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Kidney-Metabolic Factors Associated with Cognitive Impairment in Chronic Kidney Disease: A Pilot Study

Anne M. Murray, MD, MSc[1,2,3], **Yelena Slinin, MD, MS**[4], **David E. Tupper, PhD**[5,6], **Sarah L. Pederson, MA, MBA**[7], **Cynthia Davey, MS**[8], **David T. Gilbertson, PhD**[9], **Paul Drawz, MD**[10], **Ryan Mello, MD**[11], **Allyson Hart, MD**[11], **Kirsten L. Johansen, MD**[9,11], **Scott Reule, MD**[10,12], **Rebecca Rossom, MD, MS**[13], **David S. Knopman, MD**[14]

[1]The Berman Center for Outcomes and Clinical Research, Hennepin Healthcare Research Institute, Minneapolis, MN, USA

[2]Department of Medicine, Division of Geriatrics, Hennepin Healthcare, Minneapolis, MN, USA

[3]Department of Medicine, University of Minnesota, Minneapolis, MN, USA

[4]Kaiser Permanente Fremont Medical Center, Fremont, CA, USA

[5]Department of Psychology and Neuropsychology, Hennepin Healthcare Minneapolis, MN, USA

[6]Department of Neurology, University of Minnesota, Minneapolis, MN, USA

[7]Allina Health, Minneapolis, MN, USA

[8]Biostatistical Design and Analysis Center, Clinical and Translational Science Institute, University of Minnesota, Minneapolis, MN, USA

[9]Chronic Disease Research Group, Hennepin Healthcare Research Institute, Minneapolis, MN, USA

[10]Department of Medicine, Division of Nephrology and Hypertension, University of Minnesota, Minneapolis, MN, USA

[11]Department of Medicine, Division of Nephrology, Hennepin Healthcare, Minneapolis, MN, USA

Corresponding Author: Anne M. Murray, MD, MSc, The Berman Center for Outcomes and Clinical Research, Hennepin Healthcare Research Institute, and Hennepin Healthcare, 701 Park Avenue, Suite PPC4.440 Minneapolis, MN 55415, USA, Mobile: 612-385-7910, Office: 612-873-5541, amurray@bermancenter.org.

Author Contributions

A.M., D.T., P.D., R.M., A.H., K.J., S.R., R.R., and D.K. contributed to the conception and design. A.M., Y.S., D.T., S.P., S.R., R.R., and D.K. contributed to acquisition of data. A.M., D.T., C.D., D.G., P.D., R.M., A.H., K.J., S.R., R.R., and D.K. contributed to analysis and interpretation of the data. Each author contributed in the content during manuscript drafting and revision. All authors approved the final version of the manuscript.

Statement of Ethics

All study protocols were approved by relevant institutional review boards and/or Ethics Committees and were conducted in accordance with the tenets of the Declaration of Helsinki, the International Council for Harmonization guidelines for Good Clinical Practice, and any other applicable local health and regulatory requirements. All patients provided written informed consent before enrollment.

Conflict of Interest Statement

Dr. Anne M. Murray has been a consultant to Alkahest, Inc.

Dr. David S. Knopman serves on a Data Safety Monitoring Board for the DIAN study. He serves on a Data Safety monitoring Board for a tau therapeutic for Biogen but receives no personal compensation. He is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals and the University of Southern California. He has served as a consultant for Roche, Samus Therapeutics, Third Rock and Alzeca Biosciences but receives no personal compensation. He receives funding from the NIH.

All other authors list no disclosures.

[12]Department of Medicine, Nephrology Division, Minneapolis Veterans Affairs Health Care System, Minneapolis, MN, USA

[13]HealthPartners Institute, Bloomington, MN, USA

[14]Department of Neurology, Mayo Clinic, Rochester, MN, USA

Abstract

Introduction—The associations of kidney-metabolic biomarkers with cognitive impairment (CI) beyond estimated glomerular filtration rate (eGFR, in mL/min/1.73m^2) and albuminuria levels are not well understood. In exploratory analysis, our objective was to determine the extent that three kidney-metabolic factors, previously proposed as mechanisms of CI and commonly abnormal in CKD, were associated with prevalent CI in CKD participants, adjusted for kidney function measures.

Methods—The study cohort included community-dwelling individuals aged ≥45 years with CKD (eGFR <60), not requiring dialysis, recruited from four health systems. We examined the serum biomarkers bicarbonate (CO_2), TNFαR1, and cholesterol, as primary exposures. A structured neuropsychological battery conducted by trained staff measured global and domain-specific cognitive performance. Logistic regression analyses estimated the cross-sectional associations between kidney-metabolic measures and global and cognitive domain-specific moderate/severe (Mod/Sev) CI, adjusted for eGFR, urinary albumin-creatinine ratio (UACR, mg/g), demographics, comorbid conditions, and other kidney-metabolic biomarkers commonly abnormal in CKD.

Results—Among 436 CKD participants with mean age 70 years, 16% were Black, mean eGFR was 34 and median [IQR] UACR was 49 [0.0, 378] mg/g. In adjusted models, increased TNFαR1 was associated with global Mod/Sev CI [OR (95% CI) = 1.40 (1.02, 1.93); P = 0.04]; low bicarbonate (CO2 <20 mEq/L) with Mod/Sev memory impairment [3.04 (1.09, 8.47); P = 0.03], and each 10 mg/dL lower cholesterol was associated with Mod/Sev executive function/processing speed impairment [1.12 (1.02, 1.23); P = 0.02]. However, after adjustment for multiple comparisons these associations were no longer significant, nor were any other kidney-metabolic factors significant for any CI classification.

Conclusion—In exploratory analyses in a CKD population, three kidney-metabolic factors were associated with CI, but after adjustment for multiple comparisons, were no longer significant. Future studies in larger CKD populations are needed to assess these potential risk factors for CI.

Keywords

Chronic kidney disease; cognitive impairment; risk factors; inflammation; acidosis

Introduction

The graded association between declining kidney function and cognitive function is well-recognized [1–3]. However, the association of potentially modifiable kidney-metabolic factors beyond estimated glomerular filtration rate (eGFR, in mL/min/1.73m^2) and urinary albumin-creatinine ratio (UACR) with cognitive function in individuals with non-dialysis-dependent chronic kidney disease (CKD) has only begun to be explored. We sought to

further address the gap in understanding of mechanisms of cognitive impairment (CI) in CKD, by measuring kidney and metabolic-associated biomarkers in the BRain IN Kidney disease (BRINK) cohort of CKD participants [4], with mean eGFR of 34, to conduct a pilot study of risk factors for CI in CKD with an exploratory analysis.

Our objective was to determine the extent that three kidney-metabolic factors: inflammatory biomarkers, low venous bicarbonate, and total serum cholesterol, previously proposed as metabolic mechanisms of CI and commonly abnormal in CKD, were associated with prevalent global CI and cognitive domain-specific impairment in CKD participants, adjusted for eGFR and UACR. We hypothesized that inflammatory biomarkers measured in this study (IL-6, urine and serum, or TNFαR1) would be significantly associated with CI, as CKD is considered a chronic inflammatory state with associated vascular endothelial inflammatory changes [5] and given prior reports of such associations [6–8]. We also postulated low serum venous bicarbonate would be a risk factor, given its reported association with CI in the SPRINT study [9], and that as a reflection of chronic metabolic acidosis it could affect neuronal function by inducing cortical GABAergic neuronal impairment [10, 11]. Lastly, we examined total cholesterol level as a third primary exposure, given controversial previous reports of the relation between cholesterol levels and CI.

Methods

Study Design and Population

Details of the BRINK study design and population are described elsewhere [4]. Briefly, the BRINK study is an ongoing prospective cohort study of the epidemiology of CI in CKD. The BRINK CKD cohort was limited to community-dwelling participants with mild (eGFR 45-<60), moderate (eGFR 30-<45), or advanced (eGFR <30) CKD. Eligibility criteria for the BRINK study were: aged ≥45 years, could complete a 90-minute cognitive and physical function battery, and identified English as their primary language. Exclusion criteria were: recent acute psychosis, active chemical dependency, chronic high-dose narcotic use that could impair cognitive function, severe dementia (defined as unable to complete the Modified Mini-Mental State Examination [3MS]) [12], severe sensory deficits preventing completion of cognitive testing, nursing home residence, dialysis dependence, kidney transplant recipient at the time of screening, or inability to provide signed consent due to severe CI as judged by the potential participants' providers, family, or caregivers.

Participants were from four healthcare institutions in Minneapolis: Hennepin Healthcare, the University of Minnesota Medical Center, the Department of Veterans Affairs Medical Center, and HealthPartners Institute. The Hennepin Healthcare Research Institute institutional review board approved the study (approval number 11–3393 and those of the collaborating institutions).

Cognitive Function Assessment

Staff technicians trained and monitored every 6 months by a PhD neuropsychologist (co-author D.T.) and a certified psychometrist assessed participant cognitive function using

a one-hour structured battery of validated tests of memory, executive function/processing speed, and language.

Participants on psychoactive medications that could affect cognitive testing (e.g., benzodiazepines, opioids, gabapentin, muscle relaxants) were instructed not to take those medications within 6 hours prior to testing.

The battery and cognitive domains assessed included the 1) Modified Mini-Mental State Examination [12] (3MS; measures global cognitive function), 2) Hopkins Verbal Learning Test-Revised [13] (HVLTR; Immediate and Delayed verbal memory), 3) Brief Visuospatial Memory Test-Revised [14] (BVMTR; Immediate and Delayed visual-spatial/memory) [15], 4) Symbol Digit Modalities Test [15] (SDMT; attention, concentration, and processing speed), 5) Controlled Oral Word Association Test [16] (COWAT; semantic memory/language), 6) Color Trails Tests 1 and 2 [17] (CTT-1 and CTT-2; attention and executive function/processing speed), 7) Wechsler Digit Span [18] (auditory short-term memory), and for depression, 8) the Patient Health Questionnaire–9 [15] (PHQ-9) [19].

Classifying cognitive function: Cognitive function was classified according to both domain-specific and global CI performance.

Classification of cognitive domain-specific function: Cognitive domain-specific T-scores were calculated as the mean T-score of the cognitive function tests included in each domain, using published normative tables in each respective test manual or related publications for each test previously cited in this report. Tests in each domain included: a) Memory: HVLTR and BVMTR, b) Executive function/processing speed: CTT-1, CTT-2 and SDMT, and c) Language: COWAT and a 1-minute version of the Animals test from the 3MS. T-scores, with mean (SD)= 50 (10), for each individual test were obtained from the previously cited published norms that adjust for age (all), education (CTT-1, CTT-2, SDMT, COWAT), and race (COWAT). To classify domain-specific functioning, a domain-specific T-score of ≤1.0 SD below a mean of 50 (i.e., T ≥40) was classified as normal, >1.0–1.5 SD below the mean as mild CI (i.e., 35 ≤ T <40), >1.5–2.0 SD below the mean as moderate CI (i.e., 30 ≤T <35), and >2.0 SD below the mean (i.e., T <30) as severe CI. Domain-specific Mod/Sev CI was defined as a domain T-score <35.

Classification of global cognitive impairment—(Table 1): Participants were classified as having no CI (all three domain T-scores in the normal range), mild CI (one or more domain T-scores in the mild range), moderate CI (one or more domain T-scores in the moderate range), or severe CI (one or more domain T-scores in the severe range) using an algorithm that parallels standard criteria for mild CI [20] and dementia [21]. This four-level domain-based CI classification was dichotomized into Mod/Sev CI or mild CI/normal (reference group) for all risk factor analyses of global cognitive impairment.

Other Measurements

Comorbid conditions were ascertained through a medical history interview, chart review, and in some cases, physical examination or laboratory testing. Cardiovascular disease (CVD) was defined as a history of myocardial infarction, angina, congestive heart failure,

or peripheral vascular disease. Diabetes was defined by self-report, use of diabetes medications, a non-fasting glucose ≥200, or hemoglobin A1c% ≥6.5; Type 1 diabetes was not differentiated from Type 2 diabetes. Hypertension was defined by self-report, use of anti-hypertensive medications, a systolic blood pressure (SBP) ≥140, or a diastolic blood pressure (DBP) ≥90. Prior stroke and stroke symptoms were reported using the Questionnaire for Verifying Stroke-Free Status [22] and medical record data, if available. Duration of CKD was calculated as the time between CKD diagnosis per self-report (if known) and the baseline visit. Staff measured weight (kg) and height (m); body mass index was calculated as kg/m^2. Depression was defined as a score of ≥10 on the PHQ-9 [19] or self-report of depression requiring daily medication. Patients were classified as smokers if they reported smoking any cigarettes in the past month. Alcohol use/abuse was defined as self-reported alcoholic, history of alcoholism, or more than one drink/day. Current medications were obtained from their primary care provider's medication list that included potentially psychoactive medications such as opioids, antipsychotics and anti-seizure medications; participants were asked to bring this list and their medications to each visit.

We measured multiple individual kidney-metabolic biomarkers that were established or potential risk factors for CI in the general and CKD population. These biomarkers were measured using a non-fasting venous serum blood sample, or a urine sample obtained at the BRINK baseline visit (as previously described [4]). They included: UACR, hemoglobin [23, 24], phosphorous [25], calcium [26], serum (venous) bicarbonate [9, 27], cholesterol [28, 29], Il-6, urine and serum, and serum TNFαR1 (inflammation) [6–8, 30–32], parathyroid hormone (PTH) [33], and F2 isoprostane (oxidative stress) [34]. In addition, serum creatinine, hemoglobin A1c%, the APOE4 genotype, associated with Alzheimer's disease, and serum clusterin [35], a measure of neuronal apoptosis, were measured.

Statistical Analyses

Descriptive statistics of baseline characteristics and potential risk factors for Mod/Sev CI were generated overall and separately for the mild-to-moderate (eGFR 30 - <60) and advanced CKD (eGFR <30) groups. Chi-square tests and two sample t-tests were used to test for prevalence and mean differences in demographic, cognitive, and risk factor measures between participants with mild-to-moderate and advanced CKD. Logistic regression models estimated odds ratios (ORs) and 95% confidence intervals to assess unadjusted and adjusted associations between potential risk factors and Mod/Sev global and domain-specific CI in CKD.

Unadjusted logistic regression models for global and domain-specific Mod/Sev CI were performed for each potential risk factor. All adjusted models included demographic factors: age (per 10 years), sex, years of education, Black race; and risk factors significantly or marginally significantly associated with one or more of the global or domain-specific Mod/Sev CI outcomes, or recognized risk factors for CI in prior studies: Diabetes (yes/no), history of stroke or transient ischemic attack (TIA), CVD, smoking, pulse pressure (SBP minus DBP), low hemoglobin (based on World Health Organization criteria: <13 g/dL for men and <12 g/dL for women, phosphorous (per 1 mg/dL), calcium (per 1 mg/

dL), low serum bicarbonate <20 mEg/L; level also used in prior studies, and frequently used in clinical practice instead of KDOQI guidelines [27] serum bicarbonate <22 mEg/L, cholesterol (per 10 mg/dL decrease), and TNFαR1 (per 1000 pg/mL). In addition, all models were adjusted for eGFR (using the creatinine-based CKD-EPI equation, without the Black race correction factor [36] and modeled as a one-unit decrease per ml/min/ $1.73m^2$), UACR (3-level categorical variable: <30, 30–300, >300 mg/g), and PTH (per 100 pg/mL, included based on established associations of PTH with calcium, phosphorous, and hemoglobin) [33].

Although component T-scores of the cognitive domain T-scores were adjusted for age, and/or education and race, these factors were also included as covariates in adjusted regression models for domain scores to adjust for any residual effects.

Imputation for missing data was not used in analysis for baseline associations between risk factors and global or domain-specific Mod/Sev CI; thus, individuals with missing data for one or more risk factors were not included in adjusted risk factor analyses ($n = 25$). Sensitivity analyses with models excluding PTH (missing for 18 at baseline) were run for global and domain-specific models for Mod/Sev CI. In addition, sensitivity models were conducted that included use of lipid-lowering medications from their medication list.

To measure the potential effects of medications on cognitive performance, unadjusted logistic regression models were used to evaluate the association between prescribed (a) opioid medications, (b) psychoactive medications (benzodiazepines, typical and atypical antipsychotics), (c) common medications with frequent psychoactive side effects (muscle relaxants, e.g., cyclobenzaprine, carisprodol), (d) anti-epileptics (gabapentin, valproic acid), or (e) hypnotics (e.g., zolpidem) and global Mod/Sev CI. As none of these associations were significant, adjusted models were not pursued. No other associations were examined between other medication groups and CI; specifically, bicarbonate products, as no participants reported taking them on a scheduled basis (they are often ordered PRN).

An alpha significance level of 0.05 was used for all statistical tests and models to identify statistically significant results. To account for multiple testing of 18 factors in four adjusted logistic regression models (n = 72 tests), False Discovery Rate (FDR) adjusted p-values were computed using the Benjamini-Hochberg formula [37]. Both the original p-values (unadjusted for multiple comparisons) and FDR adjusted p-values are reported for adjusted model results. SAS version 9.4 (SAS Institute, Cary, NC) was used for all analyses.

Results

The BRINK CKD cohort included 436 participants; 278 (64%) with mild-to-moderate CKD (eGFR 30-<60) and 158 (36%) with advanced CKD (eGFR <30) (Table 2). The mean age of the cohort was 70 years (SD 9.9), slightly over half were male, mean education was 14 years, and 16% were Black. Participants reported mean CKD duration of 8 (SD 9.2) years, 96% had hypertension, 19% history of TIA or stroke, and 52% diabetes. The mean (SD) eGFR for the cohort was 34 (12.0), median [IQR] UACR was 49 [0.0, 377.7], 27% of the cohort had a UACR >300, and 45% low hemoglobin by World Health Organization

criteria. Characteristics are also described by CKD subgroup to demonstrate the large range of distributions of potential risk factors available for analyses with the inclusion of 36% of participants with advanced CKD.

Frequency of Global and Domain-Specific CI

The frequency of global and domain-specific cognitive impairment is described in Table 3. Overall, 30.3% had global Mod/Sev CI, 19.2% had Mod/Sev memory impairment, 12.8% had Mod/Sev executive function/processing speed impairment, and 11.2% had Mod/Sev language impairment. Among participants with Mod/Sev global CI, memory impairment (66%) was more prevalent than executive function/processing speed (42%) or language (37%) impairment. For reference, mean T-scores by cognitive domain are available in Supplementary Table 1.

Factors Associated with Global Mod/Sev CI in CKD

Odds ratios for the unadjusted and adjusted associations between demographic, kidney-metabolic, comorbidity factors and global Mod/Sev CI in the BRINK CKD cohort are reported in Table 4.

Models for Global Moderate-to-Severe CI

In unadjusted models, two kidney-metabolic factors were significantly associated with Mod/Sev CI: higher TNFαR1, and higher phosphorous; additional factors included Black race, stroke/TIA and CVD. In the fully adjusted model increased TNFαR1 (per 1000 pg/mL) was the only significant kidney-metabolic factor [OR (95% CI) = 1.40 (1.02, 1.93); P = 0.040]. Black Race [OR (95% CI) = 3.14 (1.50, 6.55); P = 0.002] was the only significant demographic factor. CKD subgroup risk factor analyses (mild-moderate and advanced CKD) were not conducted to reduce the level of multiple comparisons.

Factors Associated with Domain-Specific Mod/Sev CI

Odds ratios for adjusted associations between demographic, kidney-metabolic, comorbidity factors and domain-specific (memory, executive function/processing speed, language) Mod/Sev CI in the BRINK CKD cohort are reported in Table 5. Low bicarbonate (CO_2 <20 mEq/L) was associated with Mod/Sev impairment in the memory domain; [OR (95% CI) = 3.04 (1.09, 8.47); P= 0.03], and each 10 mg/dL lower total cholesterol was associated with impaired executive function/processing speed, [OR 1.12 (1.02, 1.23); P = 0.02]; unchanged in sensitivity models that adjusted for lipid-lowering medications. Pulse pressure was associated with Mod/Sev impaired language [1.02 (1.003, 1.04); P = 0.03].

Of the demographic risk factors (although not the focus of this report), Black race [OR 3.96 (1.74, 8.98); P = 0.001], male sex, older age, and fewer years of education were associated with impaired memory function; and Black race [OR 4.98 (1.81, 13.7); P=0.002] and smoking with impaired executive function/processing speed; none were associated with language impairment. However, after FDR adjustment for multiple comparisons, none of the kidney-metabolic factors were significantly associated with global or domain-specific CI. For demographic factors, Black race remained strongly associated with Mod/Sev global,

memory, and executive function/processing speed CI, and male gender with Mod/Sev memory CI.

Discussion

In this cohort of participants with mild-to-advanced CKD, in adjusted models that included eGFR and UACR, the inflammatory factor TNFαR1 was the only kidney-metabolic factor significantly associated with global Mod/Sev CI; Black race and history of stroke (marginally), both recognized risk factors for CI, were significant demographic factors. For domain-specific Mod/Sev CI, low bicarbonate (CO_2 <20 mEq/L) was associated with Mod/Sev impaired memory, and each 10 mg/dL lower cholesterol was associated with Mod/Sev impaired executive function/processing speed. However, after adjustments for multiple comparisons, none of the kidney-metabolic factors were significantly associated with global or domain-specific CI, as noted. Nevertheless, as this was an exploratory analysis, it is helpful to consider the potential role of each of these kidney-metabolic factors in CI that could be further explored in large CKD populations; especially as Black race - as the overwhelmingly strongest risk factor may have decreased the ability to detect significant risk factors in this cohort with its somewhat limited sample size.

Increased Serum TNFαR1 Levels and CI

It is not unexpected that the highly sensitive inflammatory marker TNFαR1α would be elevated and associated with CI, given higher TNFα levels are also associated with CKD progression [30], and the recognized association between CKD severity and CI. Elevated TNFαR1 and TNFα levels have been previously associated with CI and dementia in studies of CKD and non-CKD populations [6–8]. In a study of baseline inflammatory cytokines and change in cognitive function over more than 6 years in the Chronic Renal Insufficiency Cohort of 757 adults (mean eGFR 43), participants in the highest tertiles of hs-CRP, fibrinogen, and IL-1b had an increased risk of impairment in attention (Trailmaking A) compared with the lowest tertile of each marker in adjusted analyses [6]. Counter-intuitively, participants in the highest versus lowest tertile of TNFα had a lower risk of executive function/processing speed impairment (Trailmaking B) [6]. Studies in participants without CKD have been conflicting [6–8]. Animal studies provide evidence that TNFα acts upstream of IL-1 and provokes its production in the brain [31]. Inclusion of cognitive outcomes in clinical trials of anti-inflammatory medications (such as the recent successful CANTOS study [32] of interleukin-1β inhibition with canakinumab) in CKD cohorts may be warranted to measure their potential ability to decrease cognitive decline, in addition to reduction of cardiovascular outcomes.

Low Bicarbonate and CI

Low bicarbonate (<20 mEq/L) was significantly associated with over three-fold higher risk of Mod/Sev CI in the memory domain in the BRINK CKD cohort (before adjustment of P values for multiple comparisons). We chose the (<20 mEq/L) level as a clinically practical level for oral bicarbonate treatment frequently used in clinical practice to treat metabolic acidosis. The mean bicarbonate in the cohort was 25 (3.4) mEq/L, and 12% of those with eGFR <30, and 6% (24) of the entire cohort had a level <20 mEq/L; the low percentage of

participants affected may be because many were recruited from CKD clinics and possibly more closely followed than other CKD cohort studies. A low serum bicarbonate level indicates metabolic acidosis, a common complication in later stages of CKD with many other wide-ranging clinical consequences [38]. Fortunately, metabolic acidosis is easily treatable with oral bicarbonate therapy and commonly used in advanced CKD [27].

An association of lower bicarbonate with CI has been described in adult and pediatric CKD populations [9, 39, 40]. In the large SPRINT cohort of hypertensive older adults at high cardiovascular risk, lower levels of serum bicarbonate (<24 mEq/L) were associated with reduced global cognitive function and lower performance on executive function/processing speed in models adjusted for eGFR, but not UACR [9]. Each 1 mEq/L lower bicarbonate level was approximately equivalent to a 4.3- and 5.4-month aging effect on global cognitive and executive function/processing speed, respectively. Although these domain associations differ from our memory domain finding, it is difficult to compare these results as we used a lower bicarbonate level cut-point, the mean eGFR in the SPRINT cohort was 71 (SD 20) ml/min per 1.73 m^2 compared with 34 (SD 12) in BRINK, and we adjusted for UACR. The specificity of individual biomarker associations with domain-specific CI is also unclear. Two studies also used CO_2 <20 mEq/L as the low cut-point: one among 190 Nigerian CKD participants, mean age 45 years and similar eGFR distribution to BRINK, reported an OR of 2.1 with global cognitive function [39]; and in 865 pediatric CKD patients with lower CKD severity, CO_2 <20 mEq/L combined with high blood pressure variability was associated with worse executive function performance [40]. The mechanism by which acidosis may cause cognitive impairment is unclear. Animal models have demonstrated acidosis increases glutamate accumulation at the glutaminergic axon-astrocyte-GABergic-neuronal junction, causing increased neuronal excitotoxicity [10, 11].

Low Cholesterol and Impaired Executive Function/Processing Speed

Each 10 mg/dL decrease in cholesterol was associated with 12% higher odds of Mod/Sev impaired executive function/processing speed in our cohort. The role of cholesterol as a risk factor for CI has been controversial. High cholesterol levels in midlife are associated with higher risk of subsequent dementia; however, higher cholesterol later in life may be protective [41]. Reverse causality is a possible explanation, as low cholesterol may be secondary to the pathophysiologic processes related to dementia itself (including altered cholesterol metabolism in the brain) [42] or may reflect worse overall health and nutrition seen in later stages of dementia. Most recently, in a study of resilience factors in APOE4 positive women, levels of total cholesterol and LDL were significantly higher in APOE4 dementia-free survivors compared with non-APOE4 carriers [43].

Demographic Risk Factors and CI

Although demographic risk factors are not the focus of this report, as Black race was consistently the strongest demographic and overall risk factor for global, memory-and executive function/processing speed-specific Mod/Sev CI, with high odds ratios varying from 3.1 to 4.8, it warrants recognition. Importantly, the associations of all significant demographic factors reported in our cohort - age, male sex, Black race, smoking, and the protective effect of education - were consistent with those described in many prior

studies of CI in patients without CKD [44, 46, 47]; however, the effect size of Black race was relatively stronger. This may be attributed in part to the higher frequency of Black participants with advanced compared with mild to moderate CKD in our cohort (but reflective of the general U.S. population) [48]. In addition, we did not measure or include additional social determinants of health, believed to contribute substantially to reported elevated risks for CI in Black participants [47].

The strengths of our study include a well characterized cohort of community-dwelling participants with a range of mild-to advanced CKD and detailed testing of multiple cognitive domains to explore potential mechanisms of CI. We recruited a sample of CKD participants representative of our community CKD and U.S. CKD population [48], about half with diabetes. We measured multiple potentially modifiable serum and urine kidney-metabolic biomarkers, focusing on those commonly abnormal in moderate-to-advanced CKD, or previously proposed as mechanisms of CI. Previous studies of CI in CKD patients have primarily focused on eGFR, UACR, stroke, or cardiovascular disease [49] as risk factors for CI.

Several limitations deserve mention. CKD is a highly complex disease process with many contributing and at times collinear metabolic and vascular pathways that are difficult to isolate without a larger CKD cohort. As the risk factors for CI we identified were no longer significant after adjusting for multiple comparisons, Type 1 error may have occurred, suggesting the need for a larger sample size. As such, this analysis is exploratory; however, we believe the risk factors we have identified are highly plausible mechanisms of CI, likely amenable to interventions. The strength of Black race as a risk factor for CI likely contributed to the challenge of disentangling individual kidney-metabolic factors. As diabetes was common, and many of the outcomes of diabetes parallel those of CKD, it is difficult to separate their effects, even with adjustment for diabetes in all models; we did not distinguish between medical history of Type 1 and 2 diabetes diagnosis. Lastly, the study is cross-sectional, and thus causal inferences cannot be confirmed.

Conclusion

In a cohort of 436 older community-dwelling CKD participants with mean eGFR of 34, increased TNFαR1 was associated with global Mod/Sev CI, low bicarbonate with Mod/Sev CI in memory, and lower cholesterol with Mod/Sev CI in executive function/processing speed, but not after adjustment for multiple comparisons. Longitudinal studies in larger CKD populations are needed to determine whether these potentially modifiable risk factors for CI can be confirmed in larger cohorts. As over 20 million people in the U.S. have moderate to advanced CKD (Stages G3a-5; not on KRT [48]), if confirmed in larger study populations, these findings have large, potential clinical impact. Enabling early identification of CKD patients at elevated risk of CI is critical for clinicians and family members to decrease their risk of medication and CKD disease management nonadherence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

All datasets on which the paper's conclusions rely are fully available to editors, reviewers, and readers upon request from Dr. Anne M. Murray.

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Table 1.

Criteria for Classification of Global Cognitive Impairment Severity Using T-Scores

CI Classification	Criteria in T-Scores	Criteria in SD Ranges
Normal	T ≥40 in every cognitive domain (All domains within the normal range)	≤1 SD below the mean of 50
Mild cognitive impairment	35< = T <40 in one or more domains	>1 to 1.5 SD below the mean of 50
Moderate cognitive impairment	One or more domains 30≤ T <35	>1.5 to 2.0 SD below the mean of 50
Severe cognitive impairment	One or more domains <30	>2.0 SD below the mean of 50

For T-scores, a score of 50 is defined as normal, and 10 = 1 S.D.

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Table 2.

Baseline Characteristics of BRINK CKD Participants

Mean (SD), n (%), or Median [Q1,Q3]	**All CKD (eGFR < 60) N = 436**	**Mild-Mod CKD (eGFR 30 - <60) N = 278**	**Advanced CKD (eGFR < 30) N = 158**	**p-value (chi squared or T- Test)**
Age (years), mean (SD)	69.8 (9.9)	70.5 (9.6)	68.6 (10.4)	0.061
Gender				
Female, n (%)	207 (47.5)	142 (51.1)	65 (41.1)	0.046
Years of education, mean (SD)	14.0 (2.8)	14.3 (2.8)	13.4 (2.7)	0.002
Black race, n (%)	71 (16.3)	27 (9.7)	44 (27.9)	< 0.001
CKD Duration (years) N = 393[b], mean (SD)	7.5 (9.2)	7.4 (9.9)	7.6 (8.1)	0.811
Diabetes[c], n (%)	227 (52.1)	130 (46.8)	97 (61.4)	0.003
Hypertension (HTN)[d], n (%)	419 (96.1)	264 (95.0)	155 (98.1)	0.104
SBP mmHg, mean (SD)	133.6 (19.0)	131.9 (17.0)	136.7 (21.7)	0.017
Pulse Pressure[e], mean (SD)	64.8 (17.4)	63.1 (16.1)	67.8 (19.1)	0.010
Stroke[f] or TIA, n (%)	82 (18.8)	50 (18.0)	32 (20.3)	0.560
Smoker[g], n (%)	46 (10.6)	20 (7.2)	26 (16.5)	0.003
Alcohol Use / abuse[h], n (%)	54 (12.4)	33 (11.9)	21 (13.3)	0.665
Depression[i], n (%)	161 (36.9)	91 (32.7)	70 (44.3)	0.016
Cardiovascular Disease (CVD)[j], n (%)	229 (52.5)	135 (48.6)	94 (56.5)	0.028
BMI	32.0 (7.4)	32.4 (7.7)	31.3 (6.8)	0.122
eGFR[k] mL/min/1.73 m^2, mean (SD)	33.9 (12.0)	41.1 (7.7)	21.2 (6.2)	< 0.001
UACR (mg/g) N= 432[b] Median [Q1, Q3]	48.9 [0.0, 377.7]	23.1 [0, 121]	228.7 [34.8, 1250]	< 0.001
Creatinine (mg/dL), mean (SD)	2.0 (1.1)	1.5 (0.3)	2.9 (1.3)	< 0.001
Hemoglobin A1c%, mean (SD)	6.4 (1.4)	6.4 (1.4)	6.5 (1.4)	0.752
Hemoglobin (g/dL), mean (SD)	12.7 (1.8)	13.2 (1.5)	11.8 (1.9)	< 0.001
Low hemoglobin[l], n (%)	193 (44.5)	83 (30.1)	110 (69.6)	< 0.001
Phosphorous (mg/dL), mean (SD)	3.6 (0.7)	3.4 (0.5)	3.9 (0.8)	< 0.001

Mean (SD), n (%), or Median [Q1,Q3]	All CKD (eGFR < 60) N = 436	Mild-Mod CKD (eGFR 30 - <60) N = 278	Advanced CKD (eGFR < 30) N = 158	p-value (chi squared or T- Test)
Calcium (mg/dL), mean (SD)	9.5 (0.6)	9.6 (0.5)	9.4 (0.6)	< 0.001
PTH (N = 418[b]), mean (SD)	122.5 (198.8)	104.9 (203.2)	154.4 (187.0)	0.015
TNF αR1 (pg/mL) N = 429[b], mean (SD)	3408 (1120)	2913 (876)	4291 (953)	< 0.001
CO_2 (mEq/L), mean (SD)	25.2 (3.4)	25.7 (2.9)	24.3 (3.9)	< 0.001
Low Bicarbonate (CO_2 <20 mEq/L), n (%)	24 (5.5)	5 (1.8)	19 (12.0)	< 0.001
Total Cholesterol (mg/dL), mean (SD)	175.6 (42.9)	178.6 (43.4)	170.4 (41.7)	0.056

[a] p-value for Chi-square test of difference in prevalence (for categorical factors) or two-sample t-test for difference in means (for continuous factors);

[b] N indicated if missing more than 3;

[c] Diabetes defined as Glucose ≥200 or A1c% ≥6.5 or DM meds or self-report;

[d] Hypertension defined as SBP ≥140 or DBP ≥90 or HTN meds or self-report;

[e] Pulse Pressure = SBP minus DBP;

[f] Stroke or TIA (history of) from QVSFS;

[g] Smoker defined as any cigarettes in past month;

[h] Alcohol use/abuse defined as self-reported alcoholic or history of alcoholism or more than 1 drink /day;

[i] Depression defined as PHQ-9 ≥10 or self-report of depression requiring daily medication;

[j] Cardiovascular disease (CVD)defined as history of MI, angina, CHF or peripheral vascular disease;

[k] eGFR calculated from CKD-EPI formula without black race factor;

[l] WHO definition of low hemoglobin: <13 g/dL for men, <12 g/dL for women

Table 3.

Frequency of Global and Domain-Specific Cognitive Impairment

	All CKD (eGFR < 60) N = 436	Mild-Mod CKD (eGFR 30 - <60) N = 278	Advanced CKD (eGFR < 30) N = 158	p-value
	N (%)	N (%)	N (%)	
Frequency of Global Cognitive Impairment				
Normal	224 (51.4)	161 (57.9)	63 (39.9)	
MCI	80 (18.4)	50 (18.0)	30 (19.0)	
Moderate/Severe CI (outcome)	132 (30.3)	67 (24.1)	65 (41.1)	<0.001 [b]
Frequency of Moderate/Severe Domain-specific Cognitive Impairment [a]				
Memory (N = 432[d])	83 (19.2)	36 (13.1)	47 (29.9)	<0.001[c]
Executive function/processing speed	56 (12.8)	26 (9.4)	30 (19.0)	0.004[c]
Language	49 (11.2)	26 (9.4)	23 (14.6)	0.098[c]
Frequency of Moderate/Severe Domain-specific CI among those with Moderate/Severe Global CI	**All CKD N = 132**	**Mild-Mod CKD N = 67**	**Advanced CKD N = 65**	
Memory (N = 125[d])	83 (66.3)	36 (55.4)	47 (73.4)	0.032[c]
Executive function/processing speed	56 (42.4)	26 (38.8)	30 (46.2)	0.393[c]
Language	49 (37.1)	26 (38.8)	23 (35.4)	0.684[c]

[a] Moderate/Severe domain impairment defined as domain T-score <35;

[b] p-value for Chi-square test of Mod/Severe CI prevalence difference between mild-mod CKD and advanced CKD; p-value for Chi-square test of Moderate/Severe domain-specific CI prevalence difference between mild-mod CKD and advanced CKD;

[d] Memory domain missing for n = 4 in all CKD and for n = 3 in those with Moderate/Severe Global CI.

Table 4.

Odds Ratios for Moderate/Severe Cognitive Impairment in CKD Adjusted for eGFR and UACR

Risk Factors included in Models	Unadjusted Models All CKD N = 418–436		Adjusted Model All CKD (eGFR < 60) N = 411		
	OR (95% CI[a])	p-value	OR (95% CI[a])	p-value	FDR[b] adjusted p-value
Age (10-year increase)	1.11 (0.90, 1.36)	0.33	1.32 (1.00, 1.74)	0.05	0.31
Gender: Male vs Female	1.34 (0.89, 2.02)	0.16	1.48 (0.89, 2.47)	0.13	0.46
Years of Education (1-year increase)	0.93 (0.86, 1.003)	0.06	0.98 (0.90, 1.07)	0.63	0.95
Black Race	3.32 (1.97, 5.59)	**< 0.001**	**3.14 (1.50, 6.55)**	**0.002**	**0.04**
Diabetes [c]	1.15 (0.77, 1.74)	0.50	0.91 (0.55, 1.52)	0.72	0.99
Stroke / TIA [d]	2.10 (1.28, 3.45)	**0.003**	1.70 (0.95, 3.04)	0.08	0.36
Smoker [e]	1.73 (0.92, 3.23)	0.09	1.10 (0.50, 2.40)	0.82	1.00
CVD [f]	1.67 (1.10, 2.54)	**0.02**	1.27 (0.78, 2.06)	0.34	0.81
Pulse Pressure (SBP minus DBP)	1.01 (1.00, 1.02)	0.08	1.01 (0.99, 1.02)	0.36	0.83
Low Hemoglobin [g]	1.29 (0.85, 1.94)	0.227	0.87 (0.51, 1.47)	0.60	0.95
Phosphorous (1 mg/dL increase)	1.39 (1.04, 1.87)	**0.03**	1.32 (0.91, 1.90)	0.14	0.46
Calcium (1 mg/dL increase)	0.72 (0.50, 1.03)	0.07	1.03 (0.65, 1.63)	0.90	1.00
PTH (100 pg/mL increase)	1.03 (0.94, 1.14)	0.53	1.04 (0.93, 1.16)	0.49	0.85
Low Bicarbonate (CO_2 <20 mEq/L)	2.05 (0.89, 4.71)	0.09	1.63 (0.62, 4.27)	0.32	0.80
Cholesterol (10 mg/dL decrease)	1.02 (0.97, 1.07)	0.49	0.99 (0.93, 1.05)	0.66	0.95
TNF αR1 (1000 pg/mL increase)	1.27 (1.05, 1.53)	**0.01**	**1.40 (1.02, 1.93)**	**0.04**	0.26

[a] CI refers to Confidence Interval;

[b] False Discovery Rate;

[c] Diabetes defined as Glucose ≥200 or A1c% ≥6.5 or DM meds or self-report;

[d] Stroke or TIA (history of) from QVSFS;

[e] Smoker: any cigarettes in past month;

[f] Cardiovascular disease (CVD): history of MI, angina, CHF or peripheral vascular disease;

[g] WHO definition for low hemoglobin: <13 g/dL for men, <12 g/dL for women

Table 5.

Odds Ratios for Domain Specific Moderate/Severe Cognitive Impairment in CKD Adjusted for eGFR and UACR

Risk Factors included in Models	Memory Domain[a] N = 407			Executive Function/Processing Speed Domain[b] N = 411			Language Domain[c] N = 411		
	OR (95% CI[d])	p-value	FDR[e] adjusted p-value	OR (95% CI[d])	p-value	FDR[e] adjusted p-value	OR (95% CI[d])	p-value	FDR[e] adjusted p-value
Age (10 year increase)	**1.49 (1.04, 2.12)**	**0.03**	0.26	1.33 (0.89, 1.99)	0.17	0.52	0.94 (0.63, 1.39)	0.75	0.99
Gender: Male vs Female	**3.19 (1.65, 6.19)**	**<0.001**	**0.04**	0.53 (0.25, 1.11)	0.09	0.37	1.27 (0.63, 2.57)	0.51	0.86
Years of Education (1 year increase)	**0.88 (0.79, 0.98)**	**0.02**	0.25	1.11 (0.98, 1.26)	0.09	0.37	1.02 (0.91, 1.15)	0.73	0.99
Black Race	**3.96 (1.74, 8.98)**	**0.001**	**0.04**	**4.98 (1.81, 13.7)**	**0.002**	**0.04**	0.98 (0.35, 2.80)	0.98	1.00
Diabetes [f]	1.32 (0.71, 2.48)	0.39	0.85	0.66 (0.31, 1.38)	0.27	0.71	1.00 (0.50, 2.01)	1.00	1.00
Stroke / TIA [g]	1.29 (0.63, 2.65)	0.49	0.85	2.11 (0.98, 4.53)	0.06	0.31	1.39 (0.63, 3.09)	0.42	0.85
Smoker [h]	0.93 (0.36, 2.41)	0.88	1.00	**2.75 (1.06, 7.15)**	**0.04**	0.26	1.49 (0.55, 4.03)	0.43	0.85
CVD [i]	0.99 (0.55, 1.80)	0.98	1.00	1.63 (0.79, 3.38)	0.19	0.54	0.97 (0.49, 1.90)	0.93	1.00
Pulse Pressure (SBP minus DBP)	1.00 (0.98, 1.01)	0.62	0.95	1.01 (0.99, 1.03)	0.57	0.94	**1.02 (1.003, 1.04)**	**0.03**	0.26
Low Hemoglobin [j]	0.59 (0.30, 1.18)	0.14	0.46	1.06 (0.49, 2.26)	0.89	1.00	0.74 (0.35, 1.58)	0.43	0.85
Phosphorous (1 mg/dL increase)	1.31 (0.85, 2.02)	0.22	0.61	1.32 (0.79, 2.20)	0.29	0.74	1.02 (0.62, 1.68)	0.94	1.00
Calcium (1 mg/dL increase)	0.97 (0.55, 1.70)	0.90	1.00	0.91 (0.48, 1.75)	0.78	1.00	1.15 (0.63, 2.11)	0.65	0.95
PTH (100 pg/mL increase)	1.05 (0.92, 1.20)	0.49	0.85	0.94 (0.70, 1.25)	0.65	0.95	1.11 (0.99, 1.25)	0.08	0.36
Low Bicarbonate (CO_2 <20 mEq/L)	**3.04 (1.09, 8.47)**	**0.03**	0.26	1.11 (0.30, 4.08)	0.88	1.00	1.59 (0.46, 5.42)	0.46	0.85
Cholesterol (10 mg/dL decrease)	1.001 (0.93, 1.08)	0.98	1.00	**1.12 (1.02, 1.23)**	**0.02**	0.25	1.01 (0.93, 1.10)	0.76	0.99
TNF αR1 (1000 pg/mL increase)	1.15 (0.78, 1.71)	0.48	0.85	1.56 (0.97, 2.51)	0.07	0.36	1.18 (0.77, 1.83)	0.44	0.85

[a] Factors significant (p <0.05) or marginally significant in unadjusted memory domain models (p-value indicated for marginal associations): Gender, Years of Education, Black race, Stroke/TIA, Calcium, Low Bicarbonate, TNFαR1, Diabetes (p = 0.109), Smoker (p = 0.085), Phosphorous (p = 0.072);

[b] Factors significant or marginally significant in unadjusted executive function/processing speed domain models (p-value indicated for marginal associations): Black race, Stroke/TIA, Smoker, CVD, Phosphorous, TNFαR1, Pulse Pressure (p = 0.105), Low hemoglobin (p = 0.110), Low bicarbonate (p = 0.069) cholesterol (p = 0.062);

[c] Factors significant (p <0.05) in language domain unadjusted models: Pulse Pressure, TNFαR1;

[d] CI refers to Confidence Interval;

[e] False Discovery Rate;

[f] Diabetes defined as Glucose ≥200 or A1c% ≥6.5 or DM meds or self-report;

[g] Stroke or TIA (history of) from QVSFS;

[h] Smoker: any cigarettes in past month;

[I] Cardiovascular disease (CVD): history of MI, angina, CHF or peripheral vascular disease;

[j] WHO definition for low hemoglobin: <13 g/dL for men, <12 g/dL for women.