular events (-0.44, 95% confidence interval: -0.62, -0.26). Older adults with reduced kidney function are at increased risk of worsening cognitive function.

Keywords: 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 that kidney function is associated with cognitive impairment in cross-sectional studies (6, 7), and declines in cognitive function in longitudinal studies (8-17). Cognitive impairment is a disability that has severely limiting effects on a person's quality of life and life expectancy, and 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 them used serum creatinine as the marker of kidney function (6-15). Creatinine 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 (Health ABC) cohort found a significant association between serum concentrations of cystatin C, and cognitive function in a cohort of elderly participants (21). A publication from the Cardiovascular Health Study (CHS) showed an association between cystatin C and an outcome described as "successful aging", defined as remaining free of three major classes of disease (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 two different test batteries over six years of follow-up in the CHS. In addition, we explore 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 the competing risk of mortality. By evaluating kidney function with an outcome of cognitive impairment-free life-years (CIFLY), we more thoroughly describe this association based on an outcome that 1) is meaningful to older adults, and 2) accounts for the dual impact of kidney dysfunction on cognitive impairment and mortality. We hypothesized that baseline cystatin C-based kidney function would be associated with decline in cognitive function and CIFLY, and these associations would be mediated by clinical cardiovascular disease.

MATERIALS AND METHODS

Study Population

The Cardiovascular Health Study (CHS) is a community-based study of elderly 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 elders (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 CHS during 1992-1993; they comprise 15% of CHS participants. The eligibility criteria were: 1) age $\geq$ 65 years; 2) not institutionalized; 3) expected to remain in the current community for 3 years or longer; 4) not under active treatment for cancer; and 5) provided informed consent without requiring a proxy respondent. The 1992-93 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 1998-99. During these visits researchers conducted an interview, physical examination, health questionnaire, and collection of 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 is a measure of global cognition with a range of possible scores of 0 to 100, and the DSST is a measure of executive cognitive abilities and processing speed that ranges from 0 to 90 (24, 25). There was substantial missingness for both 3MS and DSST in this study. Of 25,920 potential person-visits, 15% were missing 3MS scores, and 19% were missing DSST. Beginning in 1996, participants who did not attend the in-person visit were contacted by phone and asked to complete the Telephone Interview for Cognitive Status, a brief telephone interview designed to identify cognitive impairment in Alzheimer's disease patients. The Telephone Interview for Cognitive Status was used to impute missing 3MS data based on the method from Arnold et al. (26). Additionally, missing 3MS values were imputed by carrying non-missing values from previous years forward one year, and non-missing values from later years backwards one year. After these imputations, only 5% of the person-visits were missing 3MS scores. We did not impute DSST scores because there was no CHS validated conversion of the Telephone Interview for Cognitive Status to DSST. We considered 3MS the primary outcome of interest, because of the missingness in the DSST, and because 3MS is more commonly used in epidemiological and clinical studies. Incident cognitive impairment was defined as a score of less than 80 on the 3MS during two consecutive visits, a score of less than 80 on the 3MS and then missing on the next visit, or missing 3MS for four consecutive years (two consecutive missing values after imputation procedure described above) (27). As an additional analysis, we created a new outcome: CIFLY, 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 (Scys), a measure that may better estimate glomerular filtration rate than serum creatinine in the elderly (19, 20). Assays were performed in serum specimens obtained from fasting participants that were stored at -70°C. Scys was measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring, Deerfield, Illinois) with a nephelometer (BNII, Dade Behring) (28). The assay remained stable, with no change in the values measured, over five cycles of freezing and thawing. The assay range was 0.195 to 7.330 mg/L. Inter-assay coefficient of variation range from 2.3 to 3.1% and intra-assay coefficient of variation range from 2.0 to 2.8%. Cystatin C-based estimated glomerular filtration rate ($eGFR_{cys}$) was calculated based on the CKD-EPI equation ($133 \times (Scys/0.8)^{-0.499} \times 0.996 \times Age$ [× 0.932 if female] for $Scys \geq 0.8$ mg/L; $133 \times (Scys/0.8)^{-1.328} \times 0.996 \times Age$ [× 0.932 if female] for $Scys < 0.8$ mg/L) (29). Prior literature has demonstrated that serum creatinine-based estimated glomerular filtration ($eGFR_{creatinine}$) rate 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, and race were determined by self-report at baseline, as well as smoking status, and education. Hypertension was assessed at baseline based on self-report, medication use, and blood pressure levels. Blood pressure and diabetes were measured annually. Diabetes was defined as a fasting glucose > 125 mg/dL or use of insulin or hypoglycemic medications, and borderline diabetes was defined as a fasting glucose between 100 and 125 mg/dL. Height and weight were measured annually by standard protocol, and body mass index was calculated as weight (in kilograms) divided by height (in meters) squared. 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 *ApoE* alleles have been published elsewhere (27). C-reactive protein was measured by immunoassay. Cardiovascular events (myocardial infarction, stroke, and congestive heart failure) were adjudicated annually by a CHS outcome-assessment committee, based on 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 and from household contacts; 100% complete follow-up for ascertainment of mortality status was achieved.

Statistical Methods

We restricted our study population to those with cystatin C measured at the 1992-93 visit (n=4,734), and excluded the 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 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 $eGFR_{cys} < 60$, $60 – 90$, and ≥ 90 ml/min/1.73m^2 and the baseline characteristics of persons were summarized across these groups. Based on linear regression models, we examined the cross-sectional association of $eGFR_{cys}$ and score of 3MS and DSST, with and without adjustment for potential confounders (age, gender, race, education, smoking, body mass index, diabetes, hypertension, C-reactive protein, depressive symptoms, and *ApoE* genotype). We next examined the longitudinal association based on linear mixed models with 3MS and DSST 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 based on the change in the magnitude of the association of interest with and without the hypothesized mediators. The association between $eGFR_{cys}$ and CIFLY 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 also performed. An analysis was performed 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 without any 3MS imputation. Another analysis using $eGFR_{creatinine}$ as the predictor of interest was performed to examine the difference between using $eGFR_{cys}$ and $eGFR_{creatinine}$. The impact of missingness of 3MS was investigated using stabilized inverse probability of censoring weights (31). We modeled the probability of censoring based on pooled logistic regression models; candidate variables were the same as the list of potential confounders above, as well as kidney function and lagged 3MS. The censoring models were fit with the Deletion/Substitution/Addition algorithm in order to identify the best fit prediction model (32). Standard errors were estimated using a bootstrap procedure based on 1000 replicates.

All analyses were conducted using R (The R Foundation, Vienna, Austria).

RESULTS

Of the 3,907 participants in our sample, 778 (20%) had $eGFR_{cys} < 60$ ml/min/m^2, 2,415 (62%) had $eGFR_{cys}$ 60 – 90 ml/min/m^2, and 714 (18%) had $eGFR_{cys} \geq 90$ ml/min/m^2 (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 non-white 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 and systolic blood pressure, but higher diastolic blood pressure. Additionally, participants with higher $eGFR_{cys}$ were less likely to have hypertension, had lower average C-reactive protein, were more likely to have depressive symptoms, were more likely to be a carrier of the *ApoE*-4 allele, and had higher average scores on the 3MS and DSST. The average number of years of follow-up was 5.3.

At baseline, $eGFR_{cys}$ was associated with 3MS score; persons with $eGFR_{cys} < 60$ ml/min/1.73m^2 had lower 3MS scores compared with participants with $eGFR_{cys} \geq 90$ ml/min/m^2. This cross-sectional association no longer reached statistical significance after adjustment for confounders (Table 2). Additionally, there were no statistically significant differences in mean 3MS score for $eGFR_{cys} \geq 90$ ml/min/1.73m^2 compared with $eGFR_{cys}$ 60 – 90 ml/min/1.73m^2. 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 at baseline, and unlike 3MS, the association among persons with $eGFR_{cys} < 60$ ml/min/1.73m^2 compared with those with $eGFR_{cys} \geq 90$ ml/min/1.73m^2 remained significant despite adjustment for confounders.

There was a highly statistically significant association between baseline $eGFR_{cys}$ and longitudinal change in 3MS over the 6 years of follow up, and this association persisted even after adjustment for confounders and hypothesized mediators. Both groups with $eGFR_{cys} < 60$

ml/min/1.73m^2 and $eGFR_{cys}$ 60 – 90 ml/min/1.73m^2 had statistically significantly faster decline in 3MS compared with $eGFR_{cys} \geq 90$ ml/min/1.73m^2 over the study period (Table 3). Participants with lower $eGFR_{cys}$ had a steeper decline in predicted 3MS over time (Figure 1). There was a longitudinal association between $eGFR_{cys}$ and DSST (Table 3); there was a steeper decrease in DSST score over the study period among participants with lower $eGFR_{cys}$ compared with higher $eGFR_{cys}$ groups, even after adjustment for potential confounders and hypothesized mediators.

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 $eGFR_{cys} < 60$ ml/min/1.73m^2 had a lower average number of life-years compared to those with $eGFR_{cys} \geq 90$ ml/min/1.73m^2 (-0.35, 95% confidence interval (CI): -0.47, -0.23). Participants with $eGFR_{cys} < 60$ ml/min/1.73m^2 also had fewer CIFLY compared with those with $eGFR_{cys} \geq 90$ ml/min/1.73m^2 (-0.44, 95% CI: -0.62, -0.26 mean change in CIFLY). The association between $eGFR_{cys}$ and CIFLY was of greater magnitude compared to the association with life-years for all comparisons; in the fully adjusted models, the estimate for CIFLY was 26% greater (-0.44 compared with -0.35) than the estimate for life-years (Table 4).

A sensitivity analysis including participants with a history of prevalent clinical cardiovascular disease had similar results compared with the main analysis (fully adjusted estimates: -0.17, 95% CI: -0.27, -0.06 mean change in 3MS score per year for $eGFR_{cys}$ 60 – 90 ml/min/1.73m^2 compared to $eGFR_{cys} \geq 90$ ml/min/1.73m^2; -0.58, 95% CI: -0.70, -0.45 for $eGFR_{cys} < 60$ ml/min/1.73m^2 compared to $eGFR_{cys} \geq 90$ ml/min/1.73m^2). Another sensitivity analysis was completed with time-dependent hypertension status included instead of hypertension status at baseline also found similar results (-0.13, 95% CI: -0.23, -0.03 mean change in 3MS score per year for $eGFR_{cys}$ 60 – 90 ml/min/1.73m^2 compared to $eGFR_{cys} \geq 90$

ml/min/1.73m^2; -0.52, 95% CI: -0.65, -0.39 for $eGFR_{cys}$ < 60 ml/min/1.73m^2 compared to $eGFR_{cys}$ ≥ 90 ml/min/1.73m^2). A sensitivity analysis examined the association between $eGFR_{cys}$ and 3MS without imputation found similar results (-0.14, 95% CI: -0.25, -0.04 mean change in 3MS score per year for $eGFR_{cys}$ 60 – 90 ml/min/1.73m^2 compared to $eGFR_{cys}$ ≥ 90 ml/min/1.73m^2; -0.55, 95% CI: -0.68, -0.42 for $eGFR_{cys}$ < 60 ml/min/1.73m^2 compared to $eGFR_{cys}$ ≥ 90 ml/min/1.73m^2). We found a strong correlation between $eGFR_{cys}$ and $eGFR_{creatinine}$ in our study population (Pearson's correlation: 0.69). A sensitivity analysis using $eGFR_{creatinine}$ failed to find a statistically significant difference in average decrease in 3MS score per year between participants with eGFR 60 – 90 ml/min/1.73m^2 compared to those with eGFR ≥ 90 ml/min/1.73m^2 (0.05, 95% CI: -0.08, 0.18), however it remained statistically significant when comparing $eGFR_{creatinine}$ < 60 ml/min/1.73m^2 to $eGFR_{creatinine}$ ≥ 90 ml/min/1.73m^2 (-0.33, 95% CI: -0.48, -0.18). Finally, a sensitivity analysis was performed to examine the impact of the remaining 3MS missingness. Based on the Deletion/Substitution/Addition algorithm we estimated the missing function as the following: $\log\left[\frac{p(not\ missing\ 3MSE)}{1-p(not\ missing\ 3MSE)}\right] = 0.506 - 0.457 * cystatin\ C + 1.166 * heartfailure + 0.037 * prior\ 3MSE\ score.$ Using the inverse probability of censoring weights, the longitudinal association was similar and remained significant in the fully adjusted model (-0.17, 95% CI: -0.30, -0.05 mean change in 3MS score per year for $eGFR_{cys}$ 60 – 90 ml/min/1.73m^2 compared to $eGFR_{cys}$ ≥ 90 ml/min/1.73m^2; -0.58, 95% CI: -0.77, -0.39 for $eGFR_{cys}$ < 60 ml/min/1.73m^2 compared to $eGFR_{cys}$ ≥ 90 ml/min/1.73m^2).

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 six years of follow-up. The longitudinal association was robust to adjustment for confounders and hypothesized mediators, including demographics, 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 cognitive impairment-free life-years.

Our findings are consistent with prior studies that have 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 found conflicting results (10, 15, 34). A study from the Rush Memory and Aging Project that 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 found that this association persisted despite controlling for cardiovascular risk factors and events, similar to the results of the current study. However, unlike the current study, these studies used serum creatinine 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 $eGFR_{creatinine}$ 60 – 90 ml/min/1.73m^2 and those with ≥ 90 ml/min/1.73m^2.

One study that used cystatin C to estimate kidney function found that among participants in the Health ABC cohort, a population of well-functioning black and white older adults, those with higher cystatin C at baseline had a greater likelihood of developing cognitive impairment over the 7-year study period (odds ratio: 1.92, 95% CI: 1.37, 2.69 for persons with cystatin C > 1.25 compared with persons with cystatin C < 1.0) (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 mortality and found that persons with $eGFR_{cys}$ < 60 ml/min/1.73m^2 had an average of 0.44 fewer years of cognitively intact life compared with persons with $eGFR_{cys} \geq 90$ ml/min/1.73m^2 over six years, even after accounting for potential confounders and mediating events. We did not find a statistically significant difference in life-years or CIFLY for persons with $eGFR_{cys}$ 60 – 90 ml/min/1.73m^2, a group that has been described as having "preclinical kidney disease" (3), compared with persons with $eGFR_{cys} \geq 90$ ml/min/1.73m^2.

It has been previously suggested that 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, and 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 by kidney function directly, 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 urinary albumin may be a limitation as some evidence suggests it may be more strongly associated with stroke and magnetic resonance imaging abnormalities (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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Conflict of Interest: The authors have no conflicts of interest to disclose.

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

	$eGFR_{cys}$ <60 (n = 778)			$eGFR_{cys}$ 60 - 90 (n = 2415)			$eGFR_{cys}$ 90+ (n = 714)		
Characteristic	Mean (sd)	No.	%	Mean (sd)	No.	%	Mean (sd)	No.	%
Age	77.5 (5.9)[c]			74.3 (4.7)[c]			72.7 (4.2)		
Females		437	56.2[c]		1451	60.1[c]		506	70.9
Non-White Race		104	13.4[c]		374	15.5[c]		214	30.0
Education									
Less than High School		236	30.4[b]		587	24.3		171	24.0
High School or GED		217	27.9		713	29.6		190	26.7
Some College or Vocational		252	32.4		837	34.7		258	36.2
Graduate or Professional		72	9.3[a]		274	11.4		93	13.1
Smoking									
Never		363	46.7		1155	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 (m^2/kg)	27.6 (5.0)[c]			26.6 (4.6)[c]			25.7 (4.2)		
Systolic Blood Pressure (mmHg)	138.9 (22.5)[c]			135.8 (20.8)			135.0 (20.0)		
Diastolic Blood Pressure (mmHg)	70.8 (11.3)[b]			71.7 (11.1)			72.3 (11.2)		
Diabetes									
Diagnosed		123	16.1		287	12.0[b]		115	16.3
Borderline		98	12.8		230	9.6		70	9.9
No Diabetes		542	71.0		1867	78.3[a]		521	73.8
Self-Reported Hypertension		390	50.2[c]		908	37.6		244	34.2
C-reactive Protein (mg/L)	7.3 (13.6)[c]			4.9 (8.4)[a]			4.1 (7.2)		
Depressive symptoms (≥ 16 on CES-D)		37	4.8		99	4.1		25	3.5

ApoE-4 allele carrier		159	22.5[a]		567	25.5	186	28.5
3MS score	88.8 (10.5)[c]			91.0 (8.9)			91.0 (9.1)	
DSST score	35.8 (14.0)[c]			40.2 (13.3)			41.3 (13.9)	
Cognitive Impairment (3MS < 80)		104	13.4[b]		196	8.1	64	9.0

Abbreviations: 3MS, Modified Mini Mental State Exam; CES-D, Center for Epidemiologic Studies Depression Scale; DSST, Digit Symbol Substitution Test; $eGFR_{cys}$, Cystatin C-based estimated glomerular filtration rate (ml/min/1.73m^2); GED, General Education Development

[a]*P* value <0.05; [b]*P* value <0.01; [c]*P* value <0.001; *P* value based on pairwise chi-square tests for categorical variables and t-tests for continuous variables; $eGFR_{cys}$ 90+ ml/min/1.73m^2 was considered the referent group

Table 2. Cross-sectional Association of Kidney Function With Mean Difference in Cognitive Function at Baseline, Cardiovascular Health Study 1992-1993

	$eGFR_{cys}$ 90+		$eGFR_{cys}$ 60 – 90		$eGFR_{cys}$ <60	
	Mean Difference	95% CI	Mean Difference	95% CI	Mean Difference	95% CI
3MS						
Model 1[d]	ref	ref	0.03	-0.75, 0.80	-2.15[c]	-3.09, -1.21
Model 2[e]	ref	ref	-0.31	-0.98, 0.36	-0.78	-1.65, 0.09
DSST						
Model 1[d]	ref	ref	-1.10	-2.24, 0.05	-5.51[c]	-6.92, -4.11
Model 2[e]	ref	ref	-0.72	-1.71, 0.26	-1.63[a]	-2.90, -0.36

Abbreviations: 3MS, Modified Mini Mental State Exam; CI, Confidence Interval; DSST, Digit Symbol Substitution Test; $eGFR_{cys}$, Cystatin C-based estimated glomerular filtration rate (ml/min/1.73m^2); ref, referent

[a] *P* value <0.05; [b] *P* value <0.01; [c] *P* value <0.001

[d] Basic model: $eGFR_{cys}$

[e] Adjusted for confounders: $eGFR_{cys}$, age, gender, race, education, smoking, body mass index, diabetes, history of hypertension, C-reactive protein, *ApoE* genotype, depression symptoms

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

	$eGFR_{cys}$ 90+		$eGFR_{cys}$ 60 – 90		$eGFR_{cys}$ <60	
	Mean Difference Per Year	95% CI	Mean Difference Per Year	95% CI	Mean Difference Per Year	95% CI
3MS						
Model 1[d]	ref	ref	-0.21[c]	-0.31, -0.10	-0.74[c]	-0.87, -0.61
Model 2[e]	ref	ref	-0.17[b]	-0.28, -0.07	-0.64[c]	-0.77, -0.51
Model 3[f]	ref	ref	-0.17[b]	-0.27, -0.07	-0.62[c]	-0.75, -0.49
Model 4[g]	ref	ref	-0.15[b]	-0.25, -0.04	-0.53[c]	-0.67, -0.40
DSST						
Model 1[d]	ref	ref	-0.17[b]	-0.27, -0.07	-0.42[c]	-0.55, -0.28
Model 2[e]	ref	ref	-0.18[b]	-0.28, -0.07	-0.42[c]	-0.56, -0.28
Model 3[f]	ref	ref	-0.15[b]	-0.25, -0.05	-0.37[c]	-0.50, -0.23
Model 4[g]	ref	ref	-0.16[b]	-0.27, -0.06	-0.37[c]	-0.51, -0.24

Abbreviations: 3MS, Modified Mini Mental State Exam; CI, Confidence Interval; DSST, Digit Symbol Substitution Test; $eGFR_{cys}$, Cystatin C-based estimated glomerular filtration rate (ml/min/1.73m^2); ref, referent

[a] *P* value <0.05; [b] *P* value <0.01; [c] *P* value <0.001

[d] Basic model: $eGFR_{cys}$ × year

[e] Adjusted for confounders: $eGFR_{cys}$ × year, age, gender, race, education, smoking, body mass index, diabetes, history of hypertension, C-reactive protein, *ApoE* genotype, depression symptoms

[f] Adjusted for hypothesized mediators: $eGFR_{cys}$ × year, myocardial infarction, stroke, congestive heart failure

[g] Adjusted for confounders and hypothesized mediators: $eGFR_{cys}$ × year, age, gender, race, education, smoking, body mass index, diabetes, history of hypertension, C-reactive protein, *ApoE* genotype, depression symptoms, myocardial infarction, stroke, congestive heart failure

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

	$eGFR_{cys}$ 90+		$eGFR_{cys}$ 60 – 90		$eGFR_{cys}$ <60	
Life Years	Mean Difference	95% CI	Mean Difference	95% CI	Mean Difference	95% CI
Model 1[d]	ref	ref	-0.08	-0.16, 0.01	-0.53[c]	-0.63, -0.43
Model 2[e]	ref	ref	-0.02	-0.11, 0.07	-0.36[c]	-0.48, -0.24
Model 3[f]	ref	ref	-0.06	-0.15, 0.02	-0.49[c]	-0.60, -0.39
Model 4[g]	ref	ref	-0.01	-0.11, 0.08	-0.35[c]	-0.47, -0.23
CIFLY						
Model 1[d]	ref	ref	-0.08	-0.22, 0.07	-0.81[c]	-0.99, -0.64
Model 2[e]	ref	ref	-0.07	-0.21, 0.08	-0.48[c]	-0.66, -0.30
Model 3[f]	ref	ref	-0.04	-0.19, 0.10	-0.70[c]	-0.88, -0.52
Model 4[g]	ref	ref	-0.04	-0.20, 0.08	-0.44[c]	-0.62, -0.26

Abbreviations: CI, Confidence Interval; CIFLY, Cognitive Impairment-free life years; $eGFR_{cys}$, Cystatin C-based estimated glomerular filtration rate (ml/min/1.73m^2); ref, referent

[a] *P* value <0.05; [b] *P* value <0.01; [c] *P* value <0.001

[d] Basic model: $eGFR_{cys}$

[e] Adjusted for confounders: $eGFR_{cys}$, age, gender, race, education, smoking, body mass index, diabetes, history of hypertension, C-reactive protein, *ApoE* genotype, depression symptoms

[f] Adjusted for hypothesized mediators: $eGFR_{cys}$, myocardial infarction, stroke, congestive heart failure

[g] Adjusted for confounders and hypothesized mediators: $eGFR_{cys}$, age, gender, race, education, smoking, body mass index, diabetes, history of hypertension, C-reactive protein, *ApoE* genotype, depression symptoms, myocardial infarction, stroke, congestive heart failure

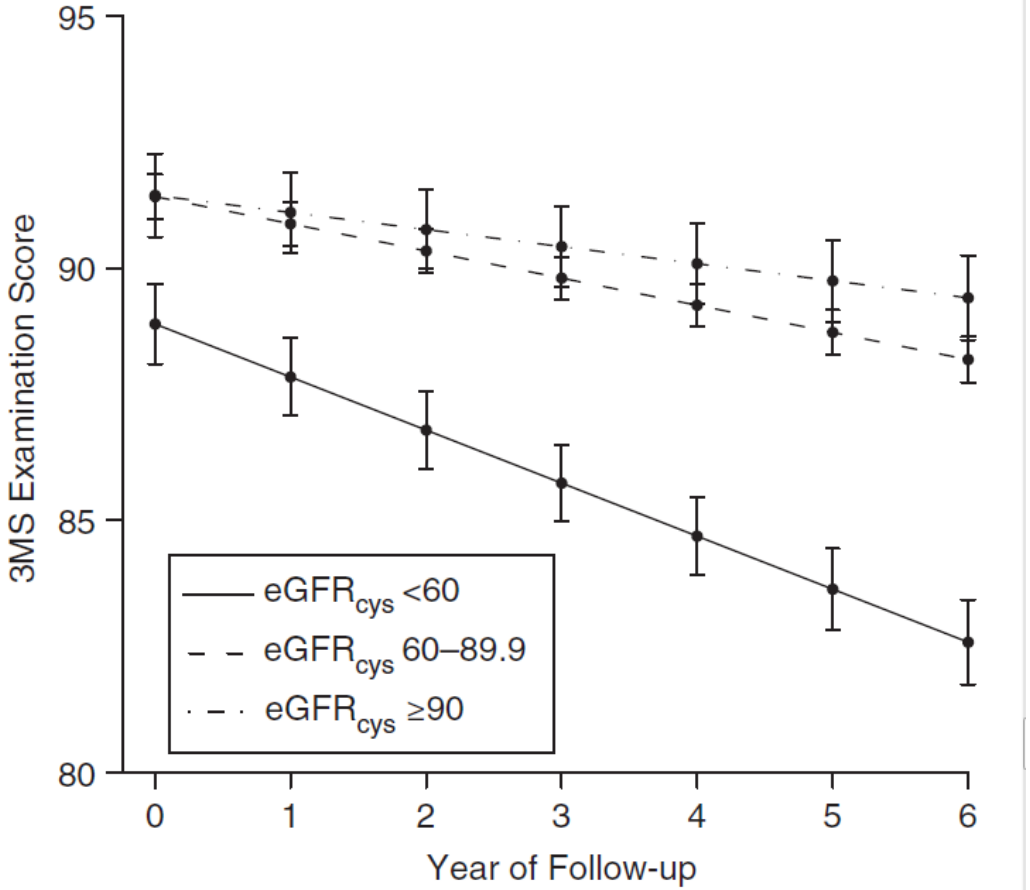

Figure 1. Baseline cystatin C–based estimated glomerular filtration rate (eGFR$_{cys}$) and predicted Modified Mini-Mental State (3MS) Examination score, Cardiovascular Health Study, 1992–1999. eGFR$_{cys}$ is measured as mL/minute/1.73 m^2. Bars, 95% confidence intervals.