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CKD Biomarkers, Cognitive Impairment, and Incident Dementia in an Older Healthy Cohort

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Key Points

- Mild albuminuria was associated with worse baseline cognitive function, cognitive decline, and increased risk for incident dementia.
- Screening cognitive tests for older persons with a urine albumin-creatinine ratio ≥3 mg/mmol could identify those at elevated risk of cognitive decline and dementia.

Abstract

Background CKD is a risk factor for cognitive impairment (CI), but reports of individual associations of eGFR and albuminuria with CI and incident dementia in healthier, older, longitudinal populations are lacking. Our goal was to estimate these associations in a large cohort of older healthy persons.

Methods In a longitudinal cohort study of older persons without prior cardiovascular disease, we estimated the associations between baseline eGFR (in ml/min per 1.73 m^2) and albuminuria, measured as urine albumin-creatinine ratio (UACR; in mg/mmol) and cognitive test scores, declines in cognitive test scores, and incident dementia using adjusted linear and linear mixed models. Cox proportional hazards regression models assessed the association between baseline kidney function and incident CI no dementia (CIND) or dementia at a median of 4.7 years.

Results At baseline, among 18,131 participants, median age was 74 years, eGFR was 74 (IQR, 63–84) ml/min per 1.73 m^2, UACR was 0.8 (IQR, 0.5–1.5) mg/mmol (7.1 [4.4–13.3] mg/g), and 56% were female. Baseline eGFR was not associated with performance on any cognitive tests in cross-sectional analysis, nor was incident CIND or dementia over a median follow-up of 4.7 years. However, baseline UACR ≥3 mg/mmol (≥26.6 mg/g) was significantly associated with lower baseline scores and larger declines on the Modified Mini-Mental State Exam, verbal memory and processing speed tests, and with incident CIND (hazard ratio [HR], 1.19; 95% CI, 1.07 to 1.33) and dementia (HR, 1.32; 95% CI, 1.06 to 1.66).

Conclusion Mild albuminuria was associated with worse baseline cognitive function, cognitive decline, and increased risk for incident CIND and dementia. Screening global cognitive tests for older persons with UACR ≥3 mg/mmol could identify those at elevated risk of cognitive decline and dementia.

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Introduction

CKD is a recognized risk factor for cognitive impairment (CI) (1–4), but reports of associations of both eGFR and albuminuria with CI and incident dementia in healthier, older populations without a history of cardiovascular disease (CVD) are limited. Decreased eGFR represents a decline in kidney function due to vascular and nonvascular etiologies and aging. Albuminuria is considered a measure of kidney damage, or glomerular angiopathy secondary to microvascular endothelial inflammation, and frequently precedes a decline in eGFR (5). Several studies have described the association between albuminuria and white matter hyperintensities in the brain—a measure of cerebral microvascular disease that is also associated with CI (6).

Vascular risk factors and associated pathology play large roles in the development of CKD and associated

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cerebrovascular disease in older populations in the United States, because over half of CKD cases are secondary to diabetes, hypertension, or both (7). However, in a population free of known CVD at baseline, the usual role of shared CVD risk factors for CKD and cerebrovascular disease in the development of CI in CKD may be weaker than in the general population. Thus, it is possible that previous estimates of the effects of CKD on cognitive function conducted in populations with high rates of CVD may not be generalizable to healthier populations.

It is important to determine to what extent eGFR and albuminuria can be used to identify those most at risk of CI in the large, and growing, portion of the older population without substantial underlying CVD, and, in turn, reduce related complications, such as medication and kidney disease management nonadherence and downstream hospitalizations. To do so, we conducted a longitudinal cohort analysis in the study population of the ASPirin in Reducing Events in the Elderly (ASPREE) trial, which was designed to enroll healthy, community-dwelling participants, free of cardiovascular events. Our goals were to estimate (*1*) the cross-sectional association between kidney function, measured by both eGFR and albuminuria (using the urine albumin-creatinine ratio [UACR]), and cognitive function at the baseline ASPREE assessment; and (*2*) the longitudinal association between baseline kidney function and change in cognitive function, incident CI no dementia (CIND), and incident dementia. We hypothesized that, in older individuals without a history of CVD or severe CKD, albuminuria would more likely be more associated than eGFR with CI, cognitive decline, and incident dementia.

Materials and Methods

Study Design and Population

We conducted a longitudinal cohort study using the ASPREE trial population in Australia and the United States. The ASPREE trial was a randomized, placebo-controlled trial of low-dose aspirin in healthy older individuals with mean 4.7 years of follow-up. We previously reported that aspirin did not reduce risk of incident dementia, mild CI, or cognitive decline (8). Full details regarding the rationale and study design for the ASPREE trial, including detailed inclusion and exclusion criteria, have been reported previously (Supplemental Appendix 1) (9).

Eligibility criteria included being free from CVD, physical disability (defined as independent in the Katz Activities of Daily Living scale), and dementia, and being expected to survive at least 5 years. Individuals with hypertension or diabetes were eligible, provided these conditions were well controlled. Individuals with a self-report or physician diagnosis of dementia at recruitment, or with a Modified Mini-Mental State Examination (3MS) (10) score of <78, were ineligible; however, it was possible that some individuals had mild levels of CI at baseline.

ASPREE participants were followed annually with in-person visits and with intermittent 6-month telephonic visits to assess change in medical conditions or study enrollment status.

ASPREE was approved by multiple institutional review boards in the United States and Australia, registered with the International Standard Randomized Controlled Trial Number Register (ISRCTN83772183) and ClinicalTrials.gov (NCT01038583), and undertaken in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Study Variables

Primary Exposures: eGFR and UACR

The primary study exposures were the kidney biomarkers eGFR and UACR. CKD was defined using Kidney Disease Improving Global Outcomes criteria of eGFR <60 ml/min per 1.73 m^2 (2,11). We calculated eGFR on the basis of serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation (12). Albuminuria was defined as a UACR ≥3 mg/mmol (≥26.6 mg/g), on the basis of a single measurement at the baseline study visit.

Cognitive Assessments and Outcome Measures

Cognitive assessments were administered by trained and accredited staff at baseline and year 1, and then biennially over the follow-up period (year 3 and year 5, or at their close-out [last] visit during the trial phase, which could be visit 3 through 7). The cognitive battery included the 3MS, a 100-point measure of global cognition (9); the Delayed Recall component for episodic memory of the Hopkins Verbal Learning Test–Revised (HVLT-R) (13), a word list of 12 items; the Controlled Oral Word Association Test (COWAT) (14) for language (scored as the total number of words beginning with F generated in 1 minute); and the Symbol Digit Modalities Test (SDMT) (15), a measure of psychomotor speed (maximum score of 110). For all cognitive tests, a higher score indicates better performance.

Incident Dementia Outcome

Individuals with a suspected dementia diagnosis (a "trigger") were referred for a dementia assessment that included further standardized cognitive tests and functional assessments. Dementia triggers were defined as a 3MS score <78 (16), a drop of more than ten points from the predicted score (17), a medical record report of memory concerns or other cognitive problems, a clinician diagnosis of dementia, or prescription of cholinesterase inhibitors in the participant's medical records.

Dementia Assessment

The dementia assessment included the Confusion Assessment Method (18), Alzheimer Disease Assessment Scale–Cognitive Subscale (19), Color Trails Test (20), Lurian overlapping figures test (21), and the Alzheimer Disease Cooperative Study Activities of Daily Living scale (22), along with the results of blood tests, brain computed tomography scanning or magnetic resonance imaging, and clinical notes from medical records (see Supplemental Appendix 2 for additional dementia assessment cognitive test results details).

The available information was reviewed by the dementia adjudication committee (consisting of a panel of neurologists, neuropsychologists, and geriatricians from Australia and the United States) who were blinded to treatment allocation. Dementia was adjudicated according to Diagnostic and Statistical Manual, Fourth Edition criteria (23). The

date of diagnosis of dementia was taken as the date the dementia trigger occurred that resulted in a confirmed dementia diagnosis by the adjudication committee.

CIND

For participants without a dementia trigger, we defined those with significant cognitive decline as CIND if they had a >1.5-SD decline in cognitive score from their own baseline value on the HVLT-R Delayed Recall, SDMT, or COWAT. This definition did not include participants with evidence of only a transient decline (*e.g.*, those with a >1.5-SD drop at one follow-up, but scoring above this threshold at a subsequent follow-up). Cognitive change was examined using the continuous scores on each of the cognitive tests over the follow-up period.

Statistical Analyses

Descriptive statistics are presented as medians (interquartile range; IQR) for continuous variables, and frequency (percentage) for categoric variables. We used linear regression models to assess the association between kidney function measures and cognitive performance at baseline. In each model, one of baseline (binary) albuminuria, UACR doubling, or a 10-U eGFR lowering were included as independent variables (specifically, eGFR measurements scaled by a factor of −10, and UACR transformed by logarithm to the base two were included as a continuous variable); these measures were chosen to reflect clinically relevant declines in kidney function. Cognitive test scores were the dependent variables. We used multivariable mixed effects models to examine the association between baseline kidney function and the rate of cognitive change over time. Each model allowed for individual variation in cognitive performances at baseline and subsequent rate of change (*i.e.*, random intercept and random slope model). We included an interaction term between visit time (years since randomization) and baseline kidney function to examine whether the rate of cognitive change depended on kidney function values at baseline.

Cox proportional hazards regression models were implemented to evaluate the effect of baseline kidney function on time to incident CIND and dementia. Cause-specific hazards were calculated, with all-cause deaths treated as competing events. Additionally, conditional covariate-adjusted survival curves (24) were presented to visualize the effect of baseline UACR levels on incidence of CIND and dementia (but not for eGFR, because initial Cox regression models demonstrated no significant association between baseline eGFR and incident CIND or dementia).

Lastly, to determine to what extent eGFR or UACR, individually or in combination, are associated with cognitive outcomes, additional analyses were performed to measure the effect of the interactions between an eGFR <60/≥60 ml/min per 1.73 m^2 and a UACR of >3/≤3 mg/mmol, and, alternatively, an eGFR of <45/≥45 ml/min per 1.73 m^2 and a UACR of >3/≤3 mg/mmol, on risks of baseline CI, cognitive decline, incident CIND, and dementia in both the cross-sectional and longitudinal models and the Cox regression models described above.

All models were adjusted for baseline characteristics: age, sex, education (<12 years or ≥12 years), treatment allocation to aspirin (versus placebo), diabetes, hypertension, and race (White/Australia, White/United States, Black, Hispanic, and other).

Participants with missing information in cognitive outcome measures, kidney function (UACR or eGFR), or any of the adjusted variables were excluded from the analyses. All analyses were performed using R version 4.0. Adjusted survival curves were computed using the survminer R package. Of note, study enrollment bias in this report was minimized due to the randomized trial recruitment design of the ASPREE study.

Results

Baseline characteristics, overall and by different eGFR levels, are shown in Table 1 for the cohort (Supplemental Figure 1). Among 19,114 ASPREE participants, 18,560 (98%) and 18,131 (95%) had baseline measurement of eGFR and UACR, respectively. Median age was 74 years, 56% were female, 74% had hypertension, and 11% had diabetes. Median (IQR) eGFR was 74 (63–84) ml/min per 1.73 m^2; 19% had an eGFR of <60 ml/min per 1.73 m^2, and 16% an eGFR of 45–60 ml/min per 1.73 m^2. Median (IQR) UACR was 0.8 (0.5–1.5) mg/mmol (7.1 [IQR, 4.4–13.3] mg/g), and UACR distribution was highly skewed: most (89%) had a UACR of <3 mg/mmol (≤26.6 mg/g), 9% had a UACR of 3 to <10 mg/mmol (88.5 mg/g), and only 3% had a UACR of ≥10 mg/mmol (88.5 mg/g) (not shown). Participants with an eGFR of <60 ml/min per 1.73 m^2 (compared with those with an eGFR of ≥60 ml/min per 1.73 m^2) tended to be older and more likely to have diabetes and hypertension.

Median follow-up time in the entire ASPREE cohort was 4.7 years; 77% (n=14,729) of the cohort completed their third annual visit for cognitive tests (*i.e.*, at least 3 years of follow-up). By the end of the trial, 237 participants in this report withdrew, 1052 were deceased, and 296 were lost to follow-up. Further details regarding number of participants with annual visits with cognitive testing each year are described in Supplemental Table 1.

Cross-Sectional Association between Kidney Function and Cognitive Function

In adjusted analyses, baseline eGFR was not associated with scores on any of the four cognitive tests (Table 2). However, UACR ≥3 mg/mmol (≥26.6 mg/g) was significantly associated with baseline scores for three of the four tests (3MS, HVLT-R, and SDMT) in adjusted models. The association with the SDMT of β=−1.24 (95% CI, −1.66 to −0.81; P<0.001) appears clinically significant, because it was more than double the size of the mean change in SDMT in all participants: −0.50 points over 4.7 years of follow-up (with baseline mean [SD] SDMT of 36.7 [10.1]; Supplemental Table 2). The association between a UACR of ≥3 mg/mmol (≥26.6 mg/g) and scores on the 3MS, at β=−0.33 (95% CI, −53 to −0.13; P=0.001), and HVLT-R, at β=−0.24 (95% CI, −0.36 to −0.11; P<0.001), were statistically significant, but the absolute score changes were minor. Similar results were seen per doubling of the UACR value.

Table 1. Baseline characteristics

Characteristic	Total Cohort (*N*=19,114)	CKD (eGFR <45 ml/min per 1.73 m^2) (*N*=606)	Mild CKD (eGFR 45 to <60 ml/min per 1.73 m^2) (*N*=2821)	All CKD (eGFR <60 ml/min per 1.73 m^2) (*N*=3427)	eGFR ≥60 ml/min per 1.73 m^2 (*N*=15,223)
Age, yr, median (IQR)	74 (71.6–77.7)	77 (73.9–82.4)	76 (72.5–80.4)	76 (72.7–80.8)	73 (71.5–77)
Age group, yr, *n* (%)					
65–74	9569 (50)	157 (26)	1049 (37)	1206 (35)	8134 (53)
75–84	8555 (45)	341 (56)	1489 (53)	1830 (53)	6513 (43)
≥85	990 (5)	108 (18)	283 (10)	391 (11)	576 (4)
Sex, *n* (%)					
Male	8332 (44)	233 (38)	1139 (40)	1372 (40)	6742 (44)
Female	10,782 (56)	373 (62)	1682 (60)	2055 (60)	8481 (56)
eGFR, ml/min per 1.73 m^2, median (IQR)	74 (63–84)	40 (36–43)	55 (51–58)	53 (48–57)	78 (69–86)
UACR, mg/mmol, median (IQR)	0.80 (0.50–1.50)	1.1 (0.6–3.3)	0.9 (0.5–1.8)	0.90 (0.50–2.00)	0.80 (0.50–1.40)
UACR <3 mg/mmol, *n* (%)	16,046 (89)	421 (73)	2274 (85)	2695 (83)	13,024 (90)
UACR ≥3 mg/mmol, *n* (%)	2085 (11)	156 (27)	404 (15)	560 (17)	1485 (10)
Education, yr, *n* (%)					
<12	8,636 (45%)	312 (51%)	1,365 (48%)	1,677 (49%)	6,710 (44%)
≥12	10,477 (55%)	294 (49%)	1,456 (52%)	1,750 (51%)	8,512 (56%)
Race, *n* (%)					
White/Australia	16,361 (86)	511 (84)	2393 (85)	2904 (85)	13,011 (86)
White/United States	1088 (6)	41 (7)	207 (7)	248 (7)	839 (5)
Black	901 (5)	35 (6)	138 (5)	173 (5)	725 (5)
Hispanic	488 (2)	7 (1)	53 (2)	60 (2)	421 (3)
Other	264 (1)	11 (2)	29 (1)	40 (1)	218 (1)
Country, *n* (%)					
Australia	16,703 (87)	523 (86)	2432 (86)	2955 (86)	13,289 (87)
United States	2411 (13)	83 (14)	389 (14)	472 (14)	1934 (13)
Diabetes, *n* (%)[a]	2045 (11)	104 (17)	390 (14)	494 (14)	1507 (10)
Systolic BP, mm Hg, median (IQR)	139 (127–151)	141 (128–153)	139 (128–152)	140 (128–152)	138 (127–150)
Diastolic BP, mm Hg, median (IQR)	77 (70–84)	75 (67–84)	77 (70–84)	77 (69–84)	77 (71–84)
Hypertension, *n* (%)[b]	14,195 (74)	551 (91)	2329 (83)	2880 (84)	10,976 (72)
Total cholesterol, mmol/L, median (IQR)	5.20 (4.60–5.90)	5.00 (4.40–5.70)	5.10 (4.50–5.90)	5.10 (4.50–5.80)	5.20 (4.60–5.90)
Current smoker, *n* (%)	735 (4)	19 (3)	94 (3)	113 (3)	610 (4)

IQR, interquartile range; UACR, urine albumin-creatinine ratio.
[a]Defined by self-report, blood glucose ≥126 mg/dl, or treatment for diabetes.
[b]Defined as the mean of three systolic BP readings >140 mm Hg, or three diastolic BP readings of >90 mm Hg, or by pharmacologic treatment for high BP.

Association between Baseline Kidney Measures and Longitudinal Change in Performance on Cognitive Testing

A mean of 3.2 annual cognitive assessments per participant was performed over a median follow-up of 4.7 years. In fully adjusted linear mixed effects, eGFR at baseline was statistically significantly associated with decline of both the 3MS and SDMT scores, but the magnitudes of the associations were clinically negligible (Table 3).

Baseline albuminuria (UACR ≥3 mg/mmol; ≥26.6 mg/g) was significantly associated with cognitive decline on all cognitive tests except the COWAT, and most strongly

Table 2. Association between kidney function and cognitive function at baseline

Outcomes	Unadjusted Analysis			Adjusted Analysis		
	N	Estimate, 95% Confidence Interval	*P* Value	*N*	Estimate, 95% Confidence Interval	*P* Value
eGFR (per 10-U decrease)[a,b]						
3MS	18,650	−0.16 (−0.21 to −0.11)	<0.001	18,638	−0.01 (−0.06 to 0.03)	0.55
COWAT	18,620	−0.07 (−0.12 to −0.03)	0.002	18,608	−0.03 (−0.08 to 0.01)	0.18
SDMT	18,571	−0.50 (−0.60 to −0.39)	<0.001	18,559	0.09 (−0.01 to 0.19)	0.09
HVLT4	18,550	−0.12 (−0.15 to −0.10)	<0.001	18,539	−0.01 (−0.04 to 0.02)	0.35
UACR (≥3 versus <3 mg/mmol)[c]						
3MS	18,131	−0.85 (−1.06 to −0.64)	<0.001	18,120	−0.33 (−0.53 to −0.13)	0.001
COWAT	18,102	−0.34 (−0.55 to −0.13)	0.001	18,091	−0.06 (−0.26 to 0.14)	0.56
SDMT	18,053	−2.62 (−3.09 to −2.16)	<0.001	18,042	−1.24 (−1.66 to −0.81)	<0.001
HVLT4	18,033	−0.53 (−0.65 to −0.40)	<0.001	18,023	−0.24 (−0.36 to −0.11)	<0.001
UACR (per two-fold increase)[d]						
3MS	18,131	−0.32 (−0.39 to −0.24)	<0.001	18,120	−0.15 (−0.23 to −0.08)	<0.001
COWAT	18,102	−0.14 (−0.22 to −0.07)	<0.001	18,091	−0.07 (−0.15 to 0.00)	0.05
SDMT	18,053	−1.09 (−1.25 to −0.92)	<0.001	18,042	−0.61 (−0.76 to −0.45)	<0.001
HVLT4	18,033	−0.18 (−0.23 to −0.13)	<0.001	18,023	−0.10 (−0.14 to −0.05)	<0.001

Models were adjusted for age, sex, education (<12 and ≥12 years), treatment, diabetes, hypertension, and race (White/Australia, White/United States, Black, Hispanic, and other). 3MS, Modified Mini-Mental State Examination; COWAT, Controlled Oral Word Association Test; SDMT, Symbol Digit Modalities Test; HVLT4, Hopkins Verbal Learning Test 4; UACR, urine albumin-creatinine ratio.

[a]eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

[b]The estimate coefficients represent an increase in the performance of each cognitive test per 10-U decrease in eGFR value.

[c]The estimate coefficients represent an increase in the performance of each cognitive test when the UACR level changed from <3 to ≥3 mg/mmol.

[d]The estimate coefficients represent an increase in the performance of each cognitive test per two-fold increase in UACR value.

associated with SDMT performance, with $\beta = -0.76$ (95% CI, −1.18 to −0.33; $P<0.001$). Similar results were seen for UACR doubling.

Longitudinal Association between Baseline Kidney Measures and Incident CIND and Dementia

Over the median 4.7 years of follow-up, 2777 cases of CIND and 563 cases of adjudicated incident dementia occurred with either baseline eGFR or UACR measures. The overall rate of incident dementia was approximately 6.8/1000 patient-years (Figure 1). We found no statistically significant association between baseline eGFR and time to CIND or dementia (Table 4). In contrast, both the binary (UACR ≥3/<3 mg/mmol [≥26.6/<26.6 mg/g]) and continuous (UACR doubling) measures of UACR were associated with an increased risk for both incident CIND and ncident dementia. Specifically, baseline albuminuria corresponded to a 19% increased risk of CIND (hazard ratio, 1.19; 95% CI, 1.07 to 1.33), and 32% increased risk of incident dementia (hazard ratio, 1.32; 95% CI, 1.06 to 1.66). These associations are further illustrated in Figure 1. Of note, the three waves of incident CIND correspond to the annual visits that, per study design, most often included the cognitive assessments (baseline, and annual visits 1, 3, and 5).

No Interactions between eGFR and UACR on Baseline Cognitive Performance, Cognitive Decline, Incident CIND, and Incident Dementia

In adjusted linear regression models that included an interaction term for an eGFR of <60/≥60 or <45/≥45 ml/min per 1.73 m^2 and UACR ≥3/<3 mg/mmol (≥26.6/<26.6 mg/g), there were no statistically significant interactions in the models for baseline cognitive function (Supplemental Table 3), cognitive decline (with a three-way interaction term for time; Supplemental Table 4), or in Cox proportional hazards regression models for incident CIND or dementia (Supplemental Table 5).

Discussion

In a population of initially healthy, community-dwelling older adults without known CVD and only 3% prevalence of eGFR <45 ml/min per 1.73 m^2, low levels of albuminuria (UACR of ≥3 mg/mmol; ≥26.6 mg/g) at study entry were associated with lower baseline cognitive function and more rapid cognitive decline over a mean of nearly 5 years. This association was seen in three of the four cognitive tests assessed: the 3MS (a global assessment), HVLT-R (verbal memory), and, especially, the SDMT (processing speed, attention, and visual scanning). More importantly, baseline albuminuria was also associated with increased rates of both incident CIND and dementia. Thus, in a relatively healthy elderly population with a median eGFR of 74 ml/min per 1.73 m^2, mild albuminuria portended a substantially increased risk of cognitive decline in cognitive domains important for day-to-day function and dementia over a period of 5 years.

Although the association of baseline albuminuria on decline in SDMT scores was relatively modest, at 1.24 lower points over 5 years, it was still approximately 2.5 times greater than the mean SDMT decline in the entire cohort. UACR ≥3 mg/mmol (≥26.6 mg/g) was also associated with a 19% increased risk of CIND, and a 32% increased risk of dementia. The lack of association

Table 3. Association between baseline kidney function and change in cognitive function

Terms	Modified Mini-Mental State Examination		Controlled Oral Word Association Test		Symbol Digit Modalities Test		Hopkins Verbal Learning Test 4	
	Estimate, 95% Confidence Interval	*P* Value	Estimate, 95% Confidence Interval	*P* Value	Estimate, 95% Confidence Interval	*P* Value	Estimate, 95% Confidence Interval	*P* Value
eGFR (per 10-U decrease)[a]								
eGFR	0.01 (−0.04 to 0.05)	0.75	−0.02 (−0.06 to 0.03)	0.52	0.13 (0.03 to 0.22)	0.008	−0.00 (−0.03 to 0.03)	0.85
Time (+5yr)	−1.26 (−1.79 to −0.74)	<0.001	0.96 (0.56 to 1.37)	<0.001	−3.41 (−4.11 to −2.71)	<0.001	−0.18 (−0.43 to 0.07)	0.16
eGFR×time	−0.11 (−0.18 to −0.04)	0.002	−0.03 (−0.08 to 0.03)	0.29	−0.11 (−0.20 to −0.01)	0.03	−0.03 (−0.07 to 0.00)	0.07
UACR (≥3 versus <3)[b]								
UACR	−0.31 (−0.50 to −0.13)	0.001	−0.09 (−0.29 to 0.10)	0.34	−1.09 (−1.49 to −0.68)	<0.001	−0.27 (−0.39 to −0.15)	<0.001
Time (+ 5yr)	−0.39 (−0.50 to −0.29)	<0.001	1.19 (1.11 to 1.27)	<0.001	−2.55 (−2.69 to −2.41)	<0.001	0.06 (0.01 to 0.11)	0.01
UACR×time	−0.67 (−0.99 to −0.35)	<0.001	−0.13 (−0.38 to 0.11)	0.28	−0.76 (−1.18 to −0.33)	<0.001	−0.25 (−0.40 to −0.09)	0.001
UACR (+two-fold)[b]								
UACR	−0.15 (−0.22 to −0.08)	<0.001	−0.07 (−0.14 to 0.00)	0.04	−0.57 (−0.72 to −0.42)	<0.001	−0.11 (−0.15 to −0.06)	<0.001
Time (+ 5yr)	−0.16 (−0.32 to 0.00)	0.05	1.22 (1.10 to 1.34)	<0.001	−2.40 (−2.61 to −2.19)	<0.001	0.15 (0.07 to 0.23)	<0.001
UACR×time	−0.28 (−0.39 to −0.16)	<0.001	−0.04 (−0.13 to 0.05)	0.35	−0.22 (−0.37 to −0.06)	0.005	−0.10 (−0.16 to −0.05)	<0.001

All models were adjusted for age, sex, education (<12 and ≥12 years), diabetes, treatment, hypertension, and race (White/Australia, White/United States, Black, Hispanic, and other). 3MS, Modified Mini-Mental State Examination; COWAT, Controlled Oral Word Association Test; SDMT, Symbol Digit Modalities Test; HVLT4, Hopkins Verbal Learning Test 4; Est, estimate; UACR, urine albumin-creatinine ratio.

[a]Number of included participants in the model for 3MS, COWAT, SDMT, and HTVLT are 18,638, 18,631, 18,606, and 18,606, respectively.

[b]Number of included participants in the model for 3MS, COWAT, SDMT, and HTVLT are 18,120, 18,114, 18,088, and 18,091, respectively.

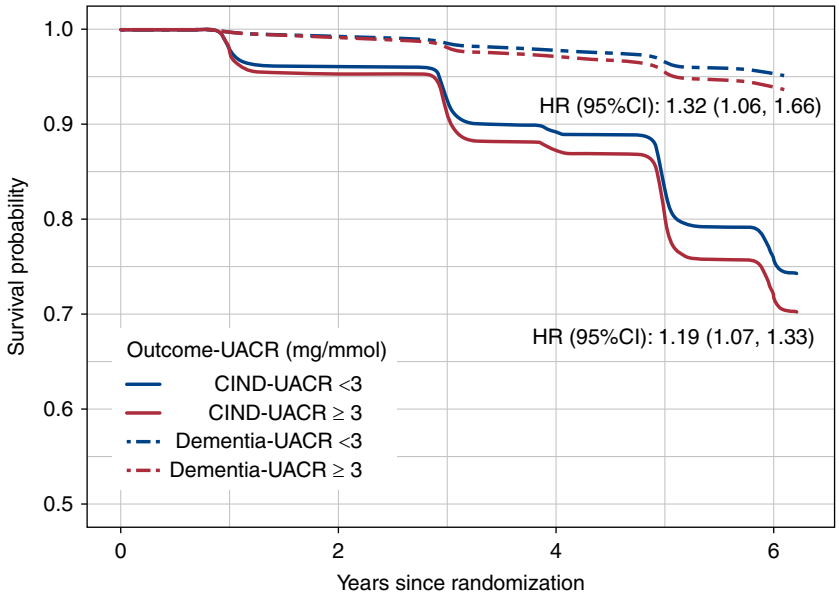

Figure 1. | Covariate-adjusted survival curves for cognitive impairment no dementia (CIND) and dementia, stratified by urine albumin-creatinine ratio (UACR) levels. Models adjusted for age, sex, education (<12 and ≥12 years), diabetes, treatment group, hypertension, and race (White/Australia, White/United States, Black, Hispanic, and other). HR, hazard ratio.

between UACR and COWAT, or verbal fluency, may be reflective of the low prevalence of poor performance on the COWAT at baseline, and on average mild decline in COWAT.

In contrast, eGFR was not associated with baseline cognitive performance on any tests. In addition, its association with longitudinal cognitive decline, seen only with the 3MS and SDMT scores, appeared modest in comparison to albuminuria, and it was not associated with incident CIND or dementia.

Finally, we found no significant interactions between lower eGFR and albuminuria on baseline cognitive function, incident CIND, or dementia. Thus, the association of albuminuria with the negative cognitive outcomes did not vary by eGFR level in this cohort with a low prevalence of eGFR <45 ml/min per 1.73 m^2.

In a systematic review of the relation of UACR with CI, in populations with less advanced CKD (eGFR >45 ml/min per 1.73 m^2), UACR was more frequently associated with CI than eGFR; however, in those with more severe CKD (eGFR <45 ml/min per 1.73 m^2), eGFR was more often a significant risk factor (25–27). For example, in the Rancho Bernardo Study of older relatively healthy men, albuminuria but not eGFR was a predictor of cognitive function measured approximately 7 years later (26).

In the BRINK (BRain IN Kidney Disease) study of 574 participants with a mean eGFR of 46 ml/min per 1.73 m^2, an eGFR of <30 ml/min per 1.73 m^2 was associated with over three-fold increased odds of severe CI in those with a UACR of <2.7 ≥3 mg/mmol (≥26.6 mg/g),mg/mmol (<30 mg/g), but not for a UACR of >2.7 mg/mmol (>30 mg/g) (4). Because 97% of the ASPREE participants had an eGFR of >45 ml/min per 1.73 m^2, our finding that UACR was a stronger risk factor than eGFR for CI and incident dementia adds to, and strengthens support for, these prior observations.

Table 4. Association between baseline kidney function and incident cognitive impairment no dementia and dementia

Characteristic	*n*	Hazard Ratio, 95% Confidence Interval	*P* Value
eGFR (per 10-U decrease)			
CIND	2777	0.98 (0.95 to 1.01)	0.15
Dementia	563	0.95 (0.89 to 1.01)	0.08
UACR (≥3 versus <3)			
CIND	2721	1.19 (1.07 to 1.33)	0.001
Dementia	557	1.32 (1.06 to 1.66)	0.02
UACR (+two-fold)			
CIND	2721	1.07 (1.03 to 1.11)	0.001
Dementia	557	1.13 (1.05 to 1.23)	0.002

All models were adjusted for age, sex, education (<12 and ≥12 years), diabetes, treatment group, hypertension, and race (White/Australia, White/United States, Black, Hispanic, and other). CIND, cognitive impairment no dementia; HR, hazard ratio; UACR, urine albumin-creatinine ratio.

Although elevated UACR in the absence of low eGFR has been identified previously as being independently associated with CI and cognitive decline, our study is novel in that our study population was free of known CVD at baseline, whereas the majority of studies have been in populations with a higher prevalence of CVD or diabetes and moderate-to-severe CKD (28,29). Thus, our results are generalizable to the growing population of older people without known CVD, and in whom there may be lower suspicion for CI due to the known increased risk for CI in those with CVD.

The pathophysiology of the associations between the kidney biomarkers eGFR and UACR and cognitive function is complex and challenging to disentangle from the underlying vascular risk factors and high inflammatory load in CKD (27,30), which, together, drive parallel trajectories of microvascular endothelial dysfunction in both the kidney and the brain, leading to high rates of vasculopathic outcomes (31,32). Albuminuria is often considered a measure of kidney damage, or glomerular angiopathy due to microvascular endothelial inflammation, which frequently precedes a decline in eGFR. Albuminuria in our study was strongly associated with lower performance on the SDMT, a measure of processing speed, both cross-sectionally and longitudinally. Lower SDMT scores are observed in patients with frontal and subcortical microvascular disease, presenting as microinfarcts or white matter hyperintensities on brain magnetic resonance imaging (30), and in vascular CI (33). Decreased eGFR is often considered a more general measure of micro- and macrovascular disease, but may also more specifically reflect the effect of kidney toxins, or uremia, on neuronal function. Both kidney biomarker paradigms result in increased risk of structural and microvascular brain pathology and secondary CI.

The strengths of our study include the large, community-based, well-characterized study cohort across two countries, including approximately 9% non-White individuals, and the absence of CVD at baseline. Our cohort study benefited from the initial rigorous clinical trial design, which included annual creatinine and UACR, regularly scheduled cognitive assessments, follow-up–triggered dementia assessments, and dementia adjudication.

Study limitations include the overall minor decline in cognitive function over the follow-up period, which may have decreased ability to detect associations between kidney function and cognitive decline, and the use of a one-time measure of UACR at study baseline. Fewer participants had cognitive assessments as the study progressed, due, in part, to some being recruited later in the study, thus decreasing their number of annual assessments before trial end, and to participants being less willing to participate in cognitive testing as they become self-aware of cognitive decline, which is frequently observed in longitudinal studies of CI. However, 77% of the cohort had reached at least 3 years of follow-up. Our results are likely not generalizable to older populations with higher CVD risk profiles and higher prevalence of advanced CKD. We are also aware that obtaining a urine specimen in older patients in the clinic setting can be difficult for some, but, at the same time, have observed that urine samples have more frequently become a part of the annual physical examination for older patients, perhaps due to the increasing awareness of the growing prevalence of CKD in older patients.

The critical translatable implication of our results is that a low level of albuminuria, now easily measured in the clinic setting, could be used to identify those at elevated risk for prevalent CI, cognitive decline, CIND, and dementia in persons ≥70 years without concomitant advanced CKD (eGFR <30 ml/min per 1.73 m^2). Importantly, baseline albuminuria identified those at increased risk of incident CIND early in the natural history of dementia, enabling interventions to decrease negative outcomes associated with cognitive decline promptly, when albuminuria is first noted.

We recommend consideration of two influential, translatable interventions in the clinic setting for those aged ≥70 years with a UACR of ≥3 mg/mmol (≥26.6 mg/g, or approximately 30 mg/g) and without an eGFR of <45 ml/min per 1.73 m^2: (*1*) screen annually for CI, and, if present, (*2*) identify a caregiver or companion to attend clinic visits with the affected patient, and to provide medication and disease management supervision in the home, or obtain home health services to ensure this. Two options for cognitive screening tests are the 8- to 10-minute Montreal Cognitive Assessment (MoCA) (34), with high sensitivity to mild and greater levels of CI (although it requires an annual brief training and certification), or the Mini-Cog assessment, a 3-minute test that detects moderate to severe CI (35). Of note, at the time of the study's design >10 years ago, ASPREE used the 3MS for global cognitive screening because the MoCA was not commonly used in large trials and the 3MS enabled easy comparisons of results between prior and concurrent studies. However, the MoCA is now frequently used as the primary global screening instrument or overall measure of cognitive function in many studies (36,37). We also chose not to use the Mini-Cog assessment because it has lower sensitivity to mild CI.

We are aware that our CI screening recommendation may be perceived to be in conflict with the recent US Preventive Services Task Force (USPSTF) recommendations against screening in asymptomatic older individuals (https://uspreventiveservicestaskforce.org/uspstf/recommendation/cognitive-impairment-in-older-adults-screening) (38), which were targeted at asymptomatic older adults regardless of their risk factors for CI. However, as discussed, we and others have demonstrated that individuals with albuminuria are at substantially increased risk of prevalent and incident CI and dementia. Second, asymptomatic does not equate to absence of CI, only absence of reported symptoms of CI. Many older individuals with memory or cognitive concerns hesitate to bring them to medical attention until brought in by family members—often after they have already reached a stage of mild-to-moderate dementia, or after a "sentinel event," such as a hospitalization with delirium (a harbinger and litmus test for dementia). In addition, the USPSTF findings were made on the basis of literature reviews that were largely inconclusive because there were inadequate numbers of robust well-designed studies to measure the outcomes of cognitive screening, but that does not mean screening is nonbeneficial,

rather it means that the studies needed to prove their benefit have not been done. In fact, one of their recommendations was to call for such studies. Early identification of CI would alert clinicians, families, and care partners to the need for increased vigilance to ensure adherence with medications and kidney disease management plans and decrease downstream risk for related hospitalizations and mortality (39,40).

In this large, healthy population of community-dwelling older people with a median eGFR of 74 ml/min per 1.73 m^2, the presence of mild albuminuria was associated with modestly lower baseline performance, greater decline on tests of global cognitive function and processing speed, and substantially increased risk of incident CIND and dementia. Our findings suggest that screening global cognitive tests could be considered for those ≥70 years with a UACR of ≥3 mg/mmol and without an eGFR of <45 ml/min per 1.73 m^2 to identify those at highest risk of cognitive decline and dementia.

Disclosures

A.M. Murray reports being a consultant to Alkahest, Inc. J.B. Wetmore reports receiving research funding from Amgen, AstraZeneca, BMS/Pfizer, Genentech, Merck, and OPKO Health; serving on advisory boards for Aurinia Pharmaceuticals, OPKO Health, and Reata Pharmaceuticals; having consultancy agreements *via ad hoc* consulting for Bristol Myers Squibb (BMS)–Pfizer Alliance; receiving honoraria from, and serving as a scientific advisor or member of, BMS-Pfizer Alliance (with occasional participation on *ad hoc* advisory boards); and receiving honoraria for academic continuing medical education from Healio and the Nephrology Self-Assessment Program. All remaining authors have nothing to disclose.

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Author Contributions

A.M. Murray was responsible for investigation; A.M. Murray, K.R. Polkinghorne, L.T.P. Thao, J.B. Wetmore, R. Wolfe, and R.L. Woods wrote the original draft; A.M. Murray, L.T.P. Thao, R. Wolfe, and R.L. Woods were responsible for formal analysis and methodology; A.M. Murray, L.T.P. Thao, and R.L. Woods were responsible for validation; A.M. Murray and R.L. Woods conceptualized the study, were responsible for project administration, and provided supervision; L. T.P. Thao was responsible for data curation, software, and visualization; and all authors reviewed and edited the manuscript.

Data Sharing Statement

All individual participant data (reidentifiable) that underlie the results reported in this article are available upon request to qualified researchers without limit of time, subject to approval and a standard data sharing agreement. Details regarding requests to access the data are available through the study website (ASPREE.org). The data will then be made available through a web-based data portal safe haven at Monash University (Melbourne, Australia). The ASPREE trial protocol and statistical analysis plan have been published (9,41).

Supplemental Material

This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0005672021/-/DCSupplemental.

Supplemental Appendix 1. ASPREE study design and population.

Supplemental Appendix 2. Incident dementia outcome and dementia assessment.

Supplemental Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram of participants in the Aspirin in Reducing Events in the Elderly (ASPREE) trial.

Supplemental Table 1. Sample sizes for those who had cognitive assessments at each annual visit (AV).

Supplemental Table 2. Summary of cognitive tests at baseline and annual visits (AV).

Supplemental Table 3. Association between renal function and cognitive function at baseline: parameter estimates for the interaction terms between eGFR and UACR.

Supplemental Table 4. Association between baseline renal function and change in cognitive function: parameter estimates for the interaction terms between eGFR and UACR and time.

Supplemental Table 5. Association between baseline renal functions and CIND and dementia: Parameter estimates for the interaction terms between eGFR and UACR.

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