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Chronic kidney disease, creatinine and cognitive functioning

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Abstract

Background. Non-dialysis-dependent chronic kidney disease (CKD) is related to cognitive impairment. Previous studies have not explored the extent of impairment across multiple cognitive domains. We examined the range of specific cognitive abilities affected by CKD and whether the associations of CKD with cognition were eliminated by statistical control for cardiovascular disease correlates of CKD.

Methods. We performed a community-based cross-sectional study with 923 individuals free from dementia and end-stage renal disease. Two groups were defined based on estimated glomerular filtration rate (eGFR): eGFR <60 mL/min/1.73 m^2 versus eGFR ≥ 60 mL/min/1.73 m^2. Outcome measures were scores from multiple clinical tests of specific cognitive abilities. The GFR classifications and serum creatinine levels were related to measures of cognitive performance using logistic and linear regression analyses with three sets of covariates: (1) basic (age, education, gender and race); (2) basic+risk factors for cardiovascular disease (CVD) and (3) basic+risk factors for CVD+stroke.

Results. An eGFR <60 mL/min/1.73 m^2 was present in 142 (15.4%) individuals; the mean (SD) eGFR in this subgroup was 49.7 (10.7). CKD was related to lower cognitive performance despite adjustment for CVD risk factors (CVD-RF). Adjusting for CVD-RF and stroke, odds ratios and 95% confidence intervals associated with performing in the lowest quartile of the distribution of the Global, Visual–Spatial Organization/Memory and Scanning and Tracking scores for the eGFR < 60 group were 1.97 (1.25, 3.10); 1.88 (1.21, 2.93) and 1.83 (1.56, 2.87), $P < 0.01$ with eGFR $\geq$ 60 group as the reference group.

Conclusions. Global performance and specific cognitive functions are negatively affected early in CKD. Targeted screening for cognitive deficits in kidney disease patients early in their disease course may be warranted.

Keywords: cardiovascular disease; chronic kidney disease; cognitive performance; serum creatinine

Introduction

End-stage renal disease (ESRD) and less advanced stages of chronic kidney disease (CKD) are associated with cognitive impairment [1–10]. The relation between CKD and cognitive impairment is an important public health issue because the prevalence of CKD in the United States increased from 10% between 1988 and 1994 to 13% between 1999 and 2004, and may rise further in the future [11].

Prior studies examining CKD and cognitive function have reported an association of CKD with general cognitive function, incident dementia and functioning cognitive abilities related to verbal learning, visual attention, mental flexibility and executive functioning [5–10]. However, these studies either used clinic-based study samples, and thus have more limited generalizability or employed a limited battery of neurocognitive tests.

The mechanisms proposed as mediators of relations between kidney function and cognition are similar to those that have been advanced to explain relations between other risk factors for cardiovascular disease and cognition, e.g. atherosclerosis, clinical stroke, silent stroke, oxidative stress and white matter lesions [7,12,13]. A number of traditional risk factors for cardiovascular disease (CVD) including blood pressure, diabetes mellitus, body mass index (BMI), smoking and low-HDL (high-density lipoprotein) cholesterol have been identified as among the most important independent risk factors for the onset of kidney disease [14].

In the present study, we examined the relations of CKD and lower renal filtration function with a broad range of cognitive functions in a dementia-free community-based population. We examined these relations before and after adjustment for major CVD-RF [14] as well as for other variables that confound relations between CKD and cognition [15–17]. We hypothesized that modest attenuation of the magnitude of relations between CKD and cognition with adjustment for major CVD-RF would occur, but that significant associations would remain.

Methods

Sample and design

The data were obtained from the sixth wave of the Maine-Syracuse Longitudinal Study (MSLS), a community-based study of CVD-RF [18,19]. Participants were recruited from the Syracuse, NY, 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 creatinine were obtained for the first time.

Beginning with 1047 study participants, individuals were excluded in the following sequence: (1) data necessary to calculate eGFR were missing ($n = 82$); (2) dementia ($n = 9$); (3) active dialysis treatment ($n = 4$) and (4) under 40 years of age ($n = 29$). The final sample consisted of 781 participants with eGFR $\geq$ 60 mL/min/1.73 m^2 and 142 participants with eGFR<60 mL/min/1.73 m^2 (CKD group). The age exclusion was employed because of a major imbalance in age between the two eGFR groups when persons < 40 years old were included.

The clinical diagnosis of dementia was determined from cognitive data and medical records using the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [20]. 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 major impairment.

Procedures

The participants completed the Center for Epidemiological Studies Depression Scale (CES-D) [21] within 1 week prior to neuropsychological testing. 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 [18,19]. Serum creatinine (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 [22,23]. Our definition of CKD in this study does not include albuminuria.

Determinations of high-sensitivity C-reactive protein (CRP), serum vitamin B$_{12}$, total cholesterol, HDL cholesterol, LDL (low-density lipoprotein) cholesterol and glucose, homocysteine (Hcy) and standard ApoE genotyping were performed as previously described [18,19,24]. To be classified as anaemic, a diagnosis of anaemia or treatment for anaemia, as established by medical records, was necessary. Haemoglobin levels and complete blood count (CBC) were not available to the study, as we did not anticipate an examination of kidney function as a risk factor at the time the data were collected.

Mean systolic BP (SBP) and diastolic BP (DBP) were based on at least 15 BP measurements (5 sitting, 5 standing and 5 reclining). Hypertension was defined as SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg regardless of medication. Additional covariates used or considered in various analyses described later were as follows: race/ethnicity, defined as African Americans versus other, treatment with antihypertensive medications, treatment with anti-cholesterol medications, diabetes mellitus, body mass index (BMI, kg/m^2), self-report of number of cigarettes smoked per week, alcohol consumption (ounces per week), triglyceride levels, plasma homocysteine (Hcy), self-reported presence of CVD confirmed by medical records and/or treatment and stroke. Diabetes mellitus was defined by treatment with insulin, oral anti-diabetic agents or fasting glucose level of 126 mg/dL (7 mmol/L) or higher. CVD was defined as the presence of any one of the following: myocardial infarction (4.3%), coronary artery disease (8.1%), heart failure (2.5%), angina pectoris (6.0%) and transient ischaemic attack (3.7%) [16,17]. Stroke, defined as a focal neurological deficit of acute onset persisting more than 24 h, was based on self-report or medical records, confirmed by record review, hospitalization or both.

Cognitive tests and domains

The cognitive outcome measures were four relatively independent and theory-based composite scores that define the following cognitive domains: Verbal Episodic Memory, Visual–Spatial Organization and Mem-

Table 1. Descriptions of the cognitive tests contributing to each composite score indexing a cognitive domain[a]

Composite scores (domains) and tests that define them	Cognitive ability measured
Verbal Episodic Memory	
Logical memory—immediate recall[b]	Immediate memory, verbal
Logical memory—delayed recall[b]	Delayed memory, verbal
Hopkins Verbal Learning Test	Verbal learning and memory
Visual–Spatial Organization/ Memory	
Visual reproductions—immediate recall[b]	Immediate recall, visual memory, and visual–spatial problem solving
Visual reproductions—delayed recall[b]	Delayed recall, visual memory and visual–spatial problem solving
Matrix reasoning[c]	Abstract reasoning and pattern recognition
Block design[d]	Visual–spatial perception, organization and construction
Object assembly[d]	Speed of visual–spatial organization
Hooper Visual Organization	Visual–spatial organization; some demands on executive function
Scanning and Tracking	
Trail making A[e]	Visual scanning and tracking; concentration and attention
Trail making B[e]	Trails A plus demands on executive function abilities
Digit symbol substitution[d]	Psychomotor performance
Symbol search[c]	Visual processing speed
Working Memory	
Digit span forward[d]	Attention and concentration
Digit span backward[d]	Attention, concentration and working memory
Letter–number sequence[c]	Information processing while holding information in memory
Controlled Oral Word Associations	Verbal fluency and executive functioning
Similarities	Verbal intelligence and abstract reasoning

[a]The tests employed in each composite score/domain define the abilities measured by that domain. A general description of the cognitive processes required by each domain of functioning may be found in the text.
[b]Origin Wechsler Memory Scale—revised.
[c]Origin Wechsler Adult Intelligence Scale III.
[d]Origin Wechsler Adult Intelligence Scale.
[e]Origin Halstead–Reitan Neuropsychological Test Battery.

ory (VSOM), Scanning and Tracking and Working Memory. Briefly, Verbal Episodic Memory is required for learning and memory of oral or written material such as instructions. Visual–Spatial Organization and Memory is required for problem solving with respect to visual–spatial relationships. Scanning and Tracking requires attention and concentration and places demands on organization and planning (executive functioning). Working Memory requires holding information in short-term memory while manipulating the information needed to execute a task [25–29].

The number of composite scores and the tests [25–29] used to define each composite (domain of cognitive functioning) were based on principal components and orthogonal rotation analyses employed in previous studies with this sample [18,19] and confirmed in the present study. The 17 tests composing the composite scores (domains) are described in Table 1. Similarities, a measure of abstract reasoning, correlated nearly equally with each of the above domains and thus was treated as a separate measure and only included in the Global composite.

Where necessary, raw test scores were first normalized (log to the base 10 transformation) to achieve a normal distribution. Each individual's original (raw) test score was then transformed to a *z* score, a linear

transformation that allows all performance measures to be expressed in the same units of measurement (SD units) and to have a distribution of scores with mean = 0 and a SD = 1 [30]. Each individual's composite scores were the sum of the equally weighted [31,32] z scores making up the composite divided by the number of tests in the composite and then re-transformed to z scores as the final step. The Global score, based on all tests, was calculated in the same way. See Supplement 1 for more details on scoring.

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.

Statistical analyses

In the first set of analyses we compared the differences between the eGFR ≥ 60 and eGFR<60 groups using logistic regression analysis, thus permitting a determination of odds ratios associated with poor performance, operationally defined as a cognitive score on any of the outcome measures falling in the lowest quartile of the distribution of test scores. This criterion for relatively poor performance (cognitive deficit) has been used in previous studies, including publication of norms [33–35]. A person performing at an average level within the lowest quartile of our sample would have a z score 1.34 SD below the mean of the entire distribution of test scores (z = −1.34).

The distributions of eGFR did not meet requirements for linear regression analysis as a continuously distributed variable [36] despite various transformations. Moreover, while the four-variable MDRD study equation is reasonably accurate for assigning participants to GFR groups based on eGFR <60 and ≥60 mL/min/1.73 m² values, it is of limited accuracy in estimating eGFR at higher levels [22,23]. Thus, following the Cardiovascular Health Study [10], in the second set of analyses we employed a normalized distribution of creatinine (1/sCR) values in linear regression analyses relating renal insufficiency to cognitive performance. Because we adjusted for factors aside from renal function that are known to influence serum creatinine (i.e. age, gender and body mass index), the observed associations of 1/sCR with cognitive performance in these multivariate models can be interpreted as representing primarily the effects of renal filtration function. Using the general linear model (SAS version 9.1), multivariable regression analyses were performed separately for each independent variable.

The statistical models were based on the identification of independent predictors of new-onset kidney disease in the Framingham Heart Study [14], many of which are also hypothesized risk factors for neurocognitive deficit [15–17]. For each of the major analyses, i.e. linear regression using 1/sCR and the logistic regression analyses using GFR groups, sets of covariates were introduced in serial stepwise order: (1) basic model = age (years) + gender + education (years) + race; (2) basic + CVD-RF model = basic model + mean SBP + diabetes mellitus + BMI + HDL cholesterol + number of cigarettes smoked per day and (3) basic model + CVD-RF model + Stroke. Additional covariates described in the results section were employed in planned secondary sets of analyses.

Residual plots, absence of non-linear trends (P-values > 0.20) and a low Variance Inflation Factor, 1.14–1.50, [36,37] confirmed the appropriateness of the straight-line fit for 1/sCR and the absence of collinearity. However, Hcy was highly correlated with creatinine, Pearson's r = 0.43, and may be a proxy for renal disease. Thus, it was not included as a covariate in the analyses.

Results

Demographic, health and kidney function characteristics of our non-demented and well-educated cross-sectional, community-based sample of middle aged to elderly adults (60% women; 7.3% African American) are presented in Table 2. Participants with CKD were older, exhibited higher CRP, higher mean SBP, higher Hcy, lower HDL cholesterol, higher creatinine, consumed moderately less alcohol and there was a higher proportion of persons with diabetes and cardiovascular disease.

Table 2. Demographic and health characteristics of participants by level of renal function

Variable	eGFR ≥ 60 mL/min/1.73 m² (n = 781)		eGFR < 60 mL/min/1.73 m² (n = 142)		P-value
	Mean	SD	Mean	SD	
Age (years)	62.3	11.7	68.5	11.6	0.0001
Education (years)	14.6	2.7	14.2	2.7	0.1341
CRP (mg/L)	4.0	4.4	5.0	5.9	0.0152
Homocysteine (mmol/L)	9.5	3.3	13.2	4.8	0.0001
Total cholesterol (mg/dL)	202.0	39.7	202.6	42.6	0.8707
HDL cholesterol (mg/dL)	53.9	15.6	51.1	14.3	0.0424
LDL cholesterol (mg/dL)	121.0	33.3	119.7	34.6	0.6737
Mean SBP, exams 1–6 (mmHg)	131.2	19.0	137.5	20.6	0.0004
Mean DBP, exams 1–6 (mmHg)	73.1	10.6	73.8	11.4	0.4590
Cigarettes/day	1.3	5.3	1.2	4.5	0.9600
BMI (kg/m²)	29.4	6.0	29.9	6.0	0.4100
Alcohol (oz/week)	1.5	2.8	1.0	1.7	0.0222
Creatinine (mg/dL)	0.9	0.2	1.4	0.7	0.0001
eGFR (mL/min/1.73 m²)	83.4	14.3	49.7	10.7	0.0001
	Percent		Percent		
Women	58.2		63.8		0.2536
African American	7.3		7.3		0.8508
Diabetes mellitus	12.6		23.9		0.0002
ApoE-ε4	26.4		27.5		0.7848
Folate deficiency (>3 ng/mL)	0.3		1.4		0.1051
B₁₂ deficiency (<200 pg/mL)	3.3		4.2		0.6010
Depressed mood (CES-D > 16)	10.3		12.1		0.5249
Anaemia	1.7		4.2		0.0742
Stroke	2.3		6.4		0.0404
Cardiovascular disease[a]	13.6		26.1		0.0002

[a]Cardiovascular disease includes a diagnosis of myocardial infarction, coronary artery disease, heart failure, angina pectoris and transient ischaemic attack.

Table 3 summarizes the odds ratios associated with performance in the lowest quartile as a function of membership in the GFR< 60 group with GFR ≥ 60 serving as the reference group. With adjustment for the basic covariate set, significantly higher odds of poor performance were associated with membership in the GFR < 60 group for the Global, VSOM and Scanning and Tracking composites and Similarities (abstract reasoning). With adjustment for the Basic + CVD-RF and the Basic + CVD-RF + Stroke covariate sets, the same significant results were obtained except for a non-significant association of CKD with Similarities. There was only a modest attenuation of odds ratios with adjustment for the covariate sets. Thus, for example, odds of performance score in the lowest quartile for the Global Composite score were 2.27, 1.97 and 1.97, respectively with adjustment for the Basic, Basic + CVD-RF and the Basic + CVD-RF + Stroke covariate sets. Results for individual test scores are summarized in Supplement 2.

Risk of cognitive deficit for persons in the GFR < 60 group can be put in further perspective by comparing them with risk associated with diabetes mellitus, an established risk factor for neurocognitive deficit [38], using the Global Composite scores as an example. The odds ratio associated

Table 3. Results of logistic regression analysis showing odds ratios (OR) and confidence intervals (CI) for performing in the lowest quartile of cognitive scores for persons with GFR < 60 (GFR ≥ 60 is the reference group) and *P*-values for differences between groups

Cognitive measure	Basic model[a]			Basic + CVD-RF[b]			Basic + CVD-RF + Stroke[c]		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Global Composite	2.27	1.47, 3.52	0.0002	1.97	1.25, 3.09	0.0032	1.97	1.25, 3.10	0.0035
Visual–Spatial Organization and Memory	2.00	1.31, 3.07	0.0016	1.88	1.21, 2 .93	0.0051	1.88	1.21, 2.93	0.0052
Verbal Memory	1.37	0.91, 2.08	0.1319	1.24	0.81, 1.90	0.3145	1.26	0.82, 1.93	0.2947
Working Memory	1.38	0.91, 2.09	0.1285	1.20	0.78, 1.83	0.4088	1.21	0.79, 1.87	0.3810
Scanning and Tracking	2.01	1.30, 3.12	0.0018	1.83	1.17, 2.87	0.0086	1.83	1.56, 2.87	0.0094
Similarities (abstract reasoning)	1.58	1.01, 2.48	0.0475	1.39	0.87, 2.21	0.1665	1.38	0.87, 2.21	0.1738

[a]Covariates in the Basic model are age, sex, education and race.
[b]Covariates in the Basic + CVD-RF model are age, sex, education, race, diabetes, SBP, BMI, cigarettes/day and HDL.
[c]Covariates in the Basic+ CVD-RF + Stroke model are age, sex, education, race, diabetes, SBP, BMI, cigarettes/day, HDL and stroke.

Table 4. Summary of *P*-values describing the significance of the regression coefficients relating creatinine to the cognitive measures and the difference (decrement) in performance (*z* scores) associated with an increment in the creatinine level from 1 to 2 mg/dL

Cognitive measure	Basic model[a]		Basic + CVD-RF[b]		Basic + CVD-RF + Stroke[c]	
	P-value	2 vs 1 mg/dL	*P*-value	2 vs 1 mg/dL	*P*-value	2 vs 1 mg/dL
Global Composite	0.009	−0.1480	0.031	−0.1207	0.040	−0.1152
Visual–Spatial Organization and Memory	0.010	−0.1551	0.026	−0.1338	0.576	−0.0377
Verbal Episodic Memory	0.373	−0.0600	0.527	−0.0426	0.028	−0.1327
Working Memory	0.117	−0.1088	0.265	−0.0774	0.280	−0.0752
Scanning and Tracking	0.009	−0.1506	0.023	−0.1303	0.042	−0.1163
Similarities (abstract reasoning)	0.148	−0.0933	0.301	−0.0666	0.577	−0.0329

[a]Covariates in the Basic model are age, sex, education, and race.
[b]Covariates in the Basic + CVD-RF model are age, sex, education, race, diabetes, SBP, BMI, cigarettes/day and HDL.
[c]Covariates in the Basic + CVD-RF + Stroke model are age, sex, education, race, diabetes, SBP, BMI, cigarettes/day, HDL and stroke.

with diabetes for deficit on the Global Composite score was 1.60 (95% CI = 1.02, 2.51); the odds ratio associated with low eGFR was considerably higher, at 2.27 (95% CI = 1.47, 3.52).

Table 4 summarizes the results of linear regression analyses employing 1/sCR as the predictor. In order to make the regression coefficients meaningful in terms of specific creatinine levels, they are expressed as the difference in performance levels (*z* scores) between 1 and 2 mg/dL creatinine (as predicted by the regression equation). The minus signs indicate a decrement in performance with an increase in creatinine from 1 to 2 mg/dL. Regardless of adjustment for the various covariates, higher levels of sCR were associated with lower cognitive performance levels for the Global, VSOM and Scanning and Tracking composites for all three sets of covariates. For example, comparing participants with creatinine levels of 1.0 mg/dL versus 2.0 mg/dL, with adjustment for age, education, gender and race, the participant with the higher creatinine level would be predicted to score −0.15 SD (15% of 1 SD lower) on the VSOM composite score (Table 4).

Composite scores do not have raw (original) scores, but the results for individual tests can be expressed as raw scores and *z* scores. Thus, the meaning of the levels of deficit expressed in *z* scores (units of SD) in Table 4 can be illustrated by comparing predicted *z* scores and original raw test scores for a test that contributed significantly to the VSOM score in the 1/sCR analysis, i.e. the Object Assembly

Test. The predicted decrement in performance for persons with 2 mg/dL creatinine versus 1 mg/dL creatinine is 1.86 raw score points (*z* = −0.20 or 20% of 1 SD).

The following covariables were added to the basic model for the logistic and linear regression analyses described above: depressed mood (CES-D > 16) [21], CRP, alcohol consumption, ApoE genotype, anti-hypertensive drugs (yes/no), anti-cholesterol drugs (yes/no) and cardiovascular disease (yes/no). The pattern of significant results was the same as that previously reported (Tables 3 and 4). Further, the pattern of results was unchanged when either mean DBP or hypertension were substituted for SBP and when total cholesterol, LDL cholesterol or triglycerides were substituted for HDL in the Basic + CVD-RF covariate set.

Discussion

The odds of performance decrement in the Global, VSOM and Scanning and Tracking performance domains of functioning were significantly higher for those with low eGFR regardless of the statistical models employed. Similarly, higher levels of creatinine were associated with lower levels of performance for the Global, VSOM and Scanning and Tracking domains even after adjustment for demographics, cardiovascular risk factors and stroke.

Poor performance on the Global score is consistent with previous studies employing the MMSE [5] or a six-item

telephone screening instrument [2] and reflects the general trend across all measures for lower levels of performance in relation to higher creatinine levels and membership in the GFR < 60 group. However, it is important to note that the Global Composite score is not directly comparable to the MMSE or telephone screening measures. The MMSE was designed to be a measure of mental status and is subject to significant ceiling effects (most test questions are insufficiently difficult) in persons who are free from dementia. While particularly useful for large population studies of kidney disease, the six-item screening instrument is a relatively insensitive measure of cognitive function and does not test specific cognitive abilities [2].

Our findings demonstrate a decreased performance level within specific domains of cognition in association with modestly lower renal function. For example, the risk of performing in the lowest quartile for Global, VSOM and Scanning and Tracking is doubled in the presence of GFR < 60 and approaches this level with adjustment of the covariates. Diabetes is well established as a risk factor for cognitive impairment [33,38], but the odds ratios associated with performance in the lowest quartile for the Global Composite score were less for diabetics (OR = 1.60) than for persons in the GFR<60 group (OR = 2.27). Given the high prevalence of CKD in the USA, the public health implications of moderate decrements in performance for CKD patients are considerable [11].

Neuropathological changes in the brain that parallel changes in kidney have been posited as mechanisms explaining relationships between CKD and cognition [34]. These include atherosclerosis, microvascular disease, clinical stroke, silent stroke, oxidative stress and white matter lesions [7,12,13,39,40]. For example, in a recent study of homebound elderly individuals, albuminuria was associated with lower levels of executive function ability and with white matter hyperintensities and white matter volume [41].

Disease-related depression can contribute to lower cognitive performance but our results were robust to statistical adjustment of depressive symptoms. The absence of neuroimaging studies in the present investigation prevents us from inferring which specific areas of the brain are associated with the observed cognitive deficits. However, it is clear that specific cognitive domains are more vulnerable to moderate CKD, i.e. VSOM and Scanning and Tracking abilities. Deficits in VSOM manifest in deficits in visual pattern recognition, immediate and delayed memory for visual materials, and organization and problem solving in a visual–spatial context [28,29]. Deficits in Scanning and Tracking reflect lowered ability in attention, concentration, visual processing speed, psychomotor performance and planning resulting in difficulty with completing an organized visual search [28,29]. In contrast, neither Working Memory nor Verbal Episodic Memory was significantly associated with CKD. Patients exhibiting the pattern of cognitive deficits seen in this study would not be expected to have difficulty in remembering well-organized specific instructions for medications and fluid and dietary restrictions presented verbally or in writing, but may experience difficulty when challenged by higher order demands on visual–spatial memory and organization, concentration, scanning and tracking, psychomotor and executive skills, e.g. aviation and air traffic control.

There are two broader concerns: (1) modest cognitive deficits, especially deficits in visual–spatial skills, are risk factors for later, more serious impairments in cognition, including dementia [42,43,44] and (2) more severe cognitive impairment extending to memory may be seen in more advanced CKD [13,45]. Earlier studies have shown that cognitive impairment is a complication of advanced pre-ESRD and ESRD patients on maintenance dialysis [1–6,13]. Our results indicate that cognitive function is reduced even in patients with only moderate reductions in GFR, and that visual–spatial organization and memory and scanning and tracking functions are particularly vulnerable. Thus awareness and treatment of cognitive deficits should begin early in the progression of kidney disease.

Limitations

The absence of haemoglobin determinations and standardization of creatinine values are limitations because the study was not designed to delineate the association of kidney disease with cognition at the time of data collection. However, our community-based study permitted us to examine relationships between CKD and cognition in a non-clinical sample, unselected for kidney disease and with blinded testing procedures.

Our participants were relatively highly educated. Education is protective of cognitive performance [46,47]; consequently, our findings may underestimate the magnitude of relations between renal function and cognition. We used eGFR data obtained on only one occasion to define CKD. However, our eGFR criterion was consistent with previous community-based studies and the Hope 2 trial that defined CKD in this manner [7–9,48]. Acute decrements in renal function would not be anticipated in our relatively healthy community-based study participants. Finally, our study was cross-sectional and thus does not allow us to determine causal directions between predictor and covariates.

Strengths

Strengths of our study include (1) a community-based sample; (2) data on CKD and multiple cardiovascular risk factors and (3) an extensive battery of neuropsychological tests organized into theoretically relevant cognitive domains.

Perspectives

Hopefully our investigation will encourage much needed longitudinal studies of cognitive decline in mild renal disease. Improvements in cognition following kidney transplant [45] offer encouragement for intervention strategies at the ESRD stage, but it is clear that early recognition and treatment of modest cognitive deficits in CKD is important [49] because patients with modest deficits are at risk for the more serious cognitive impairments typical of ESRD.

Supplementary data

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

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