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Associations Between Early Kidney Disease With Brain Magnetic Resonance Imaging and Cognitive Function in African Americans With Type 2 Diabetes Mellitus

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*The AA-DHS MIND and ACCORD MIND Investigators are listed in Murray et al¹¹ and at <http://fmri.wfubmc.edu/research/AADHSMind>, respectively.

Supplementary Material

Table S1: Demographic and laboratory characteristics of African American ACCORD MIND participants with MRI scan.

Table S2: Demographic and laboratory characteristics of AA-DHS MIND participants, by UACR.

Table S3: Demographic and laboratory characteristics of African American ACCORD MIND participants, by UACR.

Table S4: Comparison between association effect sizes of UACR and eGFR with effect of aging on cognitive function and MRI volumetric measures.

Note: The supplementary material accompanying this article (doi: _____) is available at www.ajkd.org

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Abstract

Background—Relationships between early kidney disease, neurocognitive function and brain anatomy are poorly defined in African Americans with type 2 diabetes mellitus (T2DM).

Study Design—Cross-sectional associations were assessed between cerebral anatomy and cognitive performance with estimated glomerular filtration rate (eGFR) and urinary albumin-creatinine ratio (UACR) in African Americans with T2DM.

Setting a& Participants—African Americans with cognitive testing and cerebral magnetic resonance imaging (MRI) in the African American–Diabetes Heart Study Memory in Diabetes (AA-DHS MIND; n=512; 480 with MRI) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) MIND (n=484; 104 with MRI) studies.

Predictors—eGFR (CKD-EPI creatinine equation), spot UACR.

Measurements—MRI-based cerebral white matter volume (WMV), gray matter volume (GMV), and white matter lesion volume (WMLV); cognitive performance (Mini-Mental State Examination, Digit Symbol Coding, Stroop test, and Rey Auditory Verbal Learning Test). Multivariable models adjusted for age, sex, body mass index, scanner, intracranial volume, education, diabetes duration, hemoglobin A1c, low-density lipoprotein cholesterol, smoking, hypertension and cardiovascular disease were used to test for association between kidney phenotypes and the brain in each study; a meta-analysis was performed.

Results—Mean participant age was 60.1±7.9 (SD) years; diabetes duration, 12.1±7.7 years; hemoglobin A1c, 8.3%±1.7%; eGFR, 88.7±21.6 ml/min/1.73 m²; and UACR, 119.2±336.4 mg/g. In the fully-adjusted meta-analysis, higher GMV associated with lower UACR (p<0.05), with a trend toward association with higher eGFR. Higher WMLV was associated with higher UACR (p<0.05) and lower eGFR (p<0.001). WMV was not associated with either kidney parameter. Higher UACR was associated with lower Digit Symbol Coding performance (p<0.001) and a trend toward association with higher Stroop interference; eGFR was not associated with cognitive tests.

Limitations—Cross-sectional; single UACR measurement.

Conclusions—In African Americans with T2DM, mildly high UACR and mildly low eGFR were associated with smaller GMV and increased WMLV. UACR was associated with poorer processing speed and working memory.

Keywords

African American; brain; albuminuria; chronic kidney disease (CKD); type 2 diabetes mellitus (T2DM); cognitive performance; neurocognitive function; estimated glomerular filtration rate (eGFR); urinary albumin-creatinine ratio (UACR); magnetic resonance imaging (MRI)

Compared with the general population, people with type 2 diabetes mellitus (T2DM) and advanced chronic kidney disease (CKD) have higher rates of cognitive dysfunction, more cerebral atrophy, and increased severity of white matter lesions on brain magnetic resonance imaging (MRI) scans.^{1–7} The associations of mildly reduced estimated glomerular filtration rate (eGFR) and albuminuria (typically assessed as the spot urine albumin-creatinine ratio [UACR]) on brain anatomy and function have been assessed less often, even though these disorders make up a much larger percentage of the population with CKD. Several studies from predominantly European-derived cohorts have associated subtle declines in executive function and possible MRI findings with mild kidney disease in people with diabetes.^{8, 9} The relationship between mild reductions in eGFR and low level albuminuria with brain structure and function are not well studied in African Americans with T2DM. Although it is logical to assume that these relationships would be the same as in European Americans, differences in susceptibility to T2DM, subclinical cardiovascular disease, kidney disease, and risk of cognitive decline exist between people of African and European descent.¹⁰ Brain findings may therefore differ between European Americans and African Americans and variable access to medical care may further confound relationships between brain and kidney disease in the context of diabetes.

The objective of this study was to examine whether early markers of kidney disease are associated with cognitive impairment and brain MRI changes in African Americans with T2DM. Two African American cohorts with access to medical care were analyzed. Participants had extensive cognitive function testing and brain MRI scans. In contrast to existing reports, these well characterized participants had generally preserved kidney function with low levels of albuminuria, as well as frequent receipt of medications to control blood pressure, blood sugar and serum lipids.

Methods

Setting

The African American–Diabetes Heart Study Memory in Diabetes (AA-DHS MIND) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) MIND studies evaluated cognitive performance and brain volumes with cerebral MRI in African Americans with T2DM.^{11–15} AA-DHS MIND is an observational genetic and epidemiologic study that assesses relationships between T2DM, cardiovascular disease, brain anatomy and neurocognitive function. ACCORD was designed to determine if intensive lowering of blood sugar levels, intensive lowering of blood pressure levels, or treatment of blood lipids with a fibrate drug plus a statin drug can reduce the risk of major cardiovascular disease events in patients with T2DM who are at especially high risk of cardiovascular disease.

Study Size and Participants

The sample consisted of all self-reported African Americans with T2DM enrolled in the Wake Forest School of Medicine AA-DHS MIND study and all African Americans with T2DM who were recruited in the ACCORD MIND sub-study. Detailed AA-DHS MIND methods have been reported.^{13, 14} AA-DHS consists of 717 participants with T2D actively treated with insulin and/or oral agents; those with known serum creatinine concentrations >2

mg/dL were not recruited. A total of 292 AA-DHS participants were re-examined in the AA-DHS MIND with cerebral MRI and cognitive testing and another 220 individuals meeting identical inclusion criteria were later recruited. ACCORD was a randomized, multi-center 2×2 factorial design trial that assessed two levels of hemoglobin A1c (HbA1c) control (standard versus intensive) on adjudicated major cardiovascular disease events; lipid lowering (with a statin with or without a fibrate) and blood pressure control arms (standard versus intensive) were also included. ACCORD MIND was an ancillary study that assessed the effects of blood sugar, blood pressure, and lipid lowering on cognitive function.^{11, 12} Detailed recruitment strategies have been reported for both studies.^{11–14} Medication, medical and education histories were collected and body mass index (BMI) and blood pressure recorded in all participants. These studies were approved by their respective Institutional Review Boards and adhered to the principles of the Declaration of Helsinki. All participants provided written informed consent.

Data Sources and Measurement

Biochemical Measures—Measures of HbA1c, fasting glucose and lipids were performed. Albuminuria was quantitated with a spot UACR, and eGFR was computed using the CKD-EPI (CKD Epidemiology Collaboration) equation based on isotope-dilution mass spectrometry–validated serum creatinine concentrations in each study.¹⁶

Cognitive Testing—Partially overlapping cognitive batteries were administered to AA-DHS MIND and ACCORD MIND participants. Analyses included the four cognitive tests performed in both studies. The Digit Symbol Coding test (subtest of Wechsler Adult Intelligence Scale) primarily reflects processing speed and, to a lesser extent, working memory.¹⁷ Digit Symbol Coding score was defined as the number of correct responses within 2 minutes; a higher score indicates better performance. Response inhibition, a component of executive function, was assessed with a 40-item version of the Stroop task.¹⁸ The interference score is reported, computed as [time to completion Stroop 3 + errors Stroop 3] – [time to completion Stroop 2 + errors Stroop 2], where higher scores reflect poorer executive function. The Rey Auditory Verbal Learning Test (RAVLT) is a 15-item word list recall task that tests verbal memory and learning. The RAVLT measures delayed recall, which reflects the number of words correctly recalled after a 25-minute delay ranging from 0 (worst) to 15 (best). Global cognition was assessed in the AA-DHS MIND with the Modified Mini-Mental State Examination (3MS)¹⁹ and Montreal Cognitive Assessment²⁰ and in ACCORD MIND with the Mini-Mental State Examination (MMSE)²¹. Analyses of global cognition in this report were limited to 3MS results from AA-DHS MIND and MMSE from ACCORD MIND.

Cerebral Magnetic Resonance Imaging—Detailed MRI imaging methods for the AA-DHS MIND have been reported.^{22, 23} Of 512 participants, 480 underwent MRI scanning: 61 had 1.5-T and 419 had 3.0-T MRI scans; cognitive testing was performed and kidney phenotypes determined on the day of the MRI. Fifteen individuals underwent both 1.5-T and 3.0-T scans to account for between-scanner variation, and adjustments were made in structural brain volumes based on any systematic differences in volumetric measures, as described.^{22, 23} In AA-DHS MIND, structural analysis of the T1-weighted images (for total

intracranial volume [TICV] comprised of gray matter volume [GMV], white matter volume [WMV] and cerebrospinal fluid volume; GMV; and WMV) was performed using the SPM8²⁴ new segment procedure as implemented in the VBM8 toolbox.²⁵ WMLV was computed from the fluid-attenuated inversion recovery (FLAIR) images using the lesion segmentation toolbox,²⁶ for SPM8 and an optimized threshold (k) of 0.25 as previously described.²² ACCORD MIND MRI analyses (described in next paragraph) excluded the cerebellum, while the VBM8 pipeline uses a whole brain template. In order to make the values more comparable, the VBM8 results were masked to exclude the cerebellum.

ACCORD MIND 1.5-T MRI scans were performed on participants from the study sites at Columbia University, Wake Forest School of Medicine, and the University of Minnesota. MRI scans were offered to all participants until the pre-specified sample of 640 scans was complete. Of these 640 MIND participants, 104 were African American. Scans were performed a median of 49 days after cognitive testing and kidney phenotypes had been measured. ACCORD MIND MRI included a three-dimensional fast spoiled gradient-echo T1-weighted (repetition time, 21 ms; flip angle, 30°; echo time, 8 ms), two-dimensional axial fast spin-echo FLAIR (repetition time, 8000 ms; inversion time, 2000 ms; echo time, 100 ms), and proton-density/T2-weighted (repetition time, 3200 ms; echo time_{1,2}=27 ms and 120 ms) sequences. Image data was analyzed at the ACCORD-MIND MRI Center at the Department of Radiology, University of Pennsylvania School of Medicine (R.N.B.). Processing of MRI sequences involved template registration and semi-automated segmentation.^{27–30} Using a previously validated but conservative technique called white matter lesion segmentation, abnormality maps based on structural MRI (proton density, T1-weighted, T2-weighted, FLAIR) were used to identify WML.^{27–30} White matter lesion segmentation is a support vector machine classifier trained on expert human manual segmentation of WML on FLAIR images that strongly correlates with human observer definition of WML. Both studies provided measures of GMV, WMV and WMLV.

Statistical Methods

General linear models were fitted separately for each study to test for association between measures of kidney function with MRI and cognitive test outcomes. Box-Cox³¹ transformations were applied where appropriate to ensure that the distributional assumptions of conditional normality and homogeneity of variance of the residuals were satisfied. Because different transformations were applied within AA-DHS-MIND and ACCORD-MIND, the resulting model coefficients are on different transformed scales, and are difficult to compare directly. To aid interpretation, the inverse of the Box-Cox transformation was applied separately in each dataset to provide association parameters that are interpretable on the original measurement scale.³² Standardized coefficients ($\hat{\beta}/\hat{\sigma}$) are presented, where $\hat{\beta}$ represents the parameter estimates associated with the kidney function measure and $\hat{\sigma}$ denotes the estimated residual standard deviation from the Box-Cox transformed regression model. In AA-DHS-MIND, a minimally adjusted model was fitted including age, sex, TICV and MRI scanner (1.5 T versus 3 T) as covariates for MRI outcomes. The minimally adjusted models fitted with the ACCORD-MIND data were adjusted for age, sex, total brain volume (comprised of WMV plus GMV), and further adjusted for study site. Fully adjusted

models were fitted in each dataset separately. These models, in addition to the covariates included in the minimally-adjusted model, also adjusted for education level, BMI, HbA1c and hypertension. Diagnostic tests performed on the model residuals showed that the assumptions underlying the linear models were met. Similar models were used for testing for association between the kidney function measures and cognitive tests. The minimally-adjusted models included age, sex and education level as covariates in AA-DHS-MIND, and age, sex, education level and study site in ACCORD-MIND. The fully-adjusted models were further adjusted for BMI, HbA1c, hypertension (yes/no), and low-density lipoprotein (LDL) cholesterol levels. Inverse variance meta-analysis of the results observed separately in the two studies was performed using the standardized coefficients. The approach we employed controlled for minor differences in administration or test composition between studies (*e.g.*, 3MS and MMSE). We also provide estimated I^2 values, a measure of the heterogeneity between studies.

In contrast to AA-DHS MIND where 480 of 512 (93.8%) of participants had an MRI, 104 of 484 (21.5%) of African American ACCORD MIND participants had an MRI; this rate was similar to that in all ACCORD MIND participants where 640 of 2972 (21.5%) had an MRI.

Results

A total of 996 self-reported African Americans with T2DM were evaluated with cognitive testing; 512 participants from AA-DHS MIND (480 of whom had an MRI) and 484 participants from ACCORD MIND (104 of whom had an MRI). Approximately 62% of participants were female, with mean participant age of 60.1 ± 7.9 (standard deviation) years; T2DM duration, 12.1 ± 7.7 years; HbA1c, $8.3\% \pm 1.7\%$; eGFR, 88.7 ± 21.6 ml/min/1.73 m²; and UACR, 119.2 ± 336.4 mg/g. Demographic and laboratory characteristics of AA-DHS MIND and ACCORD MIND participants, respectively, are presented in Tables 1 and 2. The demographic and laboratory results of the African American ACCORD MIND subset with an MRI (Table S1, available as online supplementary material) were similar to those of the full sample of African Americans in ACCORD MIND (Table 2).

Frequencies of kidney disease (defined as UACR >30 mg/g and/or eGFR <60 ml/min/1.73m²) were nearly identical in each study: 193 of 512 (37.7%) in AA-DHS MIND and 184 of 484 (38.0%) in ACCORD MIND. Levels of eGFR were also generally preserved (mean, 88–89 ml/min/1.73m²), with median UACRs of 10.0 mg/g in AA-DHS MIND and 13.64 mg/g in ACCORD MIND participants. Among AA-DHS MIND participants, 130 (25.4%) had UACR >30 mg/g and eGFR ≥ 60 ml/min/1.73m², 33 (6.5%) had UACR <30 mg/g and eGFR <60 ml/min/1.73m², 30 (5.9%) had UACR >30 mg/g and eGFR <60 ml/min/1.73m², and 319 (62.3%) had UACR ≤ 30 mg/g and eGFR ≥ 60 ml/min/1.73m². The number of ACCORD MIND participants with UACR >30 mg/g, eGFR <60 ml/min/1.73m², or both were 148 (30.6%), 20 (4.1%), and 19 (3.9%), respectively. Table S2 and S3, respectively, display characteristics of AA-DHS MIND and ACCORD MIND participants based on levels of UACR. Systolic blood pressure, HbA1c, and use of statins were slightly higher in ACCORD MIND participants; baseline LDL cholesterol and high-density lipoprotein cholesterol levels were similar across studies.

The results of association analyses between kidney phenotypes UACR and eGFR with cerebral volumes are reported in Table 3. Model 1 adjusted for MRI scanner, TICV (AA-DHS) or total brain volume (ACCORD), age and sex; Model 2 adjusted for the covariates in Model 1 plus level of education, BMI, HbA1c and presence of hypertension; Model 3 adjusted for the covariates in Model 2 plus diabetes duration, smoking and history of CVD; Model 4 adjusted for covariates in Model 3 plus eGFR; and Model 5 adjusted for covariates in Model 3 plus UACR. Findings are reported separately in each study and in a meta-analysis. Statistically significant associations were found in the fully-adjusted meta-analysis between higher UACR and lower GMV (standardized coefficient $\beta/\sigma = -2.0 \times 10^{-4}$; $p < 0.05$) and higher UACR and higher WMLV ($\beta/\sigma = 2.0 \times 10^{-4}$; $p = 0.05$), but not with WMV. Significant association was also present in the fully-adjusted meta-analysis between higher eGFR and lower WMLV ($\beta/\sigma = -6.0 \times 10^{-3}$; $p < 0.001$) and a non-significant trend was seen with higher eGFR and higher GMV ($\beta/\sigma = 4.0 \times 10^{-3}$; $p = 0.08$), but not with WMV.

Table 4 displays results of association analyses between kidney disease phenotypes and cognitive performance. Model 1 adjusted for age, sex and level of education. Model 2 adjusted for these covariates plus BMI, HbA1c, hypertension and LDL cholesterol. Model 3 adjusted for the covariates in Model 2 plus diabetes duration, smoking and history of CVD; Model 4 adjusted for covariates in Model 3 plus eGFR; and Model 5 adjusted for covariates in Model 3 plus UACR. Statistically significant relationships were not observed in meta-analyses between kidney disease parameters and global cognition (MMSE/3MS) or memory (RAVLT). In contrast, higher UACR was associated with poorer function on Digit Symbol Coding ($\beta/\sigma = -3.0 \times 10^{-4}$; $p < 0.001$) and revealed a non-significant trend toward higher Stroop interference ($\beta/\sigma = 2.0 \times 10^{-4}$; $p = 0.08$).

Using standardized parameters obtained in the meta-analysis, effect sizes for increases of 100 mg/g in UACR and reductions of 10 ml/min/1.73m² in eGFR were computed on cognitive performance and MRI volumes. Results were compared with the standardized effect of a year increase in age. In the fully-adjusted model, a 100 mg/g increase in UACR was equivalent to an aging effect of ~0.5 years on the Digit Symbol Coding, ~0.6 years on Stroop interference, and ~0.5 years on volume of abnormal white matter. A 10 ml/min/1.73m² reduction in eGFR corresponded to an aging effect of ~1.3 years (Table S4).

Discussion

Independent from age, severity of diabetes (HbA1c), diabetes duration, hypertension, lipid levels, smoking or prevalent cardiovascular disease, albuminuria and reduced kidney function were each significantly associated with abnormal white matter volume (increased WMLV), a marker of cerebral microvascular disease, and lower gray matter volume in African Americans with diabetes. Findings may explain the poorer performance on Digit Symbol Coding that was observed in African Americans with kidney disease. Although diabetes and advanced kidney disease (end-stage kidney disease) are known to be associated with cognitive dysfunction and cerebral microvascular disease in European Americans and African Americans, results in African Americans with T2DM having milder degrees of kidney disease have been less clear, particularly in those with access to healthcare. These cognitive performance and cerebral MRI data in African Americans with T2DM and

measures of kidney function and albuminuria encompass the largest such sample analyzed to date, to our knowledge. Diabetes, blood pressure, and lipid control were similar to those in participants from contemporary cohorts in other racial/ethnic groups, reducing the risk of bias of healthcare access on relationships.^{12, 33}

The present findings extend those from an interim AA-DHS MIND analysis in 263 participants.^{13, 14} Although kidney disease associations with the brain were generally consistent in the interim study and the present analyses, the current better-powered study detected significant associations between eGFR with abnormal white matter volume (and a trend with GMV) that was not initially evident. Moreover, the previously reported association between UACR and 3MS was no longer present (an association between UACR and Digit Symbol Coding remained). In contrast to the relationships between mild kidney disease and the brain in African Americans, European Americans in DHS MIND (374 T2DM-affected European Americans with mild-to-moderate kidney disease) lacked significant association between UACR and eGFR with brain volumes and cognitive function.³³ In addition, ACCORD MIND did not detect significant associations between baseline (or persistent) albuminuria with brain volumes after adjusting for age and systolic blood pressure in a predominantly non-African American T2DM-affected study population (67.7% European American, 17.3% African American, 8.8% Hispanic American, 6.2% other).¹⁵ Therefore, results from the ACCORD MIND and other published studies in European Americans with T2DM suggest that racial/ethnic-specific differences may exist in the relationships between mild kidney disease and the brain.³⁴ These findings warrant further study in multi-ethnic cohorts or meta-analyses.

It is possible that glycemic control modulates relationships between albuminuria and cognitive performance. In 2,957 T2DM-affected ACCORD MIND participants with HbA1c values >7.5%, a UACR >30 mg/g was associated with the poorest cognitive function, specifically with reduced RAVLT and Digit Symbol Coding.¹¹ In contrast, levels of cystatin C and eGFR were not associated with cognitive performance. In a longitudinal analysis, Barzilay *et al.* found that relatively young ACCORD MIND participants with persistent or progressive albuminuria showed significantly greater declines in the speed of information processing, relative to those without albuminuria; 16.2% of these participants were African American.¹² This finding was evident even in those with normal eGFR. We note that blood pressures differed somewhat between reports; the average baseline systolic blood pressure in participants with albuminuria in the Barzilay *et al.* report was 141 mm Hg,¹² contrasted with 144 mm Hg in those with kidney disease from the current study. Therefore, higher blood pressures in African Americans compared to non-African Americans could contribute to differences in the effect of albuminuria on brain structure and cognitive function.

Measures of brain structure and function have been shown to be poorer in persons with albuminuria and reduced eGFR, including in study populations with a low prevalence of diabetes.^{35–38} although a large European study failed to detect these associations.³⁹ The Nurses' Health Study demonstrated that among older women, even slightly increased levels of UACR (>5 mg/g) were associated with cognitive decline, whereas reductions in eGFR were not.⁴⁰ In the Systolic Blood Pressure Intervention Trial (SPRINT), cerebral MRI and cognitive testing were performed for 218 hypertensive non-diabetic study participants with

low eGFR; slightly more than 30% were African American.⁴¹ In these *non-diabetic* SPRINT participants, increasing albuminuria was associated with higher abnormal white matter volumes (WMLV); cognitive data were not provided. Excess albuminuria is a marker of endothelial dysfunction and related systemic microvascular disease. This can affect the coronary, neurologic, pulmonary and cerebral circulations.^{42–46}

Although this current analysis included the largest sample of African Americans with T2DM for cognitive performance and cerebral volumes of which we are aware, limitations exist. This was a cross-sectional analysis with a single measure of UACR. As such, causation between MRI-based cerebral changes and cognitive performance could not be demonstrated. Although it is likely that most participants had access to adequate healthcare based on baseline blood pressures and clinical data, healthcare access was not directly assessed. Associations between mild kidney disease with GMV, WMLV, and Digit Symbol Coding were stronger in the AA-DHS MIND than in ACCORD MIND. ACCORD examined several interventions in a sample limited to individuals with T2DM at high risk for CVD and with a baseline HbA1C >7.5%. AA-DHS MIND was observational, recruited a broader mix of participants and was better powered to detect MRI associations than ACCORD MIND due to the larger number of participants with cerebral imaging. Hence, ACCORD entry criteria may have resulted in a more narrowly defined group. White matter hyperintensity volume is known to be a reliable and common measure of macroscopic white matter disease; however, it is not a comprehensive measure of cerebral small vessel disease nor is it a sensitive measure of more extensive microscopic white matter integrity such as those obtained from diffusion tensor imaging.⁴⁷ Finally, the MMSE may provide a more limited assessment of memory functions than the 3MS.

We conclude that low level albuminuria and mildly reduced kidney function are associated with increased cerebral abnormal white matter volume and reduced gray matter volume in African Americans with T2DM. Poorer performance on Digit Symbol Coding (slower processing speed and working memory) was also present in those with higher levels of albuminuria. These results identify a subgroup of African Americans with T2DM who are at higher risk for developing reduced cognitive function and shed light on possible treatment pathways for reducing the burden of cognitive impairment–related disability in African Americans with diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Demographic and laboratory characteristics of African American AA-DHS MIND participants

Table 1

Variable at MIND Visit	All		Kidney disease absent*		Kidney disease present*		P
	N	Mean±SD; Median or %	N	Mean±SD; Median or %	N	Mean±SD; Median or %	
Age (years)	510	58.6 (9.6) 57.6	317	58.3 (9.4) 57.0	193	59.0 (9.8) 58.3	0.4
Female sex	511	60.9%	318	61.6%	193	59.6%	0.6
BMI (kg/m ²)	511	35.2 (8.4) 33.7	318	35.0 (8.3) 33.5	193	35.5 (8.6) 34.1	0.4
Education							0.1
Some High school or less	511	[12.7%]	318	[10.7%]	193	[16.1%]	
High school graduate	511	[26.4%]	318	[27.7%]	193	[24.4%]	
Technical school/Associate degree	511	[43.4%]	318	[41.5%]	193	[46.6%]	
College graduate/Post-graduate	511	[17.4%]	318	[20.1%]	193	[13.0%]	
Diabetes duration (years)	508	13.0 (7.7) 11.6	317	12.2 (7.5) 10.5	191	14.5 (7.8) 13.5	<0.001
Current or past smoker	508	[54.7%]	315	[54.3%]	193	[55.4%]	0.8
Systolic blood pressure (mm Hg)	511	131.5 (17.9) 131.0	318	128.7 (16.0) 130.0	193	136.2 (20.0) 133.0	<0.001
Diastolic blood pressure (mm Hg)	511	77.0 (11.3) 77.0	318	75.9 (10.4) 76.0	193	78.7 (12.5) 78.0	0.03
Hypertension	501	[85.8%]	310	[81.3%]	191	[93.2%]	<0.001
History of prior CVD	510	[22.5%]	317	[19.2%]	193	[28.0%]	0.02
eGFR (ml/min/1.73m ²)	511	88.2 (23.4) 89.0	318	94.3 (17.6) 93.0	193	78.0 (28.0) 78.0	<0.001
eGFR <60 ml/min/1.73m ²	511	[12.3%]	318	[0.0%]	193	[32.6%]	<0.001
eGFR <90 ml/min/1.73m ²	511	[50.1%]	318	[41.5%]	193	[64.2%]	<0.001
UACR (mg/g)	511	134.9 (380.6) 10.0	318	8.1 (7.2) 5.4	193	343.9 (560.6) 82.8	<0.001
UACR at MIND visit							
10–30 mg/g	511	[18.6%]	318	[27.0%]	193	[4.7%]	<0.001
>30 mg/g	511	[31.3%]	318	[0.0%]	193	[82.9%]	<0.001
30–300 mg/g	511	[21.1%]	318	[0.0%]	193	[56.0%]	<0.001
>300 mg/g	511	[10.2%]	318	[0.0%]	193	[26.9%]	<0.001
Serum glucose (mg/dL)	511	150.3 (63.8) 134.0	318	141.5 (53.0) 127.5	193	164.8 (76.4) 149.0	0.001
Hemoglobin A1c (%)	510	8.1 (2.0) 7.4	317	7.8 (1.9) 7.2	193	8.5 (2.1) 7.9	<0.001

Variable at MIND Visit	All		Kidney disease absent*		Kidney disease present*		P
	N	Mean±SD; Median or %	N	Mean±SD; Median or %	N	Mean±SD; Median or %	
LDL cholesterol (mg/dl)	296	110.1 (35.8) 107.0	188	104.6 (33.6) 101.0	108	119.6 (37.6) 115.0	<0.001
HDL cholesterol (mg/dl)	297	48.0 (13.1) 46.0	189	48.1 (12.4) 46.0	108	47.8 (14.4) 45.0	0.5
Use of statins	298	[50.3%]	190	[47.4%]	108	[55.6%]	0.2
Use of insulin	300	[37.3%]	192	[29.7%]	108	[50.9%]	<0.001
GMV (cm ³)	477	479.7 (55.3) 477.1	301	483.2 (51.1) 483.4	176	473.8 (61.5) 466.2	0.03
WMV (cm ³)	477	440.7 (58.0) 434.4	301	440.2 (56.8) 434.1	176	441.5 (60.2) 435.3	0.8
Total intracranial volume (cm ³)	477	1141.1 (123.5) 1134.6	301	1139.2 (117.6) 1129.7	176	1144.3 (133.3) 1142.3	0.7
WMLV, automated (cm ³)	474	7.3 (11.1) 2.6	300	6.8 (11.1) 2.0	174	8.3 (10.9) 3.9	<0.001
3MS, 0–100	511	85.9 (8.5) 87.0	318	86.6 (8.2) 88.0	193	84.7 (9.0) 86.0	0.03
RAVLT delayed recall, 0–15	504	6.5 (2.4) 6.2	315	6.5 (2.4) 6.2	189	6.5 (2.3) 6.6	0.9
Digit Symbol Coding, 0–133	503	50.0 (16.4) 49.0	315	51.6 (15.9) 50.0	188	47.3 (16.9) 47.0	0.003
Stroop Interference	501	34.4 (17.4) 31.0	315	33.5 (17.9) 30.0	186	36.0 (16.6) 32.5	0.07

Note: Conversion factors for units: cholesterol in mg/dL to mmol/L, $\times 0.02586$; glucose in mg/dL to mmol/L, $\times 0.05551$ 3MS, Modified Mini-Mental State Examination; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GMV, gray matter volume HDL, high-density lipoprotein; LDL, low-density lipoprotein; MIND, urine albumin-creatinine ratio; RAVLT, Rey Auditory Verbal Learning Test; WMV, white matter volume; SD, standard deviation; AA-DHS, African American–Diabetes Heart Study; MIND, Memory in Diabetes; ACCORD, Action to Control Cardiovascular Risk in Diabetes; WMLV, white matter lesion volume.

* Presence of kidney disease defined as eGFR < 60 ml/min/1.73m² and/or UACR > 30 mg/g

Table 2
Demographic and laboratory characteristics of African American ACCORD MIND participants

Variable at MIND Visit	All		Kidney disease absent*			Kidney disease present*			P
	N	Mean±SD; Median or %	N	Mean±SD; Median or %	N	Mean±SD; Median or %	N	Mean±SD; Median or %	
Age (years)	484	61.7 (5.7) 61.0	297	61.3 (5.4) 60	187	62.4 (6.0) 62	187	62.4 (6.0) 62	0.04
Female sex	484	[62.6%]	297	[63.0%]	187	[62.0%]	187	[62.0%]	0.8
BMI (kg/m ²)	484	32.7 (5.5) 32.1	297	32.4 (5.3) 31.6	187	33.2 (5.7) 32.7	187	33.2 (5.7) 32.7	0.2
Education									0.02
Some high school or less	484	[19.4%]	297	[15.5%]	187	[25.7%]	187	[25.7%]	
High school graduate	484	[30.6%]	297	[34.3%]	187	[24.6%]	187	[24.6%]	
Technical school/Associate degree	484	[30.8%]	297	[32.0%]	187	[28.9%]	187	[28.9%]	
College graduate/Post-graduate	484	[19.2%]	297	[18.2%]	187	[20.9%]	187	[20.9%]	
Diabetes duration (years)	478	11.0 (7.7) 10.0	293	9.7 (7.1) 8	185	13.2 (8.2) 12	185	13.2 (8.2) 12	<0.001
Current or past Smoker	483	[52.8%]	296	[50.3%]	187	[56.7%]	187	[56.7%]	0.2
Systolic blood pressure (mm Hg)	478	138.7 (18.7) 136.0	292	135.3 (17.0) 133.0	186	144.1 (19.9) 142.0	186	144.1 (19.9) 142.0	<0.001
Diastolic blood pressure (mm Hg)	478	77.2 (10.8) 77.0	292	76.7 (10.4) 77.0	186	78.0 (11.4) 77.0	186	78.0 (11.4) 77.0	0.5
Hypertension	484	[92.4%]	297	[89.9%]	187	[96.3%]	187	[96.3%]	0.01
History of prior CVD	484	[20.9%]	297	[18.9%]	187	[24.1%]	187	[24.1%]	0.2
eGFR (ml/min/1.73m ²)	484	89.2 (19.5) 91.3	297	94.1 (15.9) 94.6	187	81.3 (21.9) 80.9	187	81.3 (21.9) 80.9	<0.001
eGFR <60 ml/min/1.73m ²	484	[8.1%]	297	[0.0%]	187	[20.9%]	187	[20.9%]	<0.001
eGFR <90 ml/min/1.73m ²	484	[47.7%]	297	[37.7%]	187	[63.6%]	187	[63.6%]	<0.001
UACR (mg/g)	484	102.8 (282.7) 13.6	297	9.9 (6.7) 7.5	187	250.2 (414.5) 68.5	187	250.2 (414.5) 68.5	<0.001
UACR at MIND visit									
10–30 mg/g	484	[23.1%]	297	[35.0%]	187	[4.3%]	187	[4.3%]	<0.001
>30 mg/g	484	[34.5%]	297	[0.0%]	187	[89.3%]	187	[89.3%]	<0.001
30–300 mg/g	484	[25.2%]	297	[0.0%]	187	[65.2%]	187	[65.2%]	<0.001
>300 mg/g	484	[9.3%]	297	[0.0%]	187	[24.1%]	187	[24.1%]	<0.001
Serum glucose (mg/dL)	484	168.1 (63.5) 159.5	297	162.2 (58.3) 155	187	177.4 (70.2) 165	187	177.4 (70.2) 165	0.02
Hemoglobin A1c	483	8.6 (1.1) 8.3	296	8.5 (1.1) 8.3	187	8.7 (1.2) 8.4	187	8.7 (1.2) 8.4	0.1

Variable at MIND Visit	All		Kidney disease absent*		Kidney disease present*		P
	N	Mean±SD; Median or %	N	Mean±SD; Median or %	N	Mean±SD; Median or %	
LDL cholesterol (mg/dl)	484	110.1 (33.2) 105.0	297	110.3 (33.7) 104	187	109.8 (32.5) 107	0.7
HDL cholesterol (mg/dl)	484	48.5 (13.1) 47.0	297	48.7 (13.4) 47	187	48.1 (12.8) 47	0.7
Use of statins	484	[62.6%]	297	[64.6%]	187	[59.4%]	0.2
Use of insulin	484	[40.7%]	297	[33.7%]	187	[51.9%]	<0.001
GMV (cm ³)	104	439.6 (47.2) 427.2	69	441.1 (46.0) 425.4	35	436.8 (50.0) 428.1	0.5
WMV (cm ³)	104	441.1 (53.8) 434.5	69	440.7 (53.2) 435.9	35	441.7 (55.8) 431.0	0.9
Total brain volume (cm ³)	104	880.7 (87.9) 867.5	69	881.8 (88.0) 867.4	35	878.5 (88.8) 870.4	0.8
WMLV, automated (cm ³)	104	1.9 (3.4) 0.8	69	1.6 (2.8) 0.6	35	2.6 (4.4) 1.4	0.05
MMSE	484	26.2 (2.9) 27.0	297	26.3 (2.8) 27	187	26.1 (3.0) 27	0.6
RAVLT delayed recall, 0–15	484	7.1 (2.5) 7.0	297	7.2 (2.5) 7.2	187	6.8 (2.5) 6.8	0.1
Digit Symbol Coding, 0–133	479	44.5 (15.2) 45.0	294	45.9 (14.7) 47.0	185	42.3 (15.7) 42.0	0.005
Stroop Interference	480	38.0 (20.4) 34.0	295	36.6 (20.0) 32	185	40.1 (20.8) 36	0.04

Note: Conversion factors for units: cholesterol in mg/dL to mmol/L, $\times 0.02586$; glucose in mg/dL to mmol/L, $\times 0.05551$ MMSE, Mini-Mental State Examination; BMI, body mass index; eGFR, estimated glomerular filtration rate; GMV, gray matter volume HDL, high-density lipoprotein; LDL, low-density lipoprotein; UACR, urine albumin-creatinine ratio; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation; WMV, white matter volume; MIND, Memory in Diabetes; ACCORD, Action to Control Cardiovascular Risk in Diabetes; WMLV, white matter lesion volume.

* Kidney disease defined as eGFR <60 ml/min/1.73m² and/or UACR ≥ 30 mg/g.

Table 3

Association between kidney function measures with MRI volumetric measures

Outcome	Predictor	Model	AA-DHS MIND			ACCORD MIND			Meta-analysis		
			Parameter	SE	P	Parameter	SE	P	Parameter	SE	P ²
GMV (cm ³)	UACR	1	-4.0×10 ⁻⁴	1.0×10 ⁻⁴	<0.001	3.0×10 ⁻⁴	4.0×10 ⁻⁴	0.5	-4.0×10 ⁻⁴	1.0×10 ⁻⁴	<0.001
GMV (cm ³)	UACR	2	-4.0×10 ⁻⁴	1.0×10 ⁻⁴	<0.001	5.0×10 ⁻⁴	4.0×10 ⁻⁴	0.2	-3.0×10 ⁻⁴	1.0×10 ⁻⁴	<0.001
GMV (cm ³)	UACR	3	-4.0×10 ⁻⁴	1.0×10 ⁻⁴	<0.001	5.0×10 ⁻⁴	4.0×10 ⁻⁴	0.2	-3.0×10 ⁻⁴	1.0×10 ⁻⁴	0.01
GMV (cm ³)	UACR	4	-3.0×10 ⁻⁴	1.0×10 ⁻⁴	0.01	5.0×10 ⁻⁴	4.0×10 ⁻⁴	0.2	-2.0×10 ⁻⁴	1.0×10 ⁻⁴	0.05
GMV (cm ³)	eGFR	1	5.0×10 ⁻³	2.0×10 ⁻³	0.01	3.0×10 ⁻⁶	6.0×10 ⁻³	0.9	5.0×10 ⁻³	2.0×10 ⁻³	0.02
GMV (cm ³)	eGFR	2	6.0×10 ⁻³	2.0×10 ⁻³	<0.001	3.0×10 ⁻⁴	6.0×10 ⁻³	0.9	5.0×10 ⁻³	2.0×10 ⁻³	0.01
GMV (cm ³)	eGFR	3; 5	6.0×10 ⁻³	2.0×10 ⁻³	0.01	1.0×10 ⁻⁴	6.0×10 ⁻³	0.9	5.0×10 ⁻³	2.0×10 ⁻³	0.02
GMV (cm ³)	eGFR	5	4.0×10 ⁻³	2.0×10 ⁻³	0.07	6.0×10 ⁻⁴	6.0×10 ⁻³	0.9	4.0×10 ⁻³	2.0×10 ⁻³	0.08
WMV (cm ³)	UACR	1	-3.0×10 ⁻⁵	1.0×10 ⁻⁴	0.8	-3.0×10 ⁻⁴	4.0×10 ⁻⁴	0.5	-5.0×10 ⁻⁵	1.0×10 ⁻⁴	0.6
WMV (cm ³)	UACR	2	-5.0×10 ⁻⁶	1.0×10 ⁻⁴	0.9	-4.0×10 ⁻⁴	4.0×10 ⁻⁴	0.3	-4.0×10 ⁻⁵	1.0×10 ⁻⁴	0.7
WMV (cm ³)	UACR	3	4.0×10 ⁻⁵	1.0×10 ⁻⁴	0.8	-5.0×10 ⁻⁴	4.0×10 ⁻⁴	0.3	-8.0×10 ⁻⁶	1.0×10 ⁻⁴	0.9
WMV (cm ³)	UACR	4	2.0×10 ⁻⁵	1.0×10 ⁻⁴	0.9	-4.0×10 ⁻⁴	4.0×10 ⁻⁴	0.3	-2.0×10 ⁻⁵	1.0×10 ⁻⁴	0.8
WMV (cm ³)	eGFR	1	-4.0×10 ⁻⁴	2.0×10 ⁻³	0.9	3.0×10 ⁻³	6.0×10 ⁻³	0.6	1.0×10 ⁻⁴	2.0×10 ⁻³	0.9
WMV (cm ³)	eGFR	2	-7.0×10 ⁻⁵	2.0×10 ⁻³	0.9	3.0×10 ⁻³	6.0×10 ⁻³	0.6	3.0×10 ⁻⁴	2.0×10 ⁻³	0.9
WMV (cm ³)	eGFR	3; 5	-1.0×10 ⁻³	2.0×10 ⁻³	0.6	3.0×10 ⁻³	6.0×10 ⁻³	0.6	-7.0×10 ⁻⁴	2.0×10 ⁻³	0.8
WMV (cm ³)	eGFR	5	-1.0×10 ⁻³	2.0×10 ⁻³	0.6	3.0×10 ⁻³	6.0×10 ⁻³	0.6	-7.0×10 ⁻⁴	2.0×10 ⁻³	0.8
WMLV (cm ³)	UACR	1	4.0×10 ⁻⁴	1.0×10 ⁻⁴	<0.001	1.0×10 ⁻⁴	4.0×10 ⁻⁴	0.8	4.0×10 ⁻⁴	1.0×10 ⁻⁴	<0.001
WMLV (cm ³)	UACR	2	4.0×10 ⁻⁴	1.0×10 ⁻⁴	<0.001	1.0×10 ⁻⁴	4.0×10 ⁻⁴	0.8	4.0×10 ⁻⁴	1.0×10 ⁻⁴	<0.001
WMLV (cm ³)	UACR	3	4.0×10 ⁻⁴	1.0×10 ⁻⁴	<0.001	-1.0×10 ⁻⁵	4.0×10 ⁻⁴	0.9	3.0×10 ⁻⁴	1.0×10 ⁻⁴	<0.001
WMLV (cm ³)	UACR	4	3.0×10 ⁻⁴	1.0×10 ⁻⁴	0.04	-3.0×10 ⁻⁵	4.0×10 ⁻⁴	0.9	2.0×10 ⁻⁴	1.0×10 ⁻⁴	0.05
WMLV (cm ³)	eGFR	1	-8.0×10 ⁻³	2.0×10 ⁻³	<0.001	-5.0×10 ⁻³	6.0×10 ⁻³	0.4	-8.0×10 ⁻³	2.0×10 ⁻³	<0.001
WMLV (cm ³)	eGFR	2	-8.0×10 ⁻³	2.0×10 ⁻³	<0.001	-4.0×10 ⁻³	6.0×10 ⁻³	0.6	-8.0×10 ⁻³	2.0×10 ⁻³	<0.001
WMLV (cm ³)	eGFR	3; 5	-8.0×10 ⁻³	2.0×10 ⁻³	<0.001	-4.0×10 ⁻³	6.0×10 ⁻³	0.5	-8.0×10 ⁻³	2.0×10 ⁻³	<0.001
WMLV (cm ³)	eGFR	5	-7.0×10 ⁻³	2.0×10 ⁻³	<0.001	-4.0×10 ⁻³	6.0×10 ⁻³	0.5	-6.0×10 ⁻³	2.0×10 ⁻³	<0.001

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Note: Model 1 covariates: MRI scanner, total intracranial volume (AA-DHS) or total brain volume (ACCORD), age and sex; Model 2 covariates: Model 1 + level of education, body mass index, hemoglobin A1c, and hypertension; Model 3 covariates: Model 2 + diabetes duration, smoking status, history of cardiovascular disease; Model 4 covariates: Model 3 + eGFR; Model 5 covariates: Model 3 + UACR

SE – standard error; eGFR, estimated glomerular filtration rate (in ml/min/1.73m²); GMV, gray matter volume UACR, urine albumin-creatinine ratio (in mg/g); WMV, white matter volume; WMLV, white matter lesion volume; AA-DHS, African American–Diabetes Heart Study; MIND, Memory in Diabetes; MRI, magnetic resonance imaging; ACCORD, Action to Control Cardiovascular Risk in Diabetes.

Table 4

Association between kidney function measures with cognitive function

Outcome	Predictor	Model	AA-DHS MIND			ACCORD MIND			Meta-analysis		
			Parameter	SE	P	Parameter	SE	P	Parameter	SE	P ²
Digit Symbol Coding	UACR	1	-4.0×10 ⁻⁴	1.0×10 ⁻⁴	<0.001	-3.0×10 ⁻⁴	2.0×10 ⁻⁴	0.04	-4.0×10 ⁻⁴	1.0×10 ⁻⁴	<0.001
Digit Symbol Coding	UACR	2	-5.0×10 ⁻⁴	2.0×10 ⁻⁴	0.003	-3.0×10 ⁻⁴	2.0×10 ⁻⁴	0.1	-4.0×10 ⁻⁴	1.0×10 ⁻⁴	0
Digit Symbol Coding	UACR	3	-4.0×10 ⁻⁴	1.0×10 ⁻⁴	0.002	-2.0×10 ⁻⁴	2.0×10 ⁻⁴	0.3	-3.0×10 ⁻⁴	1.0×10 ⁻⁴	0.24
Digit Symbol Coding	UACR	4	-4.0×10 ⁻⁴	1.0×10 ⁻⁴	0.003	-2.0×10 ⁻⁴	2.0×10 ⁻⁴	0.3	-3.0×10 ⁻⁴	1.0×10 ⁻⁴	0
Digit Symbol Coding	eGFR	1	2.0×10 ⁻³	2.0×10 ⁻³	0.3	-2.0×10 ⁻³	2.0×10 ⁻³	0.5	6.0×10 ⁻⁴	2.0×10 ⁻³	0.7
Digit Symbol Coding	eGFR	2	5.0×10 ⁻³	3.0×10 ⁻³	0.05	-4.0×10 ⁻⁴	2.0×10 ⁻³	0.9	2.0×10 ⁻³	2.0×10 ⁻³	0.2
Digit Symbol Coding	eGFR	3	2.0×10 ⁻³	2.0×10 ⁻³	0.3	-2.0×10 ⁻³	3.0×10 ⁻³	0.5	6.0×10 ⁻⁴	2.0×10 ⁻³	0.7
Digit Symbol Coding	eGFR	5	7.0×10 ⁻⁴	2.0×10 ⁻³	0.8	-2.0×10 ⁻³	3.0×10 ⁻³	0.3	-7.0×10 ⁻⁴	2.0×10 ⁻³	0.7
3MS/MMSE	UACR	1	-2.0×10 ⁻⁴	1.0×10 ⁻⁴	0.2	2.0×10 ⁻⁵	2.0×10 ⁻⁴	0.9	-9.0×10 ⁻⁵	9.0×10 ⁻⁵	0.3
3MS/MMSE	UACR	2	-2.0×10 ⁻⁴	2.0×10 ⁻⁴	0.2	4.0×10 ⁻⁵	2.0×10 ⁻⁴	0.8	-8.0×10 ⁻⁵	1.0×10 ⁻⁴	0.5
3MS/MMSE	UACR	3	-2.0×10 ⁻⁴	1.0×10 ⁻⁴	0.1	3.0×10 ⁻⁵	2.0×10 ⁻⁴	0.9	-1.0×10 ⁻⁴	1.0×10 ⁻⁴	0.2
3MS/MMSE	UACR	4	-2.0×10 ⁻⁴	1.0×10 ⁻⁴	0.1	3.0×10 ⁻⁵	2.0×10 ⁻⁴	0.8	-1.0×10 ⁻⁴	1.0×10 ⁻⁴	0.3
3MS/MMSE	eGFR	1	4.0×10 ⁻⁴	2.0×10 ⁻³	0.8	-5.0×10 ⁻⁶	2.0×10 ⁻³	0.9	2.0×10 ⁻⁴	2.0×10 ⁻³	0.9
3MS/MMSE	eGFR	2	2.0×10 ⁻³	3.0×10 ⁻³	0.5	8.0×10 ⁻⁴	2.0×10 ⁻³	0.7	1.0×10 ⁻³	2.0×10 ⁻³	0.5
3MS/MMSE	eGFR	3	1.0×10 ⁻³	2.0×10 ⁻³	0.6	8.0×10 ⁻⁴	3.0×10 ⁻³	0.8	1.0×10 ⁻³	2.0×10 ⁻³	0.5
3MS/MMSE	eGFR	5	4.0×10 ⁻⁴	2.0×10 ⁻³	0.9	6.0×10 ⁻⁴	3.0×10 ⁻³	0.8	5.0×10 ⁻⁴	2.0×10 ⁻³	0.8
RAVLT delayed recall	UACR	1	1.0×10 ⁻⁴	1.0×10 ⁻⁴	0.4	-1.0×10 ⁻⁴	2.0×10 ⁻⁴	0.4	1.0×10 ⁻⁵	9.0×10 ⁻⁵	0.9
RAVLT delayed recall	UACR	2	-1.0×10 ⁻⁴	2.0×10 ⁻⁴	0.6	-2.0×10 ⁻⁴	2.0×10 ⁻⁴	0.2	-2.0×10 ⁻⁴	1.0×10 ⁻⁴	0.2
RAVLT delayed recall	UACR	3	6.0×10 ⁻⁵	1.0×10 ⁻⁴	0.6	-1.0×10 ⁻⁴	2.0×10 ⁻⁴	0.4	-1.0×10 ⁻⁵	1.0×10 ⁻⁴	0.9
RAVLT delayed recall	UACR	4	5.0×10 ⁻⁵	1.0×10 ⁻⁴	0.7	-2.0×10 ⁻⁴	2.0×10 ⁻⁴	0.3	-3.0×10 ⁻⁵	1.0×10 ⁻⁴	0.8
RAVLT delayed recall	eGFR	1	-7.0×10 ⁻⁴	2.0×10 ⁻³	0.7	-2.0×10 ⁻³	2.0×10 ⁻³	0.5	-1.0×10 ⁻³	2.0×10 ⁻³	0.5
RAVLT delayed recall	eGFR	2	2.0×10 ⁻³	3.0×10 ⁻³	0.5	-2.0×10 ⁻³	2.0×10 ⁻³	0.5	-2.0×10 ⁻⁵	2.0×10 ⁻³	0.9
RAVLT delayed recall	eGFR	3	-8.0×10 ⁻⁴	2.0×10 ⁻³	0.7	-3.0×10 ⁻³	3.0×10 ⁻³	0.3	-2.0×10 ⁻³	2.0×10 ⁻³	0.4
RAVLT delayed recall	eGFR	5	-5.0×10 ⁻⁴	2.0×10 ⁻³	0.8	-4.0×10 ⁻³	3.0×10 ⁻³	0.2	-2.0×10 ⁻³	2.0×10 ⁻³	0.3

Outcome	Predictor	Model	AA-DHS MIND			ACCORD MIND			Meta-analysis		
			Parameter	SE	P	Parameter	SE	P	Parameter	SE	P
Stroop Interference	UACR	1	2.0×10 ⁻⁴	1.0×10 ⁻⁴	0.05	2.0×10 ⁻⁴	2.0×10 ⁻⁴	0.2	2.0×10 ⁻⁴	9.0×10 ⁻⁵	0.02
Stroop Interference	UACR	2	3.0×10 ⁻⁴	2.0×10 ⁻⁴	0.06	2.0×10 ⁻⁴	2.0×10 ⁻⁴	0.2	3.0×10 ⁻⁴	1.0×10 ⁻⁴	0.03
Stroop Interference	UACR	3	2.0×10 ⁻⁴	1.0×10 ⁻⁴	0.05	1.0×10 ⁻⁴	2.0×10 ⁻⁴	0.5	2.0×10 ⁻⁴	1.0×10 ⁻⁴	0.04
Stroop Interference	UACR	4	2.0×10 ⁻⁴	1.0×10 ⁻⁴	0.1	1.0×10 ⁻⁴	2.0×10 ⁻⁴	0.4	2.0×10 ⁻⁴	1.0×10 ⁻⁴	0.08
Stroop Interference	eGFR	1	-3.0×10 ⁻³	2.0×10 ⁻³	0.1	-5.0×10 ⁻⁴	2.0×10 ⁻³	0.8	-2.0×10 ⁻³	2.0×10 ⁻³	0.2
Stroop Interference	eGFR	2	-5.0×10 ⁻³	3.0×10 ⁻³	0.05	2.0×10 ⁻⁴	2.0×10 ⁻³	0.9	-2.0×10 ⁻³	2.0×10 ⁻³	0.2
Stroop Interference	eGFR	3	-4.0×10 ⁻³	2.0×10 ⁻³	0.08	1.0×10 ⁻³	3.0×10 ⁻³	0.7	-2.0×10 ⁻³	2.0×10 ⁻³	0.3
Stroop Interference	eGFR	5	-3.0×10 ⁻³	2.0×10 ⁻³	0.2	2.0×10 ⁻³	3.0×10 ⁻³	0.5	-1.0×10 ⁻³	2.0×10 ⁻³	0.6

Note: Model 1 covariates: age, sex and level of education;

Model 2 covariates: Model 1 + body mass index, hemoglobin A1c, hypertension and low-density lipoprotein -cholesterol; Model 3 covariates: Model 2 + diabetes duration, smoking status, history of cardiovascular disease; Model 4 covariates: Model 3 + eGFR; Model 5 covariates: Model 3 + UACR.

SE – standard error; 3MS, Modified Mini-Mental State Examination; eGFR, estimated glomerular filtration rate (in ml/min/1.73m²); MMSE, Mini-Mental State Examination; UACR, urine albumin-creatinine ratio (in mg/g); RAVLT, Rey Auditory Verbal Learning Test; AA-DHS, African American–Diabetes Heart Study; MIND, Memory in Diabetes; ACCORD, Action to Control Cardiovascular Risk in Diabetes.