THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2018, Vol. 73, No. 3, 407–414
doi:10.1093/gerona/glx255
Advance Access publication January 4, 2018

OXFORD

Research Article

Cerebral Structure and Cognitive Performance in African Americans and European Americans With Type 2 Diabetes

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Received: June 20, 2017; Editorial Decision Date: December 19, 2017

Decision Editor: Anne Newman, MD, MPH

Abstract

Background: African Americans typically perform worse than European Americans on cognitive testing. Contributions of cardiovascular disease (CVD) risk factors and educational quality to cognitive performance and brain volumes were compared in European Americans and African Americans with type 2 diabetes.

Methods: Association between magnetic resonance imaging–determined cerebral volumes of white matter (WMV), gray matter (GMV), white matter lesions (WMLV), hippocampal GMV, and modified mini-mental state exam (3MSE), digit symbol coding (DSC), Rey Auditory Verbal Learning Test (RAVLT), Stroop, and verbal fluency performance were assessed in Diabetes Heart Study Memory in Diabetes (MIND) participants. Marginal models incorporating generalized estimating equations were employed with serial adjustment for risk factors.

Results: The sample included 520 African Americans and 684 European Americans; 56 per cent female with mean ± SD age 62.8 ± 10.3 years and diabetes duration 14.3 ± 7.8 years. Adjusting for age, sex, diabetes duration, BMI, HbA1c, total intracranial volume, scanner, statins, CVD, smoking, and hypertension, WMV (p = .001) was lower and WMLV higher in African Americans than European Americans (p = .001), with similar GMV (p = .30). Adjusting for age, sex, education, HbA1c, diabetes duration, hypertension, BMI, statins, CVD, smoking, and depression, poorer performance on 3MSE, RAVLT, and DSC were seen in African Americans ($p = 6 \times 10^{-23}$–7×10^{-62}). Racial differences in cognitive performance were attenuated after additional adjustment for WMLV and nearly fully resolved after adjustment for wide-range achievement test (WRAT) performance (p = .0009–.65).

Conclusions: African Americans with type 2 diabetes had higher WMLV and poorer cognitive performance than European Americans. Differences in cognitive performance were attenuated after considering WMLV and apparent poorer educational quality based on WRAT.

Keywords: Brain, Cognition, Educational quality, Health disparities, Minority aging.

Compared with the general population, individuals with type 2 diabetes mellitus (T2D) have higher rates of cognitive impairment and dementia (1–3). African Americans are at particularly high risk for developing T2D (www.diabetes.org). Many reports also reveal poorer cognitive performance in African Americans compared with European Americans (4, 5). It is unclear whether differences in cognitive performance relate to increased cerebrovascular disease in African Americans or whether differences in environmental factors contribute.

Magnetic resonance imaging (MRI) studies have shown increased white matter lesion burden in African Americans compared with European Americans (6, 7). This anatomic difference is likely related to exposure to more severe cardiovascular disease (CVD) risk factors in African Americans, including increased risk for T2D. Racial differences in access to healthcare were likely present in these reports, and nonbiological risk factors have proven to be important in predicting low cognitive performance and dementia risk between racial and ethnic groups (8, 9). Quality of education is one such factor and it reportedly contributes to racial differences in cognitive performance (10–12). Identifying modifiable environmental (nonbiological) risk factors for cognitive impairment provides hope for increasing cognitive reserve and reducing risk factors for dementia in minority populations.

We sought to determine the contribution of risk factors for CVD and educational quality on racial differences in brain volumes and cognitive performance between European Americans and African Americans. Participants were enrolled in the Diabetes Heart Study Memory in Diabetes (DHS MIND) and African American–DHS MIND (AA–DHS MIND) (13, 14). These cohorts include individuals with T2D and extensive CVD and vascular disease phenotypes during mid-life, and cerebral MRI and cognitive testing.

Methods

Study Population

All European American and African American DHS MIND and AA–DHS MIND participants were included. Details of the recruitment methods have been reported (13, 14). In brief, European American and African American siblings with T2D, and singletons with T2D (who had additional first-degree relatives with diabetes), were recruited in DHS MIND. Unrelated African Americans with T2D were recruited in AA-DHS MIND using the same diagnostic criteria. T2D was clinically defined as a diagnosis after the age of 30 years along with active insulin or hypoglycemic treatment in the absence of ketoacidosis. Both studies were approved by the Institutional Review Board at the Wake Forest School of Medicine (WFSM) and all participants provided written informed consent.

Examinations were performed in the WFSM Clinical Research Unit. Medical and education histories, active medications, and vital signs were recorded by study staff. Fasting blood work included plasma glucose, hemoglobin (Hb) A1c, vitamin B12, and thyroid stimulating hormone.

Cerebral MRI

Among 684 European American participants, 671 had a 1.5 Tesla (T)-MRI scan and 13 had a 3.0-T MRI. Among 520 African American participants, 434 had a 3.0-T MRI scan and 86 had a 1.5-T MRI scan.

The 1.5-T Excite HD scanner (GE Healthcare, Milwaukee, Wisconsin) was initially used in DHS MIND. High-resolution T1–anatomic images were obtained using a three-dimensional (3D) volumetric inversion recovery echo-spoiled gradient-echo sequence (repetition time [TR] 7.36 milliseconds, echo time [TE] 2.02 milliseconds, inversion time [TI] 600 milliseconds, flip angle 20°, 124 sections, field of view [FOV] 24 cm, matrix size 256 × 256, 1.5-mm slice thickness).

Due to a protocol change at the WFSM Center for Biomolecular Imaging, subsequent MRI scans were performed on a 3.0-T Skyra Scanner (Siemens, Erlangen, Germany) using a high-resolution 20-channel head or neck coil. T1-weighted anatomic images were obtained using 3D volumetric magnetization–prepared rapid acquisition gradient-echo sequence (TR 2300, TE 2.99, TI 900 milliseconds, flip angle 9°, 192 slices, voxel dimension 0.97 × 0.97 × 1 mm).

Structural T1 images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), normalized to the Montreal Neurological Institute (MNI) imaging space, and modulated with the Jacobian determinants (nonlinear components only) of the warping procedure to generate volumetric tissue maps using the Dartel high-dimensional warping and the SPM8 new segment procedure, as implemented in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html). Total GM volume (GMV), WM volume (WMV), CSF volume (CSFV), and intracranial volume (ICV = [GMV + WMV + CSFV]) were determined from the VBM8-automated segmentation procedure. Additional region of interest (ROI)–based measures were generated for the right and left hippocampus using the automated anatomical labeling atlas, as implemented in the wfu_pickatlas (15). The automated anatomical labeling atlas hippocampal ROI is not specific to the GM; it encompasses GM-, WM-, and CSF-tissue types. The hippocampal ROIs (right and left) were applied to the modulated GM- and WM-volumetric tissue maps to generate hippocampal GMV and hippocampal WMV. WM lesion (WML) segmentation was performed using the lesion segmentation toolbox for SPM8 at a threshold (k) of 0.25, as in our previous report. The lesion segmentation toolbox (16) has been validated against expert manual segmentation, as well as identifying the optimum thresholds (17). Normalization to MNI space was accomplished by coregistration with the structural T1 and applying the normalization parameters computed in the VBM8 segmentation procedure. The total WML volume (WMLV) measure was determined by summing the binary lesion maps and multiplying by the voxel volume, and values are reported in cubic centimeters.

Cognitive and Depression Testing

One investigator (K.M.S.) was responsible for quality control and training, certification, and assessment of study staff responsible for conducting cognitive tests. The cognitive function battery included the Modified Mini-Mental State Examination (18) (3MSE; range 0–100 with higher scores indicating better performance) to assess global cognitive function, the Digit Symbol Coding task from WAIS-III (19) to assess psychomotor speed and working memory (range 0–133 with higher scores indicating better performance), the Rey Auditory Verbal Learning Test (20) (RAVLT) to assess memory, from which we report the delayed recall score (0–15), the Stroop Task (21) (from which we report the interference: trial 3 time (seconds)—trial 1 time as a measure of executive function; higher scores indicating worse performance), and category fluency for animals, a measure of language and executive function. Depression was evaluated using the Center for Epidemiological Studies-Depression (CES-D) 10-item measure (22, 23), considered to have high sensitivity and specificity in patients with diabetes. The Brief Symptom Inventory

(BSI)-Anxiety (24) was used to assess anxiety. In addition to providing their level of educational attainment, AA-DHS MIND participants completed the Wide-Range Achievement Test (25) (WRAT-4) reading recognition subtest to directly assess reading grade level. WRAT was categorized into three groups (less than high school, high school graduate, and more than high school) to be comparable with self-reported education.

Statistical Analyses

Statistical analyses were completed using SAS software version 9.4 (SAS Institute, Cary, NC, USA). Summary statistics including means, standard deviations (SD), medians, and interquartile ranges were computed for the continuous characteristics, and counts and percentages were computed for discrete characteristics. The race/ethnicity comparison for the characteristics was performed using the marginal models incorporating generalized estimating equations' approaches to account for familial correlation using a sandwich estimator of the variance under exchangeable correlation.

To assess associations between race and MRI volumes, marginal models with identity link, normal distribution, and exchangeable correlation were fitted. Race was the covariate of interest. A series of models with different covariate adjustment were fitted: Model 1 adjusted for TICV and MRI scanner; Model 2 additionally adjusted for age, sex, and diabetes duration; Model 3 adjusted for all the covariates in Model 2 and body mass index (BMI) and HbA1c; and Model 4 adjusted for all covariates in Model 3 and statins, prior CVD, smoking, and hypertension. The regression coefficient estimates and their confidence intervals are reported. A strict Bonferroni correction was applied to adjust for multiple comparisons; *p*-values < .0031 (p = .05/16 tests) were considered significant for associations between race and MRI cerebral volumes.

Age- and education-adjusted normative data on the 3MSE in European Americans (26) and African Americans (27) were used to calculate percentile scores of 3MSE in the study sample. Due to the limitation of reported age ranges in the literature, percentile scores were only calculated for those whose ages were between 60 and 84 years. Cognitive impairment within this age range can be defined as the percentile score less than 8 (approximately equal to 1.5 SD below the mean). The raw 3MSE score and cognitive impairment by race, age, and education groups were presented.

To assess associations between race and cognitive performance, marginal models with log link, Poisson distributions, and exchangeable correlations were fitted. Four models were fitted: Model 1 adjusted for age, education, sex, and HbA1c; Model 2 additionally adjusted for hypertension, diabetes duration, BMI, statins, prior CVD, smoking, and depression; Model 3 adjusted for all the covariates in Model 2 and MRI scanner, TICV, and WMLV; Model 4 adjusted for all the covariates in Model 3 except that education was replaced by WRAT reading grade level in African Americans, which is presumed to be a more accurate reflection of education level than years of school attended. The exponentiated regression coefficient estimates (ie relative risk) and their confidence intervals were reported. Bonferroni-adjusted *p*-values < .0025 ($p = .05/20$ tests) were considered significant for association between race/ethnicity and cognitive performance.

Two sensitivity analyses were performed to assess whether WMLV is significantly associated with cognitive performance independent of WRAT reading grade level. First, we repeated the association analysis between race and cognitive performance with adjustment of WRAT reading first instead of education using both European Americans and African Americans. Second, we fitted the same models only in African American participants. Three Poisson models were fitted to assess the association among WRAT, WMLV, and performance on cognitive testing: (a) adjustment for age, sex, HbA1c, BMI, hypertension, statins, CVD, smoking, diabetes duration, CES-D (depression), MRI scanner, TICV, and WMLV (but not WRAT); (b) additional adjustment for WRAT, but not MRI scanner, TICV, and WMLV; and (c) adjustment for all the covariates in the initial model plus WRAT. To compare the education effect and WRAT effect, we also included Models 4 and 5 by replacing WRAT with reported education.

To address potential bias in use of 3.0-T versus 1.5-T MRI scanner, 15 African American participants underwent both a 1.5-T and a 3-T MRI to assess correlations in cerebral volumes. We next performed two sensitivity analyses. The first used data in the 15 participants to calibrate 3.0 to 1.5 T readings (calibration equation estimated using a linear regression model). All the analyses regarding WMLV-described previously were repeated. Second, we performed subgroup analyses for participants on the 1.5 T scanner only (669 European American and 86 African American).

Results

Table 1 displays demographic, clinical, imaging, and cognitive characteristics in all 1,204 participants with T2D, as well as separately in 684 European Americans from 505 families and 520 African Americans from 512 families. The cohort was 56 per cent female, with mean ± SD age 62.8 ± 10.3 years, T2D duration 14.3 ± 7.8 years, and HbA1c 7.7 ± 1.7%. Statins were taken by 51.5 per cent of participants and 53.9 per cent were current or former smokers. Prior CVD defined as myocardial infarction, stroke, transient ischemic attack, and coronary artery angioplasty or stenting or bypass grafting was reported by 31.4 per cent.

African Americans were mean 5.9 years younger than European Americans ($p < .001$), with 1.9-year shorter T2D durations ($p < .001$) due to earlier age at onset of diabetes. Compared with European Americans, African Americans reported higher levels of education, more frequent receipt of statins, and less prevalent CVD. In univariate analyses, African Americans had higher HbA1c, diastolic blood pressure, GMV, hippocampal GMV, and lower TICV and WMV than European Americans. Similar systolic blood pressures and fasting glucose levels were observed.

Relative to European Americans, African Americans had poorer performance on the 3MSE, RAVLT delayed recall, and category fluency test, without significant differences in DSC or Stroop interference. Depression scores and anxiety were also higher in African Americans than European American. Education estimates from WRAT scores differed substantially from self-reported educational attainment in African Americans (simple κ statistic for agreement = 0.03); WRAT scores were not assessed in European American participants.

Table 2 displays the relationships between brain volumes in African Americans compared with European Americans, in minimally adjusted models (with MRI scanner and TICV covariates) to fully adjusted models (with MRI scanner, TICV, age, sex, diabetes duration, BMI, HbA1c, statins, CVD, smoking, and hypertension covariates). In fully adjusted models, GMV and hippocampal GMV did not differ significantly between the races. In contrast, African Americans had higher WMLV and lower WMV in fully adjusted models, even after accounting for multiple comparisons.

Table 1. Demographic and Clinical Characteristics of Study Participants, by Race

Variable	European Americans (*N* = 684)	African Americans (*N* = 520)	Full sample (*N* = 1,204)	*p*-Value (AA vs EA)
Age, y	65.8 (9.8)	58.9 (9.6)	62.8 (10.3)	<.0001
Female	360 (52.6)	314 (60.4)	674 (56.0)	.0088
Education				<.0001
<12 (less than high school)	103 (15.1)	63 (12.1)	166 (13.8)	
=12 (high school graduate)	305 (44.7)	144 (27.7)	449 (37.4)	
>12 (more than high school)	274 (40.2)	313 (60.2)	587 (48.8)	
Education (WRAT)				
<12 (less than high school)		395 (80.9)		
=12 (high school graduate)		59 (12.1)		
>12 (more than high school)		34 (7.0)		
Ever smokers	362 (53.3)	283 (54.7)	645 (53.9)	.5866
Hypertension	606 (88.9)	440 (86.4)	1046 (87.8)	.2087
Hemoglobin A1c (%)	7.5 (1.4)	8.0 (2.0)	7.7 (1.7)	<.0001
Statin	333 (48.9)	283 (55.0)	616 (51.5)	.0353
Prior cardiovascular disease	234 (35.8)	134 (25.8)	368 (31.4)	.0003
Age of diabetes, y	50.6 (10.5)	45.6 (10.1)	48.4 (10.6)	<.0001
Duration of diabetes, y	15.2 (7.7)	13.3 (7.7)	14.3 (7.8)	<.0001
Waist (cm)	109.7 (15.7)	112.6 (17.3)	111.0 (16.5)	.0166
Hip (cm)	115.3 (15.3)	119.0 (17.2)	116.9 (16.3)	.0002
Body mass index, mean (*SD*) [kg/m^2]	32.7 (6.5)	34.7 (8.0)	33.5 (7.2)	<.0001
Systolic blood pressure (mm Hg)	130.5 (17.6)	131.6 (18.1)	131.0 (17.8)	.2656
Diastolic blood pressure (mm Hg)	71.3 (10.0)	76.8 (11.1)	73.7 (10.9)	<.0001
Glucose (mg/dL)	146.5 (54.1)	149.8 (65.1)	148.0 (59.2)	.9075
Total intracranial volume (cc)	1355 (136.8)	1293 (136.2)	1328 (139.9)	<.0001
Gray matter volume (cc)	522.1 (54.6)	553.8 (64.0)	535.8 (60.9)	<.0001
White matter volume (cc)	571.0 (69.5)	495.0 (64.9)	538.1 (77.3)	<.0001
White matter lesion volume (cc)	4.6 (8.7)	6.5 (13.1)	5.5 (10.9)	.0921
Median (IQR)	1.6 (0.2, 5.0)	1.5 (0.2, 6.4)	1.6 (0.2, 5.3)	
Hippocampal gray matter volume (cc)	8.9 (1.2)	9.2 (1.0)	9.0 (1.1)	.0002
Modified mini mental state exam	91.0 (6.9)	86.0 (8.3)	88.8 (8.0)	<.0001
RAVLT (sum of 5 trials, 0–75)	40.8 (10.2)	37.8 (8.8)	39.5 (9.7)	<.0001
Digit symbol substitution (0–133)	50.3 (16.1)	49.4 (16.4)	49.9 (16.3)	.1964
RAVLT delayed recall (0–15)	7.0 (3.5)	5.6 (3.2)	6.4 (3.5)	<.0001
Stroop (Trial 3 – Trial 1, s)	39.7 (20.2)	38.5 (17.3)	39.2 (19.0)	.3308
Median (IQR)	34.0 (28.0, 46.0)	35.0 (28.0, 47.0)	35.0 (28.0, 46.0)	
Category fluency for animals	16.6 (4.7)	15.7 (4.6)	16.2 (4.7)	.0013
Median (IQR)	16.0 (13.0, 20.0)	15.0 (13.0, 19.0)	16.0 (13.0, 19.0)	
Anxiety	4.4 (3.8)	5.0 (4.5)	4.7 (4.2)	.0124
Median (IQR)	3.0 (2.0, 6.0)	4.0 (2.0, 7.0)	3.0 (2.0, 7.0)	
Total CESD score	7.7 (5.3)	8.5 (5.6)	8.1 (5.4)	.0126
Median (IQR)	7.0 (4.0, 10.0)	7.0 (4.0, 12.0)	7.0 (4.0, 11.0)	

Notes: Data expressed as mean (*SD*) for continuous characteristics; *n* (%) for discrete characteristics; median (min–max) for variables with skewed distributions. RAVLT = Rey Auditory Verbal Learning Test; CES-D = Center for Epidemiological Studies-Depression; AA = African American; EA = European American.

Supplementary Table S1 shows the raw 3MSE score and cognitive impairment by race, age, and education groups. The proportion of participants with scores consistent with cognitive impairment was generally higher in the lower education groups and the older age groups.

Table 3 displays relationships between cognitive test performance in African Americans compared with European Americans, in minimally adjusted (with age, sex, self-reported education, and HbA1c covariates) to fully adjusted models (prior covariates + hypertension, diabetes duration, BMI, statins, CVD, smoking, and depression covariates). Significantly higher WMLV was seen in African Americans than European Americans. In addition, marked reclassification of self-reported educational attainment was observed in African Americans based on the performance of the WRAT. Therefore, sequential models were considered that further adjusted for WMLV (considering TICV and MRI scanner) and for both WMLV and WRAT. These models were analyzed to determine whether racial differences in cognitive performance were attributable to cerebral small vessel disease (WMLV) and quality of education (WRAT). Without considering WMLV and WRAT performance, significant racial differences were observed for performance on the 3MSE ($p = 7.0 \times 10^{-62}$), DSC ($p = 6.2 \times 10^{-23}$), RAVLT-delayed recall ($p = 5.2 \times 10^{-31}$), Stroop interference ($p = .001$), and category fluency for animals ($p = 6.8 \times 10^{-14}$). These racial differences were substantially reduced when WMLV was included in the subsequent model. They were nearly fully abrogated with the subsequent inclusion of WRAT reading grade level in the model. However, a significant difference remained in RAVLT performance between African Americans and European Americans even after adjustment for WRAT. These results suggest that racial differences in cognitive

Table 2. Associations Between European American and African American Race With Brain Volumes on Cerebral MRI

Variable	Covariate	β (95% CI)*	*p*-Value
White matter volume	TICV, MRI scanner	−12.65 (−19.76, −5.54)	.0005
White matter volume	Above + age, sex, diabetes duration	−12.54 (−19.85, −5.24)	.0008
White matter volume	Above + BMI, HbA1c	−13.01 (−20.50, −5.52)	.0007
White matter volume	Above + statins, CVD, smoking, hypertension	−12.70 (−20.34, −5.06)	.0011
Gray matter volume	TICV, MRI scanner	12.97 (3.79, 22.16)	.0056
Gray matter volume	Above + age, sex, diabetes duration	4.32 (−2.55, 11.18)	.2179
Gray matter volume	Above + BMI, HbA1c	4.44 (−2.72, 11.60)	.2241
Gray matter volume	Above + statins, CVD, smoking, hypertension	3.89 (−3.41, 11.18)	.2963
White matter lesion volume	TICV, MRI scanner	2.35 (−0.40, 5.10)	.0940
White matter lesion volume	Above + age, sex, diabetes duration	4.27 (1.62, 6.92)	.0016
White matter lesion volume	Above + BMI, HbA1c	4.21 (1.49, 6.93)	.0024
White matter lesion volume	Above + statins, CVD, smoking, hypertension	4.49 (1.77, 7.22)	.0012
Hippocampal GMV	TICV, MRI scanner	0.27 (0.02, 0.51)	.0336
Hippocampal GMV	Above + age, sex, diabetes duration	0.06 (−0.16, 0.28)	.6016
Hippocampal GMV	Above + BMI, HbA1c	0.02 (−0.20, 0.25)	.8316
Hippocampal GMV	Above + statins, CVD, smoking, hypertension	0.01 (−0.21, 0.24)	.9138

Notes: *African American:European American regression coefficient and 95% Confidence Interval.

BMI = Body mass index; CVD = cardiovascular disease; GMV = Gray matter volume; HbA1c = Hemoglobin A1c; MRI = Magnetic resonance imaging; TICV = Total intracranial volume.

European Americans were the reference group.

Table 3. Serially Adjusted Cognitive Testing Relationships Between African Americans and European Americans

Variable	Covariates	Relative risk (95% CI)*	*p*-Value
3MSE	Age, education, sex, HbA1c	0.51 (0.47,0.55)	7.1×10^{-69}
3MSE	Above + BMI, hypertension, statins, CVD, smoking, CES-D	0.51 (0.47,0.55)	7.0×10^{-62}
3MSE	Above + MRI scanner, TICV, WMLV	0.54 (0.46,0.63)	2.6×10^{-14}
3MSE	Above + WRAT	0.82 (0.68,0.97)	.0219
Digit symbol coding	Age, education, sex, HbA1c	0.85 (0.82,0.88)	3.4×10^{-21}
Digit symbol coding	Above + BMI, hypertension, statins, CVD, smoking, CES-D	0.84 (0.81,0.87)	6.2×10^{-23}
Digit symbol coding	Above + MRI scanner, TICV, WMLV	0.87 (0.82,0.93)	3.4×10^{-5}
Digit symbol coding	Above + WRAT	0.98 (0.91,1.06)	.6529
RAVLT-delayed recall	Age, education, sex, HbA1c	0.67 (0.63,0.72)	5.5×10^{-35}
RAVLT-delayed recall	Above + BMI, hypertension, statins, CVD, smoking, CES-D	0.69 (0.64,0.73)	5.2×10^{-31}
RAVLT-delayed recall	Above + MRI scanner, TICV, WMLV	0.70 (0.61,0.81)	5.1×10^{-7}
RAVLT-delayed recall	Above + WRAT	0.79 (0.68,0.91)	.0009
Category fluency	Age, education, sex, HbA1c	0.88 (0.85,0.91)	3.9×10^{-14}
Category fluency	Above + BMI, hypertension, statins, CVD, smoking, CES-D	0.87 (0.84,0.90)	6.8×10^{-14}
Category fluency	Above + MRI scanner, TICV, WMLV	0.90 (0.84,0.96)	.0016
Category fluency	Above + WRAT	0.99 (0.91,1.07)	.7914
Stroop interference	Age, education, sex, HbA1c	1.11 (1.06,1.17)	7.2×10^{-5}
Stroop interference	Above + BMI, hypertension, statins, CVD, smoking, CES-D	1.09 (1.04, 1.16)	.0012
Stroop interference	Above + MRI scanner, TICV, WMLV	0.99 (0.89,1.10)	.8001
Stroop interference	Above + WRAT	0.87 (0.76,0.98)	.0264

Notes: *African American:European American Relative Risk and 95% Confidence Interval.

3MSE = Modified Mini-Mental State Exam; BMI = Body mass index; CES-D = Center for Epidemiological Studies-Depression; CVD = Cardiovascular disease; HbA1c = Hemoglobin A1c; MRI = Magnetic resonance imaging; RAVLT = Rey Auditory Verbal Learning Test; TICV = Total intracranial volume; WMLV = White matter lesion volume; WRAT = Wide-range achievement test.

European Americans were the reference group.

performance between African Americans and European Americans with T2D were partially explained by more severe cerebral small vessel disease in African Americans. Poorer quality of education in African Americans appeared to account for much of the remaining difference.

We repeated the analysis shown in Table 3 adjusting for WRAT first instead of education in the full sample. The relative risks for racial difference from the partially adjusted model (with adjustment for WRAT and other factors; Model 2) and fully adjusted model (with the additional adjustment for WMLV; Model 3) did not change appreciably (Supplementary Table S2). Similarly, in the African American only analysis (Supplementary Table S3), adjustment for WRAT did not change the association between WMLV and cognitive test performance, except for 3MSE. Adjustment for WRAT improved the precision of the estimates of association between WMLV and 3MSE, which resulted in the test having a lower *p*-value. In summary, effects of WMLV and WRAT on cognitive performance generally appeared to be independent.

Furthermore, when comparing Model 5 with Model 3, the association between WRAT and cognitive test performance was stronger than the association between education and cognitive test performance. This was pronounced for the association with Stroop interference, where WRAT showed a significant association after adjusting for other covariates, whereas self-reported education level did not show any association. When adjusting for WRAT, the association between WMLV and cognitive test performance was also stronger compared with the association when adjusting for self-reported education. This reveals that WRAT reading level is more strongly associated with cognitive test performance in African Americans than self-reported education.

For the scanner sensitivity analysis, between-scanner correlation for WMLV was 0.97; therefore, results were strongly correlated. Results for calibrated WMLV analyses corresponding to Tables 2 and 3 are shown in Supplementary Tables S4 and S5. Supplementary Tables S6 and S7 display subgroup analyses for participants on the 1.5 T scanner. The sensitivity analyses results were similar to those shown in Tables 2 and 3. These results suggest that the adjustment for scanner magnetic strength to reduce the confounding effect in the models is appropriate.

Discussion

Analyses in the DHS MIND and AA–DHS MIND assessed cerebral structure and cognitive performance in African Americans and European Americans with T2D living in the same region and having similar treatment for CVD risk factors. African Americans had significantly lower volumes of white matter with greater burdens of abnormal white matter (WMLV) consistent with cerebral small vessel disease. The volume of gray matter was not significantly different between groups. Performance on cognitive testing was substantially poorer in African Americans than European Americans, even though African Americans were more likely to report education after high school than European Americans (60.2% vs 40.2%; $p < .001$). However, the poorer cognitive performance observed in nearly all domains in African Americans compared with European Americans was fully abrogated when WMLV and reading grade level in African Americans (in place of self-reported education) were included in the model. We believe that the change in relationships after consideration of WRAT reading level probably reflects poorer educational quality in African Americans, not that lower reading levels predicted cognitive decline in African Americans. We also recognize the limitation that our European American participants did not undergo WRAT testing.

These results demonstrate that potentially remediable factors contribute to the poorer performance on cognitive testing in African Americans. Higher volumes of white matter disease may be preventable with more intensive control of blood pressure, hyperglycemia, lipids, and smoking cessation (28). Despite what appeared to be relatively similar access to healthcare in these participants based on treatment with statins, achieved systolic blood pressures, and fasting blood sugars, poorer control of other risk factors may have been present in African Americans. A higher diastolic blood pressure and HbA1c were recorded in African Americans in this sample, although racial differences in the HbA1c assay may contribute; blood sugar control was not likely to be substantially different between the racial groups (29). In addition, quality of healthcare, particularly preventative healthcare, could have differed between racial groups. Ensuring quality of healthcare, improving health literacy, neighborhood safety (to engage in outdoor exercise), and availability of affordable and nutritious food options in communities where African Americans may dwell all remain critical.

A striking observation was that reclassification of education in African Americans using WRAT reading grade level led to markedly different impressions of education. Only 19 per cent of African Americans in the sample performed at or above the high school graduate level, despite 88 per cent reporting this level of formal education (Table 1). When WRAT performance was included in a final model (replacing self-reported education in African Americans), all differences in cognitive performance except for RAVLT were no longer statistically significant after accounting for multiple testing. Simply including WRAT reading grade level in the final model for cognitive testing (including the covariates age, sex, HbA1c, BMI, statins, CVD, smoking, hypertension, depression, WMLV, TICV, and MRI scanner) increased the p-value for African American versus European American effect on 3MSE from 2.6×10^{-4} to 0.02, for DSC from 3.4×10^{-5} to 0.65, for RAVLT-delayed recall from 5.1×10^{-7} to 0.0009, and for category fluency for animals from 0.002 to 0.79. In contrast, Stroop interference showed lower p-values with inclusion of WRAT (0.80 to 0.03, respectively). The only racial comparison in cognitive performance that met statistical significance after accounting for WRAT (based on multiple testing) was RAVLT-delayed recall; even here, significance was diminished by 3 orders of magnitude. African Americans in this sample had poorer basic education despite more years of formal education. This effect is likely to reflect poorer quality of education in these older African Americans residing in the mid-Atlantic region. We note that the development and progression of white matter lesions should be preventable (both in African Americans and European Americans) with intensive hypertension and blood sugar control, reductions in LDL cholesterol, and smoking avoidance. Poorer quality of education can also be reversed with appropriate and equal resources being provided to children in all schools. Therefore, results of this study are both reassuring and disturbing. The often reported poorer cognitive performance in African Americans (and other U.S. ethnic minorities), compared with European Americans, appears to relate to reversible factors, reducing cerebrovascular disease risk factors and improving the quality of education. It is also evident that equalizing treatment for vascular disease risk factors and improving the quality of education for underserved minority populations is a complex undertaking that requires extensive effort and expense. Socioeconomic factors likely play prominent roles in these findings. The 5-year average geocode-based median household income in inflation-adjusted dollars was collected in participants from 2008 to 2013 during the time they were recruited (data not shown). Adjusting for income revealed continued poorer cognitive performance in African Americans than European Americans on the 3MSE, RAVLT-delayed recall, and Digit Symbol Coding, but not on STROOP or category fluency. Thus, socioeconomic status (SES) may contribute to observed racial differences in cognitive performance, potentially based on relationships between SES and quality of neighborhood schools. However, geocode data were lacking in study participants during childhood; adult data were analyzed.

This report has strengths and some limitations. Strengths include a relatively large biracial sample with access to healthcare based on treatment for hypertension, lipids, and blood sugars and with extensive brain imaging and cognitive testing. Limitations include cross-sectional data and assessment of a type 2 diabetes–affected population. Results may not be generalizable to populations without T2D, although reports in cohorts without diabetes suggest they likely are (4, 5, 10, 30–32). Finally, WRAT testing was only performed in African American participants in the AA–DHS MIND, not in European Americans enrolled in the DHS MIND study. Therefore, direct comparisons on educational achievement level could not be

performed between the ethnic groups. However, the correlation between WRAT performance and self-reported education is likely higher in European Americans than African Americans, which suggests that the association parameters are less biased (33). Sayegh and colleagues demonstrated that race/ethnicity and educational quality significantly affect differences in WRAT score between African Americans and European Americans (34). In that report, the WRAT reading score predicted neurocognitive performance. Although this finding strengthens our conclusions, future analyses should include WRAT testing and self-reported education in participants in all racial groups. It remains uncertain whether European American background, versus African American, equates to a more uniform standard of quality of education based on years in school.

In contrast to widely recognized ethnic differences between African and European ancestral populations that contribute to higher rates of kidney disease and lower rates of osteoporosis and subclinical atherosclerosis in African Americans (35), this hypothesis generating report suggests that poorer cognitive performance in African Americans compared with European Americans may relate to environmental factors. Gray matter volumes on MRI did not differ between African Americans and European Americans in this report. It is critical that equal quality of education and access to basic and preventive healthcare be available to all in the United States. Attention to these potentially remediable factors could reduce racial disparities in cognitive dysfunction and dementia in the aging and high-risk population with diabetes mellitus.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

This work was supported by National Institutes of Health General Clinical Research Center of Wake Forest School of Medicine M01 RR07122; National Institute of Neurological Disorders and Stroke R01 NS075107 (to B.I.F.) and NS058700 (to D.W.B.); and National Institute of Diabetes and Digestive and Kidney Diseases R01 DK071891 (to B.I.F.).

Acknowledgments

The authors thank DHS MIND study participants and research coordinators.

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