# Subclinical Atherosclerosis Is Inversely Associated With Gray Matter Volume in African Americans With Type 2 Diabetes

Barry I. Freedman,[1,2] Jasmin Divers,[3] Christopher T. Whitlow,[4] Donald W. Bowden,[2,5] Nicholette D. Palmer,[2,5] S. Carrie Smith,[5] Jianzhao Xu,[2] Thomas C. Register,[6] J. Jeffrey Carr,[7] Benjamin C. Wagner,[4] Jeff D. Williamson,[8] Kaycee M. Sink,[8] and Joseph A. Maldjian[4]

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## OBJECTIVE

**Relative to European Americans, African Americans manifest lower levels of computed tomography–based calcified atherosclerotic plaque (CP), a measure of subclinical cardiovascular disease (CVD). Potential relationships between CP and cerebral structure are poorly defined in the African American population. We assessed associations among glycemic control, inflammation, and CP with cerebral structure on MRI and with cognitive performance in 268 high-risk African Americans with type 2 diabetes.**

## RESEARCH DESIGN AND METHODS

**Associations among hemoglobin $A_{1c}$ ($HbA_{1c}$), C-reactive protein (CRP), and CP in coronary arteries, carotid arteries, and the aorta with MRI volumetric analysis (white matter volume, gray matter volume [GMV], cerebrospinal fluid volume, and white matter lesion volume) were assessed using generalized linear models adjusted for age, sex, African ancestry proportion, smoking, BMI, use of statins, $HbA_{1c}$, hypertension, and prior CVD.**

## RESULTS

**Participants were 63.4% female with mean (SD) age of 59.8 years (9.2), diabetes duration of 14.5 years (7.6), $HbA_{1c}$ of 7.95% (1.9), estimated glomerular filtration rate of 86.6 mL/min/1.73 $m^2$ (24.6), and coronary artery CP mass score of 215 mg (502). In fully adjusted models, GMV was inversely associated with coronary artery CP (parameter estimate [β] −0.47 [SE 0.15], $P = 0.002$; carotid artery CP (β −1.92 [SE 0.62], $P = 0.002$; and aorta CP [β −0.10 [SE 0.03] $P = 0.002$), whereas $HbA_{1c}$ and CRP did not associate with cerebral volumes. Coronary artery CP also associated with poorer global cognitive function on the Montreal Cognitive Assessment.**

## CONCLUSIONS

**Subclinical atherosclerosis was associated with smaller GMV and poorer cognitive performance in African Americans with diabetes. Cardioprotective strategies could preserve GMV and cognitive function in high-risk African Americans with diabetes.**


[1]Department of Internal Medicine, Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC
[2]Center for Diabetes Research and Center for Genomics and Personalized Medicine Research, Wake Forest School of Medicine, Winston-Salem, NC
[3]Division of Public Health Sciences, Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC
[4]Advanced Neuroscience Imaging Research Laboratory, Department of Radiologic Sciences, Wake Forest School of Medicine, Winston-Salem, NC
[5]Department of Biochemistry, Wake Forest School of Medicine, Winston-Salem, NC
[6]Department of Pathology, Wake Forest School of Medicine, Winston-Salem, NC
[7]Department of Radiology, Vanderbilt University School of Medicine, Nashville, TN
[8]Section on Gerontology and Geriatric Medicine, Wake Forest School of Medicine, Department of Internal Medicine, Winston-Salem, NC

Corresponding author: Barry I. Freedman, bfreedma@wakehealth.edu.

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J.A.M. is currently affiliated with the Department of Radiology, The University of Texas Southwestern Medical Center, Dallas, TX.

Relative to European Americans, the effects of subclinical cardiovascular disease (CVD), glycemic control, and metabolic risk factors on cerebral structure and cognitive performance in African Americans are understudied. Improvements in vascular imaging and neuroimaging permit precise assessments of relationships between subclinical atherosclerosis (calcified atherosclerotic plaque [CP]) and cerebral structure (1). Metabolic risk factors including adiposity, inflammation, glycemic control in patients with diabetes, and CVD have been associated with alterations in cerebral structure and reduced cognitive performance (1–5).

African Americans have an increased risk for the development of type 2 diabetes (T2D) and diabetic kidney disease compared with European Americans, with paradoxically reduced rates of vascular CP and markedly lower rates of myocardial infarction when provided equivalent access to health care (6–9). In addition to different environmental exposures, evidence supports inherited contributions to ethnic-specific rates of T2D-associated subclinical atherosclerosis (10–12). Due to racial differences in susceptibility to CP, we hypothesized that relationships between subclinical CVD and brain structure might differ in populations with European and recent African ancestry. The present analyses were performed in the understudied high-risk African American population with T2D to assess relationships among subclinical CVD, cerebral structure, and cognitive performance.

## RESEARCH DESIGN AND METHODS

### Participants

African Americans who participated in the Wake Forest School of Medicine (WFSM) African American-Diabetes Heart Study (AA-DHS) and subsequently returned to participate in the AA-DHS MIND were evaluated (11,13,14). AA-DHS MIND was initiated to improve the understanding of environmental and inherited risk factors for subclinical cerebrovascular disease and to assess the relationships among CVD, cerebral volumes, and cognitive performance in African Americans. Participants with serum creatinine concentrations >2 mg/dL were not recruited because diabetic kidney disease is independently associated with CVD.

The AA-DHS recruited unrelated participants with clinically diagnosed T2D based on an age at onset of >30 years in the absence of diabetic ketoacidosis, with active diabetes treatment (with insulin and/or oral hypoglycemic agents), a fasting blood glucose of ≥126 mg/dL, a nonfasting blood glucose of ≥200 mg/dL, or a hemoglobin $A_{1c}$ ($HbA_{1c}$) of ≥6.5% (15). Hypertension was considered present if it had been diagnosed by a physician, antihypertensive medications were prescribed, or clinic blood pressures were >140/90 mmHg. Studies were approved by the WFSM Institutional Review Board, and all participants provided written informed consent.

Examinations were performed in the WFSM Clinical Research Unit. In addition to providing medical, dietary, exercise, and educational histories, vital signs and medications were recorded. Subjects had fasting blood work for the measurement of chemistries, $HbA_{1c}$, lipid profiles, hs-CRP, thyroid-stimulating hormone, vitamin $B_{12}$, and a spot urine albumin and creatinine concentration for urine albumin-to-creatinine ratio (UACR) (LabCorp, Burlington, NC). Estimated glomerular filtration rate (eGFR) was computed using the Chronic Kidney Disease Epidemiology Collaboration equation (16). After a morning snack, cognitive testing and cerebral MRI were performed (17,18). As reported, computed tomography (CT) scans of the neck, chest, and abdomen were performed to measure CP in the carotid arteries, coronary arteries, and abdominal aortoiliac bed using 4- or 16-channel multidetector CT scanners (LightSpeed Qx/i and 16 Pro; GE Healthcare, Waukesha, WI) (15).

### CP Scoring

CP was measured in the coronary, carotid, and infrarenal abdominal aorta arteries with single-detector and multidetector CT systems using a standard electrocardiogram-gated CT scanning protocol based on those currently implemented in the National Heart, Lung, and Blood Institute Multi-Ethnic Study of Atherosclerosis (MESA) (19). The calcium mass score (milligrams of calcium hydroxyapatite) is derived as the product of the density of the calcium in the plaque × the volume of CP on a pixel-by-pixel basis measured using SmartScore (GE Healthcare, Waukesha, WI). This score is highly correlated with the standard Agatston score using a 90-Hounsfield unit threshold. A minimum lesion size of 0.5 $mm^2$ (two adjacent pixels) was used for comparability between vascular territories. When scoring CP, >96% interobserver and intraobserver reproducibility were observed. Calcium mass scores of "0 mg" reflect the absence of CP in a given vascular bed. Beds that had interventions (bypass surgery, angioplasty, stent, or endarterectomy) were excluded.

### Cerebral MRI

#### *MRI Acquisition*

The initial 41 scans were performed on a 1.5-T EXCITE HD scanner with twin-speed gradients using a neurovascular head coil (GE Healthcare). High-resolution T1 anatomic images were obtained using a three-dimensional (3D) volumetric inversion recovery spoiled gradient recalled sequence (repetition time [TR] 7.36 ms, echo time [TE] 2.02 ms, inversion time [TI] 600 ms, fractional anisotropy [FA] 20°, 124 slices, field of view [FOV] 24 cm, matrix size 256 × 256, 1.5 mm slice thickness). Fluid-attenuated inversion recovery images were acquired in the axial plane (TR 8,002 ms, TE 101.29 ms, TI 2,000 ms, FA 90°, FOV 24 cm, matrix size 256 × 256, 3 mm slice thickness). Because of a change in scanners at the WFSM Center for Biomolecular Imaging, the subsequent 227 scans were performed on a 3.0-T Skyra MRI Scanner (Siemens Healthcare, Erlangen, Germany) using a high-resolution 20-channel head/neck coil. T1-weighted anatomic images were obtained using a 3D volumetric magnetization-prepared rapid acquisition gradient echo sequence (TR 2,300 ms, TE 2.99 ms, TI 900 ms, FA 9°, 192 slices, voxel dimension 0.97 × 0.97 × 1 mm). Fluid-attenuated inversion recovery images were acquired using a 3D SPACE inversion recovery sequence (TR 6,000 ms, TE 283 ms, TI 2,200 ms, FA 120°, 160 slices, voxel dimensions 1.1 × 1.1 × 1 mm).

#### *Image Segmentation*

Structural T1 images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF); were normalized to the Montreal Neurological Institute imaging space; and

were 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 (20) 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 plus WMV plus CSFV) were determined from the VBM8 automated segmentation procedure, which outputs a text file with values for native space total GMV, WMV, and CSFV. Additional region of interest (ROI)–based measures were generated for the right and left hippocampus using the automated anatomical labeling atlas (21), as implemented in the wfu_pickatlas (22). 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. All volumes were reported in cubic centimeters by summing the voxel values, multiplying by the voxel volume (in cubic millimeters), and dividing by 1,000.

#### *WM Lesion Segmentation*

WM lesion (WML) segmentation was performed using the lesion segmentation toolbox (23) for SPM8 at a threshold ($k$) of 0.25. We validated the lesion segmentation toolbox in the AA-DHS MIND against expert manual segmentation and identified the optimum threshold in this population (24). Normalization to the Montreal Neurological Institute imaging space was accomplished by coregistration with the structural T1 and application of the normalization parameters computed in the VBM8 segmentation procedure. WML volume (WMLV), reported in cubic centimeters, was determined by summing the binary lesion maps and multiplying by the voxel volume.

#### *Interscanner Variability*

To account for between-scanner variation, 15 study participants were imaged using both 1.5-T and 3.0-T MRI instruments. Imaging data from these individuals underwent identical processing for both scanners. Adjustments in all brain volumes except WMLV were made in the 41 participants who had 1.5-T MRI scans to account for any systematic differences in volumetric measures between scanners (25,26). Analyses based on WMLV were based only on the 3.0-T MRI scans ($n$ = 227), because the range of WMLV scores in this calibration subsample ($n$ = 15) did not adequately represent the distribution of WMLV scores in the full data set and adjustment could not be performed.

### Cognitive Testing

Interviewers were trained, certified, and assessed for quality control by one investigator (K.M.S.). General cognitive function was assessed with the Montreal Cognitive Assessment (MoCA) and the Modified Mini-Mental State (3MS) examination. MoCA is a screening instrument for mild cognitive dysfunction that is composed of specific items to evaluate short-term memory, visuospatial abilities, executive function, attention, concentration, working memory, and language, as well as orientation to time and place (range 0–30 [higher score is better]) (18,27). 3MS is also a general assessment instrument for assessing cognitive impairment and dementia, with items evaluating orientation, registration, attention/calculation, recall, language, spatial abstraction, and delayed recall (range 0–100 [higher score is better]) (17).

### Statistical Analyses

Calibration equations between the 1.5-T and 3.0-T MRI measures were estimated using robust linear regression (28). These equations were used to determine the corresponding 3.0-T MRI value from an MRI scan performed on a 1.5-T scanner. $R^2$ values obtained from the calibration equations also provide an estimate of the reliability of 1.5-T measurements as predictors of the 3.0-T MRI values. Since the MRI measurements serve as the dependent variables in the models, additional variation in the calibrated 1.5-T measurements do not bias the parameter estimates; they only reduce the power of the association test.

Generalized linear models were fitted to test for associations between parameters of coronary artery CP, carotid artery CP, aorta CP, $HbA_{1c}$, fasting glucose, and C-reactive protein (CRP) (independent variables) and *1*) brain volumes on MRI or *2*) cognitive performance (dependent variables). Variables derived from the brain MRI were total ICV, WMLV, GMV, WMV, CSFV, hippocampal GMV, hippocampal WMV, and hippocampal CSFV. The Box-Cox method (29) was applied to identify the appropriate transformation best approximating the distributional assumptions of conditional normality and homogeneity of the variance of the residuals. This method suggested taking the natural logarithm of CSF, WMV, and WMLV, and the use of power functions for GMV, hippocampal WMV, and hippocampal GMV. The exponents were 1.5, 2.0, and 2.5 respectively. The $\lambda$ values considered in the Box-Cox evaluation ranged between $-3$ and 3; therefore, the estimated exponents were not near the boundaries of the maximum likelihood function. The simplest models were adjusted for ICV, age at CP measurement, and time between the CT scan for measurement of CP and the MRI scan. Additional adjustments were made for sex, African ancestry proportion (estimated using ancestry informative markers that were identified from a genome-wide association study), BMI, $HbA_{1c}$, hypertension (yes/no), use of statin medications, and history of CVD.

Negative binomial regressions were fitted for MoCA and 3MS to account for the level of overdispersion. These models typically fit the observed data better than generalized linear models, while preserving the discrete nature of the observed scores, which facilitates the interpretation of observed results. The logarithm function was used to link the mean of the outcome with the predictors included in the model. The effect of age on the cognitive function outcomes was fitted using a third-degree polynomial. Parameter estimation was performed using the maximum likelihood approach, and all models reached convergence. Diagnostic tests based on the deviance residuals were performed to make sure that the model assumptions were met. The models used to test for the association between CP and cognitive function were adjusted for age, sex, education level, African ancestry proportion, time from CT scan to cognitive testing, smoking, BMI, $HbA_{1c}$, the presence of hypertension, the use of statin medications, and history of CVD. The presence of hypertension, the

use of statin medications, and history of CVD were not included in the models used to test for association between cognitive function and $HbA_{1c}$. Level of education was defined as follows: 1, less than high school; 2–5, number of years in high school (5, high school graduate); 6–9, number of years in college (9, college graduate); and 10, postgraduate degree.

Factors governing the presence of CP are not necessarily the same as those influencing the amount of plaque once the calcification process is initiated (30). Therefore, association effects were tested for both the presence and the amount of CP when present for all cerebral structure and cognitive performance measures.

Adjustment for multiple testing was performed systematically in this study, mainly because of the known correlation among the outcome variables and the predictors considered separately. Ignoring this correlation and focusing solely on fully adjusted model results, the Bonferroni-corrected significance threshold would be $1.4 \times 10^{-3}$; that is, 0.05 divided by 48 (6 outcomes times 8 predictors). However, the effective number of tests could be as low as 18.3 (4.3 among the outcomes [GMV, WMV, CSFV, WMLV, MoCA, and 3MS] and 4.26 among the predictors [3 continuous and 3 binary measures of CP plus CRP and $HbA_{1c}$]) (31).

## RESULTS

Table 1 contains demographic and cognitive characteristics of this AA-DHS MIND sample; results are shown in the full sample ($n$ = 268) and separately for those with ($n$ = 210) and without ($n$ = 58) detectable aorta CP. For individuals with detectable CP (mass score in milligrams, $>0$) in at least two of the three vascular beds, the Spearman rank correlation for amount of CP was 0.44 between the aorta and coronary arteries, 0.26 between the aorta and carotid arteries, and 0.18 between the coronary and carotid arteries. Prior CVD events were defined as carotid endarterectomy, coronary artery bypass graft surgery, coronary artery angioplasty/stent, stroke, or myocardial infarction; 23.3% of AA-DHS participants reported prior CVD events at the baseline CT study visit. Table 2 displays results of the laboratory and cerebral MRI scans in participants. The reliability coefficient ($R^2$) between MRI measures obtained on the 1.5-T and 3.0-T scanners ranged between 98% for total ICV and 92% for GMV. Among participants, 63.4% were female, with a mean (SD) age of 59.8 years (9.2). Participants had a mean (SD) T2D duration of 14.5 years (7.6), $HbA_{1c}$ of 7.9% (1.9), BMI of 34.9 kg/m$^2$ (8.2), eGFR of 86.6 mL/min/1.73 m$^2$ (24.6), and UACR of 148.6 mg/g (513) (median 9.1 mg/g). Statin medications were received by 50.4% of participants, and the mean LDL cholesterol, HDL cholesterol, and triglyceride concentrations were 109.1, 47.8, and 122.0 mg/dL, respectively. At the MIND visit, 88% of participants had a diagnosis of hypertension with mean (SD) systolic and diastolic blood pressures 131.9 mmHg (18.1) and 76.1 mmHg (10.7), respectively. Cognitive testing revealed a mean (SD) 3MS score of 86.1 (8.6) and MoCA score of 19.5 (4.0). The time between the CT and MRI scan visits varied between 1.05 and 13.8 years (median 3.6 years, mean [SD] 4.0 years [1.9]).

**Table 1—Demographic and cognitive characteristics of the AA-DHS MIND sample**

| | Full sample ($n$ = 268) | | Aorta CP absent* ($n$ = 58) | | Aorta CP present ($n$ = 210) | | |
|---|---|---|---|---|---|---|---|
| Variable | $n$ | Mean (SD) median or % | $n$ | Mean (SD) median or % | $n$ | Mean (SD) median or % | $P$ value |
| Age (years) | 267 | 59.8 (9.25) 59.56 | 58 | 52.73 (8.57) 52.81 | 209 | 61.76 (8.46) 61.78 | $3.5 \times 10^{-10}$ |
| Time between baseline CT and MIND MRI visits (years) | 267 | 4.61 (1.78) 4.28 | 58 | 4.97 (1.98) 4.77 | 209 | 4.52 (1.71) 4.19 | 0.03 |
| Female sex (%) | 268 | 63.43 | 58 | 65.52 | 210 | 62.86 | 0.71 |
| African ancestry | 265 | 0.81 (0.1) 0.82 | 56 | 0.81 (0.1) 0.82 | 209 | 0.81 (0.1) 0.83 | 0.92 |
| BMI (kg/m$^2$) | 268 | 34.85 (8.21) 33.84 | 58 | 37.72 (8.43) 35.93 | 210 | 34.06 (7.99) 32.99 | $4.3 \times 10^{-3}$ |
| Systolic blood pressure (mmHg) | 268 | 131.9 (18.08) 131 | 58 | 126.76 (14.95) 125 | 210 | 133.31 (18.64) 133 | 0.02 |
| Diastolic blood pressure (mmHg) | 268 | 76.08 (10.7) 75.75 | 58 | 78.22 (10.54) 80 | 210 | 75.5 (10.7) 74.25 | 0.04 |
| Prior coronary artery bypass graft (%) | 268 | 3.42 | 58 | 0 | 210 | 4.37 | 0.09 |
| Hypertension (%) | 267 | 88.01 | 58 | 81.03 | 209 | 89.95 | 0.06 |
| Smoking history (pack-years) | 261 | 9.55 (14.68) 1.3 | 58 | 3.2 (7.82) 0 | 203 | 11.36 (15.67) 3 | $8.4 \times 10^{-6}$ |
| Current or past smoker (%) | 267 | 49.06 | 58 | 22.41 | 209 | 56.46 | $4.7 \times 10^{-6}$ |
| Oral diabetes medication (%) | 268 | 79.85 | 58 | 84.48 | 210 | 78.57 | 0.32 |
| Insulin diabetes medication (%) | 268 | 38.43 | 58 | 36.21 | 210 | 39.05 | 0.70 |
| Statin therapy (%) | 266 | 50.38 | 57 | 35.09 | 209 | 54.55 | $9.4 \times 10^{-3}$ |
| ACE/ARB therapy (%) | 268 | 51.87 | 58 | 44.83 | 210 | 53.81 | 0.22 |
| Diabetes duration (years) | 267 | 14.48 (7.57) 12.81 | 58 | 12.93 (6.03) 11.07 | 209 | 14.91 (7.9) 13.24 | 0.09 |
| Education level | | | | | | | $1.6 \times 10^{-4}$ |
| High school education (%) | 268 | 27.99 | 58 | 20.69 | 210 | 30 | |
| Some college or a college diploma (%) | 268 | 43.28 | 58 | 43.1 | 210 | 43.33 | |
| Graduate school education (%) | 268 | 17.91 | 58 | 34.48 | 210 | 13.33 | |
| 3MS, range 0–100 | 268 | 86.05 (8.62) 87 | 58 | 88.52 (8.29) 91 | 210 | 85.37 (8.6) 87 | $5.0 \times 10^{-5}$ |
| MoCA, range 0–30 | 268 | 19.47 (4.01) 20 | 58 | 20.6 (4.68) 21 | 210 | 19.16 (3.75) 20 | 0.01 |

ARB, angiotensin receptor blocker. *Reflects Aorta CP mass score 0.

**Table 2—Laboratory and MRI lesion volumes of the AA-DHS MIND sample**

| | Full sample ($n$ = 268) | | Aorta CP absent* ($n$ = 58) | | Aorta CP present ($n$ = 210) | | |
|---|---|---|---|---|---|---|---|
| Variable | $n$ | Mean (SD) median or % | $n$ | Mean (SD) median or % | $n$ | Mean (SD) median or % | $P$ value |
| UACR at the MIND visit (mg/g) | 262 | 148.64 (513) 9.1 | 54 | 126.06 (423.36) 6.7 | 208 | 154.5 (534.57) 9.65 | 0.10 |
| CKD-EPI eGFR at the MIND visit (mL/min/1.73 $m^2$) | 263 | 86.6 (24.59) 89 | 55 | 92.56 (24.87) 91 | 208 | 85.03 (24.34) 86 | 0.08 |
| CRP at CT visit (mg/dL) | 256 | 1.04 (1.6) 0.57 | 56 | 0.88 (1.06) 0.5 | 200 | 1.08 (1.72) 0.59 | 0.72 |
| Serum glucose at the MIND visit (g/dL) | 263 | 146.75 (59.21) 133 | 55 | 152.09 (63.65) 139 | 208 | 145.34 (58.06) 131.5 | 0.63 |
| $HbA_{1c}$ at the MIND visit (%) | 262 | 7.94 (1.87) 7.4 | 55 | 8.19 (2.22) 8 | 207 | 7.88 (1.76) 7.3 | 0.57 |
| Change in $HbA_{1c}$ between CT and MRI visits (%) | 259 | −0.09 (1.81) −0.1 | 54 | 0.12 (1.74) 0.15 | 205 | −0.14 (1.83) −0.1 | 0.27 |
| HDL cholesterol (mg/dL) | 266 | 47.83 (13.21) 46 | 57 | 47.82 (13.24) 44 | 209 | 47.84 (13.23) 46 | 0.94 |
| LDL cholesterol (mg/dL) | 264 | 109.12 (36.38) 106 | 56 | 111.34 (32.13) 110 | 208 | 108.52 (37.49) 103 | 0.39 |
| Triglycerides (mg/dL) | 266 | 121.97 (91.11) 99.5 | 57 | 127.07 (138.75) 93 | 209 | 120.58 (73.37) 101 | 0.62 |
| Vitamin $B_{12}$ (pg/mL) | 263 | 673.41 (408.64) 563 | 55 | 605.67 (355.85) 506 | 208 | 691.32 (420.45) 573.5 | 0.19 |
| Thyroid-stimulating hormone (μIU/mL) | 263 | 2.01 (1.62) 1.65 | 55 | 2.05 (1.39) 1.73 | 208 | 1.99 (1.68) 1.64 | 0.53 |
| Coronary artery CP (mass score, mg) | 268 | 215.02 (502.90) 11.0 | 58 | 11.39 (39.34) 0 | 210 | 266.90 (553.00) 27.0 | $2.7 \times 10^{-8}$ |
| Coronary CP >0 mg (%) | 268 | 63.6 | 58 | 41.3 | 210 | 69.9 | $5.2 \times 10^{-5}$ |
| Carotid artery CP (mass score, mg) | 267 | 36.46 (118.42) 0 | 57 | 2.8 (12.36) 0 | 210 | 45.6 (131.96) 0 | $2.6 \times 10^{-6}$ |
| Carotid artery CP >0 mg (%) | 267 | 41.2 | 57 | 15.79 | 210 | 48.1 | $1.2 \times 10^{-5}$ |
| Total intracranial volume ($cm^3$) | 268 | 1,291.37 (131.4) 1,279.91 | 58 | 1,298.26 (132.94) 1,274.15 | 210 | 1,289.47 (131.23) 1,283.26 | 0.88 |
| CSFV ($cm^3$) | 268 | 247.33 (47.24) 240.48 | 58 | 224.56 (41.18) 216.34 | 210 | 253.61 (46.96) 244.97 | $5.7 \times 10^{-6}$ |
| GMV ($cm^3$) | 268 | 560.57 (56.11) 557.31 | 58 | 577.82 (55.36) 575.37 | 210 | 555.8 (55.51) 553.7 | $8.1 \times 10^{-3}$ |
| WMV ($cm^3$) | 268 | 485.36 (62.76) 482.74 | 58 | 495.79 (63.78) 493 | 210 | 482.48 (62.32) 476.97 | 0.16 |
| WMLV ($cm^3$) | 265 | 7.69 (14.57) 2.05 | 58 | 6.53 (19.46) 0.51 | 207 | 8.01 (12.92) 2.88 | $4 \times 10^{-4}$ |
| Hippocampal WMV ($cm^3$) | 267 | 2.81 (0.35) 2.85 | 58 | 2.9 (0.35) 2.95 | 209 | 2.79 (0.35) 2.85 | 0.05 |
| Hippocampal GMV ($cm^3$) | 267 | 9.2 (0.98) 9.29 | 58 | 9.36 (0.94) 9.4 | 209 | 9.16 (0.98) 9.25 | 0.17 |
| Hippocampal CSFV ($cm^3$) | 268 | 1.92 (1.15) 1.57 | 58 | 1.58 (0.92) 1.27 | 210 | 2.01 (1.19) 1.65 | $3.1 \times 10^{-3}$ |

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation. *Reflects Aorta CP mass score 0.

In binary analyses (aorta CP present vs. absent), GMV was lower ($P$ = 0.008), CSFV was higher ($P = 5 \times 10^{-6}$), and WMLV was higher ($P$ = 0.0004) in the 210 participants with (vs. without) aorta CP (Table 2). These association effects would remain significant even after a strict Bonferroni correction. Total ICV was not significantly different based on the presence or absence of aorta CP ($P$ = 0.88). In region-specific analyses, hippocampal WMV was lower ($P$ = 0.05) and hippocampal CSFV ($P$ = 0.003) was significantly higher in subjects with aorta CP.

Minimally adjusted models (for total ICV, age, sex, African ancestry proportion, and time between CT scan and cerebral MRI) and fully adjusted analyses (minimally adjusted models plus smoking, BMI, $HbA_{1c}$, use of statin medications, hypertension, and history of CVD) were performed to assess the relationships between continuous measures of CP in each vascular territory (coronary arteries, carotid arteries, and aorta) and cerebral volumes (Table 3). Results of the fully adjusted analyses revealed that CP in the aorta, coronary arteries, and carotid arteries were significantly associated with reduced cerebral GMV ($P$ values = 0.0018, 0.0023, and 0.0023, respectively. These association effects would remain under less stringent Bonferroni corrections that account for the correlations among the outcomes and the predictors. Although significant relationships were detected between CP and WMV, parameter estimates were small ($\beta < 10^{-5}$) and of doubtful clinical relevance. Statistically significant relationships were not detected between WMLV and CP; however, WMLV assessments were limited to the 227 participants who had undergone 3.0-T MRI scans.

Supplementary Table 1 displays the lack of significant relationships between recent glycemic control ($HbA_{1c}$ at the MRI visit) or inflammation based on CRP with GMV, WMV, or WMLV. In addition, the effects of $HbA_{1c}$ at first study visits (for CT scans) and fasting glucose concentrations at CT and MRI visits were not significantly associated with any of the reported MRI volumes (data not shown).

Hippocampal volume relationships with CP in the vascular beds, $HbA_{1c}$, and CRP were considered next. In the full model (adjusted for total ICV, age, sex, African ancestry proportion, time between CT scan and cerebral MRI, smoking, BMI, $HbA_{1c}$, use of statin medications, hypertension, and history of CVD), aorta CP was significantly and inversely associated with hippocampal GMV (parameter estimate −0.0010, SE 0.0005, $P$ = 0.0317), but

**Table 3—Relationships between brain volumes with subclinical CVD**

| Outcome ($cm^3$) | Predictor | Adjustment | Parameter estimate | SE | *P* value | Effect† |
|---|---|---|---|---|---|---|
| GMV | AorCP | TICV, age, sex, African ancestry, time from CT scan to MRI scan | −0.11 | 0.03 | $2.0 \times 10^{-4}$ | −1.91 |
| GMV | AorCP | Above + smoking, BMI, $HbA_{1c}$, use of statins, hypertension, prior CVD | −0.10 | 0.03 | $1.8 \times 10^{-3}$ | −1.80 |
| GMV | CorCP | TICV, age, sex, African ancestry, time from CT scan to MRI scan | −0.50 | 0.14 | $4.0 \times 10^{-4}$ | −2.0 |
| GMV | CorCP | Above + smoking, BMI, $HbA_{1c}$, use of statins, hypertension, prior CVD | −0.47 | 0.15 | $2.3 \times 10^{-3}$ | −1.9 |
| GMV | CarCP | TICV, age, sex, African ancestry, time from CT scan to MRI scan | −2.03 | 0.61 | $1.0 \times 10^{-3}$ | −1.64 |
| GMV | CarCP | Above + smoking, BMI, $HbA_{1c}$, use of statins, hypertension, prior CVD | −1.92 | 0.62 | $2.3 \times 10^{-3}$ | −1.57 |
| WMV | AorCP | TICV, age, sex, African ancestry, time from CT scan to MRI scan | $4.1 \times 10^{-6}$ | $1.8 \times 10^{-6}$ | 0.02 | 1.37 |
| WMV | AorCP | Above + smoking, BMI, $HbA_{1c}$, use of statins, hypertension, prior CVD | $4.9 \times 10^{-6}$ | $1.9 \times 10^{-6}$ | 0.01 | 1.50 |
| WMV | CorCP | TICV, age, sex, African ancestry, time from CT scan to MRI scan | $2.3 \times 10^{-5}$ | $8.2 \times 10^{-6}$ | $5.0 \times 10^{-3}$ | 1.72 |
| WMV | CorCP | Above + smoking, BMI, $HbA_{1c}$, use of statins, hypertension, prior CVD | $2.6 \times 10^{-5}$ | $8.7 \times 10^{-6}$ | $3.3 \times 10^{-3}$ | 1.95 |
| WMV | CarCP | TICV, age, sex, African ancestry, time from CT scan to MRI scan | $8.5 \times 10^{-5}$ | $3.5 \times 10^{-5}$ | 0.02 | 1.25 |
| WMV | CarCP | Above + smoking, BMI, $HbA_{1c}$, use of statins, hypertension, prior CVD | $8.9 \times 10^{-5}$ | $3.6 \times 10^{-5}$ | 0.01 | 1.25 |
| WMLV* | AorCP | TICV, age, sex, African ancestry, time from CT scan to MRI scan | $6.0 \times 10^{-6}$ | $4.1 \times 10^{-5}$ | 0.88 | |
| WMLV* | AorCP | Above + smoking, BMI, $HbA_{1c}$, use of statins, hypertension, prior CVD | $-6.4 \times 10^{-5}$ | $4.6 \times 10^{-5}$ | 0.16 | |
| WMLV* | CorCP | TICV, age, sex, African ancestry, time from CT scan to MRI scan | $1.7 \times 10^{-4}$ | $1.9 \times 10^{-4}$ | 0.37 | |
| WMLV* | CorCP | Above + smoking, BMI, $HbA_{1c}$, use of statins, hypertension, prior CVD | $-6.6 \times 10^{-5}$ | $2.0 \times 10^{-4}$ | 0.74 | |
| WMLV* | CarCP | TICV, age, sex, African ancestry, time from CT scan to MRI scan | $5.1 \times 10^{-4}$ | $1.1 \times 10^{-3}$ | 0.63 | |
| WMLV* | CarCP | Above + smoking, BMI, $HbA_{1c}$, use of statins, hypertension, prior CVD | $3.7 \times 10^{-4}$ | $1.1 \times 10^{-3}$ | 0.74 | |

AorCP, aorta CP; CarCP, carotid artery CP; CorCP, coronary artery CP; TICV, total ICV. *Reflects the 227 scans performed on 3.0-T MRI scanners. †Effect sizes are calculated for a quarter SD change in the predictor. SDs for aorta, carotid, and coronary CP are shown in Table 2.

not with hippocampal WMV. CP in coronary arteries and carotid arteries, CRP, and $HbA_{1c}$ were not significantly associated with either hippocampal volume in adjusted models (data not shown).

Association testing results between executive function (MoCA and 3MS) and the presence of CP, $HbA_{1c}$, and log(CRP) in fully adjusted models are displayed in Table 4. The presence of CP in coronary arteries was significantly and inversely associated with MoCA scores. Analyses testing for an association between MoCA/3MS and quantitative measures of CP did not reveal statistically significant associations in these vascular beds (data not shown).

## CONCLUSIONS

Significant inverse associations were detected between the extent of CP in the aorta, coronary arteries, and carotid arteries with cerebral GMV in African Americans with T2D. Absent were significant relationships between subclinical CVD and WMLV, a finding observed in many studies of European participants (2,32). Few reports have measured brain volumes and subclinical CVD in carefully phenotyped African American cohorts, and the present analyses are the first to include African ancestry proportion as a covariate in this admixed population. The inverse relationship between subclinical CVD and GMV may have functional implications based on lower MoCA scores in African Americans with detectable coronary artery CP.

Despite more severe conventional CVD risk factors in African Americans relative to European Americans, dramatically lower levels of CP are observed (33–37). Evidence supports a genetic contribution to these differences (6,10,11). Population-specific differences in the risk of subclinical CVD led us to assess cerebral changes that were potentially associated with subclinical CVD in African ancestry populations. WMLV, a measure of cerebral small-vessel disease, was not significantly associated with systemic atherosclerosis (large-vessel disease), glycemic control, or systemic inflammation in this African

**Table 4—Relationships between cognitive function and CP, inflammation, and glycemic control**

| Outcome | Predictor | Parameter estimate | SE | *P* value |
|---|---|---|---|---|
| 3MS | Presence of AorCP* | 0.0657 | 0.0928 | 0.06 |
| MoCA | Presence of AorCP* | 0.0444 | 0.0577 | 0.44 |
| 3MS | Presence of CorCP* | −0.0038 | 0.0713 | 0.96 |
| MoCA | Presence of CorCP* | −0.1043 | 0.0443 | 0.02 |
| 3MS | Presence of CarCP* | −0.0932 | 0.0697 | 0.18 |
| MoCA | Presence of CarCP* | −0.0210 | 0.0435 | 0.62 |
| 3MS | Log(CRP+1)* | −0.0746 | 0.0726 | 0.30 |
| MoCA | Log(CRP+1)* | −0.0574 | 0.0432 | 0.18 |
| 3MS | $HbA_{1c}$† | 0.1939 | 0.2421 | 0.42 |
| MoCA | $HbA_{1c}$† | 0.0127 | 0.1151 | 0.91 |

AorCP, aorta CP; CarCP, carotid artery CP; CorCP, coronary artery CP. *Analyses adjusted for age, sex, African ancestry proportion, time from CT scan to cognitive testing, level of education, smoking, BMI, $HbA_{1c}$, hypertension, CVD, and use of statins. †Analyses adjusted for age, sex, African ancestry proportion, time from CT scan to cognitive testing, level of education, smoking, BMI.

American population that is at high risk for cerebrovascular disease.

African Americans in the AA-DHS MIND appeared to have access to medical care based on high rates of the prescription of lipid-lowering and antihypertensive medications. This was an important strength, since we previously reported that African Americans and European Americans with T2D who had equivalent health care access also had similar MRI measures of cerebral disease burden (38). Thus, the previously identified higher levels of WM disease in African Americans from Harlem and the south side of Chicago were not likely due to enhanced biologic susceptibility to intracranial vascular disease (39) but more likely reflected poorer health care access and resultant higher blood pressures and blood sugar levels (40,41). The AA-DHS MIND cohort appears to be more comparable to non–African American T2D-affected populations with similar levels of lipid, glycemic, and blood pressure control. A report (42) in European Americans with T2D from Wake Forest University also supports that subclinical CVD was associated with poorer cognitive performance. Because all AA-DHS participants have T2D, the results may not be generalizable to African Americans without diabetes. In addition, although AA-DHS MIND is the largest study ($N$ = 268) to assess relationships between the brain and CVD in African Americans using CT and MRI scans, the somewhat modest sample size may have reduced the ability to detect additional associations.

The prospective Second Manifestations of Arterial Disease-Magnetic Resonance (SMART-MR) study (2) demonstrated that Europeans who had metabolic syndrome (prediabetes) and preexisting arterial disease (coronary artery disease, peripheral arterial disease, cerebrovascular disease, or abdominal aortic aneurysms) had significantly smaller brain tissue volumes, without more cerebral infarcts or WM hyperintensities. These results parallel those in African Americans with T2D in this report. SMART-MR participants with peripheral artery disease and cerebrovascular disease also demonstrated faster rates of brain atrophy and progression of WMLs (32). Cerebral atrophy progressed most rapidly in men and in those with cerebrovascular disease (32). Finally, smaller brain volumes found in the SMART-MR study were independently associated with risk for all causes of death, vascular death, and ischemic stroke (2). The SMART-MR study included European participants with clinical arterial disease, whereas the AA-DHS MIND examined subclinical CVD in a community-based sample of African Americans with T2D. Results were generally consistent across reports and between racial groups, suggesting that the severity of systemic vascular disease has adverse consequences on the brain.

Potential study limitations include that the AA-DHS cohort was uniformly affected by T2D; therefore, the findings may not apply to lower-risk populations lacking diabetes or with lesser burdens of CVD. The 3MS and MoCA global cognitive screening tests may not be sensitive enough to detect subtle changes. Although the relationship between MoCA and coronary CP could reflect a type I error, we believe it is likely real because lower GMVs were detected. In addition, MoCA is more sensitive to mild cognitive impairment than 3MS and was specifically designed to detect this finding rather than dementia. MoCA has a greater representation of executive function tasks than 3MS, which may be more relevant than memory or language in the setting of atherosclerosis. Additionally, MRI and CT scans were not performed at the same time. Subclinical CVD may have progressed by the time the MRI was performed, an effect that would underestimate associations.

In conclusion, the extent of subclinical CVD in African Americans with T2D was inversely associated with cerebral GMV, but not WMLV. The presence of subclinical coronary artery CP was also associated with poorer cognitive function. Glycemic control and systemic inflammation were not significantly associated with cerebral structural changes or cognitive performance in this African American cohort. The results are important given the markedly lower frequency and severity of CP in African Americans and that few studies have noninvasive measures of both subclinical CVD and cerebral MRI in African Americans with T2D. As in European populations, methods to reduce subclinical CVD have the potential to slow the atrophy of GM and improve cognitive function.

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