

REVIEW ARTICLE

Hypoglycemia as a risk factor for dementia in diabetes: A systematic review

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Abstract

Diabetes is a global health concern associated with complications such as cognitive decline and dementia. This systematic review investigated the risk of hypoglycemia and dementia in patients with diabetes. A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science for cohort studies published between January 1, 2020, and March 15, 2025. Eight studies with over 1.1 million individuals with diabetes, mainly type 2 diabetes (T2D), were included. The selected studies were conducted in various countries and had follow-up periods ranging from 5.9 to 9.14 years. This review demonstrated that hypoglycemic episodes are strongly associated with an increased risk of cognitive decline, including Alzheimer's disease, vascular dementia, and all-cause dementia. The hazard ratios ranged from 1.25 to 2.80, with multiple episodes significantly increasing the likelihood of dementia. Blood sugar fluctuations, particularly increased hemoglobin A1c levels and variability, heighten the risk of dementia. Sex-based analyses showed that women with T2D faced a higher risk of dementia linked to glycemic factors. The relationship between hypoglycemia and cognitive decline is bidirectional, with cognitive decline affecting diabetes management and leading to hypoglycemia. The findings underscore the importance of maintaining stable blood sugar levels, setting treatment goals, and incorporating cognitive assessments in diabetes care for older adults.

Keywords: Diabetes; Hypoglycemia; Dementia; Alzheimer's disease; Vascular dementia

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1. Introduction

Diabetes represents a major global health challenge, with 589 million adults aged 20–79, equivalent to roughly 1 in 9 people, affected in 2024. Projections indicate that this number could reach 853 million by 2050, with healthcare costs approaching US\$ 1 trillion.¹ India has one of the highest diabetes burdens globally, with the ICMR–INDIAB study (2019–

2021) reporting 101 million adults with diabetes and 136 million with prediabetes—showing an urgent need for scalable healthcare solutions.^{2,3} On the other hand, dementia represents another growing public health issue on a global scale, with 57 million people affected in 2021 and 10 million new cases being reported each year. Projections indicate that this number could reach 153 million by 2050.^{4,5} In India, a study found a 7.4% prevalence among those aged 60 and above, which translates to 8.8 million elderly Indians with dementia. It has been reported that the dementia prevalence varies by gender and rural–urban location, highlighting concerns regarding accessibility to care.⁶

Repeated or severe low blood sugar levels can accelerate cognitive decline through oxidative stress, neuroinflammation, excitotoxicity, and brain microvascular damage. Cognitive decline can also increase the risk of hypoglycemia through poor medication management and self-care, creating a cycle that is particularly relevant to older adults with type 2 diabetes (T2D). The effects of diabetes extend beyond microvascular complications, such as retinopathy, neuropathy, and nephropathy, and macrovascular effects, including cardiovascular and cerebrovascular diseases.⁷ It is linked to neurological issues, particularly cognitive decline and dementia.^{8,9} Alzheimer's disease (AD) and vascular dementia are more common in patients with diabetes. Research shows that diabetic patients have a 1.5–2 times higher risk of developing dementia.^{8,9} This increased risk stems from factors including hyperglycemia, insulin resistance, microangiopathy, oxidative stress, and inflammatory pathways affecting brain function.

Hypoglycemia, a deleterious side effect of glucose-lowering treatments, contributes to cognitive issues in patients with diabetes. It occurs when blood glucose drops below 70 mg/dL, causing symptoms ranging from adrenergic responses such as palpitations and sweating, to neuroglycopenic effects such as confusion and seizures.¹⁰ There are three classifications of hypoglycemia: Mild (level 1: <70 mg/dL), moderate (level 2: <54 mg/dL), and severe (level 3: A severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery).¹¹ While more frequent in insulin-dependent type 1 diabetes (T1D), hypoglycemia also affects T2D patients on intensive treatments.¹²

The Whipple triad, which includes hypoglycemic symptoms, low plasma glucose, and symptom relief after glucose administration, remains key criteria for clinical diagnosis of hypoglycemia.¹³ Research indicates that frequent hypoglycemic episodes may contribute to cognitive decline and dementia onset.⁸ This concern is significant as hypoglycemia can cause cumulative neuronal damage from repeated glucose shortages in the brain.

The pathophysiological mechanisms explain the link between hypoglycemia and dementia. Low blood glucose levels can induce oxidative stress, neuroinflammation, and neuronal apoptosis, harming brain function and accelerating neurodegeneration.⁸ Hypoglycemia can cause cognitive deficits, including memory loss and executive dysfunction. In patients with diabetes, especially older adults, these episodes increase the risk of transient ischemic attacks, microvascular damage, and vascular dementia.^{9,14}

The complexity of this issue stems from the bidirectional link between hypoglycemia and dementia. Cognitive decline leads to poor diabetes management and increased hypoglycemia risk, whereas hypoglycemic episodes may accelerate cognitive deterioration. Although this association is biologically plausible, the scientific literature has shown inconsistent findings. Some studies indicate a strong link between hypoglycemia and dementia risk, while others remain inconclusive.^{9,14} This may be due to variations in the study design, population, and diagnostic criteria.

Nurse-facilitated multidisciplinary models are crucial for breaking this cycle. Nurses specializing in lifestyle medicine and diabetes management deliver diabetes self-management education and support, adjust medications, utilize continuous glucose monitoring (CGM) for titration, develop hypoglycemia management plans, and set goals. These strategies lower hemoglobin A1C (HbA1C) levels and reduce the incidence of hyperglycemia.¹⁵ Evidence supports nurse-led self-management programs that improve HbA1c and risk factor control in healthcare settings.¹⁶ Community-based nurse-led support showed lower HbA1c levels than standard care. These approaches, including group visits and telehealth, are scalable in low-resource areas and are critical for India and low-/middle-income countries.

Psychosocial factors such as diabetes distress, health literacy, and patient-provider communication influence self-care, adherence, and glycemic control, affecting hypoglycemia risk. Poor health literacy correlates with higher HbA1c levels and complications, whereas effective communication improves self-management.¹⁷

AD comprises 60–70% of dementia cases, marked by beta-amyloid plaques and neurofibrillary tangles, causing cognitive decline.¹⁸ Vascular dementia, the second most common type of dementia in AD, stems from reduced brain blood flow and microangiopathic changes—alterations that are common in diabetic patients due to high blood sugar and endothelial dysfunction.¹⁸ Other types, such as Lewy body and frontotemporal dementia, share risk factors with diabetes, including aging and cardiovascular issues.¹⁸ Dementia symptoms include memory impairment, personality changes, confusion, and declining abilities.

As it progresses from mild forgetfulness to dependency, complications such as malnutrition, falls, and psychological distress would exacerbate.^{18,19} Thus, prevention strategies targeting modifiable risk factors, such as glycemic variability, are crucial. Brain insulin resistance in diabetes may impair glucose metabolism and promote amyloid buildup, linking diabetes to AD.^{9,14} Inflammation from high blood sugar and oxidative stress can cause vascular and neurodegenerative harm.^{9,14} Hypoglycemic episodes worsen these by depriving the brain of energy and triggering stress responses that may accelerate cognitive decline.

If hypoglycemia is identified as a modifiable risk factor for dementia, diabetes management goals must be reassessed, especially in older adults. A personalized approach emphasizing metabolic control may help prevent adverse outcomes. Understanding the neurocognitive effects of hypoglycemia may enable interventions to maintain brain health while achieving glycemic control. Patients undergoing intensive diabetes treatment often experience hypoglycemia; however, its role in cognitive decline and dementia remains unclear. Acute hypoglycemia may cause neurodegenerative changes, raising concerns about its cognitive effects. The varied results of the current studies necessitate a comprehensive literature review. Understanding this connection is crucial for guiding treatment and developing preventive measures to improve metabolic and cognitive well-being.

The primary objective of this review was to assess whether hypoglycemia serves as an independent risk factor for dementia in patients with diabetes and to evaluate its association with AD, vascular dementia, and overall dementia. The secondary objective was to examine the modifiers of this relationship, including sex differences, HbA1C variability impact, and whether hypoglycemia might increase the risk of cognitive decline. The research question was as follows: Does hypoglycemia elevate the risk of dementia in patients with diabetes, and how do demographic and clinical factors affect this relationship?

2. Methods

This systematic review examined the association between hypoglycemia and dementia risk in individuals with diabetes. The review used the patient/population, exposure, and outcome framework, focusing on adult patients with diabetes as the study sample, hypoglycemia as the exposure, and dementia, including AD, vascular dementia, or all-cause dementia, as the outcome. Studies were included if they investigated hypoglycemia as a risk factor for cognitive decline in patients with T1D or T2D. The search strategy followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.²⁰

A comprehensive literature search was performed using PubMed, Scopus, and Web of Science that investigated hypoglycemia as a potential risk factor for dementia in patients with diabetes. The search covered from January 1, 2020, to March 15, 2025, and publications were limited to the English language.

For this review, the following Boolean combinations and Medical Subject Headings were used: PubMed: (“hypoglycemia”[MeSH Terms OR “hypoglycemia”[All Fields]) AND (“dementia”[MeSH Terms OR “Alzheimer Disease”[MeSH Terms OR “vascular dementia”[All Fields]) AND (“diabetes mellitus”[MeSH Terms OR “type 2 diabetes”[All Fields OR “type 1 diabetes”[All Fields]), Scopus/Web of Science: TITLE-ABS-KEY (“hypoglycemia” AND “dementia” AND “diabetes”) OR TITLE-ABS-KEY (“cognitive decline” OR “Alzheimer’s disease” OR “vascular dementia”). Filters limited the search to human cohort studies available as full texts within the specified time frame. The search strategy identified observational cohort studies that provided original data on dementia risk following hypoglycemia in diabetic adults.

This review included cohort studies that examined the association between hypoglycemia and dementia in adults with T1D or T2D. Studies were required to identify hypoglycemia as the exposure and report dementia outcomes (AD, vascular dementia, or all-cause dementia) as primary or secondary endpoints. They were required to provide effect estimates such as hazard ratios (HRs), relative risks, or odds ratios with 95% confidence intervals (CIs). We excluded reviews, meta-analyses, theses, case reports, editorials, studies published more than 9 years, and those lacking cognitive outcome data from the search.

The study selection process was conducted in two stages: Initially, duplicates were removed, and three reviewers assessed the titles and abstracts for relevance using the online tool Rayyan (accessible at <https://rayyan.qcri.org>). Articles meeting the criteria were retrieved for full-text review. Studies were excluded if they did not define hypoglycemia, failed to evaluate dementia outcomes, or provided insufficient information. Studies were also excluded if they focused on pediatric populations or repeated previously published data without new analyses. Disagreements among the reviewers were resolved through discussion, with a fourth reviewer serving as an arbitrator when needed. The review process and exclusion reasons are detailed in the Preferred Reporting Items for Systematic Review and meta-analysis 2020 flow diagram.

Two reviewers independently assessed the methodological quality of the included studies using the National Heart, Lung, and Blood Institute Quality

Assessment Tool for Observational Cohort Studies, focusing on research question clarity, study population suitability, exposure and outcome measurement, follow-up adequacy, and adjustment for confounding variables. The Cochrane risk of bias framework was used to examine potential biases related to selection, performance, detection, attrition, and reporting outcomes. The studies were classified as having low, unclear, or high risk of bias. The inter-rater reliability between the reviewers was determined using Cohen's kappa statistic, which showed a high agreement. Discrepancies were resolved through discussion, and the bias assessment results are presented in the text and visually in a risk of bias figure.

The reviewers exhibited high inter-rater reliability. When measured using Cohen's kappa statistic ($\kappa = 0.82$), it indicated significant agreement in their independent evaluations. This value indicates that a few disagreements arose, showing that the independent evaluations were largely consistent. Few disagreements were addressed through discussion. This approach ensured that the bias

assessment was clear and dependable, enhancing the credibility of the evidence synthesis.

A statistical meta-analysis was not possible owing to variability in study populations, definitions of hypoglycemia and dementia, follow-up periods, and analytical methods. Instead, a structured narrative synthesis was conducted to describe associations across studies, report HRs and CIs, and highlight subgroup findings, such as differences by sex and effects of glycemic variability.

3. Results

A search of PubMed, Scopus, and Web of Science yielded 98 articles. After applying the inclusion and exclusion criteria, 38 records were removed due to a lack of full-text availability. Of the 60 remaining studies, 46 were excluded after relevance and eligibility screening. Fourteen studies underwent full-text review, and six were excluded due to insufficient data and/or conclusions. Eight studies met all the inclusion criteria and were included in the systematic review.²¹⁻²⁸ Figure 1 provides a summary of the selection

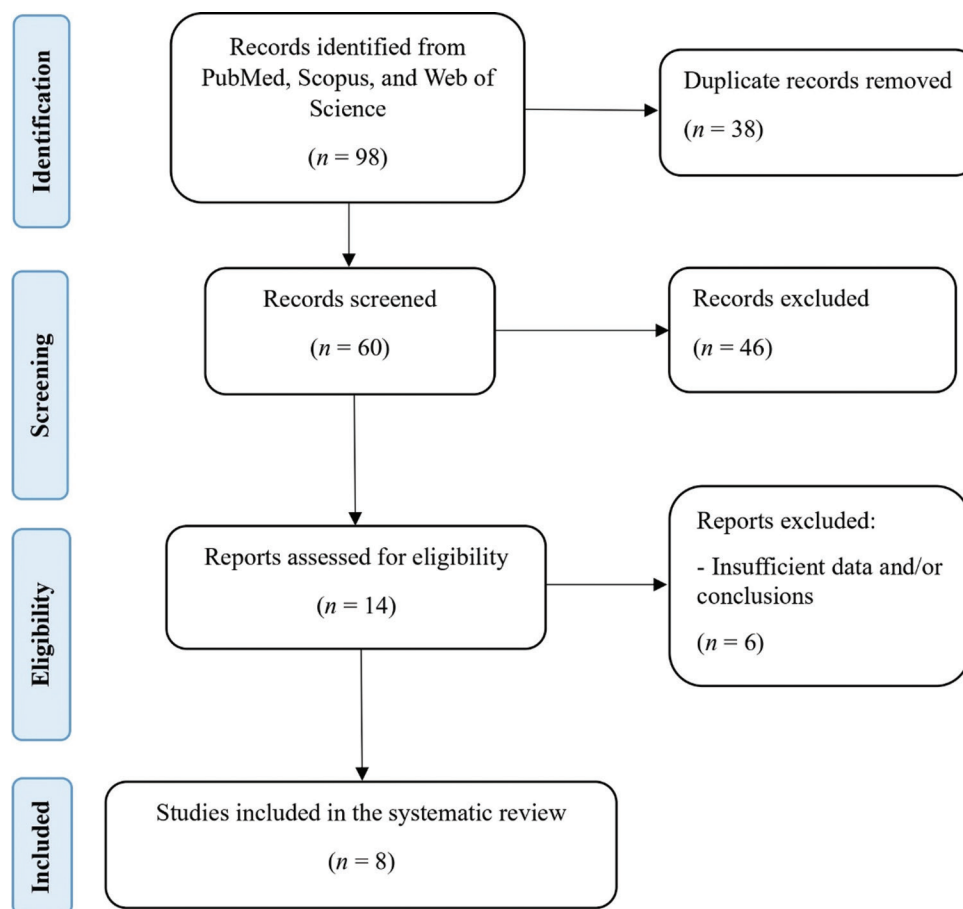


Figure 1. Flow diagram of literature search and selection of studies for systematic review (preferred reporting items for systematic review and meta-analysis flow chart)

process, and Table 1 outlines the key characteristics of the included studies.

This systematic review analyzed eight cohort studies with over 1.1 million individuals with diabetes, mainly T2D. The follow-up period ranged from 5.9 to 9.14 years. Conducted in South Korea, the US, the UK, Hong Kong, Canada, and China, these studies offer broad applicability. The research designs included cohort analyses using national health databases or healthcare systems. The key methods used were propensity score matching, time-varying Cox regression, and adjustments for clinical variables such as age, sex, HbA1C levels, diabetic complications, depression, and comorbidities.

Evidence shows a strong link between hypoglycemic episodes and an increased risk of cognitive decline, including AD, vascular dementia, and all-cause dementia.^{21–26} Studies on T1D and T2D demonstrate that hypoglycemia raises dementia risk, with HRs ranging from 1.25 to 2.80, particularly in those with recurrent episodes.^{21,23,26} A dose–response relationship revealed that while single episodes increased risk, multiple episodes significantly raised dementia likelihood.^{21,23} This pattern occurs in both mid-life and late-life hypoglycemia onset, showing that cognitive susceptibility persists throughout diabetes.²⁶ Blood glucose fluctuations, particularly increased HbA1c levels and variability, heighten the risk of dementia.^{24,25,27} Patients with poor blood glucose control (HbA1c $\geq 9\%$ or $\geq 10\%$) have a higher likelihood of dementia than those who maintain it at advised levels.²⁷ Blood sugar variability

independently predicts cognitive decline, indicating that both high glucose levels and fluctuations contribute to neurodegeneration.^{24,25}

Sex-based analyses showed that women with T2D face a higher risk of dementia linked to glycemic factors. In older women, severe hypoglycemic episodes and HbA1c fluctuations indicate AD, regardless of the initial glycemic condition and diabetes duration.²⁵ These findings highlight sex as a biological factor in assessing dementia risk in patients with diabetes. Studies examining hypoglycemia as a risk factor for dementia have revealed bidirectional causality. Patients with diabetes and dementia face an increased risk of hypoglycemia.²⁸ Cognitive decline affects medication adherence and symptom awareness, leading to hypoglycemia. This relationship between hypoglycemia and cognitive decline complicates the management of diabetes. In addition, it has been demonstrated that the combination of hypoglycemia and dementia contributes to the highest mortality risk compared to either condition alone,²³ highlighting the need for early detection of hypoglycemia and cognitive decline in older diabetic populations. Evidence analysis shows that hypoglycemia is a key risk factor for dementia in patients with diabetes. These findings emphasize the importance of maintaining stable blood glucose levels and setting personalized treatment goals, especially for older adults with cognitive vulnerabilities.

The risk of bias was assessed for eight studies across five areas: selection, performance, detection, attrition, and reporting biases (Figure 2). The selection and reporting

Table 1. Characteristics of selected studies on evaluating the association between hypoglycemia and dementia risk in patients with diabetes

Author (year)	Country	Diabetes type	Sample size	Key exposure	Follow-up duration	Dementia risk (HR, CI)
Kim <i>et al.</i> (2020) ²¹	South Korea	T2D	11,932	≥ 1 Hypoglycemic episodes	Not reported	HR: 1.254 (1.166–1.349)
Whitmer <i>et al.</i> (2021) ²²	United States	T1D	28,31	Severe hypo- and hyperglycemia	6.9 years	HR: 1.66 (1.09–2.53); HR: 6.20 with both events
Han <i>et al.</i> (2022) ²⁵	South Korea	T2D	2,032,689	Severe hypoglycemia	6.9 $\pm$ 1.7 years	HR: 1.54 (1 episode); HR: 1.80 (≥ 2 episodes)
Zheng <i>et al.</i> (2021) ²³	United Kingdom	T2D	457,902	HbA1c levels and complications	Median: 6 years	HR: 1.08 per 1% HbA1c; HR: 1.03 per SD variability
Lee <i>et al.</i> (2021) ²⁴	Hong Kong	T2D	85,514	Severe hypoglycemia, HbA1c variability	Median: 6 years	Significant in women only; AD prediction
Alkabbani <i>et al.</i> (2023) ²⁶	Canada	T2D	445,623	Severe hypoglycemia (mid vs late life)	Midlife: 9.14 years; Late-life: 6.7 years	HR: 2.85 (midlife); HR: 2.38 (late-life)
Moran <i>et al.</i> (2023) ²⁷	United States	T2D	253,211	Cumulative HbA1c exposure	Mean: 5.9 years	HR: 1.74 (HbA1c $\geq 10\%$)
Alsharif <i>et al.</i> (2023) ²⁸	United Kingdom	T2D	20,706	Dementia status (risk of hypoglycemia)	Mean: 6.11 years	HR: 2.00 (1.63–2.66)

Abbreviations: AD: Alzheimer's disease; CI: Confidence interval; HbA1c: Hemoglobin A1c; HR: Hazard ratio; SD: Standard deviation; T1D: Type 1 diabetes; T2D: Type 2 diabetes.

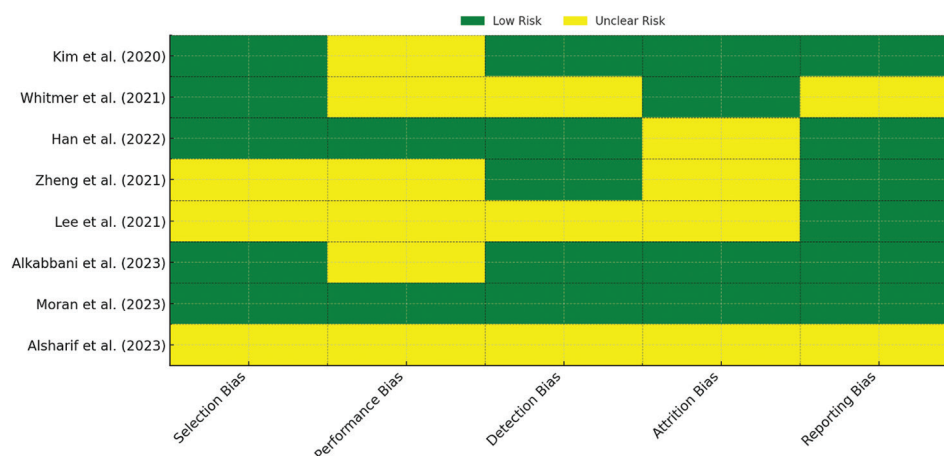


Figure 2. Risk of bias assessment across included studies for systematic review

domains showed a low risk of bias. Studies by Kim *et al.*, Alkabbani *et al.*, and Moran *et al.* exhibited a low risk of bias across most domains.^{21,26,27} However, an unclear risk of bias was noted in the performance, detection, and attrition domains. Studies by Whitmer *et al.*, Zheng *et al.*, Lee *et al.*, and Alsharif *et al.* showed an unclear risk of bias in at least three domains.^{22–24,28} The study by Alsharif *et al.* had an unclear risk of bias in all five domains, indicating a lack of methodological detail.²⁸ Han *et al.*'s study showed a low risk of bias but had an unclear risk of attrition bias.²⁵ Overall, the frequent occurrence of unclear risks, particularly in the performance and detection domains, suggests potential issues with study blinding and outcome assessment methods.

4. Discussion

This systematic review combined evidence from high-quality cohort studies, highlighting a strong link between hypoglycemia and elevated dementia risk in patients with diabetes. The studies indicate that patients with T1D and T2D who experience hypoglycemic episodes, especially if recurrent or severe, are significantly more likely to develop dementia, with HRs ranging from 1.10 to over 2.80.

The findings of this review are consistent with those of previous studies. A systematic review and meta-analysis by Huang *et al.*²⁹ that included over 1.4 million individuals with diabetes showed that hypoglycemic episodes are linked to a 44% higher risk of developing dementia than those without such episodes (adjusted HR = 1.44, 95% CI: 1.26–1.65). This association remained consistent across subgroups according to study design, location, diabetes type, HbA1C adjustment, sex, and hypoglycemic event frequency.²⁹ Lacy *et al.*³⁰ studied older adults with T1D (mean age, 67 years), and found that recent severe hypoglycemic incidents were linked to reduced global

cognitive abilities and diminished performance in language, executive function, and episodic memory. Those who experienced four or more incidents in the previous year were 3 times more likely to have impaired global cognition (odds ratio: 3.1; 95% CI: 1.26–7.63). Furthermore, severe hypoglycemia was particularly associated with executive dysfunction, although it did not correlate with other cognitive impairments.³⁰ Diabetes predicts the progression from mild cognitive impairment to dementia, raising the risk 1.52 times compared to other factors.³¹

Hypoglycemia causes cognitive decline through neuronal energy failure, oxidative stress, and excitotoxicity, affecting the hippocampus and cerebral cortex, which are crucial for memory and cognition.³² Frequent hypoglycemia leads to brain atrophy and white matter changes visible on magnetic resonance imaging scans.³³ Longitudinal studies support these findings. The ACCORD-MIND trial found that intensive glycemic control, which causes more severe hypoglycemia, was unexpectedly linked to cognitive decline and reduced brain volumes.³⁴ This underscores the need to balance glycemic goals with cognitive health, especially in older adults.

Recent findings have shown that glucose variability and absolute hypoglycemia are significant. A systematic review and meta-analysis by Chi *et al.*³⁵ indicated that increased glucose variability is associated with a heightened risk of cognitive impairment in patients with T2D. These fluctuations may result in cerebral stress, triggering inflammation and neuronal dysfunction. Gender-specific susceptibilities have also been identified. Women with T2D are more prone to cognitive alterations due to hypoglycemia, which may be linked to hormonal differences influencing neuronal metabolism and vascular reactivity.³⁶ This highlights the importance of conducting sex-stratified analyses in future studies.

Patients with hypertension, obesity, or dyslipidemia have an increased likelihood of hypoglycemia and dementia. These conditions are linked to vascular damage, endothelial dysfunction, and compromised blood–brain barrier integrity, which intensify the neurotoxic impact of hypoglycemia.^{16,18} Verhulst *et al.*³⁷ found that acute hypoglycemia reduced cognitive abilities, as shown by an 8.4% drop in correct answers to the Paced Auditory Serial Addition Test, a delay in reaction times of approximately 32 ms, and increased working memory mistakes. These effects were observed regardless of the type of diabetes, symptom awareness, duration, or HbA1c levels.³⁷

Ye *et al.*³⁸ studied nearly 4 million participants and showed that those with hypoglycemia had a 47% greater likelihood of cognitive dysfunction than those without, with each episode increasing the risk by 17.87%. A review by Meng *et al.*³⁹ demonstrated that repeated hypoglycemia causes neuronal energy deficits, excitotoxicity, and synaptic dysfunction, all of which contribute to the development of dementia. A systematic review and meta-analysis by Tabesh *et al.*⁴⁰ found a 49% higher risk of all-cause dementia and a 31% increased risk of AD in patients with hypoglycemic events. These findings highlight the epidemiological link and pathophysiological pathways through which hypoglycemia may accelerate cognitive decline, emphasizing the importance of preventing hypoglycemic episodes, particularly in older adults and those at a higher risk of neurodegeneration.

The relationship between hypoglycemia and dementia is bidirectional. Cognitive decline leads to poor diabetes management through skipping meals or insulin dosing errors, triggering hypoglycemia.²⁸ Cognitive assessments are crucial for diabetes management in older individuals with a history of hypoglycemia. These results support the need to reevaluate glycemic targets in older adults with multiple conditions. The American Diabetes Association recommends moderate HbA1c control (7.0–7.5%) for those at risk of hypoglycemia or cognitive decline.¹¹ Preventive measures, such as CGM, education, medication review, and simplified insulin regimens, should be adopted.

In addition to vascular and metabolic factors, hypoglycemia directly worsens dementia-related neuropathological processes. Animal studies showed that repeated moderate hypoglycemia accelerates tau hyperphosphorylation and amyloid-beta accumulation, key features of AD, through oxidative stress and disrupted insulin signaling.⁴¹ Hypoglycemia causes mitochondrial dysfunction, glutamate excitotoxicity, and blood–brain barrier disruption, leading to synaptic degeneration and hippocampal damage.³⁶

Concerns exist regarding the cognitive effects of rigorous glycemic control in older individuals. The ACCORD-MIND study found that patients with HbA1c <6.5% experienced more hypoglycemia and showed greater cognitive decline and brain volume reduction than those receiving standard treatment.³⁴ These results indicate the need to adjust glycemic targets based on cognitive health and age.

Despite the evidence, cognitive function assessment is not standard in diabetes care. Integrating screening tools, such as the Montreal Cognitive Assessment, into treatment plans is important for older adults with frequent hypoglycemia. CGM can identify asymptomatic hypoglycemia, reduce glucose fluctuations, and improve glycemic control in patients with diabetes. CGM use also decreases hypoglycemia frequency, aiding in the prevention of cognitive impairments.⁴²

The risk of bias analysis revealed methodological differences among studies examining hypoglycemia and dementia in patients with T2D. Studies by Kim *et al.* and Moran *et al.* showed high methodological quality with low bias risk across domains.^{21,27} These studies had defined cohort designs, standardized outcomes, and thorough follow-up data. Studies by Whitmer *et al.* and Lee *et al.* showed unclear risks in selection, performance, detection, and attrition due to insufficient details on randomization, absence of blinding, and incomplete reporting on participant attrition.^{22,24} Performance and detection biases emerged when blinding of participants and outcome assessors was not possible—a limitation of observational studies using secondary data. An unclear detection bias may indicate inconsistent methods for defining dementia outcomes. Alsharif *et al.*'s study exhibited high uncertainty, with all domains rated unclear, indicating a need for greater transparency in methodology.²⁸

A key limitation of this study is the variability in the definition of hypoglycemia and dementia outcomes. Some studies used hospital records or databases to identify hypoglycemia, while others used self-reported incidents, which may increase the risk of underreporting. Dementia diagnosis methods vary from clinical evaluations to health records, leading to potential inconsistencies. These differences make comparisons difficult and may explain the variations in effect estimates. Population differences contribute to this heterogeneity. While cohorts included patients with T2D, T1D had limited representation, focusing mainly on East Asia and Western countries. Healthcare systems, glucose monitoring access, and cultural differences in diabetes management can affect hypoglycemia detection and dementia diagnosis. In addition, follow-up periods of 5.9–9.14 years might not fully capture dementia development.

Publication bias is concerning, as studies finding positive links between hypoglycemia and dementia may be more likely to be published, potentially exaggerating the association. Selection bias could affect generalizability, particularly in database studies with incomplete records. Despite moderate-to-high quality ratings for the selected studies, unclear risks in performance and detection revealed methodological issues. The lack of blinding and incomplete reporting could compromise the validity of the results. Confounding factors, such as cognitive status, genetic predisposition, socioeconomic status, and lifestyle habits, have been inconsistently addressed. Future studies should use standardized definitions of hypoglycemia and dementia, thorough cognitive testing, and consistent confounder adjustment. CGM and harmonized diagnostic criteria would reduce misclassification bias, and diverse populations would improve generalizability.

Future research should explore the dose–response relationship between hypoglycemia and dementia risk, incorporating CGM to detect glycemic variability. There is a need to explore the biological mechanisms underlying this connection, including biomarkers of oxidative stress and brain changes, using advanced imaging. Understanding these mechanisms may help identify potential intervention targets. Studies assessing whether reducing the risk of hypoglycemia decreases the incidence of dementia are vital. Clinical trials comparing glycemic control strategies may help guide personalized management. Including diverse populations will improve the external validity. Special consideration should be given to older adults with comorbidities who are at a high risk for both conditions.

Drawing from this systematic review connecting hypoglycemia with increased dementia risk in patients with diabetes, the following recommendations are suggested: (i) Personalized glycemic targets: Clinicians should customize glycemic targets based on individual risk factors, especially in older adults with cognitive issues. For patients susceptible to hypoglycemia, maintaining a moderately controlled HbA1c range (7.0–7.5%) is recommended. Regular cognitive evaluations in diabetes care, particularly in elderly patients with severe hypoglycemic episodes, are crucial for early detection. Hypoglycemia prevention strategies, including CGM devices, simplified insulin regimens, and medication reviews, reduce the occurrence of hypoglycemia. (ii) Risk management: Assessments should include sex- and age-specific analyses to identify vulnerable subgroups, considering hormonal and vascular differences that affect dementia risk. Collaborative care involving

endocrinologists, neurologists, geriatricians, and diabetes educators is essential.

5. Conclusion

This systematic review shows that hypoglycemia is a crucial risk factor for dementia in patients with diabetes, particularly in those with T2D. Large-scale studies have demonstrated that frequent hypoglycemic events independently increase the risk of cognitive decline, including Alzheimer's and vascular dementia. The findings revealed that hypoglycemia accelerates neurodegeneration through oxidative stress and neuroinflammation, whereas cognitive decline increases the risk of inadequate diabetes management. These insights highlight the need to incorporate cognitive outcomes into diabetes care and reconsider glycemic targets for older adults with comorbidities.

Future research should aim to create predictive models that integrate clinical, metabolic, and neurocognitive elements to identify high-risk patients. Preventive measures, such as glucose monitoring, customized treatments, and cognitive evaluations, should be prioritized to mitigate hypoglycemia and its neurological effects. Large-scale prospective studies with standardized definitions and biomarker-based imaging are essential to understand the causal pathways. Implementing personalized diabetes management can enhance metabolic control and protect cognitive health in at-risk groups.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data

Not applicable.

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