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Albuminuria, Kidney Function, and the Incidence of Cognitive Impairment Among Adults in the United States

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Abstract

Background—Albuminuria and estimated glomerular filtration rate (eGFR) are each associated with increased risk for cognitive impairment, but their joint association is unknown.

Study Design—Prospective cohort study.

Setting and Participants—A US national sample of 19,399 adults without cognitive impairment at baseline participating in the REGARDS (Reasons for Geographic And Racial Disparities in Stroke) study.

Predictors—Albuminuria was assessed by the urine albumin-creatinine ratio (UACR) and GFR was estimated using the CKD-EPI (CKD Epidemiology Collaboration) equation.

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Outcomes—Incident cognitive impairment was defined as a score of 4 or less on the Six-item Screener at the last follow-up visit.

Results—Over a mean follow-up of 3.8 ± 1.5 years, UACR 30 – 299 and ≥ 300 mg/g were independently associated with 31% and 57% higher risk for cognitive impairment, respectively, relative to individuals with UACR <10 mg/g. This finding was strongest among those with high eGFR and attenuated at lower levels ($P=0.04$ for trend). Relative to an eGFR ≥ 60 ml/min/1.73m², eGFR <60 ml/min/1.73m² was not independently associated with cognitive impairment. However, after stratifying by UACR, eGFR <60 ml/min/1.73m² was associated with 30% higher risk for cognitive impairment among participants with UACR <10 mg/g but not higher UACR levels ($P=0.04$ for trend).

Limitations—single measure of albuminuria and eGFR, screening test of cognition

Conclusions—When eGFR was preserved, albuminuria independently associated with incident cognitive impairment. When albuminuria was <10 mg/g, low eGFR independently associated with cognitive impairment. Albuminuria and low eGFR are complementary but not additive risk factors for incident cognitive impairment.

Keywords

albuminuria; chronic kidney disease; cognitive impairment

Chronic kidney disease (CKD), usually marked by the presence of persistent albuminuria or an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m², is increasingly recognized as an elevated risk state for cognitive impairment and dementia ¹. As CKD is common, affecting an estimated 13% of adults in the United States ², and potentially modifiable, defining the relation between markers of CKD and risk for cognitive impairment is critical in this large at-risk population.

Both albuminuria and low eGFR are associated with elevated risk for cognitive impairment ^{3–7}. However, previous studies have produced limited and conflicting information about whether albuminuria and low eGFR are associated with cognitive impairment independent of the other, owing to investigations focused on one marker but not both, cross-sectional study designs, use of dichotomous measures for albuminuria and eGFR, and study populations with a small number of participants who have both risk factors. A better understanding of these relationships could aid in risk stratification of patients with CKD and may also provide unique insight into the causal pathways that link abnormalities of kidney structure and function with cognitive impairment. Importantly, recent investigations have highlighted independent associations between albuminuria, eGFR and macrovascular outcomes ^{8–11} that have prompted an international working group to consider revising the CKD classification system ¹². Determining whether similar relationships exist between albuminuria, eGFR and outcomes such as cognitive impairment that are strongly linked with microvascular disease ¹³, may help to inform these efforts.

We evaluated the association between albuminuria, eGFR, and the incidence of cognitive impairment in a large nationwide sample of United States (US) adults participating in the REGARDS (REasons for Geographic And Racial Disparities in Stroke) Study. We hypothesized that higher levels of albuminuria and lower levels of eGFR would be associated with higher risk for incident cognitive impairment independent of the other.

Methods

Study population

The REGARDS study is a national sample of 30,239 community-dwelling adults aged 45 years and older in the US population. Recruitment of the REGARDS cohort has been previously described¹⁴. Briefly, REGARDS participants were recruited from a commercially available nationwide list of over 250 million individuals and 120 million households (Genesys, Inc) so that approximately half of the cohort was targeted to be black, half male, and half from the stroke belt/buckle, an area of the southeastern US with stroke mortality rates 50% higher than the rest of the US. Exclusion criteria included race other than black or white, active treatment for cancer, medical conditions preventing long-term participation, severe cognitive impairment judged by the telephone interviewer, residence in or inclusion on a waiting list for a nursing home, or inability to communicate in English. For these analyses, we included all subjects enrolled between December 18, 2003 (the date cognitive function testing was incorporated into the REGARDS baseline interview) and the end of study enrollment, November 1, 2007 (25,084 subjects). Among these subjects, 697 individuals were missing cognitive data at baseline, 1621 were missing serum creatinine or urinary albumin-creatinine ratio (UACR) values, and 43 individuals had self-reported kidney failure or an estimated GFR <15 ml/min/1.73m². We further excluded 1943 individuals with cognitive impairment at baseline (defined below) and 1381 individuals without an assessment of cognitive function during follow-up, leaving 19,399 individuals in the analytic cohort.

Measurement of albuminuria and kidney function

During the baseline telephone interview demographic characteristics, health conditions and use of antihypertensive or diabetes medications, as well as verbal informed consent were obtained. During the subsequent in-home baseline examination anthropometric measurements, an electrocardiogram, phlebotomy, and written informed consent were obtained. Blood samples were shipped to a central laboratory for determination of serum creatinine and glucose. Serum creatinine measurements were calibrated to a method traceable to creatinine determined by isotope dilution mass spectrometry (IDMS) as previously described¹⁵, and these values were then employed to estimate GFR using the CKD-EPI (CKD Epidemiology Collaboration) equation¹⁶. Estimated GFR values were categorized as ≥ 90 ml/min/1.73m², 60 to <90 ml/min/1.73m², 45 to <60 ml/min/1.73m², and <45 ml/min/1.73m². UACR was measured on a random spot urine sample using the BN ProSpec Nephelometer (Dade Behring), and categorized as <10 mg/g, 10 to <30 mg/g, 30 to <300 mg/g and ≥ 300 mg/g.

Assessment of cognitive function

Starting on December 18, 2003 a six item cognitive screening examination was incorporated into the REGARDS baseline telephone interview and administered to all participants enrolled on or after that date, and then during annual follow-up telephone interviews. Designed for either in-person or telephone administration, the Six-item Screener (Item S1, available as online supplementary material)¹⁷ is a validated test of global cognitive function that includes recall and orientation items derived from the widely used Mini-Mental State Exam.¹⁸ Scores on the Six-item Screener range from 0–6. We defined incident cognitive impairment as a score of 4 or less during the last available REGARDS telephone interview. In a previous study, a score of 4 or less had a sensitivity of 74.2% to 84.0% and a specificity of 80.2% to 85.3% for a diagnosis of cognitive impairment based on extensive clinical evaluation in community and clinical samples.¹⁷

Covariates

Race was defined by participant self-report. Education was categorized as less than high school education, high school education, some college, and professional. Geographic region of residence was categorized as stroke belt, stroke buckle, or other region, as previously defined.¹⁴ Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, or the self-report of use of anti-hypertensive medications. Diabetes was defined as fasting glucose ≥ 126 mg/dL, non-fasting glucose ≥ 200 mg/dL, or self-reported current treatment for diabetes. Cerebrovascular disease was defined as self-report of stroke at baseline. Prevalent coronary heart disease was defined as ECG evidence of a prior myocardial infarction or self-report of a myocardial infarction, coronary artery bypass surgery, coronary angioplasty or coronary stenting. Alcohol and tobacco use were categorized as current versus past or never use.

Statistical Analysis

We used ANOVA and logistic regression as appropriate to assess differences in baseline characteristics across UACR categories. We used logistic regression models to evaluate the association, expressed as an odds ratio (OR) and 95% confidence interval (95% CI), between UACR and eGFR categories with incident cognitive impairment. We evaluated three different models: (1) an unadjusted model, (2) a model adjusted for all characteristics listed in the first table, and (3) a model adjusted for UACR and eGFR in addition to all characteristics listed in the first table. We constructed similar models using eGFR and log transformed UACR as continuous variables rather than categorical variables. Individuals with a urinary albumin excretion less than the detection limit for the assay used (2 mg/L) were assigned values of 1 mg/L. We also tested for interactions between UACR and eGFR, separately, with age (<65 versus ≥ 65 years, the median age at baseline in the REGARDS study), sex, and race. We determined the association between UACR and cognitive impairment within each eGFR stratum after dichotomizing UACR as <30 mg/g and ≥ 30 mg/g. Similar analyses were conducted to determine the association between eGFR <60 versus ≥ 60 ml/min/1.73m² and cognitive impairment in each UACR stratum. The trend in the association between UACR and incident cognitive impairment across eGFR categories and between eGFR and incident cognitive impairment across UACR categories was assessed by including multiplicative interaction terms. Subsequently, we determined the joint association between albuminuria and eGFR with incident cognitive impairment by comparing the odds for incident cognitive impairment in eight categories: UACR <30 and ≥ 30 mg/g and eGFR ≥ 90 , 60 to <90, 45 to <60, and <45 ml/min/1.73m². Participants with UACR <30 mg/g and eGFR ≥ 90 ml/min/1.73m² were used as the reference group.

In sensitivity analyses we used previously defined sex-specific UACR cut-points (UACR ≥ 25 mg/g in women or ≥ 17 mg/g in men) rather than the uniform cut-point of ≥ 30 mg/g¹⁹. We also substituted a more stringent definition of incident cognitive impairment, a Six-item Screener score of four or less at each of the participant's last two assessments (n=17,320 with two or more follow-up assessments), to determine if this materially changed the results. To assess whether exclusion of individuals missing follow-up data influenced the results, we conducted sensitivity analyses by classifying all individuals missing follow-up data as cases of cognitive impairment, and separately, as cognitively intact at follow-up. Lastly, as the exact date a participant developed cognitive impairment was not known (i.e., it was assessed annually), we also used interval censored regression models to calculate hazard ratios for developing cognitive impairment²⁰. All analyses were performed with SAS v9.1 (Cary, NC).

Results

Albuminuria ≥ 10 mg/g was present in 7037 (36.2%) study participants (Table 1). Individuals with albuminuria were older, more likely to be black and less likely to have a college education. They had a higher prevalence of most cardiovascular risk factors and a lower prevalence of current alcohol use. The mean eGFR was 86.3 ± 19.2 ml/min/1.73m². The distribution of albuminuria by eGFR categories is shown in Figure 1. Participants excluded from the analytic cohort due to missing follow-up cognitive assessments were older and more likely to have albuminuria and low eGFR (Table S1).

The average duration of follow-up was 3.8 ± 1.5 years over which time 1549 subjects (8.0%) developed cognitive impairment. Cognitive impairment developed in 6.6 %, 9.0 %, 12.2 % and 15.0 % of participants with UACR <10 mg/g, 10 to <30 mg/g, 30 to <300 mg/g, and ≥ 300 mg/g, respectively. After adjustment for age, sex, race, education, region, diabetes, hypertension, baseline cardiovascular disease, baseline stroke, smoking and alcohol use, UACR of 30 to 299 and ≥ 300 mg/g, compared to UACR <10 mg/g, was associated with ORs for incident cognitive impairment of 1.32 (95% CI, 1.12 – 1.55) and 1.60 (95% CI, 1.18 – 2.16) (Table 2). When log-transformed UACR was analyzed as a continuous variable, each two-fold increase in UACR was associated with 7% higher odds for developing cognitive impairment (OR, 1.07; 95% CI, 1.03–1.10) after multivariable adjustment. These associations were similar after additional adjustment for eGFR and baseline Six-item Screener score. There was no evidence for statistical interaction between UACR and age, sex, or race on the odds of incident cognitive impairment (P-values >0.1).

Cognitive impairment developed in 6.0 %, 8.9 %, 13.1 % and 14.8 % of participants with eGFR ≥ 90 , 60 to <90 , 45 to <60 and <45 ml/min/1.73m², respectively. After adjustment for age, sex, race, education, region, diabetes, hypertension, baseline cardiovascular disease, baseline stroke, smoking and alcohol use, there was no association between eGFR categories or eGFR as a continuous variable and incident cognitive impairment (Table 2). For example, compared to the referent group with eGFR ≥ 90 ml/min/1.73m², eGFR <45 was associated with 5% higher odds for incident cognitive impairment (OR, 1.05; 95% CI, 0.79 – 1.39). The ORs for incident cognitive impairment increased modestly in the eGFR range of 60 to <90 ml/min/1.73m² (ORs of 0.96 [95% CI, 0.83–1.11] for eGFR 75 to <90 and 1.10 [95% CI, 0.94–1.30] for eGFR 60 to <75 ml/min/1.73m²), but there was no evidence for a higher risk for impairment at very high eGFR values (i.e. >110 ml/min/1.73m²). Adjustment for albuminuria and additional adjustment for Six-item Screener score did not change these findings. There was no evidence for statistical interaction between eGFR and age, sex, or race on the odds of incident cognitive impairment (P-values >0.1).

In analyses stratified by eGFR, ACR ≥ 30 mg/g (versus <30 mg/g) was associated with higher odds ratios for incident cognitive impairment among individuals with an eGFR of 60 to <90 ml/min/1.73m² (OR, 1.37; 95% CI, 1.11 – 1.69) and ≥ 90 ml/min/1.73m² (OR, 1.44; 95% CI, 1.12 – 1.85) (Table 3). However the association was diminished with lower eGFR level (P=0.04 for trend across eGFR categories ≥ 90 , 60 to <90 , 45 to <60 , <45 ml/min/1.73m²). In analyses stratified by ACR, eGFR <60 ml/min/1.73m² (versus ≥ 60 ml/min/1.73m²) was associated with higher odds for incident cognitive impairment among individuals with ACR <10 mg/g (OR, 1.30; 95% CI, 1.02 – 1.66), but not at higher ACR levels (P=0.04 for trend across ACR categories <10 , 10 to <30 , 30 to <300 and ≥ 300 mg/g) (Table 4). When we categorized participants according to UACR and eGFR, individuals with UACR ≥ 30 mg/g and eGFR ≥ 60 ml/min/1.73m² and individuals with UACR <30 mg/g and eGFR <45 ml/min/1.73m² had the highest adjusted odds for incident cognitive impairment compared to the reference group with UACR <30 mg/g and eGFR ≥ 90 ml/min/1.73m² (Figure 2).

We conducted several sensitivity analyses. When we utilized sex-specific UACR cut-points, the multivariable adjusted OR for incident cognitive impairment associated with albuminuria was 1.29 (95% CI, 1.02–1.63), 1.46 (95% CI, 1.20–1.76), 1.07 (95% CI, 0.74–1.57), and 0.78 (95% CI, 0.46–1.32) for adults with eGFR ≥ 90 ml/min/1.73m², 60 to <90 ml/min/1.73m², 45 to <60 ml/min/1.73m² and <45 ml/min/1.73m², respectively. When we excluded individuals with stroke at baseline, the results were also similar (Table S2). When we utilized a more stringent definition of cognitive impairment requiring a Six-item Screener score ≤ 4 at each of the last two assessments, the magnitude of the association between albuminuria and incident cognitive impairment was strengthened, but was unchanged for eGFR. For example, among individuals with UACR 30 to <300 mg/g and ≥ 300 mg/g (versus < 10 mg/g), the odds ratio for cognitive impairment was 1.33 (95% CI, 0.97 – 1.82) and 2.24 (95% CI, 1.31–3.82), respectively, after multivariable adjustment. When we utilized a time to event model, the results were unchanged for UACR and strengthened for eGFR (Table S3). Because subjects excluded from the analytic cohort due to missing follow-up cognitive assessments were more likely to have UACR ≥ 300 mg/g and more likely to have eGFR <45 ml/min/1.73m², we also repeated the analyses after including individuals with missing follow-up cognitive assessments and classifying them as impaired, and separately, as cognitively intact. The association between albuminuria and incident cognitive impairment was similar (data not shown), while the association between eGFR <45 ml/min/1.73m² and incident cognitive impairment was strengthened when all individuals with missing follow-up assessments were classified as impaired (OR, 1.32; 95% CI, 1.05–1.65).

Discussion

In a large cohort of black and white adults, when eGFR was preserved, albuminuria independently associated with higher risk for developing cognitive impairment. When albuminuria was <10 mg/g, low eGFR independently associated with higher risk for developing cognitive impairment.

Our findings confirm the importance of albuminuria and eGFR as risk factors for cognitive impairment, and expand on previous studies to demonstrate their joint association and gradients in risk over a wide range of albuminuria and eGFR levels. In the Rancho Bernardo Study involving 1345 community-dwelling adults with a mean age of 75, ACR ≥ 30 mg/g, but not eGFR, was independently associated with cognitive decline among men, with no association between ACR, eGFR and cognitive decline among women⁴. In a cross-sectional study of 335 homebound elders with a mean age of 73, Weiner et al. noted albuminuria, assessed as a continuous variable, but not eGFR, was associated with lower cognitive function and a higher prevalence of brain small vessel ischemic disease⁵. In cross-sectional analyses from the CRIC (Chronic Renal Insufficiency Cohort) Study which included 3591 adults with a mean age of 58 and eGFR <70 ml/min/1.73m², lower eGFR, but not albuminuria, was associated with lower cognitive function²¹. Differences in the study populations or in the definition of cognitive impairment may explain the conflicting findings of previous studies. For example, the Six-item Screener used in this study evaluates memory and orientation but not executive function, a cognitive domain linked with cerebrovascular disease.

In the CKD classification paradigm, albuminuria is considered an early marker of kidney disease and low eGFR a late marker. In the current study, however, the risk for incident cognitive impairment was higher among adults with albuminuria and eGFR ≥ 60 ml/min/1.73m² (currently classified as CKD stage 1–2) as compared to individuals without albuminuria and eGFR 45–59 ml/min/1.73m² (currently classified as CKD stage 3), and comparable to or higher than the risk of incident cognitive impairment among those with

eGFR <45 ml/min/1.73m² (CKD stages 3–4). These findings are important for several reasons. First, most older adults with CKD die before progression to ESRD²². Thus, it is important for revised CKD classification methods to accurately reflect the risk for clinical outcomes beyond ESRD. Second, they highlight the heterogeneity of risk within the same CKD stage and in particular, the disproportionately high risk relative to assigned CKD stage among those with albuminuria and normal or near-normal eGFR. Third, it suggests that the pathways which link albuminuria and low eGFR with cognitive impairment are only partially overlapping. Albuminuria is a marker of microvascular dysfunction²³, whereas low eGFR may also be a marker of other novel risk factors, such as disorders of mineral metabolism, anemia, oxidative stress, altered drug disposition and others that contribute to cognitive impairment through vascular and non-vascular mechanisms. If the presence of albuminuria and low eGFR identify different pathways of risk, then this may imply a role for different therapeutic strategies to delay cognitive decline.

There may be several possible explanations for the observation that albuminuria is more strongly associated with incident cognitive impairment at higher compared to lower eGFR levels. Creatinine-based GFR estimating equations, including the CKD-EPI equation, overestimate GFR in individuals with low muscle mass, and may misclassify kidney function in malnourished individuals who are at high risk for cognitive impairment¹⁶. Alternatively, the phenotype of albuminuria with high eGFR may identify individuals with glomerular hyperfiltration. This pattern has been described in patients with and without diabetes^{24, 25}, and may be a marker of systemic microvascular hemodynamic abnormalities that contribute to accelerated loss of kidney and cognitive function. While it is possible that competing mortality risk may explain the attenuation in risk for cognitive impairment at low eGFR, we do not think this is the case because our results did not change substantively in sensitivity analyses that included individuals with missing follow-up data due to death or other causes.

Interestingly, the attenuation in risk associated with albuminuria at lower eGFR is not unique for the outcome of cognitive impairment. For example, in a large community-based study, Hemmelgarn et al. noted that the magnitude of the association between heavy albuminuria and risk for mortality, myocardial infarction or ESRD was reduced at low eGFR as compared to normal eGFR⁹. In a meta-analysis of community-based cohorts, Matsushita et al. reported a similar interaction between albuminuria and eGFR in several cohorts, although this interaction was not statistically significant after pooling data¹⁰. However, in contrast to our results, these studies found that albuminuria remained independently associated with a higher risk for mortality even among those with moderate or severe reductions in eGFR (<45 ml/min/1.73m²). A similar, independent association of albuminuria and eGFR with mortality has been noted in REGARDS²⁶. Thus it seems more likely that our findings reflect differences in microvascular versus macrovascular outcomes rather than differences in the REGARDS cohort versus other community-based cohort studies. Owing to a relatively small sample of adults with eGFR <45 ml/min/1.73m² after stratifying for albuminuria we cannot exclude the possibility that albuminuria may also be independently associated with cognitive impairment in this group.

Strengths of the REGARDS study include the large national sample of black and white adults with standardized measures of albuminuria and serum creatinine at baseline and prospective assessment of cognitive function using a validated measure. This study also has several limitations. First, albuminuria is known to have day-to-day variability²⁷. However, misclassification of some individuals would be expected to bias the results towards the null. Second, the Six-item Screener is a relatively insensitive measure of cognitive function and it does not assess executive function, a cognitive domain linked with vascular diseases. It may also misclassify some individuals due to its narrow scoring range. We attempted to reduce

this misclassification by using different definitions of cognitive impairment, with consistent results. Attrition as a result of death or loss to follow-up may have influenced the study results. We performed several sensitivity analyses after including individuals missing follow-up data, with similar findings, suggesting these results are robust to several assumptions we made in the analyses. Finally, although we adjusted for several potential confounders in these analyses, there may be residual confounding from unmeasured factors.

In summary, we found that albuminuria and low eGFR were complementary but not additive risk factors for the development of cognitive impairment. Our findings provide additional support for incorporating information about albuminuria into CKD classification methods, and suggest that the pathways mediating the association between albuminuria and low eGFR with cognitive impairment may be partially distinct.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Prevalence of albuminuria according to eGFR categories among included participants at baseline. There were N=9102 (47%), 8419 (43%), 1317 (7%) and 561 (3%) participants with eGFR ≥ 90 , 60–89, 45–59, and <45 ml/min/1.73m², respectively. Note: albuminuria is expressed as urine albumin-creatinine ratio (ACR, in mg/g). eGFR - estimated glomerular filtration rate.

Figure 2.

Adjusted odds ratios for cognitive impairment over 3.8 years, by estimated glomerular filtration rate (eGFR, in ml/min/1.73m²) and urine albumin-creatinine ratio (ACR, in mg/g). The referent category is eGFR ≥90 ml/min/1.73m² and ACR <30 mg/g. Odds ratios are adjusted for age, sex, race, education, region, diabetes, hypertension, cardiovascular disease, stroke, smoking and alcohol use. Bars represent 95% confidence intervals.

N=297, 976, 7385, and 8141, respectively for categories ACR <30 mg/g and eGFR <45, 45–59, 60–89, and ≥90 ml/min/1.73m². N=264, 342, 1033, and 961, respectively, for categories ACR ≥30 mg/g and eGFR <45, 45–59, 60–89, and ≥90 ml/min/1.73m².

Table 1

Baseline characteristics, by albuminuria status.

Baseline characteristics	Urine albumin-creatinine ratio				P-value for trend
	<10 mg/g	10 to <30 mg/g	30 to <300 mg/g	≥300 mg/g	
No. (row percentage)	12,362 (63.7%)	4,437 (22.9%)	2,181 (11.2%)	419 (2.2%)	
Age (years)	62.9 +/- 9.1	66.0 +/- 9.5	66.5 +/- 9.9	65.8 +/- 9.4	<0.001
Male sex	40.9	35.2	44.0	49.6	0.2
Black race	36.0	36.4	47.0	64.0	<0.001
Region					
Non-belt/Buckle	43.4	42.6	45.1	45.1	Ref
Stroke Belt	35.0	35.4	34.8	33.7	0.5
Stroke Buckle	21.7	22.0	20.2	21.2	0.3
Education					
< High school	8.5	11.8	15.1	14.1	Ref
High school	24.5	26.7	27.1	30.8	<0.001
Some College	27.3	27.9	27.1	30.6	<0.001
College/Professional	39.7	33.6	30.7	24.6	<0.001
Coronary Heart Disease	13.3	18.9	23.0	34.2	<0.001
Stroke	3.5	5.9	8.1	12.4	<0.001
Diabetes	13.5	23.7	36.8	60.7	<0.001
Hypertension	51.0	64.4	74.4	87.8	<0.001
Current smoking	13.0	14.2	16.5	21.6	<0.001
Current alcohol use	55.7	51.4	46.6	41.8	<0.001
eGFR (ml/min/1.73m ²)	87.8 +/-17.3	85.9 +/- 19.3	81.6 +/- 23.4	66.8 +/- 28.2	<0.001

Baseline characteristics	Urine albumin-creatinine ratio				P-value for trend
	<10 mg/g	10 to <30 mg/g	30 to <300 mg/g	≥300 mg/g	
eGFR category					
≥90 ml/min/1.73m ²	49.2	46.4	39.4	24.3	Ref
60–89 ml/min/1.73m ²	44.2	43.3	41.1	32.7	<0.001
45–59 ml/min/1.73m ²	5.2	7.5	12.0	19.1	<0.001
<45 ml/min/1.73m ²	1.4	2.8	7.5	23.9	<0.001
Six-item screener score					
5 points	20.0	22.6	25.5	29.6	<0.001
6 points	80.0	77.4	74.5	70.4	

Note: Data cover included study participants only. Continuous data presented as mean +/- standard deviation; categorical data as percentage.

Abbreviations: eGFR, estimated glomerular filtration rate; Ref, reference

Table 2

Association of UACR and eGFR with incident cognitive impairment

	Model 1	Model 2	Model 3
UACR			
<10 mg/g	1.00 (reference)	1.00 (reference)	1.00 (reference)
10-<30 mg/g	1.40 (1.23 – 1.58)	1.14 (0.99 – 1.30)	1.14 (0.99 – 1.30)
30 to <300 mg/g	1.97 (1.70 – 2.28)	1.32 (1.12 – 1.55)	1.31 (1.12 – 1.55)
≥ 300 mg/g	2.49 (1.89 – 3.29)	1.60 (1.18 – 2.16)	1.57 (1.15 – 2.14)
Per UACR doubling	1.16 (1.13 – 1.19)	1.07 (1.03 – 1.10)	1.07 (1.03 – 1.10)
eGFR			
≥ 90 ml/min/1.73m ²	1.00 (reference)	1.00 (reference)	1.00 (reference)
60 to <90 ml/min/1.73m ²	1.55 (1.38 – 1.74)	1.01 (0.89 – 1.15)	1.01 (0.88 – 1.15)
45 to <60 ml/min/1.73m ²	2.38 (1.98 – 2.85)	1.13 (0.92 – 1.39)	1.09 (0.88 – 1.34)
<45 ml/min/1.73m ²	2.74 (2.13 – 3.51)	1.15 (0.87 – 1.52)	1.05 (0.79 – 1.39)
eGFR (/20 ml/min/1.73m ² decrease)	1.37 (1.30 – 1.44)	1.04 (0.97 – 1.11)	1.02 (0.95 – 1.09)

Note: Values shown are odds ratios (95% confidence interval). mean follow-up duration is 3.8 years.

Model 1: Crude

Model 2. Adjusted for age, race, sex, education, region, diabetes, hypertension, cardiovascular disease, stroke, smoking and alcohol use.

Model 3. Model 2 + UACR (<10, 10 to <30, 30 to <300, ≥300 mg/g) or eGFR (<45, 45 to <60, 60 to <89, ≥90 ml/min/1.73m²)

Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio

Table 3

Association of albuminuria with incident cognitive impairment, by eGFR stratum

	Unadjusted	Multivariable-adjusted*
EGFR category		
≥ 90 ml/min/1.73m ²	1.83 (1.45 – 2.32)	1.44 (1.12 – 1.85)
60 to <90 ml/min/1.73m ²	1.88 (1.55 – 2.28)	1.37 (1.11 – 1.69)
45 to <60 ml/min/1.73m ²	1.28 (0.90 – 1.82)	1.10 (0.74 – 1.62)
<45 ml/min/1.73m ²	0.90 (0.56 – 1.44)	0.80 (0.48 – 1.36)
P-value for trend	0.006	0.04

Except where indicated, values shown are odds ratio (95% confidence interval). Albuminuria defined as UACR ≥30 mg/g. The referent category is UACR <30 mg/g. P-value for trend represents the interaction between eGFR as a continuous variable and UACR ≥ 30 mg/g.

* Adjusted for age, race, sex, education, region, diabetes, hypertension, cardiovascular disease, stroke, smoking and alcohol use.

Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio

Table 4

Association of eGFR <60 ml/min/1.73m² with incident cognitive impairment, by UACR stratum

	Unadjusted	Multivariable-adjusted *
UACR category		
<10 mg/g	2.13 (1.71 – 2.66)	1.30 (1.02 – 1.66)
10 to <30 mg/g	1.80 (1.36 – 2.40)	1.02 (0.74 – 1.40)
30 to <300 mg/g	1.30 (0.96 – 1.76)	0.87 (0.62 – 1.22)
≥300 mg/g	1.00 (0.58 – 1.71)	0.76 (0.41 – 1.40)
P-value for trend	<0.001	0.04

Note: Except where indicated, values shown are odds ratio (95% confidence interval). The referent category is eGFR ≥60 ml/min/1.73m². P-value for trend represents the interaction between ACR as a log-transformed continuous variable and eGFR <60 ml/min/1.73m².

* Adjusted for age, race, sex, education, region, diabetes, hypertension, cardiovascular disease, stroke, smoking and alcohol use.

Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urine albumin-creatinine ratio