Biomarkers of Renal Function and Cognitive Impairment in Patients With Diabetes

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FOR THE ACTION TO CONTROL CARDIOVASCULAR RISK IN DIABETES MEMORY IN DIABETES (ACCORD-MIND) SUBSTUDY INVESTIGATORS*

OBJECTIVE—Kidney disease is associated with cognitive impairment in studies of nondiabetic adults. We examined the cross-sectional relation between three measures of renal function and performance on four measures of cognitive function in the Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes (ACCORD-MIND) study.

RESEARCH DESIGN AND METHODS—The relationships among estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (n = 2,968), albumin/creatinine ratio (ACR) ≥30 μg/mg (n = 2,957), and cystatin C level >1.0 mg/L (n = 532) with tertile of performance on the Mini-Mental State Examination, Rey Auditory Verbal Learning Test (RAVLT), Digit Symbol Substitution Test (DSST), and Stroop Test of executive function were measured.

RESULTS—In adjusted logistic regression models, ACR ≥30 μg/mg was associated with performance in the lowest tertile, compared with the highest two tertiles, on the RAVLT (odds ratio 1.30, 95% CI 1.09–1.56, P = 0.006), equivalent to 3.6 years of aging, and on the DSST (1.47, 1.20–1.80, P = 0.001), equivalent to 3.7 years of aging. Cystatin C >1.0 mg/L was borderline associated with the lowest tertile on the DSST (1.81, 0.93–3.55, P = 0.08) and Stroop (1.78, 0.97–3.23, P = 0.06) in adjusted models. eGFR was not associated with any measure of cognitive performance.

CONCLUSIONS—In diabetic people with HbA_{1c} >7.5% at high risk for cardiovascular disease, decreased cognitive function was associated with kidney disease as measured by ACR, a measure of microvascular endothelial pathology, and cystatin C, a marker of eGFR.

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A parallel decline in renal function and cognitive function has been described in people without diabetes (1,2). For example, there is a graded association between estimated glomerular filtration rate (eGFR) and cognitive function, especially at eGFR <45 mL/min/1.73 m^2 (2,3). Albuminuria (urine albumin/creatinine ratio [ACR] ≥30 μg/mg) is also associated with cognitive impairment (4). The protein kinase inhibitor cystatin C, which colocalizes with brain β-amyloid and can be used as a measure of GFR, was recently found to be significantly associated with both baseline cognitive impairment and incident cognitive decline (5).

eGFR diminishes and albuminuria increases with age, particularly in people with diabetes, in whom these conditions are highly prevalent. At age ≥60 years, ~15% of the general population and 25% of the diabetic population have eGFR <60 mL/min/1.73 m^2, and ~15 and 35%, respectively, have albuminuria (6). Diabetes is the leading cause of chronic kidney disease (CKD) in North America (7). Up to 25% of adults aged ≥65 years have type 2 diabetes, and another 25% have impaired fasting or elevated postprandial glucose levels (8).

Diabetes is also a recognized risk factor for cognitive impairment (9,10). Previously, we reported that HbA_{1c} was significantly associated with performance on cognitive tests in the Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes (ACCORD-MIND) study (10). Given the high prevalence of diabetes, CKD, and cognitive impairment in older adults, a better understanding of the association between different measures of declining renal function and cognitive impairment in people with diabetes is important. Such an understanding may lead to better means to detect and possibly prevent cognitive decline.

We examined the cross-sectional relation between three measures of renal function and four measures of cognitive function, using data from the ACCORD-MIND study (11). We postulated that at baseline, cognitive function would be lower for *1*) participants with eGFR <60 mL/min/1.73 m^2 than for participants with eGFR ≥60 mL/min/1.73 m^2; *2*) participants with albuminuria than for participants without albuminuria; and *3*) participants with elevated cystatin C levels than for participants with lower cystatin C levels.

RESEARCH DESIGN AND METHODS

—The ACCORD trial was a randomized controlled trial of 10,251 people with established type 2 diabetes

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who were at high risk for cardiovascular disease and whose screening HbA_{1c} was >7.5%. The ACCORD trial goal was to determine whether *1*) intensive glycemic control, *2*) treatment to increase high-density lipoprotein cholesterol and lower triglycerides (in the context of good low-density lipoprotein cholesterol and glycemic control), and *3*) intensive treatment of systolic blood pressure (in the context of good glycemic control) could reduce the rate of cardiovascular events more than standard therapeutic approaches. The MIND substudy of 2,977 randomized ACCORD participants was designed to determine whether the rate of cognitive decline and structural brain change differed in people with diabetes treated with standard care compared with intensive care.

The design of ACCORD-MIND has been described (11). ACCORD participants aged ≥55 years who were fluent in English or Spanish, were willing to participate, and had been randomized into the main ACCORD trial for <45 days were invited to participate in the MIND substudy. After signing an informed consent form, eligible participants completed a 30-min battery of cognitive tests. To ensure that participants were not hypoglycemic at the time of cognitive testing, the tests were administered after breakfast and a capillary glucose level was measured before testing. If the result was <60 mg/dL (3.3 mmol/L), a snack was given and the capillary glucose measure was repeated within 15 min; if the repeat glucose level remained <60 mg/dL, the test was rescheduled for a different day. The battery was administered and scored (in English or Spanish) by certified study coordinators, and the data were entered centrally at the ACCORD-MIND coordinating center at Wake Forest University. The study protocol was approved by the research ethics board of each participating center.

Renal measures

eGFR based on serum creatinine was calculated using the Modification of Diet in Renal Disease study equation and expressed in mL/min/1.73 m^2 (12). Serum creatinine concentration was determined using the Roche Creatinine Plus enzymatic reagent on a Roche Double Modular P Analytic automated analyzer (Roche Diagnostics, Indianapolis, IN). The interassay precision for the low- and high-quality control samples was 2.2 and 1.4%, respectively. Concentrations of serum cystatin C were determined using the Siemens Diagnostics reagent on a Siemens Dade Behring BNII nephelometer (Siemens Diagnostics, Deerfield, IL). The interassay precision for the high- and low-quality control samples was 2.5 and 2.6%, respectively. Urine albumin was measured by the Dade Behring reagent on a Siemens Dade Behring BNII nephelometer, and urine creatinine was measured by the Roche reagent on a Roche Hitachi 917 chemistry autoanalyzer.

Measures of glycemic status

Baseline biochemical characteristics were measured in the ACCORD central laboratory. HbA_{1c} was measured by an automated high-performance liquid chromatography Tosoh G7 (Tosoh Bioscience, South San Francisco, CA) in a laboratory with National Glycohemoglobin Standardization Program level I certification for traceability to the Diabetes Control and Complications Trial reference.

Cognitive testing

Cognitive tests that measure performance in specific domains of interest were chosen because they are standardized and widely used, have well-established norms, and can be administered by nonneuropsychologists. Cognitive test administrators were trained in the MIND cognitive battery and certified as proficient. Administrators were recertified 6 months after initial certification and annually. Planned review of test administrator performance, which included review of audiotaped test sessions and examination of test materials and scores, provided ongoing quality assurance. Test administrators were given written feedback on their performance and retrained as needed. Because there were Spanish-speaking participants, verified translations of the tests into Spanish were provided.

The cognitive tests have been described (11). Briefly, the Digit Symbol Substitution Test (DSST) is a subtest of the Wechsler Adult Intelligence Scale (Third Edition) that assesses a wide array of cognitive domains, most prominently processing speed, visual–motor speed, capacity for learning, sustained attention, and working memory. The range of scores is 0 to 133, with increasing scores indicating better performance.

The Mini-Mental State Examination (MMSE) is a global screening tool for cognitive impairment shown to have adequate sensitivity to detect moderate cognitive impairment. It is administered in ~5 min. The range of scores is 0–30, with increasing scores indicating better performance.

The Rey Auditory Verbal Learning Test (RAVLT) assesses the ability to memorize and retrieve a list of 15 words five times (verbal memory). The delayed score is equal to the number of words remembered after a 10-min interval, with a maximum score of 15; higher scores indicate better performance.

The Stroop Test evaluates the ability to view complex visual stimuli and respond to one stimulus dimension while suppressing response to another dimension, an "executive" skill largely attributed to frontal-lobe function. Limits of 120 s are set for Stroop subtests I and II and 180 s for subtest III. The summary score for the Stroop Test is calculated as an "interference score" and is obtained by subtracting the Stroop II subtest score from the Stroop III subtest score. For both the Stroop II and Stroop III, the subset score is obtained by adding the time to complete the test and the number of errors for that trial. Higher scores indicate more impairment.

Measures of confounding variables and covariates

We adjusted the analyses for demographic factors and factors that may confound the relationship between cognitive function and the selected renal measures, including age, sex, race, education (highest attained level of the categories <12 years, high school education only, some college education, or more), previous cardiovascular event (defined as history of myocardial infarction, angina with ischemic changes on graded exercise test or positive imaging, or previous coronary revascularization procedures), time in years since diabetes diagnosis, HbA_{1c}, history of stroke, hyperlipidemia (defined as use of any lipid-lowering agent or untreated LDL cholesterol >130 mg/dL [3.38 mmol/L]), hypertension (defined as history of hypertension or use of any antihypertensive agents), alcohol consumption (defined as more than three drinks per week), and depression (defined as history of depression or score ≥10 on the Physicians Health Questionnaire 9, a screening instrument for depressive symptoms) (13).

Statistical methods

Each of the three renal measures was treated as a dichotomized variable. Participants with eGFR <60 mL/min/1.73 m^2 were classified with moderate or severe

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reduction in kidney function, and participants with eGFR ≥60 mL/min/1.73 m^2 were classified with normal or mild reduction in kidney function. Participants with ACR ≥30 μg/mg were defined as having albuminuria. We used an established cut point of 1.0 mg/L to classify patients with low versus moderate or elevated levels of cystatin C (14). Demographic and clinical characteristics were determined, and mean scores on the four cognitive tests were calculated for each of the two categories of renal function (high vs. low) for the three renal measures. Multiple logistic regression was used to estimate the independent relationship between each of the three renal measures and performance in the lowest tertile versus highest two tertiles on each of the four cognitive tests after controlling for the following covariates in sequential models: *1*) age, sex, race, and education (model 1); *2*) model 1 variables plus previous cardiovascular events including stroke (model 2); *3*) model 2 variables plus diabetes duration and HbA_{1c} (model 3); and *4*) model 3 variables plus history of hyperlipidemia, hypertension, alcohol consumption, current smoking status, BMI, and depression (model 4). Last, to measure the modifying effect of stroke on the association between renal impairment and cognitive function, we added an interaction term for stroke and renal impairment to model 4 for each of the three measures of renal function.

Because cystatin C levels were measured for only a subsample of 532 participants who were also recruited for brain magnetic resonance imaging in ACCORD-MIND, we compared participant characteristics listed in Table 1 between participants with and without measured cystatin C levels, using χ^2 and *t* test analyses for categoric and continuous measures, respectively. Participants with measured cystatin C levels were more likely to be nonwhite (31.0 vs. 26.6%, $P = 0.04$) and more educated (65.6 vs. 60% with some college or more education, $P = 0.01$) and less likely to have had a previous cardiovascular event (24.6 vs. 30.2%, $P = 0.01$), with slightly higher MMSE scores (27.6 vs. 27.4, $P = 0.05$). There were no significant

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Table 1—*Bivariate associations between baseline characteristics of the ACCORD-MIND cohort and measures of renal function*

	eGFR mL/min/1.73 m^2		ACR μg/mg		Cystatin C mg/L	
Characteristics	≥60	<60	<30	≥30	<1.0	≥1.0
n (%)	2,721 (91.7)	247 (8.3)	2,118 (71.6)	839 (28.4)	464 (87.2)	68 (12.8)
Age (years)	62.2 (5.7)	65.5 (6.2)	62.3 (5.8)	63.0 (5.9)	62.0 (5.5)	65.3 (6.9)
Age (years)						
55–64	70.6	48.6	69.7	66.2	72.6	52.9
65–74	25.6	41.3	26.3	28.5	23.9	35.3
≥75	3.8	10.1	4.0	5.4	3.4	11.8
Men	54.5	40.5	50.4	61.1	53.9	50.0
Education						
<12 years	13.3	10.5	12.0	15.7	11.4	8.8
High school/GED	25.1	33.6	26.2	25.2	22.0	32.4
Some college	34.9	31.2	34.7	34.6	33.2	33.8
College graduate	26.7	24.7	27.2	24.6	33.4	25.0
White race	72.3	76.5	73.8	69.7	67.2	80.9
Current smoker	12.1	9.4	11.2	13.4	12.3	23.9
BMI (kg/m^2)	33.0 (5.3)	33.4 (5.5)	32.8 (5.3)	33.3 (5.4)	32.6 (5.1)	33.5 (5.3)
Systolic BP (mmHg)	135.6 (17.6)	135.3 (19.6)	133.1 (16.8)	141.5 (18.8)	135.5 (17.4)	134.0 (22.5)
Urine albumin (μg)	8.3 (31.4)	17.7 (46.6)	1.3 (1.0)	29.2 (58.6)	5.8 (17.7)	27.7 (86.7)
HbA_{1c} (%)	8.3 (1.0)	8.2 (1.1)	8.2 (1.0)	8.5 (1.1)	8.2 (1.0)	8.0 (0.9)
Diabetes duration (years)	10.2 (7.2)	12.4 (8.4)	9.7 (7.1)	11.7 (7.8)	9.8 (7.3)	10.9 (6.9)
Secondary prevention	28.0	42.5	26.2	36.7	22.6	38.2
Previous stroke	4.9	7.3	4.1	7.7	3.0	4.4
Hyperlipidemia	63.7	70.9	64.6	63.4	68.1	63.2
Serum creatinine (mg/dL)	0.84 (0.18)	1.28 (0.20)	0.86 (0.21)	0.92 (0.24)	0.85 (0.18)	1.11 (0.20)
eGFR <60 mL/min/1.73 m^2			7.2	10.9	1.9	32.4
ACR >30 μg/mg*	27.6	37.3			25.3	47.1
Cystatin ≥1.0 mg/L	9.2	71.0	9.5	21.5		
Cognitive test scores						
MMSE	27.4 (2.5)	27.4 (2.5)	27.5 (2.5)	27.2 (2.5)	27.6 (2.5)	27.6 (2.2)
RAVLT†	7.2 (3.2)	7.4 (3.4)	7.4 (3.2)	6.7 (3.3)	7.3 (3.2)	6.7 (2.6)
DSST	52.7 (15.9)	51.7 (15.2)	53.9 (15.7)	49.2 (15.8)	53.8 (16.8)	49.3 (15.2)
Stroop Test‡	31.7 (16.4)	34.0 (17.1)	31.4 (16.0)	33.6 (18.2)	31.0 (16.8)	32.8 (14.9)
Depression score, PHQ9§	5.3 (4.8)	5.2 (4.6)	5.3 (4.7)	5.4 (5.0)	5.0 (4.7)	5.6 (4.5)

Values are expressed as mean (SD) or percent unless otherwise indicated. BP, blood pressure; GED, graduate equivalence degree; PHQ9, Physicians Health Questionnaire 9. *Albuminuria. †RAVLT scores reflect the delayed recall score. ‡The Stroop Test score is calculated as an "interference score" and is obtained by subtracting the Stroop II subtest score from the Stroop III subtest score. For both the Stroop II and Stroop III, the subset score is obtained by adding the time to complete the test and the number of errors for that trial. Higher score indicates worse performance on the Stroop Test. §PHQ9 score ≥10 suggests depression.

differences in age, sex, diabetes duration, hyperlipidemia, stroke, blood pressure, BMI, creatinine, or depression.

Sensitivity of conclusions to classification of the cognitive measures by categories of tertiles compared with continuous linear outcomes was investigated. We repeated each of the above logistic models using multiple regression, with the continuous cognitive measure being regressed on each renal measure and the covariates. We also calculated the effects of impaired renal function (albuminuria) on cognitive impairment as equivalent to a difference of "X" years of age at baseline, based on the cross-sectional linear regression analyses in which age was modeled as a yearly increment, which allowed a comparison across units of the various variables used in the analyses.

RESULTS—Characteristics of the ACCORD-MIND cohort by renal biomarker category are described in Table 1. Mean age of the entire cohort was 62.5 years; approximately half were women, most were white (16% African American, 7% Hispanic, 7% other race), 62% had attended college, and 5% had a history of stroke. Mean HbA_{1c} was 8.3%, and mean duration of diabetes was 10.4 years (means for total cohort not shown in Table 1). Participants with lower eGFR and higher cystatin C tended to be older. More men than women had lower eGFR and higher ACR. Participants with renal impairment, as defined by all three renal biomarkers, had longer diabetes duration and higher frequency of stroke.

Albuminuria (ACR ≥30 μg/mg) was associated with worse performance on all four cognitive tests, the MMSE, RAVLT, DSST, and Stroop (higher score on the Stroop indicates worse performance; Table 1). With the use of logistic regression, albuminuria was significantly associated with performance in the lowest tertile on the RAVLT verbal memory test in the fully adjusted model (odds ratio [OR] 1.30, 95% CI 1.09–1.56, $P = 0.006$) and with poor performance on the DSST measure of executive function and processing speed (1.47, 1.20–1.80, $P = 0.001$; Table 2). The effect of albuminuria was equivalent to an additional 3.56 years of age at baseline on RAVLT performance and to an additional 3.69 years on DSST performance (data not shown). There was no statistically significant relation of albuminuria with performance on the MMSE or Stroop after adjustment in logistic regression models (data not shown).

Table 2—*ORs for cross-sectional relation between albuminuria (ACR >30 μg/mg) and performance in the lowest tertile on the RAVLT and DSST cognitive tests

Models†	RAVLT‡	*P*	DSST	*P*
Unadjusted	1.57 (1.32–1.86)	<0.001	1.77 (1.50–2.09)	<0.001
Model 1	1.33 (1.11–1.60)	0.002	1.64 (1.35–1.99)	<0.001
Model 2	1.31 (1.10–1.57)	0.003	1.60 (1.31–1.95)	0.001
Model 3	1.29 (1.08–1.56)	0.006	1.48 (1.21–1.82)	0.001
Model 4	1.30 (1.09–1.56)	0.006	1.47 (1.20–1.80)	0.001

Values are expressed as OR (95% CI) unless otherwise indicated. *No significant associations between albuminuria and the MMSE or Stroop Test were found in adjusted models. †Model 1: age, sex, race, education; model 2: model 1 + history of cardiovascular disease including stroke; model 3: model 2 + diabetes duration, HbA_{1c}; model 4: model 3 + hyperlipidemia, hypertension, alcohol consumption, current smoking status, BMI, depression. ‡Delayed recall score.

eGFR <60 mL/min/1.73 m^2 was associated with worse performance on the Stroop (Table 1) but not with poor performance on any of the cognitive measures in fully adjusted logistic regression models.

Elevated cystatin C levels were associated with worse mean DSST and RAVLT scores (Table 1). Logistic regression results for cystatin C are shown in Table 3. Cystatin C >1.0 mg/L was associated with increased risk of poor performance on the DSST (OR 2.08, 95% CI 1.10–3.95, $P = 0.02$) and on the Stroop measure of executive function (1.78, 1.00–3.17, $P = 0.05$) in model 3, which adjusts for age, sex, race, education, history of cardiovascular events, diabetes duration, and HbA_{1c}. Significance was borderline in the fully adjusted logistic regression model (model 4, which also adjusts for hyperlipidemia, hypertension, alcohol consumption, current smoking status, BMI, and depression) on the DSST (1.81, 0.93–3.55, $P = 0.08$) and Stroop (1.78, 0.97–3.23, $P = 0.06$).

The interaction term for stroke with and without renal impairment (defined by albuminuria or cystatin C >1.0 mg/L) in the fully adjusted logistic regression models of the association of cognitive tests and albuminuria or cystatin C level was not significant.

Sensitivity analyses were performed to assess whether using linear outcome models instead of logistic models would change overall conclusions. Using adjusted linear regression models to explore the linear associations between renal function measure categories and raw scores on the four cognitive tests revealed no substantive differences in the conclusions from using adjusted logistic models with lowest tertile of cognitive performance as the outcome.

CONCLUSIONS—In a cohort of middle-aged and older persons with long-standing type 2 diabetes and at high risk for cardiovascular events, we found that albuminuria and elevated cystatin C levels were strongly associated with poor performance on a test of processing speed. Albuminuria was also strongly associated with lower scores on the verbal memory test. Elevated cystatin C levels were associated with poor performance on the test of executive function in adjusted models that did not include hyperlipidemia, hypertension, alcohol consumption, current smoking status, BMI, or depression. eGFR <60 mL/min/1.73 m^2 was not associated

Table 3—*ORs for cross-sectional relation between cystatin C >1.0 mg/L and performance in lowest tertile on the DSST and Stroop cognitive tests

Models†	DSST	*P*	Stroop Test	*P*
Unadjusted	1.70 (1.02–2.86)	0.04	2.11 (1.25–3.55)	0.005
Model 1	2.13 (1.14–4.00)	0.02	1.82 (1.03–3.21)	0.02
Model 2	2.03 (1.08–3.81)	0.03	1.73 (0.98–3.07)	0.06
Model 3	2.08 (1.10–3.95)	0.02	1.78 (1.00–3.17)	0.05
Model 4	1.81 (0.93–3.55)	0.08	1.78 (0.97–3.23)	0.06

Values are expressed as OR (95% CI) unless otherwise indicated. *No significant associations between cystatin C and the MMSE or RAVLT were found in adjusted models. †Model 1: age, sex, race, education; model 2: model 1 + history of cardiovascular disease; model 3: model 2 + diabetes duration, HbA_{1c}; model 4: model 3 + hyperlipidemia, hypertension, alcohol consumption, current smoking status, BMI, depression.

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with any measure of cognitive function, likely because of the small percentage of participants (8.3%) in that category, and only 34 participants (1.2% of the total) with eGFR <45 mL/min/1.73 m^2, the level at which most cognitive impairment has been shown to occur (3).

We are not aware of previous studies that have measured the cross-sectional association between albuminuria and specific cognitive domains in an exclusively diabetic population. However, one study of 205 Australian patients with diabetes reported a significant longitudinal association between baseline ACR and cognitive decline over 1.6 years using a clinical dementia rating scale (15). In another study of 140 patients aged 70 to 85 years with impaired glucose tolerance, baseline 24-h urinary albumin excretion rate was associated with 1-year cognitive decline on the MMSE and on tests of executive function.

In nondiabetic populations, albuminuria is associated with prevalent dementia. In the Cardiovascular Health Cognition Study, albuminuria was associated with increased odds of prevalent dementia, adjusted for prevalent cardiovascular disease and risk factors, lipid levels, C-reactive protein level, eGFR, and apolipoprotein *E-4* genotype (OR 1.58, 95% CI 1.09–2.30, $P < 0.02$) (4). In the National Health and Nutrition Examination Survey (NHANES) 1999–2002, among 2,049 participants aged >60 years, albuminuria on cross-sectional adjusted analyses was inversely associated with worse performance on the DSST, but only among those with peripheral arterial disease. Presence of both albuminuria and peripheral arterial disease had an additive effect on low scores.

Albuminuria, a measure of endothelial pathology, was associated with decreased verbal memory performance (RVALT) and impaired processing speed and executive function (DSST). These cognitive domains are affected in both Alzheimer disease and vascular cognitive impairment, but decreased processing speed and executive function are more commonly associated with vascular dementia, especially white matter disease. In brain imaging studies, albuminuria is associated (16,17) with brain atrophy, white matter disease, and lacunar infarcts, emphasizing its correlation with microvascular pathology. In addition, albuminuria is associated with elevated levels of inflammatory markers. Inflammation plays a role in the pathophysiology of Alzheimer disease and vascular cognitive impairment.

The effect of albuminuria was also equivalent to 3.6 years of aging on RAVLT performance, and to 3.7 years on DSST performance. This is not inconsequential. Every year, 10–15% of patients with mild cognitive impairment progress to dementia (18); thus, 3 years of cognitive aging can substantially accelerate the time from living independently to requiring supervised care in a nursing home.

Elevated levels of cystatin C were associated with worse performance on the DSST and Stroop Test. Cystatin C is a protein kinase inhibitor produced by all cells. As a measure of renal function, cystatin C is less dependent on muscle mass (19) than creatinine-based measures and a more reliable measure of renal function in the elderly. Although cystatin C is a measure of renal function, whether its association with cognitive impairment is due to decreased renal function or to other mechanisms is unclear. For example, cystatin C colocalizes with amyloid in the human brain, especially in areas affected earliest in Alzheimer disease (the hippocampus and entorhinal cortex) (20). Polymorphisms of the *cystatin C* gene have also been reported to be associated with risk of Alzheimer disease (21). In epidemiologic studies, higher levels of cystatin C have been associated with impaired performance on the MMSE and DSST (5). In brain magnetic resonance imaging studies, elevated cystatin C levels are associated with 25–40% increased risk of prevalent lacunar infarcts and white matter lesions (16,22).

On the basis of our findings, one may hypothesize that injury to the brain and kidneys share parallel trajectories through microvascular disease processes (3). Impaired endothelial function in the brain is manifested by defects in the blood–brain barrier and increased amyloid transport and formation (23), and by susceptibility to lacunar infarcts and white matter changes (24). In the kidney, impaired glomerular endothelial function leads to albuminuria, which in turn triggers tubulointerstitial inflammation, secondary renal fibrosis, and progression of CKD (25).

Given that our results are cross-sectional, these hypotheses cannot be proven through this study, and longitudinal data are needed. Our cystatin C findings are limited by the relatively small subsample of participants with measured cystatin C levels; further, levels were elevated for only 13%, limiting our power to detect anything but large effects. Because participants with and without measured cystatin levels differed significantly regarding race (more nonwhites with measured cystatin C), education (higher for people with measured cystatin C), history of cardiovascular events (fewer for people with measured cystatin C), and MMSE scores (higher for people with measured cystatin C), the associations between elevated cystatin C and worse cognitive performance cannot be generalized to the remainder of the ACCORD-MIND population. However, taken together, the direction of the combined differences in demographic factors between people with and without measured cystatin C overall does not suggest a higher risk of cognitive impairment for those with measured cystatin C.

In conclusion, we found that the renal biomarkers albuminuria and cystatin C were associated with impaired verbal memory and executive function in people with diabetes at high risk for cardiovascular disease. Because recent studies have indicated that impairment in these cognitive domains predicts further cognitive decline (15), use of these renal biomarkers to screen diabetic patients for cognitive decline should be considered to enable appropriate timing of potential protective interventions.

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A.M.M. researched data, contributed to discussion, and drafted the manuscript. J.I.B. contributed to discussion and to drafting, reviewing, and revising the manuscript. J.F.L. researched data and reviewed and revised the manuscript. J.D.W. contributed to discussion and reviewed and revised the manuscript. M.E.M. and S.M. researched data and reviewed and revised the manuscript. L.J.L. contributed

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