Type 2 diabetes mellitus and biomarkers of neurodegeneration

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ABSTRACT

Objective: Our objective was to investigate whether type 2 diabetes mellitus (T2DM) influences neurodegeneration in a manner similar to Alzheimer disease (AD), by promoting brain β-amyloid (Aβ) or tau.

Methods: We studied the cross-sectional associations of T2DM with cortical thickness, brain Aβ load, and CSF levels of Aβ and tau in a sample of people from the Alzheimer's Disease Neuroimaging Initiative with diagnoses of AD dementia, mild cognitive impairment, and normal cognition. All (n = 816) received MRI, and a subsample underwent brain amyloid imaging (n = 102) and CSF Aβ and tau measurements (n = 415). Analyses were performed across and within cognitive diagnostic strata.

Results: There were 124 people with T2DM (mean age 75.5 years) and 692 without T2DM (mean age 74.1 years). After adjusting for age, sex, total intracranial volume, *APO* ε4 status, and cognitive diagnosis, T2DM was associated with lower bilateral frontal and parietal cortical thickness (mL) (β = −0.03, p = 0.01). T2DM was not associated with ^{11}C Pittsburgh compound B standardized uptake value ratio (AU) in any brain region or with CSF $A\beta_{42}$ levels (pg/mL). T2DM was associated with greater CSF total tau (pg/mL) (β = 16.06, p = 0.04) and phosphorylated tau (β = 5.84, p = 0.02). The association between T2DM and cortical thickness was attenuated by 15% by the inclusion of phosphorylated tau.

Conclusions: T2DM may promote neurodegeneration independent of AD dementia diagnosis, and its effect may be driven by tau phosphorylation. The mechanisms through which T2DM may promote tau phosphorylation deserve further study. ***Neurology*® 2015;85:1123–1130**

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **CI** = confidence interval; **MCI** = mild cognitive impairment; **NC** = normal control; **PiB** = Pittsburgh compound B; **p-tau** = phosphorylated tau; **SUVR** = standardized uptake value ratio; **T2DM** = type 2 diabetes mellitus; **VBM** = voxel-based morphometry; **WMH** = white matter hyperintensity.

Type 2 diabetes mellitus (T2DM) is associated with a nearly 2-fold increased incident risk of dementia and Alzheimer disease (AD) dementia.[1,2] The possible mechanisms underlying this association include both cerebrovascular disease and neurodegeneration.[2] T2DM is also associated with neurodegenerative imaging biomarkers, namely, hippocampal[3] and whole brain atrophy.[4] Recently, we demonstrated that the association between T2DM and cognitive impairment in older age may primarily be driven by brain atrophy rather than cerebrovascular brain lesions, and that this atrophy occurs in cortical regions similar to those affected in AD dementia.[5] However, there are limited data available from in vivo studies to determine whether T2DM contributes to the accumulation of AD pathology.[6]

In AD, 2 main pathologic processes occur to promote neurodegeneration, involving β-amyloid (Aβ) and neuronal tau.[7] Abnormal cleavage of Aβ creates the nonsoluble $A\beta_{42}$ oligomers, which

Supplemental data at Neurology.org

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forms extracellular amyloid plaques that contribute to neurodegeneration.[8] Brain $A\beta_{42}$ load can be measured in vivo either by using PET neuroimaging with special ligands (e.g., ^{11}C Pittsburgh compound B [PiB]), or estimated by detecting low $A\beta_{42}$ levels in the CSF, possibly reflecting Aβ sequestration within cerebral plaques.[9] In addition, tau-related pathology is frequently seen in AD. Intracellular tau proteins stabilize neuronal microtubules, a process that is important for neuronal health. In AD, there is hyperphosphorylation of tau (p-tau) resulting in the accumulation of neurofibrillary tangles and subsequent neuronal death.[7] Elevated CSF levels of tau and p-tau are also in vivo markers of tauopathy in AD and correlate well with intracerebral AD pathology.[9,10]

The aim of this study was to explore the relationships between T2DM and biomarkers of neurodegeneration usually implicated in the development of AD. We examined the relationships between T2DM, brain atrophy, and in vivo brain and CSF biomarkers of Aβ and tau in people with AD dementia, its precursor, amnestic mild cognitive impairment (MCI), and in normal controls (NCs).

METHODS

The data used for this analysis were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (https://ida.loni.usc.edu).[9] ADNI was launched in 2003 with the primary aim of identifying MRI, PET, CSF, biochemical, clinical, and neuropsychological biomarkers of potential progression of MCI to early AD dementia.[9] ADNI aimed to recruit 800 adults between the ages of 55 and 90 years comprising 400 people with MCI, 200 people with early probable AD dementia, and 200 NCs. These cognitive diagnoses were based on criteria from the National Institute of Neurologic and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association.[11] Those with MCI had memory complaints but no significant functional impairment based on the Clinical Dementia Rating. Individuals were excluded if they had Hachinski ischemic score[12] >4 (a high risk of cerebrovascular disease contributing to cognitive impairment), were unable to undergo MRI, had other neurologic disorders, active depression, history of psychiatric diagnosis, alcohol or substance dependence in the last 2 years, had less than 6 years of education, or were not fluent in English or Spanish.

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all participants. Full details of ethics approval, study design, participant recruitment, and clinical testing have been published previously and are available at www.adni-info.org.

Clinical and genetic data. Data on demographic information, medical history, *APO* ε4 genotype, baseline cognitive diagnosis, fasting venous blood glucose levels, and medication use were downloaded from the ADNI clinical data database in August 2013. Cognitive diagnosis at baseline was used for grouping of participants. We assigned diabetes status based on fasting blood glucose ≥7.0 mmol/L according to American Diabetes Association guidelines[13] or the use of glucose-lowering agents. *APO* ε4 genotyping was performed on venous blood–derived DNA at the ADNI Biomarker Core Laboratory (University of Pennsylvania) and participants were deemed *APO* ε4–positive if they carried at least one *APO* ε4 allele.

MRI scans and image processing. The process for MRI acquisition has been described previously in ADNI publications.[14,15] In brief, all ADNI participants had a 1.5-tesla MRI performed at either screening or baseline visits between August 2005 and October 2007. The ADNI project offers scans that have been preprocessed (gradient warping, scaling, B1 correction, and N3 inhomogeneity correction) to correct for different scanners across sites.[16] In our imaging laboratory we used FreeSurfer v5.3 (http://surfer.nmr.mgh.harvard.edu/) to parcellate the cortex in these scans into 74 regions per hemisphere, based on the Destrieux atlas.[17] Quality control of FreeSurfer parcellation was performed by testing for outliers, using Bonferroni p values for studentized residuals, in a regression model predicting regional cortical thickness from age, sex, and cognitive diagnosis. Any scan in which one or more regions were detected as an outlier was inspected for processing errors. From ADNI databases, the following measures were also obtained: hippocampal volume measures (mL) using an automated tissue classifier (AdaBoost)[9]; white matter hyperintensity (WMH) volume (mL) using fully automated segmentation[18]; and the presence of MRI infarcts as identified by a specially trained physician.[19]

PiB-PET scans. PiB-PET scans were performed at 12 ADNI sites. Participants were injected with 15 ± 1.5 mCi PiB and images were acquired 50 to 70 minutes following injection. Further details of PiB-PET acquisition and the region-of-interest protocol have been summarized previously.[9] ADNI provides PiB-PET scans that have been preprocessed (coregistered, averaged, standardized image and voxel size, uniform resolution) to account for different scanners across sites.[20]

We adopted 3 methods to investigate group differences in PiB uptake/binding. For the first method, we used the regional standardized uptake value ratios (SUVRs) derived in ADNI relative to the cerebellum for 13 regions using an automated region-of-interest template.[21] The second and third analyses were conducted in our imaging laboratory. For our second form of analysis, we coregistered PiB-PET scans with the corresponding T1-weighted MRI scan using the coregistration facility of SPM (Statistical Parametric Mapping). The T1 scan was automatically parcellated into 168 regions of interest using FreeSurfer (version 5.3) and the mean PiB intensities were computed using FreeSurfer's mri_segstats command. For the third method, we used voxel-based morphometry (VBM) to compare differences in SUVR between those with and without T2DM at the voxel level.

CSF data. CSF collection and procedural protocols have been described previously.[22] Briefly, fasting CSF was collected and analyzed using a Luminex platform (Luminex Corporation, Austin, TX) with an Innogenetics immunoassay kit (INNO-BIA AlzBio3; Ghent, Belgium) that included monoclonal antibodies for A-Beta142, t-tau and p-tau_{181} (pg/mL).

Data analysis. Student t test and χ^2 tests were applied to compare demographic, clinical, and cognitive variables between T2DM and non-T2DM groups.

We studied the associations of T2DM with individual global brain MRI measures (cortical thickness, hippocampal volume,

WMH, infarcts) adjusting in each regression for age, sex, cognitive diagnosis, *APO* ε4, and total intracranial volume (analyses with infarcts were not adjusted for total intracranial volume). Linear regression was used for continuous variables and logistic regression for categorical variables.

Differences in regional thickness between T2DM and non-T2DM were tested in 148 regions of interest using a regression model with thickness as the dependent variable and T2DM status, age, sex, cognitive diagnosis, and total intracranial volume as independent variables. Significance of the T2DM status term was examined after correction for multiple comparisons using a false discovery rate ($p < 0.05$).

For PiB-PET analyses, first we compared PiB-SUVR between cognitive diagnostic groups irrespective of T2DM status to ensure consistency with previous reports from ADNI.[21] Differences in PiB-SUVR between T2DM and those without T2DM were then tested in 4 regions of interest[21] using both ADNI-provided data and our own laboratory method, with SUVR as the dependent variable and T2DM status, age, sex, and cognitive diagnosis as independent variables. For the VBM component of the PiB-PET analysis, we used a false discovery rate ($p < 0.05$) to correct for multiple comparisons.

The associations of T2DM with individual CSF measures and CSF Aβ/tau ratios were analyzed using linear regression modeling adjusting for age, sex, *APO* ε4, and cognitive diagnosis. We examined for 2-way interactions between *APO* ε4 and T2DM and cognitive diagnosis and T2DM with a test of significance of product terms. We additionally conducted sensitivity analyses by reclassifying the presence of T2DM using fasting glucose alone, or the combination of fasting glucose and the use of glucose-lowering medication, but not metformin (because this is sometimes used in those without T2DM). Further sensitivity analyses were performed using only participants in whom fasting glucose levels were available (n = 736). All the above analyses were repeated after stratifying by cognitive diagnosis.

Table 1 Participant characteristics

	T2DM	No T2DM	*p* Value
No.	124 (15)	692 (85)	
Age, y	75.5 (6.2)	74.1 (7.0)	0.58
Sex, male	85 (69)	389 (56)	0.01
Fasting glucose, mmol/L	7.3 (2.3)	5.3 (0.7)	<0.001
Average SBP, mm Hg	137 (17)	135 (18)	0.23
Average DBP, mm Hg	74 (10)	75 (10)	0.86
Weight, kg	80.7 (17)	74.0 (14.0)	<0.0001
BMI, kg/m^2	28.0 (4.8)	26.3 (4.2)	0.0001
MRI infarct	11 (9)	55 (8)	0.73
Smoker	42 (34)	279 (40)	0.18
MMSE score	26.2 (3.4)	26.2 (3.6)	0.98
ADAS-Cog score	11.7 (6.5)	11.7 (6.4)	0.94
Oral diabetes medications	75 (60)		
Insulin use	10 (8)		
Insulin and oral agent	5 (4)		
Cognitive diagnoses			
Normal control (n = 228)	38	190	
MCI (n = 397)	59	338	0.75[a]
AD dementia (n = 191)	27	164	

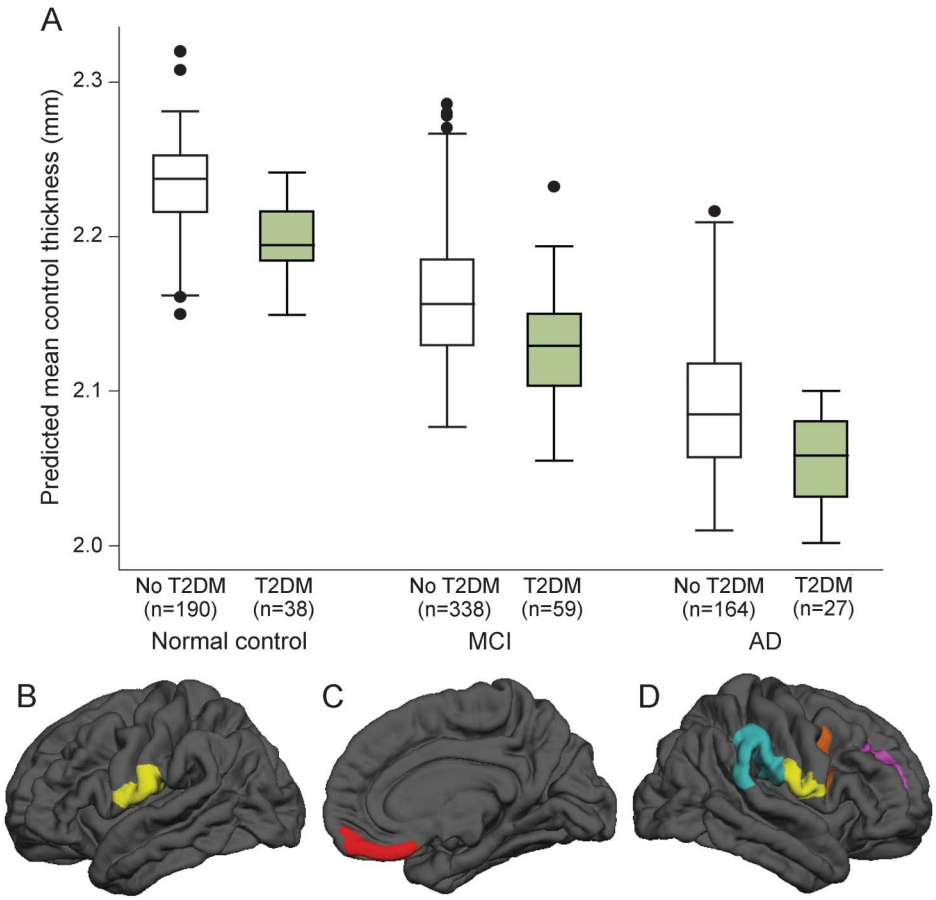
Abbreviations: AD = Alzheimer disease; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive subscale; BMI = body mass index; DBP = diastolic blood pressure; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus.
Data are n (%) or mean (SD).
[a] Chi-square test for trend of proportion of T2DM across cognitive groups.

RESULTS There were 124 people with T2DM (mean age 75.5 years, SD 6.2) and 692 without (mean age 74.1 years, SD 7.0). The numbers and proportions of T2DM in each cognitive diagnostic group were as follows: 38 of 228 (17%) cognitively NCs, 59 of 397 (15%) with MCI, and 27 of 191 (14%) with AD dementia. Group characteristics and comparisons are presented in table 1. Participants with T2DM were more likely to be male and have greater fasting blood glucose levels and body mass index than those without T2DM. A total of 75 participants used oral hypoglycemic agents to control their T2DM and 10 used insulin (5 of whom were also on oral agents).

T2DM and MRI biomarkers. Cortical thickness measures were available in 816 participants (228 NC, 397 MCI, 191 AD dementia). As expected, mean cortical thickness was greatest in NCs, followed by those with MCI and then those with AD dementia (figure 1). When adjusted for age, sex, total intracranial volume, *APO* ε4 status, and cognitive diagnosis, T2DM was associated with lower total cortical thickness (mm) (β = −0.03, 95% confidence interval [CI] −0.05 to −0.006, $p = 0.01$) but not with hippocampal volume (β = −70.90, 95% CI −248.00 to 106.19, $p = 0.43$), presence of infarct on MRI (β = 0.13, 95% CI −0.56 to 0.82, $p = 0.71$, odds ratio 1.14, 95% CI 0.57 to 2.27), or WMH volume (mL) (β = −0.12, 95% CI −0.61 to 0.38, $p = 0.64$). Regions of cortical thinning attributable to T2DM included bilateral subcentral gyri and sulci, right inferior precentral sulcus, rectus gyrus, front and middle sulcus (frontal lobe), and inferior parietal gyrus (figure 1). When stratified by cognitive diagnosis, T2DM was associated with lower cortical thickness in NCs and those with MCI (both $p = 0.04$) but not in those with AD dementia ($p = 0.77$). T2DM was associated with lower hippocampal volume in those with MCI ($p = 0.05$) but not in NCs or those with AD dementia. There was no association between T2DM and either WMH or infarcts in any of the cognitive diagnostic groups.

T2DM and ^{11}C-PiB-PET uptake. ^{11}C-PiB-PET scans were available for 102 participants (19 NC, 64 MCI, 19 AD), of whom 19 had T2DM. As expected, SUVR increased across groups from NC through MCI to AD dementia (figure 2). We did not find a statistically significant association between T2DM

Figure 1 Association of T2DM with cortical thickness (n = 816)



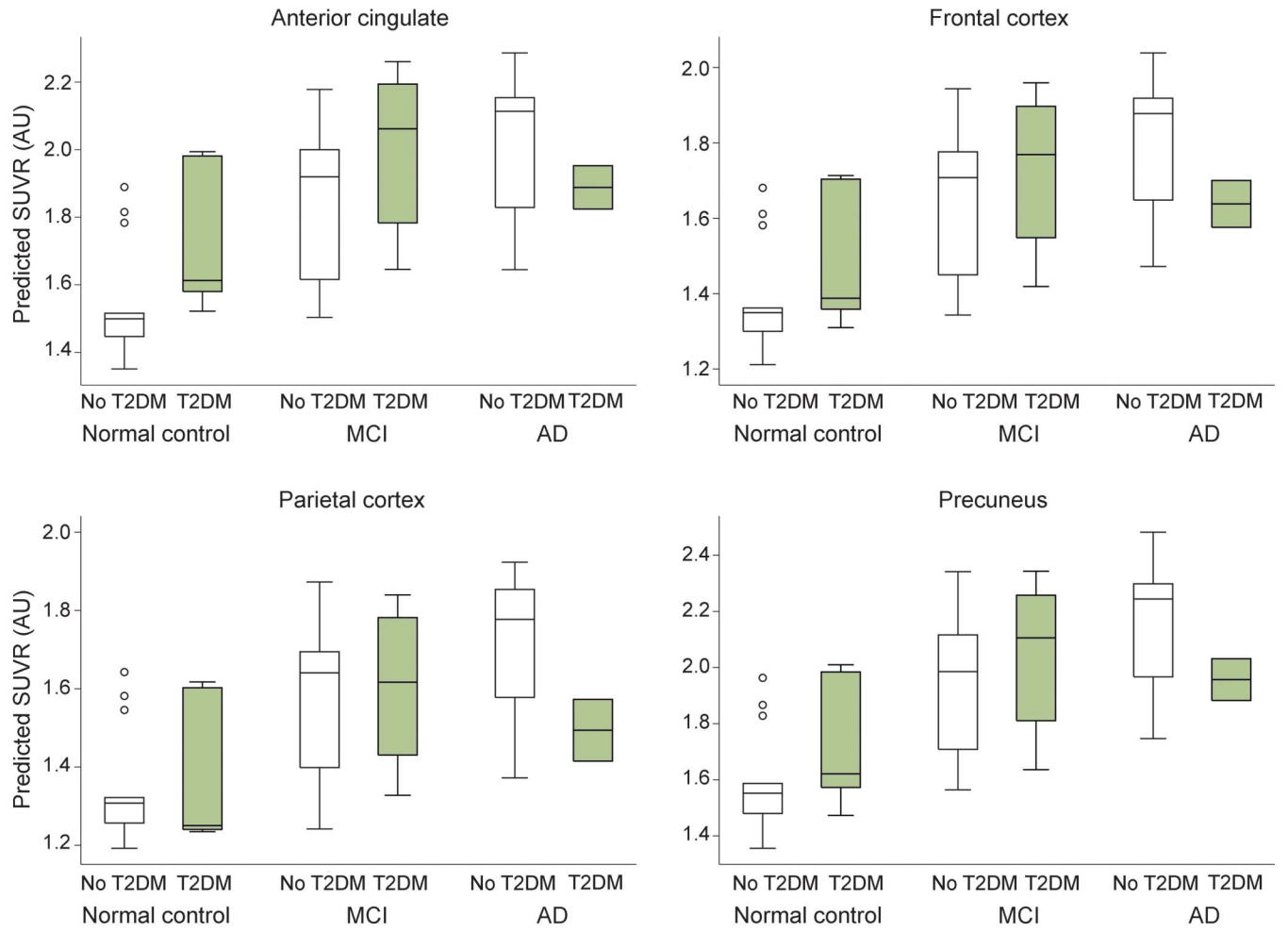
(A) Association of T2DM with cortical thickness stratified by cognitive diagnosis. Adjusted for age, sex, total intracranial volume, and *APO* ε4 status. (B–D) Regions of cortical thinning associated with T2DM. Adjusted for age, sex, total intracranial volume, *APO* ε4 status, and cognitive diagnosis. (B) Left hemisphere: lateral view. (C) Right hemisphere: medial view. (D) Right hemisphere: lateral view. Regions: yellow = subcentral gyrus and sulcus; red = rectus gyrus; orange = inferior precentral sulcus; pink = front and middle sulcus; blue = inferior parietal gyrus. AD = Alzheimer disease dementia; MCI = mild cognitive impairment; T2DM = type 2 diabetes mellitus.

and ^{11}C-PiB-SUVR when adjusting for age, sex, *APO* ε4 status, and cognitive diagnosis using either ADNI-derived data or our in-house FreeSurfer and VBM methods. Similarly, no associations were detected between T2DM and regional SUVR when the analyses were stratified by cognitive diagnosis.

CSF measures of amyloid and tau. CSF measurements were available for 415 participants (n = 114 NC, 199 MCI, 102 AD dementia), of whom 56 had T2DM (table e-1 on the *Neurology*® Web site at Neurology.org). T2DM was associated with greater CSF total tau (β = 16.06, 95% CI 1.10 to 31.02, $p = 0.035$) and p-tau$_{181}$ (β = 5.84, 95% CI 0.95 to 10.73, $p = 0.02$) when adjusted for age, sex, *APO* ε4, and cognitive diagnosis. There was no association found between T2DM and CSF Aβ$_{42}$ levels (β = −6.90, 95% CI −20.27 to 6.48, $p = 0.31$). When stratified by cognitive diagnosis (figure 3), T2DM was associated with greater CSF p-tau$_{181}$ only among those with MCI, but was not associated with CSF total tau or Aβ$_{42}$ in any of the cognitive diagnostic groups.

Among those who had both cortical thickness and CSF measures available (n = 407), the addition of total tau as a term in the regression of T2DM with cortical thickness attenuated the β coefficient of T2DM by 15% (from β = −0.039 to β = −0.033). The addition of p-tau$_{181}$ attenuated the T2DM–cortical thickness association by 15% (from β = −0.039 to β = −0.033) while the addition of Aβ$_{42}$ attenuated the association only by 4% (from β = −0.039 to β = −0.037). We did not find any interaction between *APO* ε4 and T2DM or cognitive diagnosis and T2DM status in predicting brain imaging or CSF biomarker measures. Sensitivity analysis using alternative definitions of T2DM did not result in variation from the above results, particularly in relation to the association of T2DM with cortical thickness and CSF-tau, for which the strength of the associations remained unchanged,

Figure 2 Regional associations of T2DM with Pittsburgh compound B SUVR



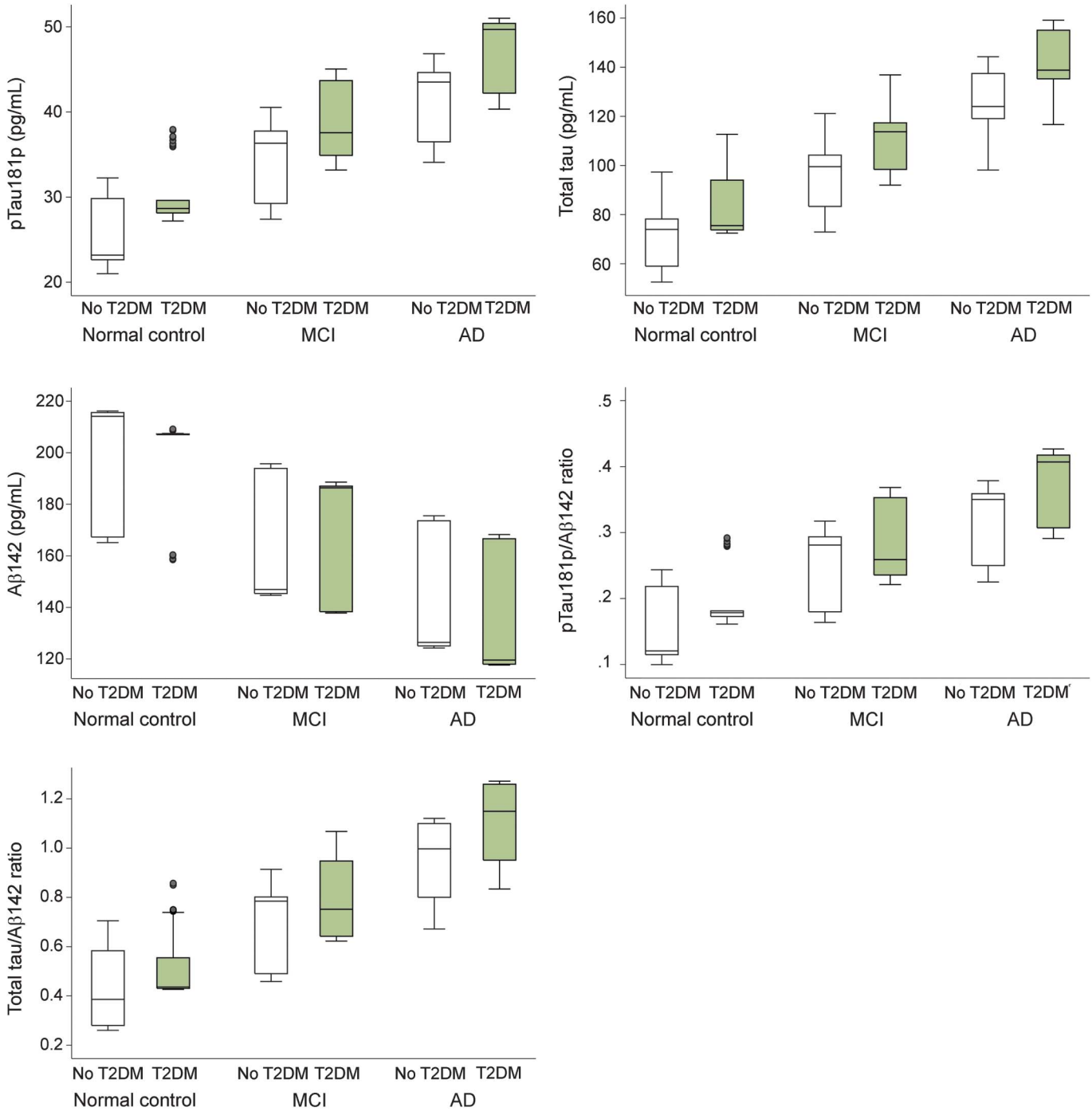
Adjusted for age, sex, cerebellum PiB uptake, *APO* ε4 status, and cognitive diagnosis. Normal control: n = 19, T2DM n = 6; MCI: n = 64, T2DM n = 11; AD: n = 19, T2DM n = 2. AD = Alzheimer disease dementia; MCI = mild cognitive impairment; SUVR = standardized uptake value ratio; T2DM = type 2 diabetes mellitus.

and for the absence of associations between T2DM and $A\beta_{42}$ measures.

DISCUSSION In this study, we examined the relationships between T2DM and in vivo mechanistic biomarkers of neurodegeneration in a sample enriched with patients with AD dementia and MCI. In addition to confirming prior findings that T2DM is associated with brain atrophy,[5,23] we now demonstrate for the first time, a strong relationship between T2DM and the amount of p-tau in the CSF. We did not find evidence of a significant relationship between T2DM and brain or CSF Aβ levels. Regression analyses suggest that the association of T2DM with cortical thickness may be partially mediated by CSF p-tau levels irrespective of cognitive diagnosis or *APO* ε4 status. Cortical thinning related to T2DM was observed in frontal and parietal cortices rather than the mesial temporal predilection for AD-related atrophy. In all, our findings suggest that the neurodegenerative effects of T2DM may be independent and possibly additive to those of AD, and driven by pathways that promote neuronal tau more than Aβ.

Our results are consistent with animal histopathologic data showing that T2DM is associated with hyperphosphorylation of neuronal tau.[24] By contrast, our results are inconsistent with data from human postmortem studies relating T2DM with AD pathology. Results from such studies suggest that the cerebral load of tau-related neurofibrillary tangles or amyloid plaques are either similar[6,25–27] or lower[28–30] in those with T2DM than in those without T2DM. The difference in results may largely be explained by factors related to study design. Previous human pathologic studies were either performed in samples from single centers[26,29,30] or with retrospective ascertainment of diabetes status[26,29,30] in people whose mean age at death was older than 80 years[25,28–30] suggesting survivor bias, or in samples who were highly educated[25,30] and with healthy lifestyles.[25,27] In the

Figure 3 T2DM and CSF biomarker levels



Adjusted for age, sex, and *APO* ε4 status. Normal control: n = 114, T2DM n = 17; MCI: n = 199, T2DM n = 25; AD: n = 102, T2DM n = 14. AD = Alzheimer disease dementia; MCI = mild cognitive impairment; T2DM = type 2 diabetes mellitus.

Honolulu-Asia Aging Study,[1] a prospective study using rigorous phenotyping of diabetes (mean age 77 years), the risk of AD pathology was greater in people with T2DM, but only among those positive for the *APO* ε4 allele. In contrast, we did not find effect modification by *APO* ε4 status, but the power to assess this interaction in our study may have been low.

There are several pathways through which T2DM may contribute to increased levels of p-tau in the brain. Chronic hyperglycemia is associated with increased production in tissues of advanced glycation end-products, which may promote protein cross-linking and stabilization of the paired helical filament tau.[31] Furthermore, hyperglycemia leads to abnormal brain glucose transport that may also contribute greater levels of p-tau.[32] Impaired insulin signaling, a hallmark of T2DM, may also contribute to increased cerebral p-tau possibly through insulin

receptor substrate 1, ERK/MAPK (extracellular signal-related kinase/mitogen-activated protein kinase), and PI3 kinase/Akt pathways.[33] Brain insulin resistance is seen in addition to the peripheral insulin resistance that characterizes T2DM.[34] The downregulation of cerebral insulin receptors leads to overactivation of the important tau phosphorylation-regulator GSK-3β. In a rat model, the administration of intranasal insulin normalized cerebral GSK-3 levels and reduced CSF p-tau levels,[35] suggesting that cerebral insulin levels have a modulatory role in tau phosphorylation.

Our study had certain limitations. The low probability of cerebrovascular disease (low Hachinski score) in the ADNI selection criteria does not allow exploration of potential vascular mechanisms.[36] While this is in a sense a limitation, it is also a strength because it facilitates better control for the confounding effects of vascular disease. The exclusion of those with a high Hachinski score may also explain the lower prevalence of T2DM (17% in cognitively NCs) than would be expected in a US sample with mean age of 75 years (approximately 25%) as per the National Diabetes Statistics Report 2014.[37] This selection bias is likely to limit the generalizability of our results. The samples of people with T2DM and PiB-PET (n = 19) or CSF studies (n = 56) were small, and hence our study may have been limited in its power to detect statistically significant associations of T2DM with brain or CSF amyloid. Thus, we cannot completely exclude the possibility that T2DM is associated with greater amyloid accumulation. However, the absence of an association between T2DM and cerebral amyloid load has also been reported in another study examining human in vivo PET-PiB uptake[27,38] and a few reports from human postmortem data.[25,39] We used 3 different approaches to PiB image analyses to increase the confidence in our null association. Furthermore, the expected increasing gradient of PiB-SUVR was observed going from normal cognition to MCI and AD dementia, making it unlikely that that measurement error could explain the null association for T2DM. In addition, we found an absence of an association between T2DM and CSF amyloid levels, consistent with the imaging findings. The absence of an association between T2DM and hippocampal or WMH volume, in contrast to results described in other studies,[3,4,40] may be attributable to the exclusion of those with a large burden of cerebrovascular disease as well as the larger proportions of those with MCI and AD dementia in ADNI than the other population-based cohorts.

Our analysis was cross-sectional, therefore limiting inferences of causality, raising the possibility that the reported brain changes may precede the development of T2DM. Further longitudinal analyses will assist in establishing whether the associations support causality. As the primary objectives of ADNI were not related to the study of T2DM, information regarding prior diagnosis of T2DM, details of duration of T2DM, and effectiveness of glucose control were unavailable, and these would have provided extra information in exploring our hypotheses. The development of T2DM in midlife may be a greater risk factor for the subsequent development of dementia.[36] The lack of data on disease duration and the older age of ADNI participants may therefore partly explain some of the null associations we report.

AUTHOR CONTRIBUTIONS

C. Moran conceived the idea for the study, conducted the analysis, and wrote the original draft of the manuscript. R. Beare conducted the analysis and contributed to the writing of the manuscript. T.G. Phan conducted the analysis and contributed to the writing of the manuscript. D.G. Bruce contributed to the writing of the manuscript. M.L. Callisaya contributed to the writing of the manuscript. V. Srikanth conceived the idea for the study, conducted the analysis, and contributed to the writing of the manuscript.

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DISCLOSURE

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