

# Association Between Cognitive Impairment and Chronic Kidney Disease in Mexican Americans

Harold M. Szerlip, MD,<sup>\*†</sup> Melissa L. Edwards, MA,<sup>\*‡</sup> Benjamin J. Williams, MD, PHD,<sup>§</sup>  
Leigh A. Johnson, PhD,<sup>\*||</sup> Raul M. Vintimilla, MPH,<sup>\*</sup> and Sid E. O'Bryant, PhD<sup>\*||</sup>

**OBJECTIVES:** To analyze the association between chronic kidney disease (CKD) and mild cognitive impairment (MCI) in Mexican Americans and to determine whether there is a blood-based proteomic profile linking CKD to MCI.

**DESIGN:** Retrospective analysis of cohort study.

**SETTING:** Health and Aging Brain among Latino Elders study.

**PARTICIPANTS:** Mexican Americans (N = 437, 105 men, 332 women).

**MEASUREMENTS:** Data were analyzed to examine the link between estimated glomerular filtration rate (eGFR) and detailed neuropsychological functioning. Serum proteomic markers were also examined.

**RESULTS:** Lower eGFR levels were associated with significantly poorer neuropsychological functioning across multiple domains. After adjusting for age, sex, education, and diabetes mellitus, participants with an eGFR less than 45 mL/min per 1.73 m<sup>2</sup> performed significantly worse than those with an eGFR from 45 to 59 mL/min per 1.73 m<sup>2</sup> or 60 mL/min per 1.73 m<sup>2</sup> and higher in processing speed ( $F = 14.1$ ,  $P < .001$ ), executive functioning ( $F = 4.5$ ,  $P = .01$ ), visuospatial skills ( $F = 4.8$ ,  $P = .009$ ), and global cognitive functioning ( $F = 6.2$ ,  $P = .002$ ). Participants with an eGFR less than 45 mL/min per 1.73 m<sup>2</sup> also performed significantly worse than those with an eGFR of 60 mL/min per 1.73 m<sup>2</sup> or greater on delayed memory ( $F = 3.8$ ,  $P = .02$ ). There was a trend toward lower eGFR levels being associated with greater risk of MCI (odds ratio (OR) = 2.4, 95% confidence interval (CI) = 0.91–6.1,  $P = .07$ ), which was stronger for men (OR = 9.6, 95% CI = 1.3–74.3,  $P = .03$ ). A serum proteomic profile consist-

ing of Factor VII, interleukin-10, C-reactive protein, and fatty acid binding protein was 93% accurate in detecting CKD-related MCI.

**CONCLUSION:** Lower eGFR was associated with significantly poorer neuropsychological functioning in Mexican Americans. A blood-based profile was generated that was highly accurate in detecting CKD-related MCI. A blood profile capable of predicting CKD-related cognitive impairment would be of benefit for the design of clinical interventions. *J Am Geriatr Soc* 63:2023–2028, 2015.

**Key words:** cognitive impairment; chronic kidney disease; neuropsychological testing; proteomics; Mexican Americans

Over the last 45 years, the Hispanic population in the United States has increased six times, making it the fastest-growing segment of the population.<sup>1</sup> Hispanics have a far greater incidence of end-stage renal disease (ESRD) than non-Hispanic whites. Data from the U.S. Renal Data System reveal that Hispanics have an incidence of ESRD that is 1.5 times as great as that of non-Hispanic whites.<sup>2</sup> Despite a clear increase in the incidence of ESRD, the incidence of chronic kidney disease (CKD) in the Hispanic population is the same as or even less than that of non-Hispanic whites.<sup>3,4</sup> This would suggest that CKD progresses faster to ESRD in Hispanic individuals. The reason for this disparity is unclear.

Analysis of data from the National Health and Nutrition Examination Surveys from 1999 to 2008 and from the Northern California Kaiser Permanente health system shows that Hispanics with diabetes mellitus have a higher urinary albumin excretion level than non-Hispanic whites.<sup>5–7</sup> In the general population with CKD, degree of albuminuria has been linked to progression of renal disease.<sup>8</sup> Analysis of data from the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria study demonstrated an association between biomarkers of endothelial dysfunction and progression from microalbuminuria to

From the \*Department of Internal Medicine, University of North Texas, Fort Worth; <sup>†</sup>Division of Nephrology, Baylor University Medical Center, Dallas; <sup>‡</sup>Department of Psychology, University of North Texas, Fort Worth; <sup>§</sup>Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas; and <sup>||</sup>Institute for Aging and Alzheimer's Disease Research, Health Sciences Center, University of North Texas, Fort Worth, Texas.

Address correspondence to Sid E. O'Bryant, 3500 Camp Bowie Blvd, Fort Worth, TX 76107. E-mail: sid.o'bryant@unthsc.edu

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macroalbuminuria.<sup>9</sup> Therefore, the greater degree of albuminuria in Hispanics may represent generalized endothelial dysfunction, which has been associated with mild cognitive impairment (MCI).<sup>10</sup> Cognitive impairment has been linked to greater mortality in individuals with and without CKD.<sup>11,12</sup> MCI may affect ability to follow medical regimens and lead to poorer ability to adhere to preventative and therapeutic regimens.<sup>13</sup>

Hispanics appear to be at greater risk of cognitive impairment than non-Hispanics at substantially younger ages.<sup>14</sup> In addition, “established” risk factors for MCI (hypertension, obesity, diabetes mellitus, dyslipidemia, apolipoprotein E 4 genotype) have not been shown to be significant for Mexican Americans.<sup>15</sup> Although it has been well established that CKD is a risk factor for cognitive decline in the general population,<sup>16–19</sup> few studies have examined this in Hispanics,<sup>20,21</sup> and these studies used general screening tools rather than detailed neuropsychological testing, which would allow for the assessment of the effect of CKD across cognitive domains.

The identification of a simple, rapid method to detect CKD-related MCI would be of tremendous value for medical management of individuals and the design of therapeutic interventions. In prior work, blood-based algorithms have been generated for the detection of MCI and Alzheimer’s disease (AD) that was more than 90% accurate, which has been validated across cohorts, species (human and animal models), tissue type (serum and brain microvessels), and assay platforms.<sup>22–25</sup> The goal of the current study was to apply the previously generated approach to the generation of a serum-based proteomic multimarker signature of CKD-related MCI in a community-dwelling cohort of Mexican Americans. It was also designed to determine whether serum proteomic markers from a previously generated blood profile of AD could be used to generate a blood profile of CKD-related cognitive impairment.

## METHODS

### Participants

Data from 437 participants (105 men, 332 women) from the Health and Aging Brain among Latino Elders (HABLE) study, an ongoing epidemiological study of cognitive aging in community-dwelling Mexican Americans were analyzed. The HABLE study uses a community-based participatory research approach, which involves partnering communities to conduct studies of human disease. The generation of locations for targeted recruitment was determined through analysis of ZIP codes in Tarrant County with the highest population density of Hispanic individuals. This research was conducted under an institutional review board-approved protocol, with each participant (or informants for cognitively impaired persons) providing written informed consent.

### Study Design

Each participant underwent an interview (medical history, medications, health behaviors), detailed neuropsychological testing, blood draw, and medical examination (review

of systems, Hachinski Ischemic Scale (HIS), brief neurological screen). The neuropsychological battery consisted of tests of global cognition (Mini-Mental State Examination (MMSE)), executive functioning (Trail-Making Test Part B (TMT-B), Executive Interview (EXIT25), clock drawing (CLOX1)),<sup>26,27</sup> language (FAS and Animal Naming),<sup>28</sup> visuospatial skills (CLOX2),<sup>27</sup> memory (Wechsler Memory Scale, Third Edition (WMS-3) Logical Memory, Consortium for the Establishment of Registry for Alzheimer’s Disease (CERAD) List Learning)<sup>28</sup> and attention (WMS-3 Digit Span, Trail-Making Test Part A (TMT-A)).<sup>29</sup> Testing was completed in English or Spanish depending on the participant’s preference. Raw scores were used in analyses. The current team has generated normative references for each of these tests for English- and Spanish-speaking Mexican Americans for diagnostic purposes (unpublished data). Normative references were constructed based on years of education and age. Cognitive diagnoses of MCI were assigned according to Mayo Clinic criteria,<sup>30</sup> which are distinguished according to subjective or informant complaints of memory changes along with one or more cognitive measures falling 1.5 standard deviation below age- and education-adjusted mean scores. Pre-MCI was defined as a score between 1.0 and 1.5 standard deviations below the mean on CERAD List Recall. All diagnoses were determined using a consensus review panel.

### Blood Collection and Processing

Fasting blood was drawn for clinical laboratory analyses. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula. Serum samples were also collected, in 10-mL tiger-top tubes, allowed to clot for 30 minutes at room temperature in a vertical position, and centrifuged for 10 minutes at 1,300 × g within 1 hour of collection. Then 1.0-mL aliquots of serum were transferred into cryovial tubes, barcode labels were firmly affixed to each aliquot, and samples placed into –80°C freezer within 2 hours of collection for storage until use in an assay.

### Biomarker Assays

All samples were assayed in duplicate using a multiplex biomarker assay platform using electrochemiluminescence (SECTOR Imager 2400A; Meso Scale Discovery, Rockville, MD, <http://www.mesoscale.com>). The Meso Scale Discovery platform has been used extensively to assay biomarkers associated with a range of human diseases, including AD.<sup>25,31</sup> Electrochemiluminescence measures have well-established properties of being more sensitive and requiring less sample volume than a conventional enzyme-linked immunosorbent assay,<sup>31</sup> the criterion standard for most assays. The markers assayed were from a previously generated and cross-validated AD algorithm<sup>22–25</sup> and included fatty acid binding protein (FABP3), beta 2 microglobulin, pancreatic polypeptide, soluble tumor necrosis factor receptor 1, C-reactive protein (CRP), vascular cell adhesion molecule 1, thrombopoietin,  $\alpha$ 2 macroglobulin, exotoxin 3, tumor necrosis factor alpha, tenascin C, interleukin (IL)5, IL6, IL7, IL10, IL18, I-309, Factor VII (FVII), thymus and activation regulated

chemokine, serum amyloid A, and intercellular adhesion molecule 1.

### Statistical Analyses

The link between eGFR levels and neuropsychological outcomes was assessed using analysis of variance (unadjusted models). In prior work, it was shown that “established” risk factors for MCI in non-Hispanic whites were not significant predictors of MCI in Mexican Americans.<sup>15</sup> In that work, diabetes mellitus status was not significantly predictive of MCI, despite the significantly greater prevalence of diabetes mellitus in Mexican Americans. Diabetes mellitus status was also not significantly related to MCI diagnosis in the HABLE cohort. Therefore, the adjusted analysis of covariance models included covariates for age, sex, and education, but models were not adjusted for diabetes mellitus. eGFR was divided into less than 45, 45 to 59, and 60 mL/min per 1.73 m<sup>2</sup> or greater based on accepted classification stages of CKD.<sup>32</sup> A two-step approach was used for the generation of a CKD-related MCI proteomic profile. First, the top markers from the previously cross-validated AD profile were applied, and then the optimal profile for CKD-related MCI from the full 21-protein profile of AD was examined. In analyses examining the utility of serum proteomic markers for detecting CKD-related MCI, logistic regression models were generated using only biomarker data. The model was run separately for those with eGFR less than 60 and 60 mL/min per 1.73 m<sup>2</sup> or greater. MCI diagnosis was used as the categorical outcome, with the predictor variables being the serum biomarkers. All serum biomarkers were transformed using Box-Cox transformation. Sensitivity (proportion of individuals correctly classified as having MCI according to the proteomic signature) and specificity

(proportion of individuals correctly classified as cognitively normal according to the proteomic signature) were calculated from the classification table output of the logistic regression model.

### RESULTS

The average age of the sample was 61.2 ± 8.3 (range 50–91) and the average education was 7.7 ± 4.3 years (range 0–18 years). Educational levels differed according to primary language (English speakers 11.3 ± 2.9 years; Spanish speakers 7.0 ± 4.1 years), which is similar to what is seen in the U.S. Mexican-American population. Average eGFR levels were 86.3 ± 17.0 mL/min per 1.73 m<sup>2</sup> (range 21–123 mL/min per 1.73 m<sup>2</sup>). eGFR categories were broken down as follows: <45 (n = 14), 45 to 59 (n = 20) and ≥60 (n = 403). Those with an eGFR of 60 mL/min per 1.73 m<sup>2</sup> or greater were significantly younger than the other two groups, with the lower eGFR groups not being significantly different from one another. Table 1 shows the demographic characteristics of the cohort.

In the unadjusted models, lower eGFR was associated with significantly poorer performance on the domains of global cognition (MMSE), memory (WMS-3 LM, CERAD Recall), executive functioning (EXIT25, CLOX1), processing speed (TMT-A), visuospatial skills (CLOX2), and language (Animal Naming) (Table 1). In the adjusted models, those with an eGFR of less than 45 mL/min per 1.73 m<sup>2</sup> performed significantly worse than those with an eGFR of 45 to 59 or 60 mL/min per 1.73 m<sup>2</sup> or higher in processing speed (TMT-A,  $F = 14.1$ ,  $P < .001$ ), executive functioning (CLOX1,  $F = 4.5$ ,  $P = .01$ ), visuospatial skills (CLOX2,  $F = 4.8$ ,  $P = .009$ ), and global cognitive functioning (MMSE,  $F = 6.2$ ,  $P = .002$ ). Those with an eGFR of less than 45 mL/min per 1.73 m<sup>2</sup> performed significantly worse

**Table 1. Demographic Characteristics and Cognitive Test Results from the Health and Aging Brain Among Latino Elders Study Sample According to Estimated Glomerular Filtration Rate**

Characteristics and Tests	Total Sample	<45 mL/min per kg <sup>2</sup> , n = 14	45–59 mL/min per kg <sup>2</sup> , n = 20	≥60 mL/min per kg <sup>2</sup> , n = 403
Age, mean ± SD	61.3 ± 8.3	71.4 ± 8.1	68.9 ± 8.5	60.4 ± 7.7
Education, years, mean ± SD	7.7 ± 4.3	6.7 ± 5.7	7.6 ± 3.4	7.7 ± 4.3
Female, %		76	75	64
Estimated glomerular filtration rate 60 mL/min per 1.73 m <sup>2</sup> , mean ± SD	86.3 ± 17.0	36.5 ± 7.5	52.1 ± 3.9	89.8 ± 12.3
Mini-Mental State Examination score, mean ± SD	25.5 ± 4.0	21.5 ± 5.9	25.9 ± 2.5	25.7 ± 3.7
TMT Part A, seconds, mean ± SD <sup>a</sup>	63.6 ± 32.4	113.3 ± 53.8	65.9 ± 22.3	61.7 ± 30.6
TMT Part B, seconds, mean ± SD <sup>a</sup>	161.3 ± 79.0	193.7 ± 84.9	198.4 ± 81.2	158.9 ± 78.4
Wechsler Memory Scale, third edition, logical memory score, mean ± SD	18.0 ± 9.0	12.4 ± 11.7	17.7 ± 8.0	18.5 ± 8.9
Consortium for the Establishment of Registry for Alzheimer's Disease recall score, mean ± SD	4.8 ± 2.4	2.7 ± 2.3	3.3 ± 2.1	4.9 ± 2.3
CLOX1 score, mean ± SD	10.7 ± 2.5	8.2 ± 2.8	10.7 ± 2.1	10.9 ± 2.4
CLOX2 score, mean ± SD	13.1 ± 1.7	11.1 ± 3.2	12.8 ± 1.6	13.2 ± 1.6
FAS score, mean ± SD	24.0 ± 10.4	21.5 ± 14.9	23.6 ± 11.4	24.3 ± 10.2
Animal naming, mean ± SD	15.4 ± 4.7	12.0 ± 5.3	14.0 ± 4.1	15.6 ± 4.6
Executive interview score, mean ± SD <sup>a</sup>	9.8 ± 4.7	13.1 ± 4.5	10.9 ± 5.7	9.6 ± 4.6

SD = standard deviation; TMT = Trail-Making Test; CLOX = clock drawing; FAS = functional assessment score.

All scores are raw values.

<sup>a</sup> Higher scores indicate poorer performance; for all other tests, higher scores indicate better performance.

than those with an eGFR or 60 mL/min per 1.73 m<sup>2</sup> or greater on delayed memory (CERAD List Recall,  $F = 3.8$ ,  $P = .02$ ). Individual differences between pairs of means are shown in Table 2.

In the logistic regression model (age, education, glucose, hemoglobin, eGFR < 60 mL/min per 1.73 m<sup>2</sup> entered into model), there was a trend toward those with an eGFR less than 60 mL/min per 1.73 m<sup>2</sup> having a greater risk of a diagnosis of MCI, but the difference was not statistically significant, probably because of sample size (odds ratio (OR) = 2.4, 95% confidence interval (CI) = 0.91–6.1,  $P = .07$ ). When the analyses were split according to sex, an eGFR or less than 60 mL/min per 1.73 m<sup>2</sup> was significantly associated with greater risk of MCI in men (OR = 9.6, 95% CI = 1.3–74.3,  $P = .03$ ).

Next, the sample was split into those with an eGFR of less than 60 mL/min per 1.73 m<sup>2</sup> ( $n = 14$  with MCI, 12 with available proteomic data) and those with an eGFR or 60 mL/min per 1.73 m<sup>2</sup> or greater ( $n = 68$  with MCI, 22 with available proteomic data) to examine the ability of the proteomic profile approach to detect CKD-related MCI. First, the top markers from previously published AD algorithm were used (IL5, IL6, IL7, IL10, tumor necrosis factor alpha, CRP, tenascin C, intercellular adhesion molecule 1),<sup>25</sup> which was 95% accurate in detecting AD. This profile was poor at detecting CKD-related MCI (sensitivity 0.50, specificity 0.87), although when the full 21-protein signature was examined, a select serum biomarker panel including FVII, IL10, CRP, and FABP was 93% accurate at identifying individuals with MCI in the group with an eGFR or less than 60 mL/min per 1.73 m<sup>2</sup> (sensitivity 86%, specificity 100%). The same set of markers was 85% accurate in detecting MCI in the group with an eGFR of 60 mL/min per 1.73 m<sup>2</sup> or less, although the 98% specificity but only 24% sensitivity biased this. Therefore, the CKD-MCI algorithm is different from an AD algorithm or an algorithm of MCI most likely due to an underlying classic amyloid pathology of AD. Three participants with CKD and 49 with an eGFR of 60 mL/min per 1.73 m<sup>2</sup> or higher were classified as having pre-MCI. The same algorithm was 100% correct at identifying individuals with an eGFR of less than 60 mL/min per 1.73 m<sup>2</sup>

with pre-MCI cases, but the serum biomarkers did not correctly identify any of the pre-MCI cases in participants with an eGFR of 60 mL/min per 1.73 m<sup>2</sup> (Table 3). The classification of each participant according to eGFR grouping (true positive, true negative, false positive, false negative) can be found in Table 4. After 12 months, two cognitively normal participants with an eGFR of less than 60 mL/min per 1.73 m<sup>2</sup> converted to MCI, and the biomarker algorithm was 100% accurate in predicting this conversion, but the algorithm did not detect any of the eight participants who were cognitively normal at baseline with an eGFR of 60 mL/min per 1.73 m<sup>2</sup> or greater who progressed to MCI.

**Table 3. Sensitivity and Specificity of Biomarker Profile in Detecting Mild Cognitive Impairment (MCI) and Pre-MCI in Individuals with Chronic Kidney Disease (CKD)**

Diagnostic Category	Sensitivity (95% CI)	Specificity (95% CI)
CKD and MCI	0.86 (0.58–0.98)	1.00 (0.78–1.00)
CKD no MCI	0.24 (0.14–0.35)	0.98 (0.81–0.88)
CKD and pre-MCI	1.00 (0.71–1.00)	1.00 (0.50–1.00)
CKD no pre-MCI	0.00 (0.00–0.00)	1.00 (0.00–0.96)

CI = confidence interval.

**Table 4. Categorization of Mild Cognitive Impairment (MCI) and Pre-MCI Using Proteomic Profile**

Estimated Glomerular Filtration Rate Predicted MCI	MCI		Pre-MCI	
	Yes	No	Yes	No
<60				
Yes	12 (100)	2 (12)	11 (100)	0 (0)
No	0 (0)	15 (88)	0 (0)	3 (100)
≥60				
Yes	16 (73)	52 (15)	0 (0)	49 (16)
No	6 (27)	306 (85)	0 (0)	258 (84)

**Table 2. Adjusted Models of Effect of Estimated Glomerular Filtration Rate on Cognitive Ability**

Cognitive Test	<45 vs 45–59 mL/min per 1.73 m <sup>2</sup>	<45 vs ≥60 mL/min per 1.73 m <sup>2</sup>	45–59 vs ≥60 mL/min per 1.73 m <sup>2</sup>
	Differences Between Pairs of Means ± Standard Deviation ( <i>P</i> -Value)		
Mini-Mental State Examination	–2.6 ± 0.9 (.005)	–4.0 ± 1.1 (<.001)	1.3 ± 0.7 (.06)
TMT Part A	36.9 ± 7.3 (<.001)	43.9 ± 9.0 (<.001)	–6.9 ± 5.9 (.24)
TMT Part B	16.1 ± 25.5 (.52)	4.9 ± 29.7 (.86)	11.2 ± 17.1 (.51)
Wechsler Memory Scale, third edition, logical memory	–2.3 ± 2.2 (.29)	–3.9 ± 2.8 (.16)	1.5 ± 1.9 (.42)
Consortium for the Establishment of Registry for Alzheimer's Disease Recall	–1.4 ± 0.6 (.03)	–0.4 ± 0.7 (.52)	–0.8 ± 0.6 (.06)
CLOX1	–1.7 ± 0.5 (.005)	–2.01 ± 0.8 (.006)	0.3 ± 0.5 (.44)
CLOX2	–1.3 ± 0.4 (.002)	–1.2 ± 0.5 (.02)	–0.1 ± 0.3 (.77)
FAS	–0.2 ± 2.6 (.92)	0.4 ± 3.2 (.88)	–0.7 ± 2.1 (.72)
Animal naming	–1.7 ± 1.1 (.14)	–1.4 ± 1.4 (.30)	–0.2 ± 0.9 (.80)
Executive interview	2.1 ± 1.3 (.10)	1.9 ± 1.6 (.22)	0.2 ± 1.0 (.84)

TMT = Trail-Making Test; CLOX = clock drawing; FAS = functional assessment score.

## DISCUSSION

Numerous studies have clearly demonstrated the association between MCI and CKD.<sup>16–19</sup> The decline in cognitive function affects all domains, including executive function, verbal memory, visuospatial skills, and attention span. In the current study, the degree of cognitive impairment appeared to be positively related to the severity of renal disease. The worse the renal function was, the greater the cognitive deficit. Cognitive impairment was also found to progress more rapidly in individuals with CKD.

The association between cognitive impairment and CKD is not surprising. Many of the same risk factors are responsible for both. In individuals with CKD and cognitive impairment, cerebrovascular disease may play a larger role in cognitive loss than Alzheimer's disease or other neurodegenerative etiologies,<sup>33</sup> and this requires additional attention, yet even after adjusting for numerous cardiovascular risk factors, CKD remains an independent risk factor for cognitive impairment.<sup>20</sup> A common pathology may be endothelial dysfunction, which is associated with MCI and CKD.<sup>10</sup> Inflammatory and metabolic determinants can cause endothelial dysfunction.

This study is the first to characterize the relationship between CKD and MCI in a Mexican-American population using detailed neuropsychological testing. Previous studies showing the association between CKD and MCI used only general, brief screening tests.<sup>20,21</sup> The importance of understanding MCI better in Mexican Americans with CKD cannot be overstated. Cognitive decline worsens disease outcomes. Mexican Americans are the fastest-growing segment of the U.S. population and have a high risk of ESRD. This excess risk may be due to socioeconomic factors, poor health literacy, poor diabetes mellitus control, lack of use of appropriate medications, and poor blood pressure control.<sup>34–36</sup> At any stage of CKD, Hispanics have higher levels of proteinuria than their non-Hispanic counterparts, suggesting a greater degree of endothelial dysfunction. In prior work, neither diabetes mellitus status nor glycosylated hemoglobin levels were related to risk of MCI in Mexican Americans,<sup>15</sup> which has held in the HABLE cohort, but given prior work demonstrating that metabolic dysfunction from a proteomic profile approach is related to AD in Mexican Americans and the link between CKD and diabetes mellitus, it is important that future work examine whether diabetes mellitus mediates the link between CKD and MCI in Mexican Americans in light of the prevalence of diabetes mellitus in this ethnic minority group.

The present study also demonstrates that a serum biomarker panel including FVII, IL10, CRP, and FABP is 93% accurate at identifying MCI in individuals with CKD (sensitivity 86%, specificity 100%). IL10 and CRP are markers of inflammation, and FABP is strongly related to metabolic functioning. In prior work examining the biomarker profile of AD in Mexican Americans, the profile was heavily weighted toward metabolic factors (e.g., FABP, glucagon-like peptide-1, pancreatic polypeptide), whereas it was shown here that the biomarker profile of CKD-related MCI is largely inflammatory in nature. Therefore, the CKD-MCI profile is significantly different from the AD profile in Mexican Americans. In addition,

the CKD-MCI profile did not predict MCI in Mexican Americans without CKD. Inflammation has been a critical factor in the AD biomarker profile in non-Hispanics, but the AD biomarker profile was not accurate in detecting CKD-related MCI. This work further highlights the need to refine the MCI nosology, specifically to target medical conditions that can affect cognition. It is likely that the biomarker profile of MCI will vary significantly from one condition (e.g., diabetes mellitus-related MCI) to the next (e.g., CKD-related MCI) and that interventions targeting cognition will therefore need to be different. Using the HIS as an index of vascular burden, HIS scores are significantly related to MCI in non-Hispanics but not Hispanics, which would suggest that, in Hispanic Americans, inflammation might play a greater role in MCI than traditional vascular factors. The greater inflammation in Hispanics may also explain their greater degree of proteinuria.

Because of the differences not only in the rate of progression of renal disease, but also in the risk factors for MCI in Hispanics, it is important to study this ethnic group in more detail to validate this group of blood-based biomarkers. Such studies will enable the association between CKD and MCI to be better characterized and will enable more-targeted interventions to be developed to prevent or at least slow the progression of CKD and MCI.

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**Author Contributions:** Szerlip, O'Bryant: conceptual design, statistical analysis, interpretation of results, drafting of manuscript. Edwards, Williams, Vintimilla, Johnson: interpretation of results, drafting of manuscript, revisions. All authors read and approved the final manuscript.

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