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Macro- and Microstructural Magnetic Resonance Imaging Indices Associated With Diabetes Among Community-Dwelling Older Adults

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OBJECTIVE—To better understand the association between diabetes and cognitive impairment, we evaluated macro- and microstructural brain MRI measures for the total brain and regions of interest (ROIs) in a group of community-dwelling elders with and without diabetes.

RESEARCH DESIGN AND METHODS—MRI measures were obtained on 308 elders (mean age 83.3 years; $n = 85$ with diabetes) from the Health ABC Healthy Brain Substudy. We performed a series of linear regressions and used standardized β values to estimate the cross-sectional association between diabetes and macrostructural (gray matter volume [GMV] and white matter hyperintensities [WMHs]) and microstructural (mean diffusivity [MD] and fractional anisotropy [FA]) measures for the total brain and ROIs. Models were adjusted for age, race, and sex; GMV values for ROIs were also adjusted for total brain volume (TBV).

RESULTS—In multivariate-adjusted models, diabetes was associated with lower total GMV ($P = 0.0006$), GMV in the putamen ($P = 0.02$ for left and right), and TBV ($P = 0.04$) and greater cerebral atrophy ($P = 0.02$). There was no association with WMHs. On microstructural measures, diabetes was associated with reduced FA for total white matter ($P = 0.006$) and greater MD for the hippocampus ($P = 0.006$ left; $P = 0.01$ right), dorsolateral prefrontal cortex ($P = 0.0007$, left; $P = 0.002$, right), left posterior cingulate ($P = 0.02$), and right putamen ($P = 0.02$). Further adjustment for stroke, hypertension, and myocardial infarction produced similar results.

CONCLUSIONS—In this cross-sectional study, elders with diabetes compared with those without had greater brain atrophy and early signs of neurodegeneration. Further studies are needed to determine whether these structural changes associated with diabetes predict risk of cognitive decline.

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Diabetes is associated with cognitive decline among older adults and has been estimated to confer ~1.54 increased risk for Alzheimer disease (1–3). Brain imaging studies may help identify markers of risk for cognitive impairment and clarify the cerebral pathology of diabetes among older adults, which is not well understood. Studies of brain differences associated with diabetes have mainly focused on macrostructural features such as volumetric measures and severity of white matter hyperintensities (WMHs). Results suggest greater brain atrophy among those with diabetes (4), with possible preferential volume loss in the medial temporal (5–7) and frontal (6,8) regions. Findings have been inconsistent regarding WMHs and diabetes in older adults (4). In addition, few studies have evaluated microstructural measures. Whether degeneration also exists at the microscopic level, possibly occurring before overt volume loss or WMHs can be detected with conventional magnetic resonance imaging (MRI), has not been established.

Diffusion tensor imaging (DTI) may be a useful tool for investigating early microstructural changes that may indicate risk of cognitive impairment. DTI provides a quantitative measure of the diffusion of water through a medium that conveys information on tissue integrity not typically visible with conventional MRI. Two commonly used DTI indices include mean diffusivity (MD) and fractional anisotropy (FA), reflecting the magnitude and degree of directionality, respectively, of water diffusion within a voxel (9). Greater MD in gray matter and decreased FA in white matter tracts are thought to reflect microstructural abnormalities, including demyelination and axonal loss (10). DTI has been shown to be sensitive in identifying early markers of age-related cognitive decline (11), mild cognitive impairment, and Alzheimer disease (10,12) and associated with cognitive performance independent of macrostructural characteristics such as gray matter volume (GMV) (11,13). Only a few known studies have used DTI to investigate microstructural brain characteristics among adults with diabetes (14,15). These studies focused on predominately middle-aged adults, with a mean age of <60 years among those with diabetes. To the best of our knowledge, DTI associations among adults with diabetes >70 years of age, when the incidence of cognitive decline and dementia increases dramatically, have not been studied.

We sought to determine whether diabetes is associated with MRI and DTI

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measures of neurodegeneration (e.g., atrophy, greater MD, reduced FA) and vascular disease (e.g., white matter changes) among a group of community-dwelling elders. We investigated indices of white matter and gray matter for the total brain and for regions of interest (ROIs) associated with memory, executive control, and processing speed. These included the hippocampus, entorhinal cortex, posterior cingulate, dorsolateral prefrontal cortex, posterior parietal cortex, and striatum, as well as substructures of the striatum: the putamen, caudate nucleus, and pallidium. We hypothesized that elders with diabetes prevalent at the time of MRI would have greater atrophy and volume of WMHs, decreased FA, and greater MD for the total brain and in ROIs compared with those without diabetes.

RESEARCH DESIGN AND METHODS

—Participants were part of the Healthy Brain Project ancillary study at the Pittsburgh site of the Health, Aging, and Body Composition (Health ABC) study, a prospective cohort study beginning in 1997–1999 of 3,075 community-dwelling elders then aged 70–79 years and living in Memphis, Tennessee, or Pittsburgh, Pennsylvania. In 2006–2007, 325 Health ABC participants, who were interested and eligible for a brain 3-Tesla MRI and who were able to walk 20 meters, participated in the Healthy Brain Project. Participants were not excluded if they had existing comorbidities. Participants in the Healthy Brain Project were similar to the Health ABC study participants of the Pittsburgh cohort, as previously reported (13). A total of 308 had measurements available for all of the macrostructural MRI variables of interest, and 281 had measurements for all of the microstructural MRI variables of interest. In addition to in-person Health ABC assessments, participants received neurocognitive testing and detailed neurologic and gait exams. All subjects provided written informed consent. The University of Pittsburgh institutional review board approved the protocol.

Diabetes

Diabetes status was determined at the time of the participant's Healthy Brain exam either at year 10 or at year 11 of the Health ABC study, by record of diabetes at the start of the Health ABC study through self-report, use of hypoglycemia medication, a fasting glucose of ≥126 mg/dL, or a 2-h glucose tolerance test >200 mg/dL in accordance with the American Diabetes Association criteria in place (2002) near the start of the Health ABC study or through record of a diabetes diagnosis during an annual Health ABC follow-up assessment by self-report, use of hypoglycemic medication, or a fasting glucose of ≥126 mg/dL.

Image acquisition

Images were obtained with a Siemens 12-channel head coil and 3T Siemens Tim Trio MR scanner at the Magnetic Resonance Research Center, University of Pittsburgh. Magnetization-prepared rapid gradient echo T1-weighted images were acquired in the axial plane (repetition time [TR] = 2,300 ms, echo time [TE] = 3.43 ms, imaging time [TI] = 900 ms, 9° flip angle, 256 × 224 mm field of view [FOV], 1 × 1 mm voxel size, 256 × 224 matrix size, 176 slices, and 1 mm thick). Fluid-attenuated inversion recovery (FLAIR) images were acquired in axial plane (TR = 9,160 ms, TE = 89 ms, TI = 2,500 ms, 150° flip angle, 256 × 212 mm FOV, 256 × 240 matrix size, 48 slices, 3 mm thick, and 1 × 1 mm voxel size). Diffusion-weighted images were acquired using a single short spin-echo sequence (TR = 5,300 ms, TE = 88 ms, TI = 2,500 ms, 90° flip angle, 256 × 256 mm FOV, two diffusion values of b = 0 and 1,000 s/mm, 12 diffusion directions, four repeats, 40 slices, 3 mm thick, 128 × 128 matrix size, 2 × 2 mm voxel size, and GRAPPA = 2). A neuroradiologist examined each MRI for neurologic abnormalities (13,16).

Image processing and analysis

GMV, WMH volume, and microstructural MRI global indices of gray matter integrity (atrophy index, relative peak height, magnetic transfer [MT] ratio, and MD) and white matter integrity (relative peak height MT ratio and mean FA) were obtained using previously published methods briefly described below (13,16).

Gray matter, white matter, and cerebrospinal fluid (CSF) were segmented on skull-stripped T1-weighted images in native anatomical space (17). GMV, WMV, and CSF volume were estimated by summing voxels classified as these tissue types. Total intracranial volume was computed as the volume inside the inner skull via brain extraction tool. Atrophy was calculated as the ratio of GMV to total intracranial volume. WMH volume was obtained from T2-weighted FLAIR image using an automated method for quantification and localization of WMHs (18). Total WMH volume was estimated by summing all the voxels classified as WMHs and normalized by brain volume. Neuroanatomical boundaries for gray matter ROIs were determined using a published atlas as previously described (16).

Diffusion tensor images were preprocessed to remove unwanted distortions due to eddy current and diagonalized to determine eigenvalues to compute FA and MD maps (19). FA maps were registered to the FMRIB58_FA template (19) using published protocols (20) similar to Tract-based Spatial Statistics (19). MD maps were also transformed (21). By use of the segmentation of white matter, gray matter, and WMHs that was obtained from the T1-weighted and T2-weighted FLAIR images, the FA and MD maps were restricted to normal-appearing white matter and normal-appearing gray matter. Scans were manually inspected, and clinically relevant infarcts were removed. Relative peak height FAs (100 bins; FA between 0.2 and 1.22 with bin size 0.0103) were calculated for the normal-appearing white matter.

Covariates

Possible covariates included self-reported age, race, sex, and high school level of education (categorized as less than high school versus high school or more) obtained from Health ABC baseline measurements. Additional measurements were obtained during the Healthy Brain exam or through the corresponding Health ABC clinic visit. Depression symptoms were assessed using the 20-item Center for Epidemiologic Studies-Depression (CES-D) scale (22). BMI (calculated as kilograms divided by the square of height in meters) was calculated from direct height and weight measurements. Hypertension, stroke, and myocardial infarction data were based on self-report, clinic data, and medication use. Apolipoprotein (apo)E genotype was determined by the 5′-nuclease assay (23) in the Human Genetics laboratory at the University of Pittsburgh, and participants were coded as e4 carriers or noncarriers.

The Modified Mini-Mental State Examination (3MS) was administered at the Health ABC visit corresponding to the MRI study visit. The 3MS is a brief general cognitive battery with components for orientation, concentration, language, praxis, and immediate and delayed memory (24). Scores range from 0 to 100

points, with lower scores indicating poorer performance.

Statistical analysis

We first performed bivariate analyses to test for associations between diabetes status and baseline characteristics. We used χ^2 analysis for categorical variables and *F* test for continuous variables.

We used linear regression models to test for associations between diabetes status and volumetric measures and DTI indices for the total brain and ROIs in each hemisphere (Table 2). Standardized *Z* scores of the neuroimaging markers were used. Linear regression analyses for DTI measures were restricted to the range of detectable abnormalities. GMV for each ROI was adjusted for total brain volume (TBV) (gray matter, white matter, and CSF in all models). Models were then adjusted for age, race, and sex. Additional adjustment was also made for stroke, hypertension, myocardial infarction, apoE e4, depression, and 3MS score. MRI measures that were highly skewed, including atrophy, WMHs, total gray matter integrity, and the GMV of the posterior cingulate, putamen, pallidium, and right posterior parietal cortex were analyzed as log transformed in all models. All analyses were conducted using SAS statistical software, version 9.2 (SAS Institute, Cary, NC), and were two tailed with the statistical significance level set at $P < 0.05$.

Table 1—*Participant characteristics by diabetes status* (N = *308*)

	No diabetes	Diabetes	*P**
N	223	85	
Age (years)	83.3 ± 2.6	83.3 ± 3.1	0.87
Black	81 (35.8)	45 (52.9)	0.006
Female	142 (62.8)	39 (45.9)	0.007
≥High school education	194 (86.2)	73 (85.9)	0.94
Stroke	22 (9.7)	13 (15.3)	0.17
Myocardial infarction	41 (18.1)	19 (22.4)	0.40
Hypertension	153 (68.0)	65 (76.5)	0.15
BMI (kg/m^2)	26.6 (4.3)	29.8 (4.1)	<0.0001
Depression score ≥16	21 (9.4)	11 (12.9)	0.36
ApoE e4	50 (23.4)	27 (32.5)	0.11
3MS	93.4 ± 6.4	92.0 ± 7.1	0.10

Data are means ± SD or *n* (%). *P value by ANOVA for continuous variables and χ^2 test for categorical variables.

RESULTS—Of the 308 participants in the study, 85 (27.6%) had diabetes. The mean (SD) age of participants was 83.3 (2.8) years, 126 (40.9%) were black, and 181 (58.8%) were female. Participants with diabetes were more likely to be of black race and male and have a higher BMI. 3MS scores were not significantly different between the two groups (Table 1).

In the unadjusted linear regression models for macro- and microstructural MRI indices for the total brain, diabetes was associated with greater atrophy (standardized β: −0.18; $P = 0.002$), lower total GMV (standardized β: −0.14; $P = 0.01$), and lower mean FA of total white matter (standardized β: −0.13; $P = 0.02$). There was no association between diabetes and WMHs ($P = 0.93$) or MD for total gray matter ($P = 0.49$). Further adjustment for age, race, and sex produced similar results (Table 2).

In linear regression models for GMV in the ROIs adjusted for TBV, diabetes was associated with smaller mean GMV in the left dorsolateral prefrontal cortex (standardized β: −0.11; $P = 0.03$) and in the left striatum (standardized β: −0.14; $P = 0.02$). Substructures of the striatum associated with diabetes included the left caudate (standardized β: −0.12; $P = 0.03$) and bilateral putamen (left standardized β: −0.16, $P = 0.005$; right standardized β: −0.16; $P = 0.005$). No other ROIs were statistically significant. The bilateral putamen remained significant after adjustment for age, race, and sex, and the left striatum and left dorsolateral prefrontal cortex were of borderline significance ($P = 0.07$ and $P = 0.06$, respectively) (Table 3).

In unadjusted linear regression models using DTI of MD, diabetes was associated with greater MD in the hippocampus (for left and right, respectively, standardized β: 0.15, $P = 0.01$, and standardized β: 0.14, $P = 0.02$), left posterior cingulate (standardized β: 0.14, $P = 0.02$), and dorsolateral prefrontal cortex (standardized β: 0.19, $P = 0.001$, for right and standardized β: 0.15, $P = 0.01$, for left). Associations with diabetes were of borderline significance for the right posterior cingulate (standardized β: 0.11, $P = 0.06$) and right putamen (standardized β: 0.12, $P = 0.06$). Further adjustment for age, race, and sex produced similar results (Table 2).

Further adjustment for hypertension, stroke, myocardial infarction, apoE e4, depression, and 3MS score produced similar results for all models. We also assessed whether there was an interaction with race; we did not find any consistent pattern, and almost all interaction terms were not significant.

CONCLUSIONS—In this cross-sectional study, we found that community-dwelling older adults with diabetes compared with those without had greater brain atrophy and early signs of neurodegeneration. Participants with diabetes exhibited smaller volumes for the total brain, gray matter, and putamen and greater brain atrophy than those without diabetes. Surprisingly, we found no difference in WMHs between the two groups. On microstructural measures, participants with diabetes compared with those without had reduced FA for total white matter and elevated MD for the bilateral hippocampus, bilateral dorsolateral prefrontal cortex, left posterior cingulate, and right putamen. This is one of the few studies to use DTI to investigate microstructural abnormalities among elders with diabetes.

Our results are supported by previous investigations of brain abnormalities on MRI among patients with diabetes. Several studies have found greater brain atrophy among those with diabetes (4), which has been correlated with cognitive decline (25). The Framingham Offspring Study demonstrated evidence of accelerated brain aging among those with diabetes. Participants with diabetes had a 1.24% difference in total cerebral brain volume, equivalent to an estimated 6

Table 2—*Association of diabetes status with global brain MRI parameters*

MRI measure	Standardized β	*P**
TBV	−0.09	0.04
GMV	−0.17	0.0006
WMHs	0.002	0.97
Atrophy	−0.13	0.02
MD of gray matter	0.07	0.26
FA of white matter	−0.16	0.006

*Adjusted for age, race, and sex.

Table 3—*Association of diabetes status with DTI and conventional MRI indices for brain ROIs*

	MD (standardized β)‡		GMV (standardized β)†	
MRI measure	Left	Right	Left	Right
Memory-related regions				
Hippocampus	0.15**	0.14**	−0.007	0.02
Entorhinal cortex	0.06	0.04	0.02	0.07
Posterior cingulate	0.14*	0.11	−0.07	0.02
Executive control/processing speed–related regions				
Dorsolateral prefrontal cortex	0.2**	0.18**	−0.1	−0.06
Posterior parietal cortex	0.04	0.04	−0.04	−0.03
Striatum	0.1	0.1	−0.11	−0.07
Putamen	0.12^	0.14*^^	−0.14*	-0.14*
Caudate nucleus	0.08	0.06	−0.1	−0.05
Pallidium	0.07Δ	0.11ΔΔ	−0.06	−0.02

Adjusted for age, race, and sex. ‡n = 278 unless otherwise indicated. †n = 308. **$P < 0.01$. *$P < 0.05$. ^n = 221. ^^n = 272. Δn = 50. ΔΔn = 60.

years of aging, than those without diabetes (26). A few studies have also reported reduced medial temporal lobe (7,27,28) and frontal cortex (6,8) volume among elders with diabetes. In our study, participants with diabetes had smaller adjusted volume in the putamen but not in other regions. Smaller putamen volume has been correlated with tests of frontal executive and language function (29). Previous studies have also demonstrated reduced putamen volume associated with Alzheimer disease progression (29,30) and with the occurrence of dementia, independent of cerebrovascular damage and hippocampal volume (31). Whether smaller putamen volume among elders with diabetes is an indicator of risk of dementia is not known and warrants further investigation.

Hypertension and cardiovascular disease are hypothesized to contribute to cerebral atrophy (32,33). In our study, adjustment for hypertension, stroke, and myocardial infarction did not significantly alter the association between diabetes and cerebral atrophy. However, we did not have information on cardiovascular risk factors in midlife, which may impact cognition in late life (34). We also did not find an association among participants with diabetes and greater volume of WMHs. Findings for WMHs among those with diabetes have been inconsistent (4). For example, participants with diabetes in the Utrecht Diabetic Encephalopathy Study had an increase in WMH volume over a 4-year period (35), while participants with diabetes in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial showed no differences in WMHs after 3 years of follow-up compared with those without diabetes (25). Discrepancies in study findings for WMHs are not understood but may result from differences in measurement techniques or specific sample characteristics (4).

Using DTI, we found additional associations among those with diabetes and abnormalities in the hippocampus, dorsolateral prefrontal cortex, and posterior cingulate and confirmed the association with the putamen. The hippocampus and prefrontal cortex may work in conjunction in memory formation and retrieval (36), and the posterior cingulate cortex has connections to several brain regions and may play a role in attention control and information exchange (37). Our results are similar to the few known studies that have used DTI to explore microstructural brain characteristics among adults with diabetes. One study found white matter microstructural abnormalities among older adults with diabetes associated with declarative memory impairments, with strong associations reported in the frontal and temporal regions (14). Another study among middle-aged adults reported associations with diabetes and microstructural abnormalities in the frontal lobe, cerebellum, temporal lobe, right caudate, cingulate gyrus, pons, and parahippocampal gyrus (15). Microstructural abnormalities may be an early marker for risk of cognitive impairment. DTI indices are sensitive to signs of age-related cognitive decline (11,38) and early indications of Alzheimer disease (12) and have been associated with cognitive performance independent of macrostructural characteristics such as GMV (11,13). Neurodegeneration in mild cognitive impairment and Alzheimer disease has also been suggested to begin in the temporal lobe, cingulum, and prefrontal regions (39). However, differences in DTI indices should be interpreted with caution, as complex fiber orientation may affect results (40) and the functional connectivity of the brain is not completely understood.

Diabetes may contribute to brain atrophy and neurodegeneration through several possible mechanisms including the formation of advanced glycation end products, inflammation, microvascular disease, hyperinsulinemia, and hyperglycemia (1,3). Diabetes is also associated with several comorbidities such as renal disease, depression, stroke, and cardiovascular disease, each of which may impair cognitive performance (3). In our study, adjustment for several comorbidities did not significantly alter the associations between diabetes and brain structural markers; however, we cannot rule out residual confounding.

Strengths of this study included extensive characterization of health-related conditions and neuroimaging data that included microstructural measures in a large and diverse sample of community-dwelling elder adults. This study also had several limitations. Because of the cross-sectional design we cannot determine causality. While our results are consistent with previous literature and based on a priori hypotheses, we conducted 22 separate analyses for MRI measures and 20 separate analyses for DTI measures and did not adjust for multiple comparisons; therefore, some findings may be by chance. The relatively small sample size limited study power, and we were not able to analyze the effect of severity or duration of diabetes on MRI outcomes. Although participants received neurocognitive testing and detailed neurologic and gait exams, we did not have formal clinical assessments for Parkinson disease, dementia, or other neurologic disorders. It was surprising that 3MS scores did not differ between the two groups, as previous studies have shown reduced cognitive performance among older adults with diabetes (3). However, the cohort was based on volunteer participation, so participants may be healthier than other community-dwelling elders. Future

longitudinal studies with larger sample sizes are needed to address these limitations and investigate the progression of neurodegeneration associated with diabetes.

In summary, this study provides evidence that diabetes is associated with structural brain changes that may increase risk for cognitive impairment. Microstructural characteristics may also be apparent before the onset of overt volume loss or impairment detected with cognitive testing. This suggests that DTI may be a useful tool for identifying early structural brain abnormalities that may serve as a biomarker for risk of cognitive decline. Longitudinal studies are needed to determine whether MRI indices predict risk of cognitive decline and impairment.

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C.M.F. researched data; performed the statistical analysis; wrote, reviewed, and edited the manuscript; and read and approved the final version of the manuscript. C.R. contributed to the research design and assisted with technical aspects of the study related to MRI, assisted with data interpretation, reviewed and edited the manuscript, contributed to the discussion, and read and approved the final version of the manuscript. E.M.S. researched data, reviewed and edited the manuscript, and read and approved the final version of the manuscript. T.H. researched data, reviewed and edited the manuscript, supervised the study, and read and approved the final version of the manuscript. E.S.S. reviewed and edited the manuscript and read and approved the final version of the manuscript. S.S. researched data, reviewed and edited the manuscript, supervised the study, and read and approved the final version of the manuscript. K.Y. planned and supervised the study, assisted with data analysis and interpretation, reviewed and revised the manuscript, contributed to the discussion, obtained funding for the study, and read and approved the final version of the manuscript. C.M.F. and K.Y. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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