Published in final edited form as:

Am J Nephrol. 2014 ; 40(3): 200–207. doi:10.1159/000367669.

Kidney disease and cognitive function: African American-Diabetes Heart Study MIND

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Abstract

Aims—Albuminuria and reduced estimated glomerular filtration rate (eGFR) associate with poorer cognitive performance in European-ancestry populations with advanced nephropathy; relationships in African Americans (AAs) with type 2 diabetes (T2D) are less clear. Tests of cognitive performance, urine albumin:creatinine ratio (UACR), and CKD-EPI eGFR were measured in unrelated AAs with T2D to determine relationships.

Methods—Cross-sectional analysis of 263 unrelated AAs with T2D recruited in the African American-Diabetes Heart Study (AA-DHS) MIND. Global cognitive function (mini-mental state exam [3MSE] and Montreal Cognitive Assessment [MoCA]), memory (Rey Auditory Verbal Learning Test [RAVLT]), executive function (Stroop, verbal fluency for animals, and Digit Symbol Copy [DSC]), UACR, and eGFR were determined. Relationships between cognitive tests and renal parameters were assessed using multivariate models, adjusted for age, gender, body mass index, hemoglobin A1c, level of education, hypertension, and LDL cholesterol.

Results—Participants had a mean±SD age of 60.2±9.7 years, 62.7% were female, T2D duration was 14.3±8.9 years, eGFR 86.0±23.2 ml/min/1.73m^2, and UACR 155.8±542.1 (median 8.1) mg/g. In adjusted models, higher UACR was associated with worse 3MSE (p=0.014), MoCA (p=0.0089), DSC (p=0.0004), Stroop performance time (p=0.003), Stroop errors (p=0.032), and

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Conflict of Interest Statement: The authors have no conflicts of interest to disclose.

Financial Disclosure: This work was supported by RO1 NS075107 (JD, JAM, BIF), NS058700 (DWB), and DK071891 (BIF).

Stroop interference (p=0.026). Higher eGFR was associated with better performance on DSC (p=0.0071).

Conclusions—In AAs with T2D, albuminuria and eGFR were associated with cognitive function, even in mild kidney disease. These data stress the need for interventions to prevent cognitive decline well before the late stages of kidney disease.

Keywords

albuminuria; glomerular filtration rate; cognition; type 2 diabetes; African Americans; kidney disease

Introduction

Chronic kidney disease (CKD) and end-stage kidney disease (ESKD) are associated with impaired cognitive performance.[1–5] Although CKD-related cerebrovascular and cardiovascular disease (CVD) contribute, uremic toxins are likely to directly impact cerebral structure and function.[6] Most published reports focus on populations of European ancestry with advanced CKD; far less is known about those of recent African ancestry. Relative to European Americans (EAs), African Americans (AAs) exhibit different biologic risk for nephropathy, calcified atherosclerotic plaque, and osteoporosis.[7] The impact of albuminuria and estimated glomerular filtration rate (eGFR) on cognitive function could vary with ancestry and ethnicity. In addition, subjects with early stage kidney dysfunction manifested by low level albuminuria and mildly reduced eGFR are underrepresented in published reports.

An extensive battery of cognitive tests was performed in African American-Diabetes Heart Study MIND (AA-DHS MIND) participants.[8] These individuals previously underwent intensive phenotyping for computed tomography to determine subclinical calcified atherosclerotic plaque for CVD, bone mineral density, and adipose tissue volumes.[9] Simultaneous with the current study, glycemic control and markers of kidney disease (and other metabolic parameters) were assessed. The present analyses focus on urine albumin:creatinine ratio (UACR) and eGFR in 263 AA-DHS MIND participants to assess relationships between mild and generally asymptomatic kidney disease and cognitive performance in the understudied AA population with type 2 diabetes (T2D).

Methods

Unrelated AAs with T2D were recruited and cognitive testing performed at Wake Forest School of Medicine (WFSM) in the family-based Diabetes Heart Study (DHS)-MIND [10] and the AA-DHS MIND.[8] DHS is a cross-sectional study of European American (EA) and AA families with siblings concordant for T2D. AA-DHS was initiated after DHS and enrolls unrelated AAs with T2D. The objectives of the two MIND studies are to improve understanding of risk factors for cognitive impairment in T2D and assess cerebral architecture using MRI, contrasting results in EAs with those in AAs. This analysis included 263 unrelated AAs, obtained by selecting all unrelated AA-DHS MIND participants (n=261) and one AA sibling from each of two DHS-MIND sib pairs concordant for T2D.

Eligible participants were AAs with a diagnosis of T2D after age 30 years and absence of diabetic ketoacidosis in the setting of: (a) active medical treatment for diabetes (insulin and/or oral hypoglycemic agents), (b) fasting blood sugar ≥126 mg/dL or non-fasting blood sugar ≥200 mg/dL, or (c) hemoglobin (Hb) A1c ≥6.5%. This study was approved by the WFSM Institutional Review Board, and it adhered to the Declaration of Helsinki. Informed consent was obtained from all individuals. In addition to recording medical histories, vital signs, and current medications, participants had fasting measures of serum creatinine, blood urea nitrogen, thyroid stimulating hormone (TSH), and vitamin B12, and a morning urine sample for albumin and creatinine determinations, all typically used in the clinical setting (LabCorp; Burlington, NC). Examinations were performed in the WFSM Clinical Research Unit. eGFR was computed with the creatinine-based CKD-Epidemiology (CKD-EPI) equation.[11]

Cognitive testing

The cognitive battery was chosen to represent a broad variety of cognitive domains, with emphasis on executive function due to the known association between vascular cognitive impairment and executive dysfunction.[12] Interviewers were trained, certified, and subsequently assessed for quality control in all cognitive tests by a single investigator (KMS). Global cognition was assessed with the modified mini-mental state examination (3MSE)[13] and the Montreal Cognitive Assessment (MoCA).[14] The Rey Auditory Verbal Learning Test (RAVLT)[15] was used to assess learning and memory. Executive function was assessed with the WAIS-III Digit Symbol Copy (DSC)[16] (measuring speed of processing and working memory), the Stroop test[17–19] (measuring response inhibition), and verbal fluency for animals. Stroop interference was calculated as the (time to complete Stroop 3) – (time to complete Stroop 2). Depression and anxiety, possible confounders in the relationship between cognitive function and CKD, were assessed with the Center for Epidemiologic Studies Depression scale CESD[20] and the Brief Symptom Inventory BSI-Anxiety[21], respectively. Testing was performed in a quiet room after a light morning snack. The cognitive battery took approximately 45 minutes to complete.

Statistical Analyses

Generalized linear models (GLM) were fitted to test for associations between renal parameters (independent variables) and measures of cognitive function (dependent variables). Renal parameters included UACR and eGFR as continuous variables. Negative binomial regressions were fitted to account for the level of over dispersion present. The logarithm function was used to link the mean of the outcome with the predictors included in the model. Models were run unadjusted and successively adjusted for age, gender, body mass index (BMI), severity of T2D (HbA1c), level of education (1=less than high school, 2–5=number of years in high school [5=graduate], 6–9 number of years in college [9=graduate], 10=post-graduate degree), hypertension status, and LDL-cholesterol. The effect of age on the cognitive function outcomes was fitted using cubic B-splines [22] coded in the R.[23] Parameter estimation was performed using the maximum likelihood approach, and all models reached convergence. Diagnostic tests based on the deviance residuals were performed to ensure that the model assumptions were met. Adjusted results refer to the model testing for association between renal and cognitive variables after adjustment for all

seven covariates. Effect sizes associated with increases of 100 mg/g in UACR and 10 ml/min/1.73m^2 in eGFR are provided. These effects were obtained by computing the exponential of the change in the predictors, which provides a rate that was then applied to the overall mean of the outcome. The overall effect is expressed as the change in the overall mean of each outcome attributable to the increase in the predictor. Finally, three-levels of outcome were assessed: normal kidney function without albuminuria (eGFR ≥60 ml/min/1.73m^2 and UACR <30 mg/g), reduced eGFR (<60 ml/min/1.73m^2), and elevated UACR (>30 mg/g) with normal kidney function (eGFR >60 ml/min/1.73m^2). This analysis was performed to discriminate the contribution of low eGFR and high UACR on cognitive outcomes in CKD, while attenuating loss of power.

Results

Table 1 contains demographic and laboratory data on all 263 participants. Participants had a mean±SD age of 60.2±9.7 years and 62.7% were female. T2D duration was 14.3±8.9 years, eGFR 86.0±23.2 ml/min/1.73m^2, UACR 155.8±542.1 mg/g (median 8.1 mg/g), TSH 2.0±1.6 milli-international units/L, and vitamin B12 level 690.0±417.3 pg/mL. Albuminuria defined as a UACR >30 mg/g was present in 25%, and defined as a UACR >300 mg/g in 9%. Levels of eGFR, in ml/min/1.73m^2, were >90 (N=117, 44.2%); 60–89 (N=116, 43.8%); 30–59 (N=30, 11.2%) and 15–29 (N=2, 0.8%). When defining kidney disease as a dichotomous trait based on an eGFR <60 ml/min/1.73m^2 and/or UACR >30 mg/g, 33.2% (N=91) of the sample had kidney disease. Of these 91 participants, 51 had CKD (abnormal renal parameters of >3 month duration), 16 had only a single study visit and lacked additional lab data, and 17 were classified with kidney disease present only at the AA-DHS MIND visit (prior and/or subsequent lab data failed to confirm kidney disease).

Table 2 presents the results of cognitive tests in those with and without kidney disease defined as a UACR ≥30 mg/g and/or eGFR <60 ml/min/1.73m^2. Participants with kidney disease had lower scores on tests of global cognitive functioning, though only the MoCA (not 3MSE) was statistically significant. Participants with kidney disease also had poorer executive function than those without, as measured by the DSC and the Stroop task. There was no significant difference in memory performance, depressive, or anxiety symptom scores between those with and without kidney disease.

Table 3 contains the results of unadjusted and fully-adjusted (for age, sex, BMI, HbA1c, level of education, hypertension status, and LDL-cholesterol) models for continuous relationships between parameters of kidney disease and cognitive tests. In fully adjusted models, higher UACR was negatively associated with higher 3MSE (p=0.014) and MoCA (p=0.0089) scores. There was no association between UACR and performance on the RAVLT or verbal fluency task. However, higher UACR was associated with worse executive function as evidenced by slower Stroop 3 times (p=0.003), more Stroop 3 errors (p=0.032), and Stroop interference (p=0.026), as well as poorer performance on the DSC (p=0.0004). This Table also suggests that every 100 mg/g higher UACR was associated with 3.21, 0.48 and 1.47 points lower in the mean 3MSE, MOCA and DSC scores, respectively. It also corresponds to an increase of 0.49 and 1.40 seconds in the processing time of Stroop 2 and Stroop 3. In the fully adjusted model, better kidney function assessed using the CKD-

EPI eGFR was associated with better DSC (p=0.007) performance. Every 10 ml/min/1.73m^2 higher eGFR was associated with a 1.23 points better DSC performance. No association was detected between eGFR and global cognitive performance or verbal memory in our participants.

Results of the three-level analysis contrasting 172 participants lacking evidence of kidney disease with: (a) 59 participants with a UACR >30 mg/g and eGFR >60 ml/min/1.73 m^2, and (b) 32 participants with an eGFR <60 ml/min/1.73 m^2 are presented in Table 4. Here, isolated albuminuria was significantly associated with longer Stroop 3 time and Interference, and with poorer DSC performance. Reduced eGFR was associated with poorer DSC performance and a trend toward more Stroop 3 errors (p=0.06).

Discussion

Several recent reports have explored the risk of cognitive impairment in patients with CKD and ESKD, as well as assessed the effects of intensive daily and nightly hemodialysis on cognitive impairment in ESKD.[24,25] The present analyses contain results of the most extensive cognitive battery employed in the understudied AA population with T2D and kidney disease to date. Greater albuminuria was associated with statistically significant worse performance on measures of global cognitive function (3MSE and MoCA), as well as speed of processing and executive function measured by DSC, Stroop 3 time, Stroop 3 errors and Stroop interference. For eGFR, better kidney function was only associated with better executive function as measured by the DSC. It is notable that markers of kidney function are associated with cognition, even though our participants have mild kidney disease.

A report in 160 patients with CKD (80 with Stage 3–4 CKD; 80 with ESKD) demonstrated that 3MSE, Trails B (Trailmaking text B), and immediate and delayed California Verbal Learning Trial (CVLT) scores were significantly lower in those with ESKD versus those with CKD.[1] Scores were also significantly lower in CKD patients compared to published results in normal individuals. Only 26 of the patients with CKD were AA. Unfortunately, the Frequent Hemodialysis Network Trials (FHN) subsequently demonstrated that frequently performed in-center hemodialysis and nocturnal hemodialysis failed to improve executive function (primary outcome, Trails B) or global cognition (secondary outcome, 3MSE) in patients with ESKD.[4] Hence, we feel there may be value to shifting the focus to reducing cognitive impairment in subjects with earlier stages of CKD.

Four reports evaluated the effects of reduced eGFR on cognitive function; however only one of these included measures of UACR. Among 1,015 Heart Estrogen/Progestin Replacement Study (HERS) participants with pre-existing coronary artery disease, only 67 subjects were AA.[2] In HERS, lower MDRD eGFR associated with impairment in global cognition, executive function, language, and memory; a 15–25% increase in risk for dysfunction was seen for each 10 ml/min/1.73m^2 decline in eGFR. Two cognitive studies have been published in Chronic Renal Insufficiency Cohort (CRIC) participants. Yaffe et al. [26] assessed 825 CRIC participants greater than 55 years old, 367 were AA. After multivariate adjustment, subjects with lower MDRD eGFR had lower scores on most cognitive domains.

Relative to older CRIC subjects with eGFR 45–59 ml/min/1.73m^2, those with eGFRs <30 were more likely to have clinically significant cognitive impairment on global cognition, naming, executive function, attention, and delayed memory, but not category fluency. Kurella Tamura and colleagues reported CRIC baseline cognitive function based on the 3MSE; 3MSE scores >1 standard deviation below the mean defined cognitive impairment. [24] Among 3,591 CRIC participants with mean MDRD eGFR 43.4±13.5 ml/min/1.73m^2, 13% had cognitive impairment. After multivariate adjustment, participants with eGFR <30 ml/min/1.73m^2 had a 47% higher odds of cognitive impairment than did those with an eGFR 45–59 ml/min/1.73m^2; however, anemia was felt to be an important contributor. Adjusting for anemia fully corrected for the effects of reduced eGFR.

The population-based Reasons for Geographic and Racial Disparities in Stroke (REGARDS) study contained large numbers of AA (and other) participants lacking baseline cognitive impairment, assessing the effects of albuminuria and CKD-EPI eGFR on incident cognitive impairment.[3] Mean follow-up was 3.8 years in these 19,399 REGARDS subjects with measures of UACR and eGFR. The validated 6-item screen (score range 0–6) was used to assess cognitive impairment (impairment was defined as a score ≤4 at most recent follow-up). This screen is a validated test of global cognitive impairment that can be administered in person or by phone and includes recall and orientation items derived from the 3MSE. Compared to those with a baseline UACR <10 mg/g, those with UACR 30–299 and >300 mg/g faced 31% and 57% increase in risk for development of cognitive impairment, respectively. Although no difference in incident cognitive impairment was observed for baseline eGFR >60 versus <60 ml/min/1.73m^2, when stratifying based on UACR <10 mg/g, an eGFR <60 ml/min/1.73m^2 was associated with a 30% increased risk. The authors concluded that UACR and eGFR were complimentary, not additive, risk factors for incident cognitive impairment. In the setting of preserved kidney function, albuminuria was independently associated with incident cognitive impairment; when UACR was <10 mg/g, eGFR <60 ml/min/1.73m^2 was independently associated.

Results in the AA-DHS MIND were broadly consistent with those in REGARDS and other studies of patients with CKD. Our sample was limited to AAs with T2D, administered a more extensive cognitive battery than prior reports, and AA-DHS MIND subjects generally had milder degrees of kidney disease than other studies, particularly CRIC. Most of the prior reports focused predominately on subjects of European ancestry with advanced nephropathy. Although markedly reduced eGFR is known to impair cognitive function, AA-DHS MIND data revealed that in AAs even mild albuminuria and reduced eGFR have significant effects on cognitive function. It is unknown whether EAs exhibit the same relationships in the presence of mild kidney disease; this is being addressed by the DHS-MIND study. Participants in the AA-DHS also had generally good access to healthcare. This was evidenced by their level of blood pressure control and frequent use of statins and anti-hypertensive medications. Many AA-DHS MIND participants are Wake Forest Baptist Health employees or their relatives. Except for REGARDS, prior studies did not evaluate the effects of albuminuria on cognitive impairment. Limitations of this report are that all subjects had T2D and it is unknown whether results generalize to the non-diabetes affected AA population. In addition, we lack data on income levels. The study was cross-sectional and follow-up is planned to permit longitudinal assessment of changes in cognitive function

and parameters of kidney disease in the future. Longitudinal assessment will also provide the opportunity to examine additional risk factors that have been postulated, e.g. serum hemoglobin, [27] but which were not evaluated in the current study. As in REGARDS, only a single measure of UACR was used for the analysis. Finally, only 58 of 91 participants with kidney disease in this report had documented albuminuria and/or low eGFR for >3 months, the duration needed to define CKD.

Albuminuria exhibited strong inverse relationships with executive function and measures of global cognitive function in AAs with T2D; while eGFR exhibited direct relationships with executive function. A discriminatory analysis showed that isolated albuminuria was associated with longer Stroop 3 time, greater Interference, and poorer DSC performance; while reduced eGFR was associated with poorer DSC performance. Memory did not appear to be significantly impacted by mild reductions in eGFR or albuminuria. This would imply that participant's mild reductions in kidney function may have concomitant cerebral vascular changes predisposing to altered cognitive performance rather than suffering from cognitive changes due to accumulation of uremic toxins. These data reveal significant associations between presence of mild kidney disease and cognitive performance in AAs. Our results stress the importance of developing interventions to prevent cognitive decline well before ESKD and late stage kidney disease.

Acknowledgments

This work was supported by RO1 NS075107 (JD, JAM, BIF), NS058700 (DWB), and DK071891 (BIF). The sponsors had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Table 1

Demographics and laboratory results of the study sample

Variable	Full Sample (N=263)		Kidney Disease absent (N=172)		Kidney Disease present (N=91)		P-value*
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	60.2	9.7	60.3	9.5	60.5	9.8	0.79
Gender (Male)	98 (37.3%)		61 (34.5%)		37 (40.7%)		0.26
Education:							0.33
Less than a high school diploma	27 (10.3%)		15 (8.7%)		12 (13.2%)		
High school diploma	76 (28.9%)		48 (27.9%)		28 (30.8%)		
Some college or college diploma	115 (43.7%)		75 (43.6%)		40 (44.0%)		
Graduate Education	45 (17.1)		34 (19.8%)		11 (12.1%)		
Body Mass Index (BMI; kg/m^2)	34.1	7.9	34.0	8.2	34.1	7.7	0.61
Age of Diabetes Diagnosis (years)	45.9	11.0	46.2	11.2	45.5	10.8	0.51
Duration of Diabetes (years)	14.3	8.9	14.1	9.2	15.0	8.3	0.29
Systolic Blood Pressure (SBP; mm Hg)	131.4	18.5	128.7	17.0	136.0	20.5	0.01
Diastolic Blood Pressure (DBP; mm Hg)	75.6	11.0	73.9	9.4	78.2	12.6	0.03
Smoking:							0.88
Never	117 (44.7%)		76 (44.4%)		41 (45.1%)		
Past	91 (34.7%)		62 (35.7%)		29 (33.0%)		
Current	54 (20.6%)		34 (19.9%)		20 (22.0%)		
Hypertension (%)	87 (34.0%)		48 (27.0%)		39 (44.3%)		0.006
Lipid Meds (%)	93 (54.7%)		57 (51.4%)		36 (60.6%)		0.25
CKD-EPI eGFR (ml/min/1.73m^2)	86.0	23.2	91.7	17.9	75.3	28	5.9×10^{-5}
C-reactive Protein (mg/dl)	1.1	1.6	0.9	1.2	1.4	2.2	0.24
Glucose (mg/dl)	147.7	60.2	142.7	54.6	156.8	69.2	0.17
Urine albumin:creatinine ratio (mg/g)*	8.06	3.21–35.46	4.74	2.37–9.67	80.99	32.61–383.32	7.0×10^{-26}
Hemoglobin A1c (%)	8.2	2.2	7.7	1.7	9.0	2.6	7.1×10^{-4}
HDL-cholesterol (mg/dl)	47.2	11.9	48.2	11.4	46.1	12.6	0.09
LDL-cholesterol mg/dl)	109.0	37.2	102.3	33.5	121.6	41.8	0.004

Variable	Full Sample (N=263)		Kidney Disease absent (N=172)		Kidney Disease present (N=91)		P-value*
	Mean	SD	Mean	SD	Mean	SD	
Serum creatinine (mg/dl)	1.0	0.3	0.9	0.2	1.2	0.4	4.8×10^{-7}
Triglycerides (mg/dl)	120.6	99.9	102.6	54.2	139.1	92.4	5.8×10^{-4}
Thyroid stimulating hormone (μIU/ml)	2.0	1.6	1.8	1.2	2.3	2.1	0.19
Vitamin B12 (pg/ml)	690.0	417.3	713.2	442.0	635.6	366.2	0.40

*median and 25^{th}–75^{th} percentiles

Table 2

Cognitive results of the sample, stratified by kidney disease status

Variable; score range (when applicable)	Full Sample (N=263)				Kidney Disease absent (N=172)				Kidney Disease present (N=91)				P-value
	N	Mean	SD	Median	N	Mean	SD	Median	N	Mean	SD	Median	
Modified Mini Mental Status Exam (3MSE); 0–100	256	84.6	9.0	84.6	165	85.1	8.8	86	91	83.75	9.32	85	0.30
Montreal Cognitive Assessment (MoCA); 0–30	261	19.9	3.9	19.9	171	20.2	3.9	21	90	19.27	3.73	19	0.05
Rey Auditory Verbal Learning Test (RAVLT) Sum; 0–75	263	38.0	9.0	38.0	172	38.0	9.5	37	91	37.96	8.06	37	0.93
RAVLT delayed recall; 0–15	259	5.4	3.2	5.4	170	5.4	3.2	5	89	5.43	3.02	6	0.64
Stroop Time (seconds) to Complete 2	262	25.89	6.86	25.89	98	26.86	6.9	25	164	25.32	6.8	24	0.04
Stroop Time (seconds) to Complete 3	256	57.4	18.4	57.4	167	55.5	17.1	53	89	60.94	20.39	58	0.01
Stroop Errors 2	262	25.89	6.86	25.89	98	26.86	6.9	25	164	25.32	6.8	24	0.04
Stroop Errors 3	258	3.4	6.3	3.4	169	3.0	5.9	1	89	4.09	7.04	1	0.06
Stroop Interference (seconds; Trial 3-Trial 2)	256	31.6	16.1	31.6	95	34.6	17.7	33.0	161	29.8	14.8	27.0	0.06
Digit Symbol Copy (DSC); 0–133	262	48.1	15.9	48.1	171	50.2	15.6	48	91	44.22	15.91	45	0.004
Verbal fluency for Animals	262	15.7	4.6	15.7	171	15.9	4.6	16	91	15.31	4.55	15	0.36
Center for Epidemiologic Studies-Depression Scale (CESD)	262	8.0	5.3	8.0	171	7.6	5.2	7	91	8.56	5.62	8	0.21
Brief Symptom Inventory-Anxiety score	262	4.9	4.5	4.9	171	4.7	4.6	4	91	5.35	4.47	5	0.17

Table 3

Cognitive test associations with urine albumin: creatinine ratio and estimated glomerular filtration rate in the full sample

Outcome	Adjustment	Means	Urine Albumin: Creatinine Ratio (UACR)						Estimated Glomerular Filtration Rate (CKD-EPI equation)					
			Estimate	SE	P-value	Factor	Effect	Change[#]	Estimate	SE	P-value	Factor	Effect	Change[*]
Modified Mini Mental Status Exam (3MSE)	Model 1	84.6	−4.2E-04	1.5E-04	0.0062	0.96	81.1	−3.47	8.6E-04	1.6E-03	0.60	-	-	-
Modified Mini Mental Status Exam (3MSE)	Model 2	84.6	−3.9E-04	1.6E-04	0.014	0.96	81.4	−3.21	−1.7E-03	1.8E-03	0.35	-	-	-
Montreal Cognitive Assessment (MoCA)	Model 1	19.8	−2.4E-04	9.4E-05	0.012	0.98	19.3	−0.46	1.3E-03	1.0E-03	0.21	-	-	-
Montreal Cognitive Assessment (MoCA)	Model 2	19.8	−2.5E-04	9.4E-05	0.0089	0.98	19.3	−0.48	−6.4E-04	1.2E-03	0.58	-	-	-
Rey Auditory Verbal Learning Test (RAVLT) sum	Model 1	38.0	−5.7E-05	6.4E-05	0.38	-	-	-	1.0E-03	6.2E-04	0.10	-	-	-
Rey Auditory Verbal Learning Test (RAVLT) sum	Model 2	38.0	−1.5E-05	6.0E-05	0.80	-	-	-	1.1E-03	6.3E-04	0.095	-	-	-
RAVLT Delayed Recall	Model 1	5.4	−1.1E-04	1.7E-04	0.50	-	-	-	2.7E-03	1.7E-03	0.10	-	-	-
RAVLT Delayed Recall	Model 2	5.4	−2.6E-05	1.8E-04	0.88	-	-	-	1.6E-03	1.8E-03	0.39	-	-	-
Stroop 2 time	Model 1	25.8	1.3E-04	6.6E-05	0.052	-	-	-	−1.3E-03	6.8E-04	0.048	0.99	25.43	−0.35
Stroop 2 time	Model 2	25.8	1.9E-04	7.1E-05	0.009	1.02	26.3	0.49	−1.5E-03	8.1E-04	0.074	-	-	-
Stroop 3 time	Model 1	57.4	1.9E-04	8.4E-05	0.022	1.02	58.5	1.12	−3.0E-03	8.5E-04	0.0004	0.97	55.67	−1.69
Stroop 3 time	Model 2	57.4	2.4E-04	8.0E-05	0.003	1.02	58.8	1.40	−1.5E-03	9.1E-04	0.091	-	-	-
Stroop 2 error	Model 1	0.5	−9.0E-05	8.6E-04	0.92	-	-	-	−6.4E-03	7.5E-03	0.39	-	-	-
Stroop 2 error	Model 2	0.5	2.5E-03	1.2E-03	0.04	1.28	0.7	0.15	−2.4E-02	1.1E-02	0.028	0.78	0.41	−0.11
Stroop 3 error	Model 1	3.4	6.4E-04	4.3E-04	0.14	-	-	-	−8.4E-03	4.3E-03	0.050	0.92	3.10	−0.27
Stroop 3 error	Model 2	3.4	1.1E-03	5.0E-04	0.032	1.11	3.7	0.38	−4.3E-03	5.2E-03	0.41	-	-	-
Interference	Model 1	31.6	2.2E-04	1.2E-04	0.061	-	-	-	−4.5E-03	1.2E-03	0.0002	0.96	30.23	−1.40
Interference	Model 2	31.6	2.9E-04	1.3E-04	0.026	1.03	32.6	0.93	−1.6E-03	1.5E-03	0.29	-	-	-
Digit Symbol Copy (DSC)	Model 1	48.4	−2.9E-04	9.3E-05	0.002	0.97	47.0	−1.36	3.5E-03	8.9E-04	<0.0001	1.04	50.11	1.74
Digit Symbol Copy (DSC)	Model 2	48.4	−3.1E-04	8.7E-05	0.0004	0.97	46.9	−1.47	2.5E-03	9.3E-04	0.0071	1.03	49.60	1.23
Verbal fluency for animal	Model 1	15.7	1.7E-05	7.7E-05	0.83	-	-	-	2.1E-03	7.6E-04	0.006	1.02	16.02	0.33
Verbal fluency for animal	Model 2	15.7	4.0E-06	8.9E-05	0.96	-	-	-	1.2E-03	9.7E-04	0.22	-	-	-

Model 1: unadjusted; Model 2: adjusted for age, sex, body mass index, hemoglobin A1c, level of education, hypertension status, and LDL-cholesterol; SE – standard error;

change based on 100 mg/g increase in UACR;

* change based on 10 ml/min1.73m^2 increase in eGFR. Transformations performed as follows: (100-3MSE)^1; (30-MoCA)^2

Table 4

Cognitive test associations with isolated UACR >30 mg/g or reduced eGFR (compared to 172 participants without kidney disease)*

Outcome	UACR >30 mg/g (N=59)			eGFR <60 ml/min/1.73m^2 (N=32)		
	Estimate	SE	p-value	Estimate	SE	p-value
Modified Mini Mental Status Exam (3MSE)	−0.03	0.10	0.8	0.07	0.13	0.6
Montreal Cognitive Assessment (MoCA)	0.07	0.06	0.2	0.07	0.08	0.4
Rey Auditory Verbal Learning Test (RAVLT) sum	0.07	0.04	0.1	−0.03	0.04	0.5
RAVLT Delayed Recall	0.16	0.10	0.1	−0.13	0.13	0.3
Stroop 1 time	0.02	0.05	0.7	0.05	0.06	0.3
Stroop 3 time	0.15	0.05	4.4×10^{-3}	0.1	0.06	0.1
Stroop 3 error	0.41	0.32	0.2	0.67	0.35	0.06
Interference	0.21	0.08	1.1×10^{-2}	0.06	0.1	0.6
Digit Symbol Copy (DSC)	−0.13	0.05	9.8×10^{-3}	−0.25	0.06	1.0×10^{-4}
Brief symptom inventory	0.16	0.18	0.4	−0.18	0.22	0.4
Center for Epidemiologic studies - Depression	0.16	0.14	0.2	−0.09	0.17	0.6
Verbal fluency for animal	−0.04	0.06	0.5	−0.03	0.07	0.7
Wide Range Achievement Test	0.05	0.09	0.6	−0.02	0.11	0.9

*Fully adjusted models; SE – standard error