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Albuminuria and cognitive performance: New evidence for consideration of a risk factor precursor model from the Maastricht Study

Merrill F. Elias
University of Maine - Main, mfelias@maine.edu

Rachael V. Torres
University of Delaware

Adam Davey
University of Delaware

Albuminuria and Cognitive Performance: New Evidence for Consideration of a Risk Factor Precursor Model From the Maastricht Study

Albuminuria has been associated with lower cognitive functioning in some studies, but not in others. Reviews[1,2] and editorials[3] have discussed possible reasons for mixed results. Variable sample sizes, limited test batteries, different study populations and experimental designs, and variable adjustment for cardiovascular risk factors and other comorbid conditions may contribute to inconsistent findings. The study by Martens et al[4] in this issue of *AJKD* supports a relationship between albuminuria and cognitive functioning and addresses a number of these methodological issues.

Martens et al[4] used data from 2,987 participants, age range 40 to 75 years, from the Maastricht Study, a study focusing on the cause, pathophysiology, complications, and comorbid conditions associated with type 2 diabetes. In cross-sectional analyses, the associations of estimated glomerular filtration rate (eGFR) and urinary albumin excretion (UAE) with cognition were assessed. Two 24-hour urine collections were used to quantify UAE, while eGFR was determined from serum creatinine and serum cystatin C levels. The neurocognitive test battery assessed memory function, information processing speed, and executive function (Table 1). In analyses adjusted for demographic characteristics, including education level, lifestyle factors, depression, and cardiovascular disease risk factors and treatments, individuals with higher UAE, defined as ≥ 30 mg/24 h, had poorer information processing speed than those with UAE < 15 mg/24 h. Associations of UAE with memory function and executive function were significant in univariate and more parsimoniously adjusted models, but were attenuated with multivariable adjustment. No significant associations were found between eGFR and cognitive outcomes following multivariable adjustment. Interaction terms suggested that for both higher UAE and lower eGFR, associations with cognitive outcomes were somewhat higher among older than among younger participants.

The interaction between albumin and age (continuously distributed) was reported for 3 cognitive measures in a secondary analysis. Specifically, for each 10-year older age and each doubling of UAE, there was a 3.1% decrease in the score for overall cognitive performance ($P = 0.01$), a 2.6% decrease in information processing speed ($P = 0.05$), and a 3.4% decrease in executive function ($P = 0.02$). Martens et al raise the possibility that this phenomenon may have been related to better cognitive or brain reserve in the younger participants. Many other explanations have been advanced, including interacting influences of age versus disease process.[5]

It is important to note that the memory domain operationally defined by Martens et al is "working memory." Many other domains of memory can be operationalized, including episodic memory (memory for places and things) and semantic memory (memory for general factual knowledge independent of personal experience). These and other memory domains are important in the differential diagnoses of vascular dementia, Alzheimer disease, and mixed-type dementia.[6] Studies comparing working, episodic, and semantic memory outcomes are needed, and it is desirable to operationally define and measure multiple cognitive domains, taking patient burden into consideration.[7,8]

As discussed, eGFR was not related to any measure of cognition in adjusted analyses. In other investigations, significant associations between eGFR and cognition have been reported and often parallel those for albuminuria.[1-3] Of note, only 3.7% of participants (n = 111) in the Martens et al study had eGFRs < 60 mL/min/1.73 m^2, the cut point for defining chronic kidney disease (CKD) stage 3, whereas 8% (n = 239) exhibited high UAE values (≥ 30 mg/24 h). The low prevalence of advanced CKD in this sample could contribute to the lack of significant findings for executive functioning and working memory because many studies report relations between kidney function and cognition only when evaluating a population with a broader range of eGFRs, including more individuals with CKD stages 3 to 5.[1-3]

This study has several strengths. In addition to its well-defined cohort, Martens et al used a carefully selected set of statistical analyses with adjustment for a substantial number of comorbid conditions, lifestyle, and cardiovascular risk factors, introduced in hierarchical blocks; used 2 measures of UAE; and included both creatinine and cystatin C levels in estimating GFR. In the rest of this editorial, we summarize the

Address correspondence to Merrill F. Elias, PhD, MPH, PO Box 40, Mount Desert, ME 04660-40. E-mail: mfelias@maine.edu

Table 1. Operational Definitions of Test of Cognitive Ability in the Martens et al[4] Study

Cognitive Domain	Description of Cognitive Domain	Test Score Measures Used to Determine Cognitive Domain (Composite) Scores[a]
Memory function	Abilities required to encode, store, and retrieve information from memory; ie, working memory as opposed to passive forms of memory	Verbal Learning Test: Immediate Recall Verbal Learning Test: Delayed Recall
Information processing speed[b]	Abilities involved in how much time it takes to detect and mentally process information and execute a correct response. Can be measured as time-expired, number of correct responses in a specific period of time, or errors	Stroop Color-Word Test Part I Stroop Color-Word Test Part II Concept Shifting Test Part A Concept Shifting Test Part B Letter-Digit Substitution Test
Executive function	Refers to a set of integrated mental processes necessary for managing behavior to achieve an optimally successful or appropriate response, including: attention, cognitive flexibility, organizing, and problem solving and planning. Places a heavy emphasis on ability to shift a response when necessary	Stroop Color-Word Test Part III Concept Shifting Test Part C
Overall cognitive performance	Refers to a composite of the individual domains included in the battery	A composite of the individual domains or test scores

[a]See Item S1 (available as online supplementary material) from Martens et al[4] for more detail on measures used and calculations of composite scores.

[b]Information processing speed could also have been classified as speed/executive function because the measures used in the Martens et al study require the use of executive function. For the information processing domain, the executive functioning test must be done with the least mistakes made in a specific time.

contributions of this study to our understanding of relations between kidney disease markers and cognitive performance, discussing these relations in the context of a risk-factor precursor model.

The attenuation in the magnitude of associations between UAE and information processing speed with adjustment for cardiovascular disease risk factors could be explained by a risk factor precursor model.[5,9] In this model, relations between albuminuria and cognitive functioning may be due to the presence of shared risk factors that precede clinically apparent kidney disease.[5,7] However, this explanation does not exclude the possibility of the continued action of these risk factors after exposure to albuminuria. Cross-sectional studies, such as performed by Martens et al, make it difficult to discover how much risk factors and their associated comorbid conditions influence cognition before versus after the development of CKD.

In our own longitudinal research using eGFR as an index of kidney function, we observed that cognitive performance declined over 4.5 years following the first detection of reduced kidney function.[7] Unfortunately, we have found few studies in which either the severity or duration of cardiovascular disease risk factors, predating the development of kidney disease defined by either by albuminuria or eGFR, were examined and adequately controlled for. Longitudinal studies are necessary to assess whether cognitive deficits associated with albuminuria and eGFR are a product of previous exposure to cardiovascular disease risk factors and events.

What does a difference in cognitive performance at the level reported by Martens et al mean in terms of treatment of and communication with a patient presenting with albuminuria? Based on the effect sizes observed, we would not argue that these patients should be singled out for special cognitive interventions. Raw test scores in this study were standardized, so the mean for each composite score is zero, with a standard deviation (SD) of 1. This allows us to present differences in cognitive functioning across each of the domains indexed in the same metric (the z score). The average difference in information processing speed between participants with elevated UAE (≥ 30 mg/24 h) and the reference group (UAE < 15 mg/24 h) was $z = -0.148$ following adjustment for lifestyle and cardiovascular disease risk factors. This translates to a 14.8% decrease in information processing speed for those with elevated UAE. These participants were performing in the 44th percentile of a normal distribution. In clinical neuropsychology, dropping from a previous level of performance by 1.0 SD (16th percentile) is often considered clinically important. In our previous study of eGFR, we defined modest and severe impairment in persons with early-stage CKD as 1.0 and 1.5 SD (7th percentile) below the mean, respectively.[8] On average, participants with albuminuria in the Martens et al study were not

cognitively impaired in the clinical sense of the word "impairment." Of course, it must be acknowledged that findings may have achieved clinical significance if more participants with advanced CKD had been included in the sample.[10]

Of note, the level of performance reported for participants in the Martens et al study is of epidemiologic significance in terms of their population-level implications. If we could eliminate even small changes in cognition associated with kidney disease through prevention and treatment, functioning would improve for many persons in the population. Modest effect sizes observed for those with albuminuria are good news in this regard because they suggest that worse cognitive performance associated with albuminuria is not insurmountable. There is a high likelihood that most patients would respond to treatment and management of cardiovascular and lifestyle variables or prevention strategies. Hopefully the Marten et al study will stimulate further research on the hypothesis that lowered cognitive performance is not caused by albuminuria, but that albuminuria serves as a proxy for cardiovascular and cerebrovascular disease and therefore identifies individuals at risk for worse cognitive performance.

Merrill F. Elias, PhD, MPH
University of Maine
Orono, Maine

Rachael V. Torres, BA
Adam Davey, PhD
University of Delaware
Newark, Delaware

REFERENCES

1. Etgen T, Chonchol M, Förstl H, Sander D. Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis. *Am J Nephrol*. 2012;35(5):474-482.
2. Elias MF, Dore GA, Davey A. Kidney disease and cognitive function. *Contrib Nephrol*. 2013;179:42-57.
3. Weiner DE. The cognition-kidney disease connection: lessons from population-based studies in the United States. *Am J Kidney Dis*. 2008;52(2):201-204.
4. Martens RJH, Kooman JP, Stehouwer CDA, et al. Estimated GFR, albuminuria, and cognitive performance: the Maastricht Study. *Am J Kidney Dis*. 2017;69(2):179-191.
5. Waldstein S, Elias MF, eds. *Neuropsychology of Cardiovascular Disease*. 2nd ed. New York, NY: Taylor and Francis; 2016.
6. Lopez OL, Wolk DA. Clinical evaluation: a systematic but user-friendly approach. In: Wahlund LO, Erkinjuntti T, Gauthier S, eds. *Vascular Cognitive Impairment in Clinical Practice*. New York, NY: Cambridge Medicine; 2009:32-45.
7. Davey A, Elias MF, Robbins MA, Seliger SL, Dore GA. Decline in renal functioning is associated with longitudinal decline in global cognitive functioning, abstract reasoning, and verbal memory. *Nephrol Dial Transplant*. 2013;28:1810-1819.
8. Torres RV, Elias MF, Seliger S, Davey A, Robbins MA. Risk for cognitive impairment across 22 measures of cognitive ability in early-stage chronic kidney disease [published online ahead of print 2016]. *Nephrol Dial Transplant*. http://dx.doi.org/10.1093/ndt/gfw005.
9. Fried L. Albuminuria and cognitive impairment. *Clin J Am Soc Nephrol*. 2012;7. (3):376-378.
10. Murray AM. Cognitive impairment in the aging dialysis and chronic kidney disease populations: an occult burden. *Adv Chronic Kidney Dis*. 2008;15:123-132.