UCSF

Title

Loss of executive function after dialysis initiation in adults with chronic kidney disease.

Authors

Kurella Tamura, Manjula
Vittinghoff, Eric
Hsu, Chi-Yuan
et al.

Loss of executive function before and after dialysis initiation in adults with chronic kidney disease

Manjula Kurella Tamura, MD, MPH[1,2], **Eric Vittinghoff, PhD**[3], **Chi-yuan Hsu, MD, MS**[4], **Karman Tam, MPH**[1], **Stephen L. Seliger, MD, MS**[5], **Stephen Sozio, MD, MHS**[6], **Michael Fischer, MD, MSPH**[7], **Jing Chen, MD, MS**[8], **Eva Lustigova, MPH**[8], **Louise Strauss, RN, BSN**[9], **Rajat Deo, MD, MTR**[10], **Alan S. Go, MD**[11], **Kristine Yaffe, MD**[3,12], and **for the CRIC Study Investigators**[*]

[1]VA Palo Alto Geriatric Research and Education Clinical Center, Palo Alto, CA

[2]Division of Nephrology, Stanford University School of Medicine; Palo Alto, CA

[3]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA

[4]Department of Medicine, Division of Nephrology; University of California San Francisco, San Francisco, CA

[5]Department of Medicine, Division of Nephrology, University of Maryland, Baltimore, MD

Correspondence to: Manjula Kurella Tamura, MD, MPH, Veterans Affairs Palo Alto Health Care System, 3801 Miranda Ave., Palo Alto, CA 94304, mktamura@stanford.edu.

[6]Division of Nephrology, Johns Hopkins University School of Medicine and Welch Center for Prevention, Epidemiology, and Clinical Research; Baltimore, MD

[7]Center of Innovation for Complex Chronic Healthcare, Jesse Brown VAMC and Edward Hines, Jr. VA, and University of Illinois Hospital and Health Sciences System; Chicago, IL

[8]Department of Medicine, Tulane University School of Medicine; New Orleans, LA

[9]Department of Medicine, University Hospitals Case Medical Center, Cleveland, OH

[10]Division of Cardiology, University of Pennsylvania, Philadelphia, PA

[11]Division of Research, Kaiser Permanente Northern California; Oakland, CA

[12]Departments of Psychiatry and Neurology, University of California San Francisco, San Francisco, CA

Abstract

The association of dialysis initiation with changes in cognitive function among patients with advanced chronic kidney disease is poorly described. To better define this, we enrolled participants with advanced chronic kidney disease from the Chronic Renal Insufficiency Cohort in a prospective study of cognitive function. Eligible participants had a glomerular filtration rate of 20 ml/min/1.73m^2 or less, or dialysis initiation within the past two years. We evaluated cognitive function by a validated telephone battery at regular intervals over two years, and analyzed test scores as z-scores. Of 212 participants, 123 did not transition to dialysis during follow-up, 37 transitioned to dialysis after baseline, and 52 transitioned to dialysis prior to baseline. In adjusted analyses, the transition to dialysis was associated with a significant loss of executive function, but no significant changes in global cognition or memory. The estimated net difference in cognitive z-scores at two years for participants who transitioned to dialysis during follow-up compared to participants who did not transition to dialysis was −0.01 (95% confidence interval −0.13, 0.11) for global cognition, −0.24 (−0.51, 0.03) for memory, and −0.33 (−0.60, −0.07) for executive function. Thus, among adults with advanced chronic kidney disease, dialysis initiation was associated with loss of executive function with no change in other aspects of cognition. Larger studies are needed to evaluate cognition during dialysis initiation.

Keywords

CKD; cognitive function; dialysis

Background

Cognitive impairment is common among patients receiving maintenance dialysis, with prevalence estimates exceeding 30%, and it may contribute to excess mortality.[1,2] However, the natural history of cognitive impairment in persons with advanced chronic kidney disease (CKD) and the effect of dialysis initiation on cognitive function remain incompletely defined.

Early studies, primarily in younger individuals with few comorbid conditions, reported that cognitive impairment associated with advanced CKD could be improved by dialysis therapy,[3,4] supporting the hypothesis that metabolites retained in kidney failure and removed by dialysis contributed to impaired cognitive function. These studies had small samples and did not always include controls, making it difficult to determine whether changes in cognitive function were due to dialysis initiation or learning effects from repeated administration of cognitive function tests.

Over the past few decades, the average age and comorbidity burden of patients starting dialysis has increased. In addition, dialysis is now initiated earlier in the course of CKD (i.e. at higher levels of estimated glomerular filtration rate (eGFR)). Coincident with these changes in demographics and practice, the predominant form of cognitive impairment may no longer be primarily attributable to retained metabolites, and rather may be related to cerebrovascular disease and vascular dementia.[1,5,6] If cerebrovascular disease is the principle factor contributing to cognitive impairment, then dialysis initiation would not be expected to improve cognitive function and it might even have deleterious effects.[7,8]

Using data collected from the Chronic Renal Insufficiency Cohort Cognition (CRIC COG) study, we aimed to evaluate the trajectory of cognitive function in a contemporary cohort of adults with advanced CKD before and after dialysis initiation. The CRIC study is well-suited to address these questions, because its prospective design reduces selection and survival biases. We hypothesized that dialysis initiation would be associated with an accelerated decline in cognitive function.

Results

Participant characteristics

Of the 212 participants included in the cohort, 123 (58%) did not transition to dialysis during follow-up, 37 (17%) transitioned to dialysis after baseline, and 52 (25%) transitioned to dialysis prior to baseline. The mean age of the cohort was 64.0 ± 10.5 years, 50.9% were male, 46.7% were white, and 57.6% had diabetes. Among participants who were not receiving dialysis at baseline, the mean eGFR was $21.3 + 7.7$ ml/min/1.73m^2. Among participants receiving dialysis at baseline, the mean number of months on dialysis was 11.6 ± 7.6. Compared to participants not receiving dialysis at baseline, participants receiving dialysis had slightly lower baseline cognitive test scores (Table 1 and Supplement Table 1).

On average, participants completed 3.1 ± 1.7 cognitive assessments over 1.4 ± 0.7 years (median 2.0, IQR 0.8–2.0). Mean absolute change in eGFR from baseline to end of study or dialysis initiation was -1.7 ± 8.9 ml/min/1.73m^2 for participants who did not transition to dialysis, and -7.5 ± 6.3 ml/min/1.73m^2 for participants who transitioned to dialysis. In analyses adjusted for age, sex, race and education, transition to dialysis was associated with loss of executive function (p-value=0.01, Table 2), and no significant changes in global cognition (p-value=0.81) or memory (p-value=0.12). These cognitive trajectories are depicted in Figure 1. In sensitivity analyses excluding participants who transitioned to dialysis prior to baseline, the results were similar (Supplement Table 2). Transition to dialysis was associated with loss of executive function (p-value=0.01) and no significant

changes in global cognition (p-value=0.69) or memory (p-value=0.30). The sensitivity analysis results were also unchanged after adjustment for baseline eGFR.

The estimated net difference in cognitive function at two years for participants who transitioned to dialysis during follow-up compared to participants who did not transition to dialysis was –0.01 (95% CI –0.13, 0.11) for global cognition, –0.24 (95% CI –0.51, 0.03) for memory, and –0.33 (95% CI –0.60, –0.07) for executive function (Figure 2). Participants who transitioned to dialysis prior to baseline had slightly larger net differences in cognitive function than participants who transitioned after baseline.

Discussion

In this study of adults with advanced CKD, transition to maintenance dialysis was associated with loss of executive function and was not associated with improvement in other aspects of cognitive function.

There may be several possible explanations for the cognitive trajectories observed in the current study. The predominant form of cognitive impairment among adults with advanced CKD may be related to vascular causes of dementia rather than retention of metabolites with central nervous system toxicity. Patients with advanced CKD have a large burden of clinical and subclinical cerebrovascular disease.[9,10] Cerebrovascular disease, in turn, is a strong correlate of cognitive impairment among patients receiving maintenance dialysis.[1,11] Our observation of accelerated decline in executive function may be consistent with this hypothesis, as impairment in this domain is often a prominent feature of vascular dementia.[12]

Our study was not able to distinguish whether accelerated decline in executive function occurred before or after dialysis initiation, and therefore we could not determine whether this finding was related to progression of CKD or dialysis initiation *per se*. The former trajectory might imply that declining kidney function and declining cognitive function are mediated by the same pathophysiologic processes. Conversely, if accelerated decline occurs after dialysis initiation, this might imply that factors associated with dialysis treatment have deleterious effects on cognitive function. These factors might include hemodynamic instability from hemodialysis treatments, brain microhemorrhages, microembolic phenomenon, and systemic inflammation. For example, in a small study, an intervention to reduce hemodynamic instability during hemodialysis treatment was associated with less ischemic brain injury in patients who recently started maintenance dialysis.[7] Clinical events occurring around the time of dialysis initiation, such as acute strokes, which increase in incidence around the time of dialysis initiation,[13] or episodes of delirium from acute illness may also contribute.

Another possible explanation for the cognitive trajectories we observed in the current study is that dialysis initiation may attenuate the acute encephalopathy of severe kidney failure, but this effect may be outweighed by the processes contributing to cognitive decline. Although it has been widely accepted that cognitive impairment improves after the initiation of maintenance dialysis therapy; evidence to support these assumptions is limited. Prior studies

which reported beneficial effects of dialysis on cognitive function were conducted more than 40 years ago, included fewer than 20 patients, and did not include a control group in pre-post assessments; thus learning effects could not be differentiated from treatment effects.[3,4] In these studies, dialysis was initiated much later in the course of CKD - a serum creatinine concentration >10 mg/d (approximately an eGFR <8 ml/min/1.73m^2 for a middle aged adult), than is typical for contemporary practice.

Alternatively, these cognitive trajectories may reflect insufficient removal of the retained metabolites which contribute to impaired cognitive function in patients with advanced CKD. Among patients receiving maintenance dialysis, more frequent hemodialysis did not improve cognitive function compared to conventional thrice weekly hemodialysis in a recent small randomized trial,[8] Because frequent hemodialysis augments the removal of small metabolites such as urea, it seems unlikely that insufficient dialytic removal of this class of metabolites contributes to cognitive decline. However, it is increasingly recognized that conventional dialysis and possibly even frequent dialysis do not efficiently remove metabolites bound to plasma proteins and those normally cleared by tubular secretion.[14] We recently identified several metabolites cleared by tubular secretion that are correlated with impaired cognitive function in patients receiving dialysis.[15] Whether more efficient removal of these retained metabolites might improve cognitive function remains unknown.

These findings are largely consistent with the trajectory of functional decline observed among older adults who start dialysis,[16,17] and could have several important implications if confirmed in larger studies. Among ambulatory patients with advanced CKD, the presence of cognitive impairment may not be an appropriate indication for initiation of dialysis if not accompanied by other traditional indications for dialysis initiation. Since we were not able to assess cognitive function immediately prior to dialysis initiation, we cannot rule out the possibility that dialysis initiation was associated with a beneficial effect on cognitive function in the short term that was not captured in our study. It is possible that certain features of cognitive impairment, such as its onset, duration and the absence of brain vascular disease on neuroimaging might identify a subgroup of patients who are more likely to improve after dialysis initiation, but this has not been carefully studied. These findings may also have implications for how patients with cognitive impairment are counseled about dialysis therapy. Loss of independence, both physical and cognitive, is rarely acknowledged but an important consideration for many older patients, especially when the burden of treatment is high.[18,19] Finally, these findings should serve to underscore the importance of advance care planning for patients with cognitive impairment who initiate dialysis. Many, if not all, will face complex medical decisions, yet few have engaged in advance care planning and even fewer have appointed a surrogate decision maker.[20]

Strengths of this study include its prospective design, which reduces survival and selection biases, the use of a validated telephone battery to assess cognitive function, the assessment of cognitive function on non-dialysis days, and the use of a control group and a one month cognitive assessment to account for learning effects from serial assessments. Several important limitations should also be acknowledged. First, while larger than previous studies, the study sample was small and the duration of follow-up was relatively short. Although we used several approaches to account for learning effects, such an effect remained apparent in

the domain of memory, and may have attenuated between-group differences. Although the differences in memory function did not reach statistical significance, the wide confidence intervals include the possibility that memory function may also worsen with dialysis initiation. Self-report of comorbidity is common in cohort studies but may contribute to under-ascertainment. In addition, because we lacked a group of patients with extremely low kidney function (i.e. GFR < 10 ml/min/1.73m^2) who did not start dialysis, we could not infer whether dialysis was the cause of cognitive decline.

In conclusion, the transition to dialysis was not associated with improvement in cognitive function among adults with advanced CKD. If confirmed in larger studies, these results suggest that the predominant causes of cognitive impairment among contemporary patients with advanced CKD are not related to dialyzable metabolites.

Methods

The CRIC Study is a prospective observational cohort study designed to evaluate risk factors for progression of CKD.[9,10] From June 2003 through May 2008, CRIC recruited 3939 persons aged 21–74 years from seven clinical centers across the United States. Participants met age-based eGFR criteria: 20–70 ml/min/1.73m^2 for ages 21–44 years, 20–60 ml/min/1.73m^2 for ages 45–64 years, and 20–50 ml/min/1.73m^2 for ages 65–74 years. Exclusion criteria included coexisting disease likely to affect survival, prior receipt of dialysis or organ transplant, residence in nursing homes or inability to provide consent. Between January 1, 2012 and February 1, 2015, CRIC participants were invited to participate in an ancillary study of cognitive function if they were fluent in English and had advanced CKD, defined as either 1) an eGFR <20 ml/min/1.73m^2 at the most recent CRIC visit, 2) an eGFR projected to fall below 20 ml/min/1.73m^2 over the subsequent year based on a CRIC prediction model using prior eGFR, proteinuria and blood pressure, or 3) initiation of dialysis within the past two years (see Supplement Figure 1 for flow diagram). We included the latter group of participants to ensure we had a sufficient sample to model the post-dialysis cognitive trajectory. Participants with hearing impairment as judged by the study coordinator were excluded. A total of 219 participants were enrolled. For these analyses, we excluded seven participants who received a pre-emptive transplant, leaving 212 participants in the analytic cohort. Compared to CRIC participants with advanced CKD prior to 2012, participants enrolled in the ancillary study were older and more likely to be female.

Institutional Review Boards at all clinical sites approved the study protocol and all participants provided written informed consent.

We assessed cognitive function over two years using a validated telephone battery administered by two trained research assistants.[11–13] The Telephone Interview for Cognitive Status modified (TICSm) evaluates global cognitive function with components for concentration, orientation, immediate and delayed memory, calculation, reasoning and judgement. The TICSm has a maximum (best) score of 41 and the delayed recall component has a maximum score of 10. The East Boston Memory test assesses verbal memory with components for immediate and delayed recall. The maximum score for each component is 12. The Digit Span backward test assesses working memory, attention, and executive

function with a maximum score of 12. The Verbal and Category fluency tests evaluate language function and aspects of executive function.[14] Higher scores indicate better cognitive function. We administered the cognitive tests at baseline (enrollment in the ancillary study), one month after baseline to capture learning effects, and then every six months for up to two years or the end of the study, August 31, 2015. For participants who were receiving hemodialysis, testing was performed on a non-dialysis day. We created z-scores for each test by subtracting the cohort baseline median score from the test score at each time point and dividing by the interquartile range. To reduce the number of outcomes, we created three summary z-scores. We used the TICSm z-score for global cognition. The memory z-score consisted of the sum of z-scores for the TICSm delayed recall, and the East Boston Memory immediate and delayed recall scores. The executive function z-score consisted of the sum of z-scores for the Digit Span, Verbal Fluency and Category Fluency tests. Higher z-scores represent better cognitive function.

We ascertained dialysis initiation through semi-annual surveillance by CRIC study personnel, supplemented by cross-linkage with the US Renal Data System. Socio-demographic and clinical characteristics were assessed at the CRIC visit immediately prior to the baseline cognitive assessment. We defined diabetes by participant self-report, use of medications for diabetes, or fasting blood glucose of 126 mg/dL. We defined hypertension by participant self-report, use of medications for high blood pressure, or a seated blood pressure of 140/80 mm Hg. We defined cardiovascular disease as participant self-report of a myocardial infarction, angina, stroke, claudication, amputation, or revascularization procedure of the coronaries or the extremities. We defined tobacco use as current versus former or never use. For participants who were not receiving dialysis at the baseline cognitive assessment, we calculated the eGFR with an equation derived from the CRIC Study, using the annual serum creatinine and cystatin C measurements corresponding to the first cognitive function assessment.[15]

We compared participant characteristics and baseline cognitive scores according to dialysis transition status: (1) did not transition to dialysis, (2) transitioned to dialysis after baseline, and (3) transitioned to dialysis prior to baseline.

We used a random-effects model to determine the change in cognitive function over time. Our base model fit separate slopes before and after the initiation of dialysis, allowed a sharp change shortly after the initiation of dialysis, and adjusted for age, sex, race, education, visit number (0, 1, 2) to model learning effects, and interactions between age, sex, race and education with time. For these models, visit number, time since baseline, dialysis status, and time since dialysis initiation were time-varying covariates. Observations occurring after kidney transplantation (N=5 participants) were censored; however, observations for 21 participants who died during follow-up were retained in the analysis. To test the joint effect of the immediate change in cognition after dialysis initiation and the change in cognitive slope after dialysis initiation, we used a statistical test with two degrees of freedom. We used this model to plot the predicted cognitive trajectory for a typical participant with advanced CKD who (1) does not transition to dialysis, (2) transitions to dialysis after 0.7 years of follow-up (the average transition time in our cohort for participants who transitioned after baseline), and (3) transitions to dialysis 11.6 months before baseline (the average transition

time in our cohort for participants who transitioned before baseline). We used a similar approach to estimate the *difference* in cognitive function at two years for a typical participant who transitioned to dialysis 0.7 years after baseline, and a typical participant who initiated dialysis 11.6 months before baseline, net of the expected cognitive function if the transition had not occurred. We used data for patients who did not transition to estimate the counterfactual difference for both groups who transitioned to dialysis. We used SAS v8.0 for all analyses (Cary, NC).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S, Smith GE, Hochhalter AK, Collins AJ, Kane RL. Cognitive impairment in hemodialysis patients is common. Neurology. 2006 Jul 25; 67(2):216–223. [PubMed: 16864811]

2. Drew DA, Weiner DE, Tighiouart H, Scott T, Lou K, Kantor A, Fan L, Strom JA, Singh AK, Sarnak MJ. Cognitive function and all-cause mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2015 Feb; 65(2):303–311. [PubMed: 25240262]

3. Teschan PE, Ginn HE, Bourne JR, Ward JW, Hamel B, Nunnally JC, Musso M, Vaughn WK. Quantitative indices of clinical uremia. Kidney Int. 1979; 15(6):676–697. [PubMed: 222935]

4. Teschan PE, Ginn HE, Bourne JR, Ward JW. Assessing the adequacy of dialysis. Proc Eur Dial Transplant Assoc. 1981; 18:697–705. [PubMed: 7329997]

5. Kurella Tamura M, Meyer JB, Saxena AB, Huh JW, Wadley VG, Schiller B. Prevalence and significance of stroke symptoms among patients receiving maintenance dialysis. Neurology. 2012 Sep 4; 79(10):981–987. [PubMed: 22875090]

6. Seliger SL, Siscovick DS, Stehman-Breen CO, Gillen DL, Fitzpatrick A, Bleyer A, Kuller LH. Moderate renal impairment and risk of dementia among older adults: the Cardiovascular Health Cognition Study. J Am Soc Nephrol. 2004 Jul; 15(7):1904–1911. [PubMed: 15213280]

7. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. Journal of the American Society of Nephrology: JASN. 2015 Apr; 26(4):957–965. [PubMed: 25234925]

8. Kurella Tamura M, Unruh ML, Nissenson AR, Larive B, Eggers PW, Gassman J, Mehta RL, Kliger AS, Stokes JB. Frequent Hemodialysis Network Trial G. Effect of more frequent hemodialysis on cognitive function in the frequent hemodialysis network trials. Am J Kidney Dis. 2013 Feb; 61(2):228–237. [PubMed: 23149295]

9. Seliger SL, Gillen DL, Longstreth WT Jr, Kestenbaum B, Stehman-Breen CO. Elevated risk of stroke among patients with end-stage renal disease. Kidney Int. 2003 Aug; 64(2):603–609. [PubMed: 12846756]

10. Seliger SL, Longstreth WT Jr, Katz R, Manolio T, Fried LF, Shlipak M, Stehman-Breen CO, Newman A, Sarnak M, Gillen DL, Bleyer A, Siscovick DS. Cystatin C and Subclinical Brain Infarction. J Am Soc Nephrol. 2005 Oct 19.

11. Sarnak MJ, Tighiouart H, Scott TM, Lou KV, Sorensen EP, Giang LM, Drew DA, Shaffi K, Strom JA, Singh AK, Weiner DE. Frequency of and risk factors for poor cognitive performance in hemodialysis patients. Neurology. 2013 Jan 29; 80(5):471–480. [PubMed: 23303848]

12. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, Powers WJ, DeCarli C, Merino JG, Kalaria RN, Vinters HV, Holtzman DM, Rosenberg GA, Wallin A, Dichgans M, Marler JR, Leblanc GG. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke. 2006 Sep; 37(9):2220–2241. [PubMed: 16917086]

13. Murray AM, Seliger S, Lakshminarayan K, Herzog CA, Solid CA. Incidence of stroke before and after dialysis initiation in older patients. J Am Soc Nephrol. 2013 Jun; 24(7):1166–1173. [PubMed: 23620399]

14. Sirich TL, Funk BA, Plummer NS, Hostetter TH, Meyer TW. Prominent accumulation in hemodialysis patients of solutes normally cleared by tubular secretion. Journal of the American Society of Nephrology : JASN. 2014 Mar; 25(3):615–622. [PubMed: 24231664]

15. Kurella Tamura M, Chertow GM, Depner TA, Nissenson AR, Schiller B, Mehta RL, Liu S, Sirich TL. Study FHN. Metabolic Profiling of Impaired Cognitive Function in Patients Receiving Dialysis. J Am Soc Nephrol. 2016 Jul 21.

16. Kurella Tamura M, Covinsky KE, Chertow GM, Yaffe K, Landefeld CS, McCulloch CE. Functional status of elderly adults before and after initiation of dialysis. N Engl J Med. 2009 Oct 15; 361(16):1539–1547. [PubMed: 19828531]

17. Jassal SV, Chiu E, Hladunewich M. Loss of independence in patients starting dialysis at 80 years of age or older. N Engl J Med. 2009 Oct 15; 361(16):1612–1613. [PubMed: 19828543]

18. Morton RL, Snelling P, Webster AC, Rose J, Masterson R, Johnson DW, Howard K. Factors influencing patient choice of dialysis versus conservative care to treat end-stage kidney disease. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2012 Mar 20; 184(5):E277–E283.

19. Fried TR, Tinetti ME, Iannone L, O'Leary JR, Towle V, Van Ness PH. Health outcome prioritization as a tool for decision making among older persons with multiple chronic conditions. Arch Intern Med. 2011 Nov 14; 171(20):1854–1856. [PubMed: 21949032]

20. Davison SN. End-of-life care preferences and needs: perceptions of patients with chronic kidney disease. Clin J Am Soc Nephrol. 2010 Feb; 5(2):195–204. [PubMed: 20089488]
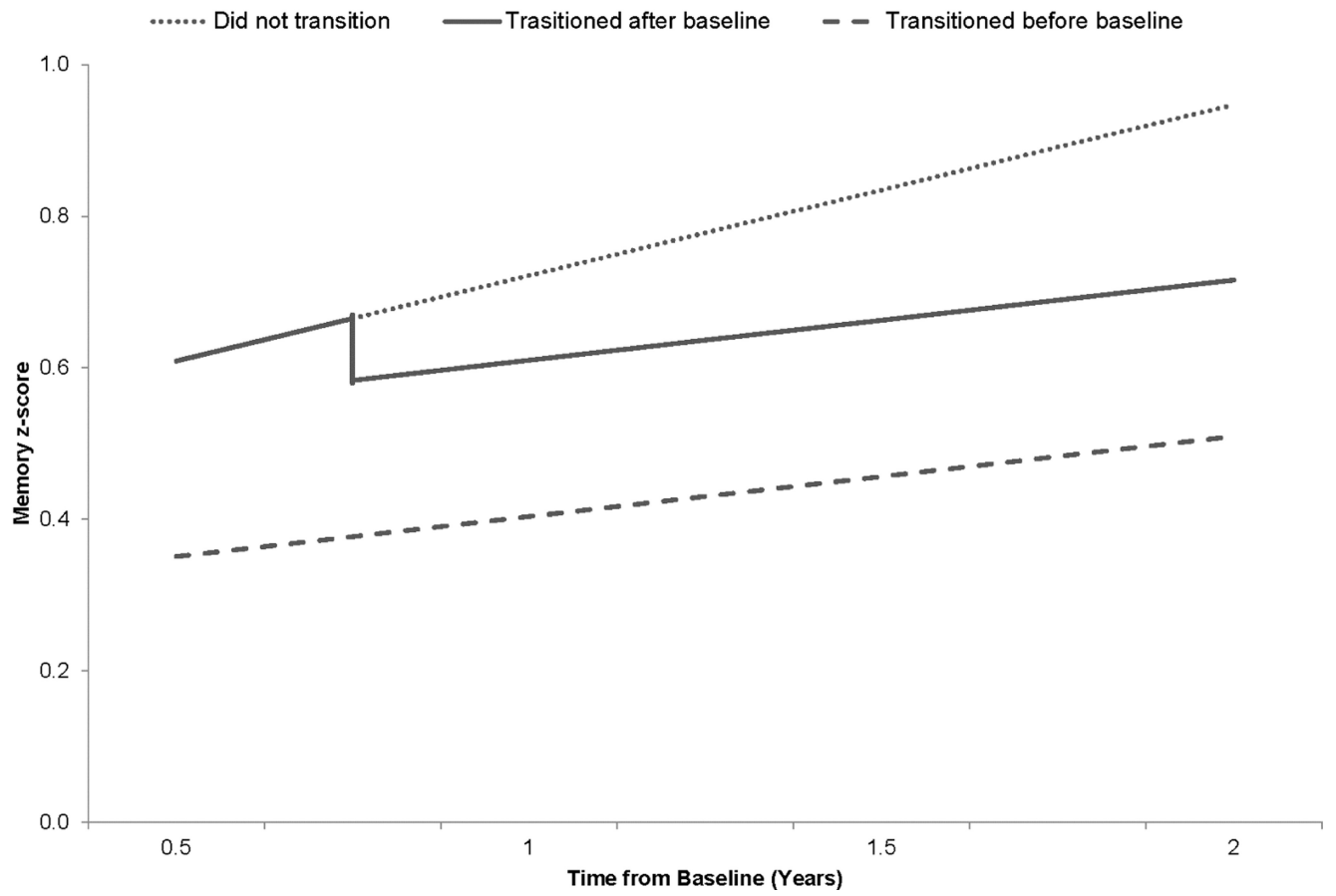
Panel A. Global cognition
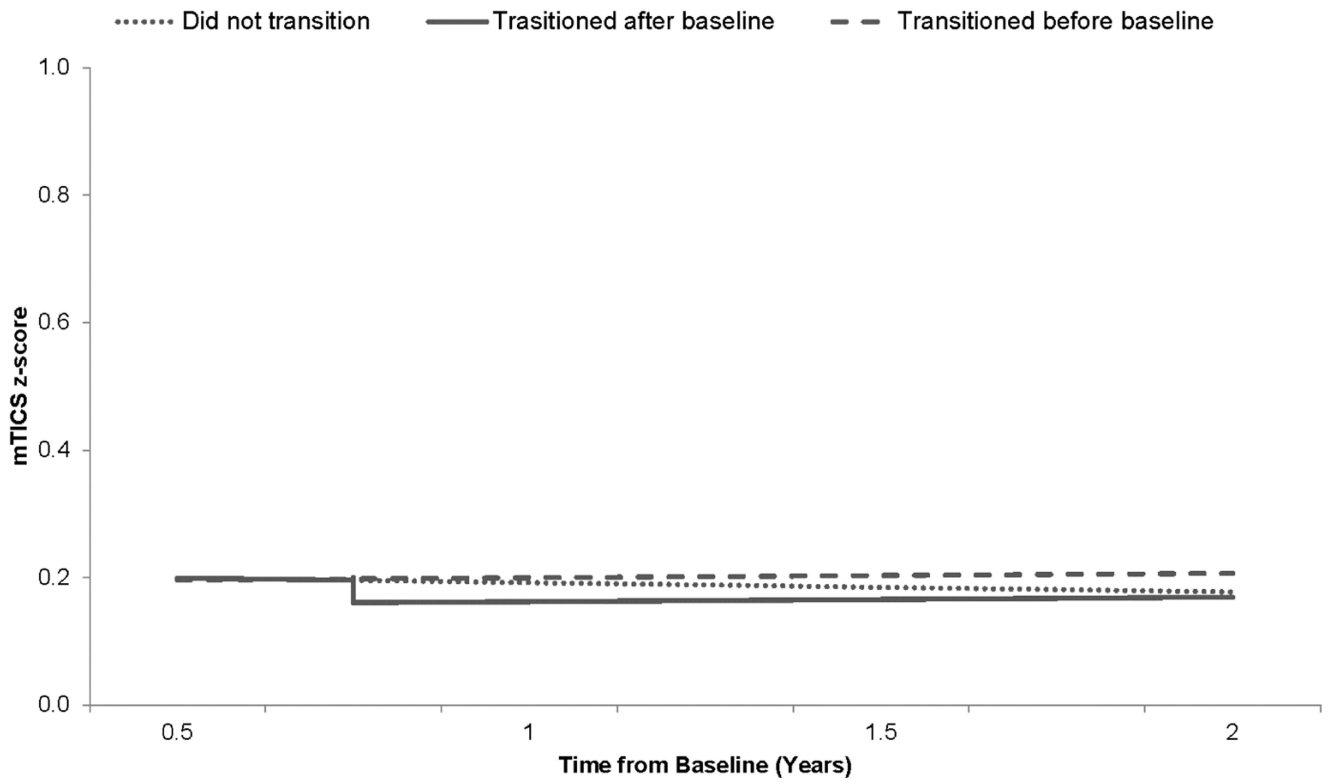
Panel B. Memory

Panel C. Executive function
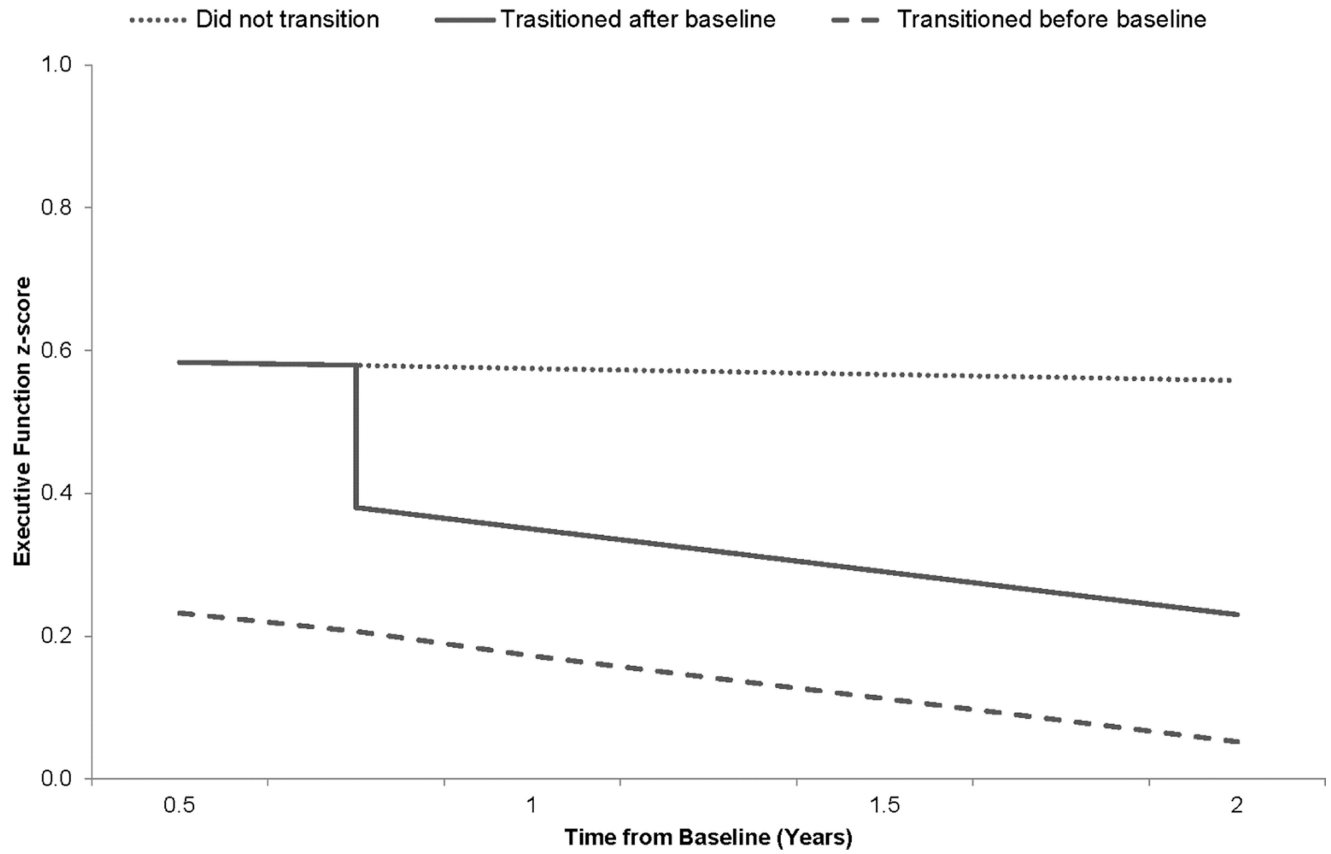
Figure 1.
Predicted trajectory of global cognitive function (Panel A), memory (Panel B) and executive function (Panel C) for participant with advanced CKD who does not transition to dialysis (dotted line), who transitions to dialysis after baseline (solid line), and who transitions to dialysis prior to baseline (dashed line).
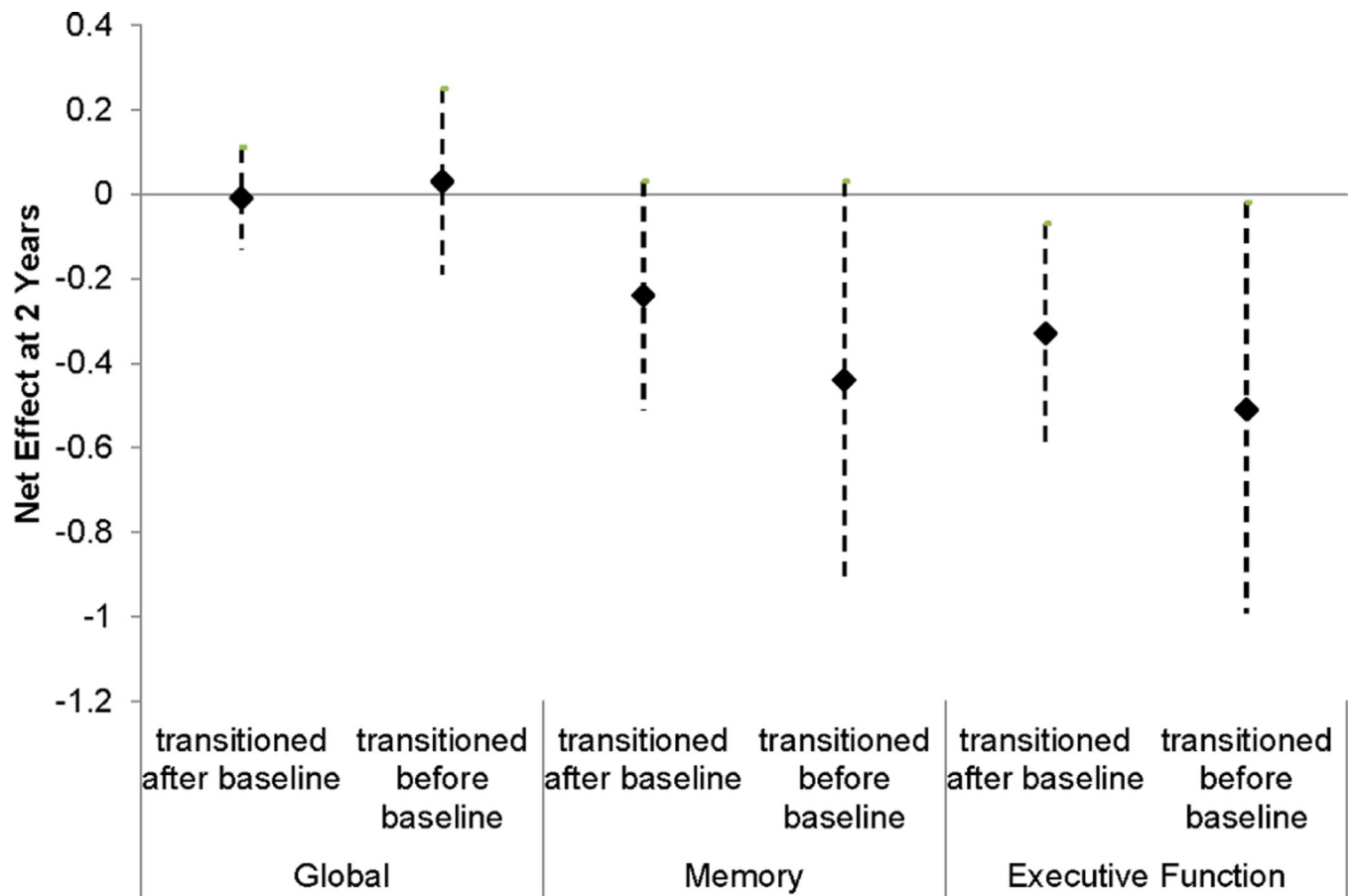
Figure 2.
Estimated net difference in cognitive function z-scores at two years for participants with advanced CKD who transition to dialysis after baseline and those who transitioned to dialysis before baseline, compared to participants who do not transition to dialysis, adjusted for age, sex, race and education. Dashed lines represent 95% confidence intervals.

Table 1

Characteristics of participants with advanced CKD at baseline, stratified by dialysis transition status. Results are presented as N (%) unless otherwise noted.

Participant characteristics	Did not transition to dialysis (N=123)	Transitioned to dialysis after baseline (N=37)	Transitioned to dialysis prior to baseline (N=52)	p-value
Age (years) [*]	64.7 ± 10.4	64.5 ± 10.5	62.0 ± 11.0	0.29
Male	63 (51.2)	16 (43.2)	29 (55.8)	0.51
Black race	54 (43.9)	19 (51.4)	40 (76.9)	<0.001
College education	82 (66.7)	27 (73.0)	26 (50.0)	0.05
Diabetes mellitus	65 (52.9)	25 (67.6)	32 (61.5)	0.23
Hypertension	120 (97.6)	37 (100.0)	52 (100.0)	0.33
Prior cardiovascular disease	47 (38.2)	15 (40.5)	19 (36.5)	0.93
Current smoker	12 (9.8)	6 (16.2)	6 (11.5)	0.55
eGFR (ml/min/1.73m^2) [*]	22.8 ± 7.3	16.1 ± 6.6	--	<0.001
Systolic blood pressure (mm Hg)	131 ± 22	140 ± 21	127 ± 22	0.02
Diastolic blood pressure (mm Hg)	70 ± 12	72 ± 13	66 ± 11	0.06
Months receiving dialysis at baseline	--	--	11.6 ± 7.6	--
Dialysis modality during follow-up [**]				--
Hemodialysis	--	29 (78.4)	43 (82.7)	
Peritoneal Dialysis	--	8 (21.6)	10 (19.2)	
Cognitive domain z-score				
Global	0.1 ± 0.7	0.1 ± 0.7	−0.2 ± 0.7	0.01
Memory	−0.1 ± 1.7	0.1 ± 1.3	−0.7 ± 2.0	0.08
Executive Function	0.2 ± 1.6	−0.002 ± 1.5	−0.1 ± 1.6	0.60

[*]
Mean ± standard deviation

[**]
Participant may have had more than one dialysis modality.

Higher z-scores indicate better cognitive function.

Abbreviations: CKD – chronic kidney disease, eGFR – estimated glomerular filtration rate

Change in cognitive function before and after dialysis initiation

Cognitive domain z-score	Rate of Change			Dialysis (vs. pre-dialysis)	p-value	p-value for joint effect
	Pre-Dialysis	Post-Dialysis	p-value			
Global	−0.01 (−0.08, 0.05)	0.01 (−0.07, 0.09)	0.60	−0.04 (−0.15, 0.08)	0.56	0.81
Memory	0.23 (0.07, 0.39)	0.11 (−0.08, 0.30)	0.24	−0.08 (−0.36, 0.20)	0.57	0.12
Executive Function	−0.01 (−0.15, 0.12)	−0.12 (−0.28, 0.04)	0.15	−0.20 (−0.44, 0.04)	0.10	0.01

Adjusted for age, sex, race, education and their interactions with time, in addition to visit number

Change in cognitive function is expressed as a change in cognitive z-score per year. A negative parameter estimate indicates declining cognitive function over time. A negative parameter estimate for dialysis indicates lower cognitive function after dialysis initiation.

*
2-degree of freedom test for the immediate effect of initiation of dialysis and change in slope