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Kidney Function and Cognitive Performance and Decline in Older Men

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Abstract

Objectives—To examine the association of kidney function with cognitive impairment and decline in elderly men.

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Design—Observational prospective cohort.

Setting—Community based.

Participants—5529 community dwelling men, aged 65 years or older (mean age 73.6 ± 5.9).

Measurements—Estimated Glomerular filtration rate (eGFR) calculated using the standardized Modification of Diet in Renal Disease (MDRD) equation; cognitive function assessed with Modified Mini-Mental State Examination (3MS) and Trail Making Test B (Trails B).

Results—At baseline, 148 (2.7%) and 494 (9.1%) men were classified as cognitively impaired and, in the 5-year prospective analysis, 931 (23%) and 432 (11.6%) met the criteria for cognitive decline at follow-up defined by 3MS and Trails B performance, respectively. In unadjusted analysis, the odds of prevalent cognitive impairment and risk of cognitive decline were significantly higher among men with eGFR of <45 and $45\text{--}59$ mL/min/ 1.73m^2 , compared to men with eGFR ≥ 60 mL/min/ 1.73m^2 . These associations were largely explained by difference in age, race, and education between the eGFR categories, with the exception of the association between reduced renal function and higher odds of impairment based on Trails B test score which persisted despite adjustment for multiple potential confounders.

Conclusion—This study found evidence of an independent association between mild to moderate reductions in kidney function and poor executive function at baseline, but not with global cognitive impairment or risk of cognitive decline in older men.

Keywords

kidney function; cognition; elderly

INTRODUCTION

Kidney function declines with age;¹ at least 35% of adults in the US aged ≥ 70 years have moderately to severely decreased kidney function.² Kidney disease has been associated with cognitive impairment and dementia in dialysis patients^{3–6} and patients with moderate chronic kidney disease (CKD).^{7–11} Individuals with CKD carry a heavy burden of traditional coronary disease risk factors, such as older age, hypertension, diabetes, and hyperlipidemia, as well as non-traditional risk factors such as hyperhomocystenemia, oxidative stress, and inflammation,^{12–14} associated with cognitive impairment in the general population.^{15–17} Kidney disease is also associated with increased risk of stroke,^{18;19} which in turn increases the risk of cognitive impairment and dementia.²⁰ Retention of uremic toxins has been implicated in decreased cognitive function, with improvement in cognitive performance with more intensive dialysis and after kidney transplantation.^{21;22} Of the studies that have reported the association between kidney function and cognitive function, only two published studies were prospective in design.^{10,11} In addition, prior studies examining the association between cognitive function and kidney disease have included only women or few men.⁹ We aimed to determine if reduced kidney function, as defined by lower glomerular filtration rate (GFR), is associated with increased odds of prevalent cognitive impairment and risk of cognitive decline in community dwelling elderly men.

METHODS

Study Participants

MrOS is a multicenter prospective study of risk factors for vertebral and non-vertebral fractures in older men. The design, measures, and recruitment methods have been described previously.^{24;25} Briefly, 5995 men 65 years or older were recruited from March 2000 to April 2002 from the populations of Birmingham, AL; Minneapolis, MN; the Monongahela

Valley near Pittsburgh, PA; Palo Alto, CA; Portland, OR; and San Diego, CA. Approval was obtained from the institutional review boards of the participating institutions, and written informed consent was obtained from all study participants. Men were excluded from the study if they could not walk without assistance, had bilateral hip replacements, did not live in or planned to move from the area surrounding the study site, or had a severe medical condition that would preclude participation in follow-up. 5529 men (92% of the cohort) with both measurement of serum creatinine and cognitive testing with Modified Mini-Mental State (3MS) examination at baseline were included in this study. Of these, 5403 men (90% of the cohort) had Trails B testing at baseline. An average (SD) of 4.6 (0.4) years later, 4833 men (97% of survivors) participated in a second visit including 654 men who completed a mailed questionnaire only and 4179 men who also attended a second clinic examination during which they underwent cognitive testing.

Estimation of Kidney Function

Serum creatinine was measured on previously thawed specimens collected by morning phlebotomy from MrOS participants at baseline examination and centrally stored at -120°C , using the Roche COBAS Integra 800 automated analyzer (Roche Diagnostics Corp., Indianapolis, IN) utilizing a variation of the Jaffe enzymatic method. This assay was calibrated daily. Inter- and intra-assay CVs were 5.3%. Kidney function was expressed as estimated glomerular filtration rate (eGFR) using standardized serum creatinine based formula derived by the Modification of Diet in Renal Disease (MDRD) equation: $\text{GFR} = 175 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.212(\text{if black}) \times 0.742(\text{if female})$.²³

We used a modification of the National Kidney Foundation – Kidney Disease Outcomes Quality Initiative kidney disease classification guidelines to define categories of kidney disease by eGFR categories.²⁶ Given a large number of subjects with eGFR between 30 and 59 mL/min/1.73m² and relatively few subjects with eGFR less than 30 mL/min/1.73m², we defined the category of eGFR between 45 and 60 mL/min/1.73m² as mild CKD and eGFRs <45 mL/min/1.73m² as moderate CKD. This classification was previously used by other studies.¹⁰ Dialysis status of participants at baseline was unknown. However, during follow up visits it became apparent that 6 individuals were on dialysis. Excluding these individuals did not alter the overall results. Results presented herein include these individuals.

Cognitive Function Testing

Cognitive function was assessed by a trained technician with the Modified Mini-Mental State Examination (primary outcome) and the Trail Making Test Part B (secondary outcome) at baseline and at the follow-up visit. The 3MS is a test of global cognitive function, with scores ranging from 0–100, with higher scores representing better cognitive function. When a cutoff of <80 is used to define cognitive impairment, it has 85–91% sensitivity and 84–97% specificity for dementia in the elderly,²⁷ and has been utilized in studies of cognitive impairment in kidney disease.^{8;10} Trails B is a test of executive function,²⁸ that assesses attention, concentration, psychomotor speed, cognitive shifting and complex sequencing function by measuring the time required to connect a series of sequentially numbered and lettered circles. Shorter completion times indicate better performance, with test scores affected by age, education and general intelligence. Better performance on Trails B test is significantly associated with the ability to perform instrumental activities of daily living (IADL) in community dwelling elderly.²⁸

For cross-sectional analyses, prevalent cognitive impairment was defined as having a baseline 3MS <80 or a Trails B time greater than 1.5 standard deviations above the mean. For prospective analyses, incident cognitive impairment was defined as having a 3MS <80 or a decline of 5 points or more on the follow-up 3MS exam (approximately one standard

deviation change), or having a change in Trails B completion time that was one standard deviation or more above the sample's mean change in completion time, between the baseline and follow-up examinations. Men with prevalent cognitive impairment at baseline as defined by a given cognitive test were excluded from longitudinal analyses examining the association between kidney function and risk of cognitive decline as defined by that test.

Other Measurements

Participants were interviewed by a trained technician at the baseline visit and completed a self-administered questionnaire. Self-reported health status and mental component summary (MCS) scale were obtained from the Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12).²⁹ A self-reported medical history of conditions listed in Table 1 was obtained. Height and weight were used to calculate a standard body mass index (kg/m^2). Ankle/arm blood pressure index was measured at baseline visit and a cutoff of ≤ 0.9 used to define peripheral arterial disease (PAD).

Statistical Analysis

Differences in baseline characteristics according to category of eGFR (<45 , $45\text{--}59$, ≥ 60 mL/min/ 1.73m^2) were compared using analysis of variance for normally distributed continuous data, Kruskal-Wallis for skewed continuous data, and chi-square tests for categorical data.

The association between renal function and cognitive impairment or decline was analyzed using logistic regression, with a test for linear trend across categories of eGFR performed. Models presented include an unadjusted base model; age-adjusted model; base model adjusted for age, education, and race; and final multivariable model further adjusting for additional variables associated with baseline renal function at $P \leq 0.10$ in univariate analyses. All models were adjusted for clinic site. Longitudinal analyses were additionally adjusted for baseline 3MS/Trails B score.

Additional analyses were performed expressing the predictor variable as four categories of eGFR (<30 mL/min/ 1.73m^2 , $30\text{--}45$, $45\text{--}59$ and ≥ 60), eGFR as a continuous variable (per 10 mL/min/ 1.73m^2), serum creatinine as a continuous variable (per 1 mg/dL), and quartiles of serum creatinine. Because the alternative definitions of the predictor variable did not substantially alter the results, only analyses using the three eGFR categories are presented in this paper. All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

Of the 5995 men in the cohort, 5529 had baseline measurements of serum creatinine and 3MS testing and were included in the cross-sectional analysis. Compared to men with complete baseline measures, 466 men without baseline serum creatinine ($N=461$) and/or cognitive function by the 3MS test ($N=5$), were older, less likely to be Caucasian, had fewer years of education, and had higher prevalence of diabetes. Men with serum creatinines who did not have baseline Trails B testing ($N=126$) were older, less educated, less likely to be Caucasian, more likely to report comorbidities, and had lower baseline 3MS scores (83.5 vs 93.6, $p\text{-value}<.001$) compared to men with baseline Trails B testing.

Characteristics of the 5529 men in the cohort by category of eGFR are presented in Table 1. 753 (13.6%) men had baseline eGFR $45\text{--}59$ mL/min/ 1.73m^2 , 204 (3.7%) had eGFR <45 mL/min/ 1.73m^2 , 28 (0.5%) had eGFR <30 mL/min/ 1.73m^2 , 6 (0.1%) men had eGFR <20 mL/min/ 1.73m^2 and only 2 (0.04%) had eGFR <10 mL/min/ 1.73m^2 . Compared to men with baseline eGFR ≥ 60 mL/min/ 1.73m^2 , those with lower baseline eGFR were older, less likely

to report their health as good or excellent, had greater functional impairment, consumed fewer alcohol drinks per week, had a higher prevalence of PAD, and were more likely to report medical conditions.

Estimated Glomerular Filtration Rate and Baseline Cognitive Function

Unadjusted baseline 3MS mean ($\pm$ SD) scores were 93.6 (5.8), 92.5 (6.0), and 91.4 (6.5), (p for trend <0.001), and unadjusted mean ($\pm$ SD) time in seconds to completion of Trails B test were 131 (57), 147 (62), and 157 (64.5) (p for trend <0.001), among participants with an eGFR $\geq$ 60, 45–59, and <45 mL/min/1.73m² respectively.

A total of 148 (2.7%) men were classified as cognitively impaired at baseline based on having a 3MS <80. Compared with men with eGFR $\geq$ 60 mL/min/1.73m², the unadjusted odds ratios [95% CI] of cognitive impairment (3MS <80) were 1.89 [1.26–2.83] among men with eGFR of 45–59 mL/min/1.73m² and 2.11 [1.08–4.11] among men with eGFR <45 mL/min/1.73m² (Table 2). The association between reduced kidney function and cognitive impairment was partially explained by older age among those with lower kidney function. Further attenuation was noted after adjustment for clinic site, education, and race.

A total of 494 (9.1%) men were classified as cognitively impaired based on the Trails B test. Compared to men with normal renal function, the unadjusted odds ratios [95% CI] of impairment were 1.74 [1.37–2.21] among men with eGFR 45–59 mL/min/1.73m² and 2.37 [1.61–3.49] among men with eGFR <45 mL/min/1.73m² (Table 2). After adjustment for the potential confounders (see Table 2) the odds ratios [95% CI] of cognitive impairment were 1.31 [1.00–1.72] among men with eGFR 45–59 mL/min/1.73m² and 1.30 [0.83–2.06] among men with eGFR <45 mL/min/1.73m² (p for trend=0.05).

Estimated Glomerular Filtration Rate and Cognitive Decline

Of the 5529 men with 3MS testing and kidney function at baseline, 1350 did not attend the follow-up visit (78 terminated, 524 died, 654 completed a self-administered questionnaire only, and 94 did not attend the follow-up visit). Compared to participants without follow-up, those who attended the follow-up visit tended to be younger, Caucasian, more educated, self-reported excellent or very good health, less likely to report history of a physician diagnosed medical condition, and had better scores on baseline cognitive testing (mean [$\pm$ SD] 3MS score of 94.1 [5.0] and mean [$\pm$ SD] time to completion of Trails B test of 126.7 [52.9] for men with follow-up as compared to 91.1 [7.6] and 158.5 [66.8] respectively for men without follow-up [P<0.001 for both]).

Of the 4179 men with baseline 3MS testing who attended the follow-up visit, 69 did not complete follow-up 3MS testing. Of the 4107 men with baseline Trails B testing who attended the follow-up visit, 159 did not complete follow-up Trails B testing. Compared to men with a given follow up testing, men without that follow-up testing were older, less educated, less likely to report their health status as excellent or good, and more likely to report a history of CVD or diabetes, for the 3MS and Trails B tests alike. In addition, 64 men, who were defined as impaired based on their baseline 3MS performance, were excluded from the prospective analysis, leaving 4046 men in the prospective analysis of cognitive decline by the 3MS performance. Similarly, 226 men who were defined as impaired based on their baseline Trails B performance were excluded, leaving 3722 participants for prospective analysis of cognitive decline by Trails B performance.

At follow-up, 931 of 4046 (23%) men met criteria for cognitive decline as defined by 3MS score <80 or a $\geq$ 5 point decline in their score and 432 of 3722 (11.6%) men met criteria for cognitive decline based on performance on the Trails B test. A total of 161 men (4.4%) met criteria for cognitive decline on both tests.

Compared with men with $\text{eGFR} \geq 60 \text{ mL/min/1.73m}^2$, the unadjusted odds ratios [95% CI] of cognitive decline as defined by 3MS score were 1.25 [1.00–1.57] among men with $\text{eGFR} 45\text{--}59 \text{ mL/min/1.73m}^2$ and 1.65 [1.07–2.53] among men with $\text{eGFR} < 45 \text{ mL/min/1.73m}^2$ (p for trend=0.004) (Table 3). This association was largely explained by older age among men with reduced renal function. Similarly, after adjustment for age, there was no association between kidney function and odds of cognitive decline as defined by the Trails B performance (Table 3).

DISCUSSION

In our study of older community dwelling men, we found an independent association between reduced eGFR , and poorer performance on Trails B testing at baseline. However, the associations between reduced eGFR and baseline cognitive impairment as measured by the 3MS test, or cognitive decline as measured by the 3MS or the Trails B tests were largely or entirely explained by older age among those with reduced renal function.

Our finding of the association between mild to moderate kidney disease and poor performance on the Trails B but not 3MS testing is in agreement with prior findings: Kurella et al showed that patients on dialysis scored worse than normal controls on both the 3MS and the Trails B tests, but those subjects with CKD performed worse on the Trails B test, but had 3MS scores not different from those of normal controls.⁸ It has been suggested that mild CKD is associated with poorer executive function and attention; where as severe CKD and ESKD are associated with a global decrease in cognitive function.^{4;8}

Our findings regarding the lack of evidence for an independent association between mild to moderate CKD and increased risk of cognitive decline as measured by the 3MS test differ from those previously reported.^{10;11} Kurella et al found a graded independent association between estimated GFR by the MDRD formula at baseline and incident cognitive impairment (similarly defined as 3MS score < 80 or > 5 point decline in 3MS score) in 3075 community dwelling elderly in the Health, Aging, and Body Composition (Health ABC) study.¹⁰ Compared with the MrOS cohort, the Health ABC study participants were more likely to have evidence of cognitive impairment at baseline (10%) and follow-up (36%), were less educated, more racially diverse, and more likely to have diabetes.¹⁰ Another cross-sectional study by Kurella et al observed an association between reduced kidney function and increased likelihood of cognitive impairment (assessed with 3MS score, Trails B test and Boston naming test) in a cohort of 1,015 postmenopausal women with a history of atherosclerotic heart disease who participated in the Heart Estrogen/Progestin Replacement Study (HERS).⁹ Differences in findings between MrOS and these two studies may be related to the lower prevalence of CKD and cognitive impairment in the MrOS cohort, use of the accepted cut offs to define impairment in the highly educated cohort, effect of gender on the association between kidney dysfunction and cognitive impairment,³⁰ or in the case of HERS, the presence of residual confounding by atherosclerotic vascular disease

We did not find an independent association between CKD and higher risk of cognitive decline in our study. The Cardiovascular Health Cognition study¹¹ revealed an independent association between elevated creatinine ($\geq 1.3 \text{ mg/dL}$ for women and $\geq 1.5 \text{ mg/dL}$ for men) with a 37% increase in risk of new diagnosis of dementia, established by extensive neuropsychiatric testing in 1013 participants and by detailed record review in 1072 participants. It is possible that we have limited our ability to observe an association by excluding the participants with baseline cognitive impairment from our analyses, and by limiting the test battery to a few cognitive domains. In addition, using unequal thresholds for impairment limited the Trails B cohort to a less impaired group of people, and could have

differentially affected the association between kidney function and cognitive decline as defined by the two tests.

While prior studies have reported a robust association between moderate to severe CKD or ESKD and cognitive dysfunction,⁸ it is unknown whether mild reduction in kidney function is an independent risk factor for global decrease in cognitive function. Very few men in the MrOS study (28 [0.5%]) had an eGFR <30 ml/min/1.73m². If cognitive dysfunction in kidney disease is the result of uremic toxin accumulation, more advanced CKD might be required before an adverse global effect on cognition is observed.

The study has a number of strengths that include comprehensive measures of the cohort baseline characteristics, outcome assessment blinded to status of renal function, as well as complete follow-up of survivors. However, this study has several limitations. Our participants are mostly white elderly community dwelling healthy men; therefore the findings might not be generalizable to other populations. The study might have been underpowered to detect an association because of healthy participant population. Plasma creatinine may be a biased marker of kidney function in the elderly, because it depends on the muscle mass and nutritional status, resulting in overestimation of kidney function in participants with malnutrition and sarcopenia; using MDRD formula that adjusts for age only partially corrects this limitation. In addition, MDRD formula underestimates GFR particularly if the GFR >60 ml/min/1.73m². These misclassifications might have skewed our findings toward the null. In addition, we did not have serial measurements of kidney function that would allow us to look at the association between change in kidney function and cognitive decline, or baseline dialysis status. Finally, while we used widely accepted measures of cognition in older people, a more comprehensive battery of neuropsychiatric testing might have increased our power to detect an association.

In conclusion, this study found an association between mild to moderate CKD and poorer executive performance at baseline, but did not find evidence of an independent association between mild to moderate CKD and likelihood of global cognitive impairment or risk of cognitive decline in older men. Further prospective studies should include participants of both genders, a spectrum of CKD severity, serial kidney function testing, as well as a more comprehensive battery of neuropsychiatric testing.

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REFERENCES

1. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. *J Am Geriatr Soc.* 1985; 33:278–285. [PubMed: 3989190]

2. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007; 298:2038–2047. [PubMed: 17986697]
3. Kurella M, Mapes DL, Port FK, et al. Correlates and outcomes of dementia among dialysis patients: the Dialysis Outcomes and Practice Patterns Study. *Nephrol Dial Transplant*. 2006; 21:2543–2548. [PubMed: 16751655]
4. Murray AM, Tupper DE, Knopman DS, et al. Cognitive impairment in hemodialysis patients is common. *Neurology*. 2006; 67:216–223. [PubMed: 16864811]
5. Pereira AA, Weiner DE, Scott T, et al. Cognitive function in dialysis patients. *Am J Kidney Dis*. 2005; 45:448–462. [PubMed: 15754267]
6. Sehgal AR, Grey SF, DeOreo PB, et al. Prevalence, recognition, and implications of mental impairment among hemodialysis patients. *Am J Kidney Dis*. 1997; 30:41–49. [PubMed: 9214400]
7. Hailpern SM, Melamed ML, Cohen HW, et al. Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: Third National Health and Nutrition Examination Survey (NHANES III). *J Am Soc Nephrol*. 2007; 18:2205–2213. [PubMed: 17554148]
8. Kurella M, Chertow GM, Luan J, et al. Cognitive impairment in chronic kidney disease. *J Am Geriatr Soc*. 2004; 52:1863–1869. [PubMed: 15507063]
9. Kurella M, Yaffe K, Shlipak MG, et al. Chronic kidney disease and cognitive impairment in menopausal women. *Am J Kidney Dis*. 2005; 45:66–76. [PubMed: 15696445]
10. Kurella M, Chertow GM, Fried LF, et al. Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. *J Am Soc Nephrol*. 2005; 16:2127–2133. [PubMed: 15888561]
11. Seliger SL, Siscovick DS, Stehman-Breen CO, et al. Moderate renal impairment and risk of dementia among older adults: The Cardiovascular Health Cognition Study. *J Am Soc Nephrol*. 2004; 15:1904–1911. [PubMed: 15213280]
12. Francis ME, Eggers PW, Hostetter TH, et al. Association between serum homocysteine and markers of impaired kidney function in adults in the United States. *Kidney Int*. 2004; 66:303–312. [PubMed: 15200438]
13. Muntner P, Hamm LL, Kusek JW, et al. The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. *Ann Intern Med*. 2004; 140:9–17. [PubMed: 14706967]
14. Shlipak MG, Fried LF, Crump C, et al. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation*. 2003; 107:87–92. [PubMed: 12515748]
15. Keller JN, Schmitt FA, Scheff SW, et al. Evidence of increased oxidative damage in subjects with mild cognitive impairment. *Neurology*. 2005; 64:1152–1156. [PubMed: 15824339]
16. eshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med*. 2002; 346:476–483. [PubMed: 11844848]
17. eunissen CE, Boxtel MP, Bosma H, et al. Inflammation markers in relation to cognition in a healthy aging population. *J Neuroimmunol*. 2003; 134:142–150. [PubMed: 12507782]
18. Koren-Morag N, Goldbourt U, Tanne D. Renal dysfunction and risk of ischemic stroke or TIA in patients with cardiovascular disease. *Neurology*. 2006; 67:224–228. [PubMed: 16864812]
19. Seliger SL, Gillen DL, Longstreth WT Jr, et al. Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int*. 2003; 64:603–609. [PubMed: 12846756]
20. Desmond DW, Moroney JT, Sano M, et al. Incidence of dementia after ischemic stroke: Results of a longitudinal study. *Stroke*. 2002; 33:2254–2260. [PubMed: 12215596]
21. Griva K, Thompson D, Jayasena D, et al. Cognitive functioning pre- to post-kidney transplantation—a prospective study. *Nephrol Dial Transplant*. 2006; 21:3275–3282. [PubMed: 16861731]
22. Jassal SV, evins GM, Chan CT, et al. Improvements in cognition in patients converting from thrice weekly hemodialysis to nocturnal hemodialysis: A longitudinal pilot study. *Kidney Int*. 2006; 70:956–962. [PubMed: 16837916]
23. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006; 145:247–254. [PubMed: 16908915]

24. Iank JB, Cawthon PM, Carrion-Petersen ML, et al. Overview of recruitment for the osteoporotic fractures in men study (MrOS). *Contemp Clin Trials*. 2005; 26:557–568. [PubMed: 16085466]
25. Orwoll E, Iank JB, Barrett-Connor E, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study--a large observational study of the determinants of fracture in older men. *Contemp Clin Trials*. 2005; 26:569–585. [PubMed: 16084776]
26. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis*. 2002; 39:S1–S266. [PubMed: 11904577]
27. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987; 48:314–318. [PubMed: 3611032]
28. Cahn-Weiner DA, Boyle PA, Malloy PF. Tests of executive function predict instrumental activities of daily living in community-dwelling older individuals. *Appl Neuropsychol*. 2002; 9:187–191. [PubMed: 12584085]
29. Ware, JE.; Kosinski, M.; Keller, SD. SF-12: How to score the SF-12 Physical and Mental Health Summary Scores. Third Ed.. Lincoln, RI: QualityMetric, Inc.; 1998.
30. Azad NA, Al BM, Loy-English I. Gender differences in dementia risk factors. *Gend Med*. 2007; 4:120–129. [PubMed: 17707846]

Table 1

Baseline Characteristics of the Study Participants by Category of eGFR for Men with Baseline 3MS Scores

Characteristic	Total cohort (n=5529)	Baseline eGFR (mL/min/1.73m ²)			P-value
		≥60 (n= 4572)	45–59 (n= 753)	<45 (n=204)	
Age groups, %					<0.001
65–69	30	34	11	12	
70–74	29	29	31	20	
75–79	24	23	30	29	
≥80	18	15	28	39	
Caucasian race, %	91	91	92	92	0.681
Education, %					0.058
Less than high school	7	7	8	9	
High school	18	18	20	21	
Some college or beyond	75	76	72	70	
Mental Component Score from SF-12 (mean ± SD)	55.6 ± 7.0	55.6 ± 6.9	55.4 ± 7.8	55.9 ± 7.0	0.654
Self-reported good or excellent health status, %	86	87	80	74	<0.001
Number of IADL impairments, %					<0.001
None	79	82	71	60	
1–2	16	15	21	29	
≥3	5	4	8	11	
Smoking status, %					0.458
Current smokers	3	4	3	2	
Former smokers	59	59	60	57	
Never smoked	37	37	37	41	
Alcohol use, drinks per week, mean ± SD	4.3 ± 6.8	4.5 ± 6.9	3.4 ± 6.4	2.2 ± 4.7	<0.001
Hypertension, %	43	40	59	68	<0.001
History of stroke, %	6	5	8	14	<0.001
Cardiovascular disease [*] , %	24	22	32	46	<0.001
Lung disease, %	11	10	12	14	0.144
Diabetes, %	11	10	14	25	<0.001

Characteristic	Baseline eGFR (mL/min/1.73m ²)				P-value
	Total cohort (n=5529)	≥60 (n= 4572)	45–59 (n= 753)	<45 (n=204)	
History of selected medical conditions [†] , %					<0.001
None	38	41	25	13	
1–2	56	54	66	65	
≥3	7	5	10	22	
Body mass index, kg/m ² , mean ± SD	27.4 ± 3.8	27.4 ± 3.8	27.6 ± 3.8	27.7 ± 4.2	0.151
Ankle/arm blood pressure index ≤0.9, %	6	5	10	21	<0.001
Serum creatinine, mg/dL, mean ± SD	1.02 ± 0.28	0.93 ± 0.13	1.30 ± 0.10	1.90 ± 0.63	<0.001

* Self-reported history of myocardial infarction, angina or congestive heart failure

[†] History of one or more selected medical conditions including hypertension, diabetes, history of stroke, cardiovascular disease, lung disease, or Parkinson's disease

Table 2

Association between eGFR and Odds of Cognitive Impairment at Baseline

Odds Ratio of Cognitive Impairment (95% CI)	Estimated Glomerular Filtration Rate* (mL/min/1.73m ²)			
	<45	45–59	≥60	P for trend
Impairment at baseline by 3MS [†]				
Crude (n=5529)	2.11 (1.08–4.11)	1.89 (1.26–2.83)	1.0 (referent)	<0.001
Age-adjusted (n=5529)	1.57 (0.80–3.11)	1.61 (1.06–2.44)	1.0 (referent)	0.025
Model 1 [‡] (n=5529)	1.37 (0.65–2.87)	1.47 (0.94–2.29)	1.0 (referent)	0.118
Model 2 [§] (n=5321)	1.24 (0.57–2.70)	1.47 (0.91–2.39)	1.0 (referent)	0.214
Impairment at baseline by Trails B				
Crude (n=5403)	2.37 (1.61–3.49)	1.74 (1.37–2.21)	1.0 (referent)	<0.001
Age-adjusted (n=5403)	1.61 (1.08–2.40)	1.33 (1.04–1.71)	1.0 (referent)	0.002
Model 1 [‡] (n=5403)	1.57 (1.03–2.39)	1.30 (1.01–1.69)	1.0 (referent)	0.007
Model 2 [§] (n=5206)	1.30 (0.83–2.06)	1.31 (1.00–1.72)	1.0 (referent)	0.050

^{*} Estimated glomerular filtration rate as calculated by MDRD Index

[†] Cognitive impairment at baseline defined as a 3MS score of <80 at the baseline visit

[‡] Model 1 adjusted for age, education and race

[§] Model 2 adjusted for age, education, race, health status, IADL impairments, alcohol use, diabetes, hypertension, stroke, cardiovascular disease, body mass index, and PAD

^{//} Cognitive impairment at baseline defined as a Trails B completion time >1.5 SD above sample mean (>221.5 s) at baseline visit

Table 3

Association between eGFR and Odds of Incident Impairment at Follow-up

	Estimated Glomerular Filtration Rate* (mL/min/1.73m ²)			
Odds Ratio for Incident Impairment (95% CI)	<45	45–59	≥60	P for trend
Incident impairment at follow-up by 3MS [†]				
Crude (n=4046)	1.65 (1.07–2.53)	1.25 (1.00–1.57)	1.0 (referent)	0.004
Age-adjusted (n=4046)	1.28 (0.83–1.97)	1.06 (0.85–1.34)	1.0 (referent)	0.271
Model 1 [‡] (n=4046)	1.27 (0.82–1.96)	1.07 (0.85–1.35)	1.0 (referent)	0.271
Model 2 [§] (n=3936)	1.18 (0.75–1.85)	1.06 (0.84–1.35)	1.0 (referent)	0.427
Incident impairment at follow-up by Trails B				
Crude (n=3722)	1.42 (0.80–2.50)	1.26 (0.94–1.70)	1.0 (referent)	0.062
Age-adjusted (n=3722)	1.05 (0.59–1.87)	1.03 (0.76–1.40)	1.0 (referent)	0.814
Model 1 [‡] (n=3722)	1.04 (0.58–1.86)	1.02 (0.75–1.39)	1.0 (referent)	0.857
Model 2 [§] (n=3630)	0.96 (0.53–1.75)	1.06 (0.77–1.45)	1.0 (referent)	0.891

* Estimated glomerular filtration rate as calculated by MDRD Index

[†] Cognitive impairment at follow-up defined as a 3MS score of <80 or a decline of >5 points at the second visit in participants with baseline 3MS score ≥80[‡] Model 1 adjusted for age, education, race and baseline 3MS score[§] Model 2 adjusted for age, education, race, health status, IADL impairments, alcohol use, diabetes, hypertension, stroke, cardiovascular disease, body mass index, PAD, and time to complete Trails B at baseline^{||} Cognitive impairment at follow-up defined as ≥1 standard deviation above the mean difference in time between baseline and follow-up (≥44.44 seconds). Each analysis examining the association between renal function and cognitive decline as defined by a given test excludes men who were defined as impaired at baseline by their score on that test