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Association of Kidney Function Measures With Signs of Neurodegeneration and Small Vessel Disease on Brain Magnetic Resonance Imaging: The Atherosclerosis Risk in Communities (ARIC) Study

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Abstract

Rationale & Objective: Chronic kidney disease (CKD) is a risk factor for cognitive decline, but evidence is limited on its etiology and morphological manifestation in the brain. We evaluated

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the association of estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (UACR) with structural brain abnormalities visible on magnetic resonance imaging (MRI). We also assessed whether this association was altered when different filtration markers were used to estimate GFR.

Study Design: Cross-sectional study nested in a cohort study.

Setting & Participants: 1,527 participants in the Atherosclerosis Risk in Communities (ARIC) Study.

Predictors: Log(UACR) and eGFR based on cystatin C, creatinine, cystatin C and creatinine in combination, or β_2-microglobulin (B2M).

Outcomes: Brain volume reduction, infarcts, microhemorrhages, white matter lesions.

Analytical Approach: Multivariable linear and logistic regression models fit separately for each predictor based on a 1-IQR difference in the predictor value.

Results: Each 1-IQR lower eGFR was associated with reduced cortex volume (regression coefficient: −0.07 [95% CI, −0.12 to −0.02]), greater white matter hyperintensity volume (logarithmically transformed; regression coefficient: 0.07 [95% CI, 0.01–0.15]), and lower white matter fractional anisotropy (regression coefficient: −0.08 [95% CI, −0.17 to −0.01]). The results were similar when eGFR was estimated with different equations based on cystatin C, creatinine, a combination of cystatin C and creatinine, or B2M. Higher log(UACR) was similarly associated with these outcomes as well as brain infarcts and microhemorrhages (odds ratios per 1-IQR-fold greater UACR of 1.31 [95% CI, 1.13–1.52] and 1.30 [95% CI, 1.12–1.51], respectively). The degree to which brain volume was lower in regions usually susceptible to Alzheimer disease and LATE (limbic-predominant age-related TDP-43 [Tar DNA binding protein 43] encephalopathy) was similar to that seen in the rest of the cortex.

Limitations: No inference about longitudinal effects due to cross-sectional design.

Conclusions: We found eGFR and UACR are associated with structural brain damage across different domains of etiology, and eGFR- and UACR-related brain atrophy is not selective for regions typically affected by Alzheimer disease and LATE. Hence, Alzheimer disease or LATE may not be leading contributors to neurodegeneration associated with CKD.

Dementia and cognitive decline constitute a growing public health issue, causing lower quality of life, loss of independence, increased caregiver burden, and premature death.[1] In addition to the heavy personal toll, estimated health care costs amount to over $150 billion annually in the United States, a financial strain similar to heart disease or cancer.[2] Therefore, it is vital to identify high-risk patients and understand the underlying disease mechanisms to facilitate prevention and treatment strategies.[3]Dementia, both vascular and age-related, as well as cognitive decline are often accompanied or preceded by brain pathologies visible on magnetic resonance imaging (MRI).[4–6] Certain brain regions including the entorhinal cortex, fusiform gyri, inferior temporal lobe, middle temporal lobe, and hippocampus are usually susceptible to neurodegenerative disease, including typical amnestic Alzheimer disease (AD) and, in later age, limbic-predominant age-related TDP-43 (Tar DNA binding protein 43) encephalopathy (LATE).[7,8] White matter hyperintensities (WMH) and lacunar infarcts are signs of small vessel disease, which is known to contribute to vascular dementia.[9,10]

Cerebral microhemorrhages have been shown to be more frequent in study participants with vascular dementia, cerebral amyloid angiopathy, and AD, depending on the hemorrhages' location.[11,12] An impaired microstructural integrity of white matter is a sign of subclinical brain damage and can be measured using diffusion tensor imaging (DTI). It is also a predictor for the development of brain atrophy and cognitive decline later in life.[13–15]

Patients with chronic kidney disease (CKD) are also at a higher risk of cognitive decline, and more advanced stages of CKD are associated with more severe cognitive impairment.[16–18] Previous studies have reported an association of kidney function measures with brain atrophy, cerebrovascular pathologies, and white matter abnormalities, but characterized the brain damage as primarily driven by vascular causes and its nature as being functional rather than structural.[19–21] An evaluation of the effects of CKD on structural outcomes, including brain MRI pathologies in regions usually susceptible to neurodegenerative disease (eg, AD and LATE), has not been performed. In addition, most previous studies based their glomerular filtration rate (GFR) estimates on creatinine, which can be influenced by non-GFR determinants of creatinine such as unusual muscle mass, protein-rich diet, or intake of supplements containing creatine.[22–25]

In this study, we investigated the cross-sectional relationship of estimated GFR (eGFR) and urinary albumin-creatinine ratio (UACR) with structural brain abnormalities visible on MRI in the Atherosclerosis Risk in Communities (ARIC) Study cohort. We examined whether the association of these kidney function measures with brain MRI abnormalities differs for pathologies that are usually associated with AD and LATE compared with those typically related to vascular dementia. We also assessed whether the association between eGFR and brain MRI changes is different depending on which markers (cystatin C, creatinine, or β_2-microglobulin [B2M])[26–28] are used for the estimation of GFR.

Methods

Study Population

In 1987–1989, the ARIC cohort study recruited 15,792 participants between 45 and 64 years old from 4 US communities (Washington County, MD; Forsyth County, NC; Jackson, MS; and Minneapolis, MN).[29] Participants with evidence of cognitive impairment and a stratified random sample of the remaining participants were invited for a brain MRI scan at study visit 5 (2011–2013) as part of the ARIC Neurocognitive Study (NCS).[10,30] For our cross-sectional analysis, we included all White or African American participants with complete data for brain MRI, eGFR, UACR, and covariates, resulting in 1,527 participants (Fig S1). This study was approved by the institutional review boards at all study sites (Johns Hopkins University, Wake Forest University, University of Mississippi Medical Center, and University of Minnesota), and all participants gave written, informed consent.

Exposures: Measures of Kidney Function

As exposures, we studied eGFR and UACR at ARIC visit 5. Creatinine was measured in plasma specimens using a modified kinetic Jaffé method, calibrated to the Cleveland Clinic laboratory measurements and standardized to an isotope-dilution mass spectrometry–

traceable method.[31,32] Cystatin C and B2M were also measured in plasma using a particle-enhanced immunonephelometric assay (Siemens Healthcare Diagnostics) followed by calibration and standardization.[33] In the primary analysis, GFR was estimated using the CKD Epidemiology Collaboration (CKD-EPI) equation based on cystatin C.[27] This was motivated by concerns that eGFR based on creatinine may be influenced by non-GFR determinants of creatinine. In a sensitivity analysis, associations with eGFR based on creatinine, a combination of creatinine and cystatin C, or B2M were also tested.[26–28] For use of creatinine and the creatinine–cystatin C combination, the 2021 CKD-EPI equations were used.[28] Urine albumin was measured in spot urine samples via a nephelometric method with either the BN-100 (Dade Behring) or the Beckman Nephelometer (Beckman Coulter).

Outcomes: Brain Imaging

Structural brain images were obtained using 3-T MRI scanners (Siemens Verio [Maryland study center], Siemens Skyra [North Carolina and Mississippi study centers], or Siemens Trio [Minnesota study center] following identical protocols.[34] The scans included sagittal T1-weighted magnetization–prepared rapid gradient-echo (MPRAGE) imaging, axial T2 fluid attenuation inversion recovery (FLAIR), and axial DTI pulse sequences. Brain volumes were estimated based on T1-weighted scans. Data processing was done at the ARIC MRI Reading Center at the Mayo Clinic (Rochester, MN).

Volumes of regions of interest (ROIs) were estimated using the FreeSurfer system (Laboratory for Computational Neuroimaging). Specifically, we evaluated the volume of the whole brain, total cortical region, as well as a meta-ROI, which includes the entorhinal cortex, fusiform gyri, inferior temporal lobe, middle temporal lobe, hippocampus, and amygdala. This meta-ROI is typically susceptible to neurodegenerative disease, including typical amnestic AD and LATE.[7,8] In our analysis, it is referred to as “temporal lobe meta-ROI.” WMH volume was measured using a semiautomated segmentation algorithm on T2-weighted FLAIR images.[35]

Brain microhemorrhages and infarcts were identified by a trained imaging technician and confirmed by a radiologist. Depending on the location, microhemorrhages were further classified as lobar (lobar or cortical gray matter) or subcortical (subcortical or periventricular) microhemorrhages; infarcts were further classified as lacunar or cortical infarcts. Fractional anisotropy (FA) is a measurement for the directional constraint of water diffusion with a unitless range from 0 to 1. Mean diffusivity (MD) is a scalar measure of how quickly water molecules diffuse (10^{-4} mm^2/s). Lower levels of FA and higher levels of MD are a sign of impaired white matter microstructural integrity.[14]

Covariates

The covariates used for adjustment in statistical models were chosen as known dementia risk factors based on previous studies.[36] Age, sex, race, education (less than high school, high school graduate or general equivalency diploma, beyond high school), and smoking status (current smoker, former smoker, never smoker) were self-reported. Additional covariates were apolipoprotein E (APOE) ε4 genotype (presence of 0, 1, or 2 alleles; genotyping was performed using the TaqMan assay [Applied Biosystems]), body mass index (in kg/

m^2), serum low-density lipoprotein cholesterol (in mmol/L, measured using an enzymatic method), hypertension (systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, or use of antihypertensive medication), diabetes (fasting glucose level ≥ 126 mg/dL with serum glucose assessed by the hexokinase method, self-report of physician-diagnosed diabetes, or use of diabetes medication), prevalent heart failure, and prior history of stroke. Information about sex, race, date of birth, self-reported education, and APOE genotype was obtained at ARIC visit 1. For all other covariates, the measurements were taken at ARIC visit 5.

Statistical Analysis

This is a cross-sectional analysis with eGFR and UACR as exposures and different brain pathologies visible on MRI as outcomes. eGFR was modeled either as a continuous or as a categorical exposure variable using standard categories of eGFR: <30, 30-<60, 60-<90 (reference category), and ≥90 mL/min/1.73 mL/min/1.73 m^2. Albuminuria was modeled as continuous UACR.

To account for skewness in the distribution, the exposure variable UACR and the outcome variable WMH were log-transformed. Logistic regression was used for binary outcomes to calculate odds ratios (ORs) with 95% CI per 1-IQR difference in the respective predictor, or to calculate ORs comparing predictor categories to the reference category. Linear regression was used for continuous outcomes to calculate regression coefficients with 95% CI per 1-IQR difference in the respective predictor or comparing predictor categories to the reference category.

Owing to the variability in the distributions and units of the continuous outcome variables, and in order to facilitate the comparison of their regression results, the continuous outcome variables were standardized before regression to have a mean of 0 and SD of 1. Models analyzing log(UACR) as a predictor were adjusted for the covariates age, sex, race, education, APOE ε4, smoking, body mass index, low-density lipoprotein cholesterol level, hypertension, diabetes, heart failure, stroke, and cystatin C–based eGFR. For brain volume measurements and WMH volume, models were further adjusted for total intracranial volume.

All statistical models were weighted to account for potential bias introduced by the stratified random sampling approach used to select participants for a brain MRI scan. We applied inverse probability weighting, using weights inversely proportional to the sampling weights. Potential interactions between exposures and race were evaluated by running separate models including interaction terms for cystatin C–based eGFR and race, as well as UACR and race.

In a sensitivity analysis, we evaluated the association of structural brain abnormalities visible on MRI with eGFR calculated using creatinine alone, a combination of creatinine and cystatin C, or B2M. $P < 0.05$ was considered statistically significant, and tests for significance were 2-tailed. All statistical analyses were performed using Stata Version 15.1 (StataCorp LLC).

Results

Participant Characteristics

Among the 1,527 participants in our analysis, the mean age was 76.4 ± 5.3 (SD) years, 879 participants (57.6%) were women, and 417 (27.3%) were African American. Among all participants, 391 (25.6%) had 1 and 40 (2.6%) had 2 APOE ε4 risk alleles. In the assessment of cognitive status at the study visit, 926 (60.6%) of the participants had no cognitive impairment, 525 (34.4%) had mild cognitive impairment, and 76 (5.0%) had dementia. Lower eGFR was associated with a higher prevalence of hypertension, diabetes, heart failure, and previous stroke. Participants with an eGFR < 30 mL/min/1.73 m^2 also showed higher levels of albuminuria compared with the rest of the study cohort (Table 1). In the study population, the mean brain volume was 1,016.0 ± 108.7 cm^3, and cortex volume was 399.1 ± 43.0 cm^3. Brain MRI scans showed infarcts in 398 (26.1%) and microhemorrhages in 371 (24.3%) participants (Table 2).

Association of Kidney Function Measures With Brain Atrophy

Lower cystatin C-based eGFR was associated with lower brain cortex volume, with a regression coefficient of −0.07 (95% CI, −0.12 to −0.02) per 1-IQR lower eGFR (equivalent to 26.10 mL/min/1.73 m^2). The association of decreased eGFR with brain atrophy in temporal lobe meta-ROIs, which identify regions of the cortex usually susceptible to neurodegenerative disease, including AD and LATE, had a regression coefficient of −0.05 (95% CI, −0.11 to 0.01) per 1-IQR lower eGFR. This effect size, though not statistically significant, was similar in direction and magnitude to that of the cortex areas excluding these ROIs (regression coefficient per 1-IQR lower eGFR, −0.07 [95% CI, −0.12 to −0.03]) (Table 2). When assessing cortex volume according to standard eGFR categories, lower eGFR was also associated with brain cortex atrophy but was only statistically significant for participants with eGFR < 30 mL/min/1.73 m^2 (regression coefficient: −0.21 [95% CI, −0.36 to −0.06]) compared with the reference group with an eGFR of 60−<90 mL/min/1.73 m^2. The effect size was again similar in direction and magnitude for atrophy in temporal lobe meta-ROIs (regression coefficient: −0.16 [95% CI, −0.35 to 0.02]; not statistically significant) compared with the remaining cortical regions (regression coefficient: −0.22 [95% CI, −0.37 to −0.07]) (Table 3).

Higher levels of albuminuria were similarly related to lower brain volume, both in temporal lobe meta-ROIs and cortex areas excluding temporal lobe meta-ROIs; for log(UACR), the regression coefficients per 1-IQR-fold (equivalent to 1.26-fold) greater value were similar to the regression coefficients per 1-IQR lower eGFR (Table 2).

Association of Kidney Function Measures With Macrovascular Damage

Associations of albuminuria with macrovascular damage were expressed in adjusted OR (AOR) per 1-IQR-fold greater log(UACR). Participants with higher levels of albuminuria were more likely to have prevalent macrovascular brain damage, such as brain infarcts (AOR, 1.31 [95% CI, 1.13–1.52]). This could also be observed for the 2 subtypes of brain infarcts evaluated in this study: cortical infarcts (AOR, 1.27 [95% CI, 1.05–1.53]) and lacunar infarcts (AOR, 1.18 [95% CI, 1.00–1.39]). In addition, there was an association

between higher levels of albuminuria and increased odds of brain microhemorrhages in general (AOR, 1.30 [95% CI, 1.12–1.51]) and subcortical microhemorrhages in particular (AOR, 1.32 [95% CI, 1.13–1.54]). For lobar microhemorrhages, the effect estimate was similar in direction and magnitude but not statistically significant (Table 2).

Although the effect estimates were not statistically significant, participants with lower eGFR had nominally greater odds of prevalent brain infarcts of any kind and lacunar infarcts (but not cortical infarcts) as well as microhemorrhages of any kind and lobar microhemorrhages (but not subcortical microhemorrhages) (Table 2).

Association of Kidney Function Measures With Microvascular Abnormalities

Reduced eGFR and greater albuminuria showed similar associations with microvascular white matter pathologies in conventional MRI and DTI (associations are expressed as regression coefficients per 1-IQR lower eGFR or per 1-IQR-fold greater UACR). The volume of WMH, which is a sign of brain small vessel disease, was higher in patients with lower eGFR (regression coefficient, 0.07 [95% CI, 0.01–0.15]) and higher log(UACR) (regression coefficient, 0.09 [95% CI, 0.03–0.15]). Impaired microstructural integrity of white matter indicates subclinical brain damage and is reflected in lower levels of FA and higher levels of MD in DTI measurements. Lower white matter FA was associated with lower levels of eGFR (regression coefficient, −0.08 [95% CI, −0.17 to −0.01]) and higher levels of log(UACR) (regression coefficient, −0.09 [95% CI, −0.16 to −0.02]). White matter MD was increased for both lower eGFR and higher log(UACR), but only statistically significant for log(UACR) (regression coefficient, 0.11 [95% CI, 0.05 to 0.17]) (Table 2).

In the analysis of standard eGFR categories, white matter FA was also lower in participants with eGFR < 30 mL/min/1.73 m^2 than in those in the reference group (regression coefficient, −0.30 [95% CI, −0.59 to −0.01]) (Table 3).

Sensitivity Analyses

To compare kidney function measurements based on different biomarkers, we repeated the analysis for continuous eGFR, but instead of using a cystatin C–based eGFR, we used GFR estimated with creatinine, a combination of creatinine and cystatin C, or B2M. The regression results for these other GFR estimates and their associations with brain volume, infarcts, microhemorrhages, and white matter lesions were similar in direction and magnitude to eGFR based on cystatin C, as was used in the main analysis (Table 2; Table S1).

In the analysis of interaction between kidney function measures and race, the interaction terms of cystatin C–based eGFR or log(UACR) with race were not statistically significant (Table S2).

Discussion

This study of 1,527 community-based participants shows that kidney function measures are significantly associated with markers of neurodegeneration and small vessel disease visible on brain MRI. These associations were robust against adjusting for known vascular risk

factors. Lower levels of eGFR and higher levels of UACR were associated with a reduction of cortical brain volume, and this association was as strong for cortical regions susceptible to AD and LATE as in the rest of the cortex. Both lower eGFR and higher UACR were also associated with greater WMH volume, a sign of small vessel disease in the brain, and impaired white matter microstructural integrity visible on DTI measurements, such as reduced white matter FA. Beyond that, the participants with higher levels of UACR had greater odds of ischemic brain damage, such as lacunar and cortical infarcts and of subcortical microhemorrhages. Increased UACR was also associated with higher MD, another sign of microstructural white matter damage. The effect sizes were generally similar in direction and magnitude when GFR estimation was based on cystatin C, creatinine, a combination of creatinine and cystatin C, or B2M.

The relationship between albuminuria and structural brain pathologies is supported by previous studies, which have found associations with reduced brain volume, increased WMH volume, and microstructural white matter damages in patients with CKD, diabetes, or other cardiovascular risk factors.[20,37–42] Our study adds an analysis of a large, biracial population-based sample, finding a significant correlation of UACR with white matter lesions, microhemorrhages, and infarcts. This contributes further evidence to previous studies linking albuminuria to cerebral small vessel disease.[20,43] An association of UACR with brain atrophy was visible in the cortex but was not selective for regions typically affected by AD and LATE. Therefore, etiologies other than AD or LATE, such as vascular damage, are likely to play a leading role as pathomechanisms for cognitive decline in patients with albuminuria.

Compared with albuminuria, the evidence linking eGFR to MRI markers of neurodegeneration is less clear. Some studies reported that albuminuria but not eGFR was associated with WMH and brain atrophy affecting both grey and white matter.[38,41] Others found marginal associations of eGFR with brain volume and white matter lesions, which were statistically significant at first but did not persist after adjusting for other factors.[44] Yet most previous studies reported significant associations of eGFR with brain atrophy,[40,45,46] microvascular damage,[20,21] and impaired white matter microstructural integrity,[39,40] which is consistent with our findings.

Mixed results of previous studies regarding the association of eGFR and brain pathologies visible on MRI may be explained by small sample sizes in some analyses and different study populations regarding age, nationality, severity of cognitive impairment, etiology of CKD, duration of CKD, as well as variation in severity of CKD in the cohort. It is noteworthy that all but one of these studies used GFR estimations based on serum creatinine, which can potentially be influenced by muscle mass, meat-based diet, or creatine dietary supplements.[22–25] Older people are more likely to have less than average muscle mass due to chronic illness, leading to low creatinine values and potential overestimation of GFR, which may blur associations with adverse outcomes. By contrast, markers such as cystatin C or B2M may be less affected by such non-GFR determinants of creatinine.[28,47]

For our main analysis, we therefore used eGFR based on cystatin C and performed a sensitivity analysis comparing the results with estimations based on creatinine, a

combination of creatinine and cystatin C, and B2M. Comparability was ensured by standardizing all changes of eGFR to their respective IQRs. However, the associations between eGFR and morphological brain abnormalities for cystatin C–based GFR estimates were similar in direction and magnitude compared with the estimates based on other biomarkers. We therefore conclude that the association between eGFR and MRI signs of neurodegeneration in our cohort is not influenced by the way GFR is estimated.

Compared to previous studies, our analysis adds a more detailed breakdown of affected brain regions. The effect size for the association of lower eGFR and reduced brain volume was similar in direction and magnitude for brain regions usually susceptible to AD and LATE and other regions of the cortex. The generalized atrophy pattern, which we observed in association with both eGFR and UACR, was not selective for regions typically affected by AD and LATE. This suggests that AD and LATE may not be leading factors in the development of brain pathologies related to CKD but may coexist with vascular etiologies of reduced brain volume. Our analysis shows statistically significant associations of decreased kidney function with brain atrophy, microvascular brain damage, and impaired white matter integrity. Hence, CKD appears to be related to various domains of macro- and microstructural brain damage suggestive of a multifactorial pathomechanism in the development of neurodegeneration and brain small vascular disease.

The strengths of our study include a large population-based sample with both White and African American participants, enhancing the generalizability of the results, as well as use of variety of filtration markers for estimating GFR and comprehensive brain imaging techniques covering different areas of morphological brain damage. However, this study also has limitations. The cross-sectional study design does not allow for inference about longitudinal effects. Although a one-time measurement of brain volume relative to intracranial volume has been used in the previous literature to measure brain atrophy, the rate of brain atrophy over time cannot be assessed.[48] Conducting MRI scans on only a part of the ARIC cohort at study visit 5 (all participants with cognitive impairment plus a stratified random sample of the remaining participants) may introduce potential selection bias. This was addressed by using inverse probability weighting. B2M can be measured by different methods, such as immunoassay, nephelometry, or turbidimetry; due to a lack of standardization, there is discordance between these methods.[49] However, we would not expect this to affect our analysis because all measurements were performed with the same immunonephelometric assay followed by calibration and standardization.[33]

A principal objective of ARIC-NCS is to characterize the morphological manifestation of dementia and cognitive decline. This study builds upon previous reports, which linked kidney function measures to dementia and cognitive decline,[16–18] and confirms the association of UACR and eGFR with structural brain damage while also providing new information about its etiology as well as its localization in the brain. Future studies need to collect longitudinal data and confirm predictors as risk factors to increase clinical applicability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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PLAIN-LANGUAGE SUMMARY

Cognitive decline is a major public health issue and common in patients with kidney disease. To better understand this condition, we measured kidney function and albuminuria in 1,527 participants from the Atherosclerosis Risk in Communities Study. The participants were also scanned for different types of brain damage using magnetic resonance imaging. We found that low kidney function and albuminuria are associated with various structural brain pathologies, such as brain atrophy, microvascular damage, and white matter defects. These results confirm the connection between kidney function and albuminuria with brain damage and provide new information about its cause and its localization in the brain.

Table 1.

Characteristics of the Study Population From the ARIC Study Cohort, Visit 5 (Ages 67–90 Years During 2011–2013)

		eGFR Category (mL/min/1.73 m^2)[a]			
Participant Characteristics[a]	**Overall**	**≥90**	**60-<90**	**30-<60**	**<30**
No. of patients	1,527	114	678	663	72
Age, y	76.4 ± 5.3	74.0 ± 4.4	75.2 ± 4.9	77.7 ± 5.4	78.6 ± 5.1
Women	879 (57.6%)	60 (52.6%)	373 (55.0%)	402 (60.6%)	44 (61 %)
African American	417 (27.3%)	49 (43.0%)	201 (29.6%)	150 (22.6%)	1 7 (24%)
Education					
< High school	223 (14.6%)	10 (8.8%)	85 (12.5%)	113 (1 7.0%)	15 (21%)
High school	618 (40.5%)	40 (35.1%)	273 (40.3%)	279 (42.1%)	26 (36%)
> High school	686 (44.9%)	64 (56.1%)	320 (47.2%)	271 (40.9%)	31 (43%)
Smoking status					
Current	73 (4.8%)	4 (3.5%)	30 (4.4%)	36 (5.4%)	3 (4%)
Former	758 (49.6%)	70 (61.4%)	324 (47.8%)	329 (49.6%)	35 (49%)
Never	696 (45.6%)	40 (35.1%)	324 (47.8%)	298 (45.0%)	34 (47%)
APOE ε4 status					
TT: 0 Alleles	1,096 (71.8%)	73 (64.0%)	469 (69.2%)	504 (76.0%)	50 (69%)
CT: 1 Allele	391 (25.6%)	35 (30.7%)	189 (27.9%)	148 (22.3%)	1 9 (26%)
CC: 2 Alleles	40 (2.6%)	6 (5.3%)	20 (2.9%)	11 (1.7%)	3 (4%)
BMI, kg/m^2	28.4 ± 5.7	26.9 ± 4.3	28.0 ± 5.7	28.9 ± 5.8	28.9 ± 6
LDL cholesterol, mg/dL	104.7 ± 34.3	112.4 ± 36.4	106.9 ± 33.9	102.3 ± 33.9	93.6 ± 35
Hypertension	1,144 (74.9%)	71 (62.3%)	486 (71.7%)	520 (78.4%)	67 (93%)
Diabetes	514 (33.6%)	32 (28.1%)	209 (30.8%)	240 (36.2%)	33 (46%)
Heart failure	162 (10.6%)	10 (8.8%)	50 (7.4%)	79 (11.9%)	23 (32%)
Stroke	57 (3.7%)	2 (1.8%)	13 (1.9%)	34 (5.1%)	8 (11 %)
Cognitive status					
No cognitive impairment	926 (60.6%)	79 (69.3%)	421 (62.1%)	394 (59.4%)	32 (44%)
Mild cognitive impairment	525 (34.4%)	31 (27.2%)	233 (34.4%)	229 (34.5%)	32 (44%)

Participant Characteristics[a]	Overall	eGFR Category (mL/min/1.73 m²)[a]			
		≥90	60-<90	30-<60	<30
Dementia	76 (5.0%)	4 (3.5%)	24 (3.5%)	40 (6.0%)	8 (11 %)
UACR, mg/g	10.5 [6.4–22.6]	9.4 [7.0–16.0]	9.7 [6.0–1 7.9]	11.1 [6.5–26.1]	37.7 [10.4–170.2]
eGFR, mL/min/1.73 m²	60.8 [47.6–73.7]	95.8 [93.6–100.3]	71.0 [65.2–78.5]	48.3 [41.0–54.4]	25.5 [21.7–28.3]

Values for continuous variables given as mean ± SD or median [IQR], for categorical variables as count (percent). Abbreviations: APOE, apolipoprotein E; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; UACR, urinary albumin-creatinine ratio.

[a]Cystatin-C–based eGFR using the CKD Epidemiology Collaboration equation.

Table 2.

Associations of eGFR and log(UACR) With Brain Pathological Changes

		eGFR, per 1-IQR (26.10 mL/min/1.73 m^2) Lower[b]		Log(UACR), per 1-IQR-fold (1.26-fold) Greater[d]	
Brain MRI Sign	**Summary Statistic[a]**	**Effect Estimate[c]**	***P***	**Effect Estimate[c]**	***P***
Brain volume					
Total brain, cm^3	1,016.0 ± 108.7	−0.05 (−0.08 to −0.01)	0.02	−0.04 (−0.07 to −0.01)	0.005
Total cortex, cm^3	399.1 ± 43.0	−0.07 (−0.12 to −0.02)	0.002	−0.06 (−0.10 to −0.03)	<0.001
Temporal lobe meta-ROI, cm^3	68.1 ± 8.5	−0.05 (−0.11 to 0.01)	0.07	−0.06 (−0.10 to −0.02)	0.002
Cortex excluding temporal lobe meta-ROI, cm^3	331.1 ± 35.4	−0.07 (−0.12 to −0.03)	0.002	−0.06 (−0.10 to −0.03)	<0.001
Brain infarcts					
Any	398 (26.1%)	1.09 (0.90 to 1.32)	0.4	1.31 (1.13 to 1.52)	<0.001
Cortical	167 (10.9%)	0.94 (0.71 to 1.25)	0.7	1.27 (1.05 to 1.53)	0.02
Lacunar	281 (18.4%)	1.13 (0.92 to 1.39)	0.2	1.18 (1.00 to 1.39)	0.04
Brain microhemorrhages					
Any	371 (24.3%)	1.02 (0.84 to 1.26)	0.8	1.30 (1.12 to 1.51)	<0.001
Lobar	144 (9.4%)	1.16 (0.84 to 1.59)	0.4	1.21 (0.99 to 1.47)	0.06
Subcortical	307 (20.1%)	0.97 (0.78 to 1.20)	0.8	1.32 (1.13 to 1.54)	<0.001
White matter lesions					
Log(WMH) volume, cm^3	17.7 ± 17.2	0.07 (0.01 to 0.15)	0.04	0.09 (0.03 to 0.15)	0.003
Fractional anisotropy	0.31 ± 0.02	−0.08 (−0.17 to −0.01)	0.03	−0.09 (−0.16 to −0.02)	0.008
Mean diffusivity, 10^{-4} mm^2/s	8.78 ± 0.55	0.04 (−0.05 to 0.12)	0.4	0.11 (0.05 to 0.17)	<0.001

Models using inverse probability weighting to account for the selection of participants invited for MRI scans. Abbreviations: APOE, apolipoprotein E; eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; ROI, region of interest; UACR, urinary albumin-creatinine ratio; WMH, white matter hyperintensities.

[a]Mean ± SD for volume measurements and continuous diffusion tensor imaging (DTI) variables; count (%) for binary lesion variables. Mean diffusivity is a scalar measure of how quickly water molecules diffuse overall. Fractional anisotropy is a measurement for the directional constraint of water diffusion with a unitless range from 0 to 1.

[b]Estimated GFR calculated using the 2012 CKD Epidemiology Collaboration cystatin C equation. Models adjusted for age, sex, race, education, APOE ε4 status, smoking, body mass index, low-density lipoprotein cholesterol level, hypertension, diabetes, heart failure, stroke, and log(UACR). Continuous outcomes were standardized before regression to have a mean of 0 and SD of 1. For brain volume measurements and log(WMH), models were further adjusted for total intracranial volume.

[c]Standardized regression coefficient shown for brain volume measures and white matter lesions; odds ratios shown for brain infarcts and brain microhemorrhages. Values in parentheses are 95% CI.

[d] Models adjusted for age, sex, race, education, APOE *e4*, smoking, body mass index, low-density lipoprotein cholesterol level, hypertension, diabetes, heart failure, stroke, and eGFR. Continuous outcomes were standardized prior to regression to have a mean of 0 and SD of 1. For brain volume measurements and log(WMH), models were further adjusted for total intracranial volume.

Table 3.

Associations of eGFR Categories With Brain Pathological Changes

	Effect Estimate by eGFR Category (mL/min/1.73 m^2)[a]			
Brain MRI Sign	**≥90**	**60–<90**	**30–<60**	**<30**
Brain volume				
Total brain	−0.00 (−0.10 to 0.09)	0 (ref)	−0.03 (−0.09 to 0.02)	−0.15 (−0.28 to −0.02)[c]
Total cortex	0.05 (−0.07 to 0.17)	0 (ref)	−0.01 (−0.07 to 0.06)	−0.21 (−0.36 to −0.06)[c]
Temporal lobe meta-ROI, cm^3	0.10 (−0.05 to 0.25)	0 (ref)	0.02 (−0.06 to 0.10)	−0.16 (−0.35 to 0.02)
Cortex excluding temporal lobe meta-ROI, cm^3	0.04 (−0.08 to 0.1)	0 (ref)	−0.01 (−0.07 to 0.05)	−0.22 (−0.37 to −0.07)[c]
Brain infarcts				
Any	0.61 (0.35 to 1.07)	1 (ref)	0.86 (0.64 to 1.16)	1.10 (0.59 to 2.02)
Cortical	1.07 (0.54 to 2.16)	1 (ref)	0.69 (0.46 to 1.04)	0.74 (0.30 to 1.83)
Lacunar	0.51 (0.25 to 1.04)	1 (ref)	1.01 (0.73 to 1.40)	1.18 (0.63 to 2.24)
Brain microhemorrhages				
Any	0.88 (0.49 to 1.57)	1 (ref)	0.98 (0.73 to 1.32)	0.75 (0.39 to 1.44)
Lobar	1.25 (0.55 to 2.82)	1 (ref)	1.53 (0.98 to 2.38)	1.51 (0.65 to 3.52)
Subcortical	0.79 (0.41 to 1.52)	1 (ref)	0.89 (0.65 to 1.21)	0.51 (0.28 to 1.05)
White matter lesions				
Log(WMH) volume	−0.02 (−0.21 to 0.16)	0 (ref)	0.03 (−0.09 to 0.14)	0.24 (−0.24 to 0.72)
Fractional anisotropy	0.03 (−0.20 to 0.25)	0 (ref)	−0.09 (−0.21 to 0.03)	−0.30 (−0.59 to −0.01)[c]
Mean diffusivity, 10^{-4} mm^2/s	0.04 (−0.17 to 0.25)	0 (ref)	0.08 (−0.03 to 0.20)	0.15 (−0.15 to 0.45)

Models using inverse probability weighting to account for the selection of participants invited for MRI scans. Models adjusted for age, sex, race, education, apolipoprotein E ε4 status, smoking, body mass index, low-density lipoprotein cholesterol level, hypertension, diabetes, heart failure, stroke, and log(UACR). Continuous outcomes were standardized before regression to have a mean of 0 and SD of 1. For brain volume measurements and log(WMH), models were further adjusted for total intracranial volume. Abbreviations: eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; ROI, region of interest; UACR, urinary albumin-creatinine ratio; WMH, white matter hyperintensities.

[a]Standardized regression coefficient shown for brain volume measures and white matter lesions. Odds ratios shown for brain infarcts and brain microhemorrhages. Values in parentheses are 95% CI. Estimated GFR calculated using the 2012 CKD Epidemiology Collaboration cystatin C equation.

[c]$P < 0.05$.