

Updates on Diabetes as a Risk Factor for Developing Dementia: A Systematic Review

Abstract

Background: There is debate over the relationship between diabetes and the main forms of dementia. The cognitive alterations associated with type 2 diabetes (T2D) mostly impact mental flexibility, mental speed, and learning and memory. **Objectives:** To ascertain the degree of the link between diabetes and dementia, we thoroughly reviewed papers on the incidence of dementia in individuals with diabetes mellitus in this study. **Methods:** PubMed, SCOPUS, Web of Science, and Science Direct were systematically searched for relevant literature. Rayyan QRCI was employed throughout this comprehensive process. **Results & interpretation:** We included ten studies with a total of 173797 participants, and 78828 (45.4%) were males. All of the included studies were prospective cohorts. For diabetic patients, early-onset diabetes, poor glycemic management, and diabetes status are risk factors for dementia development. There was also a higher chance of dementia development in those with mild to severe motor cognitive impairment and hereditary variables. Longitudinal studies that involve comprehensive evaluations of comorbid diseases and diabetes-related variables, as

well as rigorous assessments of cognition—ideally in conjunction with neuroimaging—will be necessary for this process. This method will work best with large population-based cohort studies of older adults with diabetes and with longitudinal studies of at-risk groups that look at the development of diabetes, metabolic syndrome, vascular disease, and cognitive decline.

Keywords; Diabetes mellitus; Dementia; Cognitive function; ; Systematic review.

Introduction

Global healthcare systems are facing increasing problems from dementia and diabetes due to changes in demographics and lifestyle. Fifty million individuals globally suffer from dementia, with Alzheimer's disease (AD) and vascular dementia (VaD) being the two most prevalent forms of the condition [1]. Many more people are affected by less severe kinds of cognitive dysfunction that occur before dementia develops; for example, moderate cognitive impairment (MCI) affects 6% of the population [2] and 1 in 5 persons 65 years of age or older [3]. Between dementia and age-appropriate cognition is a condition known as MCI. It is described as objective cognitive impairment in relation to age, with cognitive symptoms being of concern in an individual who is fundamentally functioning normally and is not suffering from dementia [4]. A specific subtype of MCI called amnesic MCI has been connected to the onset of Alzheimer's disease [5]. MCI is a diverse illness. Dementia is highly likely to strike people with motor cognitive impairment (MCI); after three years, 46% of them will get dementia, compared to 3% in an age-matched population [6].

The relationship between diabetes and dementia is debatable, despite the fact that the correlation between the two mild cognitive alterations and diabetes is now well

established. Diabetes and Alzheimer's disease might not coexist, according to early research that revealed a low rate of diabetes in people with the illness [7-9]. A more recent study, however, revealed that up to 80% of Alzheimer's patients may have T2D or impaired fasting glucose [10]. These contradictory findings make it abundantly evident that research on the incidence of diabetes in patients who have dementia that has already progressed is unlikely to yield accurate information about the dementia risk among diabetics. The reasons for these inconsistent results could be methodological, including survival bias of non-diabetic patients with Alzheimer's disease and the potential effects of the disease on glucose metabolism, which could mask the relationship between diabetes and more advanced dementia cases. More accurate risk estimates are obtained from population-based research comparing the occurrence of dementia in people with and without diabetes than from investigations on patients who already have dementia [11].

To ascertain the degree of the link between diabetes and dementia, we thoroughly reviewed papers on the incidence of dementia in individuals with diabetes mellitus in this study. We also looked at how much research has been done on possible moderators and mediators of dementia risk in individuals with diabetes. Underlying processes and pertinent neuropathological research are discussed.

Methodology

In carrying out this systematic review, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards were adhered to [12].

Study Design and Duration

November 2023 marked the start of this systematic review.

Search strategy

To discover the pertinent literature, a thorough search was conducted across four main databases: PubMed, SCOPUS, Web of Science, and Science Direct. We limited our search to English and considered each database's specific needs. The following keywords were transformed into PubMed Mesh terms and used to locate the pertinent studies; "Dementia," "Cognitive function," "Diabetes," "T1D," "T2D," and "Risk." The Boolean operators "OR" and "AND" matched the required keywords. Publications with full English text, available free articles, and human trials were among the search results.

Selection criteria

We considered the following criteria for inclusion in this review:

- Studies that studied the risk of diabetes in developing dementia.
- We included both T1D and T2D.
- Studies conducted between 2019 and 2023.
- We did not include studies that investigated diabetic treatments.
- Only human subjects.
- English language.
- Free accessible articles.

Data extraction

The search technique's output was double-checked using Rayyan (QCRI) [13]. By modifying the combined search results with inclusion/exclusion criteria, the researchers evaluated the relevance of the titles and abstracts. Each paper that met the requirements for inclusion underwent a careful examination by the reviewers. The authors talked about methods for resolving disputes. The approved study was uploaded using a data extraction form already created. The authors extracted data about the study titles, authors, study year, country, participants, gender, diabetes

type, and main outcomes. A separate sheet was created for the risk of bias assessment.

Strategy for data synthesis

Summary tables were created using data from relevant studies to provide a qualitative assessment of the findings and study components. After the data for the systematic review were gathered, the most efficient approach for utilizing the data from the included study articles was chosen.

Risk of bias assessment

The ROBINS-I risk of bias assessment technique for non-randomized trials of therapies was used to evaluate the caliber of the included studies [14]. The seven themes assessed were confounding, participant selection for the study, classification of interventions, deviations from intended interventions, missing data, assessment of outcomes, and choice of the reported result.

Results

Search results

A total of 522 study articles resulted from the systematic search, and 113 duplicates were deleted. Title and abstract screening were conducted on 409 studies, and 323 were excluded. 86 reports were sought for retrieval, and 2 articles were retrieved. Finally, 84 studies were screened for full-text assessment; 40 were excluded for wrong study outcomes, 32 for the wrong population type, and 2 articles were letters to the editors. Ten eligible study articles were included in this systematic review. A summary of the study selection process is presented in

Figure 1.

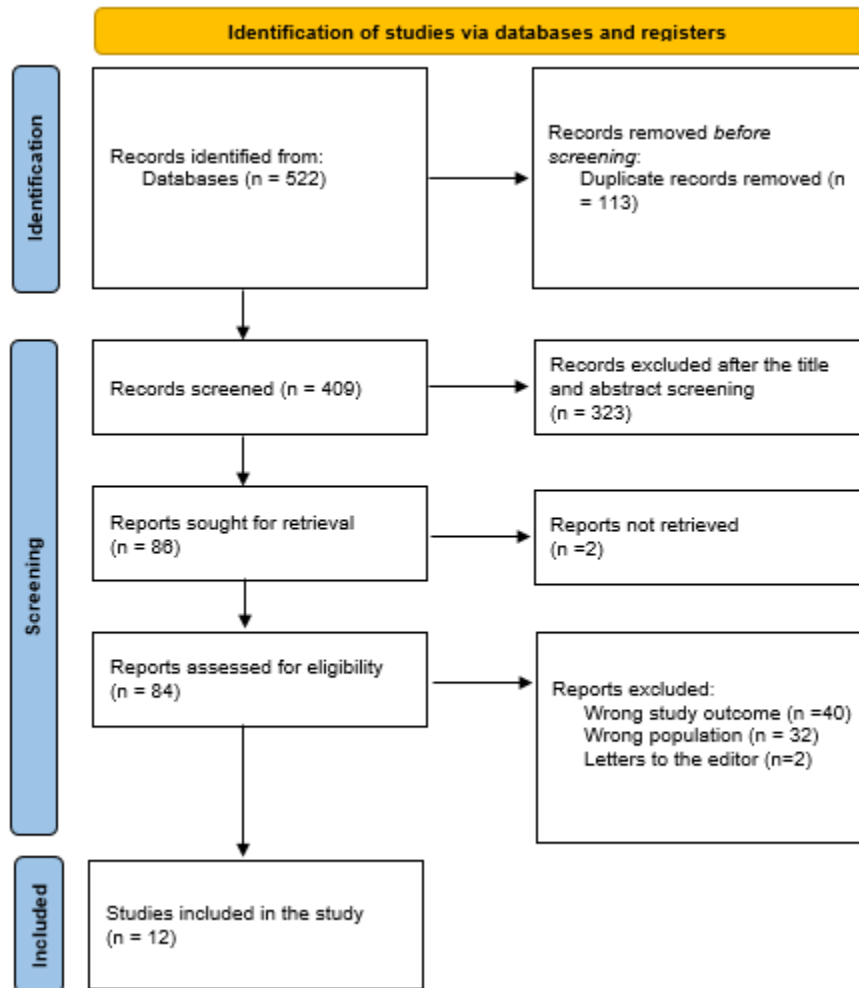


Figure (1): PRISMA flowchart summarizes the study selection process.

Characteristics of the included studies

Table (1) presents the sociodemographic characteristics of the included study articles. Our results included ten studies with a total of 173797 participants, and 78828 (45.4%) were males. All of the included studies were prospective cohorts [15-24].

Table (2) presents the clinical characteristics. Eight of the included studies stated that poor glycemic control, diabetes status, and early-onset diabetes are risk factors for developing dementia in diabetic patients. Mild to moderate motor cognitive impairment [17] and genetic factors [22] were also at an increased risk of developing dementia.

Table (1): Sociodemographic characteristics of the included participants.

Study	Study design	Country	Participants	Gender (Females)	Age
Amidei et al., 2021 [15]	Prospective cohort	UK	10095	74.6±7.2	6798 (37.6)
Shang et al., 2023 [16]	Prospective cohort	China	1376	NM	488 (35.5)
Albai et al., 2019 [17]	Prospective cohort	Romania	207	47-65.5	110 (53.1)
Reinke et al., 2022 [18]	Prospective cohort	Germany	57613	76.9±5.8	22568 (39.2)
Wang & Liu 2021 [19]	Prospective cohort	China	2389	NM	1034 (43.3)
Li et al., 2021 [20]	Prospective cohort	China	25879	59.2±7.1	19122 (73.9)
Wang et al., 2023 [21]	Prospective cohort	China	27415	60.1±7.2	17082 (62.3)
Dybjer et al., 2023 [22]	Prospective cohort	Sweden	29139	58.1±7.61	11539 (39.6)
Rawlings et al., 2019 [23]	Prospective cohort	USA	5099	75.8±5	2080 (40.8)
Li et al., 2023 [24]	Prospective cohort	China	14585	58.9±6.3	7007 (48)

Table (2): Clinical characteristics and outcomes of the included studies.

Study	Diabetes type	Main outcomes	ROBIN-I
Amidei et al., 2021 [15]	T2D	A stronger risk of dementia later in life was found to be correlated with a younger age at the onset of diabetes.	Moderate
Shang et al., 2023 [16]	T1D & T2D	People with T1D or T2D who receive their diagnosis earlier in life are more likely to experience dementia and brain volume loss.	Moderate
Albai et al., 2019 [17]	T2D	Individuals with T2D who have mild to moderate motor cognitive impairment are at an increased risk of developing dementia and should have regular cognitive evaluations. To identify MCI development in its early stages, the MMSE test can be administered regularly.	High
Reinke et al., 2022 [18]	T2D	After the initial years following diagnosis, doctors should continue to regularly monitor cognitive function in diabetes patients because later increases in dementia occur in all therapy groups.	Moderate
Wang & Liu 2021 [19]	T2D	Independent of other demographic characteristics, relatively early-onset diabetes was linked to an increased risk of stroke, AD dementia, and all forms of dementia. The age at which diabetes onset occurs may serve as a possible signal for preventive interventions, and these findings have implications for prioritizing efforts to lower the risk of dementia, AD, and stroke in people with prevalent diabetes, especially in younger adults.	Moderate
Li et al., 2021 [20]	T1D & T2D	Due to variables other than glycemic control, the length of diabetes seems to be linked to the likelihood of incident dementia. When assessing a patient's risk of dementia, clinicians should take into account not just the patient's glycemic control but also the duration of their diabetes.	Moderate
Wang et al., 2023 [21]	T2D	Among diabetes patients, a lower age at the onset of diabetes—especially <45 years old—was substantially linked to an increased risk of dementia in the future.	Moderate
Dybjær et al., 2023 [22]	T2D	This population-based study's findings indicate that some genetic risk factors for T2D are also associated with an increased risk of incident dementia, including vascular dementia. MR studies did not reveal any causative relationships between T2D and dementia, nevertheless.	High
Rawlings et al.,	T1D & T2D	Over a median follow-up of five years, poorer cognitive outcomes were linked to diabetes	High

2019 [23]		status, longer duration of diabetes, and poor glycemic management.	
Li et al., 2023 [24]	T2D	A higher risk of dementia and a smaller volume of the hippocampus were linked to higher visit-to-visit HbA1c fluctuation in middle-aged and older persons without diabetes.	Moderate

UNDER PEER REVIEW

Discussion

This systematic review of prospective studies supports the conclusion that poor glycemic control, diabetes status, and early-onset diabetes are risk factors for developing dementia in diabetic patients. **Cukierman *et al.*** also reported that individuals with diabetes exhibit a higher rate of cognitive function decrease and a higher risk of cognitive decline in comparison to those without the disease. Thus, cognitive damage must be included among the long-term effects of diabetes [25]. **Pal *et al.*** reported that MetS, diabetes, and prediabetes have all been linked to higher chances of MCI leading to dementia. For individuals with diabetes, the pooled odds ratio for progression was 1.53 (95% CI 1.20–1.97), but for those with MetS, it was 2.95 (95% CI 1.23–7.05). Statins and oral hypoglycemic medications appeared to lower the risk of dementia progression in individuals with T2D, while retinopathy and a longer history of diabetes were linked to an elevated risk [26].

Diabetes may have a variety of pathophysiological effects on the development and progression of the numerous underlying diseases linked to dementia [27]. These mechanisms include ageing itself and those shared by vascular dementia and Alzheimer's disease. It is becoming more widely acknowledged that individuals suffering from dementia, especially those who are extremely old, are likely to exhibit a variety of diseases in their brains, including Alzheimer-type dementia and vascular abnormalities [28].

Here are a few endocrinological, metabolic, and vascular disorders that are linked to diabetes and may cause these many illnesses. Mixed pathology may arise from these coupled causes. Some diabetics will have more vascular damage than other types, which might result in a type of dementia known as "pure vascular dementia," according to clinical classification. Other people may have a clinical picture of "pure Alzheimer's disease," with a predominance of amyloid-related

processes. The majority of people will have a dementia syndrome that is in between these two [26].

There are several explanations for why diabetes and cognitive deterioration are related. Firstly, it is widely known that diabetes raises the risk of cerebrovascular illness. It is also linked to dyslipidemia and hypertension. Thus, cerebrovascular illness may act as a mediating factor in the association between diabetes and cognitive decline. This needs to be carefully taken into account while evaluating patients because it can be more noticeable in the older age group. Second, depression is more common in those who have diabetes [29-31] and is challenging to diagnose clinically, apart from dementia and early stages of cognitive deterioration. Even after controlling for depression, at least one of the studies [32] found a link between diabetes and cognitive deterioration. There are several explanations for why diabetes and cognitive deterioration are related.

Third, cognitive function may be impacted by hypoglycemia. Nevertheless, there is minimal evidence to show chronic cognitive impairment related to hypoglycemia, in contrast to the acutely detrimental effects of hypoglycemia on cognition. In fact, rigorous treatment plans that were linked to a higher frequency of hypoglycemic episodes in people with T1D did not have a negative impact on cognitive function [34]. Fourth, long-term cognitive damage may also be influenced by hyperglycemia. Studies conducted after death on senile plaques removed from Alzheimer patients' brains revealed metabolic oxidation products linked to hyperglycemia [35, 36].

We also found that mild to moderate motor cognitive impairment [17] and genetic factors [22] were also at an increased risk of developing dementia. The relationship between diabetes and dementia may potentially be influenced by genetic predisposition; however, only the APOE genotype has been studied in this regard.

Two other studies [37, 38] reported the risk of dementia in persons with diabetes based on the APOE genotype, while one study [39] adjusted the risk of dementia in people with diabetes for the APOE genotype. In comparison to patients with either of these risk factors alone, patients with diabetes who carried the APOE ϵ 4 allele had a relative risk of dementia that was doubled, according to these two subsequent investigations [37, 38].

We might have underreported null outcomes that weren't explained in the published articles because risk factors that were evaluated in studies but not reported might have existed. According to the study results, it was also challenging to identify risk variables that had been treated from those that had not. The difficulty of diagnosing dementia and its various forms may have impacted the findings' accuracy. There are limits to evaluating the conversion of MCI to dementia because the only distinction between MCI and mild dementia may be how the illness affects everyday activities, and this interpretation may be biased [40]. Furthermore, diabetes itself may eventually affect a person's function and lead to frailty, which further complicates attributing the evolution of MCI to risk factors.

It may be possible to significantly improve patient outcomes by creating and assessing multi-modal interventions that use therapy approaches and lifestyle modifications to target modifiable risk factors and slow the progression of MCI to dementia in these high-risk individuals. The best time to provide such interventions, however, would be to determine whether midlife therapies are necessary or if treatment can begin after the onset of MCI. Studies reporting more specific outcome measures for the conversion of MCI to dementia would also be beneficial. It would be easier to distinguish between the worsening of frailty and the progression of cognitive impairment if there were quantifiable changes in

cognition and more information about subsequent dementia diagnoses. This would lead to a better understanding of the nature of progression and more reliable results that are less dependent on subjective interpretation.

Conclusion

For diabetic patients, early-onset diabetes, poor glycemic management, and diabetes status are risk factors for dementia development. There was also a higher chance of dementia development in those with mild to severe motor cognitive impairment and hereditary variables. Mechanistic studies exist that offer pathophysiological leads, but they do not specify which of these leads has practical significance. It is necessary to bridge the evidence gap between mechanistic and epidemiological investigations. Before appropriate treatment strategies can be established, it is necessary to identify the risk factors and mechanisms that underlie the link between diabetes and accelerated cognitive decline and dementia. Longitudinal studies that involve comprehensive evaluations of comorbid diseases and diabetes-related variables, as well as rigorous assessments of cognition—ideally in conjunction with neuroimaging—will be necessary for this process. This method will work best with large population-based cohort studies of older adults with diabetes and with longitudinal studies of at-risk groups that look at the development of diabetes, metabolic syndrome, vascular disease, and cognitive decline.

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