HHS Public Access

Author manuscript

Am J Kidney Dis. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Am J Kidney Dis. 2016 April ; 67(4): 593–600. doi:10.1053/j.ajkd.2015.11.008.

The Brain in Kidney Disease (BRINK) Cohort Study: Design and Baseline Cognitive Function

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Financial Disclosure: The authors declare that they have no other relevant financial interests.

Contributions: Research idea and study design: AMM, DET, SLP, BH, DTG, RNF, YS, KL, DSK, PV, CRJ; data acquisition: AMM, SLP, EMA, KM, LM, RR, PD; data analysis/interpretation: AMM, EJB, DET, CSD, BH, DTG, RNF, PD, CSD; statistical analysis: EJB, BH, DTG, CSD; and supervision or mentorship: AMM, SLP. 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. AMM 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.

Peer Review: Evaluated by 2 external peer reviewers, a Statistical Editor, a CoEditor, and the Editor-in-Chief.

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Abstract

Background—The Brain in Kidney Disease (BRINK) Study aims to identify mechanisms that contribute to increased risk of cognitive impairment (CI) in chronic kidney disease (CKD) patients. We describe the rationale, design, and methods of the study and report baseline recruitment and cognitive function results.

Study Design—Longitudinal observational cohort study of the epidemiology of CI in CKD. The primary aim is to characterize the association between (a) baseline and incident stroke, white matter disease, estimated glomerular filtration rate (eGFR), inflammation, microalbuminuria, dialysis initiation, and (b) cognitive decline over 3 years in a CKD cohort with mean eGFR < 45 mL/min/1.73 m^2.

Setting & Participants—Community-dwelling participants aged 45 years or older recruited from four health systems into two groups: reduced eGFR, defined as eGFR < 60 mL/min/1.73 m^2 (non-dialysis-dependent), and control, defined as eGFR ≥ 60 mL/min/1.73 m^2.

Predictor—eGFR group.

Outcomes—Performance on cognitive function tests and structural brain magnetic resonance imaging.

Measurements—Sequential cognitive and physical function testing, serum and urine biomarker measurement, and brain magnetic resonance images over 3 years.

Results—Of 554 participants, mean age was 69.3 years; 333, 88, and 133 had eGFR <45 (non-dialysis dependent, non-transplant), 45-<60, and ≥ 60 (controls) mL/min/1.73 m^2, respectively. Mean eGFR in the reduced eGFR participants was 34.3 mL/min/1.73 m^2. Baseline cognitive performance was significantly associated with eGFR in all domains except language. Participants with eGFR < 30 mL/min/1.73 m^2 performed significantly worse than those with eGFR ≥ 30 mL/min/1.73 m^2 on tests of memory, processing speed, and executive function. Participants with reduced eGFR overall scored worst on the Immediate Brief Visual-Spatial Memory Test-Revised.

Limitations—Healthy cohort bias, competing risk of death versus cognitive decline.

Conclusions—Cognitive function was significantly worse in participants with eGFR < 30 mL/min/1.73 m^2. Future BRINK analyses will measure risk factors for cognitive decline using the longitudinal data.

INDEX WORDS

cognitive impairment; renal function; estimated glomerular filtration rate (eGFR); structural brain magnetic resonance imaging; stroke; neuropsychological testing; memory; executive function; processing speed; language; attention; chronic kidney disease (CKD); brain aging; study design

The increased risk of prevalent cognitive impairment (CI) in chronic kidney disease (CKD) patients, especially those with estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 $m^{2,1}$ is well recognized.[1–5] However, the mechanisms that contribute to this increased risk have not been adequately explored. Most cohort studies of CI in CKD have primarily included patients with mild to moderate CKD (eGFR, 45-<60 mL/min/1.73 m^2), not those with eGFR < 45 mL/min/1.73 m^2, who are at higher risk of CI.[1–5] Additionally, to our knowledge, previous longitudinal studies have not followed patients through initiation of dialysis to measure its effect on CI, or included brain imaging to measure structural outcomes of CKD.

We designed the prospective Brain in Kidney Disease (BRINK) Study to address these study design and knowledge gaps. The BRINK Study is a longitudinal observational cohort study of the natural history and epidemiology of CI in CKD. Its primary goal is to improve understanding of the pathophysiology of CI in patients with moderate to severe CKD (eGFR < 45 mL/min/1.73 m^2), who are non-dialysis-dependent or without a kidney transplant at baseline. Specifically, it aims to characterize the association between (a) baseline and incident stroke, white matter disease, eGFR, inflammation, microalbuminuria, and dialysis initiation, and (b) cognitive decline over 3 years in community-dwelling CKD outpatients. Secondary aims are to: 1) measure the prevalence and severity of CI (global and individual domains) in CKD and control participants (cross-sectional at baseline), 2) elucidate risk factors for prevalent CI in CKD participants and 3) compare global and domain-specific cognitive decline over 3 years in CKD and control participants (longitudinal). The BRINK Study has completed baseline recruitment and follow-up is underway.

Although cognitive function is the primary BRINK outcome, our overall long-term goal is to describe the effect of CKD on multiple geriatric outcomes using the paradigm of CKD exposure *as a model of accelerated brain aging*. Thus, in addition to measuring the effect of CKD on cognitive function, we also measure its effect on physical function, frailty, multiple blood and urine biomarkers, and structural brain magnetic resonance imagine (MRI) outcomes. Here, we describe the design and methods of the BRINK study and report baseline recruitment results, demographics, and prevalence of domain-specific CI by eGFR status.

METHODS

Study Population: Recruitment Design

Herein we describe participants either as those with reduced eGFR (this group is further subdivided using eGFR categories) or as controls (participants with eGFR ≥ 60 mL/min/1.73 m^2) because we do not include their albuminuria status, which would be required for classifying their CKD status in accordance with the 2012 KDIGO (Kidney Disease: Improving Global Outcomes) CKD guidelines. Participants were classified into eGFR categories based on baseline BRINK visit serum creatinine and calculated eGFR, using the CKD-EPI creatinine equation[7]. Our original goal was to recruit 2 groups: 350 participants with eGFR < 45 and 100 with eGFR ≥ 60 mL/min/1.73 m^2. However, despite requiring at least two eGFRs < 40 mL/min/1.73 m^2 from medical records over the previous year to screen for eGFR <45 mL/min/1.73 m^2, some had eGFRs of 45- <60 mL/min/1.73 m^2

calculated from their BRINK baseline visit creatinine. Thus we modified our inclusion criteria to include a third group with eGFR 45- < 60 mL/min/1.73 m^2, to reflect the full range of kidney function in the community population.

We recruited three groups of community-dwelling outpatients: those with eGFR < 45 mL/min/1.73 m^2 (non-dialysis-dependent, non- transplant), those with eGFR 45-<60 mL/min/1.73 m^2, and a comparison control group with eGFR ≥ 60 mL/min/1.73 m^2 (acknowledging that the control group includes people with early CKD [ie, those with eGFR of 60–90 mL/min/1.73 m^2 and kidney damage]), with or without albuminuria. Control participants were recruited to approximate the age, race, education, diabetes status, and sex distributions (in order of priority) of the combined reduced eGFR groups.

Eligibility and Exclusion Criteria

Eligibility criteria *for reduced eGFR participants* were as follows: age 45 years or older, eGFR of < 45 or 45-<60 mL/min/1.73 m^2, ability to complete a 90-minute cognitive and physical function battery, and English as first language. Eligibility criteria *for controls* were identical, except for eGFR ≥ 60 mL/min/1.73 m^2. Exclusion criteria for all participants were recent psychosis, chemical dependency, chronic high narcotic use, inability to complete the Modified Mini–Mental State Examination[8] (3MSE) due to sensory deficits or severe CI, nursing home residence, dialysis-dependent or kidney transplant recipient at the time of screening, or inability to provide signed consent due to severe CI as judged by providers, family, or caregivers.

Participants are from four health care institutions in Minneapolis: Hennepin County Medical Center (> 65% non-white), the University of Minnesota Medical Center (> 80% white), the Department of Veterans Affairs Medical Center (> 90% white males), and HealthPartners Institute for Education and Research (80% white). The Institutional Review Boards of collaborating institutions approved the study (Hennepin County Medical Center approval no: 11–3393; University of Minnesota: 1203M11122; Veterans Affairs Medical Center: 4364-B; and HealthPartners: A12–282). At each site, we used three recruitment methods: referral by providers, screening using electronic medical records followed by letters or phone calls, and onsite posters and newsletters. Written informed consent was obtained from participants at the baseline visit.

Study Design Overview

The baseline assessment (2.5 hours) includes detailed cognitive testing, self- reported function using activities of daily living measures, a performance-based physical function battery, medical history questionnaire, and blood and urine laboratory measurements (urine albumin-creatinine ratio, multiple biomarkers). Follow-up cognitive and physical function assessments (1.5 hours) are conducted every 6 months (Table S1, available as online supplementary material).

Participant Follow-up Time

Targeted follow-up time is 3 years, but we will follow all participants for up to 4 years. We contact participants every 3 to 6 months in person or by phone to maximize retention,

monitor for stroke-related symptoms and diagnoses, and monitor dialysis status. For participants unable to attend a visit in person, as much as possible is conducted via telephone, including medical history questionnaires, the standardized Telephone Interview for Cognitive Status[9] (TICS), which correlates highly with the 3MSE,[8] and portions of a cognitive battery (Table S2). Participants who are unable to attend a visit due to acute illness are rescheduled approximately 2 weeks after the illness has resolved.

The predicted mean follow-up time is 2.6 years for non-dialysis CKD patients and 1.4 years after dialysis initiation for patients who transition to dialysis, based on predicted mortality rates of approximately 10% for CKD and 20% for incident dialysis patients[6] and estimated annual dialysis initiation rates of 13% for participants with eGFR of approximately 30 mL/min/1.73 m^2. However, because the actual mortality rates in BRINK over a mean of approximately 1.7 years of follow-up have been < 2% per year for CKD participants and 10% per year for incident dialysis patients, we anticipate longer mean follow-up times.

Study Measurements

Measurement of Cognitive Function—Cognitive function is assessed every 6 months using two alternating cognitive batteries of validated neuropsychological tests to minimize both loss of follow-up cognitive data due to death or study withdrawal, and learning effects. Cognitive battery 1 is conducted at baseline and annually; cognitive battery 2, at the 6-month follow-up and annually thereafter.

Cognitive battery 1: 1) 3MSE,[8] global cognitive function; 2) Hopkins Verbal Learning Test-Revised[10] (HVLTR), verbal memory; 3) Brief Visuospatial Memory Test-Revised[11] (BVMTR), visual-spatial/memory; 4) Symbol Digit Modalities Test[12] (SDMT) attention, concentration, and processing speed; 5) Controlled Oral Word Association Test[13] (COWAT), verbal fluency/language, semantic memory; 6) Color Trails Tests 1 and 2[14] (CTT1, CTT2), processing speed, executive function; 7) Wechsler Digit Span,[15] attention, auditory short-term memory; 8) Patient Health Questionniare-9[16] (PHQ-9), depression.

Cognitive battery 2: 1) 3MSE; 2) SDMT; 3) Wechsler Vocabulary Test,[17] word knowledge, verbal concept formation, fund of knowledge; 4) Wechsler Matrix Reasoning Test,[17] visual information processing, abstract reasoning skills; 5) Grooved Pegboard Examination,[18] manipulative dexterity; 6) PHQ-9[16].

Results of cognitive battery 1 are considered the primary cognitive results. Results of cognitive battery 2 provide missing data at the interval 6-month visits for participants who miss their next annual visit, and supplemental descriptive cognitive data to characterize the population at baseline and longitudinally. The 3MSE and SDMT are included in both batteries to enable direct measurement of changes in global cognitive function and executive function/processing speed, which is believed to be especially affected in vascular CI. To minimize practice effects, we alternate the three words for verbal recall on the 3MSE and use four alternating versions of the SDMT. In addition, in cognitive battery 1, we alternate four versions of the HVLTR, BVMTR, and COWAT. The Clinical Dementia Rating Scale[19] is triggered for participants who score < 88 on the 3MSE to estimate severity of dementia

using patient and informant interviews. Detailed descriptions of all cognitive tests appear in part *a* of Item S1.

Classifying Cognitive Function—Cognitive function is classified using individual tests to measure performance in specific cognitive domains, and the cognitive summary score to measure global CI.

Performance on individual tests: Performance is measured using raw scores and with T-scores for the following individual tests: HVLTR, BVMTR, CTT-1, CTT-2, SDMT, and COWAT. T Scores adjust for age and sometimes education (CTT-1, CTT-2, SDMT, COWAT) and race (COWAT) A score of 50 denotes normal cognition; 1 standard deviation [SD] = 10. To classify test-specific CI, T-scores of ≤ 1 SD below the mean published norm are classified as normal cognitive function; 1.0–1.49 SDs below, as mild CI; 1.5–1.99 SDs below, as moderate CI; and ≥ 2.0 SDs below, as severe CI.

Cognitive summary score: The primary continuous global cognitive outcome measure is the cognitive summary score, defined as the average of the T-scores from the HVLTR/Immediate, HVLTR/Delayed, CTT-1, CTT-2, SDMT, BVMTR/Immediate, BVMTR/Delayed, and COWAT. As for test-specific CI, a summary score of ≤ 1 SD below the mean published norm is classified as normal cognitive function; 1.0–1.49 SDs below, as mild CI; 1.5–1.99 SDs below, as moderate CI; and ≥ 2.0 SDs below, as severe CI. We are also conducting sensitivity analyses to assess including two additional cognitive tests: a) a second measure of language (semantic fluency) using the 1 minute animal list, which is already measured during the 3MS by extending the allotted time from 30 seconds to 1 minute, and b) the Wechsler Digit Span to measure attention and working memory.

The 3MSE, Wechsler Vocabulary Test, Wechsler Matrix Reasoning Test, Grooved Pegboard Examination, PHQ-9, and Wechsler Digit Span are currently not included in the cognitive summary score and thus not used to classify global CI severity, but are used to characterize the performance of the BRINK population in their associated cognitive domains.

Structural Brain MRI—Structural brain MRI is obtained to measure stroke and other structural pathology at baseline and at the 36-month follow-up. In addition, in the subsample of MRI participants who transition to end-stage renal disease, repeat MRIs are obtained within 90 days after dialysis initiation or kidney transplantation, and every 6 months thereafter (Table S2).

We conducted a power calculation (≥ 80% power, 2-sided $\alpha = 0.05$) using preliminary data from our previous CKD pilot study (not reported here) to estimate the number of magnetic resonance images needed to determine the effect of incident stroke over the 3-year follow-up (as detected on year-3 MRI) on CI (measured by change in cognitive summary score). Part *b* of Item S1 shows the number of MRIs needed to determine the effect of incident stroke over the 3-year follow-up (as detected on year 3 MRI) on CI (measured by change in cognitive summary score). This yielded a target BRINK MRI subsample size of 130 reduced eGFR (<60 mL/min/1.73 m^2) and 50 control (eGFR ≥ 60 mL/min/1.73 m^2) participants.

Reduced eGFR MRI participants were recruited on a rolling basis by enrolling MRI-eligible participants at the time of their baseline visit until the MRI recruitment goals were met. Control MRI participants were recruited to approximate the age, race, and diabetes status distributions of the combined reduced eGFR groups. Written informed consent for the MRI was obtained at the baseline BRINK visit.

MRI methods: All participants are scanned with a 1.5T Phillips Ingenia MRI scanner. Primary structural MRI outcomes assessed on FLAIR images are a) number of cortical and subcortical infarcts, and b) volume of subcortical and periventricular white matter hyperintensities. We also measure regional and total gray matter volumes and cortical thickness using magnetization-prepared rapid gradient-echo (MPRAGE) images and FreeSurfer version 5.3 (Martinos Center for Biomedical Imaging)[20], including a total of 34 regions of interest, and ventricular and hippocampal volumes as a measure of Alzheimer's disease-related neurodegeneration. Microhemorrhages are measured on T2* GRE images and defined as homogenous hypointense lesions up to 10 mm in diameter in the gray or white matter. Fractional anisotropy and medial diffusivity on diffusion tensor imaging are used to measure white matter structural integrity. Quality control operations are performed as described by Jack et al.[21] The detailed imaging protocol and imaging measures are described in part *c* of Item S1.

Incident Stroke Ascertainment—Incident stroke and transient ischemic attack (TIA) are identified using 1) the participant's electronic medical record over the duration of follow-up for discharge diagnoses of acute stroke and TIA (ICD-9 codes 430–438; ICD-10 when available), and brain MRI reports for MRIs obtained outside of the BRINK study; 2) self-report of incident stroke or TIA or symptoms using the Questionnaire for Verifying Stroke-Free Status[22] (QVSFS) (or informant report for participants with 3MSE scores < 88), administered at each 6 month follow- up visit, and additionally every intervening 3 months by phone in dialysis or transplant patients. The QVSFS will provide supplementary data for secondary analyses to classify possible strokes not noted in the medical record, acknowledging that not all strokes are diagnosed or reported; 3) among BRINK participants with a 3-year follow-up MRI or post-dialysis/transplantation MRIs, incident stroke is identified by comparing the 3-year or post-transition MRI to the baseline MRI. These strokes are further classified as symptomatic or subclinical (silent) based on the self-reported QVSFS and medical records of stroke/TIA symptoms. See part *d* of Item S1 for further details regarding the QVSFS, stroke ascertainment and adjudication.

Physical Function Assessment—The BRINK Study includes biannual measurement of self-reported and performance-based measures of physical function to assess level of independence (part *e* of Item S1).

Laboratory Measures—Non-fasting blood samples are drawn from an antecubital vein. Annual laboratory tests include the following: sodium, potassium, chloride, carbon dioxide, anion gap, albumin, calcium, creatinine, phosphorus, glucose, serum urea nitrogen, hemoglobin, hemoglobin A1c, urine albumin and creatinine, urine microalbumin-creatinine ratio, and total cholesterol; the are processed at the CLIA (Clinical Laboratory Improvement

Amendments)-certified Hennepin County Medical Center Clinical Laboratory and Pathology. Other biomarkers, measured at baseline and 36-month follow-up, include markers of inflammation (cystatin C, interleukin [IL] 6 in serum, IL-6 in urine, tumor necrosis factor α [TNF-α], and TNF-α receptor 1), 8-isoprostane (marker of oxidative stress), parathyroid hormone, 25-hydroxyvitamin D, advanced glycation end products, clusterin (marker of neuronal apoptosis, also may inhibit αβ amyloid), asymmetric dimethylarginine (marker of uremia); an endogenous inhibitor of nitric oxide synthase. Apolipoprotein E4 (APO-E4) genotype is measured at baseline only. For laboratory procedures, please see part *f* of Item S1.

Other Measures—See part *g* of Item S1 for details of the medical history interview (including history of cardiac disease); diabetes and hypertension definitions; blood pressure, electrocardiogram and BMI measurements; frailty and PHQ-9 depression measures; CHA_2DS_2-VASc scale[23, 24] for patients with atrial fibrillation; Godin Leisure-Time Exercise Questionnaire[25]; and Medication Reconciliation Assessment.

RESULTS

Baseline Characteristics

During 2011–2015, 2,177 people were assessed for eligibility; 1,420 were eligible and confirmed of which 554 were recruited into the BRINK Study (39% response rate; Figure S1). Complete demographic characteristics of non-participants are not available due to confidentiality and HIPAA (Health Insurance Portability and Accountability Act) compliance concerns. The 554 participants included 144 (26%) with severely reduced eGFR (< 30 mL/min/1.73 m^2), 189 (34%) with moderate to severely reduced eGFR (30- <45 mL/min/1.73 m^2), 88 (16%) with mildly to moderately reduced eGFR (45- <60 mL/min/1.73 m^2), and 133 (24%) classified as controls (eGFR ≥ 60 mL/min/1.73 m^2) (Table 1). Mean eGFR among all with reduced eGFR was 34.3 mL/min/1.73 m^2. Reduced eGFR participants were on average slightly older (70.4 years) than control participants (67.4 years), and there was a higher percentage of men in the group with eGFR < 30 mL/min/1.73 m^2 compared to the other groups (61.7% compared to range of 42.1%–52.1%, respectively). Race distribution was similar between groups. As expected, prevalence of diabetes, hypertension and stroke were higher among reduced eGFR participants than among controls, and systolic blood pressure was higher; education levels were lower and daily medication use tended to be higher.

Baseline Cognitive Function and Association With eGFR

Performance on individual cognitive tests revealed significant associations between eGFR groups and cognitive function in unadjusted ANOVA analyses for raw scores and T scores across all individual tests and for all cognitive domains (Table 2) In addition, as the column-based letter superscript comparisons between eGFR groups indicate, the greatest differences in global cognitive function (3MSE) and in all cognitive domains including verbal memory were between the lowest and highest eGFR groups: eGFR < 30 versus eGFR ≥ 60 mL/min/1.73 m^2. The subgroup with eGFR < 30 mL/min/1.73 m^2 represented 34% of our reduced eGFR population. Overall, reduced eGFR participants scored worst on the BVMTR/

Immediate, a test of ability to recall and reproduce a set of six polygons after 30 seconds of exposure, and best on the COWAT, a measure of verbal fluency. The T scores of 0.25–0.5 SD below norms in the groups with eGFR 30-< 45 and 45- <60 mL/min/1.73 m^2 reflect a very modest level of CI. However, at 0.75–1.0 SD below norms, the T-scores in the group with eGFR < 30 mL/min/1.73 m^2 approach criteria for the diagnosis of mild cognitive impairment, defined as 1.0–1.5 SD below norms;[26] the mean score of 92.4 on the 3MSE in this group is also consistent with this diagnosis.

DISCUSSION

The BRINK Study is an ongoing prospective cohort study of the epidemiology of CI in CKD and of CKD exposure *as a model of accelerated brain aging* on multiple geriatric outcomes. Its long-term goal is to identify mechanisms of CI in people with CKD, and to ultimately design interventions to prevent CI.

Our baseline cognitive function test results reflect a strong overall association with eGFR across all cognitive domains, but the greatest differences in performance were between participants with eGFR < 30 versus ≥ 60 mL/min/1.73 m^2. This suggests that although eGFR < 45 mL/min/1.73 m^2 is an effective cutpoint to identify CI in CKD,[1, 27] CI is most likely to occur at eGFR < 30 mL/min/1.73 m^2. This subgroup made up 34% of our reduced eGFR population; in many previous studies, it was less than 10%.[1–3, 27]

The individual cognitive test most strongly associated with eGFR was the BVMTR/ Immediate recall. The Maine-Syracuse study found similar results; tests of visual memory and scanning were strongly associated with eGFR < 60 mL/min/1.73 m^2 as was global cognitive function. [5] In contrast to other studies,[5, 28] ours found that eGFR < 45 mL/min/ 1.73 $m^2$was associated with lower performance in all cognitive domains, not only executive function, which is often reported to be the most affected by CKD due to its proposed vascular or subcortical origins. For the mild to moderate reduced eGFR groups (eGFR 30- <60 mL/min/1.73 m^2), we found significant albeit modest impairment in all cognitive domains including verbal (episodic) memory at approximately 0.25–0.5 SD below expected performance. In the group with eGFR < 30 mL/min/1.73 m^2, mean scores were 0.7 to almost 1.0 SD below norms in memory and processing speed/executive function (SDMT), but not language (COWAT). We attribute this to the high proportion of participants with eGFR < 30 mL/min/1.73 m^2 in BRINK, who are more likely to have a longer exposure to CKD and its secondary structural cerebral outcomes. Longitudinal follow-up will better measure the effect of eGFR changes on cognitive performance, adjusting for the multiple covariates measured in BRINK.

Strengths of this unique longitudinal study design include 1) a high proportion of participants with eGFR < 45 mL/min/1.73 m^2, and mean eGFR 34.3 mL/min/1.73 m^2 among participants in the group with reduced eGFR; 2) a rigorous incident stroke detection protocol to measure its role in CI; 3) serum and urine biomarker measurement at baseline and 3 years of inflammation, oxidative stress, uremia, genomic and multiple metabolic measures; 4) follow-up extending after dialysis initiation or kidney transplantation to measure effects on cognitive function; and 5) sequential structural brain MRI to measure the

association of CKD with structural MRI changes and their potentially mediating effect on CI.

We anticipated multiple specific challenges with a study population of reduced eGFR patients and adapted our study design accordingly. The study design challenges, our approach to them, and their outcomes are described in Table S3.

Remaining study limitations include a healthy cohort bias (given low loss to follow-up and mortality rates), potentially decreasing the generalizability of our results to the less healthy US CKD population; however, the prevalence of CI, extent of cognitive decline and relative effect of risk factors for CI that we identify in BRINK CKD participants may also be underestimated. The competing (high) risk of death vs. cognitive decline is a recognized challenge in our longitudinal analyses; the sickest patients who do not survive could well be those at highest risk for CI; thus, the incidence of cognitive decline and associations of risk factors with CI may be underestimated. However, we accounted for this in our sample size and follow-up time calculations, and mortality rates are much lower than predicted. Our sample size may limit our ability to match or adjust for all comorbid conditions in analyses of risk factors for CI in reduced eGFR and control participants. The association of albuminuria to cognitive function is not addressed in this report and albuminuria is not included in classification of CKD groups. This will be done in future analyses.

The results from the BRINK Study can be used to improve clinical care of CKD patients. Our baseline cognitive test results suggest that cognitive screening appears justified for patients with an eGFR < 30 mL/min/1.73 m^2, to identify those who would benefit most from medication and dietary supervision and annual reassessment of ability to live independently, and minimize negative outcomes (e.g., hospitalizations and death). Our longitudinal results will inform physicians regarding expected progression of CI in later-stage CKD patients. We anticipate that achievement of the BRINK Study's aims will enable us to pursue the identification of mechanisms and modifiable risk factors for cognitive decline in CKD and propose potential preventive interventions or treatment. Lastly, our data will begin to describe the extent to which initiating hemodialysis may accelerate cognitive decline, the potential role of incident stroke in CI after initiation,[29] and the role of dialysis dose as a risk factor for incident CI. Based on the results, alternative dialysis dosage and options for nocturnal, daily, and peritoneal dialysis delivery could be explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the BRINK Study participants and families for their generous contribution in time and commitment to the study; Rachel Vasseur and Katelyn Hanneman for their excellent work in participant recruitment and testing; and Nan Booth, MSW, MPH, ELS, for editing.

Support: Funding for this work was provided by National Institute on Aging grant R01 AG03755, Satellite Health Inc., and the Minneapolis Medical Research Foundation. The study sponsors did not play a role in study design; collection, analysis, and interpretation of data; writing the report; or the decision to submit the report for publication.

Reference List

1. Kurella-Tamura M, Wadley V, Yaffe K, et al. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Am J Kidney Dis. 2008; 52(2):227–234. [PubMed: 18585836]
2. Yaffe K, Lindquist K, Shlipak MG, et al. Cystatin C as a marker of cognitive function in elders: findings from the health ABC study. Ann Neurol. 2008; 63(6):798–802. [PubMed: 18496846]
3. Kurella TM, Xie D, Yaffe K, et al. Vascular risk factors and cognitive impairment in chronic kidney disease: the Chronic Renal Insufficiency Cohort (CRIC) study. Clin J Am Soc Nephrol. 2011; 6(2): 248–256. [PubMed: 20930087]
4. Kurella M, Yaffe K, Shlipak MG, Wenger NK, Chertow GM. Chronic kidney disease and cognitive impairment in menopausal women. Am J Kidney Dis. 2005; 45(1):66–76. [PubMed: 15696445]
5. Elias MF, Elias PK, Seliger SL, Narsipur SS, Dore GA, Robbins MA. Chronic kidney disease, creatinine and cognitive functioning. Nephrol Dial Transplant. 2009; 24(8):2446–2452. [PubMed: 19297357]
6. U.S. Renal Data System. USRDS 2006 Annual Data Report: Atlas of Chronic Kidney Disease & End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2006.
7. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150(9):604–612. [PubMed: 19414839]
8. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. J Clin Psychiatry. 1987; 48(8):314–318. [PubMed: 3611032]
9. Fong TG, Fearing MA, Jones RN, et al. Telephone interview for cognitive status: Creating a crosswalk with the Mini-Mental State Examination. Alzheimers Dement. 2009; 5(6):492–497. [PubMed: 19647495]
10. Brandt, J., Benedict, RHB. Professional manual. Lutz, FL: Psychological Assessment Resources, Inc; 2001. Hopkins verbal learning test revised.
11. Benedict, RH. Professional manual. Lutz, FL: Psychological Assessment Resources, Inc; 1997. Brief visuospatial memory test-revised.
12. Smith A. The symbol-digit modalities test: a neuropsychologic test of learning and other cerebral disorders. Learning disorders, Special Child Publications. 1968:83–91.
13. Gladsjo JA, Schuman CC, Evans JD, Peavy GM, Miller SW, Heaton RK. Norms for letter and category fluency: demographic corrections for age, education, and ethnicity. Assessment. 1999; 6(2):147–178. [PubMed: 10335019]
14. D'Elia, LF., Satz, P., Lyons Uchiyama, CL., White, T. Professional manual. Lutz, FL: Psychological Assessment Resources, Inc; 1996. Color trails test. Ref Type: Generic
15. Wechsler, D. Administration and Scoring Manual. San Antonio, Texas: The Psychological Corporation; 1997. Wechsler Memory Scale.
16. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16(9):606–613. [PubMed: 11556941]
17. Wechsler, D. The Wechsler Adult Intelligence Scale-Revised. New York, NY: The Psychological Corporation; 1981.
18. Heaton, RK., Miller, SW., Taylor, MJ., Grant, I. Psychological Assessment Resources, Inc. 2004. Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted NeuropsychologicalNorms for African American and Caucasian Adults. Professional Manual
19. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993; 43(11):2412–2414.
20. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage. 2012; 61(4):1402–1418. [PubMed: 22430496]
21. Jack CR Jr, Bernstein MA, Fox NC, et al. The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. J Magn Reson Imaging. 2008; 27(4):685–691. [PubMed: 18302232]

22. Meschia JF, Brott TG, Chukwudelunzu FE, et al. Verifying the stroke-free phenotype by structured telephone interview. Stroke. 2000; 31(5):1076–1080. [PubMed: 10797168]
23. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001; 285(22):2864–2870. [PubMed: 11401607]
24. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010; 137(2):263–272. [PubMed: 19762550]
25. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. Can J Appl Sport Sci. 1985; 10(3):141–146. [PubMed: 4053261]
26. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol. 2001; 58(12):1985–1992. [PubMed: 11735772]
27. Kurella M, Chertow GM, Fried LF, et al. Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. J Am Soc Nephrol. 2005; 16(7):2127–2133. [PubMed: 15888561]
28. Zammit AR, Katz MJ, Lai JY, Zimmerman ME, Bitzer M, Lipton RB. Association between renal function and cognitive ability domains in the Einstein aging study: a cross-sectional analysis. J Gerontol A Biol Sci Med Sci. 2015; 70(6):764–770. [PubMed: 25394616]
29. Murray AM, Seliger S, Lakshminarayan K, Herzog C, Solid CA. Incidence of stroke associated with dialysis initiation in older patients. J Am Soc Nephro. 2013; (24):1166–1173.

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Table 1

Participant characteristics at baseline

Characteristic	Study sample (*N* = 554)	eGFR < 30 (*n* = 144)	eGFR 30-< 45 (*n* = 189)	eGFR 45-<60 (*n* = 88)	eGFR ≥ 60 (*n* = 133)	*P for* between-group difference
Age, years	69.3 ± 9.9	69.0 ± 10.5	70.4 ± 9.6	70.4 ± 9.8	67.4 ± 9.5	0.04[a]
Age category						0.01[b]
45–54 y	36 (6.5)	15 (10.4)	6 (3.2)	2 (2.)	13 (9.8)	
55–64 y	142 (25.6)	36 (25.0)	54 (28.6)	22 (25)	30 (22.6)	
65–74 y	206 (37.2)	46 (31.9)	62 (32.8)	39 (44)	59 (44.4)	
≥ 75 y	170 (30.7)	47 (32.6)	67 (35.5)	25 (28)	31 (23.3)	
Male sex	278 (50.2)	88 (61.1)	88 (46.6)	46 (52)	56 (42.1)	0.009[b]
Race						0.1[b,c]
African American	71 (12.8)	29 (20.1)	16 (8.5)	11 (13)	15 (11.3)	
White	455 (82.1)	111 (77.1)	163 (86.2)	72 (82)	109 (82.0)	
Other	28 (5.1)	4 (2.8)	10 (5.3)	5 (6)	9 (6.8)	
Duration of education, y	14.4 ± 2.8	13.6 ± 2.7	14.1 ± 2.7	14.6 ± 3.1	15.4 ± 2.5	< 0.001[a]
Highest education attained						< 0.001[b]
< HS or HS graduate	178 (32.3)	61 (42.7)	71 (37.6)	28 (32)	18 (13.6)	
Some college or technical school	170 (30.8)	44 (30.8)	56 (29.6)	25 (28)	45 (34.1)	
College graduate or advanced Degree	204 (36.9)	38 (26.6)	62 (32.8)	35 (40)	69 (52.3)	
eGFR, mL/min/1.73 m^2	45.5 ± 23.5	21.3 ± 6.0	36.6 ± 3.9	50.8 ± 4.1	80.9 ± 14.3	< 0.001[a]
Urine ACR, mg/g	28 [0–193]	206.5 [34.8–1162.5]	36.3 [3.9–197.6]	16.1 [0–79.8]	3.1 [0–11.5]	< 0.001[d]
Diabetes	271 (48.9)	85 (59.0)	85 (45.0)	49 (56)	52 (39.1)	0.003[b]
Hypertension	502 (90.6)	141 (97.9)	181 (95.8)	82 (93)	98 (73.7)	< 0.001[b]
Prior stroke	89 (16.1)	27 (18.8)	33 (17.5)	16 (18)	13 (9.8)	0.2[b]
Systolic BP, mmHg	131.8 ± 18.7	135.8 ± 21.2	132.6 ± 18.0	129.9 ± 16.3	127.7 ± 17.4	0.003[a]
Diastolic BP, mmHg	68.6 ± 12.0	68.3 ± 13.8	68.5 ± 11.5	68.9 ± 11.6	69.0 ± 10.8	0.9[a]
BMI, kg/m^2	31.3 ± 7.6	31.1 ± 6.8	32.2 ± 8.0	32.6 ± 8.7	29.4 ± 6.8	0.003[a]

Characteristic	Study sample (*N* = 554)	eGFR < 30 (*n* = 144)	eGFR 30-< 45 (*n* = 189)	eGFR 45-<60 (*n* = 88)	eGFR ≥ 60 (*n* = 133)	*P for* between-group difference
No. of medications per day	9 [5–14]	11 [8–16]	10 [6–14]	9 [6–13]	5 [3–9]	< 0.001[d]
Cholesterol, mg/dL	180.2 ± 44.3	169.3 ± 41.9	179.8 ± 45.8	176.9 ± 38.2	194.8 ± 44.8	< 0.001[a]
Hemoglobin A1c, %	6.4 ± 1.4	6.3 ± 1.3	6.4 ± 1.4	6.7 ± 1.7	6.3 ± 1.4	0.2[a]
PTH, pg/mL	66.5 [35.2–120.8]	116.3 [54.8–201.5]	79.0 [45.7–118.8]	61.1 [38.0–88.0]	36.0 [23.7–53.8]	< 0.001[d]
Urine IL-6, pg/mL	1.7 [0.6–5.0]	2.9 [1.0–7.5]	1.6 [0.6–3.6]	1.4 [0.7–3.8]	1.3 [0.4–3.9]	0.001[d]
Tumor necrosis factor a, pg/mL	8.2 ±4.3	10.3 ± 4.8	8.5 ± 4.0	7.8 ± 3.9	5.6 ± 2.6	< 0.001[a]
F2-isoprostane, pg/mL	23.2 [15.3–38.9]	25.3 [16.1–44.1]	23.3 [15.7–37.4]	19.4 [14.9–30.0]	24.9 [14.5–44.1]	0.06[d]
At least one APO-E4 allele	143 (27.5)[e]	33 (25.2)	57 (33.4)	20 (24)	33 (25.6)	0.3[b]

Note: eGFRs expressed in mL/min/1.73 m2. Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation or median [interquartile range]. Conversion factors for cholesterol in mg/dL to mmol/L, ×0.02586.

[a] p-value calculated from ANOVA F-test

[b] p-value calculated from Chi-square test

[c] Groups categorized as white versus non-white

[d] p-value calculated from Kruskal-Wallis test

[e] Total sample size reduced N = 521 as genotyping is not yet complete on all participants

ACR, albumin-creatinine ratio; APO-E4, apolipoprotein E4; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HS, high school; IL, interleukin; PTH, parathyroid hormone;

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Table 2

Means of cognitive test scores overall and by eGFR group

Cognitive test	Domain	Study Sample (*N* = 554)	eGFR < 30 (*n* = 144)	eGFR 30-< 45 (*n* = 189)	eGFR 45-<60 (*n*= 88)	eGFR ≥ 60 (*n* = 133)	*p* for ANOVA F-test[†]
Raw scores							
3MS	Global	94.1 ± 5.4	92.4 ± 6.3[a]	94.1 ± 5.2[b]	94.9 ± 4.5[b]	95.6 ± 4.7[b]	< 0.001
HVLTR/Immediate	Memory	23.6 ± 5.5	21.8 ± 5.3[a]	23.8 ± 5.4[b]	24.1 ± 5.6[b]	25.0 ± 5.2[b]	< 0.001
HVLTR/Delayed	Memory	7.8 ± 3.1	7.0 ± 3.2[a]	7.9 ± 3.1[ab]	8.3 ± 2.8[b]	8.4 ± 3.0[b]	0.001
BVMTR/Immediate	Memory	17.3 ± 7.2	15.1 ± 6.7[a]	17.5 ± 7.2[b]	18.4 ± 6.5[b]	18.8 ± 7.6[b]	< 0.001
BVMTR/Delayed	Memory	6.9 ± 3.0	6.2 ± 2.9[a]	7.0 ± 2.9[b]	7.3 ± 3.0[b]	7.4 ± 3.0[b]	0.004
CTT-1	Processing speed	55.4 ± 27.5	62.0 ± 31.6[a]	54.5 ± 25.4[ab]	56.2 ± 28.6[ab]	49.3 ± 23.1[b]	0.002
CTT-2	Executive function	112.1 ± 43.8	121.6 ± 44.3[a]	111.0 ± 42.8[ab]	112.1 ± 42.0[ab]	103.1 ± 44.2[b]	0.006
SDMT	Executive function	38.4 ± 11.5	34.4 ± 11.6[a]	38.2 ± 11.3[b]	39.3 ± 10.0[bc]	42.4 ± 11.1[c]	< 0.001
COWAT	Language	36.6 ± 11.9	33.3 ± 12.3[a]	36.7 ± 11.3[b]	36.0 ± 10.7[ab]	40.2 ± 12.1[c]	< 0.001
Wechsler Digit Span	Attention	9.9 ± 2.8	9.4 ± 2.8[a]	9.8 ± 2.5[ab]	10.5 ± 3.1[b]	10.2 ± 3.0[b]	0.008
PHQ-9	Depression	4.3 ± 4.4	4.7 ± 4.4[a]	4.2 ± 4.6[ab]	5.2 ± 4.9[a]	3.2 ± 3.6[b]	0.005
T-scores[*]							
HVLTR/Immediate	Memory	46.9 ± 11.2	42.7 ± 11.3[a]	47.8 ± 10.3[b]	48.4 ± 11.6[b]	49.2 ± 11.0[b]	< 0.001
HVLTR/Delayed	Memory	45.6 ± 12.6	41.9 ± 13.3[a]	46.2 ± 12.2[b]	47.9 ± 11.4[b]	47.4 ± 12.2[b]	<0.001
BVMTR/Immediate	Memory	42.5 ± 12.4	38.6 ± 11.6[a]	42.6 ± 12.6[b]	44.8 ± 11.0[b]	44.8 ± 13.0[b]	< 0.001
BVMTR/Delayed	Memory	45.3 ± 12.8	41.8 ± 12.4[a]	46.1 ± 12.8[b]	46.9 ± 12.1[b]	46.8 ± 12.9[b]	0.002
CTT1	Processing speed	48.7 ± 11.1	46.7 ± 11.9[a]	49.4 ± 10.9[ab]	48.2 ± 9.7[ab]	50.4 ± 11.1[b]	0.03
CTT2	Executive function	47.9 ± 12.0	45.7 ± 12.6[a]	48.7 ± 11.4[ab]	47.6 ± 11.4[ab]	49.5 ± 12.2[b]	0.04
SDMT	Executive function	46.2 ± 10.8	42.3 ± 10.8[a]	46.9 ± 10.9[b]	47.4 ± 10.1[b]	48.6 ± 10.2[b]	<0.001
COWAT	Language	49.4 ± 9.9	47.1 ± 10.4[a]	50.0 ± 9.6[b]	48.7 ± 9.5[ab]	51.4 ± 9.6[b]	0.002

Note: eGFRs expressed in mL/min/1.73 m2. Values are given as mean ± standard deviation. Means within a row that do not share a superscript letter are significantly different after Tukey adjustment for multiple comparisons. Lower mean scores represent a worse outcome for all tests except CTT-1 and CTT-2 raw scores and PHQ-9.

[*] T-scores adjust for age and sometimes race (COWAT) and education (CTT-1, CTT-2, SDMT, COWAT). A score of 50 denotes normal cognition; 1 standard deviation = 10.

[†] Null hypothesis is that means are equal for all four eGFR groups.

3MSE; Modified Mini-Mental State Examination; ANOVA, analysis of variance; BVMTR, Brief Visuospatial Memory Test-Revised; COWAT, Controlled Oral Word Association Test; CTT, Color Trails Test; eGFR, estimated glomerular filtration rate; HVLTR, Hopkins Verbal Learning Test-Revised; PHQ-9, Patient Health Questionnaire-9; SDMT, Symbol Digit Substitution Test.