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Cognitive Decline and Its Risk Factors in Prevalent Hemodialysis Patients

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Abstract

Background—Cognitive impairment is common in patients treated with hemodialysis. The trajectory of cognitive function and risk factors for cognitive decline remain uncertain in this population.

Study Design—Longitudinal cohort

Setting & Participants—Three hundred fourteen prevalent hemodialysis patients

Predictors—Age, sex, race, education level, hemodialysis vintage, cause of end-stage renal disease, and baseline history of cardiovascular disease (CVD).

Outcomes—Cognitive function as determined by a comprehensive neurocognitive battery, administered at baseline and yearly whenever possible. Individual cognitive test results were reduced into two domain scores using principal components analysis, representing memory and executive function, which were used as our co-primary outcomes, and by definition have a mean of zero and standard deviation of one.

Results—Mean age was 63 years; 54% were men, 22% were black and 90% had at least a high school education. During median follow up of 2.1 (IQR, 0.9–4.2) years, 196 had at least one follow up test, 156 died and 43 received a kidney transplant. Linear mixed models and joint

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Supplementary Material

Table S1: Cognitive tests used in neurocognitive battery, categorized by primary cognitive domain.

Table S2: Unadjusted baseline score and slope of cognitive tests using linear mixed models.

Item S1: Supplemental methods.

Note: The supplementary material accompanying this article (doi: _____) is available at www.ajkd.org

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models, which accounted for competing risks from death, dropout, or kidney transplantation, showed nearly identical results. The joint model demonstrated a decline in executive function (-0.09 [95% confidence interval, -0.13 to -0.05] SD per year), while memory improved slightly (0.05 [95% CI, 0.02 to 0.08] SD per year). A significant yearly decline was also seen in the Mini-Mental State Examination (median change of -0.41 ; 95% CI, -0.57 to -0.25). Older age was the only significant risk factor for steeper executive function decline (-0.04 [95% CI, -0.06 to -0.02] SD steeper annual decline for each 10 years of age).

Limitations—Prevalent hemodialysis patients only, limited follow up testing due to high mortality rate, and exclusion of participants with severe cognitive deficits or dementia

Conclusions—Prevalent hemodialysis patients demonstrate significant cognitive decline, particularly within tests of executive function. Older age was the only statistically significant risk factor for steeper cognitive decline, which may have important clinical consequences for patient management and education. Future studies should evaluate strategies to maintain or improve cognitive function.

Index words

cognitive impairment; hemodialysis; memory; executive function; neurocognitive battery; cognitive decline; risk factor; end-stage renal disease (ESRD); disease progression; cardiovascular disease (CVD); kidney disease cerebrovascular neuropathology

Cognitive impairment is common and frequently marked in patients with end stage renal disease (ESRD) treated with dialysis, with prevalence rates of moderate cognitive impairment estimated at 30%–60%.^{1–3} Notably, cognitive impairment contributes to increased morbidity and mortality.^{3,4} A recent meta-analysis that incorporated many prior studies of cognitive function in patients with kidney disease confirmed poor cognitive performance in those receiving hemodialysis.⁵ However, as most of these prior studies in dialysis patients are cross-sectional, it remains unclear whether there is significant decline in cognitive function over time, and if so how rapidly.

Previous longitudinal studies of dialysis patients are limited by a small number of participants and a limited array of cognitive tests.^{6–8} Accordingly, there is uncertainty as to whether certain types of cognitive function, such as memory or executive function, decline at different rates. In particular, executive function, which broadly includes attention and planning, may decline faster because its pathophysiology is tied to cerebrovascular disease,⁹ a common finding in hemodialysis patients. Finally, though well established in the general population¹⁰, it is important to establish what risk factors, including dialysis-specific risk factors, are associated with worsening cognition,^{1,4,11} because this knowledge is needed to implement strategies to limit cognitive decline in this vulnerable population.

We therefore assessed cognitive function using a comprehensive battery of cognitive tests at baseline and then yearly in a cohort of maintenance hemodialysis patients. We evaluated for cognitive decline and also explored risk factors for decline, focusing additionally on memory and executive function cognitive domains.^{2,12} Our pre-specified hypotheses, based on cross-sectional data^{2,12}, was that, due to progression of vascular disease, executive function would

decline more than memory and that older age and a baseline history of cardiovascular disease (CVD) would be risk factors for steeper decline.

Methods

Study Population

Outpatients aged 18 years or older receiving maintenance in-center hemodialysis at five Dialysis Clinic Inc units and one hospital-based outpatient unit (St. Elizabeth's Medical Center) in the greater Boston area were screened for the Cognition and Dialysis Study, with study enrollment occurring from January 28th 2004 through May 31st 2012.² Eligibility criteria included English fluency as well as sufficient visual and hearing acuity needed to complete neurocognitive testing. To minimize floor effects and reflecting inability to provide informed consent, individuals with Mini-Mental State Examination (MMSE) scores ≤ 10 and/or advanced dementia based on medical record review were excluded. Temporary exclusion criteria included non-access-related hospitalization within one month of screening, receipt of hemodialysis for less than one month, and single-pool Kt/V (spKt/V) < 1.0 . The Tufts Medical Center/Tufts University Institutional Review Board approved this study (IRB# 6409), and all participants who completed the detailed cognitive testing signed informed consent. The clinical and research activities reported are consistent with the Declaration of Helsinki.

Baseline Demographics and Clinical Characteristics

Demographic, clinical and laboratory factors were ascertained at the time of cognitive testing. Education information ($< 12^{\text{th}}$ grade, high school graduate to less than 2 years of college, and ≥ 2 years of college) was obtained via patient questionnaire. History of CVD, defined as a composite of either coronary artery disease and/or peripheral vascular disease, was determined by patient history or documentation in the patient's electronic or paper chart. Patients were queried about personal history of myocardial infarction and coronary revascularization, which were used to define coronary disease, and intermittent claudication and peripheral vascular disease, which were used to define peripheral vascular disease. Additionally, Dialysis Clinic Inc electronic medical and paper records were reviewed for a history of these conditions, with specific focus on problem lists, hospital discharge summaries, cardiac test results, and procedure results. Additional medical history including primary cause of ESRD, hemodialysis vascular access type, and dialysis vintage (time since hemodialysis initiation) were obtained from the Dialysis Clinic Inc or St. Elizabeth's electronic record as were mean monthly systolic and diastolic blood pressures and body mass index (BMI). Serum albumin and spKt/V most proximate to the time of cognitive testing were obtained from participant medical records.

Neurocognitive Assessment

At study enrollment, participants were administered a battery of neurocognitive tests by research coordinators after a period of training and direct observation by the study neuropsychologist (T.S.). The same battery of tests was administered yearly to study participants whenever possible. To maintain quality and inter-rater reliability, testing was observed by the study neuropsychologist at 3–6 month intervals. To limit subject fatigue, all

testing was completed during the 1st hour of hemodialysis. Using the same battery of tests, we have previously demonstrated similar performance regardless of whether testing was performed during the first hour of dialysis or before the start of a dialysis session.¹³ When possible, neurocognitive testing was performed in a private room or in as quiet an environment as possible. The neurocognitive battery included well-validated commonly used cognitive tests (Table S1, available as online supplementary material) that possess high inter- and intra-rater reliability. The MMSE¹⁴ was used as a screening test. The neurocognitive battery consisted of the Wechsler Memory Scale, third edition (WMS-III), Word List Learning Subtest;¹⁵ the Wechsler Adult Intelligence Scale, third edition (WAIS-III), Block Design¹⁵ and Digit Symbol-Coding Subtests;¹⁵ and Trail-Making Test, parts A and B¹⁶ (Trails A and B). For Trails B, a 300-second time limit was imposed, with those unable to complete the test during this time period considered “non-completers”. In year 3 of the study, the cognitive panel was expanded to include additional verbal tests assessing both memory and executive functions, including Digit Span (forwards and backwards),¹⁵ the Mental Alternation Test,¹⁷ and the Controlled Oral Word Association Test (COWAT).¹⁸

Our pre-specified primary outcomes were change in memory and executive function over time, with risk factors for decline examined as exploratory analyses. Principal component analysis (PCA) with varimax rotation was used as a data reduction technique with 292 participants to derive composite scores for separate cognitive domains (memory or executive function) in the entire study population.¹⁹ For 18 individuals who were missing baseline results on one cognitive test (or 2 results if derived from the same test), single item imputation was performed using multivariable linear regression models based on performance on other tests in the cognitive battery. Two principal components with eigenvalues greater than two were obtained (component 1 eigenvalue, 2.87; component 2 eigenvalue, 2.29), and the resulting component scores subsequently were used as co-primary outcomes. Using this method, all component scores have a mean of zero and standard deviation of one. The first component was interpreted to reflect executive functioning, attention, and processing speed (referred to as executive function in the Results section), with the Trails A and B, Block Design, and Digit Symbol-Coding tests contributing significantly (Table S1). The second component primarily was composed of Word List Learning Recall and Recognition and was interpreted to reflect memory. Component loadings for deriving the principal component score at the baseline examination (n = 292) were used to calculate the principal component scores for follow-up testing, which included 8 patients who did not have enough data to calculate PCA scores at baseline, bringing the number of unique participants up to 300. Digit Span, Mental Alternations and the COWAT were not used to calculate the PCA because of the smaller number of individuals who completed these tests.

We obtained survival status on all patients through periodic electronic medical record monitoring as well as from each patient’s dialysis unit. Survival time was defined as the period of time elapsed from initial study enrollment until death or March 31, 2013. In a similar manner, we also collected information on censoring events such as kidney transplantation, dialysis modality change, and transfer to outside dialysis unit.

Statistical Analysis

Descriptive characteristics of the study population were reported as frequency count and proportions for categorical and binary variables, means $\pm$ standard deviations (SDs) for continuous normally distributed variables, and medians with interquartile ranges (IQRs) for skewed variables.

We used random effects mixed models to explore the change in cognitive test scores over time. We postulated a linear model with a random intercept and slope for each cognitive test in which at time j for the i^{th} patient, the cognitive test Y_{ij} is given by $Y_{ij} = (\beta_1 + b_{1i}) + (\beta_2 + b_{2i})t_j + \epsilon_{ij}$; $i=1, \dots, n$; $j=1, \dots, n_i$ where β_1 and β_2 are the population mean intercept and rate of change. Because of the high rate of dropout due to mortality and transplantation, and the fact that mortality and other causes of dropout may be informative, such that cognitive decline may have been greater in those who die before subsequent testing, we used shared random effects joint models for repeated measures and time-to-event data to estimate the rate of change in cognitive function decline adjusting for informative censoring due to mortality, transplantation, or other reasons (see Item S1 for model formula and details).²⁰ The joint models approach includes a linear mixed sub-model for the repeated measurement and a survival sub-model for time to dropout. These two models are linked using a shared random effect to account for non-informative dropout. The survival sub-model included was a stratified cause-specific Cox competing risk model with three possible end points: (1) mortality, which also included dropout due to prolonged hospitalization or being too sick to complete testing; (2) transplantation, transfer to peritoneal dialysis or transfer to a non-participating facility; and (3) no dropout. We separated out these causes of dropout to account for the fact that the association of the most proximate cognitive test with mortality and transplantation could be in opposite directions.

To explore the effect of each potential risk factor (age, sex, race, education, cause of ESRD, dialysis vintage, and baseline history of CVD) on the rate of change of the cognitive test, the linear mixed sub-model included the main effect of the covariate of interest, time since baseline as a linear term, and their product. The time effect provides the slope of the cognitive test for the reference level of the covariate, and the interaction term provides the increase/decrease in this slope for the other level of the covariate. Models were initially unadjusted and subsequently adjusted for baseline age, sex, race, education level, cause of ESRD, dialysis vintage and history of CVD. The competing risk survival sub-model was adjusted for the same covariates included in the linear mixed sub-model in addition to variables previously shown to be associated with mortality including vascular access type, serum albumin, systolic blood pressure, diastolic blood pressure, BMI and spKt/V.²¹

Significance was assessed using a two-sided α of 0.05, and results were presented with 95% confidence intervals (CIs). All analyses were performed using SAS software (version 9.3, SAS Institute Inc, Cary NC) and R language (version 3.3.1, R Foundation for Statistical Computing, Vienna Austria). The joint models were estimated using the JM package in R (version JM 1.4-4).²²

Results

Baseline Characteristics

Among nine hundred twenty nine patients screened for enrollment, 414 did not meet eligibility criteria and 201 declined participation, leaving 314 patients who had cognitive testing performed at baseline.² Three hundred participants had sufficient data to calculate memory and executive principal components for use in the joint models. The mean age of study participants at enrollment was 63 ± 16 (SD) years; 168 (54%) were men, 70 (22%) were black and 284 (90%) had at least a high school education (Table 1). During median follow up of 2.1 (IQR, 0.9–4.2) years, 196 (62%) had at least one follow up test with median number of follow-up test of 2 (IQR, 1–4), while 156 (50%) died during the study, 43 (14%) received a kidney transplant and 41 (13%) dropped out because of modality change or transfer to another dialysis unit.

Cognitive Decline

There was little overall difference in the results for the linear mixed models versus joint models; therefore only joint model results are presented in the main text (Table 2), while the linear mixed models can be found in the supplementary material (Table S2). There was a significant decline in the composite executive function factor (change of -0.09 [95% CI, -0.13 to -0.05] SD per year), while there was a significant increase over time in the composite memory factor (0.05 [95% CI, 0.02 – 0.08] SD per year; Table 2). When examining individual tests within the cognitive battery, there were declines in performance over time in multiple cognitive tests including the MMSE, Block Design, Digit Symbol, and Trails A and Trails B (Table 2), all of which, with the exception of the MMSE, either partially or primarily assess executive function. With the exception of the MMSE (change of -0.41 ; 95% CI, -0.57 to -0.25), which is a non-specific screening test, and Digits Forward, both of which showed a significant decline over time, there was either no decline or modest improvement over time for the remaining tests of memory.

Risk Factors for Cognitive Decline

Age was a strong risk factor for cognitive decline for the executive function factor in fully adjusted analyses (0.04 [95% CI, -0.06 to -0.02] –SD steeper decline per year of follow-up for every 10 additional years of age). There was no significant association between age and change in memory score (estimated difference in slope, 0.0 ; 95% CI, -0.02 – 0.01). Neither sex nor race was a risk factor for decline in memory or executive function. Baseline history of CVD and diabetes as cause of ESRD showed a nominally greater cognitive decline for executive function but not for memory, though neither was statistically significant (for history of CVD, executive function = -0.06 [95% CI, -0.12 to 0.01] steeper decline per year; for diabetes, executive function = -0.06 [95% CI, -0.13 to 0.01]). Education level and dialysis vintage were not significant risk factors for decline in either memory or executive function.

Discussion

Prevalent hemodialysis patients have significant declines in cognitive function, particularly in executive function. This decline is consistent across multiple neurocognitive tests that measure different aspects of executive function including attention and processing speed and remains consistent in competing risk analyses accounting for death, transplantation, and other censoring events such as unit transfer. We did not observe a similar pattern of decline for memory, regardless of whether competing risks were considered. Older age was associated with greater decline in cognitive function per year, while sex, race, education level, history of CVD, and cause of ESRD were not associated with steeper decline.

Multiple previous studies have examined cognitive function in cross sectional analyses of dialysis patients, showing that there is a high prevalence of cognitive impairment, with anywhere from 30% to 80% of patients demonstrating at least mild cognitive impairment. These findings were summarized in a recent meta-analysis which confirmed that patients receiving hemodialysis have significant cognitive deficits, particularly with executive function, compared to the general population.⁵ Within the general population, prior longitudinal studies have confirmed that cognitive function deteriorates over time, but such decline is predominantly within older individuals²³ For example, a longitudinal study by Jacqmin-Gadd et al demonstrated a 0.02-per-year decline in MMSE score over five years for individuals aged 65 years, in contrast to a 0.57-per-year decline for individuals aged 85 years. Comparing this report to our findings, we observed a 0.41-per-year decline in MMSE score, despite a mean age of 63 years.

There are also several previously published longitudinal studies of cognitive function in hemodialysis patients.^{6–8} A recent study by McAdams-Demarco et al identified frailty as a risk factor for cognitive decline as measured by the MMSE and Trails A and B tests, but did not include a full battery of cognitive tests and did not assess other risk factors for decline. Similarly, studies by Bossola et al and Altmann et al demonstrated a decline in cognitive scores but included a limited number of cognitive tests and did not assess risk factors.

Interestingly, our study showed a significant decline in executive function but not memory function, a finding that was consistent across multiple individual tests as well as our summary scores. This may be partially explained by common underlying cerebrovascular neuropathology in hemodialysis patients. Multiple studies show a high burden of cerebrovascular disease in dialysis patients, whether by brain imaging^{24–26} or clinical outcomes such as stroke.^{27,28} Cerebrovascular disease is more closely linked to impaired executive function than impaired memory, as seen with multi-infarct dementia^{29,30} Memory, however, is more likely to be affected by normal aging or Alzheimer's disease,³¹ the latter of which does not appear to be more prevalent in patients with kidney disease.³² We observed a modest improvement in memory score over time, which remained even when accounting for competing risks. This finding was driven largely by the results of a single test (Delayed Recall), with other tests of memory showing little change in either direction over time. We also acknowledge that this finding could be explained by two potential biases: (1) a learning or practice effect from repeated administrations of the same test, or (2) residual confounding that could occur due to survival bias.

Older age was a strong risk factor for greater decline in cognitive function, even though older patients have significantly lower cognitive scores at baseline. Consistent with findings in the general population,^{23,33} this observation may have important implications for the future of dialysis care. As the average age for incident dialysis patients is increasing and survival on dialysis improves,³⁴ cognitive impairment and cognitive decline are likely to become a more substantial source of morbidity. We saw no relationship between sex, race, education or dialysis vintage and decline in cognitive function over time. Finally, baseline history of CVD and diabetes as the cause of ESRD both showed trends towards greater decline in cognitive function, but only for executive function. Though not statistically significant, these findings are consistent with and expand upon our own previous data in hemodialysis patients,¹² as well as with findings from both cross-sectional and longitudinal studies in the general population demonstrating that CVD and CVD risk factors are a significant risk factor for cognitive impairment, likely through a pathway of cerebrovascular disease^{35,36}.

Our study has several strengths. We have a relatively large cohort for a hemodialysis population considering known problems with recruiting and retaining patients who are receiving hemodialysis. Instead of using a short screening test for assessment of cognition, we used a detailed battery of neuropsychological tests in consultation and successfully repeated these assessments at yearly intervals. Our cohort is also demographically similar to the overall US hemodialysis population,³⁴ enhancing the generalizability of our results.

There are also several limitations of this study. First, our cohort includes only prevalent hemodialysis patients, which may lead to selection bias; accordingly, we are unable to apply our findings to incident hemodialysis patients. In addition, the use of prevalent patients does not allow for determination of baseline cognitive function at hemodialysis initiation, introducing the possibility of survival bias. There are also limitations that would be associated with the inclusion of incident patients, because patients initiating hemodialysis may have worse cognitive function⁵ due to uremia, acute poor health, and concurrent hospitalization. Second, the median number of visits was two, indicating that many participants were not available for subsequent testing. Similar to many dialysis cohorts, the mortality rate was high in our study, limiting follow up testing. We have attempted to address this shortcoming by using statistical analyses incorporating competing risks to account for non-random dropout. Additionally, we excluded patients with advanced dementia from entry to the cohort, which may lead to an underestimation of the severity of cognitive impairment at baseline as well as the progression of cognitive impairment over time. We are also limited in evaluating risk factors due to our overall sample size and limited number of repeated measures, which may explain the lack of statistically significant association seen for both CVD and cause of ESRD. Finally, we administered cognitive testing during the first hour of hemodialysis. Critically, we previously demonstrated that testing during this time is equivalent to testing administered prior to the start of a hemodialysis session, and testing in subsequent years was done at the same time during dialysis, allowing for direct comparison.¹³ Cognitive testing during this time period is more convenient for patients and arguably is more clinically relevant as much of the clinical assessment and education for hemodialysis patients occurs during hemodialysis treatments.

These findings have several important implications. First, patients on hemodialysis have a high prevalence of cognitive impairment when seen at the point of care, and they are at high risk for cognitive decline. Older patients are more likely to have faster decline. Patients with known CVD or diabetes as their cause of kidney disease may also have faster decline in cognitive function, though larger studies will be required to confirm this finding. If CVD and CVD risk factors prove to be important in the pathophysiology of cognitive impairment in CKD patients, measures aimed at treatment of vascular disease may prove to be helpful in limiting further decline. Finally, discussions on complex and important topics related to care such as end of life, medication adherence, dietary restrictions, and quality of life should be initiated as early as possible, even prior to the initiation of hemodialysis, as cognitive function often will deteriorate over time. Greater awareness about the potential for cognitive decline to occur needs to be incorporated into routine dialysis care, with importance placed on involving families and caregivers in care plans and treatment decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Contributions: research idea and study design: DAD, DEW, HT, TS, MJS; data acquisition: TS, SD; data analysis/interpretation: DAD, DEW, HT, TS, AG, MJS; statistical analysis: HT; supervision or mentorship: DEW, TS, MJS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. DAD takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Table 1

Baseline characteristics of study sample

Characteristic	Value
Age (y)	62.6 ± 16.5
Female sex	146 (46.5%)
Black race	70 (22.3%)
Education level	
<12 th grade	30 (9.6%)
HS graduate—<2 y of college	172 (54.8%)
2 y of college	112 (35.7%)
Stroke	56 (17.8%)
Peripheral Vascular Disease	74 (23.6%)
Hypertension	281 (89.5%)
Diabetes	150 (47.8%)
Heart Failure	113 (36.0%)
Coronary Artery Disease	116 (36.9%)
Primary cause of ESRD	
Diabetes	109 (34.7%)
Hypertension	59 (18.8%)
Glomerulonephritis	56 (17.8%)
Other	51 (16.2%)
Unknown	39 (12.4%)
Dialysis Vintage	14.4 [6.9–35.4]
<12 mo	127 (40.5%)
12–<24 mo	79 (25.2%)
24–<36 mo	31 (9.9%)
36 mo	77 (24.5%)
Vascular Access	
Fistula	203 (64.7%)
Graft	18 (5.7%)
Catheter	93 (29.6%)
BMI (kg/m ²)	28.4 ± 7.0
Systolic BP * monthly average (mmHg)	141.3 ± 20.9
Diastolic BP * monthly average (mmHg)	73.2 ± 12.3

Characteristic	Value
spKt/V	1.51 ± 0.24
Albumin (g/dL)	3.8 ± 0.4

Note: N=314. Values for categorical variables are given as count (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range].

Data are presented either as n (%), mean ± standard deviation or median (interquartile range).

BMI, body mass index; BP, blood pressure; ESRD, end-stage renal disease; HS, high school; sp, single-pool;

* Predialysis session.

Table 2

Unadjusted baseline score and slope of cognitive tests using joint models

Type of Test	Cognitive test	No. of		Baseline (95% CI)	Slope ^ (95% CI)		p
		Unique pts	f/u visits				
Summary Scores *	Memory Function	300	645	0.0 (−0.1, 0.1)	0.05 (0.01, 0.09)	0.04	
	Executive Function	300	645	0.0 (−0.1, 0.1)	−0.09 (−0.13, −0.05)	<0.001	
Screening	MMSE	314	785	26.7 (26.3, 27.0)	−0.41 (−0.57, −0.25)	<0.001	
Primarily Memory	Short Delayed Recall	312	779	4.8 (4.5, 5.1)	0.03 (−0.07, 0.14)	0.5	
	Delayed Recall	312	774	4.5 (4.1, 4.8)	0.12 (0.01, 0.22)	0.03	
	Word Recognition	312	775	20.7 (20.4, 21.1)	−0.05 (−0.14, 0.04)	0.3	
Primarily Executive Function	Block Design	311	752	26.0 (24.8, 27.2)	−0.36 (−0.72, −0.01)	0.05	
	Digit Symbol Substitution	296	676	39.7 (37.7, 41.7)	−0.64 (−1.18, −0.10)	0.02	
	Digits Forward	187	452	9.7 (9.3, 10.0)	−0.10 (−0.20, 0.00)	0.05	
	Digits Backward	186	451	5.6 (5.3, 6.0)	−0.09 (−0.19, 0.02)	0.1	
	Trail-Making Part A	302	693	61.4 (56.8, 66.0)	6.27 (3.13, 9.41)	<0.001	
	Trail-Making Part B	299	681	170.6 (160.7, 180.6)	4.84 (1.49, 8.20)	0.006	
	Mental Alternations	187	453	20.2 (19.0, 21.4)	−0.21 (−0.51, 0.09)	0.2	
	COWAT (Animals)	187	453	15.6 (14.7, 16.5)	−0.23 (−0.48, 0.03)	0.08	
	COWAT (Supermarket)	187	454	20.9 (19.8, 22.0)	−0.29 (−0.64, 0.06)	0.1	

Note: The Digits, Mental Alternations, and COWAT tests were added halfway through study enrollment. Negative coefficients are associated with worse scores over time except on the Trail-Making tests. Bold indicates statistically significant differences over time

CI, confidence interval; MMSE, Mini-Mental State Examination; COWAT, controlled oral word association

[^] Slope is the rate of change in the cognitive test per year.

^{*} Summary scores represent a per standard deviation change

Table 3

Effect of baseline covariates on slope (faster decline) of summary cognitive scores using joint models

Risk Factors	Unadjusted Diff in Slope		Adjusted Diff in Slope	
	Estimate (95% CI)	p	Estimate (95% CI)	p
Memory Function				
Age, per 10-y older	0.00 (−0.02, 0.01)	0.8	0.00 (−0.02, 0.01)	0.8
Sex, Female vs Male	−0.01 (−0.08, 0.05)	0.7	−0.02 (−0.09, 0.05)	0.6
Race, Black vs Non-Black	0.05 (−0.02, 0.12)	0.1	0.04 (−0.03, 0.11)	0.2
History of CVD	−0.03 (−0.10, 0.04)	0.4	−0.03 (−0.10, 0.04)	0.4
Cause of ESRD, DM vs other	0.02 (−0.09, 0.05)	0.7	0.02 (−0.09, 0.05)	0.6
Education level				
HS graduate [*] vs <12 th grade	−0.02 (−0.13, 0.09)	0.7	−0.03 (−0.13, 0.08)	0.6
2 y college vs <12 th grade	0.00 (−0.12, 0.11)	0.9	−0.01 (−0.12, 0.10)	0.8
Dialysis vintage, <1 y vs 1 y	−0.03 (−0.09, 0.03)	0.3	−0.03 (−0.09, 0.03)	0.4
Executive Function				
Age, per 10-y older	−0.04 (−0.06, −0.03)	<0.001	−0.04 (−0.06, −0.02)	<0.001
Sex, Female vs Male	0.04 (−0.03, 0.11)	0.3	0.04 (−0.03, 0.10)	0.3
Race, Black vs Non-Black	0.06 (−0.02, 0.14)	0.2	0.05 (−0.03, 0.12)	0.2
History of CVD	−0.07 (−0.14, 0.01)	0.08	−0.06 (−0.13, 0.01)	0.1
Cause of ESRD, DM vs other	−0.06 (−0.14, 0.01)	0.1	−0.06 (−0.13, 0.01)	0.07
HS graduate [*] vs <12 th grade	−0.02 (−0.15, 0.11)	0.8	−0.03 (−0.15, 0.09)	0.7
2 y college vs HS graduate [*]	0.03 (−0.11, 0.16)	0.7	0.01 (−0.11, 0.14)	0.8
Dialysis vintage, <1 y vs 1 y	−0.03 (−0.10, 0.04)	0.5	−0.03 (−0.10, 0.04)	0.4

Note: Adjusted for all listed variables. A negative coefficient for difference in slope indicates a faster progression/decline in the cognitive test.

CVD = cardiovascular disease, ESRD = end-stage renal disease, DM = diabetes mellitus, HS = high school

^{*} HS graduate to <2 years of college