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RESEARCH ARTICLE

Diabetes and cortical thickness in ethnically diverse cognitively normal older adults

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Abstract

INTRODUCTION: Mechanisms linking type 2 diabetes mellitus (T2DM) with dementia are poorly understood. We examined T2DM associations with cortical thickness and hippocampal volume in ethnoracially diverse, cognitively unimpaired older adults.

METHODS: In 2171 cognitively unimpaired older adults, we examined (1) how T2DM related to cortical thickness and hippocampal volume, (2) whether associations were independent of socioeconomic factors and comorbidities, (3) whether associations were driven by hyperglycemia or hyperinsulinemia, and (4) how associations varied by self-reported race/ethnicity.

RESULTS: T2DM was correlated with thinner cortex independent of socioeconomic factors and comorbidities, and this was driven by higher hemoglobin A1c (HbA1c). Higher HbA1c levels were correlated with thinner cortex in diabetics and non-diabetics. T2DM–cortical thickness associations were strong and widespread in Hispanic participants, modest and limited to temporal regions in non-Hispanic White participants, and not present in non-Hispanic Black adults.

DISCUSSION: T2DM is associated with a thinner cortex, and this is driven by poor glycemic control.

KEYWORDS
cognitively unimpaired, aging, cortical thickness, glycemic control, hyperglycemia, hyperinsulinemia, health disparities, MRI, type 2 diabetes mellitus

Highlights

- T2DM is associated with a thinner cortex.
- The T2DM–cortical thickness relationship is likely driven by poor glucose control.
- Higher HbA1c levels correlated with thinner cortex in diabetics and non-diabetics.
- The T2DM-cortical thickness association varied by self-reported ethnicity/race.

1 | INTRODUCTION

Approximately 30% to 40% of dementia cases worldwide are attributable to modifiable risk factors,[1] including type 2 diabetes mellitus (T2DM). T2DM increases the risk of all-cause dementia, including both Alzheimer's disease (AD) dementia and vascular dementia.[2] Prior studies reported lower cortical volume and thickness among older T2DM patients compared to healthy controls, particularly in temporal and parietal regions.[3–10] However, the samples in most prior research were small or overwhelmingly non-Hispanic White (NHW), highly educated, and with relatively low rates of cardiovascular comorbidities, limiting the generalizability of their findings. This is particularly concerning given the higher prevalence of T2DM among Hispanic and non-Hispanic Black (NHB) Americans compared to NHW individuals.[11] The higher T2DM burden in these minoritized groups may also contribute to their elevated dementia risk compared to their NHW counterparts.[12,13] Examining the relationship between T2DM and brain health in diverse samples could help uncover factors contributing to disparities in dementia risk.

People with T2DM often have comorbidities, including obesity, dyslipidemia, and hypertension, which may also adversely influence brain health. It is not clear whether the previously–observed differences in brain structure between T2DM patients and healthy controls are influenced by such comorbidities. Furthermore, it remains unclear whether this relationship is driven by chronic hyperglycemia or by hyperinsulinemia, both of which are pathological features of T2DM. Chronic hyperglycemia, indexed by higher hemoglobin A1c (HbA1c) levels, is linked to higher dementia risk,[14] larger white matter hyperintensity volume, and lower hippocampal volume.[15] In contrast, higher blood insulin correlates with better cognitive performance and lower dementia severity in early AD patients.[16] However, insulin resistance, which is often accompanied by hyperinsulinemia, is associated with poor cognitive outcomes.[17] Whether hyperglycemia is associated with adverse brain outcomes independent of hyperinsulinemia remains unknown.

In an ethnoracially diverse sample of 2171 cognitively unimpaired older adults, we investigated the association between T2DM and both cortical thickness and hippocampal volume. We also explored whether these associations were independent of socioeconomic factors and related comorbidities. In T2DM-associated regions, we evaluated whether cortical thickness was related to fasting blood insulin and HbA1c levels. In diabetic participants, we examined whether poor glycemic control related to thinner cortex independent of disease severity. Finally, we investigated the relationship between T2DM and cortical thickness separately within Hispanic, NHB, and NHW participants. Our work analyzing the relationship between T2DM and cortical thickness in the context of possible mechanisms and confounding factors may help guide a personalized medicine approach to mitigate the impact of T2DM on brain health.

2 | METHODS

2.1 | Participants

We evaluated 2171 cognitively unimpaired older adults from the Health and Aging Brain Study-Health Disparities (HABS-HD) cohort. The HABS-HD is a community-based cohort study of cognitive aging in adults aged 30 years or older. Participants undergo a clinical interview, neuropsychological assessment, brain MRI, and blood draw at the University of North Texas Health Science Center. HABS-HD exclusion criteria include a diagnosis of type 1 diabetes, the presence of an active infection or other uncontrolled inflammatory condition, a current or recent cancer diagnosis, or having an active or recent severe medical condition (other than dementia or mild cognitive impairment [MCI]) that could impact cognition, such as severe mental illness (except depression), traumatic brain injury with loss of consciousness, or alcohol/substance abuse. Participants were included in our study if they (1) were cognitively unimpaired at baseline, (2) had a baseline MRI scan with usable FreeSurfer cortical segmentations, (3) had a baseline T2DM diagnostic assessment, and (4) were aged 50 years or older.

2.2 | Diagnostic criteria

Cognitive diagnoses are determined using a decision tree and verified at consensus review based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for AD[18] and established criteria for MCI.[19] Cognitively unimpaired participants have a Clinical Dementia Rating (CDR) Sum of Boxes score of 0 and have cognitive test scores that broadly fall within normal limits. Further details regarding the assignment of cognitive diagnoses can be found in the Supplementary Material.

2.3 | MRI data acquisition and processing

For each participant, we acquired a T1-weighted whole brain volumetric magnetization-prepared rapid gradient (MPRAGE). Participants

were scanned on either a 3T Siemens MAGNETOM Skyra whole-body scanner (repetition time [TR] = 2300 ms; echo time [TE] = 2.93 ms; 1.1 × 1.1 × 1.2 mm) or a 3T Siemens MAGNETOM Vida (TR = 2300 ms; TE = 2.98 ms; 1.0 × 1.0 × 1.0 mm). We used FreeSurfer software version 5.3.0 to automatically segment and parcellate 34 cortical regions on the right and left for a total of 68 cortical regions. We used HippoDeep software to segment the right and left hippocampus and to estimate intracranial volume (ICV). We quality checked gray–white matter segmentations for each cortical region using a pass–fail algorithm modified from the ENIGMA internal quality check protocol updated in April 2017. The quality control for hippocampal segmentation was performed following the recommendations of the European Alzheimer's Disease Consortium and the Alzheimer's Disease Neuroimaging Initiative (EADC-ADNI) harmonized hippocampal protocol.[20] Examples of acceptable segmentation (Figure S1), oversegmentation (Figure S2), and undersegmentation (Figure S3) of the hippocampus can be found in the Supplementary Material. All raters achieved acceptable reliability on an established test set for both cortical thickness and hippocampal volume (Cohen's $\kappa > 0.60$) before performing quality checks for this project. More information regarding our quality checking protocols for cortical thickness and hippocampal volume measures can be found in the Supplementary Material.

2.4 | Blood collection and processing procedures

HbA1c, cholesterol, and insulin were assessed using fasting blood collection, and processing was performed following international guidelines.[21] Blood tubes were centrifuged within 1 h of collection and then transferred to the Hamilton Robotics EasyBlood automation system to be processed within 2 h of the blood draw. Plasma insulin was derived using a Meso Scale Discovery kit.

2.5 | Metabolic risk measures

All medical diagnoses were determined by a licensed practitioner (nurse practitioner or physician) based on clinical labs, medical history, current medications, and direct measurements. Participants having HbA1c ≥ 6.5% or reporting a past T2DM diagnosis were classified as diabetic. Participants with a medical history of hypertension or at least two blood pressure readings of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg were classified as hypertensive. Participants having low-density lipoprotein (LDL) cholesterol ≥ 120 mg/dL, total cholesterol ≥ 240 mg/dL, triglycerides ≥ 200 mg/dL, or a past medical history of high cholesterol were classified as dyslipidemic.

2.6 | Statistical analyses

We ran statistical analyses (R studio version 2023.06.2 + 561) on bilateral average cortical thickness measures instead of on left and right regions separately to reduce statistical noise and limit the number of comparisons. However, for some individuals, certain regional segmentations failed our quality control checks resulting in missing data. To allow for bilateral averaging, we performed multivariate imputation by chained equations using the mice package in R to impute missing cortical thickness values for regions that failed our quality checks.[22] We used predictive mean matching with 10 iterations to produce five imputed datasets. We then calculated the bilateral average for each region and for each imputed dataset; statistical analyses were performed on each of the five imputed datasets, and results were pooled to generate parameter estimates.[22] Missing left or right hippocampal volume values were also imputed but were not averaged to create a bilateral measure due to possible asymmetry in hippocampal atrophy in cognitively unimpaired older adults.[23] Nine cortical regions had more than 5% missing data (Table S1), but diagnostic strip plots demonstrated adequate imputation performance in these regions (Figure S4). In 10 regions, missingness differed significantly by self-reported race and ethnicity (Figure S5), but these regions were not significantly associated with T2DM in our study.

We identified regions associated with T2DM using a separate multivariable linear regression analysis for each brain region covarying for age, self-reported sex, and MRI scanner. For hippocampal volume analyses, we additionally included ICV as a covariate. We used the Bonferroni correction to correct for 36 comparisons (34 mean bilateral cortical thickness regions and left and right hippocampus volume); comparisons with $p < .0014$ were regarded as statistically significant for all analyses. To confirm that the observed associations were independent of variance related to MRI scanner differences, we repeated

RESEARCH IN CONTEXT

1. **Systematic review**: The relevant literature was searched using PubMed. T2DM increases dementia risk, but the brain changes associated with T2DM that might underlie this relationship are not well understood. Most research linking T2DM with dementia-related neuroimaging measures has been predominantly conducted on NHW adults with limited assessment of underlying mechanisms or the influence of socioeconomic factors and common comorbidities.
2. **Interpretation**: In a large, multiethnic sample of cognitively unimpaired older adults, T2DM was correlated with thinner cortex, independently of socioeconomic factors and common comorbidities, and this was largely driven by poor glycemic control. Worse glycemic control was correlated with thinner cortex in people across the spectrum from diabetic to normal glucose control.
3. **Future directions**: Future longitudinal studies are necessary to determine whether poor glycemic control is associated with faster neurodegeneration over time and help us refine strategies to ameliorate the risk of dementia associated with T2DM.

this analysis on cortical thickness and hippocampal volume data harmonized across scanners using ComBat. ComBat is a harmonization procedure that accounts for non-biological variance in structural neuroimaging data collected across multiple scanners while preserving biological variance.[24] We also used FreeSurfer to perform an additional sensitivity analysis probing the relationship between T2DM and vertex-wise cortical thickness, while accounting for age, sex, and MRI scanner.

Next, we determined whether the observed associations were independent of socioeconomic factors (income and years of education) or related comorbidities (obesity, dyslipidemia, and hypertension). To do this, in each of the regions that were significantly associated with T2DM, we ran a multivariable linear regression with additional covariates for annual household income, years of education, and body mass index (BMI) as continuous variables and hypertension and dyslipidemia as dichotomous variables (1 = present or 0 = absent). In all subsequent analyses, we focused only on those regions that were significantly associated with T2DM in the fully adjusted model (significance at $p < .0014$ after controlling for multiple comparisons across 36 regions using the Bonferroni correction), and we refer to these regions as the T2DM-relevant regions for the remainder of the paper.

To better understand the underlying factors that may be driving the relationship between T2DM and cortical thickness, we next evaluated the relationship between cortical thickness in T2DM-relevant regions and fasting blood insulin and HbA1c levels (both log-transformed), covarying for age and sex. The correlation between HbA1c and insulin levels was not strong enough to preclude their inclusion in the same model ($r = 0.13$). We did not include fasting glucose in this analysis because glucose and HbA1c were highly correlated ($r = 0.82$). This analysis was conducted on the 1024 participants with available HbA1c and insulin levels at baseline. Since all participants with available fasting blood insulin were scanned on the same MRI scanner (Siemens MAGNETOM Skyra), we did not control for the MRI scanner in this analysis.

Next, we evaluated whether the relationship between HbA1c and cortical thickness was driven by T2DM severity more generally (rather than HbA1c values specifically) in diabetic participants alone. To do this, within diabetic participants only, we examined the association between HbA1c levels and cortical thickness, controlling for age, sex, and MRI scanner, and then reran regressions with additional covariates for self-reported T2DM duration and insulin use.

To determine whether higher HbA1c values were related to cortical thickness even for those within normal or prediabetic HbA1c levels, we also performed multivariable linear regression on non-diabetic participants only, relating HbA1c levels to cortical thickness, covarying for age, sex, and MRI scanner.

Finally, to determine whether the observed associations between T2DM and cortical thickness differed by self-reported ethnicity and race, we ran multiple linear regressions relating T2DM to cortical thickness in T2DM-relevant regions separately within the Hispanic, NHB, and NHW subsamples, covarying for age, sex, and MRI scanner, and tested for a formal interaction between the ethnoracial group and T2DM on cortical thickness.

3 | RESULTS

3.1 | Participant characteristics

Out of 3035 HABS-HD participants, 2258 were classified as cognitively unimpaired at baseline. Of those 2258 participants, 2216 had baseline MPRAGE scans. We excluded four participants due to poor scan quality, nine due to FreeSurfer gray–white matter segmentation that failed our quality control assessments globally, and 32 who lacked T2DM diagnosis status. Hippocampal segmentations were also available in all but eight participants who had bilateral hippocampus segmentation fails. Of the 2171 participants who satisfied all inclusion criteria for our study, 435 (20%) self-identified as NHB, 826 (38%) as Hispanic, and 910 (42%) as NHW, and 511 (23.5%) were diabetic. See Table 1 for participant demographic and clinical characteristics. Diabetic participants had fewer years of education, were more likely to identify as Hispanic, and reported a lower annual household income than non-diabetic participants. Additionally, diabetic participants had higher average BMI, HbA1c, glucose, and insulin and were more likely to have hypertension and dyslipidemia.

3.2 | Association between T2DM and cortical thickness in whole sample

After controlling for age, sex, and MRI scanner, T2DM was associated with thinner cortex in 22 brain regions spanning the frontal, parietal, temporal, and occipital lobes with the strongest associations seen in the middle temporal ($\beta = -0.25$; 95% confidence interval [CI]: −0.37 to −0.18; $p < .001$) and superior temporal gyrus ($\beta = -0.27$; 95% CI, −0.34 to −0.15; $p < .001$) (Table 2). Our sensitivity analysis conducted on data harmonized across MRI scanners using ComBat yielded very similar results (Table S2). Our results were also consistent with the localization of T2DM associations with cortical thickness in our vertex-wise sensitivity analysis, though vertex-wise results did not survive multiple comparisons correction (Figure S6). Almost all region-of-interest associations remained significant after also covarying for annual household income, years of education, BMI, hypertension, dyslipidemia (Table 3), and *APOE4* positivity (Table S3). A sensitivity analysis examining the relationship between T2DM and cortical thickness in T2DM-relevant regions separately for the left and right hemispheres demonstrated that most associations were evident bilaterally (Table S4).

3.3 | Associations between HbA1c and fasting plasma insulin and cortical thickness

We found that the relationship between T2DM and cortical thickness was driven mainly by poor ongoing glycemic control (demonstrated by high HbA1c) rather than by fasting insulin levels (Table S5). Higher HbA1c levels were associated with thinner cortex in all T2DM-relevant regions we identified previously (Figure 1A). Higher fasting insulin was significantly associated ($p < .0014$) with a thicker cortex in the superior parietal, inferior parietal, and lateral occipital cortex (Figure 1B; Table S5).

TABLE 1 Demographic and clinical characteristics of the 2171 participants in the sample.

	Diabetic participants	Non-diabetic participants	Statistic	*p* value
No. (%)	511 (23.5)	1660 (76.5)	NA	NA
Age, mean (SD), years	64.66 (7.93)	64.85 (8.56)	$t = 0.46$	.65
Sex			$\chi^2 = 1.11$	.29
Male, no. (%)	185 (36.2%)	559 (33.7%)		
Female, no. (%)	326 (63.8%)	1101 (66.3%)		
Education, mean (SD), years	11.8 (4.74)	14.0 (4.04)	$t = 9.42$	<.001
Self-reported race/ethnicity			$\chi^2 = 120.53$	<0.001
Non-Hispanic Black, no. (%)	117 (22.9%)	318 (19.2%)		
Hispanic, no. (%)	283 (55.4%)	543 (32.7%)		
non-Hispanic White, no. (%)	111 (21.7%)	799 (48.1%)		
Annual household income, mean (SD), US dollars	49,900 (54,300)	81,100 (100,000)	$t = 8.92$	<.001
Missing income, no. (%)	22 (4.3%)	53 (3.2%)		
Body mass index, mean (SD), kg/m^2	32.8 (6.79)	29.9 (6.37)	$t = 8.56$	<.001
Missing BMI, no. (%)	4 (0.8%)	15 (0.9%)		
Hypertension, no. (%)	405 (79.3%)	982 (59.2%)	$\chi^2 = 69.40$	<.001
Missing hypertension, no. (%)	1 (0.2%)			
Dyslipidemia, no. (%)	374 (73.2%)	1052 (63.4%)	$\chi^2 = 17.18$	<.001
Missing dyslipidemia, no. (%)	1 (0.2%)			
HbA1c, mean (SD), %	7.56 (1.76)	5.47 (0.36)	$t = 26.37$	<.001
Missing HbA1c, no. (%)	17 (3.3%)	6 (0.4%)		
Glucose, mean (SD), mg/dL	147 (59.3)	94.6 (12.1)	$t = 19.41$	<.001
Missing glucose, no. (%)	17 (0.6%)	6 (0.4%)		
Insulin, mean (SD), mLU/L	9.34 (8.15)	7.00 (6.94)	$t = 4.04$	<.001
Missing insulin, no. (%)	268 (52.4%)	873 (52.6%)		
MRI scanner			$\chi^2 = 2.97E\text{-}05$	.10
Skyra, no. (%)	321 (62.8%)	1043 (62.8%)		
Vida, no. (%)	190 (37.2%)	617 (37.2%)		
*APOE*4 status			$\chi^2 = 5.0$	.03
Positive *APOE*4, no. (%)	337 (65.9%)	1053 (63.4%)		
Negative *APOE*4, no. (%)	91 (17.8%)	382 (23.0%)		
Missing *APOE* genotype, no. (%)	83 (16.2%)	225 (13.6%)		

Note: Sex, ethnicity, race, years of education, and annual household income were self-reported. Of the 826 Hispanic participants in our sample, 819 self-identified race as White, two identified as Black, and five identified as American Indian or Alaska Native. Furthermore, of the 826 Hispanic participants, 818 self-reported ethnicity as Mexican American, three participants self-reported as Puerto Rican, two as Spanish, one as Venezuelan, one as Ecuadorian, and one as Honduran.
Abbreviation: HbA1c, hemoglobin A1c.

3.4 | Association between HbA1c levels and cortical thickness examined in diabetic and non-diabetic participants separately

When covarying for age, sex, and MRI scanner, higher HbA1c levels were associated with thinner cortex, even within diabetics (Table 4). Additional adjustments for insulin use and T2DM duration attenuated some associations, but those in the inferior parietal, superior temporal, and lateral occipital cortex remained significant (Table 4). Higher HbA1c levels were correlated with lower transverse temporal gyrus thickness even within non-diabetic participants (Table S6).

3.5 | Association between T2DM and cortical thickness by self-reported ethnicity/race

In analyses stratified by ethnoracial group (Tables S7, S8), we found that in Hispanic participants, the T2DM association with thinner cortex was significant in nearly all T2DM-relevant regions. In NHW

TABLE 2 T2DM associations with regional cortical thickness, covarying for age, sex, and MRI scanner.

Region	β	95% CI	p value	Covariates with $p < .05$
Frontal				
Superior frontal	−0.15	−0.24 to −0.05	2.09E-03*	Age**; sex**, MRI scanner**
Rostral middle frontal	−0.11	−0.21 to −0.01	.03*	Age*; MRI scanner**
Caudal middle frontal	−0.15	−0.24 to −0.06	1.36E-03**	Age**; sex**, MRI scanner**
Pars opercularis	−0.17	−0.26 to −0.09	1.25E-04**	Age**; MRI scanner**
Pars triangularis	−0.11	−0.2 to −0.02	.02*	Age**; sex*; MRI scanner**
Pars orbitalis	−0.10	−0.19 to 0.001	.05	Age**; sex**, MRI scanner**
Lateral orbitofrontal	−0.17	−0.27 to −0.07	5.94E-04**	Age**; MRI scanner**
Medial orbitofrontal	−0.05	−0.15 to 0.05	.30	MRI scanner**
Precentral	−0.22	−0.31 to −0.14	5.68E-07**	Age**; MRI scanner**
Paracentral	−0.22	−0.31 to −0.13	9.97E-07**	Age**; MRI scanner**
Frontal pole	−0.16	−0.25 to −0.06	1.88E-03*	Sex*; MRI scanner**
Parietal				
Superior parietal	−0.24	−0.32 to −0.15	1.91E-07**	Age**; sex*; MRI scanner**
Inferior parietal	−0.24	−0.32 to −0.15	8.89E-08**	Age**; sex**, MRI scanner**
Supramarginal	−0.26	−0.35 to −0.18	1.95E-09**	Age**; sex**, MRI scanner**
Postcentral	−0.22	−0.31 to −0.13	7.33E-07**	Age**; sex*; MRI scanner**
Precuneus	−0.28	−0.36 to −0.20	5.32E-11**	Age**; MRI scanner**
Temporal				
Superior temporal	−0.33	−0.42 to −0.25	3.02E-14**	Age**; MRI scanner**
Middle temporal	−0.35	−0.44 to −0.25	2.63E-13**	Age**
Inferior temporal	−0.18	−0.28 to −0.09	1.38E-04**	Age**; sex**, MRI scanner**
Banks of superior temporal sulcus	−0.25	−0.34 to −0.16	1.04E-07**	Age**; MRI scanner**
Fusiform	−0.18	−0.27 to −0.09	7.04E-05**	Age**; sex**, MRI scanner**
Transverse temporal	−0.28	−0.37 to −0.19	1.20E-09**	Age**; sex**, MRI scanner**
Entorhinal	−0.08	−0.18 to 0.01	.09	Age**
Temporal pole	−0.25	−0.35 to −0.16	2.87E-07**	Age**; MRI scanner*
Parahippocampal	−0.12	−0.22 to −0.02	.01*	Age**; sex**
Hippocampus, left	−0.12	−0.21 to −0.04	4.24E-03*	Age**; sex*; ICV**; MRI scanner*
Hippocampus, right	−0.08	−0.16 to 0.01	.07	Age**; sex**; ICV**; MRI scanner*
Occipital				
Lateral occipital	−0.28	−0.37 to −0.19	4.15E-10**	Age**; sex**; MRI scanner**
Lingual gyrus	−0.14	−0.23 to −0.04	3.74E-03*	Age**; MRI scanner**
Cuneus	−0.18	−0.27 to −0.08	2.41E-04**	Age**; MRI scanner**
Pericalcarine	−0.18	−0.27 to −0.08	2.04E-04**	Age**; sex*; MRI scanner**
Other				
Rostral anterior cingulate	−0.09	−0.19 to 0.01	.08	Age**; MRI scanner*
Caudal anterior cingulate	0.002	−0.1 to 0.10	.97	Age**; sex**; MRI scanner**
Posterior cingulate	−0.1	−0.2 to −0.01	.04*	Age**; sex**; MRI scanner**
Isthmus of cingulate	−0.16	−0.25 to −0.07	8.00E-04**	Age**; sex**
Insula	−0.21	−0.31 to −0.11	3.54E-05**	Age**

Note: Relationships between T2DM diagnostic status and regional cortical thickness or hippocampal volume using separate multiple linear regression analyses are listed for each region. All regions are listed as a bilateral mean unless otherwise noted. In all multiple linear regression analyses, we included age, sex, and MRI scanner as covariates. In the hippocampal volume analyses, we also included intracranial volume as a covariate.

Abbreviations: ICV, intracranial volume; T2DM, type 2 diabetes mellitus.

*$P < .05$; not significant at $\alpha = 0.05$ after Bonferroni correction for multiple comparisons.

**Significant at $\alpha = 0.05$ after Bonferroni correction for multiple comparisons ($p < .0014$) across all 36 regions. In all regions with a significant effect of sex, female participants had thicker cortexes than male participants.

TABLE 3 T2DM associations with regional cortical thickness, covarying for socioeconomic, vascular, and metabolic factors.

Region	β	95% CI	p value	Covariates with $p < 0.05$
Frontal				
Caudal middle frontal	−0.15	−0.25 to −0.05	2.98E-03*	Age**; sex*; MRI scanner**; BMI*
Pars opercularis	−0.15	−0.25 to −0.06	1.81E-03*	Age**; MRI scanner**
Lateral orbitofrontal	−0.18	−0.28 to −0.08	7.76E-04**	Age**; MRI scanner**; BMI*
Precentral	−0.21	−0.3 to −0.12	1.05E-05**	Age**; MRI scanner**
Paracentral	−0.22	−0.31 to −0.12	1.15E-05**	Age**; MRI scanner**
Parietal				
Superior parietal	−0.19	−0.28 to −0.09	1.01E-04**	Age**; sex*; MRI scanner**; education**; BMI*
Inferior parietal	−0.18	−0.28 to −0.09	1.03E-04**	Age**; sex**; MRI scanner**; hypertension*
Supramarginal	−0.2	−0.29 to −0.11	2.55E-05**	Age**; sex**; MRI scanner**; income*; education*; hypertension*
Postcentral	−0.17	−0.27 to −0.07	4.92E-04**	Age**; sex*; MRI scanner**; education**
Precuneus	−0.23	−0.32 to −0.14	4.25E-07**	Age**; MRI scanner**; income*
Temporal				
Superior temporal	−0.25	−0.34 to −0.15	1.48E-07**	Age**; sex*; MRI scanner**; education**; BMI*
Middle temporal	−0.27	−0.37 to −0.18	6.92E-08**	Age**; income*
Inferior temporal	−0.13	−0.23 to −0.02	0.01*	Age**; sex**; MRI scanner**; income*
Banks of superior temporal sulcus	−0.19	−0.29 to −0.09	1.62E-04**	Age**; MRI scanner**; income*
Fusiform	−0.13	−0.23 to −0.03	0.01*	Age**; sex**; MRI scanner**; income*; education**
Transverse temporal	−0.18	−0.27 to −0.08	3.03E-04**	Age**; sex**; MRI scanner**; income*; education**
Temporal pole	−0.18	−0.28 to −0.08	7.70E-04**	Age**; education*; BMI*
Occipital				
Lateral occipital	−0.23	−0.32 to −0.13	2.05E-06**	Age**; sex**; MRI scanner**; income*; hypertension*
Cuneus	−0.17	−0.27 to −0.07	8.31E-04**	Age**; MRI scanner**; education*; BMI*
Pericalcarine	−0.20	−0.3 to −0.10	6.51E-05**	Age**; sex*; MRI scanner**; BMI**
Other				
Isthmus cingulate	−0.16	−0.26 to −0.06	2.43E-03*	Age**; sex**
Insula	−0.15	−0.25 to −0.04	5.89E-03*	Age**; education*; hypertension*

Note: The relationship between T2DM to cortical thickness, covarying for age, sex, MRI scanner, years of education, annual household income, BMI, hypertension, and dyslipidemia.

Abbreviations: BMI, body mass index; T2DM, type 2 diabetes mellitus.

*$P < 0.05$; not significant at $\alpha = 0.05$ after Bonferroni correction for multiple comparisons.

**Significant at $\alpha = 0.05$ after Bonferroni correction for multiple comparisons ($p < .0014$) across all 36 regions. In all regions with a significant effect of sex, female participants had thicker cortexes than male participants.

participants, there were significant T2DM associations with thinner cortex only in the middle temporal gyrus ($\beta = -0.34$; 95% CI: −0.53 to −0.15; $p < .001$) and temporal pole ($\beta = -0.36$; 95% CI: −0.56 to −0.16; $p < .001$). T2DM was not significantly associated with cortical thickness in NHB participants even after covarying for hypertension, BMI, dyslipidemia, income, and education. There was a significant interaction in the superior temporal gyrus ($\beta = -0.37$; 95% CI: −0.59 to −0.16; $p < .001$), such that the T2DM association with thinner cortex was stronger in Hispanic than in NHB participants.

4 | DISCUSSION

In an ethnoracially diverse sample of cognitively unimpaired older adults, we found that T2DM was broadly associated with thinner cortex, with the strongest associations mainly in temporal and parietal cortex. These associations were independent of socioeconomic factors and comorbidities and were likely driven by hyperglycemia, which could have important implications for refining T2DM management guidelines to avoid the adverse effects of T2DM on brain health in older age.

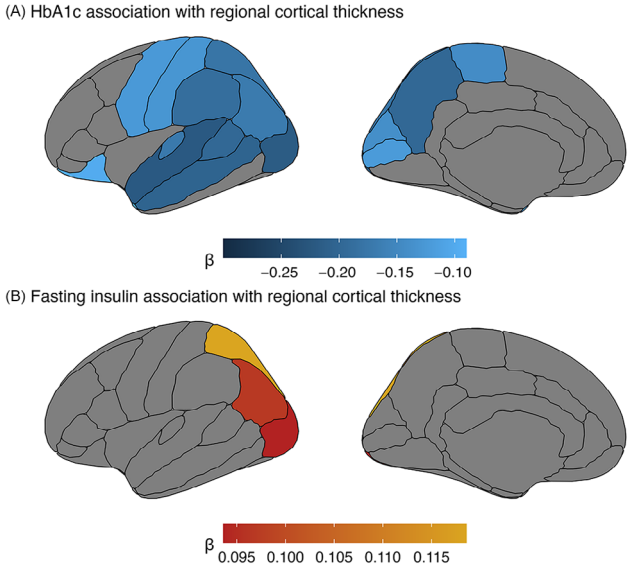

FIGURE 1 Associations between cortical thickness and HbA1c and fasting plasma insulin levels. (A) Regions in which higher HbA1c levels were associated with thinner cortex. (B) Regions in which higher fasting plasma insulin levels were associated with thicker cortex. This analysis was conducted on the 1024 participants with HbA1c and blood insulin data available. HbA1c, hemoglobin A1c.

One possible mechanism linking T2DM and chronic hyperglycemia to lower cortical thickness could be changes in cerebral glucose metabolism. Given the brain's limited capacity to store glucose, cerebral glucose metabolism presumably depends on the homeostatic function of transport systems delivering glucose from the circulation to the brain under varying physiological conditions. T2DM and elevated HbA1c levels are associated with brain hypometabolism in individuals with MCI[25] and older adults without dementia.[26] Aside from being the brain's primary energy substrate, glucose is involved in the synthesis of neurotransmitters and neuromodulators, the resolution of oxidative stress,[27] and the regulation of pathways related to autophagy and cell death.[28] Disruption of such processes due to changes in cerebral glucose metabolism in the context of chronic hyperglycemia might contribute to neurodegeneration and successive cortical thinning.

Other possible links between T2DM and lower cortical thickness include inflammation and subsequent blood-brain barrier (BBB) damage. T2DM patients exhibit elevated markers of systemic inflammation,[29–31] which, if prolonged, can damage BBB endothelial cells and their associated tight junction proteins and trigger pro-inflammatory signaling cascades in astrocytic end feet.[32] Increased BBB permeability has been reported in animal models of T2DM[33–36] and in diabetic older adults across the cognitive continuum.[37] The evidence linking BBB damage to neurodegeneration is substantial and has been thoroughly reviewed by Knox et al.[38]

We found that the relationship between T2DM and thinner cortex was likely driven by hyperglycemia rather than by hyperinsulinemia. Higher HbA1c levels were associated with a thinner cortex across all T2DM-relevant regions. The stronger correlation with HbA1c levels may partly be because we examined specifically regions associated with a T2DM diagnosis, which is itself based on HbA1c levels. Effects of hyperinsulinemia may exist in other brain regions outside the T2DM-relevant ones we examined. Interestingly, higher HbA1c levels were associated with a thinner cortex even within diabetic participants alone, regardless of disease duration or insulin use, suggesting that the association between T2DM and cortical thickness was driven by uncontrolled glucose specifically rather than disease severity more generally. We also found some HbA1c associations with cortical thickness even among non-diabetic participants alone, suggesting that elevated but clinically normal or prediabetic HbA1c levels may also be related to brain health.

Higher plasma insulin levels were associated with a thicker cortex in the superior parietal, inferior parietal, and lateral occipital areas. Brain insulin is predominantly derived from the blood,[39] though small amounts might also be produced de novo in the choroid plexus.[40] Brain insulin signaling promotes synaptic plasticity[41] and protects neurons from excitotoxicity[42] and cell death.[43] These neuroprotective actions of insulin might be underlying the positive association we observed in our study.

In analyses stratified by self-reported ethnicity and race, we found that in Hispanic participants, who had the highest HbA1c levels on average, there were strong T2DM associations with thinner cortex affecting nearly all T2DM-relevant regions. In NHW participants, who had the lowest HbA1c levels on average, associations were more modest and limited to temporal regions. The risk of cognitive impairment associated with T2DM is higher for Hispanics than non-Hispanic White adults.[44] Our results suggest that poor glycemic control and its association with widespread cortical thinning among Hispanic adults might be contributing to the observed disparities.

Interestingly, we found no association between T2DM and cortical thickness in NHB participants, whose average HbA1c levels were between those of Hispanic and NHW participants. In NHB Americans, higher HbA1c levels may overestimate glycemia,[45–47] raising concerns about the use of HbA1c as a sole diagnostic marker of T2DM due to the potential for misdiagnosis and the heightened risk of complications associated with glucose-lowering treatments if unnecessarily administered.[48] Given that a T2DM diagnosis in our study was determined largely based on HbA1c, any misclassification of NHB participants could have obscured underlying T2DM associations with cortical thickness within that group. Furthermore, social and structural determinants of health (and disease) might account for a larger proportion of the variation in cortical thickness in NHB older adults, making the relationship between diabetes and cortical thickness less evident. These factors may include housing instability, reduced access to high-quality education and nutrition, and structural racism.[49] Exposure to some social and structural factors, such as residential segregation, has a disproportionately larger impact on cognition and dementia risk in NHB communities compared to other populations.[50]

Prior studies investigating the link between T2DM and aberrant neuroimaging endophenotypes were predominantly conducted on NHW adults of high socioeconomic status who were free of many

TABLE 4 Association between cortical thickness and HbA1c in diabetics only.

	HbA1c association with cortical thickness, covarying for age, sex, and MRI scanner			HbA1c association with cortical thickness, covarying for age, sex, MRI scanner, diabetes duration, and insulin use		
Region	***β***	**95% CI**	***p* value**	***β***	**95% CI**	***p* value**
Frontal						
Lateral orbitofrontal	−0.09	−0.16 to −0.01	.02	−0.04	−0.13 to 0.05	.35
Precentral	−0.08	−0.15 to −0.02	7.43E-03*	−0.08	−0.15 to −0.01	.03*
Paracentral	−0.07	−0.13 to −0.01	.03	−0.07	−0.14 to 0.001	.05
Parietal						
Superior parietal	−0.11	−0.18 to −0.05	5.45E-04**	−0.11	−0.18 to −0.04	3.45E-03*
Inferior parietal	−0.14	−0.21 to −0.08	7.04E-06**	−0.14	−0.21 to −0.07	1.11E-04**
Supramarginal	−0.11	−0.18 to −0.05	3.66E-04**	−0.11	−0.18 to −0.04	3.55E-03*
Postcentral	−0.05	−0.12 to 0.02	.14	−0.05	−0.12 to 0.03	.21
Precuneus	−0.1	−0.16 to −0.04	1.21E-03**	−0.09	−0.16 to −0.02	8.67E-03*
Temporal						
Superior temporal	−0.15	−0.21 to −0.1	4.91E-07**	−0.17	−0.24 to −0.11	4.69E-07**
Middle temporal	−0.11	−0.18 to −0.04	1.49E-03*	−0.13	−0.21 to −0.05	1.07E-03**
Banks of superior temporal sulcus	−0.1	−0.16 to −0.04	1.82E-03*	−0.1	−0.17 to −0.02	.01*
Transverse temporal	−0.09	−0.16 to −0.03	5.49E-03*	−0.12	−0.2 to −0.05	1.18E-03**
Temporal pole	−0.04	−0.11 to 0.02	.21	−0.04	−0.12 to 0.03	.28
Occipital						
Lateral occipital	−0.16	−0.23 to −0.1	1.38E-06**	−0.14	−0.21 to −0.07	1.89E-04**
Cuneus	−0.13	−0.19 to −0.06	2.13E-04**	−0.1	−0.18 to −0.03	7.88E-03*
Pericalcarine	−0.11	−0.18 to −0.04	1.13E-03**	−0.08	−0.16 to −0.01	.03*

Note: *$P < .05$; not significant at $\alpha = 0.05$ after Bonferroni correction for multiple comparisons.
**Significant at $\alpha = 0.05$ after Bonferroni correction for multiple comparisons ($p < .0014$) across all 36 regions.
Abbreviation: HbA1c, hemoglobin A1c.

age- and T2DM-related medical comorbidities. Here, we extended prior evidence to report an association between T2DM and thinner cortex in a large sample of cognitively intact older adults with a wide range of demographic and comorbidity profiles. However, our study still had limitations. Given its cross-sectional design, we could not infer a causal relationship between T2DM and neurodegeneration. Longitudinal studies are necessary to probe whether having T2DM and persistent hyperglycemia is predictive of faster neurodegeneration over time. Furthermore, in our analysis of diabetic participants, we did not account for anti-diabetic medications beyond insulin use. Finally, our models did not account for the use of anti-hypertensive medications that might attenuate the risk of dementia associated with high HbA1c levels in people with prediabetes and T2DM.[15] Future research that addresses these limitations will help clarify some of our observed associations further. Nevertheless, our study provides substantial new evidence for an association between T2DM and an aberrant neuroimaging endophenotype in a large and ethnoracially diverse sample of cognitively unimpaired older adults and suggests that this relationship is likely driven by hyperglycemia. Future longitudinal studies probing the relationship between hyperglycemia and neurodegeneration will be crucial to our understanding of how T2DM contributes to dementia risk and will help refine disease-management strategies to ameliorate that risk.

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CONFLICT OF INTEREST STATEMENT

The authors have nothing to disclose. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants in the HABS-HD study provided informed consent, and the study protocol was approved by the Institutional Review Board at the University of North Texas Health Science Center (UNTHSC).

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SUPPORTING INFORMATION

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