Estimated GFR, Albuminuria, and Cognitive Performance

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Original Investigation

Estimated GFR, Albuminuria, and Cognitive Performance: The Maastricht Study

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Background: Reduced estimated glomerular filtration rate (eGFR) and albuminuria have been associated with worse cognitive performance. However, few studies have examined whether these associations are confined to older individuals or may be extended to the middle-aged population.

Study Design: Cross-sectional analyses of a prospective population-based cohort study.

Setting & Participants: 2,987 individuals aged 40 to 75 years from the general population (The Maastricht Study).

Predictor: eGFR and urinary albumin excretion (UAE).

Outcomes: Memory function, information processing speed, and executive function.

Measurements: Analyses were adjusted for demographic variables (age, sex, and educational level), lifestyle factors (smoking behavior and alcohol consumption), depression, and cardiovascular disease risk factors (glucose metabolism status, waist circumference, total to high-density lipoprotein cholesterol ratio, triglyceride level, use of lipid-modifying medication, systolic blood pressure, use of antihypertensive medication, and prevalent cardiovascular disease).

Results: UAE was <15 mg/24 h in 2,439 (81.7%) participants, 15 to <30 mg/24 h in 309 (10.3%), and ≥30 mg/24 h in 239 (8.0%). In the entire study population, UAE ≥ 30 mg/24 h was associated with lower information processing speed as compared to UAE < 15 mg/24 h (β [SD difference] = −0.148; 95% CI, −0.263 to −0.033) after full adjustment, whereas continuous albuminuria was not. However, significant interaction terms (*P* for interaction < 0.05) suggested that albuminuria was most strongly and extensively associated with cognitive performance in older individuals. Mean (±SD) eGFR, estimated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine–cystatin C equation ($eGFR_{cr\text{-}cys}$), was 88.4 ± 14.6 mL/min/1.73 m^2. $eGFR_{cr\text{-}cys}$ was not associated with any of the domains of cognitive performance after full adjustment. However, significant interaction terms (*P* for interaction < 0.05) suggested that $eGFR_{cr\text{-}cys}$ was associated with cognitive performance in older individuals.

Limitations: Cross-sectional design, which limited causal inferences.

Conclusions: In the entire study population, albuminuria was independently associated with lower information processing speed, whereas $eGFR_{cr\text{-}cys}$ was not associated with cognitive performance. However, both were more strongly and extensively associated with cognitive performance in older individuals.

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INDEX WORDS: Estimated glomerular filtration rate (eGFR); albuminuria; cognitive performance; kidney function; kidney disease; urinary albumin excretion (UAE); cognitive function; cognition; memory function; information processing speed; executive function; neuropsychological test battery; middle age.

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In older individuals, both reduced estimated glomerular filtration rate (eGFR) and albuminuria have been associated with lower cognitive performance,[1-17] although not consistently so.[4,14,16,18,19]

Conceptually, reduced GFR may lead to the accumulation of neurotoxins or may represent lifetime exposure to cardiovascular disease (CVD) risk factors or CVD itself,[20] whereas albuminuria may be a biomarker of generalized endothelial dysfunction.[21,22] Thereby, reduced GFR may play a direct role in the pathobiology of cognitive decline,[20] but may also, similar to albuminuria, act as a biomarker of any underlying mechanisms involved in cognitive decline.[20,22]

However, few studies[19,23-26] have examined whether the associations of eGFR[19,23-25] and albuminuria[19,26] with cognitive performance are confined to older individuals or may be extended to the middle-aged (ie, 40- to 65-year-old) population. This is important because it can be hypothesized that in middle-aged individuals, brain reserve capacity (ie, "the amount of damage that can be sustained before reaching a threshold for clinical expression"[27p449]) is higher, as a result of which changes in cognitive performance are subtle.[27,28] In addition, some studies may have been affected by residual confounding due to incomplete adjustment for CVD risk factors.

We therefore first examined the associations of eGFR and albuminuria with several domains of cognitive performance (ie, memory function, information processing speed, and executive function) in 40- to 75-year-old individuals who participated in the population-based Maastricht Study. Second, we explored whether any such associations differed by age.

METHODS

The Maastricht Study Population and Design

In this study, we used data from The Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously.[29] In brief, the study focuses on the etiology, pathophysiology, complications, and comorbid conditions of type 2 diabetes (T2DM) and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged 40 to 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry by mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM, for reasons of efficiency. The present report includes cross-sectional data from the first 3,451 participants, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of 3 months. The study has been approved by the institutional medical ethics committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (permit 131088-105234-PG) and was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent.

Kidney Function

GFR was estimated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) serum creatinine and serum cystatin C equation ($eGFR_{cr\text{-}cys}$)[30] for the primary analyses. For additional analyses, GFR was estimated by the CKD-EPI serum creatinine equation ($eGFR_{cr}$),[30] the CKD-EPI serum cystatin C equation ($eGFR_{cys}$),[30] and the isotope-dilution mass spectrometry (IDMS)-traceable 4-variable MDRD (Modification of Diet in Renal Disease) Study equation.[31] Serum creatinine was measured with a Jaffé method traceable to IDMS (due to a change of supplier, 2 instruments were used in the study, the Beckman Synchron LX20, Beckman Coulter Inc, and the Roche Cobas 6000, F. Hoffmann-La Roche Ltd). Serum cystatin C was measured with a particle-enhanced immunoturbidimetric assay standardized against ERM-DA471/IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) reference material (Roche Cobas 8000, F. Hoffman-La Roche Ltd). To assess urinary albumin excretion (UAE), participants were requested to collect two 24-hour urine samples. Urinary albumin concentration was measured with a standard immunoturbidimetric assay by an automatic analyzer (due to a change of supplier, by the Beckman Synchron LX20 and the Roche Cobas 6000) and multiplied by collection volume to obtain 24-hour UAE. A urinary albumin concentration below the detection limit of the assay (2 mg/L for the Beckman Synchron LX20 and 3 mg/L for the Roche Cobas 6000) was set at 1.5 mg/L before multiplying by collection volume. Only urine collections with a collection time between 20 and 28 hours were considered valid. If needed, UAE was extrapolated to 24-hour excretion. For this study, UAE was preferably based on the average of 2 (available in 91.3% of participants) 24-hour urine collections.

Cognitive Performance

Cognitive performance was assessed by a concise (30-minute) neuropsychological test battery.[29] For conceptual clarity, test scores were standardized and divided into 3 cognitive domains (ie, memory function, information processing speed, and executive function). A detailed description of neuropsychological tests and methods used to calculate domain scores is provided in Item S1 (provided as online supplementary material). Briefly, memory function was evaluated using the Verbal Learning Test[32] by calculating the standardized average of total immediate and delayed recall scores. The composite score for information processing speed was derived from the Stroop Color-Word Test Part I and II,[33] the Concept Shifting Test Part A and B,[34] and the Letter-Digit Substitution Test.[35] Executive function was assessed by the Stroop Color-Word Test Part III and the Concept Shifting Test Part C. If necessary, individual test scores were log-transformed to fulfill the normality assumption and/or inverted so that higher scores indicated better cognitive performance. In addition, an overall cognitive performance score was calculated as the standardized average of the 3 domain scores and used as a summary score.

Potential Confounders

We assessed fasting glucose, hemoglobin A_{1c}, cholesterol (total, high-density lipoprotein, and low-density lipoprotein), triglycerides, glucose metabolism status, body mass index, waist circumference, hip circumference, office blood pressure, 24-hour average ambulatory blood pressure, medication use, smoking behavior, alcohol consumption, educational level, (subjective) physical activity, current major depressive episode, and prevalent CVD as described previously.[29,36] Further details and definitions of potential confounders are provided in Item S1.

Statistical Analyses

All analyses were performed with IBM SPSS Statistics, version 22.0 (IBM Corp). Population characteristics were presented stratified by $eGFR_{cr\text{-}cys}$ and albuminuria categories.

Associations of $eGFR_{cr\text{-}cys}$ and albuminuria with the composite scores of cognitive performance were evaluated with multivariable linear regression analyses. $eGFR_{cr\text{-}cys}$ was analyzed as a categorical (≥90, 60-<90, and <60 mL/min/1.73 m^2) and a continuous (per 10–mL/min/1.73 m^2 lower $eGFR_{cr\text{-}cys}$) variable. Similarly, UAE was analyzed as a categorical (<15, 15-<30, and ≥30 mg/24 h) and, after log base 2 transformation, a continuous (per doubling of UAE) variable. The regression coefficients (βs) represent the standard deviation (SD) difference in the cognitive domain scores as compared to $eGFR_{cr\text{-}cys}$ ≥ 90 mL/min/1.73 m^2, per 10–mL/min/1.73 m^2 lower $eGFR_{cr\text{-}cys}$, as compared to UAE < 15 mg/24 h, and per doubling of UAE, respectively. For example, β of 0.01 is 1% of 1 SD.

We adjusted for potential confounders as follows (more details on variable handling are provided in Item S1): model 1, unadjusted model; model 2, age, sex, educational level, and glucose metabolism status; model 3, model 2 plus waist circumference, total to high-density lipoprotein cholesterol ratio, triglyceride level, use of lipid-modifying medication, smoking behavior, and alcohol consumption; model 4, model 3 plus UAE (categorical) or $eGFR_{cr\text{-}cys}$ (continuous); model 5a, model 4 plus office systolic blood pressure, use of antihypertensive medication, prevalent CVD, and depression; and model 5b, as model 5a but with replacement of office systolic blood pressure by 24-hour average ambulatory systolic blood pressure. Blood pressure, prevalent CVD, and depression may be confounders, but may also mediate an association between kidney function and cognitive performance (eg, hypertension and stroke, which are risk factors for cognitive decline,[20] may result from kidney disease[37-39]) or be descending proxies of such intermediates (eg, depression and cognitive performance may have cerebral small-vessel disease as a common cause[40]). Therefore, these variables were added in a separate model because a model including these variables is at risk of overadjustment bias.[41]

We used interaction terms added to model 1 to examine whether the associations of $eGFR_{cr\text{-}cys}$ and albuminuria with cognitive performance were modified by age (P for interaction < 0.1 was considered statistically significant).

Adjusted mean values of the composite score of information processing speed per albuminuria category were estimated with general linear models with adjustment for age, sex, educational level, and glucose metabolism status (model 2).

Several additional analyses were performed to assess the robustness of results. First, $eGFR_{cr\text{-}cys}$ was replaced with eGFR based on the MDRD Study equation, $eGFR_{cr}$, or $eGFR_{cys}$, because recent studies indicated that cystatin C–based estimates are more strongly associated with cognitive performance.[10,11] Second, we adjusted for a quadratic association between age and cognitive performance.[32-34] Third, we restricted analyses to participants with UAE ≤ 300 mg/24 h and participants with two 24-hour urine collections and excluded participants with a Mini-Mental State Examination score < 24, suggesting frank cognitive impairment.[42] Fourth, analyses were repeated with replacement of the following: office systolic blood pressure by office diastolic blood pressure, office mean arterial pressure, office pulse pressure, their 24-hour average ambulatory equivalents, and the presence of hypertension; use of antihypertensive medication by the use of specifically renin-angiotensin system inhibitors; and waist circumference by waist-to-hip ratio or body mass index. Fifth, we additionally adjusted for total or moderate to vigorous physical activity. Sixth, we used interaction terms added to model 1 to examine whether associations were modified by glucose metabolism status given the design of The Maastricht Study. Seventh, we performed multiple imputation with fully conditional specification (maximal 10 iterations, 20 data sets) under the missing at random assumption.[43,44] Continuous $eGFR_{cr\text{-}cys}$ and UAE, as well as the dependent and potential confounding variables of models 5a and 5b, were included in the imputation model. Overall cognitive performance was calculated as the standardized average of the 3 imputed cognitive domain scores.

Variance inflation factors were <2.5 for all nonmultiplicative variables.

RESULTS

Characteristics of the Study Population

Figure 1 is a flow diagram delineating the derivation of the final study population. In total, 2,987 participants had complete data for all variables in model 5a and were included in the analyses. None of the participants was on dialysis treatment. Participants with missing data (n = 420) more often had T2DM, hypertension, prevalent CVD, and a lower educational level. In addition, they had lower eGFRs estimated by cystatin C–based equations, higher UAEs, and lower scores on all domains of cognitive performance.

Table 1 shows the study population characteristics overall stratified by albuminuria categories. Table S1 shows study population characteristics stratified by $eGFR_{cr\text{-}cys}$ categories. By design, 791 (26.5%) participants had T2DM. The study population, which had a mean (±SD) age of 59.6 ± 8.2 years, was well educated (41.2% higher vocational education or university level of education). In general, participants with higher albuminuria and participants with lower $eGFR_{cr\text{-}cys}$ were older, were more often men, were less educated, more often had T2DM and CVD, and had a worse CVD risk profile.

Albuminuria and Cognitive Performance

UAE was <15 mg/24 h in 2,439 (81.7%) participants, 15 to <30 mg/24 h in 309 (10.3%), and ≥30 mg/24 h in 239 (8.0%). Participants with higher UAE had lower performance on each of the cognitive domains (Table 1).

After adjustment for age, sex, glucose metabolism status, and educational level (Table 2, model 2) and with UAE < 15 mg/24 h as the reference category, UAE ≥ 30 mg/24 h was associated with lower overall cognitive performance (β [SD difference] = −0.149; 95% confidence interval [CI], −0.256 to −0.043), lower information processing speed (β = −0.172; 95% CI, −0.286 to −0.058; Fig 2), and borderline statistically significantly lower memory function (β = −0.110; 95% CI, −0.229 to 0.008). These associations were attenuated after further adjustment for the variables of models 3 to 5, but remained statistically significant for overall cognitive performance (β = −0.110; 95% CI, −0.217 to −0.002; model 5a) and information processing speed (β = −0.148; 95% CI, − 0.263 to −0.033; model 5a).

Continuous albuminuria was not statistically significantly associated with cognitive performance after full adjustment (Table 3, model 5a).

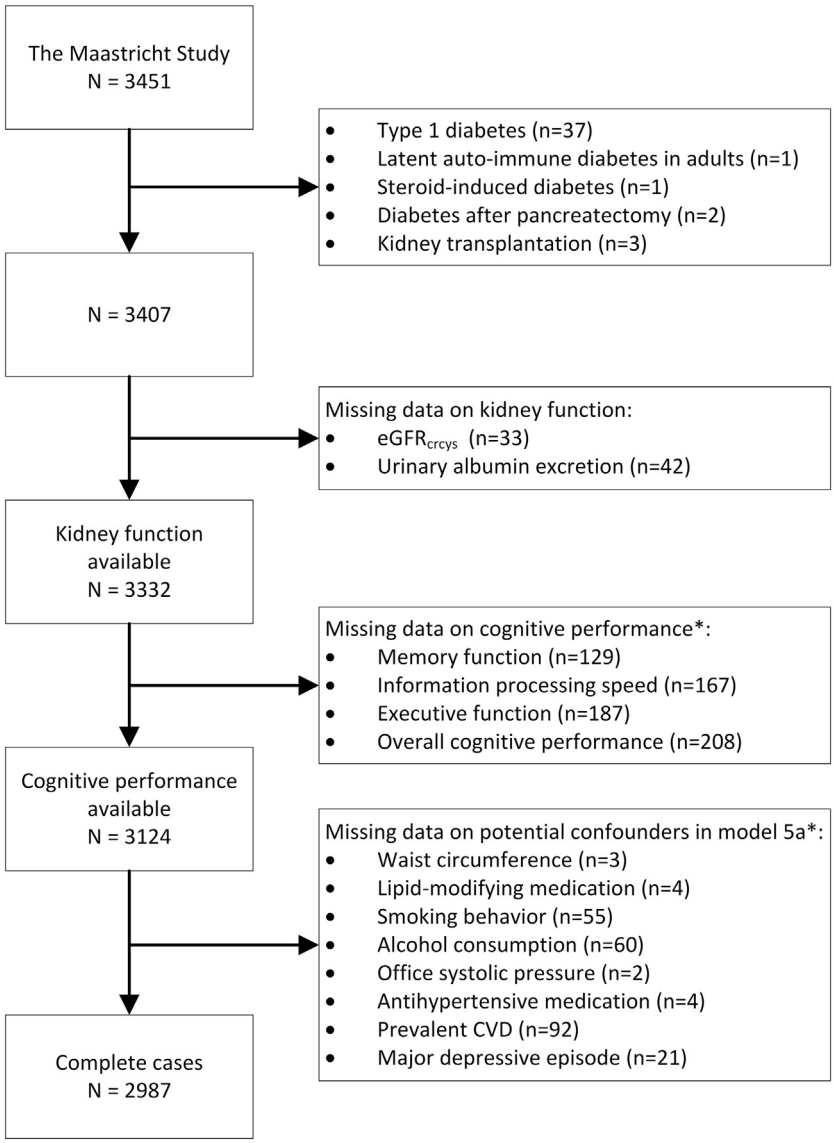

Figure 1. Flow diagram delineates the derivation of the final study population. *Categories of missing items were not mutually exclusive. Abbreviations: $eGFR_{cr\text{-}cys}$, estimated glomerular filtration rate based on creatinine and cystatin C levels; CVD, cardiovascular disease.

Results were similar when we adjusted for 24-hour average ambulatory systolic blood pressure instead of office systolic blood pressure (Tables 2 and 3, model 5b).

Albuminuria and Cognitive Performance: Test for Interaction With Age

Analyses with interaction terms showed that the association between continuous albuminuria and cognitive performance was stronger at older age, to such an extent that the interaction terms indicated a −0.038 (executive function) to −0.030 (information processing speed) difference in the β of albuminuria per 10 years older age (model 1; *P* for interaction < 0.05 for all cognitive domains except memory function). The latter implied that albuminuria was not associated with cognitive performance in 50-year-old individuals, whereas in 70-year-old individuals, it was associated with lower overall cognitive performance, information processing speed, and executive function (Table S2). Analyses stratified according to age tertiles showed a similar pattern (Table S3).

eGFR and Cognitive Performance

Mean (±SD) $eGFR_{cr\text{-}cys}$ was 88.4 ± 14.6 mL/min/1.73 m^2 (Table 1). There were 1,463 (49.0%) participants who had $eGFR_{cr\text{-}cys} \geq 90$ mL/min/1.73 m^2; 1,413 (47.3%) had $eGFR_{cr\text{-}cys}$ 60 to <90 mL/min/1.73 m^2; and 111 (3.7%) had $eGFR_{cr\text{-}cys}$ <60 mL/min/1.73 m^2. Participants with lower $eGFR_{cr\text{-}cys}$ had lower scores on each of the cognitive domains (Table S1).

After adjustment for age, sex, glucose metabolism status, and educational level (Table 4, model 2), $eGFR_{cr\text{-}cys} < 60$ mL/min/1.73 m^2 was associated with lower overall cognitive performance (β = −0.191; 95% CI, −0.346 to −0.035), lower information processing speed (β = −0.215; 95% CI, −0.381

to −0.049), and borderline statistically significantly lower memory function (β = −0.151; 95% CI, −0.323 to 0.022). After further adjustment for the variables of models 3 to 5, these associations were attenuated and no longer statistically significant.

Similarly, continuous $eGFR_{cr-cys}$ was not statistically significantly associated with cognitive performance after full adjustment (Table 5, model 5a).

Results were similar when we adjusted for 24-hour average ambulatory systolic blood pressure instead of office systolic blood pressure (Tables 4 and 5, model 5b).

eGFR and Cognitive Performance: Test for Interaction With Age

Analyses with interaction terms showed that the association between continuous $eGFR_{cr-cys}$ and cognitive performance was stronger at older age, to such an extent that the interaction terms indicated a −0.043 (overall cognitive performance) to −0.031 (memory function) difference in the β of $eGFR_{cr-cys}$ per 10 years older age (model 1, P for interaction < 0.05 for all cognitive domains). The latter implied that $eGFR_{cr-cys}$ was not associated with cognitive performance in 50-year-old individuals, whereas in 70-year-old individuals, it was associated with lower overall cognitive performance and borderline statistically significantly lower memory function and executive function (Table S4). Additional age-stratified analyses showed a similar pattern, but were hampered by a loss of statistical power (Table S5).

Additional Analyses

When $eGFR_{cr-cys}$ was replaced with eGFR based on the MDRD Study equation, $eGFR_{cr}$, or $eGFR_{cys}$, results did not materially change, except for the association of $eGFR_{cr-cys}$ with memory function, that is, point estimates as compared to $eGFR_{cr-cys}$ were smaller with creatinine-based equations and larger with the cystatin C-based equation (Table S6).

Additionally, results were not materially altered in the following scenarios (Tables S7 and S8): when we adjusted for a quadratic association between age and all scores of cognitive performance; when we replaced office systolic blood pressure with either office diastolic blood pressure, office mean arterial pressure, office pulse pressure, presence of hypertension, 24-hour average ambulatory (n = 2,644) diastolic blood pressure, mean arterial pressure, or pulse pressure; when we replaced the use of antihypertensive medication with the use of a renin-angiotensin system inhibitor or replaced waist circumference with waist-to-hip ratio or body mass index; when results were additionally adjusted for either total (n = 2,635) or moderate to vigorous physical activity (n = 2,634); when we restricted analyses to participants with UAE ≤ 300 mg/24 h (n = 2,969) and participants with 2 urine collections (n = 2,727); and when we excluded participants with a Mini-Mental State Examination score < 24 (n = 10). In addition, no interactions between either albuminuria or $eGFR_{cr-cys}$ and glucose metabolism status were found (P for interaction > 0.1), except for the association of UAE of 15 to <30 mg/24 h with overall cognitive performance (P for interaction = 0.1) and executive function (P for interaction = 0.08), and the association of $eGFR_{cr-cys} < 60$ mL/min/1.73 m^2 with information processing speed (P for interaction = 0.04) in participants with impaired glucose metabolism only. Finally, results of multiple imputation analyses were similar to complete case analyses, with the exception that lower $eGFR_{cr-cys}$ was borderline statistically significantly associated with lower memory function after multiple imputation (Table S9).

DISCUSSION

This study of the associations of eGFR and albuminuria with cognitive performance in 40- to 75-year-old individuals had 3 main findings. First, albuminuria with UAE ≥ 30 mg/24 h was associated with lower information processing speed, independent of educational level, CVD risk factors (including $eGFR_{cr-cys}$), and lifestyle factors. Second, $eGFR_{cr-cys}$ was not associated with any of the domains of cognitive performance after adjustment for educational level, CVD risk factors (including albuminuria), and lifestyle factors. Third, associations of albuminuria and $eGFR_{cr-cys}$ seemed to be modified by age, to such an extent that both were more strongly and extensively associated with cognitive performance in older individuals.

Albuminuria with UAE ≥ 30 mg/24 h was associated with information processing speed, whereas no associations were observed with memory function and executive function. As compared to continuous UAE, the categorical approach may have been less affected by the day-to-day variability in UAE and therefore nondifferential misclassification with bias toward the null. In addition, the continuous (exponential) model, although reasonable, may not have perfectly fitted the association. However, we can not exclude residual confounding with the categorical approach or the play of chance.

The absence of an association with executive function is in agreement with 2 studies in a similar age group,[19,26] but contrasts with studies in older individuals,[12-14,17] which have shown an association between albuminuria and executive function. One explanation for this discrepancy is that cognitive decline is more subtle in middle-aged individuals due to higher brain reserve capacity in this age group. The statistically significant interaction between age and albuminuria, which suggested a stronger association between albuminuria and cognitive performance, including executive function, with increasing age,

Table 1. Clinical Characteristics of Study Population Overall and Stratified According to Albuminuria Categories

		Albuminuria Category		
	Study Population (N = 2,987)	<15 mg/24 h (n = 2,439)	15-<30 mg/24 h (n = 309)	≥30 mg/24 h (n = 239)
Demographics				
Age, y	59.6 ± 8.2	59.0 ± 8.2	61.8 ± 8.2	62.4 ± 7.7
Male sex	1,527 (51.1)	1,166 (47.8)	186 (60.2)	175 (73.2)
Educational level				
Low	468 (15.7)	348 (14.3)	55 (17.8)	65 (27.2)
Intermediate	1,290 (43.2)	1,065 (43.7)	134 (43.4)	91 (38.1)
High	1,229 (41.2)	1,026 (42.1)	120 (38.8)	84 (34.7)
Prevalent CVD	481 (16.1)	352 (14.4)	61 (19.7)	69 (28.5)
Lifestyle variables				
Smoking behavior				
Never smoker	1,048 (35.1)	903 (37.0)	89 (28.8)	56 (23.4)
Former smoker	1,549 (51.9)	1,236 (50.7)	177 (57.3)	136 (56.9)
Current smoker	390 (13.1)	300 (12.3)	43 (13.9)	47 (19.7)
Alcohol consumption				
None	537 (18.0)	419 (17.2)	58 (18.8)	60 (25.1)
Low[a]	1,658 (55.5)	1,368 (56.1)	170 (55.0)	120 (50.2)
High[b]	792 (26.5)	652 (26.7)	81 (26.2)	59 (24.7)
Total physical activity, h/wk[c]	13.0 [8.3-18.8]	13.4 [8.5-18.8]	12.9 [7.5-18.6]	11.3 [6.3-18.5]
Moderate to vigorous physical activity, h/wk[c]	4.5 [2.3-8.0]	4.6 [2.8-8.0]	4.0 [1.5-8.2]	3.3 [1.5-7.3]
Metabolic variables				
BMI category[d]				
Normal weight: <25 kg/m^2	1,045 (35.0)	925 (37.9)	73 (23.6)	47 (19.7)
Overweight: 25-<30 kg/m^2	1,286 (43.1)	1,043 (42.8)	144 (46.6)	99 (41.4)
Obesity: ≥30 kg/m^2	655 (21.9)	470 (19.3)	92 (29.8)	93 (38.9)
Waist circumference, cm				
Men	101.3 ± 11.8	99.7 ± 11.1	105.3 ± 11.6	107.7 ± 13.7
Women	89.9 ± 12.8	89.3 ± 12.2	93.6 ± 16.1	96.1 ± 16.1
Waist-to-hip ratio[e]				
Men	1.00 ± 0.07	0.99 ± 0.07	1.02 ± 0.07	1.03 ± 0.08
Women	0.88 ± 0.07	0.87 ± 0.07	0.89 ± 0.08	0.92 ± 0.09
Blood pressure				
Office systolic, mm Hg	134.8 ± 18.1	133.1 ± 17.4	141.1 ± 18.2	143.7 ± 20.4
Office diastolic, mm Hg	76.3 ± 9.9	75.9 ± 9.8	77.8 ± 10.6	78.1 ± 9.7
24-h average ambulatory systolic, mm Hg[f]	119.0 ± 11.7	117.7 ± 11.0	123.1 ± 12.4	126.4 ± 13.9
24-h average ambulatory diastolic, mm Hg[f]	73.6 ± 7.2	73.2 ± 7.0	75.0 ± 8.3	75.4 ± 7.5
Hypertension	1,659 (55.5)	1,240 (50.8)	222 (71.8)	197 (82.4)
Glucose metabolism status				
Normal glucose metabolism	1,732 (58.0)	1,532 (62.8)	130 (42.1)	70 (29.3)
Impaired fasting glucose	128 (4.3)	103 (4.2)	17 (5.5)	8 (3.3)
Impaired glucose tolerance	336 (11.2)	290 (11.9)	25 (8.1)	21 (8.8)
T2DM	791 (26.5)	514 (21.1)	137 (44.3)	140 (58.6)
Fasting glucose, mg/dL[g]				
Without T2DM	96.0 ± 9.9	95.7 ± 9.7	97.7 ± 10.4	99.5 ± 10.3
With T2DM	142.8 ± 36.9	138.6 ± 31.6	143.8 ± 39.5	157.3 ± 47.4
HbA_{1c}, %[h]				
Without T2DM	5.5 ± 0.4	5.5 ± 0.4	5.5 ± 0.4	5.6 ± 0.4
With T2DM	6.9 ± 1.0	6.8 ± 0.8	7.0 ± 1.1	7.4 ± 1.4
Cholesterol				
Total, mg/dL	203.4 ± 44.6	206.3 ± 43.9	193.2 ± 46.1	186.7 ± 45.2
HDL, mg/dL				
Men	51.3 ± 14.5	52.1 ± 14.2	48.0 ± 13.6	49.6 ± 16.5
Women	67.0 ± 18.6	67.5 ± 18.5	64.3 ± 17.6	63.4 ± 20.5
LDL, mg/dL	120.2 ± 39.9	122.8 ± 39.3	112.4 ± 40.2	103.8 ± 39.8
Triglycerides, mg/dL	106.3 [77.9-152.3]	103.6 [76.2-146.1]	116.0 [86.4-169.2]	129.3 [96.5-193.1]
Total to HDL cholesterol ratio	3.7 ± 1.2	3.7 ± 1.2	3.8 ± 1.2	3.8 ± 1.2

(Continued)

Table 1 (Cont'd). Clinical Characteristics of Study Population Overall and Stratified According to Albuminuria Categories

		Albuminuria Category		
	Study Population (N = 2,987)	<15 mg/24 h (n = 2,439)	15-<30 mg/24 h (n = 309)	≥30 mg/24 h (n = 239)
Kidney function				
$eGFR_{cr-cys}$, mL/min/1.73 m^2	88.4 ± 14.6	89.2 ± 13.9	86.9 ± 16.1	82.1 ± 17.8
$eGFR_{cr}$, mL/min/1.73 m^2	84.7 ± 13.8	85.1 ± 13.3	84.1 ± 14.8	81.1 ± 16.2
$eGFR_{cys}$, mL/min/1.73 m^2	90.2 ± 16.2	91.3 ± 15.4	87.6 ± 17.7	81.7 ± 19.5
$eGFR_{MDRD}$, mL/min/1.73 m^2	80.6 ± 15.4	80.7 ± 14.9	81.5 ± 16.6	79.2 ± 19.0
UAE rate, mg/24 h	6.6 [4.0-11.7]	5.6 [3.7-8.3]	19.4 [16.6-23.9]	68.3 [41.6-114.1]
UAE category				
<15 mg/24 h	2,439 (81.7)	—	—	—
15-<30 mg/24 h	309 (10.3)	—	—	—
≥30 mg/24 h	239 (8.0)	—	—	—
Medication				
Antihypertensive medication	1,157 (38.7)	840 (34.4)	153 (49.5)	164 (68.6)
Renin-angiotensin system inhibitor	867 (29.0)	605 (24.8)	121 (39.2)	141 (59.0)
Lipid-modifying medication	1,033 (34.6)	747 (30.6)	141 (45.6)	145 (60.7)
Mental health and cognitive performance				
Current major depressive episode	109 (3.6)	69 (2.8)	23 (7.4)	17 (7.1)
Overall cognitive performance	0.00 ± 1.00	0.08 ± 0.98	−0.23 ± 1.05	−0.51 ± 1.00
Memory function	0.00 ± 1.00	0.06 ± 0.98	−0.19 ± 1.03	−0.42 ± 0.99
Information processing speed	0.00 ± 1.00	0.07 ± 0.97	−0.16 ± 1.01	−0.48 ± 1.08
Executive function	0.00 ± 1.00	0.06 ± 0.98	−0.19 ± 1.08	−0.32 ± 1.00

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range]. Conversion factors for units: fasting glucose in mg/dL to mmol/L, ×0.05551; HbA_{1c} in % to mmol/mol, 10.93 × HbA_{1c} [%] + 23.5; cholesterol in mg/dL to mmol/L, ×0.02586; triglycerides in mg/dL to mmol/L, ×0.01129.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; $eGFR_{cr}$, creatinine-based estimated glomerular filtration rate; $eGFR_{cr-cys}$, estimated glomerular filtration rate based on creatinine and cystatin C levels; $eGFR_{cys}$, cystatin C–based estimated glomerular filtration rate; $eGFR_{MDRD}$, estimated glomerular filtration rate based on 4-variable Modification of Diet in Renal Disease Study equation; HbA_{1c}, hemoglobin A_{1c} (glycated hemoglobin); HDL, high-density lipoprotein; LDL, low-density lipoprotein; T2DM, type 2 diabetes mellitus; UAE, urinary albumin excretion.

[a]Low alcohol consumption: women, 7 or fewer glasses per week; men, 14 or fewer glasses per week.

[b]High alcohol consumption: women, more than 7 glasses per week; men, more than 14 glasses per week.

[c]Available for 2,635 (total physical activity) and 2,634 (moderate to vigorous physical activity) participants.

[d]Available for 2,986 participants.

[e]Available for 2,986 participants.

[f]Available for 2,644 participants.

[g]Available for 2,985 participants.

[h]Available for 2,980 participants.

supports this view. In addition, the study population largely consisted of highly educated individuals who may be better able to maximize cognitive performance in the face of brain damage,[27,28] and information processing speed has been shown to be the domain most affected in individuals with vascular cognitive decline.[45]

Generalized endothelial dysfunction may provide an explanation for the link between albuminuria and cognitive performance.[21,22] According to this concept, endothelial dysfunction of the microcirculation on the one hand causes albuminuria, and on the other hand, cerebral small-vessel disease. It has been hypothesized that cerebral small-vessel disease increases blood-brain barrier permeability, which leads to extravasation of blood substances and subsequent neuronal damage.[22,46] Indeed, albuminuria has been associated with magnetic resonance imaging findings of cerebral small-vessel disease[47] and the latter predicts cognitive decline.[48]

Reduced GFR may lead to neuronal damage due to the accumulation of neurotoxins and/or may reflect disease processes underlying cognitive decline, for example, exposure to CVD risk factors and CVD itself.[20] The attenuation of the regression coefficients after adjustment for CVD risk factors supports the latter. However, the results of this study contrast with those of previous studies in middle-aged[23,25] and older individuals,[1,5,6,8,9] which have shown independent associations between lower creatinine-based estimates of GFR and the studied domains of cognitive performance. This is potentially explained by the younger mean age of participants in the present study population. The statistically significant interaction

Table 2. Multivariable Linear Regression Analyses of Association Between Categorical Albuminuria and Cognitive Performance

		Overall Cognitive Performance		Memory Function		Information Processing Speed		Executive Function	
Model[a]	UAE	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
1	<15 mg/24 h	Reference		Reference		Reference		Reference	
	15-<30 mg/24 h	−0.305 (−0.422 to −0.189)	<0.001	−0.252 (−0.369 to −0.134)	<0.001	−0.226 (−0.343 to −0.109)	<0.001	−0.246 (−0.364 to −0.129)	<0.001
	≥30 mg/24 h	−0.593 (−0.724 to −0.462)	<0.001	−0.481 (−0.613 to −0.350)	<0.001	−0.548 (−0.679 to −0.417)	<0.001	−0.381 (−0.513 to −0.249)	<0.001
2	<15 mg/24 h	Reference		Reference		Reference		Reference	
	15-<30 mg/24 h	−0.041 (−0.134 to 0.052)	0.4	−0.040 (−0.143 to 0.063)	0.4	0.002 (−0.097 to 0.102)	0.9	−0.057 (−0.162 to 0.048)	0.3
	≥30 mg/24 h	−0.149 (−0.256 to −0.043)	0.006	−0.110 (−0.229 to 0.008)	0.07	−0.172 (−0.286 to −0.058)	0.003	−0.075 (−0.195 to 0.044)	0.2
3	<15 mg/24 h	Reference		Reference		Reference		Reference	
	15-<30 mg/24 h	−0.036 (−0.128 to 0.057)	0.5	−0.035 (−0.138 to 0.069)	0.5	0.006 (−0.093 to 0.105)	0.9	−0.053 (−0.158 to 0.052)	0.3
	≥30 mg/24 h	−0.128 (−0.235 to −0.021)	0.02	−0.083 (−0.202 to 0.036)	0.2	−0.159 (−0.273 to −0.044)	0.007	−0.067 (−0.188 to 0.054)	0.3
4	<15 mg/24 h	Reference		Reference		Reference		Reference	
	15-<30 mg/24 h	−0.036 (−0.129 to 0.057)	0.4	−0.035 (−0.138 to 0.068)	0.5	0.006 (−0.093 to 0.105)	0.9	−0.053 (−0.158 to 0.051)	0.3
	≥30 mg/24 h	−0.124 (−0.232 to −0.017)	0.02	−0.078 (−0.198 to 0.041)	0.2	−0.158 (−0.273 to −0.044)	0.007	−0.065 (−0.186 to 0.056)	0.3
5a	<15 mg/24 h	Reference		Reference		Reference		Reference	
	15-<30 mg/24 h	−0.024 (−0.117 to 0.069)	0.6	−0.028 (−0.131 to 0.076)	0.6	0.011 (−0.089 to 0.110)	0.8	−0.038 (−0.143 to 0.067)	0.5
	≥30 mg/24 h	−0.110 (−0.217 to −0.002)	0.05	−0.068 (−0.188 to 0.052)	0.3	−0.148 (−0.263 to −0.033)	0.01	−0.050 (−0.171 to 0.071)	0.4
5b	<15 mg/24 h	Reference		Reference		Reference		Reference	
	15-<30 mg/24 h	−0.038 (−0.137 to 0.062)	0.5	−0.035 (−0.146 to 0.076)	0.5	0.006 (−0.100 to 0.112)	0.9	−0.057 (−0.169 to 0.055)	0.3
	≥30 mg/24 h	−0.133 (−0.248 to −0.018)	0.02	−0.108 (−0.237 to 0.021)	0.1	−0.177 (−0.300 to −0.054)	0.005	−0.034 (−0.164 to 0.096)	0.6

Note: Regression coefficients (βs) represent the standard deviation difference in the cognitive domain scores as compared with participants with UAE < 15 mg/24 h.

Abbreviations: CI, confidence interval; $eGFR_{cr\text{-}cys}$, estimated glomerular filtration rate based on creatinine and cystatin C levels; UAE, urinary albumin excretion.

[a]Model 1: unadjusted model; model 2: model 1 + age, sex, educational level, and glucose metabolism status; model 3: model 2 + waist circumference, total to high-density lipoprotein cholesterol ratio, triglyceride level, use of lipid-modifying medication, smoking behavior, and alcohol consumption; model 4: model 3 + $eGFR_{cr\text{-}cys}$ (continuous); model 5a: model 4 + office systolic blood pressure, use of antihypertensive medication, prevalent cardiovascular disease, and depression; model 5b: similar to model 5a but adjusted for ambulatory systolic blood pressure instead of office systolic blood pressure (missing in 343 participants).

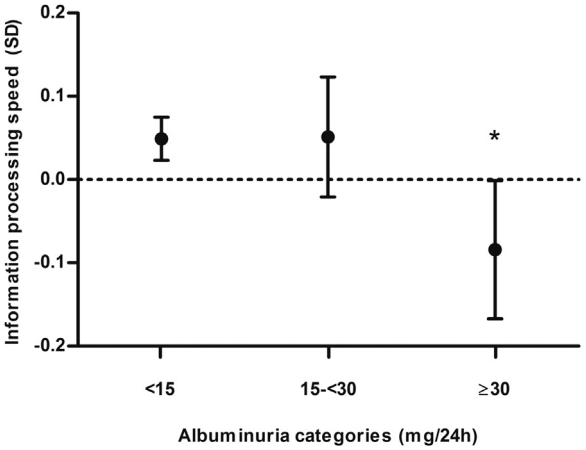

Figure 2. Association between albuminuria and information processing speed. Adjusted mean values of the composite score of information processing speed are expressed per albuminuria category. Mean values were adjusted for age, sex, educational level, and glucose metabolism status (model 2). Bars indicate 95% confidence intervals. *P* values were derived from the same models. $^{*}P < 0.01$ as compared with participants with urinary albumin excretion < 15 mg/24 h. Abbreviation: SD, standard deviation.

between age and $eGFR_{cr\text{-}cys}$, which suggested a stronger association between $eGFR_{cr\text{-}cys}$ and cognitive performance with increasing age, supports this view. Additionally, the study population largely consisted of highly educated individuals and few participants had an $eGFR_{cr\text{-}cys} < 60$ mL/min/1.73 m^2.

We used an equation based on both serum creatinine and serum cystatin C levels to estimate GFR in our primary analyses.[30] However, additional analyses showed a stronger association between eGFR and cognitive performance (ie, memory function) when an equation based on cystatin C level only was used. This is in agreement with 2 previous studies in older individuals.[10,11] A clear explanation for these results cannot be derived from this study. Cystatin C may be a more sensitive biomarker of GFR than creatinine in populations with more comorbid conditions,[49] which allows for the detection of even a subtle association between eGFR and memory function. Alternatively, cystatin C level may be associated with other determinants of cognitive decline, such as visceral adiposity and inflammation.[49]

Major strengths of the present study were its extensive assessment of cognitive performance and detailed characterization of the study population, which allowed adjustment for an extensive series of potential confounders, including 24-hour average ambulatory blood pressure. However, this study also had some limitations. First, the cross-sectional design limited causal inferences. Second, we cannot exclude residual confounding despite adjustment for an extensive series of potential confounders. For example, inflammation

Table 3. Multivariable Linear Regression Analyses of the Association Between Continuous Albuminuria and Cognitive Performance

	Overall Cognitive Performance		Memory Function		Information Processing Speed		Executive Function	
Model[a]	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
1	−0.126 (−0.152 to −0.100)	<0.001	−0.104 (−0.130 to −0.078)	<0.001	−0.108 (−0.134 to −0.082)	<0.001	−0.087 (−0.113 to −0.061)	<0.001
2	−0.019 (−0.040 to 0.002)	0.08	−0.016 (−0.040 to 0.007)	0.2	−0.016 (−0.039 to 0.006)	0.2	−0.013 (−0.037 to 0.011)	0.3
3	−0.014 (−0.035 to 0.007)	0.2	−0.011 (−0.034 to 0.013)	0.4	−0.013 (−0.035 to 0.010)	0.3	−0.010 (−0.034 to 0.014)	0.4
4	−0.013 (−0.035 to 0.008)	0.2	−0.010 (−0.034 to 0.014)	0.4	−0.012 (−0.035 to 0.011)	0.3	−0.010 (−0.034 to 0.015)	0.4
5a	−0.010 (−0.032 to 0.011)	0.3	−0.007 (−0.031 to 0.017)	0.6	−0.012 (−0.035 to 0.011)	0.3	−0.006 (−0.031 to 0.018)	0.6
5b	−0.016 (−0.040 to 0.007)	0.2	−0.014 (−0.040 to 0.012)	0.3	−0.017 (−0.042 to 0.008)	0.2	−0.007 (−0.034 to 0.019)	0.6

Note: The regression coefficients (βs) represent the standard deviation difference in the cognitive domain scores per doubling of urinary albumin excretion.
Abbreviation: CI, confidence interval.
[a]See Table 2 for descriptions of models.

Table 4. Multivariable Linear Regression Analyses of the Association Between Categorical $eGFR_{cr-cys}$ and Cognitive Performance

		Overall Cognitive Performance		Memory Function		Information Processing Speed		Executive Function	
Model[a]	$eGFR_{cr-cys}$	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
1	≥90 mL/min/1.73 m^2	Reference		Reference		Reference		Reference	
	60-<90 mL/min/1.73 m^2	−0.363 (−0.435 to −0.292)	<0.001	−0.239 (−0.312 to −0.167)	<0.001	−0.334 (−0.406 to −0.263)	<0.001	−0.300 (−0.372 to −0.228)	<0.001
	<60 mL/min/1.73 m^2	−0.943 (−1.131 to −0.755)	<0.001	−0.649 (−0.839 to −0.458)	<0.001	−0.912 (−1.101 to −0.724)	<0.001	−0.703 (−0.893 to −0.513)	<0.001
2	≥90 mL/min/1.73 m^2	Reference		Reference		Reference		Reference	
	60-<90 mL/min/1.73 m^2	−0.044 (−0.105 to 0.016)	0.2	−0.037 (−0.105 to 0.030)	0.3	−0.030 (−0.096 to 0.035)	0.4	−0.037 (−0.106 to 0.031)	0.3
	<60 mL/min/1.73 m^2	−0.191 (−0.346 to −0.035)	0.02	−0.151 (−0.323 to 0.022)	0.09	−0.215 (−0.381 to −0.049)	0.01	−0.089 (−0.264 to 0.085)	0.3
3	≥90 mL/min/1.73 m^2	Reference		Reference		Reference		Reference	
	60-<90 mL/min/1.73 m^2	−0.022 (−0.083 to 0.039)	0.5	−0.024 (−0.092 to 0.045)	0.5	−0.012 (−0.078 to 0.053)	0.7	−0.016 (−0.085 to 0.053)	0.7
	<60 mL/min/1.73 m^2	−0.138 (−0.294 to 0.017)	0.08	−0.107 (−0.280 to 0.066)	0.2	−0.177 (−0.344 to −0.011)	0.04	−0.048 (−0.224 to 0.128)	0.6
4	≥90 mL/min/1.73 m^2	Reference		Reference		Reference		Reference	
	60-<90 mL/min/1.73 m^2	−0.020 (−0.082 to 0.041)	0.5	−0.023 (−0.091 to 0.046)	0.5	−0.009 (−0.075 to 0.056)	0.8	−0.015 (−0.084 to 0.054)	0.7
	<60 mL/min/1.73 m^2	−0.118 (−0.275 to 0.039)	0.1	−0.094 (−0.269 to 0.080)	0.3	−0.152 (−0.319 to 0.016)	0.08	−0.037 (−0.214 to 0.140)	0.7
5a	≥90 mL/min/1.73 m^2	Reference		Reference		Reference		Reference	
	60-<90 mL/min/1.73 m^2	−0.017 (−0.078 to 0.044)	0.6	−0.022 (−0.090 to 0.046)	0.5	−0.003 (−0.068 to 0.063)	0.9	−0.014 (−0.083 to 0.055)	0.7
	<60 mL/min/1.73 m^2	−0.102 (−0.259 to 0.056)	0.2	−0.087 (−0.263 to 0.089)	0.3	−0.124 (−0.292 to 0.045)	0.2	−0.031 (−0.209 to 0.147)	0.7
5b	≥90 mL/min/1.73 m^2	Reference		Reference		Reference		Reference	
	60-<90 mL/min/1.73 m^2	−0.024 (−0.088 to 0.041)	0.5	−0.026 (−0.098 to 0.047)	0.5	−0.010 (−0.079 to 0.059)	0.8	−0.020 (−0.092 to 0.053)	0.6
	<60 mL/min/1.73 m^2	−0.112 (−0.279 to 0.055)	0.2	−0.094 (−0.281 to 0.093)	0.3	−0.172 (−0.350 to 0.006)	0.06	−0.002 (−0.190 to 0.186)	0.9

Note: The regression coefficients (βs) represent the standard deviation difference in the cognitive domain scores as compared with participants with an $eGFR_{cr-cys} \geq 90$ mL/min/1.73 m^2.

Abbreviations: CI, confidence interval; $eGFR_{cr-cys}$, estimated glomerular filtration rate based on creatinine and cystatin C levels.

[a]Model 1: unadjusted model; model 2: model 1 + age, sex, educational level, and glucose metabolism status; model 3: model 2 + waist circumference, total to high-density lipoprotein cholesterol ratio, triglyceride level, use of lipid-modifying medication, smoking behavior, and alcohol consumption; model 4: model 3 + UAE (categorical); model 5a: model 4 + office systolic blood pressure, use of antihypertensive medication, prevalent cardiovascular disease, and depression; model 5b: similar to model 5a but adjusted for ambulatory systolic blood pressure instead of office systolic blood pressure (missing in 343 participants).

Table 5. Multivariable Linear Regression Analyses of the Association Between Continuous $eGFR_{cr-cys}$ and Cognitive Performance

Model[a]	Overall Cognitive Performance		Memory Function		Information Processing Speed		Executive Function	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
1	−0.185 (−0.209 to −0.161)	<0.001	−0.127 (−0.151 to −0.103)	<0.001	−0.167 (−0.190 to −0.143)	<0.001	−0.150 (−0.174 to −0.126)	<0.001
2	−0.022 (−0.044 to 0.000)	0.05	−0.023 (−0.047 to 0.001)	0.06	−0.012 (−0.035 to 0.012)	0.3	−0.016 (−0.041 to 0.008)	0.2
3	−0.011 (−0.033 to 0.011)	0.3	−0.015 (−0.040 to 0.009)	0.2	−0.003 (−0.027 to 0.021)	0.8	−0.007 (−0.032 to 0.018)	0.6
4	−0.009 (−0.031 to 0.013)	0.4	−0.014 (−0.039 to 0.011)	0.3	0.000 (−0.024 to 0.023)	0.9	−0.006 (−0.031 to 0.019)	0.6
5a	−0.007 (−0.029 to 0.015)	0.5	−0.014 (−0.038 to 0.011)	0.3	0.004 (−0.020 to 0.028)	0.7	−0.005 (−0.030 to 0.020)	0.7
5b	−0.010 (−0.033 to 0.014)	0.4	−0.013 (−0.039 to 0.014)	0.3	−0.003 (−0.028 to 0.023)	0.8	−0.007 (−0.034 to 0.020)	0.6

Note: The regression coefficients (βs) represent the standard deviation difference in the cognitive domain scores per 10 mL/min/1.73 m^2 lower $eGFR_{cr-cys}$.
Abbreviations: CI, confidence interval; $eGFR_{cr-cys}$, estimated glomerular filtration rate based on creatinine and cystatin C levels.
[a]See Table 4 for descriptions of models.

markers were not available. In addition, it is important to note that, for example, blood pressure and CVD may also be intermediates in the association between kidney function and cognitive performance, possibly leading to underestimation of the evaluated associations.[41] However, the relatively small attenuation of the regression coefficients after adding these variables suggests that their role as either confounder or intermediate was small. Third, individual cognitive tests often incorporate multiple cognitive domains and their classification is therefore somewhat arbitrary.[42] In addition, although extensive, the cognitive test battery used did not specifically assess, for example, working memory, semantic memory, reasoning, and visual-spatial ability. Fourth, participants with missing data differed from included participants, and results of the complete case analyses may be conservative because the additional multiple imputation analyses also suggested an association between $eGFR_{cr-cys}$ and memory function. Finally, the absence of direct measurements of GFR precludes any definitive conclusions on the differences between the eGFR formulas and their associations with cognitive decline.

In conclusion, in the entire study population, albuminuria was independently associated with worse cognitive performance, in particular within the domain of information processing speed, whereas $eGFR_{cr-cys}$ was not associated with cognitive performance. However, both albuminuria and $eGFR_{cr-cys}$ were more strongly and extensively associated with cognitive performance in older individuals.

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Contributions: Research idea and study design: RJHM, JPK, CDAS, GN, RMAH; data acquisition: RJHM; data analysis/interpretation: RJHM, JPK, CDAS, PCD, CJHvdK, AK, AAK,

KMLL, GN, FMvdS, NCS, SJSS, MPJvB, MTS, RMAH; statistical analysis: RJHM; supervision or mentorship: JPK, CDAS, GN, RMAH. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any part of the work are appropriately investigated and resolved. RJHM takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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SUPPLEMENTARY MATERIAL

Table S1: Clinical characteristics of study population and stratified according to $eGFR_{cr\text{-}cys}$ categories.

Table S2: Multivariable linear regression analyses of association between continuous albuminuria and cognitive performance for 50- and 70-y-olds.

Table S3: Multivariable linear regression analyses of association between continuous albuminuria and cognitive performance by age tertiles.

Table S4: Multivariable linear regression analyses of association between $eGFR_{cr\text{-}cys}$ and cognitive performance for 50- and 70-y-olds.

Table S5: Multivariable linear regression analyses of association between $eGFR_{cr\text{-}cys}$ and cognitive performance by age tertiles.

Table S6: Multivariable linear regression analyses of association between eGFR and memory function using different GFR equations.

Table S7: Additional multivariable linear regression analyses of association between categorical albuminuria and cognitive performance.

Table S8: Additional multivariable linear regression analyses of association between continuous $eGFR_{cr\text{-}cys}$ and cognitive performance.

Table S9: Multivariable linear regression analyses of associations of continuous and categorical $eGFR_{cr\text{-}cys}$ and memory function after multiple imputation

Item S1: Supplemental methods and details on metrics of variables used in statistical analyses.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2016.04.017) is available at www.ajkd.org

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