

Chronic Kidney Disease Associated with Worsening White Matter Disease and Ventricular Enlargement

Prashanthi Vemuri^{a,*}, Cynthia Davey^b, Kirsten L. Johansen^{c,d}, Samantha M. Zuk^a, Robert I. Reid^e, Kaely B. Thostenson^a, Ashritha L. Reddy^a, Clifford R. Jack Jr.^a, David S. Knopman^f and Anne M. Murray^{g,h,i,*}

^a*Department of Radiology, Mayo Clinic, Rochester, MN, USA*

^b*Biostatistical Design and Analysis Center, University of Minnesota Clinical and Translational Science Institute, Minneapolis, MN, USA*

^c*Department of Internal Medicine, Nephrology Division, Hennepin Healthcare, Minneapolis, MN, USA*

^d*United States Renal Data Systems, NIDDK, Bethesda, MD, USA*

^e*Department of Information Technology, Mayo Clinic, Rochester, MN, USA*

^f*Department of Neurology, Mayo Clinic, Rochester, MN, USA*

^g*Berman Center for Clinical Research and Outcomes, Hennepin Healthcare Research Institute, Minneapolis, MN, USA*

^h*Department of Internal Medicine, Geriatrics Division, Hennepin Healthcare, Minneapolis, MN, USA*

ⁱ*Departments of Medicine and Neurology, University of Minnesota, Minneapolis, MN, USA*

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Abstract.

Background: Chronic kidney disease (CKD), a growing public health issue in the elderly, is associated with increased risk of cognitive impairment.

Objective: To investigate the mechanisms through which CKD impacts brain health using longitudinal imaging.

Methods: We identified 97 participants (74 CKD and 23 non-CKD) from the BRINK (BRain IN Kidney Disease), a longitudinal study of CKD with two MRI scans (baseline and 3-year follow-up). We measured the associations between baseline and change in kidney disease biomarkers of estimated glomerular filtration rate (eGFR) and urinary albumin to creatinine ratio (UACR), considered a measure of microvascular inflammation, and imaging outcomes of cortical thickness and ventricular volume from structural MRI, white matter hyperintensities (WMH) volume from FLAIR images, and fractional anisotropy of the corpus callosum (FACC).

Results: There were white matter-specific changes as observed by increased WMH volume and decreased FACC in CKD participants, as well as ventricular volume increase in both CKD and non-CKD groups reflective of aging-related changes. Decline in eGFR was associated with decrease in the FACC, suggesting that subtle early white matter changes due to kidney disease can be captured using DTI. An increase in UACR was associated with increase in ventricular volume.

*Correspondence to: Prashanthi Vemuri, PhD, Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, USA. Tel.: +1 507 538 0761; Fax: +1 507 284 9778; E-mail: vemuri.prashanthi@mayo.edu; Anne Murray MD, MSc, Berman

Center for Clinical Research, Hennepin County Medical Center, 701 Park Ave. Suite PPC4-440, Minneapolis, MN 55415, USA. Tel.: +1 612 873 6903; Fax: +1 612 873 1652; E-mail: amurray@bermancenter.org.

Conclusion: Our results support the role of eGFR as a measure of kidney microvascular disease which is associated with concurrent white matter damage in CKD. Future work is needed to investigate the possible link between endothelial microvascular inflammation (as measured by an increased UACR) and ventricular volume increase.

Keywords: Brain health, chronic kidney disease, diffusion tensor imaging, white matter damage, white matter hyperintensities

INTRODUCTION

It is increasingly recognized that chronic kidney disease (CKD), a growing public health issue in the elderly, has a significant impact on brain health. Associations between kidney function and brain structural abnormalities have been found in several cross-sectional studies [1–10]. In our recent cross-sectional analysis in participants of the BRINK (BRain IN Kidney Disease) [11], a longitudinal study of cognitive impairment and stroke in CKD and non-CKD in participants, we found that biomarkers of kidney disease (estimated glomerular filtration rate [eGFR] and urinary albumin to creatinine ratio [UACR]) were associated with cerebrovascular and neurodegenerative MRI brain changes, even after accounting for vascular risk factors at baseline. However, longitudinal studies are important to confirm or discern the pathological underpinnings of the brain changes observed in cross-sectional studies and will aid in understanding the impact of change in kidney biomarkers on the brain changes.

In this work, our goal was to examine the association of CKD with longitudinal brain changes. We focused on two main analyses in BRINK participants with longitudinal images: 1) change in MRI outcomes by CKD status (no CKD [eGFR \geq 60 ml/min/1.73m² and CKD [eGFR < 60 ml/min/1.73 m²]) and 2) association of baseline and change in kidney biomarkers with change in MRI outcomes. Since the brain and kidneys are end organs on parallel trajectories, subject to shared cardiovascular risk factors, with microvascular pathologic processes [12], we hypothesized that participants with CKD would experience significant worsening of MRI biomarkers indicative of cerebrovascular disease (CVD). We assessed longitudinal changes in structural MRI in temporal lobe meta region of interest (ROI) which are typically observed in the elderly due to aging and pathology, and white matter hyperintensities (WMH) from FLAIR and fractional anisotropy of the corpus callosum (FACC) using diffusion tensor imaging (DTI) as markers of white matter disease indicative of vascular damage. DTI is a sensitive marker of microstructural changes in the brain and has been shown to

be associated with worsening cerebrovascular disease [13]. We chose the FACC as we previously found that FACC is a useful biomarker of CVD. Specifically, the loss of microstructural integrity in the corpus callosum was associated with worsening of systemic vascular health and cerebrovascular injury even after accounting for Alzheimer's disease pathologies (which are common in elderly) [14]. More recently, we reported that FACC is a significant predictor of cognitive decline [15]. In addition, we included ventricular volume as a non-specific marker of aging and neurodegeneration. We limited the sMRI cortical thickness regions to temporal lobe meta ROI because this has been widely used to investigate neurodegeneration in the context of aging and dementia and also our cross-sectional analyses confirmed that the primary region associated with worsening kidney disease markers was temporal lobe thickness [11].

METHODS

MRI cohort in the BRINK study

BRINK is a longitudinal observational cohort study of the epidemiology of cognitive impairment and stroke in patients with CKD and an eGFR < 60 ml/min per 1.73 m² [15]. The primary goals of BRINK are to gain further knowledge regarding the epidemiology, natural history, and pathophysiology of cognitive impairment in people with CKD (eGFR < 60 ml/min per 1.73 m²) who have not yet transitioned to dialysis and have not received a kidney transplant. BRINK participants were recruited from four healthcare institutions in Minneapolis: Hennepin HealthCare, the University of Minnesota Medical Center, the Department of Veterans Affairs Medical Center, and HealthPartners Institute for Education and Research. To establish participants' CKD status, we screened the electronic medical records of potential participants at each of institution for at least one eGFR < 60 (minimal or no CKD) ml/min/1.73 m² during the previous year. Participants were then classified into CKD groups using serum creatinine collected at their baseline BRINK visit and the CKD-EPI creatinine equation [13].

The Institutional Review Boards of collaborating institutions approved the study (Hennepin Health-Care approval #: 11-3393, U of M: 1203M11122, VA: 4364-B, and HealthPartners: A12-282). Informed consent for the BRINK study and BRINK MRI was obtained from all participants at the time of the baseline BRINK visit. The inclusion and exclusion criteria as well as assessments are discussed in detail in the Supplementary Material.

Definition of renal biomarkers and longitudinal change

eGFR

Prior to August 2020, eGFR for BRINK participants was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation with serum creatinine, age, a sex coefficient, and a race coefficient for Blacks [16]. The race coefficient has the result of *increasing* eGFR by 14–16% over eGFR calculated without the race coefficient for Black participants [17]. Researchers at several medical schools no longer report estimated GFR with adjustment for race to prevent systemic assignment of higher eGFR values for Blacks than for non-Blacks with the same age, sex, and creatinine values (<https://medicine.uw.edu/news/uw-medicine-exclude-race-calculation-egfr-measure-kidney-function>). Recent studies have described the potential effects of removing the race coefficient, including increased estimated prevalence of CKD in US Black cohorts, and decreased eligibility for kidney transplants due to higher estimated eGFRs in Black CKD patients [18]. To minimize potential bias due to the race coefficient [19], eGFR for BRINK participants was calculated using the CKD-EPI equation without the race coefficient at both baseline and 3-year follow up. Although this will result in a lower eGFR estimate for Blacks in the study, as we are measuring change in eGFR using the same eGFR measure, it is likely to have minimal effect on the results of our analyses of the relation between change in eGFR and MRI outcomes.

UACR

Urinary albumin creatinine ratio was calculated from urinary albumin and creatinine collected at baseline and year 3 study visits using a single spot urine sample. Prior to Ln transformation of UACR, the constant 1 was added to UACR values to allow for Ln transformation of UACR = 0 values [20].

Longitudinal change in eGFR

Three-year within-participant longitudinal change in eGFR was defined as change in eGFR from baseline on the natural log (Ln) scale. For adjusted models, change in eGFR was calculated as baseline Ln eGFR minus year 3 Ln eGFR so that a positive difference represented a decrease from baseline; for unadjusted analyses and graphical representation, change in eGFR was calculated as year 3 eGFR minus baseline eGFR. A binary measure of eGFR change (not Ln transformed) was defined as a 3 ml/min/1.73 m² or greater annualized *decrease* in eGFR versus less than a 3 ml/min/1.73 m² annualized decrease or an increase in eGFR over 3 years. Change in eGFR measures were missing for 3 in the overall BRINK MRI longitudinal cohort who did not have year 3 creatinine values.

Longitudinal change in UACR

Three-year within-participant longitudinal change in UACR was defined as change in UACR from baseline on the Ln scale. Change in UACR was calculated as year 3 Ln UACR minus baseline Ln UACR so that a positive difference represented an increase from baseline. A binary measure of UACR change was defined as a 30% or greater *increase* from baseline in UACR (not Ln transformed) versus less than a 30% increase or a decrease in UACR over 3 years where percent increase was defined as [year 3 UACR – baseline UACR]/baseline UACR. Change in UACR measures were missing for 7 in the overall BRINK MRI longitudinal cohort who did not have year 3 UACR values.

Imaging changes on MRI

All participants were scanned on a single 1.5T Phillips Ingenia MRI scanner at baseline and follow-up. The image acquisition and processing details are provided in the Supplementary Material.

Cortical thickness in temporal lobe meta-ROI and ventricular volume

Cortical thickness and ventricular volume using MPRAGE images were estimated using longitudinal FreeSurfer version 5.3 [21]. The average of fusiform, middle temporal, inferior temporal, and entorhinal thicknesses was computed and used as a composite temporal ROI to evaluate neurodegeneration related to aging and pathology seen in the elderly [22].

White matter hyperintensities

White matter hyperintensities (WMH) volume on FLAIR images were segmented using a semi-automated method and then were edited for segmentation errors by a trained image analyst (SMZ). We used total intracranial volume (TIV) estimated using SPM to account for head size. The details on the estimation of WMH volume and TIV can be found in Graff-Radford et al. [23, 24].

Diffusion tensor imaging

The pre-processing details can be found in Vemuri et al. [14]. Briefly, Advanced Normalization Tools (typically known as ANTS) [25] was used to non-linearly register an in-house atlas to each participant's FA image to compute regional median FA and mean diffusivity values in the atlas regions (where the entire corpus callosum was delineated). We considered fractional anisotropy in the corpus callosum (FACC) as the primary DTI measure because corpus callosum is the largest commissural fiber pathway important for cognitive performance and is significantly influenced by worsening vascular health [14]. Mean diffusivity has been widely shown to be non-specific. Therefore, we considered FA as an indicator of early white matter changes.

Definition of longitudinal change in MRI outcomes

Three-year within-participant changes in temporal ROI thickness, FA corpus callosum, and WMH volume were defined as year-3 value minus baseline value so that a positive difference represented an increase from baseline for all MRI outcomes. Prior to Ln transformation of WMH values, the constant 1 was added to WMH values to allow for Ln transformation of WMH values = 0 [20].

Data availability

Data from BRINK, including data from this study, are available upon reasonable request.

Statistical analysis

Descriptive statistics for study participant baseline characteristics, biomarkers, and MRI outcomes include Mean (SD), Median [IQR] for continuous variables and frequency (%) for categorical variables. Chi-square, Fisher's exact, Wilcoxon rank-sum, and two sample *t*-tests were used to evaluate baseline characteristic differences between CKD and control

groups. Paired *t*-tests were used to assess unadjusted change from baseline to year 3 in MRI outcomes, Ln eGFR, and Ln UACR for the overall longitudinal MRI cohort as well as for CKD and Control groups.

Linear regression models evaluated associations in the overall cohort and in the CKD group between: 1) baseline eGFR, 2) baseline Ln UACR, 3) change in Ln eGFR over 3 years, 4) change in Ln UACR over 3 years and change in MRI outcomes. Models for change in MRI outcomes were adjusted for relevant variables from the literature (also described in the literature)—sex, Black race, age, years of education, baseline smoker or alcohol use/abuse, baseline cerebrovascular risk factor score (ranges from 0–6), and baseline pulse pressure. In addition, models of the association between either baseline eGFR or baseline UACR and change in MRI outcomes also included both baseline eGFR and baseline Ln UACR. Similarly, models of change in Ln eGFR or Ln UACR included both baseline eGFR and Ln UACR, as well as change in Ln eGFR and Ln UACR. In this way the MRI outcome models mirrored those of the baseline BRINK MRI publication, in which joint models were used to include the effect of, e.g., eGFR on the MRI outcome, adjusted for UACR [11]. Models for WMH volume and ventricular volume were also adjusted for TIV. Penalized maximum likelihood regression models evaluated the associations in the overall cohort between baseline eGFR, baseline Ln UACR, change in Ln eGFR, change in Ln UACR, and incident infarctions and microhemorrhages (MCH). To fully adjust for several potentially important confounders and address possible issues with sparse data bias, we used penalized maximum likelihood models. With only two time points (baseline and 3-year), the linear regression of the delta (change in predictors and outcomes) was appropriate to model the associations between change in MRI outcomes and change in eGFR and UACR [26].

An alpha significance level of 0.05 identified statistically significant results. No adjustments for multiple comparisons were applied in order to reduce interpretation errors [27]. All statistical analyses were conducted using SAS software, v9.4, copyright © 2016, by SAS Institute, Inc. Cary, NC, USA.

RESULTS

There were 242 BRINK participants with valid baseline MRI scans (240 were included in the 2017 BRINK baseline MRI paper [11] plus 2 for whom

Table 1
Baseline characteristics for MRI cohort

	MRI cohort N = 97	All CKD (eGFR < 60) N = 74	Control (eGFR ≥ 60) N = 23	p ¹
Age Mean (SD)	66.7 (9.1)	67.9 (8.6)	62.8 (9.9)	0.020
Years of education Mean (SD)	15.0 (2.4)	14.7 (2.6)	15.7 (1.8)	0.091
Male N (%)	55 (56.7)	43 (58.1)	12 (52.2)	0.616
AA race N (%)	7 (7.2)	3 (4.1)	4 (17.4)	0.052
SBP mm Hg ² Mean (SD)	128.9 (15.3)	130.2 (15.3)	124.7 (14.7)	0.128
DBP mm Hg ³ Mean (SD)	67.9 (9.5)	67.6 (9.7)	68.8 (8.9)	0.612
Pulse Pressure mm Hg ⁴ Mean (SD)	61.0 (14.9)	62.6 (15.3)	55.9 (12.8)	0.059
Cholesterol mg/dL Mean (SD)	183.1 (43.8)	178.2 (45.0)	198.7 (36.4)	0.051
HTN ⁵ N (%)	82 (84.5)	69 (93.2)	13 (56.5)	<0.001
Diabetes ⁶	42 (43.3)	34 (46.0)	8 (34.8)	0.345
Hyperlipidemia ⁷ N (%)	69 (71.9)	58 (79.5)	11 (47.8)	0.003
Cardiovascular disease ⁸ N (%)	33 (34.0)	29 (39.2)	4 (17.4)	0.054
Stroke/TIA ⁹ N (%)	10 (10.3)	8 (10.8)	2 (8.7)	1.00
Afib ¹⁰ N (%)	6 (6.2)	6 (8.1)	0 (0.0)	0.331
CV RF score ¹¹ N (%)				<0.001
0	9 (9.3)	3 (4.1)	6 (26.1)	
1	17 (17.5)	9 (12.2)	8 (34.8)	
2	21 (21.7)	19 (25.7)	2 (8.7)	
3	24 (24.7)	20 (27.0)	4 (17.4)	
4	19 (19.6)	18 (24.3)	1 (4.4)	
5	7 (7.2)	5 (6.8)	2 (8.7)	
CV RF score ¹⁰ Mean (SD)	2.5 (1.4)	2.8 (1.3)	1.7 (1.6)	<0.001
Smoker ¹² N (%)	5 (5.2)	3 (4.1)	2 (8.7)	0.589
Alcohol use/abuse ¹³ N (%)	14 (14.4)	11 (14.9)	3 (13.0)	1.00
UACR ¹⁴ mg/g Median [IQR]	21.7 [0.0, 129.4]	42.3 [0.0, 264.1]	0.0 [0.0, 0.0]	<0.001
LN (UACR ¹⁴ + 1) Mean (SD)	2.8 (2.6)	3.5 (2.5)	0.8 (1.7)	<0.001
eGFR ¹⁵ Mean (SD)	47.1 (21.3)	36.7 (8.8)	80.8 (12.7)	<0.001
LN eGFR ¹⁵ Mean (SD)	3.8 (0.4)	3.6 (0.3)	4.4 (0.2)	<0.001

¹Chi-square test or Fisher's exact test (AA race, HTN, Stroke/TIA, Afib, CV RF score, smoker, alcohol use) for categorical variables and two-sample *t*-test or Wilcoxon rank sum test (baseline UACR) for continuous variables; ²Average of up to 3 SBP readings; ³Average of up to 3 DBP readings; ⁴Pulse Pressure = SBP - DBP; ⁵Hypertension (HTN) defined as SBP ≥ 140 or DBP ≥ 90 or HTN meds or self-report; ⁶Diabetes defined as Glucose ≥ 200 or A1c ≥ 6.5 or DM meds or self-report; ⁷Hyperlipidemia defined as cholesterol > 240 or on lipid lowering meds; ⁸Cardiovascular disease defined as history of MI, angina, CHF, or peripheral vascular disease; ⁹History of Stroke or TIA from QVSFS; ¹⁰History of A fibrillation (Afib); ¹¹Cerebrovascular risk factor score (CV RF) defined as the sum of HTN, diabetes, hyperlipidemia, CVD, stroke or TIA, Afib; ¹²Smoker defined as any cigarettes in past month; ¹³Alcohol use/abuse defined as history of alcoholism or more than 1 drink per day; ¹⁴Urinary albumin/creatinine ratio; ¹⁵CKD-EPI equation for eGFR without race factor. LN, natural log scale; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.

baseline MRIs were completed after that analysis). Baseline demographic characteristics and biomarkers for the overall longitudinal MRI cohort, CKD, and control groups (total $n = 97$) are included in Table 1 along with *p*-values for group-wise comparisons. Mean age of the cohort was 67 years; those with CKD were about 5 years older ($p = 0.02$), on average, than the control group. Just over half of the cohort was male, and 7% were Black. Mean eGFR was 36.7 (8.8) ml/min/1.73 m² in the CKD group and 80.8 (12.7) ml/min/1.73 m² in the control group; median UACR in the CKD group was 42.3 [0.0, 264.1], and 0 in controls. There was significantly greater prevalence of hypertension, hyperlipidemia, and overall cerebrovascular risk factor score but not diabetes in the CKD group compared to controls. About 10% of the

cohort carried a history of stroke or TIA, and its prevalence did not vary substantially by CKD status. Mean (SD) time elapsed between baseline and year 3 MRI was 3.0 (0.1) years, with a range of 2.7 to 3.4 years. Potential participation bias in this study is addressed in detail in the Supplementary Material.

Change in eGFR and UACR over three years

The 3-year change (decline) in eGFR was significant in both the CKD and control groups ($p < 0.001$) (Table 2). Mean decline in eGFR among the CKD participants was 3.4 (7.8) ml/min/1.73 m², going from a mean of 36.4 (8.5) to 33.0 (10.9) ml/min/1.73 m², compared with a larger mean decline in eGFR of 7.7 (8.5) ml/min/1.73 m² in controls, going from a

Table 2
Three-year change from baseline in eGFR and UACR

	MRI cohort	All CKD (eGFR < 60)	Control (eGFR ≥ 60)
eGFR			
<i>N</i> for change ¹	<i>N</i> = 94	<i>N</i> = 71	<i>N</i> = 23
Baseline Mean (SD)	47.3 (21.5)	36.4 (8.5)	80.8 (12.7)
Year 3 Mean (SD)	42.8 (21.0)	33.0 (10.9)	73.1 (14.5)
Year 3 – baseline change Mean (SE)	–4.42 (8.12)	–3.4 (7.8)	–7.7 (8.5)
LN (Baseline) Mean (SD)	3.76 (0.43)	3.56 (0.26)	4.38 (0.16)
LN (Year 3) Mean (SD)	3.64 (0.48)	3.44 (0.35)	4.27 (0.21)
Difference ² on LN scale Mean (SE)	–0.12 (0.22)	–0.12 (0.25)	–0.11 (0.12)
<i>p</i> -value ³ for mean LN change	<0.001	<0.001	0.0003
≥ 3 unit ⁵ decrease/year <i>N</i> (%)	27 (28.7%)	17 (23.9%)	10 (43.5%)
UACR			
<i>N</i> for change ¹	<i>N</i> = 90	<i>N</i> = 69	<i>N</i> = 21
Baseline Mean (SD)	169.2 (356.5)	213.8 (395.3)	22.6 (70.8)
Year 3 Mean (SD)	328.8 (785.8)	420.4 (877.4)	27.8 (81.3)
Year 3 – baseline change Mean (SE)	159.6 (522.5)	206.6 (589.6)	5.15 (25.0)
LN (Baseline) Mean (SD) ⁴	2.81 (2.57)	3.40 (2.50)	0.87 (1.74)
LN (Year 3) Mean (SD) ⁴	2.95 (2.84)	3.60 (2.78)	0.83 (1.86)
Difference ² on LN scale Mean (SE)	0.14 (1.65)	0.20 (1.74)	–0.05 (1.33)
<i>p</i> ³ for mean LN change	0.415	0.343	0.873
>30% increase ⁵ in 3 years <i>N</i> (%)	31 (34.4%)	30 (43.5%)	1 (4.8%)

¹Baseline data limited to those with 3-year eGFR/UACR data; ²LN (Year 3) – LN (baseline); ³*p*-value for paired *t*-test of mean change; ⁴1 added to baseline and year 3 UACR prior to LN transformation; ⁵eGFR annualized decrease and UACR 30% increase calculated from non-LN transformed values. LN, natural log scale; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.

mean of 80.8 (12.7) to 73.1 (14.5 ml/min/1.73 m²). A higher percentage of controls (43.5%) also declined ≥ 3 ml/min/1.73 m² in eGFR/year compared with CKD participants (23.9%). However, the prevalence of diabetes in the control group was 36%, as they were preferentially recruited to seek to approximate the prevalence of diabetes among the CKD group (46%); thus, diabetes may have contributed to their greater than anticipated eGFR decline. In addition, the higher baseline eGFR in the control group meant they had more potential to decrease their eGFR and still fall within the control group category of eGFR > 60.

UACR increased over 3 years in the overall cohort, but none of the Ln UACR increases were significant in either the overall cohort CKD or control groups. For the CKD group, the mean increase in UACR was 206.6 (589.6) mg/g from 213.8 (395.3) to 420.4 (877.4) mg/g, compared with controls at 5.15 (25.0) mg/g. In addition, approximately 43.5% of the CKD experienced >30% increase in UACR over 3 years, compared with only 5% (1 person) in the control group.

Change in MRI outcomes over three years

Baseline and change in the MRI outcomes of temporal lobe thickness, WMH volume, ventricular

volume, and FACC are shown in Table 3. There was no significant change in temporal lobe thickness over 3 years in the overall cohort or in either the CKD or control groups. Among both the total MRI cohort and CKD group but not controls, mean Ln WMH volume increased from baseline to year 3 (*p* < 0.001 for both) and mean FACC decreased from baseline to year 3 (*p* < 0.001 for both). Ventricular volume increased in all groups (*p* < 0.0001), capturing age related shrinkage of the brain across all participants. In sensitivity analyses, we did not find any significant change in frontal lobe thickness over 3 years in either the CKD or control groups.

In the overall MRI cohort, three CKD participants incurred a new infarction and seven participants had incident MCHs; 5 were CKD and 2 were control participants (noting that one 3-year CKD MRI was excluded from the study analyses due to a new large cortical infarct). Even though these numbers were small, there were higher odds of incident infarctions with increase in Ln UACR over three years in the unadjusted penalized maximum likelihood model [OR (95% CI) was 2.13 (1.14, 3.95) with *p* = 0.017], but this association was no longer statistically significant in the adjusted model. There were no other significant associations between kidney measures (at baseline or change over 3 years) and infarctions or MCHs (data not shown).

Table 3
MRI Outcomes: baseline, 3 years, and change over 3 years

MRI outcome	BRINK longitudinal MRI cohorts		
	Overall	All CKD (eGFR < 60)	Control (eGFR ≥ 60)
Temporal lobe meta-ROI, μm , Mean (SD)			
<i>N</i> for change	<i>N</i> = 96	<i>N</i> = 74	<i>N</i> = 22
Baseline	2,876 (195.0)	2,850 (205.9)	2,964 (119.3)
Year 3	2,879 (212.6)	2,843 (218.9)	3,003 (131.0)
Difference (Year 3 – Base)	3.26 (126.8)	-7.29 (119.7)	38.73 (145.9)
p^1 for mean change	0.802	0.602	0.227
WMH volume, cc Mean (SD)			
<i>N</i> for change	<i>N</i> = 95	<i>N</i> = 72	<i>N</i> = 23
Baseline	21.2 (18.2)	23.1 (19.8)	15.1 (9.7)
Year 3	25.3 (23.0)	28.0 (25.1)	16.8 (11.7)
Difference (Year 3 – base)	3.88 (7.16)	4.58 (7.75)	1.67 (4.33)
Difference on Ln scale ²	0.15 (0.24)	0.17 (0.24)	0.09 (0.22)
p^1 for mean LN change	<0.001	<0.001	0.078
Ventricular volume, cc Mean (SD)			
<i>N</i> for change	<i>N</i> = 96	<i>N</i> = 74	<i>N</i> = 22
Baseline	29.8 (15.7)	31.8 (16.6)	23.0 (9.6)
Year 3	32.5 (17.3)	34.8 (18.3)	24.8 (10.2)
Difference (Year 3 – base)	2.72 (2.70)	2.98 (2.98)	1.85 (1.08)
Difference on Ln scale	0.085 (0.067)	0.087 (0.073)	0.079 (0.042)
p^1 for mean LN change	<0.0001	<0.0001	<0.0001
FA corpus callosum Mean (SD)			
<i>N</i> for baseline, year 3, change	<i>N</i> = 94	<i>N</i> = 71	<i>N</i> = 23
Baseline	0.633 (0.044)	0.628 (0.045)	0.649 (0.034)
Year 3	0.624 (0.049)	0.616 (0.050)	0.647 (0.038)
Difference (Year 3 – Base)	-0.0095 (0.015)	-0.0117 (0.014)	-0.0027 (0.015)
p^1 for mean change	<0.001	<0.001	0.403

¹ p from paired t -test of mean change; ²Difference on LN scale calculated from WMH+1: LN (year 3 WMH+1) – LN (baseline WMH+1); LN, natural log scale; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio; WMH, white matter hyperintensity; FA, fractional anisotropy.

Associations between kidney biomarkers and change in MRI outcomes

The linear regression adjusted associations between baseline and change in kidney biomarkers and 3-year change in MRI outcomes are shown in Table 4. Both UACR and eGFR were included in the models together. These identified no statistically significant associations between the predictors of either baseline eGFR or UACR or change in eGFR or UACR from baseline and 3-year change in temporal lobe thickness or WMH volume, in the overall cohort or in the CKD group (even though WMH volume increased in both groups). The only significant eGFR associations were seen with FACC as the outcome, where 3-year change (decline) in Ln eGFR was associated with decline in FACC in both the overall cohort ($p=0.035$) and in the CKD cohort ($p=0.016$); annualized decrease in $\text{eGFR} \geq 3 \text{ ml/min/1.73 m}^2$ was also significantly associated with decrease in FACC in the CKD cohort, but not in the overall cohort. The only significant Ln UACR associations were found for Ln UACR

increase > 30% and increase in ventricular volume, in both the overall cohort ($p=0.002$) and in the CKD group ($p=0.005$).

Change in FACC by change in Ln eGFR over 3 years in the overall MRI cohort as well as change in ventricular volume by change in UACR over 3 years in the overall MRI cohort is shown in Fig. 1, demonstrating the associations found in the regression models. Figure 2 illustrates the increase in WMH volume on FLAIR images between baseline and 3 years in a BRINK CKD participant. The increases were seen in both periventricular and diffuse WMH volume over time.

DISCUSSION

In this longitudinal study of brain changes related to kidney disease, we found: 1) WM-specific changes as observed by WMH volume increase and microstructural integrity decrease in participants with CKD; 2) greater decline in eGFR was associated

Table 4
 Linear regression adjusted¹ associations between 3-year change in MRI outcomes² and eGFR and UACR (baseline and change): Overall and All CKD MRI cohorts

	Temporal lobe meta-ROI 3-year change		WMH (Ln) 3-year change		Ventricular volume (Ln) 3-year change		FA corpus callosum 3-year change	
	B (SE)	<i>p</i>	B (SE)	<i>p</i>	B (SE)	<i>p</i>	B (SE)	<i>p</i>
Overall MRI cohort								
Baseline model ³ (N)	96		94		96		94	
Baseline eGFR ⁴	-0.77 (0.76)	0.316	0.0021 (0.0015)	0.169	0.0001 (0.0004)	0.894	-0.0001 (0.0001)	0.118
Baseline Ln UACR ⁵	-1.78 (6.44)	0.782	-0.0034 (0.0125)	0.788	-0.0006 (0.0037)	0.880	-0.0006 (0.0007)	0.404
3-year change model ⁶ (N)	89		87		89		87	
Ln eGFR 3-year change ⁴	120.79 (66.29)	0.072	0.074 (0.127)	0.562	0.015 (0.036)	0.677	-0.016 (0.0076)	0.035
Ln UACR 3-year change ⁵	-8.46 (8.84)	0.342	0.023 (0.017)	0.185	0.009 (0.005)	0.076	-0.0003 (0.001)	0.773
Threshold change model ⁷ (N)	89		87		89		87	
eGFR annualized decrease \geq 3 units	18.59 (34.57)	0.592	0.096 (0.064)	0.139	0.027 (0.017)	0.114	-0.0027 (0.0039)	0.482
UACR increase > 30%	-27.16 (32.21)	0.402	0.080 (0.062)	0.199	0.054 (0.016)	0.002	-0.0016 (0.0037)	0.664
CKD cohort								
Baseline model ³ (N)	74		72		74		71	
Baseline eGFR ⁴	-1.22 (1.71)	0.481	0.003 (0.004)	0.359	-0.0002 (0.0011)	0.852	0.0001 (0.0002)	0.713
Baseline Ln UACR ⁵	-1.73 (6.89)	0.803	-0.010 (0.014)	0.463	-0.0004 (0.0044)	0.932	-0.0011 (0.0008)	0.180
3-year change model ⁶ (N)	69		67		69		66	
Ln eGFR 3-year change ⁴	112.0 (67.52)	0.103	0.058 (0.137)	0.676	0.004 (0.041)	0.922	-0.0188 (0.0075)	0.016
Ln UACR 3-year change ⁵	-7.55 (9.41)	0.426	0.024 (0.019)	0.220	0.011 (0.006)	0.060	-0.0007 (0.0011)	0.512
Threshold change model ⁷ (N)	69		67		69		66	
eGFR annualized decrease \geq 3 units	-19.10 (39.58)	0.631	0.103 (0.077)	0.190	0.037 (0.022)	0.096	-0.0096 (0.0044)	0.033
UACR increase > 30%	-26.0 (32.83)	0.432	0.081 (0.066)	0.222	0.055 (0.019)	0.005	-0.0019 (0.0037)	0.604

¹All models were adjusted for covariates: age, gender, AA race, years of education, baseline CV risk factor score, pulse pressure, smoker/alcohol use; models for WMH and ventricular volume were also adjusted for TIV; ²MRI outcome change defined as Year 3 minus baseline; ³Baseline models include both baseline eGFR and baseline Ln UACR adjusted for covariates listed above; ⁴Baseline eGFR and change in Ln eGFR were modeled so that positive covariates reflect an increase in MRI outcome associated with 1 unit lower eGFR at baseline or 1 unit decrease in Ln eGFR over 3 years; ⁵Baseline Ln UACR and change in Ln UACR were modeled so that positive covariates reflect an increase in MRI outcome associated with 1 unit higher Ln UACR at baseline or 1 unit increase in Ln UACR over 3 years; ⁶3-year change models include 3-year change in Ln eGFR, 3-year change in Ln UACR, baseline eGFR, baseline Ln UACR, and covariates listed above; ⁷Threshold change models include eGFR annualized decrease \geq 3 units, UACR increase > 30%, baseline eGFR, baseline Ln UACR, and covariates listed above. LN, natural log scale; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio; WMH, white matter hyperintensity; FA, fractional anisotropy.

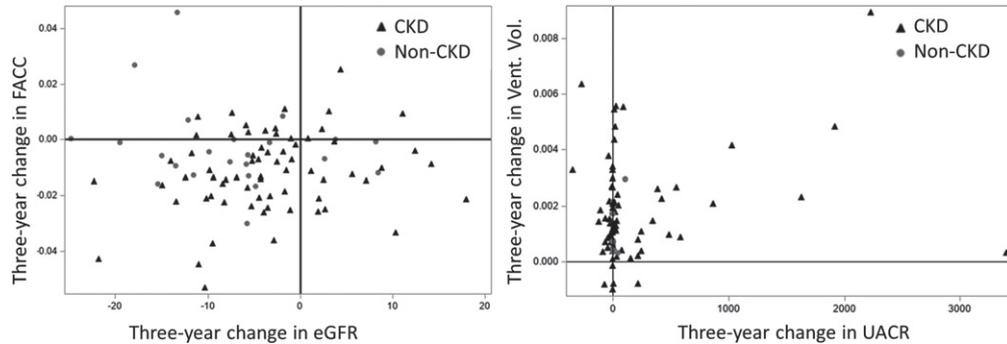


Fig. 1. In full MRI cohort: (Left) Change in fractional anisotropy of corpus callosum (FACC) by change in Ln eGFR over 3 years. (Right) Change in ventricular volume by change in UACR (not log transformed) over 3 years. CKD are represented by black triangles, Non-CKD are represented as grey circles. All changes were defined as 3-year minus baseline so that positive values represent an increase and negative values represent a decrease.

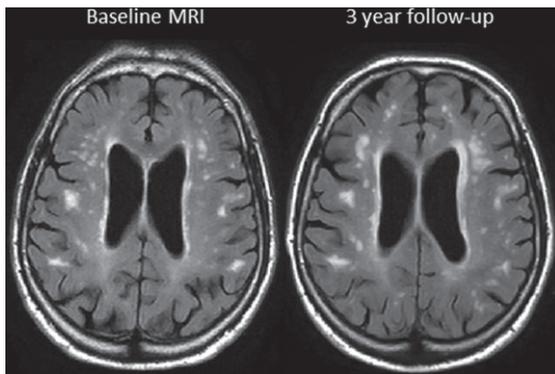


Fig. 2. FLAIR MRI scans at baseline and 3 years in a CKD subject whose eGFR decreased from 38.1 to 34.8 units.

with significant decline in the WM microstructural integrity of the FACC, suggesting that subtle early brain changes due to kidney disease can be captured using DTI; and 3) increase in UACR was associated with increase in ventricular volume across all participants.

Brain changes may be specific to WM in CKD patients

These results support our hypothesis that CKD progression exerts its influence on cognitive function in part through small vessel disease mechanisms resulting in measurable WM changes. WM changes seen in aging and dementia are linked to progressive small vessel disease in the elderly. There are several causes that include hypoperfusion, altered water content, blood-brain barrier dysfunction, myelin damage, and axonal disruption [28]. While WMH are the most commonly studied CVD related MRI changes, there is recent evidence that diffusion MRI can capture

changes even in normal appearing WM associated with myelin damage, axonal loss, and gliosis that have been shown to be predictive of cognitive performance [13, 29]. We and others have found that DTI related changes in tissue microstructure can be reflective of progressive WM damage above and beyond the information provided by WMH [15, 30, 31].

In group-wise differences of change in structural MRI outcomes (Table 3), we found that mean WMH volume significantly increased and mean FACC significantly declined in participants with CKD, but not in controls. Although there was no significant association of baseline eGFR or UACR or change in these biomarkers with WMH volume, decline in eGFR was significantly associated with change (decline) in FACC (Table 4 and Fig. 1), suggesting the utility of DTI in capturing kidney biomarker-related early brain changes in patients with CKD. Importantly, in our baseline BRINK MRI study cross-sectional analyses, eGFR was also strongly associated with FA in the frontal, temporal, and parietal lobes in models unadjusted for UACR, but these associations were no longer significant after adjusting for UACR.

The lack of significant associations between baseline UACR or change in UACR with any WM outcome was likely attributable in large part to lack of substantial change from baseline in UACR, coupled with wide UACR ranges and standard deviations in both the overall cohort and CKD group. However, we found a strong association between increase in ventricular volume and increase in UACR. Figure 1 illustrates that except for one participant, most CKD participants with increase in UACR also had significant increase in ventricular volume over three years suggesting that change in UACR reflected concurrent brain changes, specifically ventricular volume increase.

We were surprised to find no significant temporal lobe changes over three years (Table 3). These results differed from the baseline paper [11] where we found significant cortical thickness differences between CKD and controls. Therefore, the lack of sufficient sample size cannot be ruled out. However, ventricular volume increased in all groups, suggesting there was age-related non-specific degeneration throughout the brain in all groups. Many of the previous studies examining the relation between kidney function and structural MRI changes were done in diabetic cohorts, although it has recently been reported that metabolic syndrome has little impact on increase in WMH [24]. Findings from the ACCORD MIND study in 502 older persons with type 2 diabetes were consistent with ours in that baseline and persistent albuminuria were not independently associated with significant changes in global or regional gray matter volumes or WMH [32]. However, albuminuria was associated with brain atrophy and WMH in a cohort of hypertensive sibships [33].

The high attrition rate reflects the malignancy of severe CKD for those missing 3-year MRI in the 'other reasons' group. However, the attrition limitation also lends important insights to understanding the biology underlying the temporal competition between study-ending complications of CKD and ongoing participation in the longitudinal study. Thus, the observed longitudinal imaging outcomes likely represent the less-affected survivors overall and underestimate the brain imaging consequences of CKD. In turn, participants with less severe CKD have measurable brain consequences because they survived long enough to develop them.

Change in eGFR may be reflective of early WM changes

In this longitudinal study, there was a clear increase in WMH in participants with CKD in parallel with a consistent decrease in FACC in CKD participants over time. Though we did not have sufficient power to determine the odds of infarctions and MCHs in adjusted models for CKD, the worsening of WMH and FACC supports their role as early measures of WM changes, reflective of declining kidney function and worsening CVD. We previously found that the FACC was a predictor of cognitive decline even after adjusting for WMH and was a robust marker of CVD [14]. Further, the finding of an association between change in eGFR and change in FACC further support our hypothesis that CKD participants have greater

CVD structural MRI changes in comparison to temporal lobe cortical thinning due to other aging and pathological processes.

UACR, ventricular volume, and inflammation

As kidney function declines systemic inflammatory burden increases, UACR is considered a biomarker for endothelial vascular and systemic inflammation [34, 35]. There is evidence of an association between midlife systemic inflammation and greater ventricular volume in late-life [36]. Therefore, the additional association of a >30% increase in UACR with increased ventricular volume may suggest links between high levels of inflammation seen in CKD and reflected by elevated UACR levels and the concurrent diffuse atrophy measured by ventricular volume.

In sensitivity analyses (not shown here), we found that the 10 subjects with >400 units increase in UACR had slightly elevated baseline interleukin-6 (IL-6) serum marker, which is an indicator of systemic inflammation (1.99 versus 1.25; $p=0.108$). Our results suggest that further investigations on the longitudinal changes in systemic and brain markers may shed light on the role of inflammation along the CKD-brain axis.

Limitations

We anticipated that we might observe an association between change in eGFR or UCAR and MCH or infarcts, given the vascular pathophysiology and high rate of micro- and macrovascular outcomes commonly described in CKD cohorts. However, the unexpectedly small number of participants with an incident MCH and infarcts prevented analysis of these relations, perhaps due to a healthy survivor effect of the remaining CKD participants and lower prevalence of atrial fibrillation in the MRI cohort compared to those missing 3-year MRI. Even though the mortality rate at 3 years in the CKD group was high at 12%, we had predicted a higher rate of approximately 18%, based on projections from the United States Renal Data System [37]. Moreover, the baseline MRI prevalence of cortical stroke was 12% in the CKD group compared with 4% in the controls ($p=0.05$), and the odds of a cortical infarct were 1.23 higher for a 10% decrease in eGFR (95% CI 1.06 to 1.43; $p=0.008$) in joint models adjusted for UACR [11], again suggesting selective dropout due to infarcts.

The low retention rate of 40% in the MRI cohort limited power for comparisons between CKD and Controls. This was due in part to loss to follow up and study withdrawal due to high comorbidity burden commonly observed in CKD cohorts, transition to dialysis (8% of baseline participants), and the 12% mortality rate, but also to the halt in study operations associated with funding limitations between BRINK 1 and BRINK 2. The higher mortality in the group of interest (in our case CKD) has been a problem in longitudinal epidemiological studies of aging and dementia because we likely underestimate the observed brain changes based on less severe participants who remain in the study. Although all analyses were adjusted for diabetes, and diabetes was reasonably matched for (46% versus 35% of the controls), the microvascular effects of diabetes are difficult to dissect from those of progressive CKD. Though we had decreased power due to smaller sample size in this BRINK longitudinal study, the confirmation of our results through two different analyses (group comparison and association with kidney biomarkers) lends support to our findings.

CONCLUSION

In a longitudinal MRI cohort of CKD and control participants, decline in eGFR over 3 years was strongly associated with decreased WM microstructural integrity, specifically by FACC, and a 30% increase in UACR was strongly associated with ventricular volume. Our results support the role of eGFR as a measure of kidney microvascular disease and predictor of FACC changes which may be a possible early marker of microvascular brain damage in CKD. Further studies in larger samples of moderate CKD populations over a longer period are needed to elucidate the structural brain pathology underlying cognitive changes in CKD.

DISCLOSURE STATEMENT

Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/21-0604r1>).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: <https://dx.doi.org/10.3233/JAD-210604>.

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