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TYPE 2 DIABETES MELLITUS AS A RISK FACTOR FOR DEMENTIA AND ALZHEIMER'S DISEASE: A NARRATIVE REVIEW

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ABSTRACT

Background

Type 2 diabetes mellitus (T2DM) is associated with cognitive impairment and dementia. The underlying mechanisms and the effectiveness of preventive interventions remain incompletely understood.

Aim

To review the association between T2DM and dementia risk, with particular emphasis on Alzheimer's disease.

Materials and Methods

This narrative review included 53 publications identified through PubMed and Google Scholar searches conducted in May and June 2026, covering publications from January 2015 to June 2026. Reference lists were screened for additional sources. Eligible publications were written in English, with an exception for Polish national clinical guidelines. Publications without accessible full texts were excluded. Evidence was synthesized narratively.

Results

T2DM was associated with increased dementia risk, with a generally stronger association for vascular dementia than for Alzheimer's disease. Proposed mechanisms included cerebral insulin resistance, oxidative stress, inflammation, and vascular injury. However, the evidence did not establish that T2DM directly causes Alzheimer's disease. Longer diabetes duration, hypoglycaemia, and greater HbA1c variability were associated with higher dementia risk, while findings concerning mean HbA1c required cautious interpretation. Cognitive impairment may compromise diabetes self-management. Evidence concerning antidiabetic medications differed across drug classes and study designs. A meta-analysis of randomized trials reported a lower risk of dementia or cognitive impairment with GLP-1 receptor agonists, but limitations in outcome ascertainment and follow-up restrict its implications for prevention.

Conclusions

T2DM is associated with increased dementia risk. Cognitive difficulties should be considered within comprehensive diabetes care, but the reviewed evidence does not establish a specific glycaemic target or pharmacological intervention for dementia prevention. Further trials with adequate follow-up and systematic assessment of cognitive outcomes are needed.

Keywords: Type 2 Diabetes Mellitus; Dementia; Alzheimer Disease; Risk Factors; Cognitive Dysfunction.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most common chronic metabolic diseases and represents a major public health challenge of the 21st century. According to the 11th edition of the International Diabetes Federation (IDF) Diabetes Atlas, in 2024 approximately 589 million adults worldwide were living with diabetes, and this number is projected to increase to approximately 853 million by 2050 [1]. T2DM is a multifactorial disorder that develops on the basis of insulin resistance, progressive pancreatic β-cell dysfunction, and coexisting metabolic abnormalities [2]. The pathophysiology of T2DM involves impaired insulin secretion and action, chronic hyperglycemia, dyslipidemia, low-grade chronic inflammation, and endothelial dysfunction. The most important risk factors for the development of the disease include older age, overweight and obesity, physical inactivity, unhealthy diet, positive family history, hypertension, and other components of the metabolic syndrome [2]. Preservation of normal cognitive functions, such as memory, attention, learning, and executive functions, is one of the fundamental prerequisites for independent functioning in older adults.

Dementia is a clinical syndrome resulting from diseases or injuries of the brain that lead to impairment of memory, executive functions, orientation, language, and activities of daily living. In ICD-11, dementia is classified within neurocognitive disorders, and its diagnostic requirements include marked impairment in at least two cognitive domains [8,15]. Alzheimer's disease is the most common cause of dementia, accounting for approximately 60-70% of cases. The World Health Organization (WHO) reports that in 2021 approximately 57 million people worldwide were living with dementia, with nearly 10 million new cases occurring annually [3]. Alzheimer Europe estimated that approximately 9.1 million people were living with dementia in the EU27 in 2025, with this number projected to rise to approximately 14.3 million by 2050 [11]. Dementia therefore represents not only a major health problem but also a significant social, economic, and caregiving burden [3,10]. The association between T2DM and dementia is also influenced by shared risk factors such as advanced age, obesity, hypertension, dyslipidemia, and physical inactivity [4].

In recent years, there has been growing interest in the potential association between type 2 diabetes mellitus and the development of dementia, including Alzheimer's disease. This hypothesis is supported by shared pathophysiological mechanisms, primarily insulin resistance, oxidative stress, chronic low-grade inflammation, and vascular dysfunction [4,5]. Impaired insulin signaling within the central nervous system may lead to disrupted neuronal energy metabolism, impaired neuroplasticity, and accelera-

tion of neurodegenerative processes [5]. At the same time, chronic hyperglycemia and the associated overproduction of reactive oxygen species contribute to neuronal damage, while vascular alterations may result in reduced cerebral perfusion and further aggravation of neural tissue injury [5]. Some authors have referred to Alzheimer's disease as "type 3 diabetes," emphasizing the role of impaired insulin signaling in neurodegeneration; however, this term remains hypothetical and is not formally recognized [5,6].

AIM

To review the association between type 2 diabetes mellitus and dementia risk, with particular emphasis on Alzheimer's disease.

Objectives

1. To summarize epidemiological evidence and proposed pathophysiological mechanisms.
2. To assess diabetes-related factors associated with cognitive impairment.
3. To discuss clinical implications and evidence concerning preventive strategies.

METHODS

A narrative literature review was conducted to examine the association between type 2 diabetes mellitus (T2DM) and the risk of dementia, with particular emphasis on Alzheimer's disease. PubMed and Google Scholar were searched in May and June 2026 for publications published between 1 January 2015 and 30 June 2026. Additional relevant publications were identified by screening the reference lists of selected articles. The PubMed search strategy combined Medical Subject Headings (MeSH) terms with title/abstract keywords. The following search query was used: Diabetes Mellitus, Type 2; type 2 diabetes; type 2 diabetes mellitus and Dementia; Alzheimer Disease; dementia; Alzheimer; cognitive decline; cognitive impairment.

Google Scholar was searched using combinations of terms related to type 2 diabetes mellitus, dementia, Alzheimer's disease, cognitive decline, insulin resistance, and neurodegeneration. Additional publications were identified by screening the reference lists of selected articles.

Eligible publications included original observational studies, randomized controlled trials, systematic reviews, meta-analyses, narrative reviews, and clinical guidelines addressing epidemiological associations, potential mechanisms, or clinical implications of T2DM and cognitive disorders in adults. Publications written in English were eligible. Polish national clinical guidelines were included as a prespecified language exception.

Case reports and studies involving children were excluded. Publications without an accessible full text were also excluded. This access-based exclusion criterion may have introduced selection bias. A total of 53 publications were included, and the evidence was synthesized narratively.

RESULTS

Type 2 Diabetes Mellitus and Its Impact on the Central Nervous System

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by the coexistence of insulin resistance and progressive pancreatic β-cell dysfunction, leading to persistent hyperglycemia [1,3]. From an epidemiological perspective, it represents the predominant form of diabetes, accounting for more than 90% of all cases [1]. Its clinical significance results not only from its high prevalence but also from long-term organ complications affecting the cardiovascular system, kidneys, visual system, and the central nervous system [1,3].

In the pathogenesis of T2DM, a key role is played by peripheral tissue insulin resistance, particularly in skeletal muscle, adipose tissue, and the liver, as well as the gradual decline in insulin secretory capacity of pancreatic β-cells [3]. The consequence of these disturbances is chronic hyperglycemia, which promotes oxidative stress, inflammatory responses, and vascular injury [2,4]. Insulin also plays important roles within the central nervous system. Its receptors are widely expressed in multiple brain regions, including the hippocampus and cerebral cortex, which are involved in learning, memory, and executive functions [4,5].

Insulin signaling contributes to neuronal survival, synaptic plasticity, and neuronal energy metabolism [4,5]. Impairment of insulin action in the brain may therefore lead to reduced synaptic transmission efficiency, impaired long-term potentiation, and disturbances in memory processes [5]. In this context, insulin should be regarded not only

as a metabolic hormone but also as a neuromodulatory factor essential for normal central nervous system function [2,5].

The association between T2DM and cognitive decline is well documented. The World Health Organization (WHO) identifies diabetes as an important, modifiable risk factor for dementia [6]. Individuals with T2DM exhibit an increased risk of memory impairment, slowed information processing, attentional deficits, and reduced executive functioning [2,6]. From a mechanistic perspective, cerebral insulin resistance may lead to reduced neuronal glucose uptake, impaired intracellular signaling, and disrupted synaptic processes [4,5]. The literature emphasizes that the impact of T2DM on cognitive function is multifactorial, involving metabolic, vascular, and neurodegenerative components [2,4].

An important element of the pathogenesis is also the accumulation of advanced glycation end-products (AGEs), which are formed under conditions of chronically elevated glucose levels and exert their effects via RAGE receptors, thereby enhancing inflammatory responses and endothelial dysfunction [2,4]. As a consequence, neuroplasticity is impaired, cerebral perfusion is reduced, and the brain becomes more susceptible to neurodegenerative processes [4,6].

Complications of Type 2 Diabetes Mellitus Relevant to the Development of Cognitive Impairment

Complications of T2DM that are particularly relevant in the context of cognitive impairment include microvascular, macrovascular, and neuropathic complications [2,3]. Damage to cerebral small vessels, chronic cerebral hypoperfusion, white matter lesions, and cerebrovascular events may contribute to the development of vascular or mixed dementia [2,7]. Population-based studies have demonstrated that T2DM is associated with an increased risk of dementia, particularly vascular dementia, and that the magnitude of this risk is influenced, among other factors, by the quality of glycemic control [7]. Vascular alterations, dyslipidemia, and hypertension, which frequently coexist with T2DM, further impair brain function by disrupting cerebral blood flow autoregulation and damaging the blood–brain barrier [5,6].

Association Between Type 2 Diabetes Mellitus and the Risk of Developing Dementia and Alzheimer's Disease

Observational studies and meta-analyses associate diabetes mellitus, including type 2 diabetes mellitus (T2DM), with an increased risk of cognitive impairment and dementia

[12,13,17,24]. Xue and colleagues reviewed 144 prospective studies and reported increased risks across several cognitive outcomes [12]. A 2024 meta-analysis reported a pooled relative risk of 1.59 (95% CI 1.40–1.80) for dementia in individuals with diabetes compared with those without diabetes, although heterogeneity was substantial (I^2 = 96.4%) [13]. In the Danish registry study, adjusted hazard ratios were 1.98 for vascular dementia and 1.13 for Alzheimer's disease, indicating a stronger association with vascular dementia in that population [24]. These findings support an epidemiological association but do not, by themselves, establish causality.

Among individuals with T2DM, diabetes duration, glycaemic measures, and hypoglycaemic episodes have been investigated as factors associated with dementia risk [9,13,21]. Higher HbA1c levels and greater HbA1c variability were associated with increased dementia risk in the UK cohort study [21]. The systematic review by Tabesh and colleagues also found associations of hypoglycaemia, greater HbA1c variability, and longer diabetes duration with higher dementia risk, although the pooled estimate for HbA1c did not reach statistical significance [9]. Findings concerning diabetes duration should be interpreted according to the duration categories and reference groups used. The increased risk reported for diabetes duration below five years compared with no diabetes does not establish that recently diagnosed diabetes carries a greater risk than longstanding diabetes [13].

The RAMP-DM cohort study reported that participation in a structured diabetes-care programme was associated with a lower risk of dementia, whereas a higher mean HbA1c level was associated with a higher incidence of dementia [14]. These findings support a relationship between diabetes management and cognitive outcomes. However, because the study was observational, they do not establish that participation in the programme itself prevented dementia. The observed association may also have been influenced by differences in healthcare engagement, comorbidity management, socioeconomic factors, or other characteristics of the participants.

The association between T2DM and AD is generally weaker and less consistent than the association between T2DM and VaD [12,13,23]. Observational studies have proposed several biological pathways that could contribute to this relationship, including impaired cerebral insulin signalling, oxidative stress, chronic inflammation, mitochondrial dysfunction, and alterations in amyloid-β and tau metabolism [16,22,27]. These mechanisms provide biological plausibility but do not establish that T2DM directly causes AD. Moreover, Mendelian randomization studies have not consistently demonstrated a direct causal relationship between genetic liability to T2DM and AD [24,25,34,35]. Accordingly, the term "type 3 diabetes" should be regarded as an infor-

mal hypothesis describing a possible role of impaired cerebral insulin signalling rather than as a formally recognized disease entity [16,22].

The strongest and most consistent epidemiological association has been observed between T2DM and VaD [12,13]. Diabetes-related endothelial dysfunction, atherosclerosis, cerebral small-vessel disease, and impaired cerebral perfusion may contribute to white-matter lesions, microinfarcts, and disturbances in cerebrovascular regulation [7,14,16,22,27]. These vascular abnormalities may be associated with deficits in attention, information-processing speed, and executive functions. In addition, hypertension, cardiovascular disease, and other diabetes-related vascular complications may further increase the risk of cognitive impairment and dementia [32,33].

Nevertheless, vascular and neurodegenerative pathologies frequently coexist, and mixed dementia is common in clinical practice [3,16]. Consequently, the association between T2DM and dementia may reflect the combined effects of vascular injury, neurodegenerative processes, and shared risk factors rather than a single pathological pathway. This overlap also limits the ability of observational studies to distinguish the independent contribution of diabetes to specific dementia subtypes.

Overall, the available evidence supports an association between T2DM and an increased risk of dementia. The association appears to be strongest for VaD and weaker, although still clinically relevant, for AD. The interpretation of these findings requires a clear distinction between epidemiological associations, proposed biological mechanisms, and the effects of preventive or therapeutic interventions.

Pathogenetic Mechanisms Linking Type 2 Diabetes Mellitus to the Development of Dementia

Insulin signalling in the central nervous system contributes to synaptic plasticity, neuronal survival, neurotransmitter regulation, and processes involved in learning and memory [22]. Cerebral insulin resistance may disrupt intracellular pathways that support these functions. However, impaired insulin signalling should not be equated with a general reduction in insulin-dependent neuronal glucose uptake, nor should peripheral insulin resistance be assumed to imply cerebral insulin resistance in every patient with T2DM.

The term “type 3 diabetes” has been proposed to describe the potential contribution of impaired cerebral insulin signalling to Alzheimer’s disease. It is not a recognised diagnosis and should not imply that Alzheimer’s disease is a form of T2DM [22].

Mendelian randomization studies have investigated whether genetic liability to T2DM contributes causally to Alzheimer's disease [25,26]. Their findings should be distinguished from evidence concerning the consequences of prolonged hyperglycaemia, hypoglycaemia, or vascular complications. They do not establish that the association between T2DM and Alzheimer's disease is predominantly mediated through a single metabolic or vascular pathway.

Chronic hyperglycaemia may promote oxidative stress, mitochondrial dysfunction, and inflammatory responses [22]. These processes may damage neuronal lipids, proteins, and DNA and impair synaptic function. Hyperglycaemia may also increase the formation of advanced glycation end-products, which can promote endothelial dysfunction and inflammatory responses [30]. Microglial activation and increased production of pro-inflammatory cytokines may further contribute to neuroinflammation and neuronal injury [27,28,30]. Nevertheless, observational associations between glycaemic disturbances and cognitive outcomes do not, by themselves, demonstrate the molecular mechanisms responsible for neuronal damage [19,20].

Vascular injury represents another important pathway linking T2DM with cognitive impairment. Endothelial dysfunction, diabetic microangiopathy, macroangiopathy, and chronic cerebral hypoperfusion may contribute to white-matter damage, microinfarcts, and impaired perfusion of neural tissue [22,24,30,32]. These abnormalities may affect executive functions, attention, and information-processing speed. Coexisting hypertension and cerebrovascular disease may further increase the vascular burden. Vascular and neurodegenerative pathologies may also coexist, contributing to cognitive impairment through multiple interacting mechanisms rather than through a single disease pathway.

Experimental studies suggest that impaired insulin signalling may influence amyloid-β metabolism and tau phosphorylation [22]. Competition between insulin and amyloid-β for insulin-degrading enzyme has been proposed as a possible mechanism affecting amyloid-β clearance. In addition, impaired insulin signalling may activate pathways involving glycogen synthase kinase-3β, thereby promoting tau hyperphosphorylation [30,31]. However, the contribution of these mechanisms to Alzheimer's pathology in individuals with T2DM remains uncertain. They provide biological plausibility but should not be presented as inevitable consequences of T2DM or as evidence that diabetes directly causes Alzheimer's disease.

Risk Factors for Dementia in Patients with T2DM

The risk of dementia among individuals with T2DM is influenced by the duration of diabetes, the quality and stability of glycaemic control, hypoglycaemic episodes, obesity, metabolic syndrome, and coexisting cardiovascular or cerebrovascular disease [20,21,31-33,36-38].

Longer diabetes duration has been associated with a higher risk of cognitive decline and dementia, potentially reflecting prolonged exposure to hyperglycaemia and the cumulative effects of diabetes-related complications [31]. Higher HbA1c levels and greater glycaemic variability have also been associated with an increased risk of dementia [21,31]. Conversely, more stable glycaemic control has been associated with more favourable cognitive outcomes in cohort studies [21]. These findings should be interpreted cautiously, as observational associations may be influenced by age, comorbidity, treatment intensity, and overall disease severity.

Hypoglycaemia represents an additional risk factor, particularly among older adults and individuals with longstanding diabetes [20,22,31]. Previous hypoglycaemic episodes have been associated with an increased risk of cognitive impairment, dementia, and Alzheimer's disease [20]. The directionality of this association may be complex, because cognitive impairment can itself increase the risk of medication errors, inadequate nutrition, and subsequent hypoglycaemia.

Obesity and metabolic syndrome have also been associated with dementia risk, although their effects may depend on the overall metabolic and vascular profile of the individual [36–38]. Current evidence suggests that an adverse metabolic profile, rather than excess body weight alone, may be more relevant to cognitive risk [37]. Metabolic syndrome has been associated with an increased risk of both all-cause dementia and vascular dementia [38].

Cardiovascular and cerebrovascular comorbidities are important determinants of dementia risk in patients with T2DM. The coexistence of stroke, coronary artery disease, atrial fibrillation, or heart failure is associated with a further increase in dementia risk [32,33]. These findings indicate that the cognitive risk profile of individuals with T2DM is substantially influenced by their overall vascular burden. Table 1 summarizes key clinical evidence linking T2DM to increased dementia risk, highlighting associations with glycaemic control, hypoglycaemia, diabetes management, and antidiabetic treatments alongside major study limitations.

Table 1. Key clinical evidence linking T2DM with dementia risk

STUDY	DESIGN AND POPULATION	FACTOR/COMPARISON	MAIN COGNITIVE OUTCOME	MAIN RESULT, RR/HR/OR (95% CI)	MAIN LIMITATIONS
Xue et al., 2019 [12]	Systematic review/meta-analysis; 144 prospective studies	Diabetes versus no diabetes	Cognitive impairment and dementia	Diabetes associated with approximately 1.25–1.91-fold higher risk; AD: RR 1.43 (1.25–1.62)	Observational studies; substantial heterogeneity and residual confounding
Cao et al., 2024 [13]	Meta-analysis; 15 studies, 10,103,868 participants	Diabetes versus no diabetes	All-cause dementia	RR 1.59 (1.40–1.80)	Very high heterogeneity; variable adjustment and outcome definitions
Cao et al., 2024 [13]	Meta-analysis of observational studies	Diabetes duration <5 years versus no diabetes	All-cause dementia	RR 1.29 (1.20–1.39)	Duration categories inconsistently defined; possible reverse causality
Zheng et al., 2021 [21]	UK cohort; 457,902 people with diabetes	HbA1c, HbA1c variability and complications	Incident dementia	Per 1% increase in HbA1c: HR 1.08 (1.07–1.09); hypoglycaemia: HR 1.30 (1.22–1.39)	Residual confounding; observational design; incomplete HbA1c data
Song et al., 2022 [19]	Meta-analysis; 5 studies, 577,592 participants	Higher versus lower HbA1c variability	Incident dementia	HbA1c SD: HR 1.19 (1.06–1.32); high versus low CV: HR 1.18 (1.08–1.28)	Retrospective studies; different variability measures
Huang et al., 2022 [53]	Meta-analysis; 10 cohorts, 1,407,643 participants	Hypoglycaemia versus no hypoglycaemia	Incident dementia	HR 1.44 (1.26–1.65)	Mainly severe hypoglycaemia; possible bidirectional association and confounding
Wang et al., 2024 RAMP-DM [14]	Matched retrospective cohort; 55,618 people with T2DM	RAMP-DM versus usual care	All-cause dementia, AD and vascular dementia	All-cause dementia: aHR 0.72 (0.68–0.77); AD: 0.85 (0.76–0.96); vascular dementia: 0.61 (0.51–0.73)	Non-randomised design; healthy-user and health-care-engagement bias
Kuate Defo et al., 2024 [23]	Umbrella review; 100 reviews and 27 cohort/case–control studies	Antidiabetic medications versus non-use or alternative treatment	Incident dementia	Lower risk reported with metformin, TZDs, GLP-1RAs and SGLT2 inhibitors; estimates varied by drug and comparator	Confounding by indication, treatment-selection bias and heterogeneity

Note: The evidence base is dominated by prospective and retrospective observational studies; therefore, the reported associations should not be interpreted as proof of causality. Effect estimates are presented as reported in the original studies and may not be directly comparable because of differences in outcome definitions, comparator groups, adjustment sets, and follow-up duration.

The Importance of Type 2 Diabetes Mellitus Control in the Prevention of Cognitive Impairment and Dementia

In patients with type 2 diabetes mellitus, appropriate metabolic control is important not only for the prevention of classical vascular complications but also for reducing the

risk of cognitive impairment and dementia. Observational data indicate that higher HbA1c levels, greater glycaemic variability, and more frequent hypoglycaemic episodes are associated with an increased risk of dementia [14,20,29,40]. In a large cohort study from Hong Kong, a multidisciplinary diabetes care programme was associated with a reduced risk of all-cause dementia, Alzheimer's disease, and vascular dementia, while mean HbA1c levels in the range of 6.5–7.5% were associated with a more favourable cognitive risk profile [14]. Similarly, in the Kaiser Permanente study, the highest dementia risk was observed in individuals with HbA1c values ≥9% in most measurements, whereas more stable and lower HbA1c levels were associated with reduced risk [39].

In addition, HbA1c variability itself has been shown to increase dementia risk even when mean glycaemic values appear acceptable [40]. A large meta-analysis including over 7 million individuals with diabetes demonstrated a consistent relationship between hypoglycaemia, HbA1c levels, HbA1c variability, and diabetes duration with dementia risk: longer disease duration, higher HbA1c, and greater glycaemic variability were all associated with increased cognitive risk [9]. These findings indicate that dementia prevention in T2DM relies not only on achieving lower glucose levels, but primarily on maintaining stable, individualized metabolic control while avoiding both chronic hyperglycaemia and hypoglycaemia [14,40].

Modification of Cardiovascular Risk Factors

Control of type 2 diabetes mellitus should be implemented as part of a broader strategy for cardiovascular risk reduction. This is particularly important because vascular and cerebrovascular diseases significantly mediate the development of dementia in patients with T2DM [32,33]. In a large study based on the UK Clinical Practice Research Datalink (CPRD), the presence of cardiovascular comorbidities in patients with T2DM—especially stroke, heart failure, atrial fibrillation, and hypertension—was associated with a further increase in dementia risk [32]. Similarly, a Danish analysis showed that the coexistence of diabetes and coronary artery disease was associated with a higher risk of dementia, particularly vascular dementia, than either condition alone [33]. These findings indicate that the prevention of stroke, atherosclerosis, and other vascular complications has a direct impact on the preservation of cognitive function. In clinical practice, this requires a comprehensive approach including antihypertensive therapy, lipid control, weight reduction, promotion of physical activity, and optimal management of coexisting cardiovascular diseases [32,33].

Lifestyle in the Prevention of Cognitive Impairment

Lifestyle modification is one of the most important components of prevention for both diabetes mellitus and its neurological complications. In the context of cognitive function, diet, physical activity, and broadly defined "neurocognitive hygiene" have the strongest evidence base [41-43]. The Mediterranean diet is one of the most extensively studied dietary patterns with potential neuroprotective effects. A 2025 meta-analysis demonstrated that high adherence to this diet is associated with a reduced risk of cognitive impairment, dementia, and Alzheimer's disease [42]. Cohort studies and systematic reviews suggest that its beneficial effects may be mediated through reductions in oxidative stress, improvement of endothelial function, attenuation of inflammatory processes, and favourable effects on insulin sensitivity [44,45].

Regular physical activity is also associated with favourable effects on cognitive function. In studies of individuals with newly diagnosed type 2 diabetes mellitus, physical activity has been linked to a lower risk of all-cause dementia, Alzheimer's disease, and vascular dementia [43]. Meta-analyses in older adults with T2DM suggest that exercise may improve overall cognitive performance [46]. In addition, systematic reviews indicate that physical activity may modestly delay cognitive decline in the general population, with particularly pronounced effects on executive functions and memory. In clinical practice, this implies that dementia prevention in patients with T2DM should include not only glycaemic control but also lifestyle interventions that support both cardiovascular and neurocognitive health [41,45].

Potential Neuroprotective Effects of Antidiabetic Medications

In recent years, interest has increased in the potential neuroprotective effects of certain antidiabetic medications. However, it should be emphasized that most available evidence is observational in nature, and findings are not always fully consistent. For this reason, these agents should not currently be considered pharmacological prevention of dementia, although they may represent a beneficial component of a broader therapeutic strategy [23]. Metformin is the most extensively studied drug in this regard. Some cohort studies and meta-analyses suggest that its use is associated with a lower risk of dementia, particularly with longer duration of therapy [47–50]. Proposed mechanisms include improved insulin sensitivity, activation of AMP-activated protein kinase (AMPK), reduction of oxidative stress, and attenuation of inflammatory processes [49,50]. Nevertheless, the results are not entirely consistent, and further well-designed prospective studies are required. Glucagon-like peptide-1 receptor agonists

(GLP-1 RAs) have also attracted considerable interest. A meta-analysis of randomized clinical trials showed that GLP-1 RAs were associated with a reduced risk of dementia, whereas the overall effect across all antidiabetic medications was not significant [47]. More recent observational studies also suggest a potential protective effect of this drug class, although results vary depending on the population and methodology [51,52]. Potential mechanisms include anti-inflammatory effects, improvement of endothelial function, weight reduction, and favourable metabolic effects. For sodium-glucose cotransporter-2 (SGLT2) inhibitors, the data are promising but still insufficient for definitive conclusions. Some analyses suggest a possible reduction in dementia risk; however, meta-analyses of randomized trials have not confirmed a significant class-wide effect [23,47]. Their potential cognitive benefit is most likely indirect, mediated through improvements in cardiovascular and metabolic profiles. Overall, research on antidiabetic drugs as potential dementia-preventive agents is encouraging but requires confirmation in large prospective and randomized trials. At present, the most important principle remains that antidiabetic therapy should be regarded as part of comprehensive metabolic and cardiovascular risk management, rather than as a standalone neuroprotective strategy [23,47].

DISCUSSION

The evidence reviewed supports an association between T2DM and dementia, but the strength of this association differs by dementia subtype. In the Danish registry study, adjusted hazard ratios were 1.98 for vascular dementia and 1.13 for Alzheimer's disease in individuals with T2DM compared with those without diabetes [24]. This difference is consistent with an important vascular contribution, although it does not establish that vascular injury explains the entire association. In the same study, Mendelian randomization did not identify a significant association between genetic liability to T2DM and Alzheimer's disease [24]. Thus, observational associations and biologically plausible mechanisms should not be interpreted as proof that T2DM directly causes Alzheimer's disease. Genetic analyses also address a different exposure from the accumulated consequences of hyperglycaemia and vascular complications.

Findings concerning diabetes duration require careful interpretation. The 2024 meta-analysis reported increased dementia risk in the category with diabetes duration below five years, but substantial heterogeneity limits a simple interpretation of this result [13]. The 2025 review of glycaemia-related factors associated longer diabetes duration

with higher dementia risk [9]. These findings should not be reduced to opposing claims that either short or long duration is uniformly more harmful. Interpretation depends on the reference groups, duration categories, and populations studied. An elevated risk early after diagnosis does not establish that this risk exceeds that associated with longer disease duration.

The evidence also requires distinctions between individual glycaemic measures. The 2025 review associated hypoglycaemia and HbA1c variability with increased dementia risk. Although individual studies reported higher risk at higher HbA1c levels, the pooled HbA1c estimate from three studies was not statistically significant, with an HR of 1.18 and a 95% CI of 0.97 to 1.45 [9]. These results do not establish a specific HbA1c target for dementia prevention or demonstrate that progressively lowering HbA1c improves cognitive outcomes. They support attention to both hyperglycaemia and hypoglycaemia rather than treating mean HbA1c as the sole indicator of cognitive risk.

Comprehensive diabetes care may be relevant to cognitive outcomes. In the RAMP-DM study, participation in a multidisciplinary programme was associated with lower all-cause dementia incidence, with an adjusted HR of 0.72 compared with usual care [14]. However, this was an observational comparison. Propensity score matching and statistical adjustment cannot exclude residual confounding or determine which programme components contributed to the association. The finding therefore supports further evaluation of integrated care, rather than establishing the programme as a proven dementia prevention intervention.

Evidence concerning antidiabetic medications is not uniform. Hui and colleagues found no statistically significant overall association between metformin use and dementia or Alzheimer's disease in their pooled analysis, with substantial heterogeneity [18]. This limits a general claim that metformin provides established neuroprotection. Observational medication comparisons also require attention to treatment selection and differences between comparator groups.

The randomized evidence provides a more specific, but still qualified, finding. Seminer and colleagues found no significant overall reduction in dementia or cognitive impairment across the evaluated therapies. GLP-1 receptor agonists showed a significant association with a lower risk, whereas SGLT2 inhibitors did not [47]. However, dementia diagnoses were generally reported as adverse events rather than systematically assessed outcomes, event rates were low, and follow-up was relatively short. No significant reduction in Alzheimer dementia was demonstrated. These limitations prevent in-

terpreting the GLP-1 findings as established prevention of Alzheimer's disease and support the need for trials designed specifically to assess cognitive outcomes [47].

The clinical relevance of this review lies in recognizing cognitive risk within comprehensive diabetes care. Cognitive difficulties may compromise self-management and should be considered when assessing treatment complexity and the support a patient requires. Nevertheless, the reviewed evidence does not establish a particular glucose-lowering regimen for dementia prevention. Future studies should distinguish incident dementia from changes in cognitive test performance and evaluate whether metabolic or cardiovascular interventions produce sustained cognitive benefits.

Limitations

This narrative review used PubMed and Google Scholar and excluded publications without accessible full texts. These choices may have influenced the evidence selected. The reported search and selection procedures do not establish comprehensive coverage of the literature, and no formal assessment of study quality or risk of bias is described.

The review combines original studies, systematic reviews, meta-analyses, and guidelines. Differences in populations, comparison groups, dementia definitions, glycaemic measures, and adjustment for confounders limit direct comparison. Overlap of primary studies between the included reviews was not assessed, so repeated findings should not be treated as independent confirmation. These limitations restrict the review to a descriptive and critical synthesis rather than definitive causal conclusions.

CONCLUSIONS

Type 2 diabetes mellitus is associated with an increased risk of cognitive impairment and dementia, with a generally stronger association for vascular dementia than for Alzheimer's disease. Metabolic and vascular disturbances may contribute to this relationship, but the available evidence does not establish that T2DM directly causes Alzheimer's disease. Longer diabetes duration, hypoglycaemia, and greater HbA1c variability are associated with higher dementia risk, while findings concerning mean HbA1c require cautious interpretation.

Cognitive impairment may complicate diabetes self-management and recognition of hypoglycaemia. Comprehensive care should therefore consider cognitive difficulties

alongside individualized glycaemic management, cardiovascular risk factors, and lifestyle. However, this review does not establish a specific glycaemic target or intervention for preventing dementia.

Evidence concerning the cognitive effects of antidiabetic medications differs across drug classes and study designs. Current findings do not establish metformin, GLP-1 receptor agonists, or SGLT2 inhibitors as treatments for dementia prevention. Further trials with adequate follow-up and systematic assessment of cognitive outcomes are needed.

DISCLOSURE

Author Contributions

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