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Adiposity is inversely associated with hippocampal volume in African Americans and European Americans with diabetes

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Abstract

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Aims—To assess associations between body mass index (BMI), waist circumference (WC), and computed tomography-determined volumes of pericardial, visceral, and subcutaneous adipose tissue with magnetic resonance imaging-(MRI) based cerebral structure and cognitive performance in individuals with type 2 diabetes (T2D).

Methods—This study was performed in 348 African Americans (AAs) and 256 European Americans (EAs) with T2D. Associations between adiposity measures with cerebral volumes of white matter (WMV), gray matter (GMV), white matter lesions, hippocampal GMV, and hippocampal WMV, cognitive performance and depression were examined using marginal models incorporating generalized estimating equations. All models were adjusted for age, sex, education, smoking, HbA1c, hypertension, statins, cardiovascular disease, MRI scanner (MRI outcomes only), and time between scans; some neuroimaging measures were additionally adjusted for intracranial volume.

Results—Participants were 59.9% female with mean (SD) age 57.7(9.3) years, diabetes duration 9.6(6.8) years, and HbA1c 7.8(1.9) %. In AAs, inverse associations were detected between hippocampal GMV and both BMI (β [95% CI] -0.18 [$-0.30, -0.07$], $p=0.0018$) and WC (-0.23 [$-0.35, -0.12$], $p=0.0001$). In the full bi-ethnic sample, inverse associations were detected between hippocampal WMV and WC ($p<0.0001$). Positive relationships were observed between BMI ($p=0.0007$) and WC ($p<0.0001$) with depression in EAs.

Conclusions—In patients with T2D, adiposity is inversely associated with hippocampal gray and white matter volumes.

Keywords

African American; adiposity; brain; cognition; hippocampus; type 2 diabetes

1. Introduction

Compared to the general population, patients with type 2 diabetes (T2D) are at higher risk for cognitive impairment, dementia, and depression (Crane et al., 2013; Reijmer et al., 2010). Magnetic resonance imaging (MRI)-based neuroimaging in T2D-affected individuals revealed higher volumes of white matter lesions (WMLV), lower volumes of gray matter (GMV) and white matter (WMV), and reduced white matter fractional anisotropy; these findings may contribute to cognitive dysfunction (Lucatelli et al., 2015; Moran et al., 2013; Moulton et al., 2015). Relationships between brain volumes and cognitive performance were observed in the Diabetes Heart Study (DHS) MIND and African American–DHS MIND, two cohorts containing European Americans (EAs) and African Americans (AAs) with T2D (Hsu et al., 2015; Whitlow et al., 2015). Of note, glycemic control and systemic inflammation were not associated with cerebral structure or cognitive performance in these cohorts (Freedman et al., 2015).

Obesity is associated with reduced brain volumes (Raji et al., 2010) and poorer cognitive performance (Whitmer et al., 2005). Body mass index (BMI), waist circumference (WC), and volumes of abdominal visceral adipose tissue (VAT) are established indices of cardio-metabolic risk that independently predict cardiovascular disease (CVD) (Shah et al., 2014; Wormser et al., 2011). Higher BMI is also associated with lower brain volume (Raji et al.,

2010; Taki et al., 2008; Yokum et al., 2012). Debette *et al.* reported that total brain volume was inversely associated with visceral adiposity (Debette et al., 2010); whereas Kurth *et al.* observed that WC was more sensitive than BMI for effects on cerebral GMV in a small sample of healthy individuals (Kurth et al., 2013). Recent work has demonstrated inverse associations between hippocampal function and central adiposity in children (Khan et al., 2015). Most prior studies focused on adiposity in low risk populations without T2D. Because obesity is often present in patients with T2D and since adiposity measures most strongly associated with cerebral structure are unclear, relationships between multiple measures of adiposity with brain volumes (GMV, WMV, WMLV, hippocampal GMV, and hippocampal WMV), cognitive performance, and depression were assessed in AAs and EAs with T2D.

2. Material and Methods

2.1. Study Population

Participants included EAs and AAs enrolled in the DHS-MIND and AA-DHS MIND, ancillary studies to the DHS and AA-DHS, respectively (Hsu et al., 2015; Whitlow et al., 2015). These studies were designed to identify environmental and inherited risk factors for subclinical cerebrovascular disease and cognitive decline in cohorts enriched for T2D. All AAs and EAs in these studies with a cerebral MRI and computed tomography (CT) scan for adipose tissue volumes were included in the analyses. Details of participant recruitment from internal medicine and endocrinology clinics at Wake Forest Baptist Medical Center and community recruiting programs in northwestern North Carolina between 1998 and 2006 have been reported (Freedman et al., 2015; Hsu et al., 2015). Briefly, EA and AA siblings concordant for T2D, and singletons with T2D who had additional siblings with diabetes were recruited in the DHS. Unrelated AAs with T2D were recruited in the follow-up AA-DHS using the same diagnostic criteria. T2D was defined as a clinical diagnosis after the age of 30 years in the absence of historical evidence of ketoacidosis, with active insulin or hypoglycemic treatment, and/or a fasting blood glucose of ≥ 126 mg/dL, a non-fasting blood glucose of ≥ 200 mg/dL, or a hemoglobin A1c (HbA1c) of $\geq 6.5\%$. Participants known to have a serum creatinine concentration >2 mg/dL were not recruited. A comparison of clinical characteristics in those enrolled in the MIND study versus those not included in this analysis is shown in Supplementary Table S1. There were more females, and fewer individuals with hypertension and prior CVD among current study participants. The two studies were approved by the Institutional Review Board at the Wake Forest School of Medicine (WFSM) and all participants provided written informed consent.

2.2. Clinical measures

Examinations were performed in the WFSM Clinical Research Unit. In addition to providing a medical history and level of education, vital signs and medications were recorded. WC was measured in duplicate unless there was a difference of more than two centimeters between the first and second measurement, in which case a third measurement was taken and the average of all three measures was used in the analysis. Height (m) and weight (kg) were measured and BMI calculated. Participants had fasting blood work for measurement of plasma glucose, HbA1c, and lipid profiles. Lab testing was performed at LabCorp

(Burlington, NC). The HbA1c assay was performed on the Roche Tina Quant. Enzymatic methods were used to measure fasting glucose, total cholesterol, triglyceride, and HDL-cholesterol concentrations; values for LDL-cholesterol were computed.

2.3. Adipose tissue imaging

Pericardial adipose tissue (PAT), VAT, and subcutaneous adipose tissue (SAT) were measured from volumetric CT. Variability related to slice location was reduced using Volume Analysis software (Advantage Windows Workstation, GE Healthcare, Waukesha, WI). As reported, a threshold of −190 to −30 Hounsfield Units (HU) was used to define fat-containing tissue (Divers et al., 2010; Wheeler et al., 2005). CT scans were performed prior to brain MRI in all participants.

2.4. Cerebral MRI

Among EA participants, 206 had a 1.5 Tesla (T)-MRI scan, 5 had a 3.0-T MRI scan and 45 had only cognitive testing (failure to complete the MRI due to claustrophobia). Among AA participants, 236 had a 3.0-T MRI scan, 76 had a 1.5-T MRI scan, and 36 had only cognitive testing (failure to complete the MRI as above). A 1.5-T Excite HD MRI scanner (GE Healthcare, Milwaukee, Wisconsin) was used initially (Hsu et al., 2015; Whitlow et al., 2015). 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 ms, echo time [TE] 2.02 ms, inversion time [TI] 600 ms, flip angle 20°, 124 sections, field of view [FOV] 24 cm, matrix size 256 × 256, 1.5 mm slice thickness). Because of a change in scanners 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/neck coil [8]. T1-weighted anatomic images were obtained using a 3D volumetric magnetization prepared rapid acquisition gradient echo sequence (TR 2300 ms, TE 2.99 ms, TI 900 ms, 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 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 GMV, 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 (Maldjian et al., 2003). 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 (Schmidt et al., 2012) for SPM8 at a threshold (k) of 0.25, as our previous report (Freedman et al., 2015). The lesion segmentation toolbox has been validated against expert manual segmentation, as well as identifying the optimum thresholds. Normalization to Montreal Neurological Institute 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.

2.5. Cognitive and depression testing

A single investigator (KMS) was responsible for quality control and training, certification, and assessment of study staff responsible for conducting cognitive tests. A battery of cognitive function assessments were performed, including Modified Mini-Mental State Examination (3MS), the Digit Symbol Coding, the Rey Auditory Verbal Learning Test (RAVLT)-delayed recall, the Stroop Task (trial 3-trial 1), and Letter Fluency measured via the Controlled Oral Word Association Task (COWA). These methods assess multiple aspects of cognitive and executive function, as described (Hsu et al., 2015; Sink et al., 2015b; Whitlow et al., 2015). Depression was evaluated using the Center for Epidemiologic Studies-Depression (CES-D) 10 item measure, considered to have high sensitivity and specificity in patients with diabetes (Roy et al., 2012).

2.6. 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 ranges were computed for the continuous characteristics, and percentages were computed for discrete characteristics. WMLV was inverse square root transformed to better approximate the normality assumption. The ethnicity comparison for the characteristics were performed using the marginal models incorporating generalized estimating equations (GEE) approaches to account for familial correlation using a sandwich estimator of the variance under exchangeable correlation. Because the study samples were subsets of DHS-MIND and AA-DHS-MIND, comparisons between those who participated in this study and those who did not was also performed using marginal models.

To assess associations between MRI volumes and adiposity measures, marginal models with identity link and normal distribution were fitted. Adiposity measures were the covariates of interest; they were standardized for the purpose of comparisons. All models were adjusted for age, sex, ethnicity, education, smoking, hypertension, HbA1c, statins, prior CVD, MRI scanner (1.5-T vs. 3.0-T) and time between CT and MRI scans (on average 5.5 years; treated as a continuous variable). Models examining WMLV, GMV, and WMV were additionally adjusted for total ICV to control for brain size. Interactions between ethnicity and adiposity were tested. If the interaction term was not significant, it was removed from the model and the overall association with the full sample (AA+EA) was reported. If the interaction term was significant, analyses stratified by ethnicity were reported. The regression coefficient estimates and their associated standard errors were reported in the full cohort and separately in AAs and EAs. A Bonferroni correction was applied to adjust for multiple comparisons; p-values <0.002 (p=0.05/25 tests) were considered significant for associations between measures of adiposity and MRI cerebral volumes.

To assess associations between adiposity and cognitive performance and depression, marginal models were fitted with log link and Poisson distributions. All models were

adjusted for age, sex, ethnicity, education, smoking, hypertension, HbA1c, statins, CVD, and time between scans. Interactions between ethnicity and adiposity were tested. The exponentiated regression coefficient estimates (i.e., relative risk) and their standard errors were reported in the full cohort and separately in AAs and EAs. Bonferroni-adjusted p-values <0.0014 ($p=0.05/30$ tests) were considered significant for associations between adiposity and cognitive testing.

Because this study sample was randomly selected from the parent studies, sensitivity analyses were conducted using the propensity score to reduce potential selection bias. The propensity score was estimated using the marginal model with logit link and a binomial distribution, where the enrollment variable (enrollment in this study versus not enrolled) was the outcome variable and age, sex, ethnicity, education, BMI, hypertension, HbA1c, and prior CVD were the predictor variables. The propensity score was categorized based on quintiles and included as a covariate in the main association analyses (D'Agostino, 2007).

3. Results

A total of 1,219 individuals with T2D were enrolled in the DHS and AA-DHS. Of these, 604 also participated in the related MIND studies with cerebral MRI and cognitive testing.

Table 1 displays demographic and clinical characteristics in the full cohort ($N=604$) and separately in each ethnic group (348 AAs from 334 families; 256 EAs from 218 families). Among all participants, 59.9% were female, with a mean (SD) age of 57.7 years (9.3). Participants had a mean (SD) T2D duration of 9.6 years (6.8). At the MIND visit, 81.3% had a diagnosis of hypertension and 56.1% of participants were current or former smokers. Statins were taken by 45.4% of participants and 29.6% had prior CVD (myocardial infarction, stroke, transient ischemic attack, coronary artery angioplasty/stenting/bypass grafting). No significant differences were observed in the aforementioned characteristics between EA and AA participants, except for age. Although AA participants were younger than EAs, they had similar durations of T2D. Relative to EAs, AAs had higher educational attainment (55.7% vs. 29.7% greater than high school) and higher HbA1c (8.1[2.1]% vs. 7.4[1.5]%). As expected, AAs had higher HDL-cholesterol, BMI, and WC than EAs, along with lower triglyceride levels (Messiah et al., 2013). Compared to EAs, AAs also had lower volumes of VAT and PAT (both $p<0.0001$), with higher volumes of SAT ($p=0.0150$), as reported (Demerath et al., 2011; Katzmarzyk et al., 2010; Carroll et al., 2008).

The mean (SD) time between CT and MRI scans was 5.5 (2.0) years. The median WMLV in AA and EA participants was 1.6 and 2.0 respectively, without statistically significant differences between groups.

Compared to EAs, AAs had lower 3MS and RAVLT-delayed recall cognitive testing scores (all $p<0.0001$), without significant differences in DSST "total digit", Stroop, or letter fluency assessed by COWA testing. The median (IQR) CES-D depression scores also did not differ significantly between AA and EA participants.

Table 2 displays associations between standardized adiposity measures and brain MRI. No relationships differed significantly between ethnic groups, except VAT with WMV

(interaction $p < 0.0020$). However, associations between VAT and WMV were non-significant in AAs and EAs. A trend toward significant ethnic differences was observed between BMI and WC with hippocampal GMV; here association between BMI and hippocampal GMV (parameter estimate [CI] $-0.18 [-0.30, -0.07]$, $p = 0.0018$) and between WC and hippocampal GMV ($-0.23 [-0.35, -0.12]$, $p = 0.0001$) were significant in AAs (but not EAs) adjusting for age, sex, education, smoking, hypertension, HbA1c, statins, CVD, MRI scanner, total ICV, and time between CT and MRI scans. In the full sample, inverse associations were detected between hippocampal WMV and WC (regression coefficient estimate [95% confidence interval] $-0.07 [-0.10, -0.04]$, $p < 0.0001$). No measure of adiposity was significantly associated with GMV, WMV, or WMLV.

Table 3 displays relationships between standardized adiposity measures and cognitive testing. Interactions between ethnicity and adiposity were non-significant (all $p > 0.0014$). There was a trend toward a significant ethnic difference between WC and digit symbol coding (interaction $p = 0.0137$) and between BMI and Center for Epidemiologic Studies-Depression (CES-D) Scale (interaction $p = 0.0450$). An inverse relationship was present between WC and digit symbol coding in EAs ($p = 0.0007$), but not in AAs. The CES-D Scale assessing depression was positively associated with both BMI (relative risk estimate [95% CI]: $1.21 [1.08, 1.36]$, $p = 0.0007$) and WC ($1.19 [1.10, 1.28]$, $p < 0.0001$) in EAs, but not AAs. Significant associations were not observed for other adiposity measures and cognitive testing. The sensitivity analyses that explored sampling using propensity scores were consistent with the primary analysis (data not shown).

4. Discussion

Correlations were assessed between multiple measures of obesity and directly measured adipose tissue volumes with cerebral structure and cognition performance in a bi-ethnic population with T2D. Several adiposity measures were significantly and inversely associated with hippocampal GMV and hippocampal WMV; however, they were not associated with total GMV, WMV, or WMLV. Although ethnic differences in statistical significance were not observed for relationships between the five adiposity measures with hippocampal GMV and hippocampal WMV (yielding a total of 10 comparisons), nominal associations ($p < 0.05$) were more often significant within the AA sample (9 of 10) than the EA sample (2 of 10). Hence, results in the AA cohort appear to have driven significant findings. Depression based on the CES-D was positively associated with BMI and WC in EAs with T2D, with a trend toward association in the full bi-ethnic sample.

Several reports detected associations between measures of adiposity and brain structure. Much of the focus has been on visceral adiposity (Debette et al., 2010; Widya et al., 2015) due to the accompanying metabolic derangements of insulin resistance, hypertension, and pro-inflammatory and pro-thrombotic states. These likely relate to the release of adipokines and inflammatory cytokines, including interleukin-6 and TNF α , and by altered free fatty acid metabolism in the portal circulation. Prior studies focused predominantly on middle-aged and healthy subjects. In contrast, we failed to detect significant relationships between measurements of adiposity with GMV, WMV, and WMLV (except for a weak inverse association between WC and WMV that did not meet Bonferroni correction threshold) in

this T2D-affected sample. The major significant inverse association in this sample was between adiposity and the hippocampal ROI. We note that the longitudinal RUN DMC prospective cohort study with 503 participants demonstrated that low WMV and low hippocampal volumes were the major predictors of dementia, not GMV or WMLV (van Uden et al, 2015).

In contrast to the general absence of significant associations between adiposity and cognitive performance measured by 3MS, digit symbol coding, RAVLT, and Stroop in this T2D-affected cohort, BMI was positively associated with the severity of depression in EAs ($p=0.0007$) and nominally significant in AAs ($p=0.0389$). Several studies reported associations between obesity and diabetes with depression (Ali et al., 2006; Luppino et al., 2010). However, it was unclear which adipose tissue depot was most strongly associated with depression in the present study of T2D-affected individuals. Other studies reported significant associations between waist-hip ratio and WC with depression (Rivenes et al., 2009; Zhao et al., 2011), suggesting a role for abdominal adiposity in the regulation of mood. Large population-based studies have reported that depressive symptoms are associated with CT-assessed visceral adiposity (Murabito et al., 2013; Remigio-Baker et al., 2014). A study of 4,333 middle-aged Japanese men suggested that depressive symptoms were related to accumulation of visceral adipose, not subcutaneous adipose (Yamamoto et al., 2016). Potential mechanisms underlying these associations include hypothalamic-pituitary-adrenal axis (HPA-axis) dysregulation with hyper-cortisolemia (Yokoyama et al., 2015), inflammation (Miller et al., 2002), and the influences of lifestyle and behaviors (Lovell et al., 2014).

The present report revealed consistent associations between BMI and WC with lower hippocampal volumes and higher depression scores. Of interest, BMI and WC displayed stronger effects than VAT. Significant reductions in hippocampal GMV (by approximately 10%) have been reported in patients with depression (Campbell et al., 2004; Colla et al., 2007). One longitudinal study (Chan et al., 2016) suggested that reductions in hippocampal volume were “neural markers” for depression. They postulated this could relate to the effects of an adverse environment on neurobiological pathways from the serotonin transporter gene proceeding through variation in hippocampal volume to produce depression (Little et al., 2015). In a recent genome-wide-association analysis including 339,224 individuals, a pathway analysis provided strong support for an important role of the central nervous system in susceptibility to obesity (Locke et al., 2015). This analysis identified 97 loci that were associated with BMI, 56 of which were novel. A role for genes expressed in the hypothalamus was confirmed in the regulation of body mass; however, genes expressed in the hippocampus and limbic systems were even more strongly associated. These findings support hippocampal volumes as potential links to the association between obesity and depression. Our results extend existing studies regarding the association of adiposity measures with CES-D depression scores, and highlight the importance of higher BMI and WC as more sensitive risk factors for depression in patients with T2D. These results may be related to the lower hippocampal GMV and hippocampal WMV seen with higher WC and BMI.

Strengths of this study included a well-defined cohort of AAs and EAs with ten year mean durations of T2D. This permitted ethnic disparities to be considered. Participants appeared to have had good access to healthcare, based upon high rates of receiving statins and anti-hypertensive medications. In addition, PAT, VAT, and SAT were determined by multi-slice CT providing precise volumetric measures. CES-D, cognitive performance testing, and cerebral MRI were performed at a single visit; allowing for the simultaneous assessment of depression and cognitive performance. To reduce confounding, analyses employed extensive adjustment for covariates, including educational attainment, known to associate with cognitive function. In addition, brain volumes were normalized to total ICV and strict adjustment for multiple comparisons was performed.

This study also has limitations. Adiposity measures were collected on average 5.5 years earlier than the MRI and cognitive testing; hence, lack of association between adiposity measures with brain structure and function could relate to the time difference. BMI and WC were also measured on the day of the MIND visit, when the MRI and cognitive battery were administered. The mean annual change in BMI between the two study visits was -0.02 ($SD=0.69$) and the mean annual change in WC was 0.44 cm ($SD=2.03$), both minimal. Therefore, we repeated the association analysis between cerebral volumes and cognitive testing using BMI and WC on the same day and results were consistent (data not shown). Nominal associations not meeting strict Bonferroni-adjusted levels of significance were not highlighted, but may still have biological relevance. In contrast to previous reports in non-diabetic individuals (generally middle-aged or healthy populations) (Debette et al., 2010; Debette et al., 2014; Gunstad et al., 2008; Kurth et al., 2013), this study assessed anthropometric measures for association with brain structure and cognitive performance in a typical T2D-affected population. Our findings may differ from other studies due to the effects of diabetes and cannot be generalized to non-diabetic populations. In addition, only a random subset of parent DHS and AA-DHS participants was included in the MIND study. These individuals were more often female and had less hypertension and CVD compared to non-participants. Thus, this study sample may be healthier than the general T2D-affected population. In order to reduce the potential for bias, we adjusted for gender, hypertension and CVD in the primary models, and also performed a sensitivity analysis. Results from the sensitivity analysis were consistent with the primary observations. Caution should also be applied in the application of these results to populations with different ethnic backgrounds. Finally, performance on cognitive testing may differ between AAs and EAs and further studies are required to refine differences and define dementia (Sink et al., 2015a). It is unclear how educational attainment, differences in the quality of education, and differences in nutrition and food intake between groups contributed to results. Future longitudinal studies will be required to explore the causal and temporal nature of changes in adiposity and neuroimaging parameters, especially in relation to the clinical outcomes of cerebral vascular disease and depression.

In conclusion, measures of adiposity were inversely associated with hippocampal GMV and hippocampal WMV in AAs and EAs with T2D. Total volumes of gray matter, white matter and WMLV were not associated with adiposity in this cohort. Positive relationships were observed between BMI and WC with depression in patients with T2D (albeit not meeting

strict Bonferroni-corrected levels in AAs); however, other measures of cognitive performance were not associated with measures of adiposity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and clinical characteristics of study participants, by ethnic group

	European American (N=256)	African American (N=348)	Full Sample (N=604)	P-value
<u>Demographic information</u>				
Age, years	60.7 (8.4)	55.5 (9.3)	57.7 (9.3)	<0.0001
Female, n (%)	146 (57.0)	216 (62.1)	362 (59.9)	0.38
Body mass index, mean (SD) [kg/m ²]	32.2 (6.1)	35.7 (8.8)	34.2 (8.0)	<0.0001
Waist circumference (cm)	106.5 (16.8)	111.7 (19.5)	109.5 (18.6)	0.0004
Duration of Diabetes, years	9.3 (6.1)	9.9 (7.3)	9.6 (6.8)	0.60
Ever smoking, n (%)	144 (56.3)	194 (55.9)	338 (56.1)	0.86
Hypertension, n (%)	211 (82.4)	280 (80.5)	491 (81.3)	0.63
Education, n (%)				<0.0001
<12(less than high school)	42 (16.4)	43 (12.4)	85 (14.1)	
=12(high school graduate)	138 (53.9)	111 (31.9)	249 (41.2)	
>12(more than high school)	76 (29.7)	194 (55.7)	270 (44.7)	
Statin, n (%)	106 (41.4)	168 (48.3)	274 (45.4)	0.08
Prior CVD, n (%)	85 (34.1)	88 (26.3)	173 (29.6)	0.12
Time between scans, years	6.4 (1.5)	4.9 (2.1)	5.5 (2.0)	<0.0001
<u>Laboratory data</u>				
Hemoglobin A1c (%)	7.4 (1.5)	8.1 (2.1)	7.8 (1.9)	<0.0001
Glucose (mmol/L)	7.9 (2.7)	8.1 (3.5)	8.0 (3.2)	0.66
Total Cholesterol (mmol/L)	4.8 (1.0)	4.7 (0.9)	4.8 (1.0)	0.34
HDL-cholesterol (mmol/L)	1.1 (0.3)	1.3 (0.3)	1.2 (0.3)	<0.0001
LDL-cholesterol (mmol/L)	2.7 (0.8)	2.9 (0.9)	2.8 (0.9)	0.0358
Triglycerides (mmol/L)	2.2 (1.4)	1.4 (1.0)	1.7 (1.3)	<0.0001
<u>Measurements of adiposity by CT</u>				
Visceral Fat (cm ³)	288.6 (161.3)	177.3 (74.4)	226.3 (132.6)	<0.0001
Subcutaneous Fat (cm ³)	426.8 (256.2)	452.7 (188.2)	441.3 (220.9)	0.0150
Pericardial Fat (cm ³)	130.7 (54.6)	87.4 (40.5)	106.5 (51.9)	<0.0001
<u>Cerebral magnetic resonance imaging</u>				
Total intracranial volume (cc)	1345 (137.9)	1288 (132.4)	1311 (137.4)	<0.0001
Gray matter volume (cc)	510.8 (51.7)	544.6 (63.6)	530.9 (61.3)	<0.0001
White matter volume (cc)	577.6 (69.0)	498.5 (64.5)	530.6 (76.9)	<0.0001
White matter lesion volume (cc)	4.2 (6.4)	7.2 (14.3)	6.0 (11.9)	0.18
Median (IQR)	2.0 (0.3, 5.0)	1.6 (0.2, 7.1)	1.7 (0.2, 6.1)	
Hippocampus gray matter volume (cc)	8.5 (1.1)	9.2 (1.0)	8.9 (1.1)	<0.0001
Hippocampus white matter volume (cc)	3.4 (0.3)	2.8 (0.4)	3.1 (0.4)	<0.0001
<u>Cognitive function test scores</u>				
Modified mini mental state exam (3MS)	90.5 (7.1)	85.8 (9.0)	87.8 (8.6)	<0.0001
Digit symbol coding	47.8 (15.2)	48.0 (16.4)	47.9 (15.9)	0.51
Rey auditory-verbal learning task (RAVLT)	41.4 (9.8)	38.2 (9.2)	39.5 (9.6)	<0.0001

	European American (N=256)	African American (N=348)	Full Sample (N=604)	P-value
Stroop (trial 3 - trial 1)	34.6 (19.1)	33.1 (18.5)	33.7 (18.7)	0.17
Median (IQR)	29.0 (23.0, 44.0)	29.0 (22.5, 40.0)	29.0 (23.0, 41.0)	
Letter Fluency	10.3 (4.0)	10.7 (4.4)	10.6 (4.3)	0.17
Total CES-D score	7.4 (5.2)	8.0 (5.5)	7.8 (5.4)	0.17
Median (IQR)	6.0 (4.0, 10.0)	7.0 (4.0, 11.0)	7.0 (4.0, 11.0)	

Data expressed as mean (SD) for continuous characteristics; n (%) for discrete characteristics; median (min - max) for variables with skewed distributions. CVD: cardiovascular disease; COWA: Controlled Oral Word Association; CES-D: Center for Epidemiologic Studies-Depression.

Table 2
Associations between brain imaging with adiposity (standardized), in European Americans and African Americans

Outcome	Adipose Measure	European American Estimate (CI)	p-value	African American Estimate (CI)	p-value	Full sample Estimate (CI)	p-value	Interaction p-value
GMV	BMI	-1.46 (-6.84, 3.92)	0.60	1.19 (-2.73, 5.11)	0.55	0.22 (-2.94, 3.38)	0.89	0.56
	WC	0.24 (-4.56, 5.04)	0.92	-0.18 (-4.53, 4.16)	0.93	-0.13 (-3.32, 3.07)	0.94	0.99
	PAT	0.58 (-3.82, 4.99)	0.80	0.29 (-4.15, 4.73)	0.90	0.14 (-2.95, 3.23)	0.93	0.71
	VAT	-1.39 (-4.84, 2.07)	0.43	0.58 (-5.83, 6.98)	0.86	-0.49 (-3.40, 2.42)	0.74	0.53
	SAT	1.35 (-3.31, 6.00)	0.57	3.52 (-1.71, 8.74)	0.19	2.50 (-0.71, 5.72)	0.13	0.83
WMV	BMI	-3.79 (-8.88, 1.30)	0.14	1.83 (-2.21, 5.87)	0.38	0.65 (-12.68, 13.97)	0.92	0.60
	WC	-4.44 (-8.69, -0.19)	0.0407	-2.82 (-7.29, 1.66)	0.22	-5.48 (-10.65, -0.31)	0.0377	0.05
	PAT	-1.37 (-5.75, 3.01)	0.54	-0.05 (-4.79, 4.70)	0.99	3.41 (-5.55, 12.36)	0.46	0.14
	VAT	2.29 (-0.91, 5.49)	0.16	1.40 (-5.23, 8.03)	0.68	5.25 (-2.31, 12.82)	0.17	0.0008
	SAT	-3.20 (-7.32, 0.91)	0.13	-0.43 (-5.77, 4.91)	0.87	-3.67 (-13.66, 6.32)	0.47	0.14
WMLV	BMI	-0.03 (-0.17, 0.11)	0.69	0.01 (-0.02, 0.03)	0.44	0.01 (-0.01, 0.03)	0.48	0.50
	WC	-0.03 (-0.08, 0.02)	0.18	0.00 (-0.03, 0.03)	0.96	-0.01 (-0.03, 0.01)	0.54	0.43
	PAT	-0.04 (-0.10, 0.02)	0.18	0.00 (-0.04, 0.03)	0.86	-0.01 (-0.04, 0.01)	0.29	0.83
	VAT	-0.03 (-0.09, 0.03)	0.33	0.03 (-0.02, 0.08)	0.20	0.01 (-0.02, 0.04)	0.61	0.15
	SAT	-0.06 (-0.13, 0.00)	0.06	-0.01 (-0.05, 0.02)	0.48	-0.01 (-0.04, 0.02)	0.47	0.94
HGMV	BMI	-0.05 (-0.25, 0.15)	0.61	-0.18 (-0.30, -0.07)	0.0018	-0.15 (-0.25, -0.05)	0.0036	0.05
	WC	-0.02 (-0.19, 0.16)	0.85	-0.23 (-0.35, -0.12)	0.0001	-0.13 (-0.24, -0.01)	0.0325	0.0081
	PAT	0.01 (-0.13, 0.16)	0.88	-0.17 (-0.31, -0.03)	0.0178	-0.08 (-0.17, 0.02)	0.14	0.19
	VAT	-0.1 (-0.23, 0.03)	0.13	-0.27 (-0.48, -0.07)	0.0079	-0.11 (-0.22, 0.00)	0.0415	0.20
	SAT	-0.01 (-0.21, 0.18)	0.89	-0.15 (-0.3, 0.00)	0.0485	-0.08 (-0.21, 0.05)	0.23	0.06
HWMV	BMI	-0.06 (-0.12, 0.00)	0.0350	-0.06 (-0.1, -0.01)	0.0079	-0.05 (-0.09, -0.02)	0.0033	0.59
	WC	-0.08 (-0.12, -0.04)	<0.0001	-0.07 (-0.12, -0.03)	0.0018	-0.07 (-0.1, -0.04)	<0.0001	0.42
	PAT	-0.04 (-0.09, 0.01)	0.14	-0.06 (-0.12, -0.01)	0.0262	-0.04 (-0.08, -0.01)	0.0250	0.21
	VAT	-0.01 (-0.05, 0.03)	0.57	-0.07 (-0.15, 0.00)	0.06	-0.02 (-0.05, 0.02)	0.27	0.94
	SAT	-0.02 (-0.06, 0.01)	0.23	-0.09 (-0.14, 0.03)	0.0022	-0.04 (-0.08, 0.01)	0.0126	0.45

Estimates are per standard deviation increment in the full cohort: 8.0 kg/m² BMI, 18.6 cm WC, 51.9 cm³ PAT, 132.6 cm³ VAT, and 220.9 cm³ SAT. Adjusted for age, sex, education, smoking, hypertension, HbA1c, statins, CVD, time between scans, and MRI scanner type in ethnicity-specific analyses. Additional adjustment was performed for ethnicity in the full-sample analysis. P-values (<0.0020) were considered significant (**bolded**). BMI: body mass index; WC: waist circumference; PAT: pericardial adipose tissue; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; GMV: gray matter volume; WMV: white matter volume; WMLV: white matter lesion volume; HGMV: hippocampal gray matter volume; HWMV: hippocampal white matter volume.

Table 3

Associations between cognitive performance and depression with adiposity (standardized), in European Americans and African Americans

Outcome	Adipose measure	European American RR (CI)	p-value	African American RR (CI)	p-value	Full sample RR (CI)	p-value	Interaction p-value
3MS	BMI	0.94 (1.05, 0.85)	0.27	0.99 (1.02, 0.96)	0.62	0.98 (1.03, 0.93)	0.47	0.93
	WC	0.95 (1.03, 0.88)	0.22	0.95 (0.99, 0.92)	0.0052	0.95 (1.00, 0.90)	0.07	0.73
	PAT	0.96 (1.03, 0.89)	0.22	0.99 (1.03, 0.95)	0.70	0.97 (1.02, 0.92)	0.21	0.24
	VAT	0.98 (1.06, 0.90)	0.60	1.00 (1.05, 0.94)	0.87	0.98 (1.04, 0.93)	0.60	0.66
	SAT	1.01 (1.08, 0.94)	0.79	0.95 (0.99, 0.91)	0.0191	0.98 (1.04, 0.93)	0.47	0.11
Digit symbol coding	BMI	0.95 (0.91, 1.00)	0.0364	1.01 (0.99, 1.02)	0.48	0.99 (0.97, 1.01)	0.28	0.0241
	WC	0.94 (0.91, 0.97)	0.0007	0.98 (0.97, 1.00)	0.08	0.97 (0.94, 0.99)	0.0034	0.0137
	PAT	0.96 (0.92, 0.99)	0.0092	0.99 (0.97, 1.01)	0.47	0.97 (0.94, 0.99)	0.0137	0.20
	VAT	0.98 (0.96, 1.01)	0.20	1.04 (1.00, 1.07)	0.0250	0.99 (0.97, 1.02)	0.52	0.08
	SAT	0.99 (0.97, 1.02)	0.55	1.00 (0.98, 1.02)	0.90	1.00 (0.97, 1.02)	0.69	0.91
RAVLT delayed recall	BMI	0.92 (0.86, 0.98)	0.0062	0.99 (0.95, 1.04)	0.68	0.97 (0.93, 1.01)	0.14	0.27
	WC	0.95 (0.89, 1.02)	0.16	0.95 (0.91, 1.00)	0.07	0.96 (0.92, 1.01)	0.10	0.42
	PAT	0.97 (0.92, 1.02)	0.27	0.96 (0.89, 1.02)	0.18	0.96 (0.92, 1.01)	0.10	0.68
	VAT	0.98 (0.93, 1.02)	0.28	0.96 (0.87, 1.05)	0.39	0.97 (0.93, 1.01)	0.19	0.59
	SAT	0.97 (0.93, 1.02)	0.30	0.95 (0.89, 1.02)	0.16	0.97 (0.93, 1.01)	0.12	0.57
Stroop (trial 3- trial 1)	BMI	1.07 (0.97, 1.17)	0.16	0.97 (0.95, 0.99)	0.0010	1.00 (0.95, 1.04)	0.90	0.08
	WC	1.05 (0.98, 1.11)	0.16	0.97 (0.95, 0.99)	0.0040	1.00 (0.95, 1.05)	0.98	0.05
	PAT	1.03 (0.96, 1.11)	0.38	1.06 (1.03, 1.08)	0.0001	1.04 (0.99, 1.10)	0.09	0.81
	VAT	1.01 (0.96, 1.07)	0.63	0.98 (0.94, 1.02)	0.26	1.01 (0.96, 1.07)	0.61	0.27
	SAT	1.02 (0.97, 1.08)	0.41	0.95 (0.92, 0.97)	0.0001	1.00 (0.96, 1.05)	0.97	0.16
Letter fluency	BMI	0.97 (0.91, 1.03)	0.35	0.96 (0.93, 1.00)	0.0360	0.97 (0.93, 1.00)	0.06	0.72
	WC	0.99 (0.95, 1.03)	0.58	0.97 (0.93, 1.00)	0.06	0.98 (0.94, 1.01)	0.20	0.50
	PAT	1.01 (0.96, 1.06)	0.64	0.95 (0.9, 0.99)	0.021	0.98 (0.94, 1.02)	0.30	0.28
	VAT	1.03 (0.99, 1.07)	0.18	0.97 (0.91, 1.03)	0.31	1.01 (0.97, 1.05)	0.58	0.50
	SAT	1.03 (0.98, 1.07)	0.22	0.93 (0.89, 0.97)	0.0024	0.99 (0.95, 1.02)	0.42	0.0085
CES-D scale	BMI	1.21 (1.08, 1.36)	0.0007	1.04 (1.00, 1.08)	0.0389	1.08 (1.02, 1.15)	0.0116	0.0450
	WC	1.19 (1.10, 1.28)	<0.0001	1.06 (1.02, 1.11)	0.0066	1.10 (1.04, 1.17)	0.0017	0.11
	PAT	1.02 (0.94, 1.11)	0.61	1.08 (1.02, 1.13)	0.0058	1.04 (0.98, 1.11)	0.22	0.23

Outcome	Adipose measure	European American RR (CI)	p-value	African American RR (CI)	p-value	Full sample RR (CI)	p-value	Interaction p-value
	VAT	1.01 (0.94, 1.08)	0.85	1.08 (1.00, 1.17)	0.0396	1.01 (0.96, 1.07)	0.67	0.27
	SAT	1.03 (0.97, 1.09)	0.37	1.05 (0.99, 1.11)	0.08	1.03 (0.98, 1.08)	0.30	0.62

Estimates are per standard deviation increment in the full cohort: 8.0 kg/m² BMI, 18.6 cm WC, 51.9 cm³ PAT, 132.6 cm³ VAT, and 220.9 cm³ SAT.

Adjusted for age, sex, education, smoking, hypertension, HbA1c, statins, CVD, and time between scans in ethnicity-specific analyses.

Additional adjustment was performed for ethnicity in the full-sample analysis.

Additional adjustment for African ancestry proportion was performed in African Americans. P-values less than 0.0014 (=0.05/30) were considered significant (**bolded**).

EA: European American; AA: African American; BMI: body mass index; RR: relative risk; WC: waist circumference; PAT: pericardial adipose tissue;

VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; 3MS: Modified Mini-Mental State Examination; RAVLT: Auditory-Verbal Learning Test; COWA: Controlled Oral Word Association; CESD: Center for Epidemiologic Studies Depression.