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Decline in renal functioning is associated with longitudinal decline in global cognitive functioning, abstract reasoning and verbal memory

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ABSTRACT

Background. Decreased estimated glomerular filtration rate (eGFR) and higher serum creatinine (sCR) levels have been associated with longitudinal decline in global mental status measures. Longitudinal data describing change in multiple domains of cognitive functioning are needed in order to

determine which specific abilities are most affected in individuals with impaired renal function.

Methods. We conducted a 5-year longitudinal study with 590 community-living individuals (mean age 62.1 years, 60.2% female, 93.2% white, 11.4% with diabetes mellitus, mean eGFR 78.4 mL/min/1.73 m²) free from dementia, acute stroke and end-stage renal disease. To measure longitudinal change-over-

time, cognitive performance measures were regressed on eGFR adjusting for baseline eGFR and cognitive performance, comorbidity and vascular risk factors. Outcome measures were scores from 17 separate tests of cognitive abilities that were used to index 5 theoretically relevant domains: verbal episodic memory, visual-spatial organization and memory, scanning and tracking, working memory and similarities (abstract reasoning).

Results. Declines in eGFR values were associated with cognitive declines, when adjusted for eGFR and cognitive function scores at baseline. Change in renal functioning over time was related to change observed in global cognitive ability [$b = 0.21$ SD decline per unit $\ln(\text{eGFR})$, 95% CI: 0.04–0.38, $P = .018$], verbal episodic memory [$b = 0.28$ SD decline per unit $\ln(\text{eGFR})$, 95% CI: 0.02–0.54, $P = 0.038$] and abstract reasoning [$b = 0.36$ SD decline per unit $\ln(\text{eGFR})$, 95% CI: 0.04–0.67, $P = 0.025$]. Decline in cognitive functioning in association with declining renal functioning was observed despite statistical adjustment for demographic variables and CVD risk factors and the exclusion of persons with dementia or a history of acute stroke.

Conclusions. Early detection of mild to moderate kidney disease is an important public health concern with regard to cognitive decline.

INTRODUCTION

Cognitive declines are seen in end-stage renal disease (ESRD) in patients on chronic hemodialysis [1–3] and 1-year decline in cognitive test performance was greater in hemodialysis patients than non-kidney diseased elderly patients [4]. Several studies have shown elevated risk of dementia in patients with ESRD [5, 6]. However, modest cognitive declines appear to begin prior to the point where mild or modest kidney disease has progressed to ESRD. There is evidence that the rate of cognitive decline is associated with deterioration in kidney function [7, 8].

Most studies of associations between mild kidney disease and cognition have been conducted at a single point in time or have been cross-sectional with regard to the interaction of kidney disease with age [8–15]. Four studies have examined the association between modest renal dysfunction and longitudinal change in cognitive test performance and one [16] reported that decreased kidney function was associated with more accelerated cognitive decline on the Telephone Interview on Cognitive Status-M score Test [17]. While it includes questions assessing attention, language, calculation and recall from memory, this telephone assessment instrument provides a 6-item global assessment score [17]. It does not permit a determination of which cognitive domains are adversely influenced by renal disease.

Individuals with an estimated glomerular filtration rate (eGFR) <60 exhibited poorer baseline performance on the MMSE and higher rates of cognitive impairment over a 2- to 4-year period [2, 18]. Faster eGFR decline was associated with an accelerated global cognitive decline on the MMSE and higher risk for incident dementia with a vascular component

[19] and modest renal impairment was associated with 9.9% greater incidence of cognitive impairment on the 6CIT [20], a 6-question screening scale [21]. Both tests are intended as screening scales and neither provides detailed information on which cognitive abilities are related to renal function.

In a prior cross-sectional study published in this journal [9], we employed a battery of 17 neuropsychological tests to examine the relations of renal function with the global performance level and specific domains of cognitive performance. Lower eGFR and higher serum creatinine levels (sCR) were associated with lower performance on the global score and two major domains of functioning: visual-spatial organization and memory (VSOM) and scanning and tracking (ST). The purpose of the current study was to identify which domains of change in cognitive functioning were associated with longitudinal changes in renal functioning over 5 years. We hypothesize that *change in renal functioning over time* will be associated with change in global cognitive functioning over the same time period; the literature is not sufficient to allow us to predict which specific domains will show the strongest association [22].

METHODS

Sample and design

Data were obtained from the sixth and seventh waves of the Maine-Syracuse Longitudinal Study (MSLS), a community-based study of cardiovascular risk factors (CVD-RF) in relation to cognitive functioning. Participants were recruited originally from the Syracuse New York area for studies of cognition and blood pressure with no requirements for participation other than non-institutionalization, absence of diagnosed psychiatric disorder and/or alcoholism. Between 2001 and 2006 (wave 6), data necessary to examine a broad range of cognitive measures and CVD-RF, including sCR, were obtained for the first time.

Our baseline sample included 1081 subjects who were recruited at wave 6. Change in research funding necessitated that individuals in this group who moved out of New York State ($n = 137$) be excluded and an additional 319 participants were lost to follow-up. Beginning with the 625 study participants who remained after attrition, 35 were excluded in the following sequence if they met the following exclusionary criteria: (i) data for study variables were missing ($n = 21$); (ii) history of acute stroke at baseline ($n = 12$), dialysis at baseline ($n = 2$) or probable dementia at baseline ($n = 0$). The final sample consisted of 590 participants (see Supplementary Figure 1). Clinical diagnosis of dementia was based on cognitive data and medical records and a multidisciplinary dementia review for each patient using the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Exclusion of dementia cases was based on our interest in characterizing relationships between kidney disease and cognition in persons who vary in cognitive ability, but who have not suffered catastrophic impairment. Dementia was excluded by virtue of other exclusions listed above. Prevalent stroke,

defined as a focal neurological deficit of acute onset persisting for >24 h was based on self-report and record reviews (with permission) confirmed by hospitalization, treatment for stroke or both.

Procedures

Following a fast from midnight, a blood sample was drawn in the morning, followed by a light breakfast, medical history, multiple automated blood pressure measurements (GE Dinamap 100DPC-120XEN) and neuropsychological assessment. All assay methods have been defined previously [9]. sCR was determined using a two-point rate test type on a Johnson and Johnson Vitros Instrument. Coefficients of variation for these procedures were <5.0%. The eGFR was estimated using the four-variable (sCR, age, sex and ethnicity)

Modification of Diet in Renal Disease (MDRD) study equation; renal impairment was defined as an eGFR <60 mL/min/1.73 m² and we defined clinically relevant change in renal functioning as a decline >3 mL/min/1.73 m²/year following a criterion from the Cardiovascular Health Study [23, 24], which represents a magnitude of change that is more than three times greater than the rate previously described in studies of aging, and is beyond the range of noise in measurement. We also estimated models using the CKD-Epi [25] and Mayo Clinic Quadratic (MCQ) [26] equations for purposes of sensitivity analyses. Albuminuria was not collected as part of the MSLS. Determinations of total cholesterol and HDL cholesterol were performed as previously described [9]. Hemoglobin levels and complete blood count were not available to the study, as we did not anticipate an

Table 1. Descriptions of the cognitive tests derived from factor analysis used in this study

Test composite/tests included in the composite	Latent cognitive variable tested
Global composite (z-score)	Global composite of cognitive performance
Visual-spatial organization and memory	
Visual reproductions, immediate recall ^a	Immediate recall, visual memory and visual-spatial problem solving
Visual reproductions, delayed recall ^a	Delayed recall, visual memory and visual-spatial problem solving
Matrix reasoning ^b	Abstract reasoning and pattern recognition
Block design ^c	Visual-spatial perception, organization and construction
Object assembly ^c	Speed of visual-spatial organization
Hooper visual organization	Visual-spatial organization; some demands on executive function
Scanning and tracking	
Trail Making A ^d	Visual scanning and tracking
Trail Making B ^d	Complex visual scanning, tracking and executive function
Digit symbol substitution ^c	Psychomotor performance
Symbol search ^b	Visual processing speed
Verbal memory	
Logical memory, immediate recall ^a	Immediate memory, verbal
Logical memory, delayed recall ^a	Delayed memory, verbal
Hopkins Verbal Learning Test	Verbal learning and memory
Working memory	
Digit span forward ^c	Attention and concentration
Digit span backward ^c	Attention, concentration and working memory
Letter-number sequence ^b	Working memory
Controlled oral word associations	Verbal fluency and executive functioning
Similarities ^c	Abstract reasoning ^e
^a Origin WMS-R. ^b Origin WAIS III. ^c Origin WAIS. ^d Origin Halstead Reitan NP test battery. ^e Excluded from the factor analysis.	

examination of kidney function as a risk factor at the time the data were collected.

The mean systolic BP (SBP) and diastolic BP (DBP) were based on at least 15 BP measurements (five sitting, five standing and five reclining), and were adjusted for hypertensive medications using Tobin's method [27]. Additional covariates used or considered in various analyses described later were as follows: age, sex, years of education, race/ethnicity, defined as African Americans versus other, diabetes mellitus (DM) defined by treatment with insulin, oral anti-diabetic agents or fasting glucose level of 126 mg/dL (7 mmol/L) or higher, body mass index (BMI, kg/m²) and self-report of the number of cigarettes smoked per day including a score of zero indicating no smoking. Results were identical when we substituted or included a dichotomous indicator of the smoking status in the analyses.

The University of Maine IRB approved the protocol for this investigation. Informed consent for data collection was obtained from all participants and we adhered to the Declaration of Helsinki.

Cognitive tests and domains

The cognitive outcome measures included four relatively independent and theory-based composite scores derived by factor analysis and the Similarities Test (abstract reasoning) [28]. Composite scores defined domains of: verbal episodic memory (VM), VSOM, ST, working memory (WM) and Similarities, a measure of abstract reasoning and strong correlate of verbal intelligence [29]. Results are presented in z-score metric, and the content of composites is presented in Table 1. Initial training of examiners and studies of inter-reliability indicated correlations >0.95 for three examiners employed. At waves 6 and 7 no more than two senior psychological examiners were employed, and trained to our initial criterion of >0.95 scoring agreement. Examiners were blind to any diagnostic categories including cognitive impairment. All test protocols were forwarded to a secure scoring and data management laboratory where they were checked for scoring errors by two trained examiners supervised by a senior project psychologist.

Statistical analyses

Change in the eGFR was the independent variable of interest. Because eGFR is non-linearly associated with cognitive functioning, we used log-transformed eGFR in order to meet linearity assumptions. Using multiple linear regression analyses, continuously distributed cognitive outcome scores (Global, VSOM, WM, VM, ST and Similarities) obtained at follow-up were regressed onto measures of change in the eGFR and a set of covariates. As in our cross-sectional paper [9], the variables included as covariates in the regression models were based on the identification of independent predictors of new-onset kidney disease in the Framingham Heart Study [30], many of which are risk factors for cognitive decline, particularly hypertension and DM. The final model developed on this basis included the following demographic factors and vascular risk factors in addition to the eGFR: age (years)+sex + education(years) + race + meanSBP + DM +

BMI + HDL cholesterol + number of cigarettes smoked per day. For the longitudinal analyses of the present study, both baseline and follow-up renal functioning were included in the model along with the baseline cognitive status. Other risk factors, reported later, were employed in sensitivity analyses in this paper.

Essentially, regression models adjust follow-up cognitive measures for the baseline status of both renal functioning and cognitive performance. This well-recognized method of longitudinal analysis [31] is identical to predicting change in cognitive functioning from change in renal functioning adjusting for baseline renal functioning. Thus, this approach allowed us to determine whether individuals with greater change in renal functioning exhibited more change in cognitive functioning than individuals with less change in renal functioning, given that they had the same initial value. Analyses were conducted using Stata12 [32]. We present results in terms of the baseline and follow-up status because they align directly with raw values (e.g. an individual with baseline eGFR of 90 mL/min/1.73/m², follow-up eGFR of 60 mL/min/1.73/m²), consistent with what physicians have available from patients' charts. To evaluate the potential effects of sample selection bias, we implemented Heckman's selection-bias procedure [33]. Results were identical to OLS regression models using Heckman's procedure. Selection was predicted only by baseline cognitive functioning, age and systolic blood pressure, which were adjusted for in all models.

RESULTS

Baseline characteristics

Attrition. Compared with individuals lost to follow-up or excluded ($n = 491$), individuals included in the analyses ($n = 590$) were significantly higher on baseline values for each cognition measure (global: 0.122 versus -0.167 , $P = 0.001$; VSOM: 0.083 versus -0.144 , $P = 0.001$; VM: 0.098 versus -0.147 , $P = 0.001$; WM: 0.058 versus -0.087 , $P = 0.004$; ST: 0.083 versus -0.133 , $P = 0.001$; Similarities: 0.122 versus -0.167 , $P = 0.001$). They were also less likely to have DM (11 versus 16%, $P = 0.020$) or hypertension (59 versus 68%, $P = 0.002$), to have lower DBP (69.9 versus 71.5, $P = 0.012$) and higher HDL (54.4 versus 51.5, $P = 0.004$). Individuals included in the analyses had slightly higher renal functioning (78.4 mL/min/1.73 m² versus 75.8 mL/min/1.73 m², $P = 0.034$), but there were no differences in the prevalence of renal impairment (Fisher's exact $P = 0.076$). There were no differences in other study variables. The prevalence of renal impairment at follow-up was 31.9 versus 13.7% at baseline.

Descriptive statistics. Descriptive statistics for all variables in the regression models are shown in Table 2 by clinically significant change in renal functioning (>3 mL/min/1.73 m²/year). Compared with individuals who did not experience a clinically significant decline in renal functioning, individuals who experienced a clinically significant decline in renal functioning had a higher eGFR at baseline (86.3 mL/min/1.73 m² versus 73.9 mL/min/1.73

Table 2. Descriptive statistics for study variables by clinically significant longitudinal change in the eGFR (>3 mL/min/1.73 m²/year)

Variable	No clinically significant change in the eGFR (<i>n</i> = 372)		Clinically significant change in the eGFR (<i>n</i> = 218)		<i>P</i> -value
	<i>M/Mdn</i>	<i>SD/IQR</i>	<i>M/Mdn</i>	<i>SD/IQR</i>	
Follow-up					
Global	0.06	0.98	0.04	0.99	0.802
VSOM	0.05	0.79	0.02	0.81	0.694
VM	0.05	0.90	−0.01	0.89	0.436
WM	0.04	0.76	0.03	0.72	0.924
ST	0.01	0.86	0.05	0.94	0.579
Similarities	0.14	0.93	0.02	0.98	0.143
eGFR (mL/min/1.73 m ²)	67.9	19.1	62.4	16.9	0.001
Baseline					
Global	0.12	0.90	0.13	0.88	0.853
VSOM	0.09	0.75	0.08	0.73	0.891
VM	0.12	0.82	0.06	0.80	0.370
WM	0.04	0.72	0.08	0.71	0.542
ST	0.06	0.77	0.12	0.83	0.405
Similarities	0.12	0.92	0.12	0.90	0.986
eGFR (mL/min/1.73 m ²)	73.9	18.6	86.3	19.5	0.001
Age (years)	62.4	12.0	61.6	11.6	0.433
Education (years)	14.7	2.7	14.5	2.7	0.441
SBP (mmHg)	128.5	20.3	133.0	23.3	0.017
DBP (mmHg)	69.6	10.0	70.6	9.3	0.244
BMI (kg/m ²)	29.4	5.8	29.6	6.4	0.614
HDL (mg/dL)	54.4	15.6	54.3	15.9	0.909
LDL (mg/dL)	123.1	34.2	118.0	31.8	0.072
Triglycerides (mg/dL)	139.6	99.5	141.1	123.6	0.872
Total cholesterol (mg/dL)	205.1	40.6	198.7	37.7	0.059
# Cigs/week	7.94	34.2	10.8	36.7	0.345
Female	0.58	0.49	0.64	0.48	0.191
Black	0.07	0.26	0.06	0.24	0.613
Diabetes	0.10	0.30	0.13	0.34	0.283
Hypertension	0.57	0.50	0.63	0.48	0.165
Global, global composite; VSOM, visual-spatial organization; ST, scanning and tracking; VM, verbal memory; WM, working memory; Similarities, WAIS similarities; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoproteins; LDL, low density lipoproteins. Means for dichotomous variable are proportions.					

m², $P = 0.001$), a lower eGFR at follow-up (62.4 mL/min/1.73 m² versus 67.9 mL/min/1.73 m², $P = 0.001$) and higher baseline SBP (133.0 mmHg versus 128.5 mmHg,

$P = 0.017$). The level of renal functioning at baseline was not associated with *change* in cognitive functioning for any of the cognitive measures.

Changes in renal function and changes in global cognitive performance

As noted previously, these change-over-time scores were derived by adjusting for baseline renal function and baseline global performance scores. Lower renal function was associated with lower adjusted cognitive performance at follow-up (representing cognitive decline from baseline) for each measure of the eGFR (MDRD, CKD-Epi, MCQ). For all models, a positive coefficient indicates a corresponding direction of change, such as that a greater decline in renal functioning is associated with a greater decline in cognitive performance.

The longitudinal associations between changes in renal functioning and changes in cognitive performance are log-linear; thus, in terms of global cognitive functioning, an individual with the eGFR of 90 mL/min/1.73/m² at baseline and follow-up would be expected to perform 0.10SD above the mean (54 percentile), whereas an individual with the eGFR of 90 mL/min/1.73/m² at baseline and 60 mL/min/1.73/m² at follow-up would be expected to perform 0.02 SD above the mean (51 percentile), and an individual with the eGFR of 60 mL/min/1.73/m² at baseline and 30 mL/min/1.73/m² at follow-up would be expected to perform 0.10 SD below the mean (46 percentile). Consequently, in terms of global cognitive functioning, our results are highly consistent across definitions of renal functioning. Across much of the observed range of the eGFR, a 30-unit decline in the eGFR is equivalent to ~7 years difference in age with regard to the rate of decline in global cognitive functioning.

Changes in renal function and changes in specific cognitive domains

The change in the eGFR was not statistically significantly associated with VSOM, ST or WM scores for any of the analyses performed (all *P*-values > 0.05). Findings for the other cognitive domains and abstract reasoning are summarized below. We present findings for renal functioning defined by MDRD, CKD-Epi and MCQ in Table 3 and below. Results for all covariates included in the multiple regression models are shown separately for MDRD (Supplementary Table S1), CKD-Epi (Supplementary Table S2) and MCQ (Supplementary Table S3). Any differences across definitions of renal function are considered below.

Verbal episodic memory. A greater decline in renal functioning was associated with a greater decline in VM performance (Table 3). Results were consistent across MDRD and CKD-Epi, but a statistically significant association was not found when the MCQ was used to define renal functioning. In terms of VM, an individual with the eGFR of 90 mL/min/1.73/m² at baseline and follow-up would be expected to perform 0.11 SD above the mean (54 percentile), whereas an individual with the eGFR of 90 mL/min/1.73/m² at baseline and 60 mL/min/1.73/m² at follow-up would be expected to perform 0.00SD above the mean (50 percentile), and an individual with the eGFR of 60 mL/min/1.73/m² at baseline and 30 mL/min/1.73/m² at follow-up would be expected to perform 0.16 SD below the mean (44 percentile). Across much of the range of

Table 3. Change per unit increase and *P*-values for change in domains of cognitive functioning

Measure of change in eGFR	Global			Verbal memory			Similarities		
	Change per unit increase	95% CI	<i>P</i> -value	Change per unit increase	95% CI	<i>P</i> -value	Change per unit increase	95% CI	<i>P</i> -value
MDRD	0.21	0.04–0.38	0.018	0.28	0.02–0.54	0.038	0.36	0.04–0.67	0.025
CKD-Epi	0.21	0.05–0.37	0.012	0.29	0.05–0.54	0.018	0.31	–0.01–0.63	0.055
MCQ	0.22	0.02–0.41	0.028	0.23	–0.04–0.50	0.092	0.22	–0.12–0.57	0.203
>3 mL/min/1.73 m ² per year	0.08	0.01–0.15	0.021	0.07	0.05–0.17	0.149	0.14	0.02–0.26	0.018

Note: Comparison for >3 mL/min/1.73 m² per year is ≤3 mL/min/1.73 m² per year. Unit of increase for independent variable (eGFR) is change in logged eGFR (ln(mL/min/1.73 m²)). Models also adjust for baseline cognitive functioning, baseline renal functioning, age, sex, education, race, systolic blood pressure (mmHg), diabetes mellitus, body mass index (kg/m²), high density lipoproteins (mg/dL), total cholesterol (mg/dL) and # cigarettes/day. All coefficients have been scaled to represent the association between greater renal impairment and decline in cognitive functioning.

eGFR values, they suggest that a 30-point decline in the eGFR is equivalent to ~7 years difference in age on the rate of a decline in VM.

Similarities. A greater decline in renal functioning was associated with a greater decline in abstract reasoning performance only when renal functioning was defined by MDRD. In terms of Similarities, an individual with the eGFR of 90 mL/min/1.73/m² at baseline and follow-up would be expected to perform 0.14 SD above the mean (56 percentile), whereas an individual with the eGFR of 90 mL/min/1.73/m² at baseline and 60 mL/min/1.73/m² at follow-up would be expected to perform at the mean (50 percentile), and an individual with the eGFR of 60 mL/min/1.73/m² at baseline and 30 mL/min/1.73/m² at follow-up would be expected to perform 0.07 SD below the mean (47 percentile). Across much of the range of eGFR values, they suggest that a 30-point decline in the eGFR is equivalent to ~6 years difference in age for abstract reasoning.

In a secondary set of analyses, we evaluated whether additional covariates [depressed mood using clinically relevant depressive symptomatology on the Center for Epidemiologic Studies Depression scale [34], weekly alcohol consumption (ounces), the presence of APOE ε4 allele and cardiovascular disease] should be added to the regression models using a forward stepwise procedure with $\alpha = 0.05$. None of these variables significantly improved the model. We also conducted a series of sensitivity analyses replacing: SBP with DBP or the diagnosis of hypertension; and HDL with LDL or triglycerides. The number of associations with the eGFR changing between significance and non-significance (5) was consistent with what would be expected by chance.

Clinically relevant decline in renal functioning and cognitive change

In addition to treating renal functioning as a continuous variable, we also estimated models using a dichotomous indicator of clinically relevant change in renal functioning in addition to baseline cognition and renal functioning. As can be seen in Table 3, clinically significant decline in renal functioning was associated with a significant decline in global cognitive functioning and Similarities. Individuals experiencing a clinically significant decline in renal functioning would be predicted to perform 0.08 SD lower on global cognitive functioning and 0.14 SD lower on similarities than individuals with similar characteristics who did not experience a clinically significant decline in renal functioning. There were no associations with clinically significant declines in renal functioning and VSOM, VM, WM or ST.

We note that baseline eGFR is higher in the group experiencing clinically significant change. Our results do not appear to be consistent with regression to the mean given that clinically significant change in renal functioning was not associated with change in cognitive functioning and because all models were adjusted for baseline renal and cognitive functioning. Our results are identical regardless of whether we model change score or follow-up adjusting for baseline scores.

Further baseline eGFR is virtually uncorrelated with the extent of change in renal functioning.

DISCUSSION

Associations between more rapid decline in eGFR and more rapid decline in cognitive performance over an average of 5 years were seen for Global Cognitive Functioning, VM and Similarities (abstract reasoning). Associations between eGFR and global performance have been reported in previous longitudinal studies but with the MMSE [18]. The MMSE is a useful screening device for dementia but is less sensitive than the measures of cognitive performance in the present study in persons free from dementia and stroke. Moreover, while individual items (questions) on the MMSE assess attention, language, calculation and recall for memory these individual items do not assess other important specific abilities, particularly executive functioning [35, 36], nor does the MMSE have high specificity with regard to specific cognitive abilities and domains (collections of abilities). It is known that the MMSE has a low ceiling of measurement and thus is more effectively used to detect change-over-time in less-educated and very elderly individuals; it lacks specificity. It simply does not tap the range of abilities measured by our global composite score [35]. The telephone interview lacks specificity because there are only six items. The reliability and validity of cognitive testing instruments are a direct function of the number and breadth of the questions on the test [37].

The two specific cognitive domains that declined longitudinally in association with a decline in the eGFR were Similarities and VM. Similarities, a measure of verbal abstract reasoning, is highly correlated with the verbal ability scale of the Wechsler Adult Intelligence Scale [29] and its other constituent measures. The VM composite is, in our study, indexed by measures of new verbal learning and immediate and delayed verbal memory for standardized reading material.

The levels of decline on these tests were modest and clearly do not reach the level of clinically significant cognitive declines such as may be seen in patients undergoing dialysis [38]. Modest decline over time was also seen in relation to lower renal function in the NOMAS study [6], which followed 2172 subjects (mean age 75 years) for a period of 2.9 years on a 6-point telephone interview scale. For each 0.1 mg/dL increase in baseline sCR, telephone interview scores declined an average of 0.04 points per year while the decline was 0.023 point per year for age. The authors conclude that for 60–90 mL/min CCL and eGFR categories, declines in performance were equal to ~8 years of aging. For the global composite score in our study, the difference in cognitive functioning associated with a decline of 30 mL/min/1.73/m² translates into approximately a 0.10 SD or 5 percentile difference. However, a decline of 0.10 SD is epidemiologically important as the follow-up period of 5 years was relatively short. Examining decline in performance from a different perspective, the influence of a 30-unit decline in the eGFR is equivalent to decline associated with an additional 6 years of age. While decline in cognition of this magnitude may not be of immediate concern

to the individual patient, it is clearly a concern at the population level as an estimated 7.5 million persons in the USA alone have moderate renal disease [39]. Modest changes in cognitive performance over 5 years are observed with hypertension and with higher systolic and diastolic BP (mmHg) as independent variables, but over many years, decline may continue in a progressive fashion, leading to greater cognitive impairment [40, 41].

The relatively modest decline in cognitive functioning may relate to early diagnosis and good quality care. Community physicians have been associated with the MSLS longitudinal study from the beginning. Following medical examination and cognitive testing each participant received a medical report including laboratory results and was instructed to consult her or his physician. While there was no evidence of significant improvement in BP and other indicators of cardiovascular health, neither was there a change for the worse in these measures; in fact, there was evidence for improvement in total cholesterol (from 202.8 to 187.1 mg/dL, $P < 0.0001$). Our findings that the eGFR at baseline was not associated with decline over time in cognitive performance, but decline in renal function was, are consistent with a previous study employing a large ($n = 7839$) sample [19].

The modest magnitude of association between declines in renal functioning and cognitive declines reported in this paper are typical of what is seen when BP and hypertension are related to cognitive performance changes over time [41]. Modest association with cognition is essentially good news as it indicates that even after decline begins, there is adequate time to intervene and prevent conversion from kidney disease to disease requiring dialysis.

It is well known that major CVD risk factors contribute to lower cognitive function, and it is possible that key risk factors such as hypertension could contribute directly to both renal functional decline and cognitive decline. We adjusted for a number of these risk factors (obesity, BP, lipids and DM) in our primary models, but the associations of renal functional decline with a decline in specific cognitive domains persisted. Moreover, secondary sets of analyses with additional CVD-RF did not alter relations between renal disease and cognitive performance seen using our primary regression model. Clearly, there are many other potential mediators between renal disease and cognitive performance that we did not adjust for due to the absence of the necessary data, e.g. covert brain vascular disease, and vascular calcification, anemia, pro-inflammatory cytokines, oxidative stress and endothelial dysfunction [8, 42–48].

Study limitations

We used eGFR data measured at two time points only, but this is consistent with previous community-based studies including the HOP2 trial [8, 43, 44, 49–51].

The MDRD formula for the calculation of the eGFR has not been validated for eGFRs >60 mL/min/1.73 m², but the use of other methods of calculating eGFR and the inverse of sCR (Supplementary Table S4) led to similar conclusions. In addition, the fact that individuals retained at follow-up had higher cognition means that these results may have

underestimated the association between cognitive decline and decline in renal function; however, Heckman selection models did not suggest bias because our models adjusted for the strongest predictors of non-response, but the possibility of bias cannot be further ruled out. The absence of hemoglobin and urine albumin determinations and the lack of standardization of sCR values are limitations resulting from the fact that the MSLS was not originally designed to specifically study kidney disease and cognitive functioning. Kidney disease became a more prevalent comorbidity as our study participants grew older. Our subjects are relatively highly educated and persons lost to the study from attrition were less able cognitively, and in generally poorer health. Consequently, we may have underestimated the magnitude of relations between renal function and change in performance that occur in a higher risk population. We cannot definitively conclude that change in renal functioning is causing changes in cognitive functioning. However, theory does suggest that individuals who experience a greater decline in renal functioning should experience greater declines in cognition and this is what we observe here after adjusting for relevant covariates. The findings are statistically significant and of importance for the population but do not rise to the level of clinically significant decline. This has been the case in many studies of the association between CVD-RF and cognitive performance [52, 53].

Study strengths

The strengths of our study included are as follows: (i) a community-based sample that was not selected for kidney disease; (ii) data on CVD risk factors except for alcohol and cigarette smoking was based on objective measurement or, in the case of stroke, self-report and confirmation by records or hospitalization. Unlike previous studies, measures of global ability and specific cognitive domains (collections of like abilities) were based on multiple tests measuring those constructs. We are thus able to describe skills that show decline over ~4.5–5 years and thus should be monitored carefully in the clinical setting.

Perspectives

It is encouraging to find, in this and other longitudinal studies, that *cognitive* decline associated with declines in renal function over 5 years is modest and does not reach a level of clinical significance, although the underlying associations could potentially be somewhat larger than observed here because loss-to-follow-up may have restricted the range of change in cognitive and renal functioning observed. In the present study, we reach this generalization from results for global composite scores, and cognitive domain composite scores each based on multiple tests. Results suggest that even clinically relevant declines in renal functioning are unlikely to interfere with understanding of the disease or ability to comply with treatment regimens associated with modest kidney disease. Stated differently, overall, there is a window of opportunity to treat the disease free from issues stemming from major cognitive impediments. On the other hand, no amount of cognitive decline is acceptable either within-

individuals or in a population of individuals and thus early diagnosis and treatment of kidney disease is very important.

SUPPLEMENTARY DATA

Supplementary data are available online at <http://ndt.oxfordjournals.org>.

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CONFLICT OF INTEREST STATEMENT

None declared.

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