Brain Structure Among Middle-aged and Older Adults With Long-standing Type 1 Diabetes in the DCCT/EDIC Study

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

Individuals with type 1 diabetes mellitus (T1DM) are living to ages when neuropathological changes are increasingly evident. We hypothesized that middle-aged and older adults with long-standing T1DM will show abnormal brain structure in comparison with control subjects without diabetes.

RESEARCH DESIGN AND METHODS

MRI was used to compare brain structure among 416 T1DM participants in the Epidemiology of Diabetes Interventions and Complications (EDIC) study with that of 99 demographically similar control subjects without diabetes at 26 U.S. and Canadian sites. Assessments included total brain (TBV) (primary outcome), gray matter (GMV), white matter (WMV), ventricle, and white matter hyperintensity (WMH) volumes and total white matter mean fractional anisotropy (FA). Biomedical assessments included HbA_{1c} and lipid levels, blood pressure, and cognitive assessments of memory and psychomotor and mental efficiency (PME). Among EDIC participants, HbA_{1c}, severe hypoglycemia history, and vascular complications were measured longitudinally.

RESULTS

Mean age of EDIC participants and control subjects was 60 years. T1DM participants showed significantly smaller TBV (least squares mean ± SE 1,206 ± 1.7 vs. 1,229 ± 3.5 cm^3, $P < 0.0001$), GMV, and WMV and greater ventricle and WMH volumes but no differences in total white matter mean FA versus control subjects. Structural MRI measures in T1DM were equivalent to those of control subjects who were 4–9 years older. Lower PME scores were associated with altered brain structure on all MRI measures in T1DM participants.

CONCLUSIONS

Middle-aged and older adults with T1DM showed brain volume loss and increased vascular injury in comparison with control subjects without diabetes, equivalent to 4–9 years of brain aging.

The adverse effects of type 1 diabetes mellitus (T1DM) on brain structure in children (1,2), young adults (3,4), and middle-aged adults (5–7) have been described. These studies have often, but not invariably, shown smaller gray matter (GMV) and white matter (WMV) volumes, as well as white matter microstructure changes that

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are usually localized to a small number of brain regions that tend to differ across studies (3–5,7–10). Although there is an extensive literature on brain structure in older adults with type 2 diabetes (11,12), there is little information about similar outcomes associated with aging among individuals with T1DM (13). Improvements in treatment have allowed patients with T1DM to live longer and reach an age when neuropathological changes become increasingly evident in the population without diabetes. Consequently, this study was undertaken to evaluate whether long-standing T1DM results in structural changes that may make the brain more vulnerable to aging-related neuropathology. To do so, we compared MRI scans and neurocognitive assessments from a large group of older adults participating in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (EDIC) study (14,15) with those of adults without diabetes of similar age and education level recruited from the community.

DCCT/EDIC (14,15) affords an unparalleled opportunity to use longitudinal data collected over an average of 32 years in a well-characterized cohort to examine important questions about the extent to which metabolic and vascular exposures are associated with mid- and later-life brain structure that may affect risk for future cognitive decline. We address three research hypotheses: *1*) compared with subjects without diabetes, participants with T1DM will have more global tissue loss/atrophy indicated by smaller total brain volume (TBV) (primary outcome), as well as smaller GMV and WMV, smaller ventricle volumes, more microstructural injury to white matter tracts indicated by lower total white matter mean fractional anisotropy (FA), and more vascular injury, indicated by greater white matter hyperintensity (WMH) volume; *2*) among participants with T1DM, prior assignment to conventional rather than intensive diabetes therapy during DCCT, higher persistent HbA_{1c} levels, history of severe hypoglycemia, or the presence of micro- and/or macrovascular risk factors and complications will be associated with measures of brain structural abnormality; and *3*) brain structure measures will be correlated with specific domains (memory and psychomotor and mental efficiency [PME]) of cognitive functioning.

RESEARCH DESIGN AND METHODS

DCCT/EDIC Participants and Control Subjects Without Diabetes

In the DCCT, a total of 1,441 T1DM participants (1983–1989; mean age 27 years [range 13–39]) were randomized to intensive or conventional diabetes therapy for assessment of effects on diabetes-associated complications (14). Baseline exclusion criteria included hypertension, hyperlipidemia, cardiovascular disease, neuropathy requiring medical intervention, and a history of recurrent severe hypoglycemia. The DCCT ended after an average of 6.5 years of follow-up having demonstrated the benefit of intensive glycemic therapy (14). In 1994, 96% of the surviving DCCT cohort enrolled in EDIC, an ongoing, long-term observational study (15).

We estimated that 400 EDIC participants and 100 control subjects would provide ∼85% power to detect a 0.34 SD difference in a quantitative outcome between the two groups, with use of a two-sided *t* test at $P = 0.05$. Accounting for ∼5% potentially missing data, in 2018–2019, after an average follow-up of 32 years, 425 of the 1,190 actively participating EDIC participants were randomly selected across initial DCCT treatment and cohort strata (i.e., $n = 106$ from each of the four DCCT treatment and cohort combinations) and invited to enroll in the MRI study (Supplementary Fig. 1). Exclusion criteria included end-stage renal disease, visual acuity worse than 20/40 corrected in both eyes, pacemakers and implanted neurostimulators, severe claustrophobia, other known or suspected metallic foreign object in the body, or body weight in excess of 350 lbs.

A demographically similar comparison group of adults without diagnosed diabetes or serious current illnesses, including no prior history of stroke, was recruited from the community at each participating EDIC site. We randomly selected 100 of the 425 EDIC participants across the four strata (i.e., $n = 25$ from each of the four DCCT treatment and cohort combinations) and matched control subjects by ethnicity and race, age within 5 years, and educational attainment. Three control subjects with HbA1c levels ≥6.5% were excluded.

The final sample included 416 EDIC participants and 99 control subjects without diabetes (Supplementary Fig. 1). The characteristics of participants enrolled in the MRI study were similar to those of the surviving cohort at the time of the MRI study (Supplementary Table 1). The study was approved by institutional review boards at all centers, and all participants and control subjects provided written informed consent.

Evaluations, Risk Factors, and Coexisting Complications

Potential risk factors for changes in brain structure were assessed in EDIC participants and control subjects with standardized methods (15). Assessments were obtained longitudinally for EDIC participants (quarterly during DCCT and annually during EDIC) and cross-sectionally at the time of the MRI for control subjects. Clinical measures included a detailed medical history with biometrics and laboratory studies. Among EDIC participants, severe hypoglycemia was defined as the cumulative number of events leading to coma or seizure within the 3 months prior to each DCCT/EDIC study visit based on self-report. The presence of kidney disease (16), proliferative diabetic retinopathy (17), neurologic complications (18), and cardiovascular disease (19) was determined as previously described. (See Supplementary Material for more detailed descriptions of definitions and ascertainment.)

MRI Protocol

Example images from MRI scans are shown in Supplementary Fig. 2. MRI studies were performed at 26 of 27 EDIC clinical sites at 24 imaging centers with Siemens Healthineers (10 Prisma, 2 Trio, and 1 each Biograph, Verio, Skyra, and Vida), Philips (4 Achieva), and GE (3 Discovery MR750, 1 Signa Excite HDxt) 3 Tesla scanners. Imaging parameters included the following: T1 and T2, field of view 250 mm (Siemens, GE) or 256 mm (Philips), slices = 176 (Siemens, GE) or 170 (Philips), native resolution 1 mm isotropic; T2 fluid-attenuated inversion recovery (FLAIR), field of view 250–258 mm, slices = 160 (Siemens, Philips) or 176 (GE), native resolution 1 mm isotropic (Siemens, GE) or 1 × 1 × 2 mm (Philips); and diffusion tensor imaging (DTI), 30 directions, native resolution 2.2 mm isotropic. Scanner performance was stable across quarterly Alzheimer's Disease Neuroimaging Initiative (ADNI) phantom analyses. All scans were reviewed by a radiologist for clinically meaningful findings warranting follow-up. Eight scans (seven of EDIC participants and one of a control subjects) were excluded from analyses due to structural lesions that affect study MRI outcome measures: five due to encephalomalacia, one meningioma with mass effect, one neurodevelopmental abnormality, and one likely multiple sclerosis.

MRI analysis was performed by trained analysts masked to other participant data using a semiautomated computational pipeline. Preprocessing included magnetic field intensity inhomogeneity correction (20) followed by a multiatlas skull-stripping method (21), which was applied with use of both T1 and T2 images for the estimation of total intracranial volume (ICV). For two participants, subcentimeter meningiomas were manually excluded from the brain mask. TBV, a sum of all brain parenchymal volume including cerebrum, cerebellum, and brainstem, was derived with a multiatlas, multiwarp label-fusion method (22) where 145 anatomic regions of interest were segmented on the basis of T1 scans. A previously described deep learning–based segmentation method was used to determine WMH volume (23). DTI images were denoised (24), and the tensor was reconstructed using multivariate linear fitting with motion correction (25). Total white matter mean FA was extracted from scalar FA maps. FA (values 0–1) is affected by axon tract structural integrity; decreases in FA are associated with pathology.

The primary outcome for this study was TBV, a global measure of neurodegeneration/atrophy. Predefined secondary outcomes of interest included additional measures of GMV, WMV, ventricle and WMH volumes, and total white matter mean FA.

Cognitive Protocol

EDIC cognitive test administration, scoring, and quality control procedures have previously been described (26,27). The assessment included an abbreviated battery consisting of a subset of PME tests found to be particularly sensitive to diabetes (26) and tests of memory known to be sensitive to normal aging and mild cognitive impairment (28). Tests included the Logical Memory subtest from the Wechsler Memory Scale, Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale, Trail Making Test Part B, Verbal Fluency (FAS), and the Grooved Pegboard test (28,29). Cognitive tests were acquired within a mean of 46 days of the MRI (median 0 [interquartile range 0–40]), with 66% of tests occurring within 7 days. Control subjects were evaluated one time, whereas DCCT/EDIC participants were evaluated five times over 32 years. For both EDIC participants and control subjects, a standardized z score was calculated for each of the test variables with use of the means and SDs of the DCCT/EDIC cohort from the DCCT baseline evaluation (1983–1989). z scores in each domain were averaged to obtain a summary score. These standardized scores provide a unit-free measurement of the relative difference in performance compared with the total DCCT/EDIC cohort at the referent DCCT baseline assessment.

In EDIC participants, capillary blood glucose levels were measured immediately prior to cognitive testing and the MRI scan to ensure absence of acute hypoglycemia. Participants with blood glucose levels $\leq$70 mg/dL were provided a snack; scanning/testing commenced when blood glucose values were $\geq$90 mg/dL.

Statistical Analysis

Differences in demographic and clinical characteristics between EDIC participants and control subjects were tested with the Wilcoxon rank sum test for quantitative characteristics or the χ^2 test for categorical characteristics. Linear mixed models were used to estimate mean differences in MRI outcomes between groups after adjustment for ICV, age, and scanner. Cohen d effect size was calculated by division of the difference in means between EDIC participants and control subjects by the pooled SD. We estimated the additional number of years of age that would yield the same difference in each MRI outcome as the difference between EDIC participants and control subjects by taking the ratio of the β-coefficient estimate for subject group to that for age from a linear mixed model that included both factors, with adjustment for ICV and scanner (30).

Among EDIC participants only, we used ANCOVA models to assess DCCT treatment group differences in MRI outcomes and linear regression models to assess other covariate effects on the mean of each MRI outcome. Quantitative covariates were characterized as the time-weighted mean of all follow-up values from DCCT baseline to the MRI visit. Categorical covariates were defined as any report prior to the MRI visit. Comprehensive multivariable regression models were developed for each MRI outcome with use of a backward elimination, where variables significant at $P < 0.10$ were retained at each step; the final multivariable models retained covariates significant at $P < 0.05$. Signed t values are presented and correspond to the magnitude and directionality of the association. With our large sample size, t values and z values converge to a normal distribution. Both are used to differentiate covariate effects with a $P < 0.0001$ (two sided) equivalent to a $|z| \geq 3.89$. All analyses were adjusted for ICV, age, and scanner.

Due to the skewed distribution for WMH volume, we applied an inverse hyperbolic sine transformation (asinh), which is similar to a log transformation but can accommodate values of zero and was used for all formal hypothesis testing. However, since interpreting the point estimates for WMH volume after this transformation is challenging, we also present estimates for WMH volume using a linear model with a sandwich estimate for the variance-covariance matrix that is robust to model misspecification (31).

Separately for EDIC participants and control subjects, linear regression models were used to evaluate the individual associations of each MRI measure with summary z scores for each cognitive domain after adjustment for ICV, age, sex, years of education, and scanner. Here, MRI variables were treated as exposures (independent variables). In pooled analyses, using linear mixed models, we tested for an interaction between each MRI measure and subject group to evaluate whether the associations of MRI measures with cognitive domains differed between EDIC participants and control subjects.

All analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC).

Data and Resource Availability

Data collected for the DCCT/EDIC study through 30 June 2017 are available to the public through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Central Repository (https://repository.niddk.nih.gov/studies/edic/). Data collected in the current cycle (July 2017–June 2022) will be available within 2 years after the end of the funding cycle.

RESULTS

Comparison of T1DM Participants and Control Subjects

EDIC participants had a median age of 60 years (range 44–74) at the time of the MRI, with 21% older than 65 years of age. EDIC participants and age-matched control subjects were similar for most demographic variables (Table 1). Relative to control subjects, EDIC participants had less education and a greater proportion received treatment for hypertension and hypercholesterolemia. Control subjects had higher diastolic blood pressure and a less favorable lipid profile, consistent with the self-reported treatment differences.

EDIC participants had significantly smaller TBV relative to control subjects (least squares mean ± SE 1,206 ± 1.7 vs. 1,229 ± 3.5 cm^3, $P < 0.0001$) (Table 2 and Supplementary Fig. 3). In addition, GMV and WMV were significantly smaller in the EDIC cohort, while ventricle and subarachnoid cerebrospinal fluid (CSF) volumes were greater. EDIC participants also had significantly greater WMH volumes compared with control subjects (2.68 ± 0.17 vs. 2.20 ± 0.27 cm^3, P = 0.0003). Cohen *d* for these comparisons ranged from 0.37 to 0.67. We estimated that the brain volumetric findings in EDIC participants were equivalent to findings that would be found in control subjects who were 4.4–8.6 years older. Total white matter mean FA was not significantly different between groups. We reran the analyses presented in Table 2 with stratification by age above and below 65 years. There were no significant interactions between subject group (EDIC participant vs. control) and age above and below 65 years (data not shown). The results remained the same in models with further simultaneous adjustment for sex, alcohol use, and BMI (Supplementary Table 2). Additionally, excepting total GMV, these findings also persisted after adjustment for years of education, diastolic blood pressure, and lipids (data not shown).

Factors Associated With Brain Structure

Among EDIC participants, no significant group differences were observed in MRI

Table 1—Characteristics of EDIC participants and control subjects without diabetes enrolled in the MRI study (2018–2019)

	EDIC participants	Control subjects	*P*
N	416	99	
Demographic			
Age at diagnosis of T1DM (years)	21.8 ± 7.7	—	—
Age (years)	59.6 ± 6.4	59.8 ± 6.9	0.7483
Age, median (range)	60 (44–74)	60 (45–76)	
Age >65 years	20.9	23.2	0.6129
Female sex	44.2	53.5	0.0950
White race	96.6	96.7	0.9598
Education (years)	15.6 ± 1.9	16.2 ± 1.5	0.0172
Professional or technical occupation	58.7	66.0	0.1917
Married or remarried	81.9	84.5	0.5371
Behavioral			
Current cigarette smoker	8.0	5.1	0.3189
Occasional or regular alcohol use	53.5	64.7	0.0452
Physical			
BMI (kg/m^2)	28.2 ± 5.1	27.9 ± 4.7	0.6926
Waist circumference (cm)	94.7 ± 13.9	93.7 ± 13.8	0.4260
ICV (cm^3)	1441.4 ± 142.7	1427.2 ± 139.7	0.4066
Blood pressure			
Systolic blood pressure (mmHg)	123.1 ± 14.5	120.0 ± 13.9	0.0509
Diastolic blood pressure (mmHg)	68.7 ± 8.8	75.2 ± 8.9	<0.0001
Any treated hypertension	86.5	22.2	<0.0001
Lipids			
Total cholesterol (mg/dL)	170.8 ± 35.7	197.6 ± 40.8	<0.0001
Triglycerides (mg/dL)	70.0 ± 42.6	96.3 ± 47.7	<0.0001
HDL cholesterol (mg/dL)	65.5 ± 20.7	61.5 ± 19.1	0.0777
LDL cholesterol (mg/dL)	91.4 ± 29.4	117.0 ± 35.0	<0.0001
Any treated hyperlipidemia	86.0	24.2	<0.0001
Glycemia: HbA_{1c} (%)	7.7 ± 1.1	5.5 ± 0.3	<0.0001

Data are means ± SD or percentages unless otherwise indicated. Differences between the participants and control subjects were tested with use of the Wilcoxon rank sum test for quantitative characteristics or χ^2 test for categorical characteristics.

Table 2—MRI outcomes among EDIC participants and control subjects without diabetes

	EDIC participants	Control subjects	*P*	Cohen *d*	Equivalent years of age
N	416	99			
TBV (cm^3)	1,206 ± 1.7	1,229 ± 3.5	<0.0001	−0.67	7.1
GMV (cm^3)	647 ± 1.7	660 ± 3.4	0.0008	−0.37	4.4
WMV (cm^3)	538 ± 1.5	549 ± 2.8	0.0002	−0.38	—
Ventricle volume (cm^3)	34 ± 0.7	26 ± 1.5	<0.0001	0.53	8.6
Subarachnoid CSF volume (cm^3)	198 ± 1.6	182 ± 3.2	<0.0001	0.47	6.4
WMH volume (cm^3)*	2.68 ± 0.17	2.20 ± 0.27			
WMH asinh volume (cm^3)*	1.37 ± 0.04	1.03 ± 0.08	0.0003	0.46	7.9
Total white matter mean FA†	0.409 ± 0.001	0.414 ± 0.002	0.0579	−0.22	6.2

Data are least squares means ± SE from linear mixed models with adjustment for ICV, age, and scanner. We calculated Cohen *d* effect size by taking the difference in means between EDIC participants and control subjects and dividing by the pooled SD. We estimated the additional number of years of age that would yield the same difference in each MRI outcome as the difference between control subjects without diabetes and T1DM participants by taking the ratio of the β-coefficient estimate for subject group (1 = participant, 0 = control) to that for age from a linear mixed model that included both factors. The equivalent years of aging is not presented for WMV, since age was not a significant factor in the model. *WMH was assessed in *N* = 381 EDIC participants and *N* = 82 control subjects; an inverse hyperbolic sine transformation was used to normalize the distribution (asinh). †Total white matter mean FA was assessed in *N* = 363 EDIC participants and *N* = 80 control subjects and was not adjusted for ICV.

outcomes based on original DCCT treatment assignment (Supplementary Table 3). Therefore, all EDIC participants were pooled.

We investigated associations between risk factors and structural MRI outcomes in multivariable analyses, adjusting for ICV, age, and scanner (Table 3). There were no significant associations of severe hypoglycemia resulting in seizure or coma with MRI outcomes. After adjustment for all other covariates listed in Table 3, higher HbA_{1c}, higher diastolic blood pressure, and lower pulse rate were independently associated with smaller GMV. In addition, higher systolic blood pressure and a history of proliferative diabetic retinopathy were both associated with greater ventricular and WMH volumes. Higher diastolic blood pressure was associated with smaller TBV and a history of microalbuminuria with lower mean FA. Unexpectedly, higher BMI and a history of peripheral neuropathy correlated with greater GMV. Age was included as a continuous variable in our analyses. We reran the final multivariable model for TBV (our primary outcome), substituting the continuous age variable with a binary age variable of above and below 65 years of age. The interpretation and significance of the final multivariable model remained the same (data not shown). The minimally adjusted associations can be found in Supplementary Table 4. Among the lipid variables, there was a marginally significant association between HDL-to-LDL ratio and TBV. The association did not remain significant in the multivariable model (Table 3).

Relationship Between Cognition and Brain Structure

Among EDIC participants, smaller TBV was significantly associated with poorer PME but not with immediate or delayed memory (Table 4). Lower mean FA and greater ventricle, subarachnoid CSF, and WMH volumes were also associated with worse PME. In addition, decreased GMV was significantly associated with poorer performance within all three cognitive domains. There were no significant associations between MRI measures and cognitive domains among control subjects (Supplementary Table 5). In pooled analyses with a combination of EDIC participants and control subjects, no significant interactions were found between MRI measures and subject group except for a marginally significant interaction between mean FA and subject group ($P = 0.027$) for PME.

CONCLUSIONS

This work provides clear evidence that older adults with a long history of T1DM manifest reduced GMV and WMV and greater ventricle and WMH volume compared with adults without diabetes who are otherwise similar in age and demographics. The brain volumes of EDIC participants appeared similar to those of individuals without diabetes who are 4–9 years older. These effects, as indexed by Cohen *d*, are moderately large and consistent with the hypothesis that diabetes may accelerate brain aging. It is noteworthy that a similar pattern of accelerated aging was found when we assessed changes in cognitive function over the 32-year follow-up of the entire cohort from DCCT baseline to the current assessment (29).

Higher HbA_{1c} levels and vascular factors (elevated diastolic blood pressure) are most strongly associated with smaller GMV. Systolic blood pressure and proliferative diabetic retinopathy are associated with greater ventricle and WMH volumes. Prior episodes of severe hypoglycemia are unrelated to volumetric measures. Moreover, greater ventricular volume, and smaller volumes of virtually all other brain measures, are significantly associated with poorer performance on cognitive tests requiring psychomotor speed and mental flexibility. To a lesser extent, smaller GMV and WMV are also associated with poorer memory, as reflected in the moderate size of the linear regression *t* values. However, at the current average age of the EDIC cohort, T1DM may not yet exert a strong effect on memory.

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Table 3—Multivariable models for MRI outcomes among EDIC participants (*n* = 416)

	TBV (cm^3), model R^2 = 0.91				GMV (cm^3), model R^2 = 0.76				Ventricle volume (cm^3), model R^2 = 0.28				WMH asinh volume (cm^3), model R^2 = 0.16				Total white matter mean FA, model R^2 = 0.11			
	β	SE	*t*	*P*	β	SE	*t*	*P*	β	SE	*t*	*P*	β	SE	*t*	*P*	β	SE	*t*	*P*
Age (per 1 year)	−3.37	0.28	−12.14	<0.0001	−2.96	0.27	−11.01	<0.0001	0.93	0.12	7.56	<0.0001	0.04	0.01	6.12	<0.0001	−0.001	0.000	−3.71	0.0002
Sex (men vs. women)					13.45	4.81	2.80	0.0054												
Education (per 1 year)									1.42	0.42	3.35	0.0009								
HbA_{1c} (per 1%)*					−5.64	2.14	−2.63	0.0088												
BMI (per 1 kg/m^2)*	1.65	0.51	3.24	0.0013	1.48	0.49	3.03	0.0026												
Systolic blood pressure (per 5 mmHg)*									1.42	0.50	2.83	0.0049	0.05	0.02	2.17	0.0306				
Diastolic blood pressure (per 5 mmHg)*	−5.68	1.90	−2.99	0.0029	−7.87	1.92	−4.10	<0.0001												
Pulse rate (per 1 bpm)*					0.73	0.28	2.59	0.0101												
Sustained AER ≥30 mg/24 h (yes vs. no)†																	−0.006	0.003	−2.06	0.0399
PDR (yes vs. no)†									4.43	1.81	2.45	0.0146	0.20	0.09	2.20	0.0283				
Peripheral neuropathy (yes vs. no)†					10.95	3.90	2.80	0.0053												

Data are β-coefficients, SEs, *t* values, and *P* values from five separate multivariable regression models evaluating the association of all of the risk factors entered into the model together with each MRI outcome (dependent) and with further adjustment for ICV, age, and scanner. Covariates that did not enter into any of the five models were not included in the table. β estimates are equal to the difference in means between groups or the slope of the association (e.g., increase or decrease in MRI outcome for every unit change in the covariate). The signed *t* value corresponds to the magnitude and directionality of the association. WMH was assessed in *N* = 381 EDIC participants; an inverse hyperbolic sine transformation was used to normalize the distribution (asinh). Total white matter mean FA was assessed in *N* = 363 participants and was not adjusted for ICV. AER, albumin excretion rate; eGFR, estimated glomerular filtration; PDR, proliferative diabetic retinopathy. *Risk factors were characterized as the time-weighted mean values of all follow-up values since DCCT baseline up to the MRI study visit. †Any report between DCCT baseline and the MRI study visit.

We also observed several somewhat unexpected relationships between predictors and volumetric measures. Higher BMI was associated with greater TBV and GMV. Most prior studies have found higher BMI to be associated with smaller global brain volumes (32). However, some studies found no significant relationship (33) and there is evidence of heterogeneity in the relationship of BMI to brain volumes with respect to brain regions and sex (32,34). In the EDIC subsample, it is unclear whether the BMI-TBV and BMI-GMV results indicate a different effect in T1DM or are related to sampling. Similarly, having a history of peripheral neuropathy, which is known to be associated with higher HbA_{1c} values, was associated with greater, rather than smaller, TBV in these analyses. In addition, we did not find any significant associations between lipids and brain structure, with the exception of a marginal association between HDL-to-LDL ratio and TBV in marginally adjusted analyses. This may be due to the fact that EDIC participants had better lipid control (Table 1) than control subjects. Associations between hypercholesterolemia and brain morphometry have been inconsistent. In one recent large study from the UK Biobank, Cox et al. (35) also did not find significant associations with hypercholesterolemia and brain volumetric measures similar to those in our study (TBV, total GMV). Much prior work has identified regional structural associations between hypercholesterolemia and brain volume, so it is possible that there is insufficient power in global brain measures.

It is likely that decreases in cortical volume have been developing over an extended period of time in our cohort. Previous studies of children and young to middle-aged adults with T1DM have often, but not invariably, reported smaller GMV or WMV that are usually localized to a handful of brain regions that tend to differ across studies (3–5,7–10). A higher prevalence of WMH and cerebral small vessel disease has also been reported in some studies of middle-aged adults with T1DM but not others (36,37). Smaller GMV and WMV were sometimes correlated with measures of hyperglycemia (3,7) and/or hypoglycemia (3,4), but this has not been a universal finding, perhaps because of limited statistical power or other methodological differences.

Table 4—Association of MRI measures with cognitive domains among EDIC participants (n = 415)

	Immediate memory				Delayed recall				Psychomotor and mental efficiency			
	β	SE	*t*	*P*	β	SE	*t*	*P*	β	SE	*t*	*P*
TBV (per 10 cm^3)	0.009	0.012	0.75	0.4513	0.013	0.014	0.91	0.3640	0.062	0.014	4.40	$<$0.0001
GMV (per 10 cm^3)	0.031	0.012	2.53	0.0117	0.028	0.014	2.00	0.0460	0.048	0.015	3.30	0.0011
WMV (per 10 cm^3)	−0.029	0.014	−2.02	0.0445	−0.020	0.017	−1.20	0.2309	0.022	0.017	1.26	0.2073
Ventricle volume (per 10 cm^3)	−0.028	0.028	−1.02	0.3092	−0.017	0.032	−0.55	0.5824	−0.159	0.032	−4.97	$<$0.0001
Subarachnoid CSF volume (per 10 cm^3)	−0.004	0.013	−0.34	0.7367	−0.011	0.015	−0.73	0.4688	−0.036	0.015	−2.36	0.0186
Hippocampus volume (per 1 cm^3)	0.094	0.068	1.37	0.1703	0.055	0.078	0.70	0.4829	0.275	0.080	3.42	0.0007
WMH asinh volume (per 1 cm^3)*	−0.020	0.060	−0.33	0.7439	−0.004	0.070	−0.06	0.9496	−0.228	0.069	−3.30	0.0011
Total white matter mean FA (per 0.01 unit)†	0.014	0.020	0.68	0.4957	0.019	0.023	0.81	0.4161	0.084	0.023	3.57	0.0004

Data are β-coefficients, SEs, *t* values, and *P* values from individual linear regression models evaluating the association of each MRI measure (independent) with each cognitive domain (dependent), with adjustment for ICV, age, sex, years of education, and scanner. β estimates are equal to the slope of the association (e.g., increase or decrease in cognitive domain for every unit change in the covariate). The signed *t* value corresponds to the magnitude and directionality of the association. *WMH was assessed in *N* = 380 EDIC participants; an inverse hyperbolic sine transformation was used to normalize the distribution (asinh). †Total white matter mean FA was assessed in *N* = 362 EDIC participants and was not adjusted for ICV.

Correlations between MRI parameters and cognition have also been reported previously, particularly with tasks requiring psychomotor speed and mental flexibility (5,6,38). Our study differs from prior studies because it incorporates extensive longitudinal data about the biomedical status of the participants with diabetes. This includes information on metabolic control, hypoglycemia, and development of complications over an extended period of time.

Developmental delays in brain maturation have been reported soon after diagnosis of T1DM, as demonstrated in longitudinal research with children. For example, younger children with early onset of diabetes showed significantly less growth in GMV, cortical surface area, and WMV throughout the cortex and cerebellum over a 2-year follow-up period (2). Older children and adolescents with a somewhat later onset age did not, as a group, show appreciable volumetric differences in brain development over a 2-year period compared with children without diabetes, but those who had experienced more hyperglycemia showed a greater decline in whole brain gray matter, whereas those who experienced severe hypoglycemia showed a greater decrease in occipital/parietal white matter (1).

Because our MRI assessments were conducted once, ∼28–34 years after entry into the DCCT/EDIC study, we cannot accurately estimate when these brain changes began in our cohort or determine how quickly they progressed. However, cognition has been assessed periodically over a 32-year follow-up period. Although relatively modest changes in cognition were detected over the first 18 years of study, between study years 18 and 32 there was a fivefold drop in performance on measures of PME, with smaller declines on tests of memory. Given the strong associations we found between multiple measures of brain morphology and cognition, it is conceivable that the rate of brain atrophy has also been accelerating during that same period in this sample.

This study has several strengths. We evaluated brain structure in a large group of well-characterized participants with T1DM who were initially recruited when they were 13–39 years of age and were subsequently followed over an average of 32 years. The DCCT/EDIC study incorporated an extensive assessment of biomedical risk factors and diabetes complications, detailed neuroimaging, and cognitive assessments, allowing for predictive modeling of interrelationships between brain structure, cognitive function, and metabolic factors. While the participants were randomized to different levels of treatment and glycemic control during DCCT, the mean HbA_{1c} values of the original treatment groups have been indistinguishable for $>$20 years during EDIC (39). Throughout follow-up, participants have had a wide range of exposures to hyperglycemia, severe hypoglycemia, and other metabolic alterations common to T1DM, as well as the development of diabetes complications and comorbidities (40). The EDIC cohort is largely intact, with 94% of the living participants still actively followed. Control subjects were matched to be similar in age and demographics to EDIC participants and were studied with identical neuroimaging and cognitive testing protocols. Moreover, the volumetric findings from our control subjects were quite consistent with data from other general population studies (41).

This study also has limitations. Scanner factors resulted in decreased sample size for FA because some sites could not acquire high-quality DTI. Generalization of our findings to other adults with diabetes may be limited because the EDIC cohort consists of participants with T1DM who met stringent inclusion and exclusion criteria, were willing to participate in a long-term clinical study, and are highly motivated to monitor their health, highly educated, and almost entirely non-Hispanic White. As a consequence, EDIC participants may have more optimal long-term diabetes management that may lead to an underestimation of the extent of brain changes that might be seen in a sample of T1DM adults drawn from the general population.

The findings from the current research suggest that overall, middle-aged and older adults with T1DM show early signs of mild cognitive dysfunction and changes in brain structure consistent with being ~5 years older than their actual age, on average. These cognitive and brain structural changes are small in magnitude and for most do not yet manifest as clinically significant or otherwise adversely affect their quality of life or ability to function. However, it is likely that a subgroup will show changes in cognitive ability that can affect their daily lives and capabilities and that this subgroup may be larger than would be found among otherwise healthy individuals of the same age. Therefore, screening for mild cognitive impairments would seem to be useful in clinical practice. These could be done at periodic visits with questions about any changes in memory and other cognitive skills, augmented by brief, simple screening tests that can be done in the office. If these suggest cognitive impairment, referral to a neurologist or neuropsychologist may be warranted. These questions need to be handled carefully and, when possible, include a significant other because the patient may underplay the concerns or not realize their extent. It should be emphasized that the standard recommendations for care of diabetes appear to benefit cognitive function even while this report does not show that effect in the assessment of brain structure. While brain structural changes may become impactful as T1DM patients continue to age, the observed changes are overall small, and these results do not suggest that brain MRI should be routinely performed for patients with T1DM in this age-group.

In summary, this study indicates that EDIC participants who are on average 60 years old manifest global reductions in brain volume compared with control subjects without diabetes. The brain volumes of EDIC participants appear similar to those of individuals without diabetes who are 4–9 years older. Moreover, these global structural differences are associated with reduced PME. Our findings suggest that diabetes-related persistent hyperglycemia, as assessed on the basis of HbA_{1c} levels over time, and vascular factors disrupt some aspects of global brain integrity. These factors and severe hypoglycemic events may affect specific brain regions to a greater extent, as demonstrated in other studies of younger adults with T1DM (1,3,11).

It remains to be determined whether the observed reductions in brain volume and increases in WMH volume increase vulnerability to future age-related neurocognitive disease in aging patients with T1DM. Since the benefits of improved care have led to people with T1DM living longer, healthier lives overall, future research is needed to examine whether the brain changes found in the current research may continue or accelerate with aging or result in greater susceptibility to other age-related pathology that may affect the cognitive trajectory of T1DM patients. The EDIC cohort provides an opportunity to provide patients, families, and caregivers valuable information about the interaction of T1DM and aging.

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