Published in final edited form as:

J Diabetes Complications. 2018 October ; 32(10): 916–921. doi:10.1016/j.jdiacomp.2018.05.017.

Relationships between cerebral structure and cognitive function in African Americans with type 2 diabetes

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Author contributions: Research idea/study design: BIF, JD, JAM; Data acquisition: BIF, JAM, CTW, BCW, JX, SCS, KMS, RNB, LCL, LJL, JIB, RMC, MDS; Data analysis/interpretation: JD, KMS, BIF, CEH, TMH, FCH, JDW, NDP, MEM, JX, LJL, JIB; Statistical analysis: JD, MEM, LJL, FCH, JAM; Supervision: KMS, CEH, TMH, LJL; Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Disclosure: No author has a disclosure relevant to this work.

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Declarations

Ethics approval and consent to participate: 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.

Consent for publication: all authors consented to publication of this manuscript.

Availability of data and material: the data and materials included in this manuscript were readily available to all authors.

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Abstract

Background—Relationships between cognitive function and brain structure remain poorly defined in African Americans with type 2 diabetes.

Methods—Cognitive testing and cerebral magnetic resonance imaging (MRI) in African Americans from the Diabetes Heart Study Memory IN Diabetes (AA-DHS MIND) (n=480) and Action to Control Cardiovascular Risk in Diabetes (ACCORD) MIND (n=104) studies were examined for associations. Cerebral gray matter volume (GMV), white matter volume (WMV) and white matter lesion volume (WMLV) and cognitive performance (Mini-mental State Exam [MMSE and 3MSE], Digit Symbol Coding (DSC), Stroop test, and Rey Auditory Verbal Learning Test [RAVLT]) were recorded. Multivariable models adjusted for age, sex, BMI, scanner, intracranial volume, education, diabetes duration, HbA1c, LDL-cholesterol, smoking, hypertension and cardiovascular disease assessed associations between cognitive tests and brain volumes by study and in a meta-analysis.

Results—Mean(SD) participant age was 60.1(7.9) years, diabetes duration 12.1(7.7) years, and HbA1c 8.3(1.7)%. In the fully-adjusted meta-analysis, lower GMV associated with poorer global performance on MMSE/3MSE ($\hat{\beta}=7.1\times10^{-3}$, SE 2.4×10^{-3} , $p=3.6\times10^{-3}$), higher WMLV associated with poorer performance on DSC ($\hat{\beta}=-3\times10^{-2}$, SE 6.4×10^{-3} , $p=5.2\times10^{-5}$) and higher WMV associated with poorer MMSE/3MSE performance ($\hat{\beta}=-7.1\times10^{-3}$, SE 2.4×10^{-3} , $p=3.6\times10^{-3}$). No brain volume was significantly associated with RAVLT performance.

Conclusions—In African Americans with diabetes, smaller GMV and increased WMLV associated with poorer performance on tests of global cognitive and executive function. These data suggest that WML burden and gray matter atrophy associate with cognitive performance independent of diabetes-related factors in this population.

Keywords

African American; diabetes; brain; cognitive performance; magnetic resonance imaging

Introduction

Cognitive impairment commonly develops in individuals with type 2 diabetes mellitus.^{1,2} Relative to the general population, adults with type 2 diabetes have higher rates of cognitive dysfunction and their risk of dementia is 1.5-2.5 times greater.³⁻⁵ People with diabetes also have greater evidence of microvascular disease involving the brain, kidneys, eyes and peripheral nervous system.^{1,2,6-8} It remains unclear whether cognitive performance in people with diabetes is related to cerebral microvascular disease or metabolic disorders,⁹ especially

in African Americans who have a higher risk of cognitive impairment and dementia than European Americans.¹⁰

Most data relating diabetes to brain structure and cognitive function comes from populations of European descent, revealing that type 2 diabetes is associated with greater total brain atrophy,^{11,12} including gray matter volume (GMV) loss in the cerebrum,¹² putamen,¹² medial temporal¹³⁻¹⁵ and frontal regions.^{14,16} Diabetes is also associated with enlargement of the ventricles and white matter lesions (WML).¹⁷ WML and other microvascular pathologies appear to play an important role in the relationships between type 2 diabetes, cognitive impairment, and Alzheimer's Disease (AD).¹⁸ As diabetes increases the risk for microvascular damage^{19,20} in the form of cerebral small vessel disease (including WML), it appears likely that cerebral small vessel disease may be a major factor in the associations between diabetes and poorer cognitive performance and could explain the increased risk for dementia in this population. Whether the same holds true for African Americans has been largely unexplored.

Data from multi-ethnic cohorts with type 2 diabetes suggest that diabetes is associated with greater brain atrophy and WML; these findings also associated with poorer cognitive performance.^{21,22} Analyzing these data in African Americans is especially important due to their greater risk for developing type 2 diabetes, diabetes-related complications and AD compared to European-derived populations.^{10,23-25} These complications include cardiovascular disease (CVD),²⁶⁻²⁸ structural brain abnormalities,^{22,29} and cognitive dysfunction.^{22,30,31} Further, recent data demonstrate that African Americans have a greater risk for AD pathology,^{32,33} cognitive decline and dementia,¹⁰ and are more likely to have 'mixed dementia' with concomitant cerebral small vessel disease and AD pathology.^{33,34}

We previously reported that poorer cognitive performance was associated with reduced GMV and higher WML volume in a small cohort of African Americans with type 2 diabetes.²² The present analyses examined the consistency of relationships between brain volumes and cognitive performance in African Americans with type 2 diabetes; it included two of the largest cohorts with brain imaging and cognitive data to better define associations in this understudied and high-risk population.

Methods

Study Participants

The Wake Forest School of Medicine African American-Diabetes Heart Study Memory IN Diabetes (AA-DHS MIND) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) MIND studies collected cognitive performance data and cerebral magnetic resonance imaging (MRI)-determined brain volumes in African Americans with type 2 diabetes.¹¹⁻¹⁵ The data included in this report consists of all self-identified African Americans with diabetes enrolled in AA-DHS MIND and ACCORD MIND. AA-DHS is an observational study in 717 individuals with type 2 diabetes receiving treatment with insulin and/or oral agents. Of these; 292 enrolled in the AA-DHS MIND and we recruited an additional 220 participants meeting identical inclusion criteria (512 total AA-DHS MIND participants with cerebral MRI and/or cognitive testing). 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 CVD 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 analyzing the effects of glycemic control, blood pressure and lipid lowering on cognitive function.^{11; 12} Data from ACCORD MIND was from baseline assessments occurring within 45 days of randomization. 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. The two 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.

Biochemical Measures

In AA-DHS MIND, HbA1c, fasting glucose and lipid measurements were performed at LabCorp (Burlington, NC). In ACCORD MIND, HbA1c was measured by a Tosah G7 automated high performance liquid chromatograph and fasting glucose was measured enzymatically on a Hitachi 917 autoanalyzer.

Cognitive Testing

Cognitive batteries administered to AA-DHS MIND and ACCORD MIND participants partially overlapped to include four cognitive tests common to both. These included the Digit Symbol Coding task which informs processing speed, and to a lesser extent working memory.³⁵ DSC scores were the number of correct responses in 120 seconds; higher scores reflect better performance. The 40-item version of the Stroop task was used to assess response inhibition, a component of executive function.¹⁸ The interference score was computed as: [time to completion Stroop 3 + errors Stroop 3] – [time to completion Stroop 2 + errors Stroop 2]; higher scores reflect poorer executive function. The third overlapping cognitive test was the 15-item word list recall task, Rey Auditory Verbal Learning Test (RAVLT), which assesses verbal memory and learning. The RAVLT score was calculated as the average number of words recalled (0-15) over the immediate, short, and delayed recall trials. Finally, global cognition was assessed in AA-DHS MIND with the Modified Mini-Mental State Examination (3MSE)¹⁹ and in ACCORD MIND with the Mini-Mental State Examination (MMSE).²¹

Cerebral Magnetic Resonance Imaging (MRI)

AA-DHS MIND MRI scans imaging methods have previously been reported.²²⁻²³ Of 512 participants, 61 had MRI performed on a 1.5-Tesla (T) scanner and 419 on a 3.0-T machine (total 480 with MRI). Fifteen individuals underwent both 1.5T and 3.0T scans to account for between-scanner variation. Adjustments were made in brain volumes between scanners based on systematic differences in volumetric measures, as previously described.²²⁻²³ Structural analysis of T1-weighted images (for total intracranial volume [TICV], gray matter volume [GMV], and white matter volume [WMV]) in AA-DHS MIND was performed using the SPM8²⁴ new segment procedure as implemented in the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm.html>). WMLV was computed from the fluid attenuated inversion

recovery (FLAIR) images using the lesion segmentation toolbox (LST) toolbox,²⁵ for SPM8 and an optimized threshold (k) of 0.25 as previously described.²²

ACCORD MIND 1.5T MRI scans were performed on 104 African Americans (from 640 participants with MRI scans) at Columbia University, Wake Forest School of Medicine, and the University of Minnesota. ACCORD MIND MRI included a three-dimensional fast spoiled gradient-echo T1W (TR=21 ms, FA=30°, TE 8 ms), two-dimensional axial fast spin-echo FLAIR (TR=8000 ms, TI=2000 ms, TE=100 ms), and proton density (PD)/T2 weighted (TR=3200 ms, TE_{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. Nick Bryan, MD). Processing of MRI sequences involved template registration and semi-automated segmentation.²⁶⁻²⁹ Using a previously validated but conservative technique called White Matter Lesion Segmentation (WMLS), abnormality maps based on structural MRI (PD, T1, T2, FLAIR) were used to identify WML.²⁶⁻²⁹ WMLS is a support vector machine classifier trained on expert human manual segmentation of WML on FLAIR images that strongly correlates with human observer delineation of WML. Both studies provided measures of total brain volume (TBV), GMV, WMV and WMLV. In order to harmonize MRI volumetrics, all brain volumes excluded the cerebellum.

Statistical Analysis

General linear models (GLM) were fitted separately for each study to test for associations between MRI brain volumes and cognitive test scores. Box-Cox³⁰ transformations were applied where appropriate to ensure that the distributional assumptions of conditional normality and homogeneity of variance of the residuals were satisfied. Because image processing and cognitive tests differed between cohorts, study-specific transformations were applied within AA-DHS-MIND and ACCORD-MIND; therefore, the resulting model coefficients are on different transformed scales, and are difficult to directly compare. Scaled coefficients ($\hat{\beta} / \hat{\sigma}$) are presented to assist in interpretation, where $\hat{\beta}$ represents the parameter estimates associated with the MRI volumetric measure and $\hat{\sigma}$ denotes the estimated residual standard deviation from the Box-Cox transformed regression model.³¹ In AA-DHS-MIND, a minimally adjusted model was fitted including age, sex, TICV, education level and MRI scanner (1.5T vs. 3T) as covariates for MRI outcomes. The minimally adjusted models fitted with the ACCORD-MIND data were further adjusted for performance site. Sequentially adjusted models were fitted in each dataset separately. In addition to the covariates included in the minimally-adjusted models, subsequent models adjusted for BMI, HbA1c at the time of MRI, hypertension (yes/no), and LDL cholesterol, diabetes duration, prior CVD and smoking which comprised the fully-adjusted model. Diagnostic tests performed on the model residuals showed that the assumptions underlying the GLM were met. Inverse variance meta-analysis of the results observed separately in the two studies was performed using the standardized coefficients. To account for multiple comparisons for the primary hypothesis (gray matter and white matter volumes and 4 cognitive tests [2 brain volumes $\times$ 4 cognitive tests = 8]), we set alpha at 0.05/8 or 6.3×10^{-3} . The heterogeneity statistic (I^2) was used to describe the percentage of total variation across studies due to heterogeneity rather than chance; a value of 0% indicates no observed heterogeneity, and larger values show

increasing heterogeneity. The meta-analysis controlled for minor differences in administration or test composition between studies (*e.g.* 3MSE and MMSE).

Results

In this analysis, a total of 584 African Americans with type 2 diabetes, cognitive testing, and brain MRI were analyzed, including 480 from AA-DHS MIND and 104 from ACCORD MIND. In the combined sample, 60.6% were female with mean (SD) age 60 (7.9) years, diabetes duration 12.1 (7.7) years, HbA1c 67.22 (18.58) mmol/mol (8.3 [1.7]%), eGFR 1.48 (0.36) mL/s (88.7 [21.6] min/1.73m²), and urine albumin-to-creatinine ratio 13.48 (38.03) mg/mmol (119.2 [336.4] mg/g). Demographic and laboratory characteristics of AA-DHS MIND and ACCORD MIND participants, respectively, are presented in Table 1 and Table 2. Systolic blood pressure, HbA1c, and use of statins were slightly higher in ACCORD MIND participants; duration of diabetes was slightly lower in ACCORD MIND participants; baseline LDL-cholesterol and HDL-cholesterol levels were similar across studies. Brain volumes and cognitive test scores for African Americans were generally consistent across the two cohorts, similar to published data from ACCORD (mean($\pm$ SD): TBV=925($\pm$ 96) and WMLV= 2.10($\pm$ 3.88)^{36,37} and consistent with published normative data for African Americans in this age range (ranges: MMSE, 24-30³⁸; 3MSE, 89-91;³⁹ RAVLT, 6-7;⁴⁰ DSC, 59-63;⁴¹ and Stroop 31-35⁴²).

Table 3 displays brain volume associations with cognitive test performance in African Americans with diabetes separately in each study and in the meta-analysis. In the fully-adjusted meta-analysis, greater WMLV was significantly and consistently associated with poorer performance on the DSC (Meta-analysis $\hat{\beta}=-3\times 10^{-2}$, SE=6.0 $\times 10^{-3}$, p=5.2 $\times 10^{-5}$), with a trend toward association with poorer performance on the 3MSE/MMSE that missed significance considering multiple testing ($\hat{\beta}=-2.0\times 10^{-2}$, SE=6.4 $\times 10^{-3}$, p=8.3 $\times 10^{-3}$). Lower GMV was associated with poorer 3MSE/MMSE performance ($\hat{\beta}=7.1\times 10^{-3}$, SE=2.4 $\times 10^{-3}$, p=3.6 $\times 10^{-3}$), with a trend toward higher Stroop interference ($\hat{\beta}=-6.6\times 10^{-3}$, SE=2.5 $\times 10^{-3}$, p=7.5 $\times 10^{-3}$). Higher WMV was associated with poorer 3MSE/MMSE performance ($\hat{\beta}=-7.1\times 10^{-3}$, SE=2.4 $\times 10^{-3}$, p=3.6 $\times 10^{-3}$), with a trend toward higher Stroop interference ($\hat{\beta}=6.6\times 10^{-3}$, SE 2.5 $\times 10^{-3}$, p=7.5 $\times 10^{-3}$). The low heterogeneity ($I^2<0.15$) of significant associations between the cohorts for WMLV and DSC, as well as for GMV and 3MSE/MMSE suggests these relationships were consistent and reliable between studies. Brain volumes were not significantly associated with RAVLT performance.

Discussion

Poorer performance on tests of global cognitive function, executive function, and processing speed were associated with a greater WM and WML burden and smaller GMV in African Americans with type 2 diabetes. These associations were independent of participant characteristics, clinical aspects of diabetes and recent glycemic control.

There is a paucity of data on brain structure and cognitive performance in African Americans with type 2 diabetes. In multi-ethnic cohorts, type 2 diabetes is associated with brain atrophy and WML burden, which are in turn associated with poorer cognitive

performance.^{21,22} We previously reported in the DHS MIND study that the extent of white matter disease is similar between African Americans and European Americans with type 2 diabetes.⁴³ WML burden was associated with poorer cognitive performance in European American participants (DSC, RAVLT and semantic fluency) and with DSC and Stroop interference in African Americans.^{21,22} Lower GMV was associated with poorer performance on 3MSE in both African Americans and European Americans.^{21,22} Relationships between poorer cognitive performance on tests of global cognitive function and executive function with greater WML and smaller GMV were replicated here in a meta-analysis including larger numbers of African American participants in the AA-DHS MIND and ACCORD MIND.

Prior reports have been unable to demonstrate an association between measures of glycemic control (HbA1c) with brain volumes of gray matter, white matter and WML and cognitive testing in African Americans and European Americans.^{22,44} Among African Americans in ACCORD MIND and AA-DHS MIND, addition of HbA1c to the models did not attenuate any of the observed associations. This observation generally fits with ACCORD trial results where individuals with diabetes who had intensive (versus standard) glucose control did not appear to have altered trajectories if cognitive decline or global brain structural abnormalities during follow-up.⁴⁵ This highlights the need for alternative treatments and approaches focused on preventing development of cerebral small vessel disease and brain atrophy in individuals with type 2 diabetes.

Strengths of this work include analysis of cognitive and brain structure relationships in African Americans with longstanding type 2 diabetes from the two largest existing such cohorts. Several reports reveal poorer cognitive performance in African Americans compared to European Americans.^{46,47} Further, African Americans with diabetes tend to have poorer performance on cognitive tests compared to African Americans without diabetes.²² However, little is known about the characteristics that may contribute to these differences. This study demonstrates that poorer cognitive performance among African Americans with type 2 diabetes is associated with greater burden of WML and lower GMV; characteristic structural abnormalities that have consistently been associated with poorer cognitive performance, cognitive decline and dementia in cohorts with and without diabetes. Consideration of diabetes duration and metabolic factors, including recent glycemic control, BMI, LDL-cholesterol and smoking, failed to explain the observed associations between cognitive performance and brain structural abnormalities in African Americans with type 2 diabetes. These findings provide additional evidence that WML burden and GMV are important risk factors for poorer cognitive performance in individuals with type 2 diabetes. These findings are supported by initial biomarker imaging studies of AD pathology in patients with type 2 diabetes suggesting that these patients have more cerebral small vessel disease and not increased burdens of cerebral β -amyloid.^{48,49} Further studies investigating the driving factors that lead to increased WML in diabetes are required.

This study also has limitations. The larger standard errors of parameter estimates and smaller number of African Americans in ACCORD MIND (versus AA-DHS MIND) limited statistical power to detect significant relationships in this cohort; this limitation was addressed by performing a meta-analysis. The use of a meta-analytic approach enabled the

assessment of the strength of reported associations in each cohort separately while providing measures of reproducibility and heterogeneity across cohorts. The heterogeneity of results varied across combinations of cognitive test and brain volumes with the least confidence in 3MSE/MMSE and Stroop cognitive tests and for white matter lesion volume. The subtle differences in the tests administered (MMSE versus 3MSE) and the differences in processing methods for white matter lesion segmentation between cohorts may have produced minor systematic bias. Further, the differences in sample sizes caused the larger cohort, AA-DHS MIND to weight more on the meta-analytic results. However, it is important to note at these limitations generally affected magnitude, not direction of the observed associations in these two cohorts. While brain volumes and cognitive test scores generally fell well within the normal range for African Americans of this age, the AA-DHS MIND study did not collect data for the purpose of cognitive adjudication. The potential impact of a history of past hypoglycemic events on changes in brain volume could not be assessed in this study. The results are cross-sectional and inferences on longitudinal change or atrophy patterns could not be assessed. Longitudinal MR data from ACCORD show that individuals with a shorter duration of diabetes and intensive glycemic control had significantly attenuated declines in GMV in areas of the frontal and temporal lobes;⁵⁰ incident hypoglycemic events over 40 months of follow up were associated with less total brain atrophy and no increase in abnormal white matter.³⁷ Type 2 diabetes is associated with enlargement of the ventricles and increase in WML over time;¹⁷ affected individuals also had greater longitudinal increases in these measures over follow-up.¹⁷

Conclusions

Cognitive impairment is a common complication in patients with type 2 diabetes. In addition, diabetes is associated with a progressive loss of brain volume and poorer cognitive performance in European-derived populations. In multi-ethnic type 2 diabetes-affected cohorts, diabetes is associated with greater evidence of brain atrophy and WML; both are associated with poorer cognitive performance. The current analysis of the two largest cohorts of African Americans with type 2 diabetes reveals consistent evidence of associations between poorer performance on global and executive function tests and brain structural abnormalities, including greater evidence of white matter disease and gray matter atrophy.

Acknowledgements:

The authors thank all study participants and research staff at Wake Forest School of Medicine AA-DHS MIND¹⁴ and ACCORD MIND¹⁵ study sites. Support for this work was provided by NIH Grants R01 DK071891; R01 NS075107; R01 MD009055. ACCORD MIND was funded through an intra-agency agreement between NIA and NHLBI (AG-0002) and the NIA Intramural Research Program. ACCORD was funded by NHLBI (N01-HC-95178; N01-HC-95179; N01-HC-95180; N01-HC-95181; N01-HC-95182; N01-HC-95183; N01-HC-95184). Abbott Laboratories, Amylin Pharmaceuticals, AstraZeneca, Bayer Healthcare, Closer Healthcare, GlaxoSmithKline, King Pharmaceuticals, Merck, Novartis, Novo Nordisk, Omron Healthcare, Sanofi - Aventis, and Schering-Plough provided study drugs, equipment, or supplies.

Funding: NIH Grants R01 DK071891; R01 NS075107; R01 MD009055. ACCORD MIND was funded through an intra-agency agreement between NIA and NHLBI (AG-0002) and the NIA Intramural Research Program. ACCORD was funded by NHLBI (N01-HC-95178; N01-HC-95179; N01-HC-95180; N01-HC-95181; N01-HC-95182; N01-HC-95183; N01-HC-95184). Abbott Laboratories, Amylin Pharmaceuticals, AstraZeneca, Bayer

Healthcare, Closer Healthcare, GlaxoSmithKline, King Pharmaceuticals, Merck, Novartis, Novo Nordisk, Omron Healthcare, Sanofi -Aventis, and Schering-Plough provided study drugs, equipment, or supplies.

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Table 1:
Demographic and laboratory characteristics of AA-DHS MIND participants

Variable	All		
	N	Mean (SD)	Median
Age at the MIND visit (years)	482	58.79 (9.59)	57.7
Gender (Female) (%)	483	60.7%	
Body Mass Index at the MIND visit (BMI; kg/m ²)	483	34.72 (7.99)	33.5
Less than High School completion (%)	483	11.4%	
High School graduate (%)	483	26.5%	
Technical School / Associate degree (%)	483	43.7%	
College graduate including graduate education (%)	483	18.4%	
Diabetes duration at the MIND visit (years)	480	13.14 (7.71)	11.7
Current or Past Smoker at the MIND visit (%)	480	54.6%	
Systolic Blood pressure at MIND baseline	483	131.22 (18.16)	131.0
Diastolic Blood pressure at MIND baseline	483	76.90 (11.25)	77.0
Hypertension (%)	473	85.8%	
CKD-EPI eGFR at the MIND visit (mL/s)	481	1.47 (0.39)	1.49
Urine ACR at the MIND visit (mg/mmoL)	480	14.86 (43.37)	1.11
Serum glucose at the MIND visit (mmol/L)	481	8.37 (3.59)	7.38
HbA1c at the MIND visit (mmol/mol)	480	64.81 (22.19)	57.38
LDL-cholesterol (mmol/L)	274	2.84 (0.94)	2.75
HDL-cholesterol (mmol/L)	275	1.24 (0.34)	1.19
Statins	276	50.7%	
Insulin (%)	278	37.1%	
Gray matter volume	480	480.0 (55.4)	477.5
White matter volume	480	441.2 (58.7)	435.1
Total brain volume	480	921.2 (101.7)	910.8
Automated white matter lesions volume	478	7.44 (11.30)	2.6
Modified mini-mental state exam 3MSE (0–100)	483	85.79 (9.20)	87.0
Rey Auditory Verbal Learning Test RAVLT (0–15)	483	6.48 (2.36)	6.3
Digit symbol coding (0–133)	476	49.57 (16.38)	48.5
Stroop interference	473	40.82 (18.32)	38.0

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

Variable	All		
	N	Mean (SD)	Median
Age at the MIND visit (years)	103	61.07 (5.81)	60.0
Gender (Female) (%)	103	[60.2%]	
Body Mass Index at the MIND visit (BMI; kg/m ²)	103	32.46 (5.31)	31.0
Less than High School completion (%)	103	13.6%	
High School graduate (%)	103	27.2%	
Technical School / Associate degree (%)	103	35.9%	
College graduate including graduate education (%)	103	23.3%	
Diabetes duration at the MIND visit (years)	103	10.58 (7.92)	8.0
Current or Past Smoker at the MIND visit (%)	103	52.4%	
Systolic Blood pressure at MIND baseline	102	137.47 (19.89)	134.5
Diastolic Blood pressure at MIND baseline	102	76.86 (10.49)	76.0
Hypertension (%)	103	93.2%	
CKD-EPI eGFR at the MIND visit (mL/s)	103	1.49 (0.29)	1.53
Urine ACR at the MIND visit (mg/mmol)	103	10.27 (30.70)	1.44
Serum glucose at the MIND visit (mmol/L)	103	9.31 (3.69)	8.44
HbA1c at the MIND visit (mmol/mol)	103	67.55 (11.80)	65.03
LDL-cholesterol (mmol/L)	103	2.89 (0.92)	2.82
HDL-cholesterol (mmol/L)	103	1.27 (0.35)	1.24
Statins	103	62.1%	
Insulin (%)	103	35.9%	
Gray matter volume	103	440.12 (47.17)	428.1
White matter volume	103	441.79 (53.55)	435.9
Total brain volume	103	881.92 (87.40)	867.6
Automated white matter lesions volume	103	1.93 (3.46)	0.8
Mini-mental state exam MMSE (0–30)	103	26.61 (2.58)	27.0
Rey Auditory Verbal Learning Test RAVLT (0–15)	103	7.45 (2.49)	7.5
Digit symbol coding (0–133)	103	47.13 (15.07)	46.0
Stroop interference	102	34.32 (16.76)	30.0

Table 3:
Association between MRI volumetric measures and cognitive function

Outcome	Predictor	Model	AA-DHS-MIND			ACCORD-MIND			Meta-analysis		
			Parameter	SE	P-value	Parameter	SE	P-value	Parameter	SE	P-value
DSC	Gray matter volume (cm ³)	1	8.6×10 ⁻⁴	2.1×10 ⁻³	0.68	4.9×10 ⁻⁴	4.5×10 ⁻³	0.91	8.0×10 ⁻⁴	1.9×10 ⁻³	0.67
DSC	Gray matter volume (cm ³)	2	1.8×10 ⁻³	2.8×10 ⁻³	0.52	1.8×10 ⁻³	4.7×10 ⁻³	0.71	1.8×10 ⁻³	2.4×10 ⁻³	0.46
DSC	White matter volume (cm ³)	1	-8.6×10 ⁻⁴	2.1×10 ⁻³	0.68	-4.9×10 ⁻⁴	4.5×10 ⁻³	0.91	-8.0×10 ⁻⁴	1.9×10 ⁻³	0.67
DSC	White matter volume (cm ³)	2	-1.8×10 ⁻³	2.8×10 ⁻³	0.52	-1.8×10 ⁻³	4.7×10 ⁻³	0.71	-1.8×10 ⁻³	2.4×10 ⁻³	0.46
DSC	White matter lesion volume (cm ³)	1	-0.02	4.6×10 ⁻³	1.1×10 ⁻⁵	-0.06	0.03	0.04	-0.02	4.60×10 ⁻³	3.2×10 ⁻⁶
DSC	White matter lesion volume (cm ³)	2	-0.03	6.6×10 ⁻³	9.1×10 ⁻⁵	-0.04	0.03	0.28	-0.03	6.40×10 ⁻³	5.2×10 ⁻⁵
3MSE/MMSE	Gray matter volume (cm ³)	1	3.2×10 ⁻³	2.1×10 ⁻³	0.12	9.6×10 ⁻³	4.6×10 ⁻³	0.04	4.3×10 ⁻³	1.9×10 ⁻³	0.02
3MSE/MMSE	Gray matter volume (cm ³)	2	5.5×10 ⁻³	2.8×10 ⁻³	0.05	0.01	4.8×10 ⁻³	0.02	7.1×10 ⁻³	2.4×10 ⁻³	3.6×10 ⁻³
3MSE/MMSE	White matter volume (cm ³)	1	-3.2×10 ⁻³	2.1×10 ⁻³	0.12	-9.6×10 ⁻³	4.6×10 ⁻³	0.04	-4.3×10 ⁻³	1.9×10 ⁻³	0.02
3MSE/MMSE	White matter volume (cm ³)	2	-5.5×10 ⁻³	2.8×10 ⁻³	0.05	-0.01	4.8×10 ⁻³	0.02	-7.1×10 ⁻³	2.4×10 ⁻³	3.6×10 ⁻³
3MSE/MMSE	White matter lesion volume (cm ³)	1	-0.01	4.6×10 ⁻³	0.02	-0.07	0.03	0.03	-0.01	4.5×10 ⁻³	7.2×10 ⁻³
3MSE/MMSE	White matter lesion volume (cm ³)	2	-0.01	6.5×10 ⁻³	0.02	-0.07	0.03	0.03	-0.02	6.4×10 ⁻³	8.3×10 ⁻³
RAVLT	Gray matter volume (cm ³)	1	3.0×10 ⁻³	2.1×10 ⁻³	0.15	-1.3×10 ⁻³	4.5×10 ⁻³	0.78	2.3×10 ⁻³	1.9×10 ⁻³	0.23
RAVLT	Gray matter volume (cm ³)	2	3.2×10 ⁻³	2.8×10 ⁻³	0.25	1.8×10 ⁻³	4.7×10 ⁻³	0.7	2.9×10 ⁻³	2.4×10 ⁻³	0.23
RAVLT	White matter volume (cm ³)	1	-3.0×10 ⁻³	2.1×10 ⁻³	0.15	1.3×10 ⁻³	4.5×10 ⁻³	0.78	-2.3×10 ⁻³	1.9×10 ⁻³	0.23
RAVLT	White matter volume (cm ³)	2	-3.2×10 ⁻³	2.8×10 ⁻³	0.25	-1.8×10 ⁻³	4.7×10 ⁻³	0.7	-2.9×10 ⁻³	2.4×10 ⁻³	0.23
RAVLT	White matter lesion volume (cm ³)	1	-7.6×10 ⁻³	4.6×10 ⁻³	0.1	-0.05	0.03	0.08	-8.6×10 ⁻³	4.6×10 ⁻³	0.06
RAVLT	White matter lesion volume (cm ³)	2	-7.3×10 ⁻³	6.5×10 ⁻³	0.26	-0.05	0.03	0.15	-8.8×10 ⁻³	6.4×10 ⁻³	0.17
Stroop	Gray matter volume (cm ³)	1	-5.9×10 ⁻³	2.1×10 ⁻³	5.2×10 ⁻³	4.7×10 ⁻³	4.5×10 ⁻³	0.3	-4.0×10 ⁻³	1.9×10 ⁻³	0.04
Stroop	Gray matter volume (cm ³)	2	-9.6×10 ⁻³	2.9×10 ⁻³	9.0×10 ⁻⁴	1.5×10 ⁻³	4.8×10 ⁻³	0.75	-6.6×10 ⁻³	2.5×10 ⁻³	7.5×10 ⁻³
Stroop	White matter volume (cm ³)	1	5.9×10 ⁻³	2.1×10 ⁻³	5.2×10 ⁻³	-4.7×10 ⁻³	4.5×10 ⁻³	0.3	4.0×10 ⁻³	1.9×10 ⁻³	0.04
Stroop	White matter volume (cm ³)	2	9.6×10 ⁻³	2.9×10 ⁻³	9.0×10 ⁻⁴	-1.5×10 ⁻³	4.8×10 ⁻³	0.75	6.6×10 ⁻³	2.5×10 ⁻³	7.5×10 ⁻³
Stroop	White matter lesion volume (cm ³)	1	8.6×10 ⁻³	4.6×10 ⁻³	0.06	0.07	0.03	0.03	9.9×10 ⁻³	4.5×10 ⁻³	0.03
Stroop	White matter lesion volume (cm ³)	2	5.1×10 ⁻³	6.5×10 ⁻³	0.43	0.06	0.03	0.1	7.0×10 ⁻³	6.3×10 ⁻³	0.27

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DSC = digit symbol coding, 3MSE/MMSE - (modified) mini-mental state exam, RAVLT - Rey Auditory Verbal Learning Test
Model 1 covariates: MRI scanner, total intracranial volume, level of education, age and sex
Model 2 covariates: Model 1 + body mass index, hemoglobin A1c, hypertension, smoking, CVD, diabetes duration and LDL-cholesterol