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Association of Kidney Function Biomarkers with Brain MRI Findings: The BRINK Study

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Abstract

Background—Chronic kidney disease (CKD) studies have reported variable prevalence of brain pathologies, in part due to low inclusion of participants with moderate to severe CKD.

Objective—To measure the association between kidney function biomarkers and brain MRI findings in CKD.

Methods—In the BRINK (BRain IN Kidney Disease) study, MRI was used to measure gray matter volumes, cerebrovascular pathologies (white matter hyperintensity (WMH), infarctions,

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SUPPLEMENTARY MATERIAL

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microhemorrhages), and microstructural changes using diffusion tensor imaging (DTI). We performed regression analyses with estimated glomerular filtration rate (eGFR) and urine albumin to creatinine ratio (UACR) as primary predictors, and joint models that included both predictors, adjusted for vascular risk factors.

Results—We obtained 240 baseline MRI scans (150 CKD with eGFR <45 in ml/min/1.73 m^2; 16 mild CKD: eGFR 45–59; 74 controls: eGFR ≥ 60). Lower eGFR was associated with greater WMH burden, increased odds of cortical infarctions, and worsening diffusion changes throughout the brain. In eGFR models adjusted for UACR, only cortical infarction associations persisted. However, after adjusting for eGFR, higher UACR provided additional information related to temporal lobe atrophy, increased WMH, and whole brain microstructural changes as measured by increased DTI mean diffusivity.

Conclusions—Biomarkers of kidney disease (eGFR and UACR) were associated with MRI brain changes, even after accounting for vascular risk factors. UACR adds unique additional information to eGFR regarding brain structural and diffusion biomarkers. There was a greater impact of kidney function biomarkers on cerebrovascular pathologies and microstructural brain changes, suggesting that cerebrovascular etiology may be the primary driver of cognitive impairment in CKD.

Keywords

Cerebrovascular disease; chronic kidney disease; infarctions; magnetic resonance imaging

INTRODUCTION

Chronic kidney disease (CKD) is a growing public health issue in the elderly, and pathophysiological interactions between kidney and brain function are associated with cognitive impairment. CKD stages are defined by a reduction in renal function as measured by estimated glomerular filtration rate (eGFR) in ml/min/1.73 m^2, or the presence of proteinuria, measured as urine albumin to creatinine ratio (UACR) [1–5]. There is a strong graded cross- sectional relation between eGFR and cognitive function in patients with CKD as renal function declines below eGFR of 60 ml/min/1.73 m^2 [2–5]. Previous structural magnetic resonance imaging (MRI) studies in non-dialysis CKD patients have reported variable prevalence of vascular pathologies and concomitant global and region-specific atrophy [6–9], in part due to substantive differences in patient populations and range of CKD severity. Most CKD cohort studies have primarily included patients with mild CKD (Stage 3a: eGFR 45–59 ml/min/1.73 m^2) rather than those with lower renal function (Stages 3b-5: eGFR <45 ml/min/1.73 m^2) who are at higher risk of both cognitive impairment and brain pathology. In addition, few studies have included a control group of mild CKD to non-CKD participants. The primary goal of this study was to investigate the association between kidney function biomarkers and structural brain changes in participants of the BRINK (BRain IN Kidney Disease), a longitudinal study of cognitive impairment and stroke in CKD patients. In this study, our primary goal was to assess the cross-sectional association between baseline eGFR and baseline BRINK MRI measures of cortical thickness, cerebrovascular, and diffusion changes. We included BRINK participants with normal and mild CKD, and oversampled for moderate to severe CKD to capture the effect of lower eGFR <45 ml/min/

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1.73 m^2 on MRI findings. In this study, eGFR was our primary variable of interest but we also analyzed associations with UACR because eGFR and UACR are considered complementary markers of CKD [10, 11].

METHODS

BRINK study design overview

All MRI participants were enrolled in the BRINK study. Details of the BRINK study design are described elsewhere [12]. Briefly, 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 m^2. The primary goals of BRINK are to gain further knowledge regarding the epidemiology, natural history, and pathophysiology of cognitive impairment in people with moderate to severe CKD (eGFR < 45 ml/min per 1.73 m^2) who have not yet transitioned to dialysis or renal transplant. Specifically, its primary aim is to characterize the association between (a) baseline and incident stroke, white matter (WM) disease, eGFR, inflammation, microalbuminuria, and dialysis initiation and other potential risk factors and (b) cognitive decline over 3 years in community-dwelling CKD outpatients. BRINK has completed baseline recruitment and follow-up is underway.

BRINK participant recruitment

BRINK participants were recruited from four healthcare institutions in Minneapolis: Hennepin County Medical Center, the University of Minnesota Medical Center, the Department of Veteran's Affairs Medical Center, and HealthPartners Institute for Education and Research.

Eligibility criteria

To establish participants' CKD status, we screened the electronic medical records of potential participants at each of their institutions for at least one eGFR <45 (moderate to severe CKD), 45–59 (mild CKD), or > 60 (minimal or no CKD) ml/min/1.73 m^2 during the previous year. Participants were then classified by CKD group using serum creatinine collected at their baseline BRINK visit and the CKD-EPI creati-nine equation [13]. Serum creatinine was measured at baseline using non-fasting blood samples drawn from an antecubital vein, and processed at the CLIA-certified Hennepin County Medical Center Clinical Laboratory and Pathology. Level of proteinuria was described using the UACR, which was measured using a single spot urine sample collected at baseline visit.

Inclusion criteria for BRINK CKD participants were as follows: age ≥ 45 years; eGFR <45 ml/min/1.73 m^2 (moderate to severe CKD) or eGFR 45–59 ml/min/1.73 m^2 (mild CKD); ability to complete a 90-min cognitive and physical function battery; and English as the primary language. Inclusion criteria for non-CKD were identical to those for CKD except that eGFR must be ≥ 60 ml/min/1.73 m^2. Exclusion criteria for all participants were: recent acute psychosis, active chemical dependency, chronic narcotic use, severe dementia (defined as unable to complete the Modified Mini-Mental State Examination), legally blind (unable to complete written cognitive testing), deaf (unable to hear instructions), residing in a nursing home, dialysis-dependent or renal transplant recipient at the time of screening, or

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inability to provide signed consent due to severe cognitive impairment as judged by the potential participants' providers, family, or caregivers.

The Institutional Review Boards of collaborating institutions approved the study (HCMC 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. To determine number of brain MRIs needed, 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 MRIs needed to determine the effect of incident stroke during the 3-year follow-up (as detected on year-3 MRI) on cognitive impairment (measured by change in cognitive summary score). This yielded a target BRINK MRI subsample size of 130 with eGFR <60 mL/min/1.73 m^2 and 50 control (eGFR ≥ 60 mL/min/1.73 m^2) participants. However, to improve MRI study power while staying within the study's budget constraints, the goal number of baseline MRI was increased to a subsample of 245, or approximately 44% of all BRINK participants (N = 556). The flow chart of the BRINK MRI participant recruitment is shown in Supplementary Figure 1.

BRINK MRI study population

BRINK MRI participants were recruited on a rolling basis by enrolling MRI-eligible BRINK participants at the time of their baseline visit until MRI recruitment goals were met. Informed consent for the MRI was obtained at their baseline visit. The non-CKD MRI participants were recruited to approximate the age and race distributions of the combined BRINK MRI CKD and mild CKD groups. A lower percentage of participants with mild CKD than the entire cohort had brain MRIs because we had initially intended to only compare a sample of CKD patients with the non-CKD patients. However, on confirming the baseline eGFRs of 16 of the CKD MRI participants with repeat serum creatinines, their eGFRs were greater than 45, reclassifying them as mild CKD.

Definition of participant characteristics

Diabetes is defined as non- fasting glucose ≥ 200, A1c ≥ 6.5, self-reported diabetes, or taking diabetes medications. Hypertension was defined as systolic blood pressure ≥ 140, diastolic blood pressure ≥ 90, self-reported hypertension, or taking antihypertensive medications. Atrial fibrillation (AFIB) was defined as either current per annual BRINK EKG reviewed by a study cardiologist, or history of AFIB. Cardiovascular disease (CVD) was ascertained by self- reported history of angina, myocardial infarction, cardiac stent placement, angioplasties, CABG/CAD surgery, congestive heart failure, or peripheral vascular disease. Stroke or transient ischemic attack (TIA) was ascertained as self-reported history of stroke or TIA. Smoking was defined as current smoker versus past or never smoked. Alcohol intake was defined as > 1 drink/day or history of or current alcoholism.

All participants were scanned on a 1.5T Phillips Ingenia MRI scanner. The image acquisition details were published in the study design paper [12] and also provided in the Supplementary Material. Quality control was performed on each protocol that was acquired for each subject and the outcome measures were only included for those participants who

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passed quality control. The image processing and outcome measures used in this paper are presented here for each of the MRI scans.

Cortical thickness and hippocampal volume

Cortical thickness using MPRAGE images was estimated using FreeSurfer version 5.3 [14]. Regional FreeSurfer thicknesses were averaged to obtain the regions of interest (ROIs): frontal, parietal, temporal, occipital, and overall cortical. Additional structural MRI outcomes included hippocampal volume and ventricular volume.

Brain infarcts and white matter hyperintensities

Brain infarcts were assessed on FLAIR images by a trained image analyst (SMZ) and confirmed by radiologists (CRJ or KK) blinded to all clinical information. Subcortical infarcts included infarcts in WM, deep gray matter (GM) nuclei, cerebellum, and brain stem not involving the hemispheric infarcts. Only cortical infarcts ≥ 1 cm in largest diameter were considered as outcome measures. Inter-rater reliability of the FLAIR assessments was excellent [15]. As previously described, white matter hyperintensities (WMH) on FLAIR images were segmented using an automated method that were edited by trained image analyst (SMZ) [16]. We recently conducted a WMH reliability study in which five different image analysts reviewed 14 different scans on two separate occasions. The correlation between two ratings of the same scan by different analysts was an estimated 0.96 while the correlation between two ratings of the same scan by the same analysts was an estimated 0.97 indicating high reliability of WMH measurement. The outcome measures from FLAIR scans used here were: cortical infarcts, subcortical infarcts, and WMH volume as a measure of WM disease burden.

Microhemorrhages

Methods for detecting microhemorrhages (MCH) using T2* images have previously been published [17]. All MCH were identified by a trained image analyst (SMZ) and also secondarily confirmed by radiologists (CRJ or KK) experienced in reading T2* GRE images. A MCH was defined as homogenous hypointense lesions up to 10 mm in diameter in the GM or WM on T2* GRE images. Occasionally it is not possible to make a definitive decision, e.g., when distinguishing a MCH from a vascular flow void. In such instances, the MCH was labeled as “possible MCH” and not included in the analyses in this paper. The inter-rater agreement between the two radiologists on definite versus not-definite MCH is 85%, which corresponds to good agreement (κ = 68%). We were only interested in number of definite MCH for this study.

Diffusion tensor imaging (DTI)

In addition to structural and cerebrovascular changes, we also looked at diffusion changes using DTI. DTI measures the diffusion properties of water molecules in the brain and therefore is useful in visualizing subtle WM tracts and microstructural changes due to mild hypoxic-ischemic injury [18]. The two measures available from DTI are fractional anisotropy (FA), which measures degree of directionality of the diffusion process (the FA of highly directional normal WM tracts is one and FA decreases with WM degeneration) and

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mean diffusivity (MD), which measures the magnitude of the diffusivity (there is increased MD with GM and WM loss due to unrestricted motion of the water molecules). We used an in-house methodology described here to obtain regional FA and MD from each individual's DTI scan: Each volume of the DTI images was registered to the first volume (a b0) using affine transformations to correct for head motion and minimize distortions due to eddy currents. To attenuate ringing effects the images were slightly smoothed, making the resolution 3.6 × 3.6 × 2.7 mm. The images were then brain-extracted and corrected for EPI distortion by deformably registering them to undistorted (and higher resolution) T1 weighted images of the subjects [19]. Finally, the undistorted and smoothed images are used to fit diffusion tensors with a weighted least-squares algorithm. From the tensors maps of the FA and MD were generated. An in-house created atlas for the four lobes and corpus callosum was registered to each subject's image and subdivided by the subject's T1-based GM and WM segmentations in order to carry out an ROI based analysis. We only report FA in the WM, and MD in the WM and GM separately for each of the regions.

Statistical analyses

To evaluate the effect of kidney disease on brain structures and pathology, we first looked for group differences between CKD and control participants in all outcomes, and then used a regression approach to assess the relationship between continuous eGFR, UACR, and all outcomes. Each of the methods applied are described below. In the demographics table, comparisons are made across all the groups, and if this p-value was significant we report p-values from pairwise comparisons.

Group wise differences for all outcomes

The structural MRI outcomes and WMH volume group-wise differences between CKD and control participants were summarized by the area under the receiver operating characteristic curve (AUC), and p-value based on the Wilcoxon rank-sum test. We report hippocampal and ventricular volume as a percent of total intracranial volume (TIV). To test for differences between CKD and control participants in MCH and infarctions outcomes, we computed Chi-square tests categorizing the outcome as either absent or present.

Regression analysis approach for structural MRI, WMH, and DTI outcomes

To assess the effect of eGFR on hippocampal volume, overall, and regional cortical thicknesses, WMH volume, and DTI-based measures, we fit linear regression models with the outcome on the log-scale and adjusted for the covariates of interest. The log of outcome was modeled to account for skewness in the data and to allow us to interpret the results on the percent scale. For those same reasons, we model log of eGFR and log of UACR. By using this transformation, we can report the effect of a 10% decrease in eGFR and 10% increase in UACR in terms of percentage change in the outcome. We fit models with eGFR alone and UACR alone, and finally both eGFR and UACR in the same model. To remain consistent, we estimated the regression models for 10% change in UACR and eGFR but it should be noted that a larger change in UACR, e.g., approximately 20%, may be more clinically relevant, as range of UACR is large, from zero to thousands (mg/ml).

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To fully adjust for a number of potentially important confounders and address possible issues with sparse data bias, we used penalized maximum likelihood (PML) [20] After appropriate scaling of covariates, we reasoned a priori that a one-unit change in the covariate or a change from absent to present would be associated with no more than a 50% change in the response with high probability. All models were adjusted for age, sex, education, race, diabetes, hypertension, cholesterol, systolic blood pressure, diastolic blood pressure, stroke/TIA, AFIB, CVD, smoking, and alcohol use.

Regression analysis approach for infarctions

To assess the relation between eGFR and infarctions, we used logistic regression models, as few participants had multiple infarctions and the spread of the count of infarctions was small. We report the relative increase in odds of an infarction for a 10% decrease in eGFR or 10% increase in UACR. We fit models with eGFR alone and UACR alone, and finally both eGFR and UACR in the same model. As with the continuous outcome models, we used PML estimation to adjust for age, sex, education, race, diabetes, hypertension, cholesterol, systolic blood pressure, diastolic blood pressure, stroke/TIA, AFIB, CVD, smoking, and alcohol use. We used a penalty that assumed a *priori* the odds ratio (OR) for scaled covariates was between 0.10 and 10 [20].

Regression analysis approach for microhemorrhages

To assess the relation between eGFR and number of MCH, we used a negative binomial regression model where we report the relative rate (RR) for a 10% decrease in eGFR or 10% increase in UACR. The negative binomial regression model is a widely used generalization of the Poisson regression model that accounts for overdispersion or positively skewed counts. We fit models with eGFR alone and UACR alone, and finally both eGFR and UACR in the same model. This model used PML to adjusted for age, sex, education, race, diabetes, hypertension, cholesterol, systolic blood pressure, diastolic blood pressure, stroke/TIA, AFIB, CVD, smoking, and alcohol use. We used a penalty that assumed a priori the RR for scaled covariates was between 0.10 and 10 [20].

RESULTS

The demographics of the participants in the study are presented in Table 1. There were 240 total participants, but due to image quality concerns or processing failures, the number of participants excluded in each regression analysis ranged from 1 to 10 participants. Distributions of age, gender, race, and diabetes were similar between participants with mild CKD and controls without CKD. Several vascular risk factors and education were significantly different between the CKD and control participants ($p < 0.001$). When we compared the BRINK MRI cohort to BRINK participants without MRI, we found that eGFR, age, and gender distributions were similar, but those in the MRI cohort were more likely to be white (86% versus 79%; $p = 0.01$), less likely to have diabetes (43.8% versus 52.9%; $p = 0.03$), had higher education ($p = 0.01$), and there was a higher proportion of mild CKD in the non-MRI group (22.9%) compared to the MRI group (6.7%, $p < 0.0001$) (not shown). The correlation between UACR and eGFR was high as expected (rank correlation was –0.5).

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Structural MRI outcomes

Box plots summarizing group-wise differences between CKD and control participants in terms of volumes and cortical thickness measures are shown in Fig. 1 along with the AUC and corresponding *p*-values. In these unadjusted dichotomous analyses, global, frontal, and temporal thicknesses were significantly lower in CKD compared to control participants ($p < 0.05$) with AUC values near 0.6. Hippocampal volume showed trend level differences in CKD versus control participants ($p = 0.06$).

In the adjusted regression models (adjustment for age, sex, education, race, diabetes, hypertension, cholesterol, systolic blood pressure, diastolic blood pressure, stroke/TIA, AFIB, CVD, smoking, and alcohol use), a 10% change in eGFR was not associated with reduction in regional or overall cortical thickness or volume. In contrast, a 10% increase in UACR was associated with lower cortical thickness in all lobes except for the occipital lobe and lower hippocampal volume ($p < 0.05$) (Fig. 2A, B). Even after additionally adjusting for eGFR, 10% increase in UACR was associated with 0.03% lower temporal lobe thickness, 0.07% lower hippocampal volume, and 0.13% increased ventricular volume ($p < 0.05$) (Table 2). For many of the cortical thickness measures, the joint effects of UACR and eGFR are the same or attenuated towards zero (shown by the triangles in Fig. 2A) when compared to the independent models suggesting that we may need to have a larger sample size to detect a significant effect of eGFR and UACR in the joint models.

WMH

In the dichotomous analysis, there was a significantly higher burden of WMH volume in CKD patients compared to control subjects (AUC = 0.60, $p = 0.02$) (Fig. 1). In continuous analysis with adjusted regression models, a 10% decrease in eGFR was associated with about a 2.8% increase in WMH volume and 10% increase in the UACR was associated with about 0.32 % increase in WMH volume ($p < 0.01$). In the joint models, the effect of UACR was significant ($p = 0.02$) and there were trend level effects of eGFR ($p = 0.09$) (Fig. 2B and Table 2).

DTI

Box plots summarizing group-wise differences between CKD and control participants in DTI (FA in WM, MD in WM and GM) are shown in Supplementary Figs. 2 and 3 along with the AUC and corresponding *p*-values. In these unadjusted dichotomous analyses, regional WM FA was decreased in frontal, parietal, and temporal lopes ($p < 0.05$) and trend level decreases in corpus callosum ($p = 0.053$) (Table 2). In addition, MD was significantly increased in both the WM and GM throughout the brain. In the adjusted regression models, WM FA was significantly decreased and GM and WM MD increased throughout the brain in both independent models of eGFR and UACR ($p < 0.05$) (Fig. 2C). In the joint models, the estimates were similar and in many cases attenuated towards zero, suggesting that the effects may be detectable with larger sample sizes. In the joint models of eGFR, only higher UACR was significantly associated with higher WM MD throughout the brain as well as higher GM MD in the temporal and occipital lobes.

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Infarctions

We found that the frequency of cortical infarctions in CKD patients (12%) was significantly higher than in controls (4%) ($p = 0.05$). There was no statistical difference ($p = 0.27$) between the presence of subcortical infarctions in CKD patients (21%) and controls (15%). Based on the adjusted logistic regression model, we found that the odds of a large cortical infarction were 1.15 times higher for a 10% decrease in eGFR (95% CI, 1.01 to 1.31; $p = 0.033$) (Fig. 3). This association between decrease in eGFR and large cortical infarctions and was even more significant in the joint model with UACR (Table 3), where the odds of a cortical infarct were then 1.23 higher for a 10% decrease in eGFR (95% CI 1.06 to 1.43; $p = 0.008$).

Microhemorrhages

We found that the proportion of CKD subjects with MCH (22%) was higher compared to the proportion of controls with MCH (12%) but the difference was marginally significant ($p = 0.08$). Based on the negative binomial regression adjusted models, we found that the relative rate of MCH in CKD subjects compared with controls was not significant (Fig. 3 and Table 3).

DISCUSSION

In this cross-sectional analysis of 240 subjects, we found evidence that kidney disease biomarkers are associated with significant changes in neurode-generation, cerebrovascular, and diffusion-related biomarkers, even after accounting for traditional vascular risk factors. Lower eGFR was associated with greater WMH burden, increased odds of cortical infarctions, and worsening diffusion changes throughout the brain, but only the association with cortical infarctions persisted in the joint model with UACR included. UACR provided additional information even after adjusting for eGFR, related to temporal lobe atrophy, WMH, and whole brain microstructural changes as measured by DTI MD. While eGFR is routinely used to assess kidney function, UACR may prove to be a more powerful kidney disease biomarker for measuring the impact of kidney disease on brain changes.

The associations between cerebrovascular disease and kidney function we found here were consistent with the majority of the literature [9, 21–29]. However there is conflicting evidence on the extent of the impact of kidney disease on cerebrovascular events (for review, see [7]). One of the main reasons for the discrepancies is the variability in the severity of CKD studied. CKD studies generally include patients with mild CKD [2, 5], resulting in a lower likelihood of detecting substantial amounts of imaging abnormalities. In this study, the inclusion of patients along the entire range of CKD with oversampling of moderate to severe CKD aided us in establishing the association of CKD with brain changes.

Some literature has suggested no association between CKD and cerebrovascular disease after adjusting for the traditional vascular risk factors [7, 28]. Here we found that even after adjusting for these shared traditional risk factors for both cerebrovascular disease and CKD (age, sex, education, race, diabetes, hypertension, cholesterol, systolic blood pressure, diastolic blood pressure, stroke/TIA, AFIB, CVD, smoking, and alcohol use), the association

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between cerebrovascular disease and eGFR was still significant. Even though we used a broad spectrum of adjustment covariates, our aim was to obtain the estimates of the impact of eGFR and UACR on the brain with minimal bias or confounding. This reduction in bias can often come at the cost of increased variance and model instability, but PML estimation is recommended as the most principled method to counter this problem and is an important aspect of this work [30]. Due to the high prevalence of hypertension in this cohort, we also performed a sensitivity analyses by dichotomizing the participants by hypertension and no-hypertension, and found estimates of the impact of eGFR on brain changes in the dichotomized models similar to the impact of eGFR with the hypertension in the model, supporting the use of PML estimation.

Albuminuria is increasingly being viewed as a marker of systemic endothelial dysfunction [11]. Since UACR is highly correlated with eGFR, we found similar results in the independent models with UACR and eGFR as outcomes. However in the joint models, UACR provided additional information regarding temporal lobe atrophy and DTI even after adjusting for eGFR. These results suggest that UACR may be able to provide additional and non-overlapping information to eGFR and may be more reflective of vascular endothelial damage due to inflammation. The greater impact of UACR on cortical thinning compared to eGFR was also recently noted by Cho et al. [31]. The impact of UACR related changes in the medial temporal lobe structures that are vulnerable to aging provides evidence that kidney disease has a significant impact on brain aging [32].

The estimates of the impact of eGFR and UACR in joint models were attenuated compared to the estimates in independent UACR and eGFR models. This suggests that we may require a larger sample size to detect a significant effect of both eGFR and UACR in the joint models. However we found that the joint models were helpful in understanding the additional effects of each kidney disease biomarker, while controlling for the other. Two recent papers looked at the joint effect of UACR and eGFR [10, 11] and also observed a similar trend of attenuated impact of UACR and eGFR in joint models.

Overall, our results indicate that the effect of CKD on brain changes is independent of their shared vascular risk factors. The brain and kidneys are end organs on parallel trajectories, subject to shared vascular risk factors, with microvascular pathologic processes mediated by inflammatory and oxidative processes taking place in similar low-resistance vascular beds and endothelial structures [33]. Impaired endothelial function in the brain is manifested by defects in the blood-brain barrier [34] and susceptibility to MCH, lacunar infarcts, and WMH, and in the kidney by impaired glomerular filtration and secondary protein ‘leakage’, or proteinuria.

In groupwise differences (Fig. 1), there were decreased GM volumes in CKD compared to non-CKD participants. However, in the regression analyses with eGFR after adjustment for vascular risk factors this effect disappeared or greatly reduced, suggesting that the association of brain volume change with kidney function may be weak and possibly secondary or downstream to ischemic disease, due in turn to the shared risk factors. In the regression analyses with UACR, however, the impact on temporal lobe atrophy was still significant, suggesting that UACR may be a stronger biomarker for neurodegenerative

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mechanisms, or that the temporal lobe changes may are the first neurodegenerative changes seen in the natural history of the progression of CKD and structural MRI changes. Recent literature on the effect of kidney function on GM suggests that the impact on GM is minimal in mild-moderate stages of CKD and significant in end stage renal disease [8, 35, 36], lending support to our results.

DTI is a sensitive marker of microstructural changes in the brain. Recent work has shown that diffusion changes may be sensitive markers of vascular dysfunction [10, 37–40]. Baseline FA changes have been shown to be predictive of subsequent WMH incidence on subsequent FLAIR scans [41]. Microstructural damage was observed in subjects with vascular dementia with normal appearing GM [40]. In spontaneously hypertensive rats, loss of structural integrity on DTI correlated with cognitive impairment seen at subsequent time points [39]. The DTI and cerebrovascular changes we observed in this paper supports the hypothesis that initial stages of CKD may accelerate cerebrovascular disease, independent of shared vascular risk factors. These cerebrovascular changes (infarcts and WMH) and subsequent neurodegeneration seen in later stages of CKD may be the proximate correlates of cognitive impairment seen in late stage CKD patients. Further longitudinal imaging studies are necessary to elucidate these mechanisms.

The strengths of our study are the prospective design and inclusion of a large proportion of participants with moderate to severe CKD participants and non-CKD controls. There are some limitations to this study. 1) While we had sufficient numbers of participants with moderate and severe CKD, we had lower numbers of mild CKD patients, at least relative to those without MRI in the BRINK study. This made a thorough assessment of a possible nonlinear eGFR dose effect unfeasible, although in our analyses we found linear models adequately characterized the relationship between eGFR and imaging outcomes. As our primary goal was to measure the effect of moderate to severe CKD on brain pathology, we do not believe this has substantially affected our findings. 2) The issue of multiple comparisons issues cannot be avoided specifically for structural MRI and DTI. Since we did not want to make any *apriori* assumptions, we tested the associations in larger composite regions to reduce the number of multiple comparisons. The approach utilized here to investigate whole brain changes may be better to improve our understanding of the impact of CKD on the brain.

CONCLUSION

We found that both eGFR and UACR as biomarkers of kidney disease were associated with brain changes, even after accounting for vascular risk factors. UACR adds unique additional information to eGFR regarding brain structural and diffusion changes. There was a greater impact of kidney function biomarkers on cerebrovascular pathologies and microstructural brain changes suggesting that cerebrovascular etiology may be the primary driver of cognitive impairment in CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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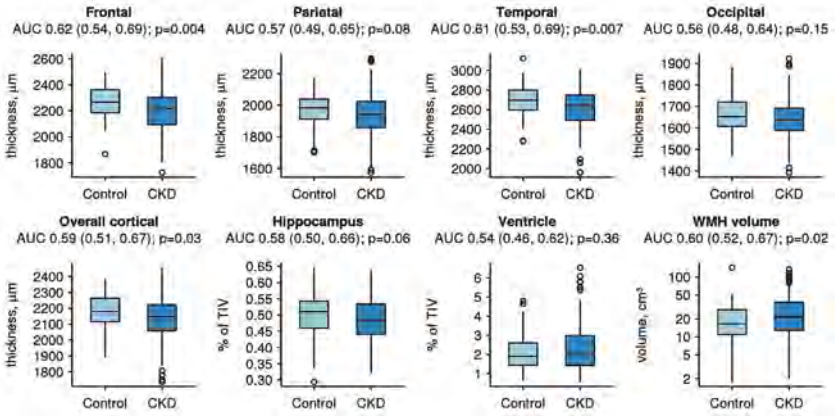

Fig. 1.

Box plots of regional and overall thicknesses, hippocampal and ventricle volumes divided by total intracranial volume (TIV), and white matter hyperintensity (WMH) volumes. WMH volume is on the log scale to account for skew in the data. Group-wise differences are summarized by the non-parametric area under the receiver operating characteristic curve (AUC) and *p*-value based on the Wilcoxon rank-sum/Mann-Whitney U test.

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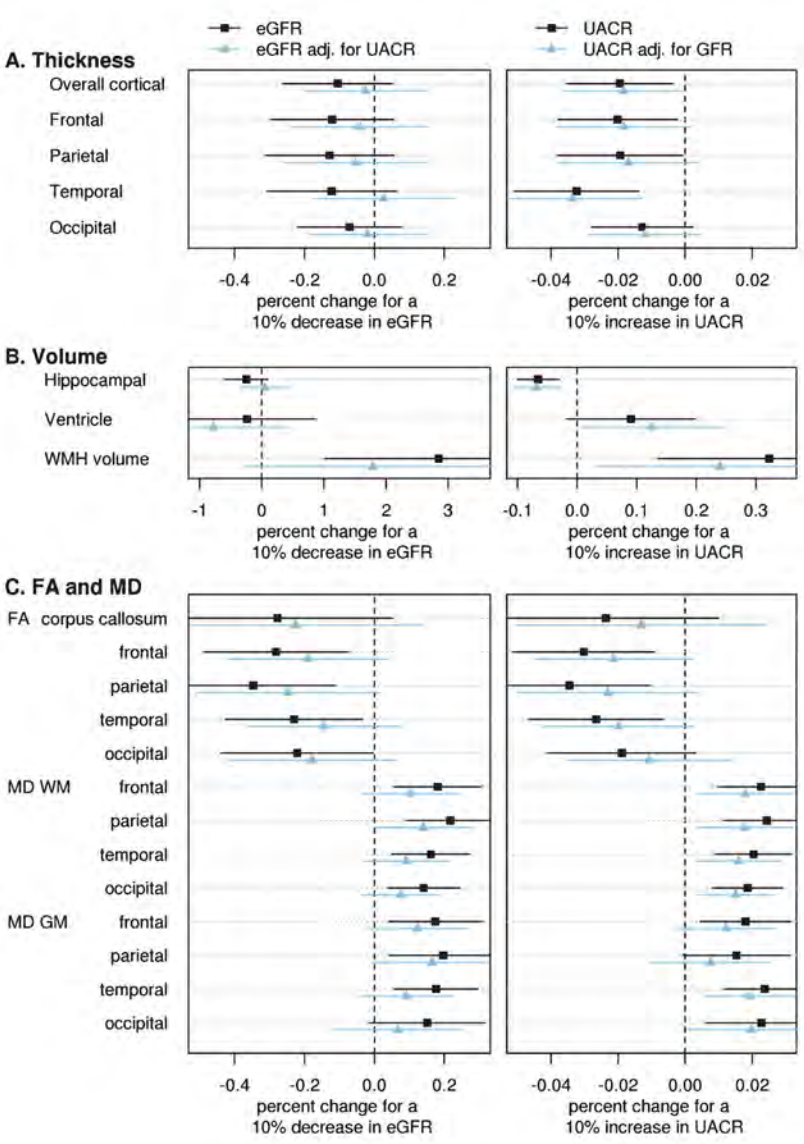

Fig. 2.

Percentage change (95% confidence interval, CI) in MRI outcome measures thickness (A), volume (B), and fractional anisotropy (FA) and MD (C) for a 10% decrease in eGFR or 10% increase in UACR. Estimates are from linear regression models adjusting for age, sex, education, race, diabetes, hypertension, cholesterol, systolic blood pressure, diastolic blood pressure, stroke/TIA, AFIB, CVD, smoking, and alcohol use. We fit models with GFR alone and UACR alone, and finally both GFR and UACR in the same model. The left panels show the effect of eGFR alone (black square) and the effect of eGFR after adjusting for UACR from the joint model (light blue triangle). The right panels show the effect of UACR alone (black square) and the effect of UACR after adjusting for eGFR from the joint model (light blue triangle).

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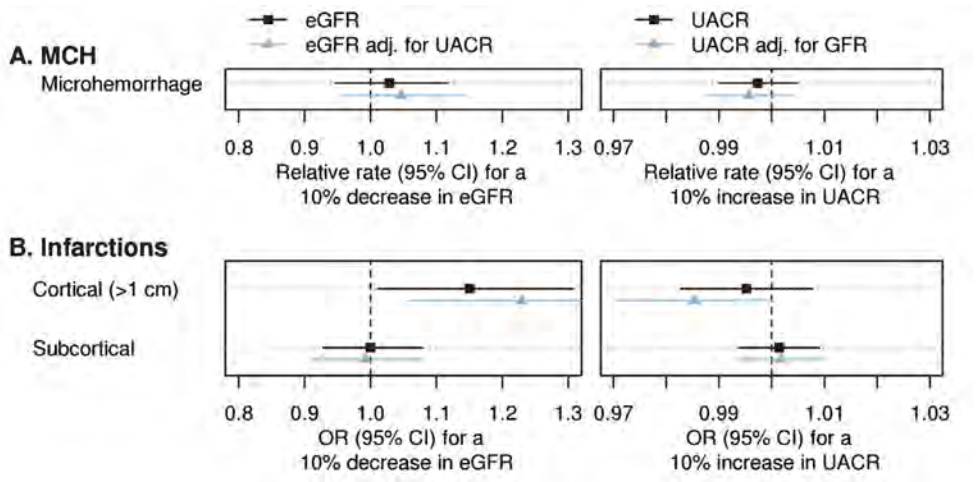

Fig. 3.

RR and OR (95% CI) for microhemorrhage (MCH) and infarctions (respectively) for a 10% decrease in eGFR or 10% increase in UACR after adjusting for age, sex, education, race, diabetes, hypertension, cholesterol, systolic blood pressure, diastolic blood pressure, stroke/TIA, AFIB, CVD, smoking, and alcohol use. We fit models with GFR alone and UACR alone, and finally both GFR and UACR in the same model. The left panel shows the effect of eGFR alone and the effect of eGFR after adjusting for UACR from the joint model (black square). The right panels show the effect of UACR alone and the effect of UACR after adjusting for eGFR from the joint model (light blue triangle).

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Table 1

Characteristics of participants by group

	All	CKD	Mild CKD	Control	p
No. of subjects (%)	240	150 (62%)	16 (7%)	74 (31%)	
Age, years					0.35[a]
Mean (SD)	69 (9)	70 (10)	71 (10)	68 (8)	
Range	45 to 94	45 to 92	58 to 94	47 to 88	
Male, n (%)	127 (53)	82 (55)	12 (75)	33 (45)	0.08[b]
Race, n (%)					0.92[c]
African-American	19 (8)	13 (9)	1 (6)	5 (7)	
White	207 (86)	128 (85)	14 (88)	65 (88)	
Other	14 (6)	9 (6)	1 (6)	4 (5)	
Education, years					<0.001[d]
Mean (SD)	15 (3)	14 (3)	15 (3)	16 (2)	
Range	5 to 22	5 to 22	12 to 22	11 to 20	
Diabetes, n (%)	105 (44)	69 (46)	10 (62)	26 (35)	0.09[e]
Hypertension, n (%)	214 (89)	145 (97)	15 (94)	54 (73)	<0.001[b]
Cholesterol, mean (SD)	183 (45)	176 (45)	173 (34)	199 (44)	<0.001[a]
SBP, mmHg, mean (SD)	133 (18)	135 (18)	128 (12)	130 (17)	0.09[a]
DBP, mmHg, mean (SD)	69 (11)	68 (12)	68 (10)	70 (10)	0.57[a]
Stroke or TIA, n (%)	29 (12)	22 (15)	2 (12)	5 (7)	0.21[b]
Atrial fibrillation, n (%)	31 (13)	19 (13)	2 (12)	10 (14)	0.95[b]
Cardiovascular disease, n (%)	97 (40)	78 (52)	7 (44)	12 (16)	<0.001[e]
Smoker, n (%)	22 (9)	16 (11)	2 (12)	4 (5)	0.33[b]
Alcohol use, n (%)	39 (16)	24 (16)	2 (12)	13 (18)	0.96[b]
GFR					–
Mean (SD)	47 (25)	30 (9)	51 (4)	79 (14)	
Median (IQR)	38 (30, 68)	32 (25, 37)	51 (49, 54)	77 (70, 87)	
Range	7 to 124	7 to 44	45 to 59	60 to 124	

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	All	CKD	Mild CKD	Control	p
UACR					–
Mean (SD)	372 (1003)	560 (1223)	140 (313)	43 (172)	
Median (IQR)	28 (2, 193)	84 (18, 512)	25 (13, 82)	0 (0, 11)	
Range	0 to 9632	0 to 9632	4 to 1229	0 to 1081	

[a] ANOVA;

[b] Fisher exact test;

[c] Fisher exact test, categorized as African-American versus not;

[d] ANOVA, test for difference between CKD and control has p-value ≤ 0.001;

[e] Chi-squared test.

CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; TIA, transient ischemic attack; GFR, glomerular filtration rate; UACR, urine albumin to creatinine ratio.

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Table 2

Estimate of effect (standard error, SE) in MRI outcomes for a 10% worsening in eGFR or UACR

		eGFR	eGFR	UACR	UACR
Response	**Model**	**estimate (SE)**	***p*-value**	**estimate (SE)**	***p*-value**
Thickness overall cortical	eGFR	–0.106 (0.08)	0.19	–	–
Thickness overall cortical	UACR	–	–	**–0.019 (0.01)**	**0.02**
Thickness overall cortical	Joint	–0.024 (0.09)	0.78	**–0.018 (0.01)**	**0.04**
Thickness frontal	eGFR	–0.121 (0.09)	0.18	–	–
Thickness frontal	UACR	–	–	**–0.02 (0.01)**	**0.03**
Thickness frontal	Joint	–0.039 (0.1)	0.69	–0.018 (0.01)	0.07
Thickness parietal	eGFR	–0.128 (0.09)	0.17	–	–
Thickness parietal	UACR	–	–	**–0.019 (0.01)**	**0.04**
Thickness parietal	Joint	–0.053 (0.11)	0.61	–0.017 (0.01)	0.11
Thickness temporal	eGFR	–0.122 (0.09)	0.20	–	–
Thickness temporal	UACR	–	–	**–0.032 (0.01)**	**<0.001**
Thickness temporal	Joint	0.027 (0.1)	0.80	**–0.034 (0.01)**	**0.002**
Thickness occipital	eGFR	–0.071 (0.08)	0.35	–	–
Thickness occipital	UACR	–	–	–0.013 (0.01)	0.10
Thickness occipital	Joint	–0.019 (0.09)	0.82	–0.012 (0.01)	0.17
Hippocampal volume	eGFR	–0.248 (0.18)	0.16	–	–
Hippocampal volume	UACR	–	–	**–0.065 (0.02)**	**<0.001**
Hippocampal volume	Joint	0.048 (0.2)	0.80	**–0.068 (0.02)**	**<0.001**
Ventricle volume	eGFR	–0.239 (0.56)	0.67	–	–
Ventricle volume	UACR	–	–	0.091 (0.06)	0.10
Ventricle volume	Joint	–0.776 (0.61)	0.20	**0.127 (0.06)**	**0.04**
WMH volume	eGFR	**2.849 (0.94)**	**0.002**	–	–
WMH volume	UACR	–	–	**0.323 (0.1)**	**<0.001**
WMH volume	Joint	1.792 (1.05)	0.09	**0.24 (0.11)**	**0.02**
FA corpus callosum	eGFR	–0.277 (0.17)	0.10	–	–
FA corpus callosum	UACR	–	–	–0.024 (0.02)	0.17
FA corpus callosum	Joint	–0.225 (0.19)	0.23	–0.013 (0.02)	0.49

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		eGFR	eGFR	UACR	UACR
Response	**Model**	**estimate (SE)**	***p*-value**	**estimate (SE)**	***p*-value**
FA frontal	eGFR	**–0.281 (0.11)**	**0.008**	–	–
FA frontal	UACR	–	–	**–0.03 (0.01)**	**0.005**
FA frontal	Joint	–0.189 (0.12)	0.11	–0.021 (0.01)	0.08
FA parietal	eGFR	**–0.346 (0.12)**	**0.004**	–	–
FA parietal	UACR	–	–	**–0.034 (0.01)**	**0.005**
FA parietal	Joint	–0.248 (0.13)	0.06	–0.023 (0.01)	0.09
FA temporal	eGFR	**–0.231 (0.1)**	**0.02**	–	–
FA temporal	UACR	–	–	**–0.027 (0.01)**	**0.009**
FA temporal	Joint	–0.144 (0.11)	0.20	–0.02 (0.01)	0.08
FA occipital	eGFR	**–0.221 (0.11)**	**0.047**	–	–
FA occipital	UACR	–	–	–0.019 (0.01)	0.09
FA occipital	Joint	–0.179 (0.12)	0.15	–0.011 (0.01)	0.40
MD WM frontal	eGFR	**0.181 (0.06)**	**0.005**	–	–
MD WM frontal	UACR	–	–	**0.023 (0.01)**	**<0.001**
MD WM frontal	Joint	0.103 (0.07)	0.15	**0.018 (0.01)**	**0.01**
MD WM parietal	eGFR	**0.217 (0.06)**	**<0.001**	–	–
MD WM parietal	UACR	–	–	**0.024 (0.01)**	**<0.001**
MD WM parietal	Joint	0.14 (0.07)	0.051	**0.018 (0.01)**	**0.01**
MD WM temporal	eGFR	**0.162 (0.06)**	**0.005**	–	–
MD WM temporal	UACR	–	–	**0.02 (0.01)**	**<0.001**
MD WM temporal	Joint	0.091 (0.06)	0.15	**0.016 (0.01)**	**0.01**
MD WM occipital	eGFR	**0.141 (0.05)**	**0.007**	–	–
MD WM occipital	UACR	–	–	**0.019 (0.01)**	**<0.001**
MD WM occipital	Joint	0.076 (0.06)	0.19	**0.015 (0.01)**	**0.01**
MD GM frontal	eGFR	**0.175 (0.07)**	**0.01**	–	–
MD GM frontal	UACR	–	–	**0.018 (0.01)**	**0.009**
MD GM frontal	Joint	0.123 (0.08)	0.10	0.012 (0.01)	0.11
MD GM parietal	eGFR	**0.197 (0.08)**	**0.01**	–	–
MD GM parietal	UACR	–	–	0.015 (0.01)	0.06
MD GM parietal	Joint	0.166 (0.09)	0.06	0.008 (0.01)	0.40

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		eGFR	eGFR	UACR	UACR
Response	**Model**	**estimate (SE)**	***p*-value**	**estimate (SE)**	***p*-value**
MD GM temporal	eGFR	**0.177 (0.06)**	**0.004**	–	–
MD GM temporal	UACR	–	–	**0.024 (0.01)**	**<0.001**
MD GM temporal	Joint	0.092 (0.07)	0.17	**0.019 (0.01)**	**0.005**
MD GM occipital	eGFR	0.151 (0.08)	0.07	–	–
MD GM occipital	UACR	–	–	**0.023 (0.01)**	**0.007**
MD GM occipital	Joint	0.067 (0.09)	0.47	**0.02 (0.01)**	**0.04**

The eGFR columns describe percent change and *p* values in response to a 10% decrease eGFR while holding UACR fixed. The UACR columns describe percent change and *p*-values in response to a 10% increase in UACR, while holding eGFR fixed. Estimates were adjusted for age, sex, education, race, diabetes, hypertension, cholesterol, systolic blood pressure, diastolic blood pressure, stroke/transient ischemic attack, atrial fibrillation, cardiovascular disease, smoking, and alcohol use. eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio; WMH, white matter hyperintensities; FA, fractional anisotropy; MD, mean diffusivity; WM, white matter; GM, gray matter.

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Table 3

Relative rate (RR) and odds ratio (OR) (95% CI) for microhemorrhages (MCH) and infarctions (respectively) for a 10% worsening in estimated glomerular filtration rate (eGFR) or urine albumin to creatinine ratio (UACR)

		eGFR	eGFR	UACR	UACR
Response	**Model**	**RR or OR (95% CI)**	***p*-value**	**RR or OR (95% CI)**	***p*-value**
MCH					
Microhemorrhages (RR)	eGFR	1.028 (0.95, 1.12)	0.507	–	–
Microhemorrhages (RR)	UACR	–	–	0.997 (0.99, 1.01)	0.486
Microhemorrhages (RR)	Joint	1.047 (0.96, 1.15)	0.322	0.996 (0.99, 1.0)	0.309
Infarctions					
Large cortical infarctions (OR)	eGFR	**1.15 (1.01, 1.31)**	**0.033**	–	–
Large cortical infarctions (OR)	UACR	–	–	0.995 (0.98, 1.01)	0.453
Large cortical infarctions (OR)	Joint	**1.23 (1.01,1.43)**	**0.008**	0.985 (0.97, 1.0)	0.062
Subcortical infarctions (OR)	eGFR	1 (0.93, 1.08)	0.993	–	–
Subcortical infarctions (OR)	UACR	–	–	1.001 (0.99, 1.01)	0.723
Subcortical infarctions (OR)	Joint	0.992 (0.91, 1.08)	0.858	1.002 (0.99, 1.01)	0.691

The eGFR columns describe percent change and *p* values in the response to a 10% decrease eGFR while holding UACR fixed. The UACR columns describe percent change and *p*-values in response to a 10% increase in UACR, while holding eGFR fixed. Estimates were adjusted for age, sex, education, race, diabetes, hypertension, cholesterol, systolic blood pressure, diastolic blood pressure, stroke/transient ischemic attack, atrial fibrillation, cardiovascular disease, smoking, and alcohol use.