

Supplementary Material

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

Inclusion Criteria and Assessments

Serum creatinine was measured at baseline using non-fasting blood samples drawn from an antecubital vein and processed at the CLIA certified Hennepin HealthCare Clinical Laboratory. Proteinuria was described using the UACR, which was measured using a single spot urine sample collected at the baseline visit. Inclusion criteria for BRINK CKD participants were as follows: age ≥ 45 years; eGFR < 60 ml/min/1.73 m², with the goal to recruit approximately 2/3 of the CKD sample with an eGFR < 45 ml/min/1.73 m² (Stage 3b- 5; non- dialysis- dependent); 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 m². Of note, non-CKD subjects with previously diagnosed diabetes were over-sampled; i.e., preferentially recruited to seek to approximate the known high prevalence of diabetes among CKD patients (approximately 50% in the U.S. CKD population) and thus decrease potential confounding by diabetes on the effect of CKD on cognitive impairment. 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 kidney transplant recipient at the time of screening, or inability to provide signed consent due to severe cognitive impairment as judged by the potential participants' providers, family, or caregivers.

BRINK MRI participants were a subset of BRINK participants who 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. The non-CKD MRI participants were recruited to approximate the age and race distributions of the BRINK MRI CKD group. BRINK participants with a baseline MRI who did not transition to dialysis or withdraw from the study prior to their year 3 visit were eligible for a year 3 MRI. The study populations of interest for this analysis included two longitudinal MRI cohorts 1) Overall: all BRINK participants with usable baseline and year 3 MRI scans and 2) BRINK CKD (eGFR <60) participants with usable baseline and year 3 MRI scans.

Cardiovascular disease was ascertained by self-reported history of angina, myocardial infarction, heart failure, or peripheral arterial disease. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, self-reported hypertension, or taking antihypertensive medications. Hyperlipidemia was defined as serum total cholesterol > 240 mg/dL or on lipid-lowering medications. Diabetes was defined as non-fasting glucose ≥ 200 mg/dL, hemoglobin A1c $\geq 6.5\%$, self-reported diabetes, or taking diabetes medications. Atrial fibrillation (Afib) was defined as self-reported history of Afib or current (e.g., baseline) Afib per BRINK EKG reviewed by a study cardiologist. Stroke or transient ischemic attack (TIA) was ascertained as self-reported history of stroke or TIA. A cerebrovascular (CV) risk factor score, ranging from 0–6, was defined as the sum of cerebrovascular risk contributing factors (the presence of at least one of the four components of self-reported history of angina, myocardial infarction, heart failure, or peripheral arterial disease), hypertension, hyperlipidemia, diabetes, Afib, Stroke/TIA. Pulse pressure was defined as SBP minus DBP and considered as a single variable in the model as a measure of arterial

stiffness, as previously published [1]. Though hypertension is a significant risk factor for WMH, we considered it as part of the CV risk factor score because the majority of participants (84.5%) had hypertension at baseline. Smoking was defined as smoking any cigarettes in the past month. Alcohol use/abuse was defined as self-reported history of alcoholism or current alcohol consumption of more than 1 drink per day. A combination variable for smoker or alcohol use/abuse was defined as either smoking or alcohol use/abuse versus neither. Since these two covariates separately as well as combined resulted in similar results, we combined them to reduce the number of adjustment variables. We did not analyze specific medication effects due to sample size limitations.

Imaging: Acquisition and Processing

All participants were scanned on a single 1.5T Phillips Ingenia MRI scanner at baseline and follow-up. The image acquisition details were: T1 MPRAGE for measuring gray matter changes [TR=8.6 ms, TE=3.9 ms, Flip Angle=8, Matrix=192 x 192, slice thickness=1.2 mm, Slices per Volume=170]; FLAIR MRI for measuring white matter hyperintensity [TR=6,000 ms, TE=140 ms, Flip Angle=90, Matrix=256 x 204, slice thickness=5 mm, Slices per Volume=35]; and diffusion tensor imaging (DTI) for measuring white matter microstructural changes [Single-shot echo-planar pulse sequence in the axial plane, with TR=7838 ms, TE=95 ms, Flip Angle=90, slice thickness=2.7 mm, Slices per Volume=60, Number of Volumes=34, 33 diffusion encoding directions with strength $b=1000$ s/mm² and one non-diffusion weighted (b_0) T2w images]. Quality control was performed on each protocol that was acquired for each subject and the outcome measures were only included for those participants who passed quality control on these outputs of standard tools.

The same protocol was used for acquisition at baseline and follow-up. Quality control was performed on each protocol that was acquired for each subject, and the outcome measures were only included for those participants who passed quality control. The image processing and outcome measures used in this paper are presented here for each of the MRI scans.

Potential Participation Bias

Potential participation bias was addressed in the baseline BRINK MRI cohort analysis which reported that, compared to BRINK participants without a baseline MRI, the baseline BRINK MRI cohort was more likely to be white (86% versus 79%), less likely to have diabetes (43.8% versus 52.9%), had higher education ($p=0.01$), and a lower proportion with Mild CKD (6.7% versus 22.9%). The retention rate for those with a baseline MRI was 40% (98/242) with 144 missing a 3 year MRI due to following reasons: 32 (22%) were lost-to-follow-up or withdrew from the study, 17 (12%) deceased, 12 (8%) transitioned to dialysis, 7 (5%) were out of window for a year 3 MRI, 8 (6%) were not eligible for a year 3 MRI for medical reasons, and 68 (47%) had a scheduled year 3 MRI date during the March 2017–July 2018 funding gap between BRINK I and BRINK II. Year 3 MRI scans were completed for 98 of those with a baseline MRI, one of which was excluded due to massive cortical infarction, resulting in an overall 3-year longitudinal MRI analysis sample size of 97. Compared to those in the longitudinal MRI cohort ($n=97$), those with only a baseline MRI ($n=145$) were older [71.0 (9.0) versus 66.7 (9.1) years, $p=0.0003$], had higher mean baseline SBP [136.4 (18.0) versus 128.9 (15.3) mmHg, $p=0.0009$], were more likely to be in the Control group [53 (36.6%) versus 23 (23.7%), $p=0.004$], have a history of or current atrial fibrillation [26 (18.1%) versus 6 (6.3%), $p=0.008$] and either smoke or use/abuse alcohol [40 (27.6%) versus 16 (16.5%), $p=0.045$] (data not shown).

However, those missing 3 year MRI were composed of two subgroups that differed substantially: those who missed the 3 year MRI during the funding gap period (N=68) (corresponding to end of recruiting period when more Controls were recruited at baseline 3 years earlier) and those without a 3 year MRI due to other reasons such as medical illness, cortical infarction, starting dialysis, LTFU, or death (N=77).

REFERENCE

- [1] Sedaghat S, Mattace-Raso FUS, Hoorn EJ, Uitterlinden AG, Hofman A, Ikram MA, Franco OH, Dehghan A (2015) Arterial stiffness and decline in kidney function. *Clin J Am Soc Nephrol* **10**, 2190-2197.