

Kidney function is associated with the rate of cognitive decline in the elderly



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ABSTRACT

Objective: We tested the hypothesis that impaired kidney function in the elderly is associated with a more rapid rate of cognitive decline.

Methods: Baseline serum was used to calculate estimated glomerular filtration rate (eGFR), using the Modification of Diet in Renal Disease formula, for 886 elderly without dementia participating in the Rush Memory and Aging Project, a prospective, observational cohort study. Kidney function was also dichotomized into impairment or no impairment based on eGFR < or ≥ 60 mL/min/1.73 m². Structured cognitive testing was performed at baseline and at annual evaluations, using a battery of 19 cognitive tests summarized into global cognition and 5 cognitive domains.

Results: In mixed-effects models adjusted for age, sex, and education, a lower eGFR at baseline was associated with a more rapid rate of cognitive decline (estimate 0.0008, SE <0.001, $p = 0.017$). The increased rate of cognitive decline associated with a 15-mL/min/1.73 m² lower eGFR at baseline (approximately 1 SD) was similar to the effect of being 3 years older at baseline. Impaired kidney function at baseline was associated with a more rapid rate of cognitive decline (estimate -0.028 , SE <0.009, $p = 0.003$). The increased rate of cognitive decline associated with impaired kidney function at baseline was approximately 75% the effect of ApoE4 allele on the rate of cognitive decline. Baseline kidney function was associated with declines in semantic memory, episodic memory, and working memory but not visuospatial abilities or perceptual speed.

Conclusion: Impaired kidney function is associated with a more rapid rate of cognitive decline in old age. *Neurology*® 2009;73:920-927

GLOSSARY

AD = Alzheimer disease; **BMI** = body mass index; **CRN** = creatinine; **eGFR** = estimated glomerular filtration rate.

Kidney function decreases with age and is common in the elderly.¹⁻³ There is growing evidence that even mild decreased kidney function is associated with an increased risk of cardiovascular and cerebrovascular events.³⁻⁶ Recent cross-sectional studies also suggest that impaired kidney function is associated with cognitive impairment in the elderly.⁷⁻⁹ However, there have been few longitudinal studies examining the association of impaired kidney function with the course of cognitive decline, and results from studies that have been reported are conflicting.^{10,11}

To test the hypothesis that impaired kidney function is associated with a more rapid rate of cognitive decline, we used data from more than 850 older participants without dementia in the Rush Memory and Aging Project.^{12,13} Linear mixed-effect models were used to examine the associations of baseline kidney function with baseline level and annual rate of change in global cognition. Kidney function was assessed with a continuous measure, estimated glomerular filtration rate (eGFR), and a dichotomized measure of kidney function (not impaired if eGFR ≥ 60 mL/min/1.73; impaired if eGFR <60 mL/min/1.73 m²). In secondary analyses, we

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considered covariates that might influence the association of kidney function and cognition. Finally, we examined whether the association of kidney function and cognition varied among 5 different cognitive abilities.

METHODS Participants. All participants were from the Rush Memory and Aging Project, recruited from more than 40 residential facilities across the metropolitan Chicago area. Participants agreed to annual testing and blood draw at baseline and signed an anatomic gift act for autopsy at the time of death.¹² Each person underwent a uniform structured clinical evaluation, which included medical history, neurologic examination, and cognitive testing. Annual follow-up evaluations were identical in all essential details to the baseline examination. The study began in 1997, and the overall follow-up rate is approximately 95% of survivors. Because of the rolling admission and mortality, the duration of follow-up and number of examinations varies across participants. Further, because the collection of serum was not added until 2002, eGFR could only be calculated on a subset of participants. To maintain the temporal relation between measures of eGFR and cognitive testing, we included the first serum creatinine (CRN) as the predictor and considered the cognitive testing obtained at that evaluation the “baseline” for this study; all subsequent cognitive testing examinations available for each participant were used to estimate the rate of change in cognition (mean 3.4 [SD 1.4] examinations/participant).

Inclusion in these analyses required 1) valid serum CRN, 2) the absence of dementia based on clinical cognitive testing, and 3) 1 or more follow-up evaluations with cognitive data to calculate change in cognition. At the time of these analyses, 1,062 participants had a valid serum CRN measure at baseline evaluation, and of these, 83 had clinical dementia at their baseline evaluation and 80 were not eligible for follow-up examination (29 persons died before their first follow-up and 51 had not yet reached their first follow-up). Of 899 who were eligible for follow-up examination, 13 had missing follow-up, data yielding a participation rate of >98%. This left 886 participants for the following analyses with an average of 3.4 years of follow-up (SD 1.39 years, range 1–5 years). Their baseline characteristics and cognitive testing are summarized in table 1.

Protocol approval, registration, and patient consents.

The study received approval from an ethical standards committee on human experimentation (Institutional Review Board Rush University Medical Center). Written informed consent was obtained from all participants.

Cognitive testing and diagnosis of dementia. Trained technicians administered 19 cognitive tests as described previously, from which a composite measure of global cognition and subscale measures of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial abilities were constructed.¹³ The individual tests and domain scores are provided in table 1. Clinical diagnoses were made in a 3-step process. Cognitive testing was scored by a computer and reviewed by a neuropsychologist to diagnose cognitive impairment. Then participants were evaluated by a physician who used all cognitive and clinical data to classify persons with respect to dementia, mild cognitive impairment, and no cognitive impairment as previously described.¹⁴ Dementia required a history of cognitive decline and evidence of impairment in at least 2 cognitive domains.¹⁴ Diagnosis-specific cognitive testing scores are summarized in table e-1 on the *Neurology*[®] Web site at www.neurology.org.

Kidney function. Serum CRN was determined using an Olympus AU4500 instrument at Quest Laboratories (Wood

Table 1 Characteristics of the cohort at baseline* (n = 886)

Age, y	80.6 (7.46)
Sex (% male)	223 (25.2%)
Education, y	14.4 (2.99)
Mini-Mental State Examination	27.9 (2.14)
eGFR1, mL/min/1.73 m ²	59 (15.8)
Impaired kidney function	460 (51.9%)
Episodic memory (composite)	0.17 (0.67)
Word List Recall	17.3 (4.39)
Word List Delay	5.3 (2.41)
Word List Recognition	9.5 (1.22)
Immediate Story Recall	9.4 (1.80)
Delayed Story Recall	8.9 (2.19)
Logical Memory Ia	11.2 (4.44)
Logical Memory IIa	9.4 (4.76)
Semantic memory (composite)	0.12 (0.63)
Boston Naming	13.9 (1.30)
Reading Test	12.3 (3.11)
Verbal Fluency	33.0 (8.85)
Working memory (composite)	0.10 (0.72)
Digit Span Forward	8.2 (2.02)
Digit Span Backward	6.2 (2.00)
Digit Ordering	7.1 (1.61)
Perceptual speed (composite)	0.07 (0.79)
Symbol Digit	36.7 (10.80)
Number Comparison	23.9 (7.60)
Stroop Color Naming	18.2 (7.61)
Stroop Word Naming	49.4 (13.22)
Visuospatial abilities (composite)	0.12 (0.78)
Line Orientation	10.1 (3.17)
Progressive Matrices	10.1 (2.03)
BMI, kg/m ²	27.3 (5.25)
Physical activity, h/wk	3.2 (3.62)
Social activity (composite)	2.6 (0.62)
Hemoglobin, mg/dL	13.3 (1.31)
Vascular diseases (sum)	0.4 (0.70)
Myocardial infarction	114 (12.9%)
Congestive heart failure	46 (5.9%)
Claudication	82 (9.3%)
Stroke	101 (11.4%)
Vascular risk factors (sum)	1.2 (0.80)
Smoking	356 (40.2%)
Diabetes	120 (13.5%)
Hypertension	563 (63.5%)
Depressive symptoms	1.2 (1.74)
Medications	
Anticholinergics	346 (39.2%)

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Antidepressants	129 (14.6%)
Antipsychotics	15 (1.7%)
Anxiolytics	54 (6.1%)
Hypnotics	72 (8.1%)
Antihypertensive	345 (38.9%)

*Mean (SD) or number (percentage) as noted.
eGFR = estimated glomerular filtration rate; BMI = body mass index.

Dale, IL, USA) and was not recalibrated to be traceable by isotope dilution mass spectrometry. CRN was used to estimate the glomerular filtration rate (eGFR) using the 4-variable Modification of Diet in Renal Disease formula^{15,16}: for white men, $eGFR = 186 \times (CRN) - 1.154 \times (age) - 0.203$, and for white women, eGFR is 0.742 the white male value for the same CRN and age. For black participants, the white value is multiplied by 1.212. Kidney function was dichotomized into not impaired if $eGFR \geq 60 \text{ mL/min/1.73 m}^2$ vs impaired if $eGFR < 60 \text{ mL/min/1.73 m}^2$.¹⁶

Comorbidities and other covariates. Sex and race was recorded at the baseline interview. Age in years was computed from self-reported date of birth, and date of the baseline cognitive examination. Education (reported highest grade or years of education) was obtained at the time of the baseline cognitive testing. Weight and height were measured and recorded at each visit. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Hemoglobin was measured using a Beckman/Coulter LH750 automated processor at Quest Laboratories, as previously described.¹⁷ Physical activity was assessed using questions adapted from the 1985 National Health Interview Survey. Hours per week spent engaged in each of 5 activities was calculated.¹² Social activity was based on the frequency of participation in 6 items involving social interaction.¹⁸ We summarized vascular risk factors as the sum of hypertension, diabetes mellitus, and smoking. Vascular disease burden was the sum of myocardial infarction, congestive heart failure, claudication, and stroke.¹² Depressive symptoms were assessed with the 10-item version of the Center for Epidemiologic Studies–Depression Scale.¹² At the baseline examination, participants receiving anticholinergics, antidepressants, antipsychotic, anxiolytics, hypnotics, and antihypertensive medications were identified using the Medi-Span[®] system (Medi-Span, Inc., Indianapolis, IN).⁸

Statistical analyses. Pearson correlations were used to assess the bivariate associations of kidney and cognitive function with other covariates. The Wilcoxon rank sum test was used to compare men and women. We used a series of linear mixed-effects models to examine whether kidney function was related to the rate of change in cognition during the study period.¹⁹ The initial model included a term for both linear cognitive change (time in years since baseline) as well as a quadratic term for quadratic change in global cognition (time \times time) as well as terms for baseline eGFR, age, sex, and education and their interactions with time and time \times time. Because there were no significant interactions between time \times time with the terms for eGFR, age, and education, we did not retain these quadratic interaction terms in subsequent models. However, terms for sex \times time \times time were included in those models in which there were significant interactions (global cognition, episodic memory, and se-

Variable	eGFR	p Value
Sex†	$t[884] = 5.60$	<0.001
Age	$r = -0.34$	<0.001
Education	$r = 0.04$	0.253
Body mass index	$r = -0.02$	0.542
Hemoglobin	$r = 0.23$	<0.001
Physical activity	$r = 0.07$	0.040
Social activity	$r = 0.14$	<0.001
Vascular risk factors	$r = -0.11$	0.001
Vascular diseases	$r = -0.22$	<0.001
Depressive symptoms	$r = -0.04$	0.238

*Pearson correlation coefficients.

†t test.

eGFR = estimated glomerular filtration rate.

matic memory). The term for eGFR indicates its association with baseline level of global cognition. The term $eGFR \times \text{time}$ indicates the effect of a 1-mL/min/1.73 m² lower eGFR at baseline on the rate of cognitive decline. Next, we added terms for a number of possible covariates that might confound the association between eGFR and global cognition. We used both linear and quadratic terms for BMI and hemoglobin, because both high and low BMI or hemoglobin may be associated with adverse health outcomes.¹⁷ We repeated the core model using dichotomized kidney function. Finally, we examined the relation of both measures of baseline kidney function with the level and rate of change of 5 cognitive subscales.¹³ Models were examined graphically and analytically and assumptions were judged to be adequately met.²⁰ Programming was performed in SAS[®] (SAS Institute Inc., Cary, NC).²¹

RESULTS Descriptive properties of baseline kidney function and global cognition. The distribution of eGFR was approximately normal, averaging 59 mL/min/1.73 m² (SD 15.8; Q1, Q3: 50, 68), and higher values indicate better kidney function. eGFR was higher in men and was related to age, hemoglobin, physical activity, social activity, and vascular risk factors and diseases but not to education, BMI, or depressive symptoms (table 2).

On average, global cognition was 0.12 (SD 0.52; Q1, Q3: -0.24, 0.51). Global cognition was related to age ($r = -0.27$, $p < 0.001$) and education ($r = 0.40$, $p < 0.001$); women had higher levels of global cognition ($t[884] = 2.63$, $p = 0.009$).

Kidney function and the rate of change in global cognition. We used a linear mixed-effect model to examine the association of eGFR and the rate of change of global cognition. On average, global cognition showed both linear decline (time: coefficient -0.079, SE 0.020, $p < 0.001$) and nonlinear decline (time \times time: coefficient -0.009, SE 0.002, $p <$

Table 3 Impaired kidney function and rate of change in global cognition

Term	Model 1*			Model 3*		
	Coefficient	SE	p Value	Coefficient	SE	p Value
Age	-0.020	0.002	<0.001	-0.018	0.002	<0.001
Age × time	-0.004	0.001	<0.001	-0.004	0.001	<0.001
eGFR	-0.0012	0.001	0.265	-0.0017	0.001	0.122
eGFR × time	0.0008	<0.001	0.017	0.0008	<0.001	0.015

Term	Model 2*			Model 4*		
	Coefficient	SE	p Value	Coefficient	SE	p Value
Age	-0.020	0.002	<0.001	-0.017	0.002	<0.001
Age × time	-0.004	0.001	<0.001	-0.004	0.001	<0.001
Impaired kidney function	0.021	0.032	0.515	0.025	0.033	0.451
Impaired kidney function × time	-0.028	0.009	0.003	-0.027	0.009	0.004

*Models 1 and 2 are based on linear mixed-effect models and show the estimates for the cross sectional association of kidney function (estimated glomerular filtration rate [eGFR] or dichotomized kidney function) with the level of global cognition as well as their association with the rate of change in cognitive function (time). These models also included a linear term (time in years since baseline) and quadratic term (time × time) for global cognitive decline and adjusted for age, sex, and education and their interactions with time and a term for the interaction of sex with time × time. The continuous measure eGFR is calculated from age and serum creatinine via the Modification of Diet in Renal Disease formula. Impaired kidney function is coded as impaired (1) if eGFR < 60 mL/min/1.73 m² and as not impaired (0) if eGFR ≥ 60 mL/min/1.73 m².

*Models 3 and 4 included all the terms listed above in models 1 and 2 but also included terms to adjust for the following covariates and their interaction with time in a single model: body mass index (BMI), BMI², serum hemoglobin, serum hemoglobin², physical activity, late-life social activity, vascular risk factors, vascular diseases, and depressive symptoms. The cross-sectional estimates for each of these terms and their interactions with time are included in table e-2.

0.001). eGFR was not associated with the baseline level of global cognition (model 1, table 3). However, a 1-mL/min/1.73 m² lower baseline eGFR was associated with about an additional 0.001 unit/y decline in global cognition, as indicated by the coefficient of the term eGFR × time (model 1, table 3). Because baseline age was also associated with cognitive decline in this model, we can contextualize the size of the effect of baseline eGFR by comparing the additional increase in the rate of cognitive decline associated with baseline eGFR to the cognitive decline associated with baseline age. Their respective coefficients indicate that a 15-mL/min/1.73 m² decrease in eGFR at baseline (approximately 1 SD) was associated with an equivalent rate of cognitive decline associated with a participant being 3 years older at baseline (eGFR × time: 0.0008 × 15 mL = age × time: -0.0040 × 3 years).

We repeated these analyses, adding terms to determine whether the association of eGFR and global cognition varied by demographic variables. No significant interactions were found (results not shown). After excluding participants with severely reduced eGFR (<30 mL/min/1.73 m², n = 29),¹⁶ eGFR re-

mained associated with cognitive decline (eGFR × time: estimate 0.001, SE <0.001, *p* = 0.004).

Impaired kidney function and the rate of change in global cognition. To examine the association of impaired kidney function and cognition, we repeated our core model using dichotomized kidney function. Impaired kidney function at baseline was not associated with level of global cognition (impaired kidney function, model 2, table 3), but was associated with the rate of change in global cognition (impaired kidney function × time, model 2, table 3). The additional rate of cognitive decline associated with impaired kidney function was approximately 75% of the effect associated with the apoE4 allele genotype (impaired kidney function × time: -0.028 vs ApoE4 × time: -0.037). The effects of both kidney function and apoE4 allele remained significant even when considered together in a single model (results not shown). Finally, a trichotomous classification of impaired kidney function¹¹ (moderate/severe impairment <45 mL/min/1.73 m², n = 153; mild impairment >45 to <60 mL/min/1.73 m², n = 307; and no impairment >60 mL/min/1.73 m², n = 426) was also significantly related to cognitive decline (estimate -0.019, SE 0.006, *p* = 0.023).

Kidney function, other covariates, and the rate of change in global cognition. Because other factors may affect either kidney function or cognition, we repeated the core models (models 1 and 2, table 3), adding terms for several possible confounders that did not substantially affect the associations between eGFR or impaired kidney function and cognitive decline (table 3 and table e-2).

Because medications might affect cognitive function, we added terms for medications to model 1. The association between eGFR and cognitive decline was unchanged after including terms for anticholinergics, antidepressants, antipsychotic, anxiolytics, hypnotics, and antihypertensive medications in a single model (GFR1 × time: estimate 0.0007, SE 0.0003, *p* = 0.026).

Kidney function and the rate of change in different cognitive abilities. To examine whether kidney function was related to specific cognitive abilities, we repeated model 1 in table 3, replacing global cognition with 5 cognitive abilities including episodic memory, the hallmark of Alzheimer disease (AD), and 4 others, including semantic memory, working memory, perceptual speed, and visuospatial abilities. Baseline eGFR was not associated with the level of cognitive function in any of the 5 domains (table 4). However, eGFR was related to the rate of change in episodic memory, semantic memory, and working memory but not perceptual speed or visuospatial abilities (ta-

Table 4 Kidney function and rate of change for different cognitive abilities*

Cognitive ability	eGFR				Impaired kidney function			
	Term	Coefficient	SE	p Value	Term	Coefficient	SE	p Value
Episodic memory	Age	-0.023	0.003	<0.001	Age	-0.023	0.003	<0.001
	Age × time	-0.005	0.001	<0.001	Age × time	-0.005	0.001	<0.001
	eGFR	-0.0008	0.0001	0.551	Impaired kidney function	0.008	0.043	0.855
	eGFR × time	0.0008	0.0004	0.043	Impaired kidney function × time	-0.023	0.011	0.042
Semantic memory	Age	-0.016	0.003	<0.001	Age	-0.015	0.003	<0.001
	Age × time	-0.003	0.001	<0.001	Age × time	-0.003	0.001	<0.001
	eGFR	-0.0002	0.0001	0.141	Impaired kidney function	0.032	0.040	0.430
	eGFR × time	0.0001	0.0004	<0.001	Impaired kidney function × time	-0.033	0.010	0.001
Working memory	Age	-0.009	0.003	0.006	Age	-0.008	0.003	0.007
	Age × time	-0.003	0.001	<0.001	Age × time	-0.003	0.001	<0.001
	eGFR	-0.0001	0.0002	0.444	Impaired kidney function	0.031	0.047	0.503
	eGFR × time	0.0009	0.0004	0.032	Impaired kidney function × time	-0.036	0.011	0.002
Perceptual speed	Age	-0.034	0.003	<0.001	Age	-0.033	0.003	<0.001
	Age × time	-0.006	0.001	<0.001	Age × time	-0.006	0.001	<0.001
	eGFR	-0.0001	0.0002	0.394	Impaired kidney function	0.030	0.049	0.538
	eGFR × time	0.0004	0.0004	0.291	Impaired kidney function × time	-0.017	0.012	0.146
Visuospatial abilities	Age	-0.012	0.003	<0.001	Age	-0.011	0.003	<0.001
	Age × time	-0.004	0.001	<0.001	Age × time	-0.004	0.001	<0.001
	eGFR	-0.0003	0.0002	0.055	Impaired kidney function	0.074	0.047	0.116
	eGFR × time	0.0006	0.0005	0.218	Impaired kidney function × time	-0.017	0.014	0.237

*The linear mixed-effect models described in table 3 (models 1 and 3) was repeated 5 times, replacing the outcome global cognition with each of 5 different cognitive abilities for both measures of kidney function (glomerular filtration rate [eGFR] or impaired kidney function). The interactions between both measures of kidney function and the rate of change of each of the 5 cognitive abilities are shown. The continuous measure eGFR is calculated from age and serum creatinine via the Modification of Diet in Renal Disease formula. Impaired kidney function is coded as impaired (1) if eGFR <60 mL/min/1.73 m² and as not impaired (0) if eGFR ≥60 mL/min/1.73 m².

ble 4). Similar results were obtained using impaired kidney function (table 4).

DISCUSSION In a cohort of more than 850 community-dwelling older adults without dementia, decreased level of eGFR or the presence of impaired kidney function at baseline was associated with a more rapid rate of cognitive decline. This association between impaired kidney function and cognitive decline persisted after excluding participants with severely impaired function (eGFR <30 mL/min/1.73 m²). The association of kidney function and cognition persisted even after controlling several potential confounders. Further analyses showed that kidney function was related to specific cognitive abilities, including episodic memory, semantic memory, and working memory, but not perceptual speed or visuo-

spatial abilities. These findings suggest that there are common pathophysiologic processes between kidney dysfunction and brain dysfunction in the elderly. From our studies, we cannot distinguish between the existence of a pathophysiologic process affecting both brain and kidney and a mechanism of brain injury that is initiated by kidney disease.

Although there is a well-known association between severe kidney disease and cognitive impairment, until recently less severe kidney dysfunction has not been considered a risk factor for cognitive impairment in the elderly. Rather, it was thought that cardiovascular risk factors and diseases accounted for many of the adverse health consequences that occur concurrently with mild kidney dysfunction.²²⁻²⁶ However, accumulating evidence

suggests that after controlling for traditional vascular risk factors, impaired kidney function is associated with lower cognitive function.⁷⁻⁹ Cross-sectional studies have observed a link between kidney function and cognition; however, there are conflicting reports about the course of cognitive decline with impaired kidney function. Several longitudinal studies have reported that moderate kidney disease is associated with cognitive decline, but one recent study did not find an association between kidney function and cognitive decline over 5 years.^{10,11,27} The current study supports findings from prior studies reporting a link between kidney function and cognitive decline in elders.^{10,27} Although the optimal screening for and staging of kidney function in the elderly remain controversial, more than half of the participants in the current study had decreased kidney function.^{28,29} Further, the association between kidney function and cognition was robust and persisted in analyses using both a continuous and a dichotomized measure of kidney function as well as after adjusting for chronic disorders and medications known to affect kidney and cognitive functions. Given the paucity of modifiable risk factors for age-related cognitive decline, these results have important public health implications because they suggest that impaired kidney function is a risk factor for cognitive decline in old age.

Importantly, previous studies that have examined the association of kidney function with cognition have used different cognitive screening instruments. A novel feature of the current study is the availability of a detailed cognitive battery that allows for an examination of the association of kidney function with decline in 5 different cognitive systems.¹³ Some previous studies have suggested that kidney dysfunction may preferentially affect executive cognitive function.¹¹ In the current study, kidney function was related to decline of semantic memory and working memory. Thus, these results provide some support for the association of executive cognitive abilities and kidney function, because working memory is a component of executive function, and semantic memory supports executive function. However, in this study, kidney function was not related to the rate of change in perceptual speed. Further, kidney function was related to change in episodic memory, often the earliest sign of AD. Taken together, these findings may suggest a more generalized association between kidney and cognitive function in old age. Subclinical vascular disease in the kidney and brain may account for the association of cognitive dysfunction and decreased kidney function. These results underscore the need to elucidate the biology underlying the association of kidney function and cognition in our aging population.

The basis for the relationship between kidney function and cognition is uncertain. Although kidney function may represent a true risk factor for cognitive decline, declining kidney function and cognition in the elderly may also derive from a common pathogenesis. Kidney dysfunction is associated with the prevalence of traditional cardiovascular risk factors such as elevations in homocysteine^{30,31} and inflammatory and procoagulant biomarkers,³² which are important biomarkers or mediators of cerebrovascular disease which leads to impaired cognition.³³ This is particularly true for executive cognitive functions and working memory, but infarcts also are associated with episodic memory impairments.³⁴ Further kidney dysfunction is associated with white matter hyperintensities and silent infarctions and, although our results persisted after adjustment for vascular risk factors and diseases, it is possible that subclinical cerebrovascular disease underlies the association of kidney function and cognition in this study.^{35,36} Because impaired kidney function is associated with anemia, this may imply some degree of cerebral hypoxia, which can also lead to decreased cognition.³⁷ Erythropoietin has been reported to have neuroprotective effects, so lower levels of erythropoietin in impaired kidney function may lead to degeneration in cognitive pathways.³⁸ Finally, kidney dysfunction is associated with metabolic abnormalities such as hyperparathyroidism, which may also contribute to cognitive dysfunction.³⁹ Further studies are needed to determine the biologic basis for the association of kidney function and cognition.

The current study has some limitations. First, we did not have measures of inflammatory markers, direct measures of kidney function, or measures of nutritional status. Although we adjusted for common health conditions, there is a possibility that subclinical disease may also have contributed to cognitive decline. Finally, our results are based on a selected cohort that may differ in important ways from the general population, underscoring the need to investigate these findings in other cohorts. However, confidence in these findings is enhanced by several factors. Participants included a large number of older persons initially free of dementia who were examined annually via detailed evaluations for up to 6 years, with more than 90% follow-up participation in survivors. Annual cognitive assessments included multiple tests that allow for composite measures of global cognition, 5 cognitive systems, and investigation of cognitive change over time.

AUTHOR CONTRIBUTIONS

Statistical analysis was performed by Aron S. Buchman in consultation with Sue Leurgans, PhD, Senior Statistician in the Rush Alzheimer's Disease Center.

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DISCLOSURE

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