Provide a comprehensive narrative review of the bidirectional relationship and shared pathophysiological mechanisms between type 2 diabetes, central insulin resistance, and the development of Alzheimer's disease or vascular dementia.

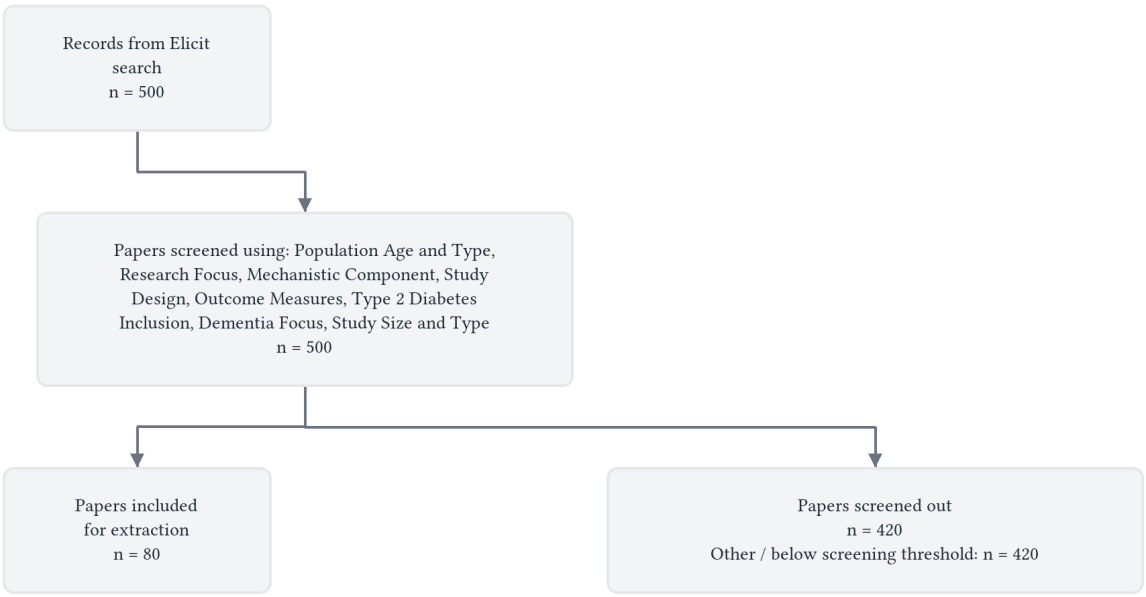
Type 2 diabetes and Alzheimer's disease are linked by a genuine bidirectional relationship in which peripheral insulin resistance elevates dementia risk primarily through cerebrovascular pathology and a convergent brain insulin resistance state (”type 3 diabetes”), sharing core mechanisms of impaired PI3K/Akt-GSK-3β signaling, neuroinflammation, oxidative stress, mitochondrial dysfunction, amyloid-β and tau dysregulation, and blood-brain barrier breakdown—with the relationship strongest for vascular dementia, substantially amplified by ApoE ε4 status, and most amenable to intervention during the midlife preclinical window before a self-perpetuating feedforward loop between Aβ toxicity and insulin resistance becomes established.

Abstract

Type 2 diabetes mellitus (T2DM) consistently elevates the risk of both Alzheimer's disease (AD) and vascular dementia, with a pooled adjusted risk ratio of 1.57 (95% CI: 1.41–1.75) for AD [1] and relative risk increases of approximately 2.3–2.5 for vascular dementia [2, 3]. The relationship is bidirectional: AD pathology independently promotes brain insulin resistance and impairs peripheral glycemic control through hypothalamic dysfunction and hepatic insulin receptor downregulation [4, 5], while over 80% of AD patients exhibit T2DM or abnormal serum glucose [6]. The shared pathophysiological architecture linking these conditions is extensive and multi-layered. Disrupted insulin signaling—operating through the PI3K/Akt and MAPK pathways, with overactivation of GSK-3β—drives both amyloid-β accumulation and tau hyperphosphorylation [6, 7], and the concept of ”type 3 diabetes” captures the observation that AD brains exhibit a state of intrinsic insulin deficiency and resistance that can arise either downstream of peripheral T2DM or through independent neurodegeneration [8, 9]. Additional shared mechanisms include neuroinflammation mediated by TNF-α and JNK-dependent IRS-1 serine phosphorylation [10], mitochondrial dysfunction and oxidative stress [11, 12], advanced glycation end products acting through RAGE [13], amylin cross-seeding with Aβ [14], and blood-brain barrier breakdown driven by hyperglycemia [15].

Despite the strength of the epidemiological signal, neuropathological studies do not consistently show that T2DM increases the cerebral burden of prototypical AD lesions [2]; rather, T2DM appears to lower the pathological threshold for clinical dementia primarily through cerebrovascular disease, such that existing amyloid and tau pathology becomes clinically manifest at lower burden when vascular injury is present [1, 16]. The ApoE ε4 allele substantially modifies the relationship, strengthening the T2DM–AD association and attenuating responses to insulin-based therapies [1, 17]. Therapeutic exploitation of shared mechanisms—particularly through GLP-1 receptor agonists, intranasal insulin, and thiazolidinediones—shows preclinical promise and early clinical signals, but trial results in established AD have been inconsistent [3, 17], consistent with the evidence that brain insulin resistance becomes self-perpetuating via a positive feedback loop between Aβ toxicity and impaired insulin signaling once neurodegeneration is advanced [9]. Prevention strategies targeting midlife metabolic risk, before this loop is established, are therefore likely to offer greater benefit than treatment of symptomatic disease [18, 19].

Flow Diagram



Paper search

We performed a semantic search across over 138 million academic papers from the Elicit search engine, which includes all of Semantic Scholar and OpenAlex.

We ran this query: "Provide a comprehensive narrative review of the bidirectional relationship and shared pathophysiological mechanisms between type 2 diabetes, central insulin resistance, and the development of Alzheimer's disease or vascular dementia."

The search returned 500 total results from Elicit.

We retrieved 500 papers most relevant to the query for screening.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population Age and Type**: Does the study involve human adults (≥18 years) with type 2 diabetes, central insulin resistance, Alzheimer's disease, or vascular dementia?
- **Research Focus**: Does the study investigate the relationship between type 2 diabetes/central insulin resistance and Alzheimer's disease or vascular dementia?
- **Mechanistic Component**: Does the study explore shared pathophysiological mechanisms, molecular pathways, or biological processes linking diabetes and dementia?

- **Study Design**: Is the study design one of the following: systematic review, meta-analysis, randomized controlled trial, cohort study, case-control study, cross-sectional study, or mechanistic/experimental study?
- **Outcome Measures**: Does the study report cognitive outcomes, dementia incidence, neuroimaging findings, biomarkers, or mechanistic endpoints related to neurodegeneration?
- **Type 2 Diabetes Inclusion**: Does the study include type 2 diabetes components (i.e., is it NOT exclusively focused on type 1 diabetes only)?
- **Dementia Focus**: Does the study examine Alzheimer's disease or vascular dementia (i.e., is it NOT focused solely on mild cognitive impairment, depression, or other non-dementia cognitive conditions)?
- **Study Size and Type**: Is the study NOT an individual case report or small case series with fewer than 10 participants?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

At abstract screening, the number of papers excluded for each primary reason was:

- **Other / below screening threshold**: n = 420

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Study Type**:

  Extract the type of evidence provided for the relationship between type 2 diabetes, central insulin resistance, and dementia, including:

- Epidemiological (cohort, case-control, cross-sectional)
- Clinical (intervention trials, observational studies)
- Preclinical/translational (animal models, cell culture)
- Mechanistic/molecular studies
- Narrative/systematic reviews
- Mixed methods approaches

- **Bidirectional Relationships**:

  Extract evidence for bidirectional relationships between type 2 diabetes and dementia (AD/vascular dementia), including:

- T2D $\longrightarrow$ dementia development (risk ratios, hazard ratios, effect sizes)
- Dementia $\longrightarrow$ T2D development or worsening glycemic control
- Strength and direction of associations
- Temporal relationships
- Population characteristics where relationships were observed
- Any evidence contradicting bidirectional relationships

- **Shared Pathophysiology**:

  Extract all shared pathophysiological mechanisms between type 2 diabetes and Alzheimer's disease/vascular dementia, including:

- Insulin signaling dysfunction (peripheral and central)

- Protein misfolding and aggregation (amyloid, tau, amylin)
- Neuroinflammation and cytokine pathways
- Oxidative stress and mitochondrial dysfunction
- Advanced glycation end products (AGEs)
- Vascular pathology and cerebrovascular disease
- Growth factor signaling (IGF, TGF)
- Apoptosis and cell death pathways
- Metabolic dysfunction
- Any other mechanistic overlaps identified

- **Brain Insulin Resistance**:

  Extract specific mechanisms of central/brain insulin resistance in the context of dementia development, including:

- Brain insulin receptor dysfunction
- Insulin transport across blood-brain barrier
- CNS glucose metabolism alterations
- Brain insulin signaling pathway disruptions (PI3K, MAPK, etc.)
- Regional brain differences in insulin sensitivity
- Relationship to 'type 3 diabetes' concept
- Neuronal vs glial insulin resistance
- Impact on memory and cognitive function

- **Dementia Subtypes**:

  Identify which dementia types are addressed and their specific relationships to diabetes/insulin resistance:

- Alzheimer's disease specifically
- Vascular dementia specifically
- Mixed dementia
- Other dementia types
- Whether mechanisms differ between AD and vascular dementia
- Cognitive domains affected (memory, executive function, etc.)

- **Key Findings**:

  Extract the main conclusions about the diabetes-dementia relationship and shared mechanisms, including:

- Novel mechanistic insights discovered
- Strength of evidence for each proposed mechanism
- Clinical implications of the relationships
- Gaps in current understanding identified
- Consistency with other research
- Population-specific findings
- Temporal aspects of disease development

- **Therapeutic Implications**:

  Extract any therapeutic approaches or implications arising from the diabetes-dementia relationship, including:

- Antidiabetic medications tested for dementia (insulin, metformin, etc.)

- Insulin sensitizers in AD treatment
- Lifestyle interventions targeting both conditions
- Prevention strategies based on shared mechanisms
- Drug repurposing opportunities
- Biomarkers for early detection
- Treatment targets identified from mechanistic studies

Results

Characteristics of Included Studies

The 80 sources included in this review span publication years from 2004 to 2026, with the majority published between 2014 and 2025. All are review articles rather than primary empirical studies; the predominant design is narrative or systematic review, with several sources explicitly synthesizing epidemiological, clinical, preclinical, and mechanistic evidence. One source (Vagelatos & Eslick, 2013) is a formal meta-analysis embedded within a systematic review [1], and one (Atabi et al., 2025) reports a PRISMA-guided systematic review incorporating 213 peer-reviewed articles [20]. The remainder are narrative reviews of varying scope, some drawing exclusively on mechanistic and molecular literature [21, 22], others integrating epidemiological cohort data with translational findings [3, 7, 23, 24]. Full texts were available for the majority of sources; abstracts only were available for a subset, as noted in the table below.

Study	Full Text Retrieved?	Study Type	Primary Focus
N. Vagelatos & G. Eslick, 2013 [1]	No (abstract only)	Systematic review and meta-analysis	T2D as risk factor for AD; cerebrovascular confounders
Shreyasi Chatterjee & A. Mudher, 2018 [25]	Yes	Narrative review	Shared pathological traits: insulin resistance, Aβ, tau, autophagy
M. Michailidis et al., 2022 [26]	Yes	Narrative review	AD as type 3 diabetes; disrupted insulin signaling
Milagros Rojas et al., 2021 [27]	Yes	Narrative review	Pathophysiological and pharmacotherapeutic links; antidiabetic drugs in AD
Xiaohua Li et al., 2015 [28]	No (abstract only)	Narrative review	Epidemiology, mechanisms, and clinical trials of antidiabetic agents in AD
Lin Li & C. Hölscher, 2007 [23]	Yes	Narrative review	Common molecular processes in AD and T2D
Rim Hamzé et al., 2022 [29]	Yes	Narrative review	Molecular links; GSK3β and DYRK1A as shared therapeutic targets

Study	Full Text Retrieved?	Study Type	Primary Focus
Jessica Lynn et al., 2021 [30]	No (abstract only)	Narrative review	Shared mechanisms linking T2D and AD; active clinical trials
Omar Yaxmehen Bello-Chavolla et al., 2019 [3]	Yes	Narrative review	Epidemiological, clinical, and preclinical pathophysiological links
S. Arnold et al., 2018 [31]	Yes	Narrative review	Brain insulin resistance; concepts and conundrums
J. Luchsinger & D. Gustafson, 2009 [32]	No (abstract only)	Narrative review	Adiposity, T2D, and AD epidemiology
Sima Kianpour Rad et al., 2018 [21]	No (abstract only)	Narrative review	Insulin signaling kinases linking T2D and AD
F. D. De Felice & S. Ferreira, 2014 [10]	Yes	Narrative review	Inflammation, defective insulin signaling, mitochondrial dysfunction
S. M. de la Monte & J. Wands, 2005 [33]	Yes	Narrative review	Insulin and IGF signaling in the CNS and AD
B. Neth & S. Craft, 2017 [18]	Yes	Narrative review	Insulin resistance and AD: bioenergetic linkages
Inês Sebastião et al., 2014 [34]	Yes	Narrative review	Insulin as a bridge between T2D and AD; antidiabetic drugs
G. Verdile et al., 2015 [35]	No (abstract only)	Narrative review	Role of T2D in neurodegeneration; clinical and experimental evidence
D. A. Butterfield et al., 2014 [12]	Yes	Narrative review	Oxidative stress as a key link between T2D and AD
S. M. de la Monte & J. Wands, 2008 [8]	Yes	Narrative review	AD as type 3 diabetes; evidence reviewed
S. Pugazhenthi et al., 2017 [36]	No (abstract only)	Narrative review	Common neurodegenerative pathways in obesity, diabetes, and AD
Ricardo Augusto Leoni de Sousa et al., 2020 [37]	No (abstract only)	Narrative review	IRS-1/IRS-2 distinctions; update on T2D–AD links
Mayuren Candasamy et al., 2020 [38]	No (abstract only)	Narrative review	AD as type 3 diabetes; therapeutic avenues
Ahmad Raza et al., 2025 [15]	Yes	Narrative review	Hyperglycemia, oxidative stress, BBB breakdown in T2D-driven AD
Zenghui Wei et al., 2021 [6]	Yes	Narrative review	Multiple mechanisms by which insulin resistance exacerbates AD

Study	Full Text Retrieved?	Study Type	Primary Focus
Vanita Rani et al., 2016 [39]	No (abstract only)	Narrative review	AD as brain-specific diabetic condition
Fengqin Xu & Jingshan Shi, 2025 [40]	No (abstract only)	Narrative review	Insulin signaling and oxidative stress bridging T2D and AD
A. M. de Matos et al., 2018 [41]	No (abstract only)	Narrative review	Therapeutic and preventive molecules targeting overlapping mechanisms
E. Barone et al., 2021 [42]	No (abstract only)	Narrative review	Oxidative stress, brain insulin resistance, and AMPK dysfunction
M. Kamal et al., 2014 [43]	Yes	Narrative review	Aberrant insulin signaling and inflammation linking AD and T2D
Aniket Kakkar et al., 2026 [44]	No (abstract only)	Narrative review	Mechanistic insights into the diabetes–Alzheimer's nexus
M. Potenza et al., 2021 [45]	Yes	Narrative review	Mitochondrial dysfunction as a common path
Viplav Kshirsagar et al., 2020 [46]	No (abstract only)	Narrative review	Insulin resistance as a connecting link; miRNA, leptin, gangliosides
F. Alam et al., 2016 [47]	No (abstract only)	Narrative review	Bridging pathophysiology and management of T2D and AD
K. Akter et al., 2011 [48]	Yes	Narrative review	Shared pathology and treatment; clinical trials
Jonathan Chang-Cheng Shieh et al., 2020 [49]	No (abstract only)	Narrative review	Insulin signaling and AGEs linking T2D and AD
Bhumsoo Kim & E. Feldman, 2015 [50]	Yes	Narrative review	Insulin resistance as key link in metabolic syndrome and AD
A. Jayaraman & C. Pike, 2014 [51]	Yes	Narrative review	Multiple mechanisms; ApoE and testosterone as modifiers
Maria Isabel Gomez-Coral, 2024 [52]	Yes	Narrative review	Impact of T2DM on AD development
Manthan Suthar & A. Korobova, 2026 [53]	No (abstract only)	Narrative review	Insulin resistance to neurodegeneration; type 3 diabetes

Study	Full Text Retrieved?	Study Type	Primary Focus
Vishvas N. Patel et al., 2022 [13]	Yes	Narrative review	Emerging pathophysiological mechanisms; an updated overview
P. Bharadwaj et al., 2017 [14]	No (abstract only)	Narrative review	Roles of Aβ, amylin, and tau linking T2D and AD
C. Caruso et al., 2012 [54]	No (abstract only)	Narrative review	Insulin action and AD; cognitive implications
Elena Ribe & Simon Lovestone, 2016 [7]	Yes	Narrative review	Insulin signaling in AD and diabetes: epidemiology to molecular links
J. Zemva & M. Schubert, 2011 [55]	No (abstract only)	Narrative review	Central insulin and IGF-1 signaling; diabetes-associated dementia
M. Lanna et al., 2014 [56]	No (abstract only)	Narrative review	Interactive role of insulin and Aβ peptide in AD
S. Rosenzweig, 2020 [57]	No (abstract only)	Faculty Opinion/Narrative review	Brain insulin resistance in T2D and AD
J. Luchsinger, 2010 [58]	No (abstract only)	Narrative review	T2D and related conditions in relation to dementia; prevention opportunity
Evelyn B. Lazar et al., 2021 [59]	No (abstract only)	Narrative review	Gut dysbiosis, insulin resistance, and AD
J. Folch et al., 2018 [4]	Yes	Narrative review	Brain insulin receptor in late-onset AD
S. De La Monte, 2017 [60]	No (abstract only)	Narrative review	Insulin resistance and neurodegeneration; new therapeutics for AD
C. Carlsson, 2010 [19]	No (abstract only)	Narrative review	T2DM, dyslipidemia, and AD
S. De La Monte, 2012 [9]	Yes	Narrative review	Brain insulin resistance and deficiency in amyloid-related neurodegeneration
Arantxa Rodríguez-Casado et al., 2025 [61]	No (abstract only)	Systematic/critical review	Cellular and molecular common pathogenic mechanisms in T2D–AD
Gauri Desai et al., 2014 [62]	No (abstract only)	Narrative review	Pancreas–brain axis; disrupted mechanisms linking T2D and AD

Study	Full Text Retrieved?	Study Type	Primary Focus
M. Yarchoan & S. Arnold, 2014 [63]	Yes	Narrative review	Repurposing diabetes drugs for brain insulin resistance in AD
G. Biessels & F. Despa, 2018 [2]	Yes	Narrative review	Cognitive decline and dementia in diabetes; mechanisms and clinical implications
C. Benedict & C. Grillo, 2018 [17]	Yes	Narrative review	Insulin resistance as therapeutic target in AD
Antoniya Hachmeriyan et al., 2025 [64]	Yes	Narrative review	Insulin resistance as a risk factor for cognitive dysfunction
E. Rhea et al., 2023 [65]	Yes	Narrative review	Brain insulin resistance and cognitive decline in AD
C. Kahn & R. Suzuki, 2010 [66]	No (abstract only)	Narrative review	Insulin action in the brain and AD pathogenesis
Sami Gabbouj et al., 2019 [67]	Yes	Narrative review	Altered insulin signaling in AD; PI3K-Akt pathway
Rachel A. Whitmer, 2007 [68]	No (abstract only)	Narrative review	T2D and risk of cognitive impairment and dementia
Fereshteh Atabi et al., 2025 [20]	Yes	Systematic review	Type 3 diabetes: bridging metabolic dysfunction and AD
Fuzhou Wang et al., 2014 [69]	Yes	Narrative review	Vascular dysfunction linking T2D and AD
M. Nicolls, 2004 [70]	No (abstract only)	Narrative review	Clinical and biological relationship between T2DM and AD
P. Moreira et al., 2007 [11]	Yes	Narrative review	Brain mitochondrial dysfunction as a link between AD and diabetes
J. Luchsinger, 2008 [71]	Yes	Narrative review	Adiposity, hyperinsulinemia, diabetes, and AD: epidemiological perspective
L. Arab et al., 2011 [72]	Yes	Narrative review	Aberrant insulin regulation in the brain; treating diabetes for AD
M. Alsaleem et al., 2025 [73]	Yes	Narrative review	Fenofibrate and PPAR-α in T2D and AD
A. Tyagi & S. Pugazhenthi, 2021 [5]	Yes	Narrative review	Targeting insulin resistance to treat cognitive dysfunction

Study	Full Text Retrieved?	Study Type	Primary Focus
A. Cole et al., 2007 [22]	No (abstract only)	Narrative review	Molecular connexions between dementia and diabetes; GSK-3
R. Sandhir & Smriti Gupta, 2015 [74]	No (abstract only)	Narrative review	Molecular and biochemical trajectories from diabetes to AD
Haya Majid et al., 2025 [75]	No (abstract only)	Narrative review	Metabolic mechanisms linking T2DM to AD; BCAA role
Dominick Shoha et al., 2026 [76]	No (abstract only)	Narrative review	Cellular and molecular mechanisms in diabetes-associated neurodegeneration
Kubis-Kubiak Am et al., 2019 [77]	No (abstract only)	Narrative review	Crucial players in AD and diabetes; friends or foes
Ying Dai & M. Kamal, 2014 [78]	No (abstract only)	Narrative review	Fighting AD and T2DM: pathological links and treatment strategies
P. Riederer et al., 2017 [24]	Yes	Mixed-methods consensus review	Diabetic brain and cognition; AD and VaD
J. Luchsinger, 2012 [16]	No (abstract only)	Narrative review	T2D and cognitive impairment: linking mechanisms
L. Exalto et al., 2012 [79]	No (abstract only)	Narrative review	T2D, vascular dementia, and AD: update
Prita R. Asih et al., 2017 [80]	Yes	Narrative review	Multiple mechanisms linking T2D and AD; testosterone as modifier

The literature base is dominated by narrative reviews, consistent with the primarily mechanistic and epidemiological research questions addressed. The two most methodologically rigorous sources in terms of formal synthesis are the Vagelatos & Eslick (2013) meta-analysis and the Atabi et al. (2025) PRISMA-guided systematic review. The remaining sources vary substantially in their evidentiary scope: some integrate all levels of evidence from epidemiology through molecular biology [2, 3, 7], while others focus narrowly on a single mechanistic pathway such as mitochondrial dysfunction [11] or vascular biology [69]. The temporal range of the literature—from Nicolls (2004) to sources dated 2026—allows observation of how the field's conceptual framework has evolved, particularly the consolidation of the "type 3 diabetes" hypothesis [8, 9, 20].

Thematic Analysis

Theme 1: Epidemiological Evidence for the T2D–Dementia Association

The epidemiological foundation of the T2D–dementia relationship rests on a substantial body of cohort and case-control data synthesized across multiple reviews. The most quantitatively rigorous estimate comes from the Vagelatos & Eslick (2013) meta-analysis of 15 epidemiological studies encompassing 2,122,883 subjects, yielding a pooled adjusted risk ratio of 1.57 (95% CI: 1.41–1.75) for Alzheimer's disease associated with T2DM, with a population-attributable risk of 8% [1]. This figure falls within the range reported across individual sources: Michailidis et al. (2022) cite a 45–90% increased risk of dementia in T2DM [26]; Rojas et al. (2021) report a relative risk of 1.56 (95% CI: 1.41–1.73) and a hazard ratio of 2.05 (95% CI: 1.18–3.57) for incident AD in subjects with T2DM versus normal glucose tolerance [27]; and Raza et al. (2025) summarize a meta-analysis finding a 73% higher risk of dementia in individuals with T2DM [15].

The risk differential between Alzheimer's disease and vascular dementia is an important and consistent finding. Bello-Chavolla et al. (2019) report that T2DM increases risk of AD by approximately 50% (RR 1.5, 95% CI 1.2–1.8) but risk of vascular dementia by more than twofold (RR 2.5, 95% CI 2.1–3.0) [3]. Biessels & Despa (2018) similarly report risk ratios of 1.53 for AD and 2.27 for vascular dementia in diabetes [2]. Jayaraman & Pike (2014) report a 1.5-fold increase for AD and a 2.5-fold increase for vascular dementia [51], and Luchsinger (2010) notes that associations are consistently stronger for vascular dementia than for late-onset Alzheimer's disease [58]. Riederer et al. (2017) estimate a 60% greater risk for dementia overall in individuals with T2DM [24].

Early antecedent metabolic states also carry risk. Hyperinsulinemia alone—in the absence of frank T2DM—has been linked to increased AD risk in several studies synthesized by Luchsinger & Gustafson (2009) [32] and Luchsinger (2008) [71]. Li & Hölscher (2007) note that hyperinsulinemia doubles the risk of AD [23], and Akter et al. (2011) report that patients with insulin resistance showed a 30% higher likelihood of developing AD (OR = 1.3; 95% CI: 0.35–2.9), rising to an adjusted OR of 1.4 (95% CI: 1.01–2.33) after controlling for age [48]. Tyagi & Pugazhenthi (2021) synthesize evidence that having diabetes for five or more years increases dementia risk by 40–60%, and that midlife insulin resistance is an independent risk factor for later brain amyloid accumulation [5]. Diabetic patients who require insulin face roughly double the risk reported in non-insulin-requiring diabetics, with Patel et al. (2022) summarizing evidence that dementia risk is doubled in T2DM and quadrupled in insulin-dependent patients [13].

A number of genetic and comorbid factors modulate these associations. The ApoE ε4 allele represents the most consistently documented modifier: Vagelatos & Eslick (2013) found that the pooled adjusted risk ratio for the T2DM–ApoE ε4 interaction reached 2.91 (95% CI: 1.51–5.61) for AD risk, with individual studies reporting odds ranging from 2.4 to 4.99 [1]. Smoking comorbid with T2DM was associated with odds of 14, and hypertension comorbid with T2DM with odds of 3 for AD [1]. Jayaraman & Pike (2014) additionally identify low testosterone as an independent AD risk factor that may cooperatively regulate pathological interactions between T2DM and dementia [51].

Theme 2: Bidirectional Relationships

The relationship between T2DM and dementia is increasingly characterized as bidirectional, though the evidence is stronger and more consistent for the T2D → dementia direction than for the reverse. In the T2D → AD direction, the epidemiological and mechanistic literature reviewed above converges on a genuine risk elevation. The reverse direction—whereby AD pathology worsens glycemic control and potentially promotes peripheral insulin resistance—is supported by a smaller but mechanistically coherent body of evidence. De la Monte & Wands (2008) argue that T2DM's aggregate effects fall short of mimicking AD but that AD-type pathology produces brain insulin resistance independently of peripheral metabolic disease [8]. De la Monte (2012) explicitly describes a positive feedback loop in which insulin resistance drives amyloid-β accumulation and amyloid-β fibril toxicity in turn drives brain insulin

resistance, potentially explaining why anti-Aβ monotherapy clinical trials have been disappointing [9].

Several sources report that Aβ and hyperphosphorylated tau—the cardinal neuropathological hallmarks of AD—may contribute to pancreatic β-cell dysfunction and reduce insulin sensitivity in peripheral tissues, thereby promoting T2DM [14]. Folch et al. (2018) describe evidence that Aβ42 generated in the brain can impact the hypothalamus, inducing peripheral hyperglycemia through downregulation of the hepatic insulin receptor [4]. Xu & Jingshan Shi (2025) summarize the bidirectional relationship explicitly: T2DM elevates AD risk and AD exacerbates glucose metabolism abnormalities in T2DM [40]. Wei et al. (2021) note that over 80% of AD patients have T2DM or abnormal serum glucose, and that insulin resistance accelerates AD progression while AD exacerbates insulin resistance [6]. Alsaleem et al. (2025) similarly note that T2DM patients have a 50–75% chance of developing AD, while AD neuropathology accelerates peripheral insulin resistance and T2D progression [73].

There are nonetheless important qualifications. Biessels & Despa (2018) make the critical neuropathological observation that while T2DM increases the risk of clinically diagnosed AD and vascular dementia, it does not increase the cerebral burden of prototypical AD pathologies—neurofibrillary tangles and neuritic plaques—suggesting that the elevated dementia risk in T2DM is mediated substantially by non-amyloid mechanisms [2]. Luchsinger (2012) reaches a similar conclusion from autopsy data, finding that the association between T2DM and vascular cognitive impairment is robust but the causal link to late-onset Alzheimer's disease remains contested [16]. Arab et al. (2011) note that postmortem studies of diabetic brains often demonstrate decreased rather than increased AD pathology, a finding that appears contradictory to the epidemiological risk elevation but may reflect competing pathological processes [72].

Theme 3: Shared Pathophysiological Mechanisms

Insulin Signaling Dysfunction Disrupted insulin signaling is the most widely cited shared mechanism across the literature, present in virtually all 80 sources reviewed. In the brain, insulin receptors are distributed with particular density in the hippocampus, entorhinal cortex, hypothalamus, and olfactory bulb—precisely the regions most vulnerable to early AD neurodegeneration [4, 43, 50]. In T2DM, peripheral insulin resistance gradually reduces insulin transport across the blood-brain barrier, decreasing cerebrospinal fluid insulin concentrations and depriving neurons of insulin's trophic and metabolic signals [6, 45]. De la Monte & Wands (2005) describe the resultant state as ”neuronal insulin resistance”: reduced activation of Akt, increased activation of GSK-3β, and hyperphosphorylation of tau [33].

The key downstream signaling nodes disrupted in both conditions are the PI3K/Akt and MAPK pathways. Gabbouj et al. (2019) identify decreased levels of PI3K subunits and blunted Akt kinase phosphorylation in AD brains, and note that AD mouse models fed a Western diet show altered PI3K subunit levels consistent with insulin resistance [67]. Folch et al. (2018) describe alterations spanning PI3K, Akt, GSK-3β, and MAPK pathways in late-onset AD [4], while Ribe & Lovestone (2016) connect reduced PI3K activation to increased GSK-3 activity and consequent tau phosphorylation [7]. Hachmeriyan et al. (2025) outline six distinct mechanisms by which insulin resistance affects cognitive function: effects on hippocampal plasticity, altered amyloid precursor protein (APP) metabolism, elevated tau protein concentration, enhanced brain inflammation, oxidative stress as an early precipitant of brain insulin resistance, and genetic factors related to ApoE ε4 expression [64].

A particularly illuminating molecular distinction is noted by de Sousa et al. (2020): failure to activate IRS-1 is the hallmark of AD, whereas inhibition of IRS-2 is the principal feature in T2DM, suggesting that while both conditions impair insulin signaling, they do so at distinct nodes of the same pathway [37]. This distinction may partly explain why peripheral T2DM and brain insulin resistance do not always co-occur in a simple linear fashion.

The Concept of "Type 3 Diabetes" The designation of AD as "type 3 diabetes"—first systematically articulated by de la Monte & Wands (2008)—is endorsed or discussed in the majority of included sources [8, 9, 20, 53, 76]. The concept holds that AD represents a form of diabetes that selectively involves the brain, with molecular and biochemical features overlapping with both type 1 (insulin deficiency) and type 2 (insulin resistance) diabetes mellitus [8]. De la Monte (2012) argues that extensive disturbances in brain insulin and IGF signaling represent early and progressive abnormalities that could account for the majority of molecular, biochemical, and histopathological lesions in AD, and that the soaring rates of peripheral insulin resistance associated with obesity and T2DM plausibly drive the current AD epidemic through a shared metabolic pathway [9]. Atabi et al. (2025), in their PRISMA-guided systematic review of 213 articles, confirm that insulin resistance was consistently identified as a key pathological driver, impairing brain glucose uptake, amyloid-β clearance, and tau phosphorylation [20]. Transcriptomic data additionally implicate non-coding RNAs—including MEG3 and MALAT1—in modulating insulin sensitivity and glucose homeostasis, linking metabolic imbalance to neuronal dysfunction at the epigenetic level [20].

Protein Misfolding and Aggregation: Aβ, Tau, and Amylin The canonical AD pathological proteins—amyloid-β and hyperphosphorylated tau—are directly modulated by insulin signaling. Impaired insulin signaling increases expression of amyloid precursor protein (APP) and accumulation of APP-Aβ, while simultaneously reducing activity of insulin-degrading enzyme (IDE), which catabolizes both insulin and Aβ [6, 9]. Wei et al. (2021) describe how insulin resistance increases reactive oxygen species production through the AGE/RAGE pathway, triggering Aβ accumulation, and separately dysregulates GSK-3β, leading to tau hyperphosphorylation [6]. In peripheral hyperinsulinemia, insulin competes with Aβ for IDE, thereby impeding Aβ clearance and promoting plaque formation [71].

Amylin (islet amyloid polypeptide, IAPP), co-secreted with insulin from pancreatic β-cells, deserves particular attention as a direct molecular bridge. Bharadwaj et al. (2017) and Neth & Craft (2017) describe how amylin accumulates within islet β-cells as a major pathological feature of chronic T2DM, contributing to β-cell toxicity and reduced insulin secretion; in parallel, amylin accumulates in the brains of AD patients and may interact with Aβ to exacerbate neurodegeneration [14, 18]. Li & Hölscher (2007) note structural similarity between APP and IAPP as a basis for shared physiological roles [23]. This cross-seeding between amylin and Aβ provides one of the most direct molecular links between pancreatic pathology in T2DM and cerebral pathology in AD.

Neuroinflammation and Cytokine Pathways Chronic low-grade inflammation is a shared feature of T2DM, obesity, and AD, and multiple reviews identify it as a mechanistic intermediary [10, 13, 43]. De Felice & Ferreira (2014) describe how peripheral low-grade inflammation in T2DM and obesity induces insulin resistance, and how proinflammatory signaling—particularly TNF-α-mediated activation of JNK and subsequent serine phosphorylation of IRS-1—impairs neuronal insulin signaling, contributing to synapse deterioration and memory loss [10]. Pugazhenthi et al. (2017) discuss cross-talk between peripheral and central inflammation, noting that damage to the blood-brain barrier (BBB) with aging allows infiltration of peripheral immune cells into the brain, exacerbating neuroinflammation and cognitive dysfunction [36]. Shoha et al. (2026) characterize chronic inflammation as the central bridge linking hyperglycemia, insulin resistance, and metabolic dysfunction in the brain to Aβ plaque formation, tau tangles, and neuronal damage [76]. Kamal et al. (2014) demonstrate convergence on inflammatory biomarkers: elevated CRP and TNF-α are common to both T2DM and AD, and anti-cholinesterase agents may reduce these inflammatory markers and provide therapeutic benefit in both conditions [43].

Oxidative Stress and Mitochondrial Dysfunction Oxidative stress and mitochondrial dysfunction represent a third major shared axis. Butterfield et al. (2014) position oxidative stress as a pivotal link between T2DM and AD, arguing that insulin resistance generates reactive oxygen species (ROS) that trigger Aβ accumulation and concurrently dysregulate GSK-3β to promote tau phosphorylation [12]. Moreira et al. (2007) identify brain mitochondrial dysfunc-

tion specifically as the key link, noting that the brain's high energetic requirements make it particularly vulnerable to deficits in mitochondrial electron transport, and that both insulin resistance and Aβ impair mitochondrial function through overlapping pathways [11]. Neth & Craft (2017) add that brain glucose hypometabolism—detectable by FDG-PET potentially decades before AD symptoms—may reflect early mitochondrial failure driven by insulin resistance, and that an initial hypermetabolic response may paradoxically precede the hypometabolism characteristic of established AD [18]. Barone et al. (2021) focus on the interplay among oxidative stress, brain insulin resistance, and AMPK dysregulation, arguing that oxidative damage to proteins regulating insulin signaling produces metabolic dysfunction through AMPK impairment, critically contributing to AD neurodegeneration [42].

Advanced Glycation End Products (AGEs) and the RAGE Axis Chronic hyperglycemia in T2DM generates advanced glycation end products (AGEs) through non-enzymatic glycation reactions. AGEs and their receptor RAGE are detected in AD brains and in the senile plaques and neurofibrillary tangles of AD patients [71, 72]. Pugazhenthi et al. (2017) identify the AGE/RAGE axis as providing critical links between diabetes and AD through amplification of neuroinflammation and mitochondrial damage [36]. Shieh et al. (2020) focus on sirtuins as the mechanism by which AGEs induce insulin resistance in diabetic cells, and note that the same sirtuin pathways are affected in neurodegenerative conditions, suggesting a molecular convergence point [49]. Patel et al. (2022) detail how AGEs formed by non-enzymatic glycation between Aβ and tau protein specifically enhance neurodegenerative disease progression through activation of pro-inflammatory mediators including IL-1β, IL-6, and TNF-α [13].

Vascular Pathology and Cerebrovascular Disease Cerebrovascular disease and vascular dysfunction represent a distinct but overlapping mechanism, particularly important for understanding the stronger epidemiological association between T2DM and vascular dementia compared to AD [51, 58]. Vagelatos & Eslick (2013) establish from clinico-neuropathological studies that cerebral infarcts are more common in those with T2DM and dementia, that they reduce the number of AD lesions required for clinical dementia manifestation, and that they do not interact synergistically with AD-type pathology—implying that the excess risk of clinically diagnosed AD in T2DM is substantially mediated through cerebrovascular pathology rather than direct augmentation of amyloid or tau burden [1]. This is corroborated by Biessels & Despa (2018), who note that mixed vascular and neurodegenerative pathologies, often on a background of AD pathology, characterize most cases of dementia in T2DM [2].

Wang et al. (2014) provide a focused analysis of endothelial dysfunction as a shared etiological factor, arguing that T2DM engenders a chronic pro-inflammatory state involving leukocyte-derived cytokines and endothelial chemotactic agents that produces vascular and organ dysfunction; within the CNS, dysregulated endothelial nitric oxide (NO) expression is presented as a critical vasodilatory, anti-inflammatory, and antioxidant mechanism whose failure underlies both T2DM-related and comorbid AD-related vasculopathies [69]. The BBB is specifically compromised by hyperglycemia-induced oxidative stress and inflammatory mediators, impairing insulin transport into the brain and allowing entry of peripheral pro-inflammatory cells [15, 44]. Raza et al. (2025) describe how T2D-associated vascular insults—including BBB breakdown and decreased brain perfusion—create conditions conducive to neurotoxicity and accelerated amyloid deposition [15].

Growth Factor Signaling: IGF and Related Pathways Insulin-like growth factor-1 (IGF-1) signaling is closely intertwined with insulin signaling in the brain and is disrupted in both T2DM and AD. De la Monte & Wands (2005) describe how downregulation of the IGF-1 receptor and its associated IRS proteins in AD brains parallels the IGF-1 signaling abnormalities seen in peripheral T2DM, and how experimental depletion of neuronal insulin receptors produces features of AD-type neurodegeneration [33]. Zemva & Schubert (2011) report that AD brains show substantially downregulated expression of insulin receptor, IGF-1 receptor, and IRS proteins, and note—significantly—that reducing insulin/IGF-1 signaling in C. elegans models decreases Aβ toxicity through two transcription factor

pathways (DAF-16 and HSF-1), raising the interpretive complexity of whether reduced signaling is pathogenic, compensatory, or protective depending on context [55].

Autophagy, Apoptosis, and Proteostasis Failure Autophagic dysfunction represents an additional shared mechanism emphasized in several reviews. Chatterjee & Mudher (2018) identify autophagy dysregulation as a pathophysiological trait common to both diseases, noting that it indirectly impacts Aβ and tau functions in neurons and that pro-autophagy drugs represent a potential shared therapeutic target [25]. Alsaleem et al. (2025) describe autophagy dysregulation as a consequence of PPAR-α signaling disruption common to both T2DM and AD [73]. The GSK-3β kinase—overactivated in both conditions—plays a central role not only in tau hyperphosphorylation but also in APP processing via the γ-secretase complex, and is discussed by Hamzé et al. (2022) and Cole et al. (2007) as a particularly attractive shared therapeutic target [22, 29]. DYRK1A, another kinase involved in both pancreatic β-cell dysfunction and AD neuropathology, is identified by Hamzé et al. (2022) as a second potential common therapeutic node [29].

Novel and Emerging Mechanistic Insights Several more recently described mechanisms extend the classical pathways above. Majid et al. (2025) identify overexpression of branched-chain amino acids (BCAA) as disrupting glycolysis, the TCA cycle, and oxidative phosphorylation, reducing acetyl-CoA availability, increasing ROS production, and contributing to Aβ and tau accumulation—linking BCAA dysregulation to both metabolic and neurodegenerative disease [75]. Lazar et al. (2021) propose gut dysbiosis as an upstream mechanism that induces peripheral and cerebral insulin resistance through inflammatory pathways and can amplify AD-promoting processes, adding a gastrointestinal dimension to the T2D–AD nexus [59]. Kshirsagar et al. (2020) discuss roles for miRNA, leptin, and gangliosides in modulating insulin resistance in both conditions [46]. Alsaleem et al. (2025) detail PPAR-α dysregulation as a shared mechanism across T2DM and AD, proposing fenofibrate as a candidate agent for modulating both conditions [73]. Asih et al. (2017) highlight the role of age-related decline in testosterone—operating through effects on mitochondrial efficiency, cerebral bioenergetics, and Aβ regulation—as an additional modifier that may mediate part of the excess AD risk associated with metabolic syndrome [80].

Theme 4: Dementia Subtypes and Differential Mechanisms

The distinction between AD and vascular dementia is relevant both epidemiologically and mechanistically, though most included reviews focus disproportionately on AD. As noted above, the relative risk increase associated with T2DM is consistently larger for vascular dementia than for AD [2, 51, 71]. Luchsinger (2012) argues that cerebrovascular disease is the best-supported mechanistic link between T2DM and cognitive impairment, and that a causal relationship with late-onset AD specifically remains unproven despite epidemiological associations [16]. Exalto et al. (2012) corroborate this from neuropathological data: while epidemiological studies link T2DM to both AD and vascular dementia, neuropathological studies attribute the increased dementia risk primarily to vascular lesions [79]. Riederer et al. (2017) conclude that mixed dementia—involving both amyloid pathology and cerebrovascular pathology—is the most frequent pattern in T2DM-associated dementia [24], consistent with the broader recognition that the Alzheimer's disease-versus-vascular dementia distinction is itself an oversimplification in elderly diabetic patients.

Mechanistically, AD and vascular dementia are distinguished by their proximal pathologies: AD involves amyloid-β plaque formation and tau tangle-driven neurodegeneration, while vascular dementia involves microvascular disease, lacunar infarcts, and white matter injury [24, 43]. However, T2DM promotes both: it accelerates amyloid and tau pathology through the insulin signaling mechanisms described above, and simultaneously produces microvascular disease, endothelial dysfunction, and BBB breakdown through hyperglycemia and dyslipidemia [3, 69]. The cognitive domains affected also differ somewhat: Biessels & Despa (2018) note that processing speed and executive function are the domains most prominently affected in diabetes-associated cognitive dysfunction, while episodic memory is

more specifically impaired in AD [2], and Riederer et al. (2017) detail that T2DM-associated dementia encompasses deficits in memory, executive function, attention, and information-processing speed [24].

Theme 5: Therapeutic Implications Arising from Shared Mechanisms

The shared pathophysiology described above has generated an extensive investigative agenda around repurposing antidiabetic agents for AD treatment or prevention. Insulin itself—delivered intranasally to circumvent the BBB and avoid peripheral hypoglycemia—is the most extensively discussed candidate, with evidence suggesting improvement in memory in both healthy adults and AD patients [17, 54]. Benedict & Grillo (2018) summarize evidence that intranasal insulin improves cognitive function and brain health in MCI or early AD, with effectiveness modified by ApoE ε4 status: ApoE ε4-positive individuals show attenuated or absent responses, while ApoE ε4-negative individuals demonstrate clearer benefit [17, 29].

GLP-1 receptor agonists are highlighted across many sources as particularly promising [5, 15, 24, 53]. These agents—including liraglutide and exenatide—act on GLP-1 receptors expressed in the brain and have demonstrated neuroprotective effects in preclinical models and encouraging signals in early clinical studies. Yarchoan & Arnold (2014) frame GLP-1 agonists as among the most promising diabetes drugs to repurpose for AD given their multi-factorial activity on brain insulin signaling, inflammation, and neurogenesis [63]. Metformin's role is discussed but contested: while it reduces peripheral insulin resistance and has been associated in some observational studies with lower dementia risk [2], concerns exist about whether it crosses the BBB effectively and whether its indirect effects on insulin sensitivity are sufficient to modify brain pathology [17]. Thiazolidinediones (TZDs), particularly pioglitazone and rosiglitazone, improve insulin sensitivity via PPAR-γ activation and have been evaluated in several AD trials; Folch et al. (2018) discuss pioglitazone and intranasal insulin as the most clinically advanced candidates for late-onset AD [4]. SGLT2 inhibitors have emerged as more recent candidates with putative neuroprotective properties [5, 15].

Beyond pharmacology, lifestyle interventions—physical activity, Mediterranean-type diets, glycemic control through caloric restriction—are discussed across multiple reviews as practical preventive strategies targeting shared metabolic and inflammatory pathways [3, 15, 52]. Bello-Chavolla et al. (2019) identify lifestyle intervention, particularly physical activity, as a promising approach to ameliorate the impact of disability and frailty on T2DM-related dementia [3].

Biomarker development is recognized as a critical gap. Suthar & Korobova (2026) identify cerebrospinal fluid biomarkers and PET imaging as providing diagnostic insights into the insulin–brain connection [53], while Raza et al. (2025) point to the plasma p-tau/Aβ42 ratio as an emerging early detection biomarker [15]. Patel et al. (2022) propose glutathione as a potential biomarker for early AD detection in T2DM patients given shared oxidative stress pathways [13].

Synthesis

The Central Interpretive Problem

The literature reviewed here presents an apparent tension between robust epidemiological evidence that T2DM increases dementia risk and inconsistent neuropathological evidence that T2DM augments the hallmark lesions of AD. This tension is central to understanding the field and warrants systematic resolution.

The epidemiological signal is genuine and large: a pooled relative risk of ~1.5–1.6 for AD and ~2.3–2.5 for vascular dementia, replicated across geographies and study designs [1–3]. Yet Biessels & Despa (2018) explicitly state that "T2DM does not increase the burden of the latter [prototypical AD pathologies]" [2], and Luchsinger (2012) notes

that autopsy studies are ”few and conflicting” [16]. Arab et al. (2011) go further, citing postmortem evidence of decreased AD pathology in diabetic brains [72].

These findings are not necessarily contradictory. The most parsimonious explanation—consistent with the evidence synthesized by Vagelatos & Eslick (2013), Biessels & Despa (2018), and Luchsinger (2012)—is that T2DM predominantly increases dementia risk through cerebrovascular mechanisms that lower the pathological threshold for clinical dementia. Vagelatos & Eslick's finding that cerebral infarcts reduce the number of AD lesions required for clinical dementia manifestation but do not interact synergistically with AD-type pathology [1] is the key mechanistic statement: individuals with T2DM do not necessarily have more amyloid plaques or tangles at death, but they have more cerebrovascular pathology that makes existing AD lesions clinically manifest at lower burden. This ”dual hit” model—cerebrovascular disease lowering the phenotypic threshold for AD expression—accounts for the epidemiological risk elevation without requiring that T2DM be a direct driver of amyloid or tau accumulation.

However, this vascular explanation cannot be the complete story. The molecular evidence for direct insulin signaling–mediated promotion of Aβ production and impaired clearance, tau hyperphosphorylation via GSK-3β, and inflammatory neurodegeneration is mechanistically compelling and supported by animal models [6, 8, 9]. The resolution likely lies in recognizing that different mechanistic pathways dominate at different disease stages and in different populations. In individuals with mild-to-moderate T2DM primarily managed through oral agents, cerebrovascular pathology may dominate. In individuals with severe, long-standing, insulin-dependent T2DM, direct metabolic effects on brain insulin signaling, mitochondrial function, and neuroinflammation may become increasingly important contributors to a neurodegenerative phenotype more resembling AD proper [5, 13].

The brain insulin resistance that de la Monte & Wands designate ”type 3 diabetes” [8] may represent a distinct pathological entity that can arise either as a consequence of peripheral T2DM (via reduced insulin transport across the BBB, hyperinsulinemia-induced receptor downregulation, and inflammatory impairment of IRS-1 signaling) [6, 64] or through intrinsic neurodegeneration independently of peripheral metabolic disease [9, 31]. In this framework, T2DM represents one upstream driver of brain insulin resistance among several, which explains why not all AD patients have T2DM and not all T2DM patients develop AD.

Population and Genetic Modifiers

The ApoE ε4 allele acts as a critical effect modifier that may substantially explain heterogeneity in findings. In ApoE ε4 carriers, the T2DM–AD association appears stronger [1], intranasal insulin treatment is less effective [17], and the relationship between diabetes duration and amyloid pathology is more pronounced [5]. This suggests that in ApoE ε4 carriers, the direct amyloid-promoting consequences of insulin resistance may be more penetrant, while in ApoE ε4-negative individuals, cerebrovascular mechanisms may dominate. Studies that do not stratify by ApoE status will therefore average across mechanistically distinct subgroups, producing attenuated and inconsistent effect estimates for both epidemiological and therapeutic outcomes [28, 29].

Gender represents another dimension of heterogeneity: Jayaraman & Pike (2014) note increased AD risk in women with metabolic syndrome and discuss the role of estrogen and androgen in modulating the T2DM–AD relationship [51], while Asih et al. (2017) detail evidence that low testosterone in men contributes independently to both T2DM and AD risk [80]. Atabi et al. (2025) note gender differences in cognitive impairment patterns in diabetic individuals—cognitive impairment is more common in diabetic women but better memory performance compared to men—suggesting sex-specific mechanistic pathways [20].

The Temporal Dimension

The temporal relationship between T2DM and AD remains incompletely characterized, though several important observations emerge. Brain glucose hypometabolism detectable by FDG-PET can precede AD symptoms by decades [18], and Hamzé et al. (2022) note that alteration of glucose metabolism and insulin signaling in the brain may induce early neuronal loss and synaptic plasticity impairment years before clinical manifestation [29]. Midlife T2DM and insulin resistance carry greater excess dementia risk than late-life T2DM, with Luchsinger & Gustafson (2009) and Carlsson (2010) both emphasizing midlife vascular risk factors as targets for prevention that exert their effects decades later [19, 32]. Conversely, the paradoxical finding that adiposity in old age is associated with reduced rather than increased dementia risk—in contrast to midlife adiposity—suggests that the relevant exposure window is early-to-mid adulthood rather than late life [32, 71].

The positive feedback loop described by de la Monte (2012) and supported by several other sources—whereby insulin resistance promotes Aβ accumulation and Aβ toxicity in turn promotes brain insulin resistance [9, 17] —implies that by the time clinical AD is manifest, the initiating metabolic insult may be difficult to identify and the disease may be self-perpetuating regardless of the status of peripheral T2DM. This has critical implications for therapeutic timing: interventions targeting insulin resistance are most likely to be effective in the preclinical or early disease window, before the feedback loop becomes self-sustaining. The consistent finding that clinical trials of insulin sensitizers in established AD have yielded inconsistent results [3, 28, 72] is consistent with this model of diminishing therapeutic opportunity as disease progresses.

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