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RESEARCH ARTICLE

Is diabetes associated with increased pathological burden in Alzheimer's disease?

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Abstract

Introduction: We examined the association between Alzheimer's disease (AD) and type 2 diabetes mellitus (DM) and hypothesized that diabetes is associated with an increased pathological burden in clinically and pathologically diagnosed AD.

Methods: All data were obtained from the Uniform Data Set (UDS) v3, the Neuropathology Data Set, and the Researcher's Data Dictionary-Genetic Data from the National Alzheimer's Coordinating Center. The dataset (37 cases with diabetes and 1158 cases without) relies on autopsy-confirmed data in clinically diagnosed AD patients who were assessed for diabetes type in form A5 or D2 during at least one visit. Differences in scores were explored using a general linear model. Effect sizes were calculated using sample means and standard deviations (Cohen's *d*).

Results: The presence of diabetes was associated with a lower Thal phase of amyloid plaques (A score; 4.6 ± 0.79 vs. 4.3 ± 0.85, $P < .05$) and lower Braak stage for neurofibrillary degeneration (B score; 5.58 ± 0.72 vs. 5.16 ± 0.96, $P < 0.05$) but not for density of neocortical neuritic plaques (CERAD score-C score). The National Institute on Aging–Alzheimer's Association Alzheimer's disease neuropathologic change (ABC score) was not different between AD+DM and AD-DM.

Discussion: This pilot study found a significantly lower Thal phase of amyloid plaques and Braak stage for neurofibrillary degeneration in AD-confirmed individuals with diabetes compared to those without. Thus type 2 DM is not associated with increased AD pathology in clinically and pathologically confirmed cases of AD.

KEYWORDS
Alzheimer's disease, Alzheimer's disease neuropathologic change (ABC score), Braak neurofibrillary stage (B score), neuritic plaque score (C score), Thal phase (A score), type 2 diabetes mellitus

1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder pathologically defined by the presence of neurofibrillary tangles (NFTs) in the brain as well as senile plaques that primarily consist of amyloid beta (Aβ) peptides.[1] Type 2 diabetes mellitus (T2DM), which is also pervasive among aging populations, is characterized by insufficient insulin secretion by the pancreas and insulin resistance.[2] Although these two diseases are often linked at the epidemiological and clinical levels, a solid molecular connection explaining this relationship has yet to be established.[3,4] Our study set out to supply compelling evidence that provides a tangible, pathophysiological link between two devastating chronic diseases that negatively impact the lives of millions worldwide.

Studies have investigated the relationship between T2DM and AD at the pathophysiological level, specifically whether T2DM catalyzes the onset of AD, but the literature is inconclusive. For example, Heitner and Dickson could not demonstrate a neuropathological connection between diabetes and AD,[5] whereas Beeri et al. reported that individuals with T2DM had less AD neuropathology than nondiabetics.[6] Some studies have failed to discover an association between T2DM and AD pathogenesis altogether and instead found a relationship between diabetes and cerebrovascular pathology.[7–11] Matsuzaki et al., however, revealed a positive association between biological irregularities associated with T2DM and the acceleration of senile plaque formation.[12] The breadth of inconsistency surrounding this controversial topic indicates that further exploration is both needed and warranted. Further, no previous study has used the dataset from the National Alzheimer's Coordinating Center.

Research indicates that T2DM and AD share several pathophysiological mechanisms.[13] Insulin resistance has been identified as a critical mechanistic link between the two diseases.[14] Peripheral insulin resistance, a staple of the T2DM pathology, generates a hyperglycemic microenvironment within the body, as well as a state of chronic hyperinsulinemia.[15] Perpetually elevated peripheral insulin levels downregulate insulin receptors found at the blood-brain barrier, which creates a hypoglycemic microenvironment within the brain.[16] GLUT4, in particular, is an insulin-sensitive glucose transporter abundant in this region that increases glucose uptake into the brain. The downregulation of this transporter and other insulin receptors decreases neural glucose metabolism, reduces the presence of neural insulin, and establishes a state of central insulin resistance.[17] Insulin-degrading enzyme (IDE) is responsible for insulin degradation, but it is also a key Aβ-degrading enzyme found within the brain.[18] This enzyme has a much higher affinity for insulin than Aβ, so the surplus of peripheral insulin generated by insulin resistance competitively inhibits IDE and decreases the level of Aβ clearance in the brain.[19] Intact Aβ peptides aggregate into senile plaques and also interact with tau protein signaling pathways that promote tau hyperphosphorylation and cause NFT formation within neurons, which exacerbates the AD pathology.[20]

It has been suggested that T2DM and AD may share pathogenic mechanisms that similarly impact cognition and are downstream from amyloid in AD, such as increased inflammation and oxidative stress, dyslipidemia, impaired mitochondrial and synaptic function, and impaired brain insulin signaling.[21] These T2DM-related abnormalities can produce an AD clinical phenotype in the absence of amyloid. Understanding these associations is imperative for anti-amyloid treatment trials enrolling patients clinically diagnosed with AD and for other precision medicine approaches to prevent and treat AD and related disorders. Concerning tau, although neuropathological studies do not indicate increased NFT deposition in T2DM, several large studies have documented increased cerebrospinal fluid (CSF) tau.[22] Co-localization of tangles and insulin resistance markers have also been reported in neuropathological studies of AD.[23]

The pathophysiological link between T2DM and AD is undeniable and deserves meticulous exploration. The purpose of the study was to examine the relationship between the diseases through biological mechanisms in which T2DM relates to and promotes AD pathology. This study tested the hypothesis that T2DM is associated with an increased pathological burden in clinically and pathologically diagnosed AD.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors did an extensive PubMed search to read and understand the literature that explores the connection between type 2 diabetes mellitus (DM) and Alzheimer's disease (AD) pathology. To publish this paper, the content was submitted to the National Alzheimer's Coordinating Center for review and approval because the data were acquired from the Alzheimer's Disease Resource Center network.
2. **Interpretation**: The pathophysiological link between T2DM and AD is undeniable and deserves meticulous exploration. The purpose of the study was to examine the relationship between the diseases through biological mechanisms in which T2DM relates to and promotes AD pathology. This study tested the hypothesis that T2DM is associated with an increased pathological burden in clinically and pathologically diagnosed AD. Our findings do not confirm our hypothesis.
3. **Future Directions**: Further investigations are need to determine how T2DM affects AD pathologically and clinically.

2 | METHODS

2.1 | Study sample

All data were obtained from the Uniform Data Set (UDS), the Neuropathology Data Set, and the Researcher's Data Dictionary-Genetic Data from the National Alzheimer's Coordinating Center (NACC), a

database funded by the National Institute on Aging (NIA) that includes information from participants enrolled at 1 of 31 Alzheimer's Disease Centers (ADCs); the current version of the UDS (UDS-3) data began in September 2015. In addition to providing standardized UDS and neuropathology forms to ADCs, the NACC also provides coding guidebooks that serve as manuals of operation for both databases. These were first developed under the close guidance of the ADC Clinical Task Force and the Neuropathology Core Leaders. They were then ratified by all ADCs for common adoption as content and as instruction for standardized data collection instruments and procedures. Thus, the intent is that all ADCs consult these guidebooks when filling out forms. Of course, there is variability across both centers and clinicians. However, this variability is likely to be significantly lower than if medical records were abstracted alone or each site were allowed to follow their unique exam procedures. There is also variability in stain or procedural choices for neuropathology data, but there are relatively standardized methods of examination and documentation for pathologic features. Montine et al. examined AD neuropathological evaluations across a subset of ADCs and found data that have a high agreement despite potential modifications made for modest improvements at different ADCs.[24]

The analyzed sample was restricted to data from the initial visits for all participants with confirmed AD and who were evaluated through self-report and clinician assessment for diabetes type in form A5 or D2 during at least one visit. In UDS-3, there is a specific opportunity to formalize the clinician's report of comorbid conditions in form D2. Still, clinicians are not required to conduct tests to verify that comorbid conditions like T2DM are present. This potential variability in data collection is addressed by researchers through the comparison of responses on form A5 with those on form D2 and through the examination of reported medications. For situations in which information captured in a particular visit might be inaccurate, comparisons across forms provide a valuable method for increasing the likelihood of drawing a correct conclusion. Many of these sorts of checks are also accomplished by the NACC's quality assurance/quality control processes.

Confirmed AD was defined as having Braak stages III–VI and moderate/frequent neuritic plaques at autopsy and a primary diagnosis of AD dementia at any clinical visit. The UDS was collected via a standardized evaluation of subjects during an office visit, a home visit, or telephone conversations with a trained clinician or clinic personnel. The information needed was provided by either the subjects themselves or their informants during an annual assessment. Written informed consent was obtained from all subjects and informants. All data in the NACC database was gathered with institutional review board approval of the 31 individual ADCs.

This investigation analyzed data gathered by the NACC, which was established in 1999 in response to a call for a permanent AD data-coordinating center and database. In addition to making this information available to researchers, the NACC seeks to maintain and increase the research capability of the NACC database, facilitate and conduct research using NACC data, collaborate with national or international efforts on AD and other dementias, and maintain the NIA-required administrative coordination of ADC meetings and ADC communications.[25]

The NACC's data request website provided all of the data necessary for this study. The proposal posed in the query questioned whether T2DM is associated with an increased pathological burden in clinically and pathologically diagnosed AD dementia. To facilitate the acquisition of pertinent variables, the following keywords were used: "Alzheimer's disease," "type 2 diabetes mellitus," "Thal phase (A score)," "Braak neurofibrillary stage (B score)," "Neuritic plaque score (C score)," and "Alzheimer's disease neuropathology change (ABC score)." The start date of the UDS (September 2005) was used, and the data freeze includes data up to June 2019.

AD participants who came to autopsy were assessed based on their diabetic status (absent or recent/active). Participants were placed in either the DM status absent or recent/active group. Differences in A, B, and C scores, as well as the composite ABC score, were explored between subjects with and without T2DM using one-way analysis of variance (ANOVA).

2.2 | Analyses

Sample descriptive statistics were calculated as a function of DM status for age, education, sex, and race. Differences in demographics were explored between groups using ANOVA for continuous variables and Chi-square for categorical variables. Differences in AD pathology were explored via separate one-way ANOVA using A, B, and C scores, and composite pathology scores (e.g., ABC Score) as dependent variables and DM status as the independent variable. Any demographic variables differing between groups were entered as covariates. A generalized linear model, which models data based on any distribution, was used to explore differences in scores. As such, response variables were not normalized and instead derived from an exponential distribution. Cohen's *d* was also calculated as a measure of effect size.

3 | RESULTS

The demographic composition of the subjects analyzed is shown in Table 1. A total of 1195 subjects had pathology-confirmed AD, completed a baseline visit, and had a known diabetes status. Of this sample, 3.1% had active T2DM. For AD-confirmed individuals with T2DM, the mean age was 75.7 ± 10.3 years. Mean years of education was 15.6 ± 4.0; 32.4% of the subjects were female. For AD-confirmed individuals without T2DM, the mean age at baseline was 73.5 ± 10.3 years, and the mean years of education for the group were 15.4 ± 3.0; 50.3% of the subjects were female.

The mean scores at different pathology stages for AD-confirmed individuals with T2DM and AD-confirmed individuals without T2DM are displayed in Table 2. Individuals with pathology-confirmed AD and T2DM had a significantly lower Braak stage for neurofibrillary degeneration ($F\,[1, 1193] = 11.79$, $P = .001$) and a significantly lower Thal phase of amyloid plaques ($F\,[1, 1193] = 5.34$, $P = .021$). Recent or active

TABLE 1 Demographics by diabetic status

Demographic data by group				
	DM status	N	Mean	Std. deviation
Age (years)	Absent	1158	73.5	10.3
	Recent/active	37	75.7	6.7
Education (years)	Absent	1146	15.4	3.0
	Recent/active	37	15.6	4.0
Sex (% female)	Absent	50.3%	—	—
	Recent/active	32.4%	—	—
Race (% non-White)	Absent	7.0%	—	—
	Recent/active	16.2%	—	—

Abbreviation: DM, diabetes mellitus.
*= $P < .05$

TABLE 2 Descriptive statistics for pathology staging by group

	DM status	N	Mean	Std. deviation
Thal phase for amyloid plaques (A score)*	Absent	1158	4.60	0.790
	Recent/active	37	4.30	0.845
Braak stage for neurofibrillary degeneration (B score)*	Absent	1158	5.58	0.718
	Recent/active	37	5.16	0.958
Density of neocortical neuritic plaques (CERAD score; C score)	Absent	1158	2.79	0.407
	Recent/active	37	2.78	0.417
NIA-AA Alzheimer's disease neuropathologic change (ADNC; ABC score)	Absent	1158	2.90	0.549
	Recent/active	37	2.73	0.450
Density of diffuse plaques (CERAD semiquantitative score)	Absent	1158	3.03	1.165
	Recent/active	37	3.27	1.465

Abbreviations: AA, Alzheimer's Association; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DM, diabetes mellitus; NIA, National Institute on Aging.
*= $P < .05$

T2DM was also associated with a lower NIA–Alzheimer's Association (NIA-AA) Alzheimer's disease neuropathologic change (ADNC) score. However, the difference was not statistically significant. Individuals with pathology-confirmed AD and T2DM also had a slightly higher density of diffuse plaques than AD-confirmed individuals without T2DM, though the difference was not significant ($F [1, 1193] = 1.54$, $P = .215$). Individuals with pathology-confirmed AD and T2DM did not differ in density of neocortical neuritic plaques from those without T2DM ($F [1, 1193] = .01$, $P = .92$).

4 | DISCUSSION

This study tested the hypothesis that T2DM is associated with an increased pathological burden in clinically and pathologically diagnosed AD. Based on the analysis of the dataset we obtained from the NACC and assessment of the differences in pathology staging between AD-confirmed individuals with T2DM and those without an AD confirmation, numerous key findings were identified. Contrary to our hypotheses, we found that the presence of T2DM is not associated with increased AD pathology in clinically and pathologically confirmed cases of AD. Instead, recent or active T2DM was associated with a lower Thal phase of amyloid plaques. The presence of T2DM was also associated with a lower Braak stage for neurofibrillary degeneration. AD-confirmed individuals with T2DM were found to have no difference in the density of neocortical neuritic or diffuse plaques. Collectively, these data suggest that there is no increased amyloid burden in AD individuals with T2DM than without T2DM.

Evidence supporting the notion that T2DM catalyzes AD pathogenesis is appealing from a molecular standpoint. A critical enzyme involved in blood glucose regulation is glycogen synthase kinase-3β (GSK-3β), and it is regulated by insulin in the phosphoinositol-3-kinase/Akt signaling pathway.[26] Individuals with T2DM overexpress GSK-3β; excessive activation of this enzyme causes signaling pathway impairment that creates a hyperglycemic microenvironment and insulin resistance.[27] The overexpression of GSK-3β also contributes to tau protein hyperphosphorylation, which is involved in accelerating AD neuropathology.[28] Hyperglycemia has been implicated in the

formation of reactive oxygen species (ROS), and research suggests that T2DM depletes cellular antioxidant systems found within the body.[29] These conditions establish endogenous oxidative stress, which has a deleterious impact on many biological systems, leads to mitochondrial dysfunction, and catalyzes both Aβ production and aggregation in the brain.[30] Chronic hyperglycemia and oxidative stress work synergistically to amplify the production of advanced glycation end-products (AGEs) in individuals with T2DM.[31] AGEs, which are also found within Aβ-plaques and NFTs, accelerate Aβ deposition in the brain through their attachment to multi-ligand receptors called RAGE. Activation of RAGE receptors stimulates the expression of an enzyme needed for Aβ production (i.e., β-site amyloid precursor protein-cleaving enzyme 1 [BACE1]) and facilitates the migration of circulating Aβ peptides into the brain.[32,33] RAGE receptor activation also generates ROS and inflammatory responses intended to counteract the reactive species, which creates a perpetuating cycle of increased AGE production and subsequent inflammation.[34] Valente et al. observed that *post mortem* brain samples exhibiting T2DM, and AD showed increased amounts of AGEs, RAGEs, and Aβ plaques compared to brains that only displayed AD.[35]

Many studies do not support a relationship between T2DM and increased AD pathology, and our report concurs with these findings. Overall, rigorous neuropathological studies have shown that insulin resistance, pre-diabetes, and T2DM are not associated with amyloid load or that amyloid load is unaffected by diabetic status in adults with mild cognitive impairment or AD.[30] This lack of association is likely impacted by differences in methodology and research design.[36] Pruzin et al. could not demonstrate a connection between diabetes and AD neuropathology at either regional or global levels.[37] Their investigation was designed as a longitudinal cohort study that enrolled older Catholic clergy members, Rush Memory and Aging Project participants from the Chicagoland area, and black participants from the Chicagoland area.[37] Although these cohorts included subjects from a single center and relied on a common neuropathology protocol, major demographic and geographic specificities are associated with each group. dos Santos Matioli et al. did not find any association between diabetes and two measures of AD neuropathology: Braak-Braak (BB) scores for NFTs and Consortium to Establish and Registry for Alzheimer's Disease (CERAD) scores for neuritic Aβ plaques.[38] The Vantaa study found that residents of Vantaa, Finland, who were 85 years old with T2DM were less likely to have NFTs and Aβ plaques. In contrast, the Honolulu-Asia Aging Study discovered that Japanese-American men with T2DM born between 1900 and 1919 who were living in Oahu, Hawaii had more Aβ plaques in their hippocampus and more NFTs in their cerebral cortex and hippocampus but only if they were carriers of the apolipoprotein E (*APOE*) ε4 allele.[7,39]

This study is not without limitations that could introduce biases. First, because this is a cross-sectional study using *post mortem* data, we were restricted to data provided by the database. Therefore, it was uncontrolled insofar as it did not control for age, race, or sex. There are several pieces of information that we did not incorporate into our analysis that could certainly affect the results we obtained, including lifestyle habits, genetic factors, comorbidities, and medication usage. Participants with T2DM may have died from reasons other than dementia and thus had a lower chance of being included in the examined sample, which exposes the study to survival biases. Second, after classifying our participants, we found a massive discrepancy in sample size. Only 37 out of 1195 total individuals were identified as AD patients with T2DM as captured by the UDS forms, representing only 3.1% of our entire sample population. The general prevalence of diabetes in the United States population is 8.2% and even 25% in the elderly; therefore, diabetes is likely underrepresented in our dataset and may depict an unusual sample of diabetic individuals.[40] Other biases include a large dementia clinic-based sample, an unclear rate of loss to follow-up and autopsy rate, a highly educated sample, and too few subjects to examine racial disparities despite T2DM being twice as common in minorities. Finally, the data are collected from 31 centers with variability in data collection despite harmonization.

Next, because our study accounted for only five different measures of pathological staging, other neuropathological mechanisms connecting T2DM to the promotion of the AD pathology may exist that were not investigated. Our study also only measured AD neuropathology within the entire cortex and did not consider the effect that T2DM has on specific regions within the brain that could possess increased amyloid or neurofibrillary pathology. Furthermore, although our analysis included data acquired from a national database, it was performed in a high-income country. As suggested by dos Santos Matioli et al.,[38] this fact may not allow this study to apply to individuals in low- and middle-income countries, who are subject to different environmental and social stressors, as well as different racial and genetic backgrounds and susceptibilities. Last, the NACC database obtains information from convenience cohorts that are taken from 31 ADCs. These ADCs rely on differing eligibility criteria when determining who is enrolled into the clinical core of the Center. ADCs also typically enroll individuals with higher socioeconomic statuses and fewer minorities, especially in the Neuropathology cohort. Because participants in the ADCs are not representative of individuals in the general community, the interpretability of these data is compromised and subjected to selection bias.

Future studies should consider the impact of genes associated with the T2DM pathology that may provide valuable insights regarding the enhanced production of Aβ plaques. The *APOE* ε4 allele, specifically, has been identified by many studies as a critical associative factor between T2DM and AD.[12,38,39,41,42] Luchsinger et al. demonstrate the strong predictive relationship between *APOE* ε4 genotype and Aβ burden; carriers of the allele were more likely to possess intermediate and high levels of Aβ compared to non-carriers.[43] Future treatments for individuals with T2DM should target physiological processes implicated in increased Aβ generation within the brain. As a result, the progression of the AD pathology may be hindered or stopped altogether. Future investigations should also explore deposition patterns through various neuroimaging techniques; the visualization of the neuropathological hallmarks of AD may provide insight as to how T2DM affects AD pathogenesis or its progression within different parts of the brain. Takenoshita et al. relied on positron emission technology to identify clinically diagnosed AD patients with T2DM with neuronal damage devoid of Aβ neurotoxicity.[44] The neuronal damage and

subsequent dementia were instead attributed to a suspected form of pure tauopathy.[44] Identifying aberrant brain imaging patterns through neuroimaging will be significant for the future of clinical practice when considering T2DM, AD, and the interaction between the two diseases because it affects diagnoses, treatment methods, and overall patient care. Taken together, this body of work suggests that many adults with T2DM express AD-like symptoms at lower levels of amyloid burden, perhaps due to the added impact of vascular or tau abnormalities in midlife; however, AD pathology appears to be potentiated by T2DM-related factors such as insulin resistance.

More extensive research needs to be performed on this complex and multifactorial relationship to provide conclusive answers that explain their connection and elucidate improved understandings of these pervasive conditions; through this needed exploration, future preventive methods and treatment, as well as health-care delivery, can be revolutionized to better serve the needs of patient populations across the world.

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CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Kaviyon Sadrolashrafi assisted in data acquisition and analysis and drafted a significant portion of the manuscript, Justin Miller assisted in data acquisition and analysis, Suzanne Craft drafted a significant portion of the manuscript, Boris Decourt drafted a significant portion of the manuscript, Abdu Adem drafted a significant portion of the manuscript, Jeffrey R. Wilson assisted in analysis, and Marwan N. Sabbagh conceived of the project and assisted in data acquisition and analysis and the drafting of the manuscript.

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