Received: 28 August 2025 | Revised: 18 March 2026 | Accepted: 19 March 2026

DOI: 10.1002/alz.71471

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

REVIEW ARTICLE

How does type 2 diabetes modify the risk of Alzheimer's disease?

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Funding information
Lucas Papaw Foundation

Abstract

Type 2 diabetes (T2D) and Alzheimer's disease (AD) are both increasing exponentially worldwide. T2D has also been identified as one of 14 modifiable risk factors for dementia, but the mechanism is unknown. T2D could promote dementia via vascular or AD neuropathological changes, and mechanistic hypotheses include central insulin resistance and T2D's peripheral inflammation promoting central inflammation. Here we examine these different hypotheses by reviewing the recent literature in combination with re-analysis of *post mortem* brain tissue molecular data. Collectively, recent studies and single-cell transcriptomic data suggest that peripheral lipid anomalies and inflammation seen in T2D act together to reduce brain–blood barrier integrity, facilitating aberrant immune signaling between the periphery and the brain. The subsequent promotion of AD-specific microglial subtypes is the most likely mechanism linking T2D and AD. These AD-specific microglial subtypes may be reduced by therapeutic targeting of triggering receptor expressed on myeloid cells 2–apolipoprotein E signaling pathway.

KEYWORDS
Alzheimer's disease, glucose, lipids, microglia, transcriptomics, Type 2 diabetes

Highlights

- T2D is one of 14 modifiable risk factors where meta-analyses suggest they increase the risk of dementia and specifically the most common form, AD
- The original hypothesis for this association was that AD represented central insulin resistance, so-called type 3 diabetes.
- Studies using human *post mortem* tissue now suggest that T2D promotes anomalies in lipid metabolism in specific microglial subtypes that, in turn, promote AD neuropathologic change.
- Upregulation of TREM2–APOE signaling can reverse these changes and represents novel therapeutic avenue for AD.

1 | INTRODUCTION

Alzheimer's disease (AD) is a rapidly growing health concern worldwide due to an aging population and a lack of effective disease-modifying drugs for a large percentage of the population at risk of AD.

AD is the most common form of dementia and manifests due to a progressive loss of neurons and the spread of AD pathology, now referred to as AD neuropathological change (ADNC) across the brain.[1] ADNC is characterized by two hallmark entities: extracellular amyloid beta (Aβ) plaques and intraneuronal neurofibrillary tangles (NFTs or just "tangles"). Aβ accumulation is thought to accelerate NFT formation, and the spread and extent of the latter is correlated with the extent and severity of the disease.[2–6] NFT formation ultimately leads to neuron death and the symptoms of AD,[7] although other mechanisms may contribute to this process.[8–11] ADNC is also characterized by reactive glia, both microglia and astrocytes,[12,13] often referred to as neuroinflammation and vascular changes.[14,15]

As the symptoms of AD result from the irreversible loss of neurons, the most effective treatments or preventive strategies need to be started pre-symptomatically, when neuronal dysfunction remains confined to regions like the hippocampus, and reversible. This requires pre-symptomatic diagnosis tools. There is now considerable optimism that amyloid imaging using positron emission tomography (PET), in combination with plasma biomarker assays that assess Aβ variants, phosphorylated tau species and non-specific indicators of neuron (e.g., neurofilament light [NfL]) and glial (e.g., glial fibrillary acidic protein [GFAP] and YKL-40 [also known as chitinase-3-like protein 1 {CHI3L1}]) damage or neuroinflammation, can identify high-risk individuals before any symptomology.[16–18]

Amyloid-modifying treatments (AMTs) successfully clear the brain of Aβ but have only moderate success in slowing the rate of cognitive decline.[19] Current research priorities in AD are addressing these issues through more nuanced AMTs and/or adjunctive early treatment targets. Other than targeting Aβ, therapies against NFT formation or gliosis or treatments that promote neuronal resistance to these hallmark pathologies may be useful, but the exact molecular targets remain elusive.[20] The major knowledge gap in AD is why, in the absence of mutations, most patients develop AD. Enormous research efforts in the last 40 years have been devoted to addressing that issue, including a myriad of genetic and epidemiological studies. AD is often said to represent ~60% of dementia cases, but it is important to consider here that most sporadic cases seen at autopsy have mixed pathology. This mix may include combinations of ADNC, Lewy body pathology, TAR DNA-binding protein 43 inclusions, and vascular pathologies: cerebral amyloid angiopathy (CAA),[15] microinfarcts, arteriosclerosis, and atherosclerosis.[14,21]

In terms of risk factors, the possession of the apolipoprotein E ε4 allele (*APOE* ε4) is by far the largest genetic risk factor,[22] and this has been shown repeatedly including in the large United Kingdom Biobank study (UKB).[23] APOE ε4 is known to promote intraneuronal Aβ accumulation,[24] plaques,[25] NFTs,[26] gliosis,[27] CAA, and other types of vascular pathology.[28,29] Whether any of these routes is more important than others, or if alternative mechanisms exist, is unknown.

For environmental factors meta-analyses aggregated in a series of Lancet Commission reports suggest there are 14 modifiable lifestyle factors.[30] The total risk associated with these factors or population-attributable fraction (PAF) was calculated at 45.3% with the high low-density lipoprotein (LDL) (bad) cholesterol and hearing loss rated as having the highest individual effects (7%), while diabetes (type 2 diabetes [T2D]) had less of an impact across the population (2%).

Exploring T2D effects on the brain may uncover new mechanisms, or a common mechanism shared with other risk factors such as *APOE4*. While treatment of middle-aged T2D could reduce AD and potentially the converse in the elderly.[31] If there is a causal association, then T2D may act centrally, promoting ADNC, or systemically, through metabolic dysregulation, or a combination of both such as via cerebrovascular injury and inflammation. We previously reviewed the link between T2D and AD,[32] where we started to question whether insulin resistance (IR) was the common pathomechanism between the two diseases, that is, AD was equivalent to type 3 diabetes.[33] Here we re-evaluate the T2D–AD connection through a combination of a review of the recent literature and a re-analysis of molecular data from human *post mortem* brain tissue studies (see Figure 1 for overview).

2 | ALZHEIMER'S DISEASE

2.1 | The pathogenesis of AD

Autosomal-dominant forms of AD (ADAD) occur in individuals with mutations in one of three genes, but these are rare and account for fewer than 2% of total AD cases. The proteins encoded by these genes are all involved in the production of Aβ, either encoding the amyloid precursor protein (*APP*) or the gamma-secretase catalytic subunit (*PSEN1* or *2*).[34] Under normal conditions APP is proteolytically degraded via non-amyloidogenic and amyloidogenic pathways, with the former being more active.[35] The amyloidogenic pathway produces an array of different sized proteolytic products collectively referred to as Aβ. The longest is 42 amino acids in length (A$\beta_{1\text{-}42}$) and more aggregation-prone and neurotoxic than the most common variant A$\beta_{1\text{-}40}$.[36–38] The clinical and pathological similarities between ADAD and sporadic AD led Hardy and colleagues to propose the amyloid cascade hypothesis for explaining sporadic cases.[39,40] More specifically, they proposed that soluble A$\beta_{1\text{-}42}$ oligomers were the likely cause.[39] In ADAD there is a relative increase in the production of A$\beta_{1\text{-}42}$. Cerebrospinal fluid (CSF) and plasma show a reduction in the A$\beta_{1\text{-}42}$/A$\beta_{1\text{-}40}$ ratio[41,42] thought to indicate an increase in A$\beta_{1\text{-}42}$ aggregation within the brain.[43] In sporadic cases, the amyloid hypothesis suggests that clearance rather than production is the issue, and it goes onto suggest a linear mechanism where A$\beta_{1\text{-}42}$ oligomers adversely affect neurons, causing ionic dyshomeostasis, imbalance in kinase/phosphatase activity, hyperphosphorylation of tau, NFT formation, and neuron death. The process is repeated in new brain regions as ADNC spreads in a

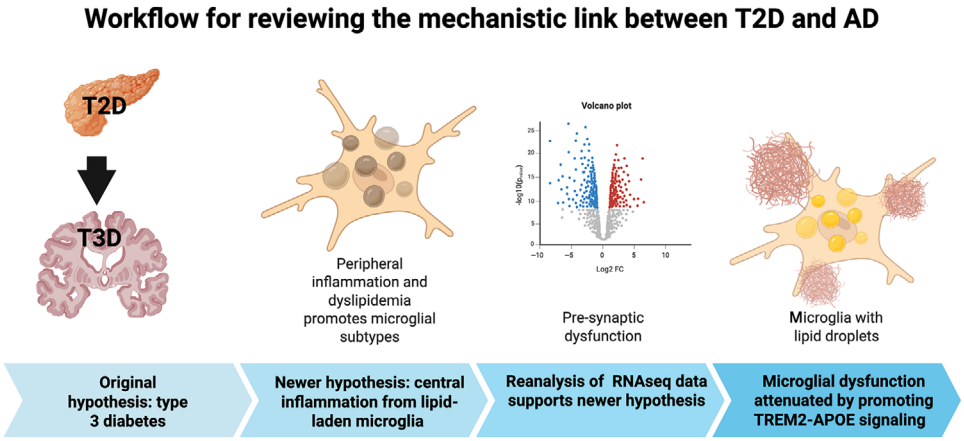

FIGURE 1 Workflow for reviewing link between type 2 diabetes (T2D) and Alzheimer's disease (AD). A flowchart gives an overview of the approach used for this review. Early literature suggested that AD represented a state of central insulin resistance, and the term type 3 diabetes was coined. The review considers more recent evidence and particularly that coming from single-cell studies where a subtype of lipid droplet-laden microglia has been shown to promote AD pathology. A re-analysis of RNA sequencing data from our own work and the ROSMAP study suggests that T2D is more likely to promote AD through these dysfunctional microglia subtypes than via central insulin resistance. The review concludes by exploring whether promoting TREM2–APOE signaling could reverse the microglial anomalies in AD. Created in BioRender.

prion-like fashion.[44,45] However, the exact mechanisms linking events within the cascade are not entirely clear, including why clearance of Aβ metabolism is disrupted in the first place. What has become clear with the success of AMTs is that Aβ accumulation is part of the problem, but the relatively modest effects on dementia suggest that solving the Aβ component alone is insufficient to prevent the disease.

2.2 | Genetics of AD

The cause of sporadic AD has been generically described as resulting from a complex interaction between genetic variants and environmental (lifestyle) factors. This might well be true, but even the UKB, with its 500,000 participants, remains underpowered to fully test this hypothesis. There are 75 known genetic risk loci including the *APOE* gene.[46] The epsilon 4 variant of *APOE* (*APOE4*) has an unusually large effect size among common genetic variants linked to late-onset neurodegenerative diseases.[47] *APOE4* homozygotes ($\varepsilon 4/\varepsilon 4$) are at 12 times greater risk compared with those with the commonest *APOE3/3* genotype,[22] and their lifetime risk is as high as 60%.[48] Recently it was suggested that *APOE4* homozygosity should be considered a genetic form of AD.[48] Others suggest that common forms of AD can be aetiologically,[49] clinically,[50] and pathologically[51,52] demarcated into APOE4-dependent and independent forms. Known genes at the other loci identified in genome-wide association studies (GWASs) can be functionally grouped into three categories: lipid metabolism, synaptic vesicle trafficking, and (innate) immune function.[53] Immune function is interesting as some researchers regard AD as a chronic neuroinflammatory disease and many of the genes within these loci are expressed primarily in microglia.[54] These functional categories might not be mutually exclusive either, with recent studies suggesting that lipid dysmetabolism in microglia may be an important component of AD pathogenesis.[55–59]

2.3 | APOE and AD

APOE is the major apolipoprotein in the brain and is physiologically known for transporting cholesterol from astrocytes to other cells, including neurons.[60] Cholesterol and APOE are both made by astrocytes and are assembled extracellularly prior to their wider distribution. One of many outcomes from single-cell transcriptomic studies is that microglia also express APOE, and this is upregulated with aging and in AD.[61] The exact mechanism by which APOE4 has such a large effect on AD risk is currently unknown. The most popular working hypothesis is that it binds, relative to the other two isoforms (APOE2 and 3) poorly to Aβ or that, once it is bound to Aβ, it binds more poorly to its receptors, including low-density lipoprotein receptor (LDLR) and low-density lipoprotein receptor-related protein 1 (LRP1 also called APOER), resulting in ineffective clearance from the brain.[62]

Peripherally, APOE is synthesized by the liver and macrophages, with its major physiological role being the return of very-low-density lipoprotein remnants to the liver via binding to the hepatic LDL receptors. Mutations in APOE and homozygosity at APOE2 can cause type III hyperlipoproteinemia because of impaired clearance by the liver.[63] APOE variants also appear to impact the immune system by affecting T-cell and macrophage function, as has been described in atherosclerosis.[64] Of the three major receptors for APOE (LDLR, low-density lipoprotein receptor-related protein 1B [LRP1B] and low-density lipoprotein receptor-related protein 8 [LRP8 also called APOER2]), LRP1B is the most highly expressed one in the brain and, along with APOE4, is known to be associated with dementia in Parkinson's disease, likely through differential APP processing and Aβ accumulation.[65] As an aside, an *APOE* variant called the Christchurch mutation prolongs the onset of symptoms associated with the *PSEN1* E280A (Paisa) mutation by three decades.[66] This variant (R136S) is on the *APOE3* background (APOE3ch). APOE3ch was shown to phenocopy APOE2 by displaying reduced LDL receptor binding.[67] This

seemingly contradicts the idea that APOE4 has its effect on AD risk through a relatively poorer clearance of Aβ from the brain parenchyma. However, a recent study suggested that rather than just clearance, LDL receptors may be involved in APP metabolism and Aβ production. They showed how the three APOE isoforms interact differently with LDL receptors on neurons, with APOE4 promoting lysosomal dysfunction potentially via build-up of the aging pigment lipofuscin.[67] Guo and colleagues further suggested that rather than clearance of Aβ from endothelial cells, the issue is the relative ease by which APOE4 (and Aβ) is internalized by neurons, followed by its aggregation and overloading of the neuronal endo-lysosomal system. We have similarly shown in 3xTg-AD mice that Aβ accumulates in the cytosol of neurons, because of reduced degradation in lysosomes, secondary to lipid accumulation that in turn results from the loss of lysosomal acid lipase (LAL). Lower LAL was also seen in AD *post mortem* brain tissue.[68]

One recurring idea in AD is that plaques develop subsequently to intraneuronal Aβ accumulation, cell death, and plaque formation.[69] The role of microglia here is also interesting. Microglia respond to Aβ plaques by forming lipid droplets, which, when excessive, decrease their phagocytic efficacy against Aβ.[58] In triple mutant APPPS1-21: APOE3ch mice, more microglia clustered around plaques and had the effect of suppressing tau seeding from injected AD-tau brain extract,[70] although Aβ load was higher than the APPPS1-21 mice, so APOE3ch rescue might not be wholly phagocytosis-related. Microglia may also respond to intraneuronal Aβ/lipid accumulation by upregulating their phagocytic machinery.[71] Under the conditions of dyslipidemia associated with T2D, microglia similarly show accelerated lipid droplet formation.[72] More recently it was suggested that triglyceride biosynthesis and storage in lipid droplets were necessary for microglia to become activated,[73] but in the case of *APOE4* carriers, lipid droplets become excessive and promote disease-associated microglial states.[59,73] Inhibiting triglyceride biosynthesis restored homeostasis in APOE4-derived microglia, suggesting a future potential therapeutic direction, which is discussed further below.

APOE4 is associated with Aβ plaque load in AD,[74] but it is also a major risk factor for CAA.[75] CAA is thought to occur in 80% of AD cases, and this figure may be higher.[76,77] CAA is a build-up of insoluble Aβ in the tunica media of leptomeningeal and cortical arteries[78] and is thought to result from ineffective clearance to the bloodstream by lipid receptors on the abluminal surface of cerebral endothelial cells. However, CAA is largely due to $A\beta_{1\text{-}40}$ and is most prominent in the occipital lobe, which suggests an alternative pathomechanism to the plaques.[79,80] We confirmed the importance of APOE4 as a risk factor for CAA using the Religious Orders Study and Memory and Aging Project (ROSMAP) study data, and particularly in the posterior parts of the brain, which is consistent with other studies.[81] Using ROSMAP bulk tissue RNA sequencing (RNAseq) data we demonstrated that *APOE4* carriers showed prominent enrichment of vascular pathways. This included genes such as adrenomedullin (*ADM*) and claudin-5 (*CLDN5*), pointing to a mechanism involving APOE, Aβ, and blood–brain barrier (BBB) integrity[82] (also see below for analysis of T2D using ROSMAP data). The obvious questions are whether vascular-related factors, such as T2D, obesity, and hypertension, operate via a vascular or ADNC mechanism and, then, whether either or both are APOE4-dependent. At least one pathology study suggested that a direct effect on ADNC was unlikely,[83] but this has not been observed universally and particularly in *APOE4* carriers.[84]

A further variation on the APOE4 and Aβ binding theme is that APOE4 (with bound Aβ) is less effectively phagocytosed by microglia via receptors including triggering receptor expressed on myeloid cells 2 (TREM2). APOE is both bound by TREM2 but also downstream to TREM2 in a pathway that regulates the switch between their homeostatic state and reactive states such as neurodegenerative disease-associated microglia (DAM).[27] A mouse model with conditional expression of the three human *APOE* variants showed that APOE4 was poor at switching on the DAM phenotype in response to Aβ deposition.[85] APOE4 microglia, relative to those with APOE3, had minimal interaction with plaques, and this seemed to be due to lipid droplet formation in the latter, consistent with that seen in an AD mouse model.[59] In a double-mutant tau P301S/ApoE4 mouse that showed prominent tau pathology,[86] the reduction of microglial lipid accumulation with Liver X Receptor (LXR) agonist or ATP-Binding Cassette Transporter A1 (Abca1) overexpression strongly reduced the tauopathy.[87] This is interesting as other studies support the idea that microglial dysfunction is the bridge between Aβ accumulation and tau hyperphosphorylation (and thus NFT formation) in adjacent neurons. Furthermore, the protective APOE3ch variant suppresses tau pathology spread via microglia.[70] Interestingly, a recent proteomics study combining data from induced pluripotent stem cell (iPSC)-derived brain organoids, CSF, plasma, and *post mortem* brain tissue suggested that APOE4 promoted a pro-inflammatory immune signature in the brain that is not specific to AD.[88] APOE4 effects for modifying AD risk probably do not operate purely via microglia, but this does provide a common mechanism for explaining how key genetic signals in AD associated with APOE4, neuroimmune dysfunction, lipid metabolism, and vesicle (lysosome) cycling could all contribute to AD pathogenesis.[89] As discussed below, it may also provide the basis by which T2D increases AD risk.

2.4 | Environmental factors and AD

The latest consensus report on modifiable risk factors suggests that 14 factors are reproducibly (meta-analyses) associated with all-cause dementia and these collectively account for 45% of risk.[30] These factors include hypertension, smoking, obesity, physical inactivity, alcohol, and diabetes, as well as recently added vision loss and elevated LDL cholesterol. A general challenge in medical research is to bridge the gap between epidemiological findings and underlying biological mechanisms, and this process has been termed translational epidemiology.[90]

We previously used a feature selection algorithm to explore the leading genetic loci and lifestyle AD risk factors using the UKB.[23] We compared predictive performance against the 12 so-called Livingston factors that were available at the time.[91] The *APOE4* signal had by far the largest effect, with the next largest risk factors being other genetic variants within the "*APOE* locus," followed by the liver enzyme

function index – the AST:ALT ratio.[23] Interestingly, in non-*APOE4* carriers, there was no additional factor(s) whose effect sizes increased to compensate for the lack of APOE4. Moreover, the 12 modifiable factors[91] (now 14[30]) were not among the top 25 ranked features. In contrast, another group applied an alternative feature selection method to the UKB data and did find that some of these 12 factors predicted AD.[92] Factors these two UKB studies have in common are age, *APOE4*, liver enzymes (GGT rather than AST), number of medications, and insomnia. The latter study noted smaller effects with two other modifiable factors – alcohol consumption and physical inactivity[92] – while our study alternatively found an association with air pollution.[23] Despite the fact that the mean age of the UKB cohort is still relatively young (~73 years) and future AD cases will be greater among non-*APOE4* controls, T2D did not directly modify risk in either study. We further opined that prominent risk factors, such as the number of medications and number of co-morbidities, may be synonymous with frailty, and it was possible that other modifiable factors, including diabetes, influenced cognition through this general form of attrition rather than by promoting ADNC.[93–96] Overall, the UKB data suggest that outside of aging and *APOE4*, AD is the result of many factors with small effects, and heterogeneity between patients is highly likely.

3 | PATHOGENESIS OF T2D

3.1 | In the periphery

Under physiological conditions, the post-prandial elevation of blood glucose is counteracted by the production of insulin from the pancreas and the glucose transporter GLUT4 (encoded by solute carrier family member 2A4 gene; *SLC2A4*)-mediated uptake into skeletal muscle, liver, and adipose tissue.[97] T2D is defined by hyperglycemia due to resistance to this action of insulin and, ultimately, the inability by pancreatic β cells to produce a compensatory secretory response.[98] Risk factors include obesity (and specifically intra-abdominal fat accumulation), Western diet, inactivity, aging, and genetics, many of which are among the "Livingston 14."[30] Like AD, T2D is undergoing an exponential increase in prevalence worldwide, with 589 million affected currently and 700 million people predicted to be affected by 2045.[99]

Pancreatic beta cells respond to glucose via the GLUT2 transporter (encoded by *SLC2A2*). The liver, skeletal muscle, and adipose tissue respond via the GLUT4 receptor, which translocates to the cell surface following insulin binding to its receptor (INSR). In adipose tissue, GLUT4-mediated glucose uptake activates glycolysis to produce the lipogenic pathway substrate glyceryl-3-phosphate. This combines with free fatty acids (FFAs) to form triglycerides that are stored in droplets. Adipose insulin resistance (IR) essentially reverses this process with FFAs released into the cytoplasm of myocytes and adipocytes, resulting in stress and efflux of FFAs into the bloodstream, promoting lipid accumulation elsewhere. In skeletal muscle and liver, insulin binding activates the insulin signaling pathway via phosphorylation of AKT (also known as protein kinase B) and then glycogen synthetase kinase 3β (GSK3β) to promote glycogen synthesis and inhibition of glucose production via forkhead box protein O1 (FOXO1).[100] Again, with IR, these processes are reversed, with pro-inflammatory molecules like C-reactive protein (CRP) released from hepatocytes, creating conditions of oxidative stress and tissue damage and the liver also exporting more atherogenic lipoproteins.[101]

3.2 | Central effects of T2D

The brain is not immune to lipid droplet formation, especially in microglia.[72] This is thought to promote neurodegenerative disease.[102] In mice, at least, high-fat diets also lead to lipid droplets that promote microglial activation,[103] while intermittent fasting had the opposite effects and in a mutant APP mouse reduced Aβ accumulation through enhanced phagocytosis.[104] One way that peripheral metabolic anomalies could interact directly with the brain is through the hypothalamus and its interconnections with other brain regions. It has been proposed that hypothalamic microglia act as sensors of excess nutrient consumption, relating signals to hypothalamic nuclei to regulate appetite and energy balance.[105] This integrated process is likely to involve tanycytes, cells associated with the ependyma in the medial eminence that also transduce leptin signaling to mediobasal hypothalamic neurons.[106] Lipid droplets in murine hypothalamic microglia accumulate in leptin receptor-deficient mice, those on high-fat diets, and streptozotocin-induced T2D mice, with the latter due to high glucose.[107] Microglial lipid droplets promote inflammation via TREM1 and neuron damage and this can be prevented by blocking TREM1. TREM1 also binds Aβ[108] but amplifies pro-inflammatory responses in microglia,[109] the opposite effect to TREM2. ADNC is seen in the hypothalamus, but it tends to be specific to certain regions including the tuberomammillary nucleus and lateral hypothalamic area.[2] A 2024 study confirmed these findings but found that Aβ load was associated with a lower body mass index during life.[110]

3.3 | Is AD type 3 diabetes?

GSK3β, is also known as tau kinase I, and this and other similarities between the known pathomechanisms of T2D and AD suggested to some researchers that AD could develop from, or represents, central IR. De La Monte and colleagues even coined the term type 3 diabetes for AD.[111] There is reasonable evidence of insulin signaling anomalies in AD derived from pharmaceutically induced mouse models of AD (e.g., STZ-induced) and *post mortem* brain tissue.[112,113] Yet, in weighing up the likelihood that central IR as a key pathomechanism for AD, it is important to note that the brain is not an insulin-sensitive organ.[114] Glucose uptake into the brain is via the receptor GLUT1 (encoded by *SLC2A1*) on cerebral endothelial cells and occurs across a concentration gradient. GLUT1 is also responsible for uptake into astrocytes, while neurons rely on GLUT3 (encoded by *SLC2A3*).[115] Some neurons in the hypothalamus express the insulin-sensitive GLUT4 (encoded by *SLC2A4*), and this may be important in whole-body glucose homeostasis.[116] Insulin does reach the brain and

is largely transported across the BBB via the insulin receptor, although there is also some local expression. However, insulin seems to act as a neurotrophic factor similarly to insulin-related growth factor 1 (IGF-1) or IGF-II. A review of all *post mortem* studies suggested to us that the increase in insulin signaling was an attempted neuroprotective action that proved inadequate to preventing the progression of AD.[33] Consistent with this conclusion, we then showed an upregulation of INSR and IGF1 receptor (IGF1R) in *post mortem* brain tissue using RNAseq and digital PCR, and this seemed contrary to the idea of central IR.[117] That being said, central glucose dysregulation in AD is supported by imaging[118] and pathological studies[119] but is probably functionally independent of insulin.[120]

4 | T2D AND AD

4.1 | Genetic connections

In a 2017 literature review, we suggested that T2D was a risk factor for both vascular dementia (VaD) and AD.[32] It was not clear whether T2D as a risk for ADNC occurred by promoting tau or Aβ pathology, but to us a tau-dependent pathway seemed more likely.[32] In 2024, a study using the Alzheimer's Disease Neuroimaging Initiative dataset showed that the 12% of participants with both mild cognitive impairment (MCI) and diabetes had increased both amyloid and tau PET signals, decreased entorhinal and middle temporal cortical volumes, and worsened cognition (Clinical Dementia Rating [CDR] scores).[121]

In 2023, Wang and colleagues used the UKB to explore the effect size of diabetes on both AD and VaD.[122] Of 466,207 participants, 27,415 (5%) had a diagnosis of diabetes (using self-reported data; UKB data field no. 2976), 7026 had all-cause dementia, 2949 had AD (0.6%), and 1587 had VaD (0.3%). They reported a hazard ratio (HR) of 1.87 for all-cause dementia, 1.85 for AD, and 2.86 for VaD. As the mean age of UKB participants at baseline is 56.3 years (~71 years in 2023), most participants who were going to develop T2D would already have done so (mean age at onset ~45years[123]), with the converse being true for AD. In 2025, we re-explored these relationships in the UKB, with 4815 participants having a clinical diagnosis of AD and 47,377 with T2D (using ICD code [E11]-based data; UKB data field no. 130709). There was a difference in risk for all-cause dementia in midlife (<60 years) between T2D versus controls (adjusted HR, 1.14 95% confidence interval [CI] [1.02, 1.27]; $p = 0.018$) but less than previously reported from self-reported data (Figure 2). The effect disappeared for a similar late-life comparison (≥60 years; adjusted HR, 1.11, 95% CI [0.96, 1.30]; $p = 0.15$).

A meta-analysis suggested that carriers of the *APOE2* allele rather than *APOE4* were at higher risk of T2D.[124] A recent exploration of the UKB data also showed that *APOE4* carriers were at greater risk of hypercholesterolemia, ischemic heart disease and AD, but protected against obesity and T2D. Whereas *APOE2* was protective for hypercholesterolemia and ischemic heart disease[125] and neutral for T2D. AD had the largest "dose-dependent" risk effect across the different *APOE* variants in the UKB participants with a 29-fold difference between

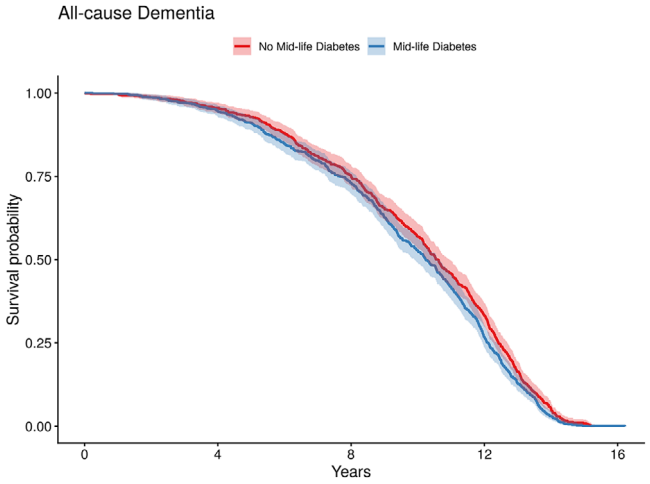

FIGURE 2 Impact of midlife diabetes on risk of dementia. A Kaplan–Meier survival curve demonstrates the relationship between all-cause dementia in UK Biobank participants with a diagnosis of diabetes during midlife (<60 years) (blue) and controls (red). A log-rank test showed that those with a history of midlife type 2 diabetes were more likely to develop dementia ($p = 0.014$). The Kaplan–Meier survival curve was generated using the survminer package, ggplot2 in R (version 4.4).

$\varepsilon 4/\varepsilon 4$s and $\varepsilon 2/\varepsilon 2$s. Similar patterns were seen with biomarkers where serum cholesterol, LDL, and white matter volume were highest for $\varepsilon 4/\varepsilon 4$s while BMI, waist circumference, and hippocampal volume were highest for $\varepsilon 2/\varepsilon 3$s. This suggests that the relationship between T2D and APOE4 is complex but that when T2D does occur in *APOE4* carriers that an additive effect meaning AD becomes highly likely. It is worth noting that the increased effect size for VaD combined with a lack of association with *APOE4* suggests that T2D is consistent with the idea that T2D influences cognition through vascular effects rather than ADNC per se.

As discussed above, AD risk genes can be grouped into three biological processes: cholesterol metabolism, endocytosis, and innate immunity. Furthermore, it has been suggested that microglial phagocytosis or efferocytosis could be a common pathogenetic hub for these three processes.[53] In contrast, there are10-fold more susceptibility loci known for T2D.[126] However, common loci between AD and T2D are surprisingly few. For example, a cross-trait analysis of GWAS data in 2019 showed almost no genome-wide correlations between the two phenotypes, other than with a combined trait of fasting insulin and fasting glucose.[127] Ghu and colleagues further suggested that the latter was likely the result of pleiotropism rather than causation. A 2025 study using an approach called "local analysis of variant association," where the authors had previously shown no global genetic correlations,[128] did find two shared causal variants between T2D and AD: HLA-DRB1 encoding a major histocompatibility class II protein complex subunit and mitochondrially encoded cytochrome C oxidase III pseudogene 1 (MTCO3P1).[129] A dual disease risk from *HLA-DRB1* is consistent with the idea of immune dysfunction in AD pathogenesis. Recently colleagues from the University of Western Australia used twin approaches called "linkage disequilibrium score regression"

analysis and "single nucleotide polymorphism (SNP) effect concordance analysis" to show that genetic overlap was greater than would be expected by chance alone (conference proceedings).[130] Their comparison of recent AD[131] and T2D[132] studies (excluding the *APOE* loci) showed significant SNP effect concordance ($p = 0.001$) and effect direction ($p = 2.67 \times 10^{-7}$). Whether pleiotropy alone could alternatively explain the T2D risk effect seems unlikely, but it does lend itself to greater exploration of genotypes including HLA-DRB1 and MTCO3P1 when considering who is at greater risk and prioritized for T2D treatments in middle age as a preventive measure.

4.2 | Finding pathomechanisms retrospectively via treatments

Deriving therapeutic targets from a comprehensive knowledge of pathomechanisms is the basis of rational drug design and prevention strategies. However, an equally valid and often more rapid strategy has been through serendipitous observations of off-label effects of drugs in trials for other conditions. This was the case with statins and cardiovascular disease treatment showing early promise against AD.[133] A current example is the glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs). Along with T2D there have been concomitant effects seen in obesity[134] and even brain diseases such as alcohol use disorder.[135] The demand for obesity treatment in those without diabetes is increasing and may surpass the intended use for T2D.[136] The mechanism of action in alcohol use disorder remains obscure, with one hypothesis suggesting an influence on the ghrelin system.[137] Along with glucose-dependent insulinotropic polypeptide (GIP), GLP-1 is an incretin hormone that stimulates insulin release after nutrient intake.[138] The effect on weight loss is thought to occur by slowing gastric emptying and promoting a feeling of satiety and via activation of GLP-1 receptor-expressing (pro-opiomelanocortin [POMC]/cocaine- and amphetamine-regulated transcript [CART]) neurons in the arcuate nucleus of the hypothalamus.[139] GLP-1RAs have been proposed to have other beneficial effects on the brain by reducing neuroinflammation, improving cognition and neuroprotection.[140] This latter has created optimism that this class of drugs may be effective, either indirectly or directly, in lowering the risk of AD,[141] and this is supported by a review of electronic health records in the United States.[142] GLP-1R activation leads to reduced tumor necrosis factor (TNF or TNF-α) via α_1-adrenergic, δ-opioid, and κ-opioid receptor signaling,[140] and all are co-expressed in the arcuate nucleus. The consensus report on modifiable risk factors in dementia also reviewed the impact of diabetic medications on dementia risk,[30] and from 27 cohort studies they concluded that AD risk (in T2D patients) was reduced by sodium-glucose cotransporter-2 (SGLT2) inhibitors, GLP-1RAs, and dipeptidyl peptidase 4 (DPP-4) inhibitors, but not metformin.[143] The mechanism of action for metformin is complex with multiple sites of action, but largely in the liver, via AMP-activated protein kinase (AMPK) to enhance insulin sensitivity and lowering cyclic adenosine monophosphate (cAMP) and gluconeogenic enzyme activity.[144] Whereas SGLT2 inhibitors have a more direct effect by increasing glucose excretion from the kidneys, DPP-4 inhibitors work by increasing GIP and GLP-1 as DPP-4 is the enzyme responsible for proteolytic degradation of these incretin hormones.[145] It is not clear whether persons with T2D might benefit from these medications, but there are currently three trials where individuals with MCI are being given metformin (Clinicaltrials.gov, NCT04098666) or GLP-1RA (NCT04777396 and NCT04777409). Having said this, the sponsor of both GLP-1RA trials recently announced that neither trial of oral semaglutide for early-stage symptomatic AD met their primary endpoints. On a positive note, they reported improvements in AD biomarkers, but not in the CDR–Sum of Boxes (CDR-SB) score that measured cognitive decline in these trials. Given the substantial evidence for benefits in T2D and obesity, these results appear to downplay the idea that controlling metabolic disease alone can slow or prevent AD.

4.3 | T2D causes peripheral and central inflammation

T2D could act peripherally, centrally, or in combination by inducing changes in the cerebrovasculature. The brain has long been considered an immune privileged site through seminal work including that of Medawar.[146] This conclusion was explained by the relative impermeability of the BBB and by a lack of lymphatics in the brain, meaning central antigen presentation was not relayed back to the immune organs to initiate an acquired immune response. It is now known that lymphatics are present in the meninges[147] and that a lymphatic-like, paravascular pathway does exist in the brain called the glymphatics.[148] Therefore, partial immune privileged is perhaps a better way to conceive how the brain interacts with the periphery.[149] The major component of the BBB are tight junctions between the endothelial cells. These sit on a basement membrane and are adjacent to the perivascular space on the arterial side of the cerebrovasculature. This space is separated from the parenchyma by the glial limitans made up of the endfeet of astrocytes sitting on their own basement membrane. It is commonplace for T cells, B cells, and peripheral macrophages to transit through the perivascular space and potentially communicate with brain cells via ligand-receptor crosstalk.[150] Astrocytes as gatekeepers to the parenchyma are dynamically involved in preventing peripheral immune cells from crossing into the brain parenchyma.[151] Peripheral immune cells, with sufficient stimuli, can produce proteases that break down endfeet connections with their basement membrane, allowing their diapedesis. As observed in the early work of Medawar, this is more likely when the immune system has been inoculated with, or exposed to, that same foreign antigen.[146]

T2D causes local toxicity via intracellular oxidative stress and dyslipidemia that result in vascular damage.[152] In AD, ischemic changes can lead to increased Aβ production,[153] while BBB dysfunction reduces Aβ clearance. Cerebrovascular endothelial cells, in response to injury, can also induce astrocyte reactivity directly,[154] and this presumably has follow-on effects to other brain cells. Astrocytes themselves may be functionally impaired by soluble Aβ,[155] while Aβ is also known to promote oxidative stress, so there may be a dual hit to the BBB. The

reverse also appears to be true, as AD mouse models show that vascular damage has an additive effect on plaque formation.[156] CAA also needs to be considered when assessing cerebrovascular dynamics during AD. T2D exacerbates CAA,[157] and metformin can reverse the latter effect[158] through the production of insulin degrading enzyme (IDE). IDE is one of several proteases that degrade Aβ in the brain,[159,160] and competition for the enzyme has been suggested as a mechanism by which hyperinsulinemia leads to Aβ accumulation in the brain.[161]

As an aside, the BBB as a bidirectionally semipermeable barrier has implications for both therapeutic delivery and peripherally monitoring the severity of brain diseases like AD. Non-invasive techniques such as PET imaging and CSF biomarkers are advancing AD diagnosis, but plasma biomarkers, including phosphorylated tau 217 (p-tau217), are particularly enticing because of their general accessibility.[162] As discussed in the introduction, glial damage markers (e.g., GFAP) can identify high-risk individuals before any symptomology.[16–18] GFAP and YKL-40 are likely to reflect the state of neuroinflammation providing an adjunctive marker of disease severity (cognitive decline) along with p-tau181 and the A$\beta_{1\text{-}42}$:A$\beta_{1\text{-}40}$ ratio[163,164] or a non-invasive means for monitoring potential immunomodulatory treatments (e.g., microglial TREM2–APOE signaling activation to increase Aβ phagocytosis) or the successful engagement by anti-amyloid or anti-tau antibodies.[165] Furthermore, in T2D patients, increases in GFAP and NfL over time, but not the A$\beta_{1\text{-}42}$:A$\beta_{1\text{-}40}$ ratio or p-tau181, were recently shown to predict cognitive decline, suggesting that neuroinflammation, either primary or subsequent to peripheral inflammation, may be the bridge between T2D and AD.[166] Future research that employs "neuroinflammation" markers like GFAP and YKL-40 comparing cognitive decline in pre-symptomatic subjects or MCI with or without T2D would be very instructive for clarifying this area.

Another possibility for how chronic peripheral inflammation in T2D promotes central inflammation is crosstalk between perivascular macrophages (PVMs) and microglia. A seminal study in 2018 suggested that immune tolerance of microglia can be achieved via peripherally applied stimuli.[167] Recently it was also shown that PVMs express osteopontin (OPN; encoded by the gene *SPP1*) that stimulate microglia to upregulate phagocytosis in the presence of Aβ oligomers.[168] OPN expression is a key characteristic marker of those microglial subsets involved in the maintaining brain tissue integrity.[169] Our recent crosstalk analysis of single-cell data from *post mortem* brain samples suggests that SPP1 may be part of the TREM2–APOE network.[170] As a microglial surface receptor, TREM2 senses damaged myelin[171] and APOE-bound Aβ.[172] Our work suggests that it also binds neuronally derived ligands such as semaphorin 6D (SEMA6D) that might be expressed by neurons stressed due to their proximity to Aβ plaques. The network regulates physiological phagocytic responses, including synaptic pruning in the embryological brain and myelin turnover in adulthood.[173] Ongoing synaptic stripping in the adult brain remains more controversial,[174] but constant turnover of myelin seems essential for normal adult brain function (and plasticity).

The preceding discussion considers several possibilities whereby T2D could modify the risk of AD, including by directly promoting ADNC or by promoting the vascular changes that accompany almost all late-onset forms of AD. It could even be that T2D is one of many comorbidities seen in aged individuals that results in cognitive frailty.[175] It is also possible that it operates through multiple mechanisms, with heterogeneity in relative importance of each seen among AD patients. Treatment with T2D drugs could serendipitously reduce or slow the onset of AD, but a more comprehensive understanding of pathomechanisms may lead to more nuanced treatment options. Our approach to gaining a better understanding of the role of T2D in promoting AD has been through interrogating transcriptomic data with systems biology approaches. In the next section of the review, we look at bulk tissue and single-cell RNAseq data from *post mortem* brain tissue along with crosstalk analysis of the latter to see whether a particular hypothesis is supported.

5 | EXPLORING HUMAN *post mortem* BRAIN DATA

5.1 | Bulk tissue RNA sequencing

We predicted that comparisons of *post mortem* tissues from different regions of the AD brain with different levels of plaques and NFTs would reveal that Aβ- or tau-dependent gene expression patterns could be derived directly in the human brain.[176] We hypothesized that expression of tau-related proteins would be higher in the precuneus with its ~2.5 times increased tau load compared to the primary visual cortex and that insulin signaling pathway components would be downregulated.[117] Our results showed that the insulin/insulin-like growth factor (IGF1) signaling pathway was largely unaffected except for a marginal increase in *IGF1*. The bulk tissue RNAseq data were generated from cases and controls without a history of T2D, but in a follow-up digital PCR study of the original RNAseq work, we looked at 26 AD cases and 22 controls that included three controls and one case with T2D. Here, *INSR* and *IGF1R* were higher in both regions in AD brains with *IGF1R* transcripts correlated with NFT-positive neurons.

We recently re-analyzed our 2021 study data using an updated bioinformatics workflow, incorporating newer versions of quality control, alignment, and quantification tools, including using *Salmon* for transcript quantification (see data availability statement for more details).

In more severely affected precunei, there were 52 differentially expressed genes (DEGs) (false discovery rate [FDR] < 0.05) with the highest ranked pathways being "neurotransmitter secretion" and "signal release from synapse" (see Supplementary File 1 for a full list of DEGs and affected Gene Ontology Biological Pathways (GO-BP); scripts are available at: https://github.sydney.edu.au/Sydney-Brainomics/T2D-AD-REVIEW). In terms of the various T2D hypotheses, *IGF1R* was upregulated, but no other components of the insulin signaling pathway were among the DEGs. The increase in insulin/IGF1 signaling was unexpected and seemingly incongruent with the idea of AD being type 3 diabetes.

5.2 | Validation of bulk tissue RNAseq

For validation of our re-analyzed bulk tissue RNAseq results, we turned to the ROSMAP study, the largest neuropathologically confirmed study of aged brains in the world, with ~500 participants having undergone bulk tissue RNAseq[177] from their middle frontal gyrus. In a first report of these data, Mostafavi and colleagues found that most DEGs were associated with clinical dementia status rather than ADNC. They performed a variation on a typical RNAseq analysis (to derive DEGs) by initially splitting their data into gene co-expression modules and then testing the modules for their association with cognitive status and ADNC. The most prominent modules associated with cognitive decline could be generally classified as relating to the regulation of the cell cycle and chromatin modification while they prioritized two genes, *INPPL1* (encoding inositol polyphosphate phosphatase like 1) and *PLXNB1* (encoding plexin B1), that were both expressed in astrocytes and involved in insulin signaling and synaptic plasticity, respectively. A recent study confirmed the increased expression of INPPL1 in the AD brain and that this correlated with Aβ load,[178] while *INPPL1* variants have been associated with T2D.[179–181] PLXNB1 regulates the interaction between reactive astrocytes and plaques and, when increased, restricts the access of phagocytic microglia,[182] while Mostafavi and colleagues went on to analyze single-cell data from the ROSMAP study[183] to show that a reactive astrocyte subtype was upregulated by PLXNB1 (pre-print).[184]

Again, using the updated tools applied to our own bulk tissue data (see data availability statement for more details), we re-analyzed the ROSMAP data. Specifically, we compared all demented cases with ADNC (n = 315) versus resistant controls with no ADNC (n = 208), and this yielded 3939 DEGs (FDR < 0.05; 2394 upregulated, 1545 downregulated). As per the precuneus in our study, the top 10 GO-BP included "neurotransmitter secretion" and "signal release from synapse" with five of the top 10 pathways in common between the two regions (see Supplementary file 2 for a full list of DEGs and GO-BP; scripts are available at: https://github.sydney.edu.au/Sydney-Brainomics/T2D-AD-REVIEW). This suggests that the same pathogenic processes are occurring irrespective of when the brain region is affected during disease progression.

Given the size of the ROSMAP study, it was also possible to look at comparisons of cases and controls relative to their T2D status. Our comparison of controls (n = 221) and AD cases without diabetes (n = 309) resulted in 1420 DEGs and GO-BPs almost identical to the preceding full case-control comparison – the highest ranked pathway being "regulation of synaptic vesicle priming" and three out of 10 of the top pathways in common (also see Supplementary file 3 for full lists). Whereas a comparison of cases (n = 60) and controls (n = 79) with T2D resulted in far fewer DEGs (389 at FDR < 0.05), with the highest ranked GO-BPs being "response to molecule of bacterial origin" and "cortical actin cytoskeleton organization." In fact, there were only four GO-BPs in total, the other two being "lipopolysaccharide-mediated signaling pathway" and "response to lipopolysaccharide" (also see Supplementary file 4 for full lists). Lastly, as the most disparate group comparison possible, we compared controls without diabetes (n = 221) and cases with diabetes (n = 60), and this yielded 2826 DEGs (FDR < 0.05), with the highest ranked GO-BP being "cell-matrix adhesion" (also see Supplementary file 5 for full lists; the scripts for all analyses are also available at: https://github.sydney.edu.au/Sydney-Brainomics/T2D-AD-REVIEW). Actin filament-based pathways were also highly ranked here, in common with the full cohort comparison, but synaptic vesicle regulation was less prominent and there were no immune signals at all. Comparing controls with and without diabetes was not helpful in clarifying the T2D transcriptomic signature in AD because there were no DEGs. Overall, the ROSMAP data show that the non-demented brain of individuals with T2D is like demented individuals with ADNC. The difference was related to pathways associated with the immune response to pathogens. Interestingly, and as a potential window into the earliest AD changes, a comparison of controls with ADNC versus those without (135 DEGS; FDR < 0.05) had the lipid-related "regulation of ketone metabolic process," "regulation of fatty acid metabolic process," and "regulation of fatty acid oxidation" as the top ranked GO-BPs.

5.3 | The age of single-cell science

Bulk tissue RNAseq has been largely superseded by single-cell studies or, in the case of human *post mortem* (frozen) tissue, single-nucleus RNAseq (snRNAseq). Single-cell datasets are composed of a multitude of individual nuclear transcriptomes, and cluster-based algorithms are used to segregate these into cell types and then cell subtypes. Our first study with US collaborators compared the moderately affected superior parietal cortex in sporadic and ADAD cases and controls and found evidence in ADAD of deficits in "transport across the BBB" and "cytokine-mediated signaling" in astrocytes.[61] DEGs can be derived through a pseudo-bulk tissue analysis, and we found astrocytes and neurons lost functionality, while microglia had increased activity in AD. We were able to split microglia into nine different subtypes, including a pro-inflammatory subtype, characterized by high OPN expression (see below).

Microglia in AD have been shown to have both protective (early)[185] and disease-promoting roles (later), with the TREM2-APOE signaling pathway being critical in regulating these dual behaviors.[27] Disease-promoting microglia have been shown to promote neuritic Aβ plaque load[186] and link Aβ accumulation with tau hyperphosphorylation,[187] tau seeding, and spreading.[188] As discussed above, Mostafavi and colleagues have also analyzed snRNAseq data from the ROSMAP study.[183] Their findings appear to link lipid and immune pathways in AD by showing that two different lipid-associated microglia subtypes drive Aβ accumulation and mediate the effects of Aβ on the tau proteinopathy. Both subtypes expressed APOE while one had relatively high TREM2 and OPN. They used the term lipid-associated microglia to describe their relatively high expression from genes associated with increased cholesterol storage, lipid metabolism, and catabolism. Perturbations in microglial lipid homeostasis provides a potential mechanism whereby T2D and peripheral dyslipidemia, by impacting BBB permeability and

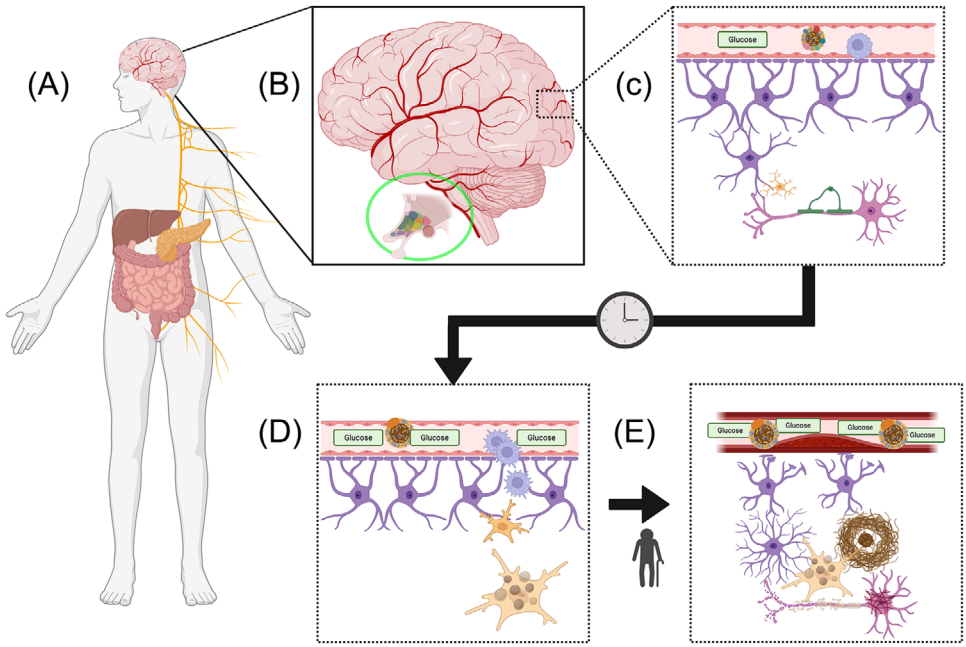

FIGURE 3 Type 2 diabetes and the increased risk of Alzheimer's disease: an intersection of inflammation and lipid anomalies. A schematic shows a proposed pathway for how type 2 diabetes (T2D) promotes Alzheimer's disease (AD). (A) The body and brain are bidirectionally connected by humoral and neural pathways. The brain–liver–gut axis is connected via the vagus nerve. The vagus sends efferents to, and receives afferents from, the viscera, including the liver (brown) and pancreas (orange). The gut microbiome works in concert with enzymes to break down carbohydrates, fats, and proteins. Excess fats and sugar, stables of Western diets, increase gut leakiness and inflammation. The gut also releases peptides such as ghrelin and GLP-1 that control appetite and insulin secretion. Nutrients reach the liver via the hepatic portal vein, where they are stored or modified. Excess sugar and fats from the gut can exceed liver capacity, causing fat accumulation and steatitis. The pancreas secretes insulin in response to the post-prandial hyperglycemia, but chronic hyperglycemia results in insulin resistance in insulin-sensitive organs, such as the liver and muscle, and over time the loss of beta cells and T2D. (B) The brain monitors the gut via the vagus nerve and via the bloodstream. The brain is surrounded by a blood–brain barrier (BBB), which is impermeable to most molecules, unless they are small. Glucose is transported across the BBB via GLUT1 receptors in the endothelial cells, which are not insulin sensitive. There are also areas of the brain, around the third ventricle, called circumventricular organs. Here the BBB is more permeable, allowing adjacent neurons to detect nutrients, electrolyte hormones, chemokines, and cytokines in the blood and cerebrospinal fluid (CSF). These neurons connect to the visceral regulatory centers, including the hypothalamus and onto the hypothalamus pituitary axis (HPA) (green circle). The HPA becomes hyperactive in T2D, further diminishing insulin resistance and promoting inflammation. (C) Under normal conditions, glucose uptake occurs across a concentration gradient. The brain uses 70% of glucose produced and 20% of oxygen, although it is only 2% of body mass. Glucose and oxygen use is highly correlated with brain activity through a process called neurovascular coupling. The key cells involved in regulating this process are astrocytes, which have their endfeet connected to blood vessels and to synapses. Astrocyte endfeet are tightly bound together, forming the inner part of the BBB. On the arterial side of the brain, the two parts of the BBB are separated by a perivascular space where immune cells like macrophages (gray) interact with the cells in the parenchyma. Astrocytes (purple) communicate among themselves but also with other brain cells, including microglia, neurons, and oligodendrocytes. Microglia (yellow) are the brain's macrophages, which constantly survey their territory monitoring brain function and potential injury. Oligodendrocyte (green) processes are filled with a special lipid substance called myelin that wraps around neurons, providing insulation that greatly increases conduction speed of action potentials. (D) T2D is characterized by excess serum glucose and bad (low-density lipoprotein [LDL]) cholesterol. Hyperglycemia and hyperlipidemia cause widespread inflammation, including in the cerebrovascular endothelium. This promotes BBB leakiness with inflammatory mediators and even immune cells moving more freely into the parenchyma. Perivascular macrophages can also signal directly to microglia and induce activated states. These external stimuli promote disease-associated microglia characterized by lipid droplet formation that display reduced Aβ phagocytosis. (E) Over time, T2D with excess glucose, LDL cholesterol, toxic lipids like ceramide, inflammatory mediators, and immune cells leads to chronic peripheral and BBB leakiness, shifting microglia toward an inflammatory phenotype. The prolonged neuroinflammatory milieu perturbs neuron and glial functions including maintenance of synapses and myelin and Aβ plaque removal. The neurons specifically respond with upregulation of their stress machinery, but this becomes dysregulated over the decades where, among other changes, kinase and phosphatase activity becomes unbalanced. One protein, called tau, when abnormally hyperphosphorylated, is highly prone to self-aggregation and forms fibrillar structures called neurofibrillary tangles (NFTs) in the soma of the neurons. These NFTs eventually "strangle" the neurons, leading to their death. Neuron loss in areas like the hippocampus results in the early amnestic symptoms of AD. T2D also leads to atherosclerosis and microangiopathy in the cerebrovasculature, which, in combination with AD neuropathologic change, causes dementia. Created in BioRender.

inducing peripheral-central immune cell-aberrant signaling, could increase AD risk.[183]

snRNAseq still lacks spatial context, but this issue has been resolved with the development of spatially resolved transcriptomics (SRT) or just spatial transcriptomics (ST).[189] This is essentially a combination of histology and ST where the expression of cells and cell subtypes can be derived relative to their proximity to hallmark pathologies like plaques and NFTs. Chen and colleagues were the first to employ ST using frozen *post mortem* tissue from the middle temporal gyrus of AD brains.[190] They found using the first-generation Visium platform (standard) that three novel DEGs (e.g., *KIF5A*, *PAQR6*, and *SLC1A3* encoding kinesin family member 5A, progestin and adipoQ receptor family member 6, and solute carrier family 1 member 3, respectively). The latter is also known as EAAT1 and, along with EAAT2, is responsible for astrocytes' removal of glutamate from the synaptic cleft). There were also 11 previously reported DEGs associated with AD pathology.

6 | CONCLUSION

T2D is one of 14 known modifiable risk factors that promote late-onset dementia. As most dementia cases are AD, or at least ADNC is responsible for most of the cognitive decline in dementia, it is likely that T2D promotes ADNC per se, notwithstanding additional effects via cerebrovascular damage. We had previously suggested that T2D may specifically promote tau pathology, although the mechanism was unknown.[32] We further hypothesized that this might be because of central IR, where the expression of kinases like GSK3β are increased, resulting in the hyperphosphorylation of tau. However, our bulk tissue RNAseq work suggested that insulin/IGF1 signaling was upregulated in the AD brain rather than downregulated, as might be expected if AD were type 3 diabetes.[117] Bulk tissue RNAseq has been superseded by snRNAseq, and this has uncovered at least 16 types of microglia across different disease states.[183] In AD, such work is increasingly pointing to lipid dysmetabolism in disease-associated subtypes that show reduced Aβ phagocytosis while promoting tau pathology by subjecting adjacent neurons to their chronic inflammatory milieu. The microglial TREM2–APOE signaling network appears to be a pathogenetic hub in this process (see Figure 3 for an overview of how T2D is predicted to modify AD risk). For example, T2D is characterized by peripheral lipid dysmetabolism and lipotoxicity that can lead to inflammation, insulin resistance, oxidative stress, ceramide and amyloid accumulation, endoplasmic reticulum stress, ferroptosis, and autophagy. T2D could promote AD through this toxic nutrient profile, causing vascular damage and BBB leakage, or through peripheral priming of microglia to these disease-associated states. It may well be a combination of all three, and work continues to try and isolate the actual mechanism.

Another important consideration is that all these pathological events seen peripherally with T2D are also happening centrally in AD.[191] For example, there is a body of evidence linking T2D and AD through pathological lipid pathways where ceramide is a hypothesized key bioactive metabolic mediator, providing a rationale for targeting ceramide metabolism to prevent or treat T2D and AD.[192] Whether T2D promotes AD directly through central effects or indirectly via peripheral inflammation, or both, it does appear that lipid dyshomeostasis, manifesting as excess lipid droplets in microglial subtypes, has probably displaced central IR as the most likely pathomechanism. This same mechanism may also explain the potent effect of *APOE4* on AD risk.[57] Given work has already shown that microglial lipid accumulation reduces Aβ load in an AD mouse model,[59] there is reason for optimism that attenuating lipid anomalies in microglia could prove an important therapeutic avenue for AD. In terms of therapeutic avenues, upregulating TREM2–APOE signaling looks particularly promising for reversing microglial anomalies. A monoclonal antibody designed to activate TREM2 and microglial phagocytosis, AL002 (Alector; NCT04592874), has progressed to Phase II trials.[193] However, it failed to meet its primary endpoints for patients with MCI or mild AD, which may reflect the current treatment regime or a narrower than predicted therapeutic window due to the supposed dual role for microglia in early versus late AD[27] or because TREM2's regulatory role in microglial dynamics is complex.[194] Other monoclonal antibodies are undergoing preclinical work, such as CGX101, with or without a transferrin receptor binding site,[195,196] so this is a rapidly developing area. In the meantime, it will be very interesting to see whether strategies that reduce T2D risk, such as intermittent fasting,[104] with peripheral and central roles can have an additional impact on reducing the prevalence of AD, although the early reports from GLP1-RA trials in early AD have been disappointing.

ACKNOWLEDGMENTS

The authors would like to thank all the donors and their families for their kind gift, which has made this review possible. This work was funded by the kind support of the Lucas' Papaw Foundation. We would like to acknowledge all the participants involved in the ROSMAP study and the Rush Alzheimer's Disease Center for making the data available. Study data were provided by the Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago under Project # 5031 ("The role of vascular factors in the pathogenesis of Alzheimer's disease"). The ROSMAP bulk brain RNA-seq counts were concurrently obtained from the AMP-AD Knowledge Portal, as part of the *RNAseq Harmonization Study*; Synapse: syn21241740. Access to both data followed the implementation of data use agreements between the PI institution's (University of Sydney) and Rush University Medical Center (RUMC) and Sage Bionetworks (Synapse). UK Biobank data was explored using the UK Biobank Resource under Application Number 49777. This work was funded by the Lucas Papaw Foundation (GS).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

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How to cite this article: Sutherland GT, Chen A, Nguyen-Hao H-T, et al. How does type 2 diabetes modify the risk of Alzheimer's disease?. *Alzheimer's Dement*. 2026;22:e71471. https://doi.org/10.1002/alz.71471