



Review Article

Cardiovascular Disorders, Hypertension, and Stroke as Risk Factors for Mild Cognitive Impairment in Older Adults With Type 2 Diabetes: A Systematic Review and Meta-Analysis

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Abstract

Introduction: This study investigated whether cardiovascular diseases (CVD), hypertension, and stroke contribute to the risk of developing mild cognitive impairment (MCI) in older adults living with diabetes.

Methods: Studies examining the association of CVD, hypertension, and stroke with MCI were systematically searched in PubMed, Web of Science, Scopus, and Embase for articles published up to 2025 in English or Persian. After duplicate removal, studies were screened against predetermined inclusion and exclusion criteria. Data were analyzed using Comprehensive Meta-Analysis software (Version 2). Publication bias was evaluated using Egger's test, and heterogeneity was assessed via the I^2 statistic. Pooled effect sizes were reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Twenty studies from 10 countries, encompassing 36,094 participants, met the eligibility criteria. Depending on heterogeneity, either a fixed-effects model ($I^2 < 50\%$) or a random-effects model ($I^2 > 50\%$) was applied. In univariate analyses, CVD (OR=1.485; 95% CI: 1.106–1.993; $I^2=89.37\%$), hypertension (OR=1.474; 95% CI: 1.273–1.707; $I^2=38.24\%$), and stroke (OR=1.592; 95% CI: 1.290–1.965; $I^2=69.88\%$) were each significantly associated with an increased likelihood of cognitive impairment. However, after adjusting for clinically relevant confounders identified from previous research and available study-level data, only the association between stroke and MCI remained statistically significant (OR=1.711; 95% CI: 1.305–2.244; $I^2=32.54\%$), whereas the associations with CVD and hypertension weakened and were no longer significant.

Conclusion: These findings indicate that among older adults with diabetes, hypertension and stroke are linked to a higher risk of MCI. However, the observed associations for CVD and hypertension diminish when potential confounding factors are considered, suggesting that shared underlying mechanisms may account for these relationships. Although causal inferences are limited by the observational nature of the included studies, maintaining healthy blood pressure and cardiovascular risk factors remains essential for supporting cognitive health. Further longitudinal and interventional studies are needed to clarify causal pathways and guide future prevention strategies.

Keywords: Type 2 diabetes, Mild cognitive impairment, Aging



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Introduction

Type 2 diabetes mellitus (T2DM) has emerged as a major global health concern, with its prevalence rising sharply alongside global population aging (1-3). Today, older adults constitute more than half of the total diabetic population, and estimates indicate that the number of older individuals diagnosed with T2DM will more than double by 2045 (4). In addition to metabolic abnormalities, diabetes is linked

to a range of long-term complications—including frailty, functional decline, and cognitive deficits—that markedly impair quality of life in later adulthood (5, 6).

Among the neurological outcomes associated with T2DM, cognitive decline is viewed as a continuum extending from mild cognitive impairment (MCI) to dementia. MCI represents an intermediate state between normal age-related cognitive changes and dementia, characterized



by measurable deficits in memory or other cognitive functions without substantial disruption of daily activities (7). Dementia, in contrast, reflects a more advanced and progressive decline accompanied by significant functional impairment. Epidemiological evidence suggests that older adults with diabetes face a 1.5–2.5-fold increased risk of cognitive impairment and dementia compared to non-diabetic individuals (8). The prevalence of MCI in this population exceeds 40%, emphasizing its relevance as an early—and potentially modifiable—stage of cognitive deterioration (9).

The biological pathways linking T2DM to cognitive dysfunction are complex and interconnected. Chronic hyperglycemia exacerbates oxidative stress and systemic inflammation, processes that contribute to both microvascular and macrovascular damage (10, 11). These vascular abnormalities impair cerebral blood flow, disrupt blood–brain barrier integrity, and accelerate neurodegenerative mechanisms, ultimately elevating vulnerability to cognitive decline. Cardiovascular disease (CVD), hypertension, and stroke—key macrovascular complications of diabetes—likely serve as key pathological mediators through mechanisms such as endothelial dysfunction, atherosclerosis, and cerebral hypoperfusion (12–14).

Although several meta-analyses have assessed diabetes as a risk factor for cognitive decline in the general population, few have specifically examined how individual cardiovascular comorbidities influence cognitive vulnerability among older adults with diabetes. Moreover, existing findings remain inconsistent regarding which cardiovascular factors exert the strongest impact on MCI risk. Clarifying these associations is of paramount clinical importance, as identifying modifiable cardiovascular risk factors may support earlier detection and prevention strategies designed to mitigate cognitive decline in elderly individuals with T2DM.

Accordingly, this systematic review and meta-analysis was undertaken to synthesize and quantify the independent associations of CVD, hypertension, and stroke with MCI in older adults with T2DM.

Methods

Although the review protocol was not registered in a public registry (e.g., PROSPERO), all methodological procedures strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations to ensure methodological transparency and reproducibility (12). The workflow included a structured search across multiple databases, reference management and duplicate removal via EndNote, preliminary title and abstract screening, assessment of methodological quality using the Newcastle–Ottawa Scale (NOS), full-text eligibility assessment, systematic data extraction through a standardized form, and final synthesis and reporting. Two reviewers independently evaluated titles and abstracts; disagreements were resolved through consultation with a third reviewer. Although inter-rater

agreement statistics (such as Cohen’s kappa) were not calculated, a calibration phase was completed beforehand to ensure consistent application of the eligibility criteria.

Search Strategy and Eligibility Criteria

Eligible studies were observational investigations (cross-sectional, case-control, or cohort designs) that evaluated the association between CVD, hypertension, or stroke and MCI in older adults diagnosed with T2DM. Studies were required to report quantifiable effect size estimates—specifically odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs)—alongside corresponding 95% confidence intervals (CIs). When necessary, non-OR effect estimates were converted into ORs to facilitate quantitative pooling. Only English-language articles were included. Studies employing non-observational designs, lacking relevant effect size measures, and representing duplicate cohorts were excluded.

A comprehensive search was conducted across PubMed, Web of Science, Scopus, and Embase. Search terms were generated using previous literature and Medical Subject Headings (MeSH), then refined to align with the study’s research objectives and Population, Exposure, Comparator, Outcome (PECO) framework (13). The core search strategy incorporated the following terms: cognitive disorder, mild cognitive impairment, cognitive dysfunction, type 2 diabetes mellitus, T2DM, older adult, elderly, and senior.

Study Selection

All citations identified across databases were imported into EndNote, where duplicates were removed. Two reviewers independently and blindly assessed titles and abstracts against the predefined eligibility criteria. Discrepancies were resolved by consulting a third reviewer. Full-text articles meeting eligibility requirements were then evaluated based on the PECO criteria for final selection.

Quality Assessment

The methodological quality was evaluated using the NOS, which comprises eight items across three primary domains: selection, comparability, and outcome. Each item, except comparability, receives one point; comparability may receive up to two points, producing a total score ranging from zero to nine. Studies were classified as low (0–2), moderate (3–5), or high quality (6–9) (14).

Data Extraction

Data extraction was performed using standardized forms, capturing sample size, baseline demographic variables (first author, publication year, study location, and mean age), and reported ORs for each cardiovascular risk factor. Quantitative analyses were conducted using Comprehensive Meta-Analysis (Version 2). Heterogeneity exceeded 50% ($I^2 > 50\%$); pooled effect sizes were derived using a random-effects model based on the Der Simonian–Laird method; otherwise, a fixed-effects model was applied. Sensitivity analyses were conducted using a leave-one-out approach, in which each study was sequentially removed to

verify that the overall results were not disproportionately influenced by a single dataset. Publication bias was assessed through Egger's regression test ($P < 0.05$) and visually examined via funnel plots.

Results

The initial database search identified 2,360 records. Following duplicate removal ($n = 890$), the remaining citations were screened through title and abstract review. A total of 93 studies underwent full-text assessment, resulting in 20 studies meeting all predefined criteria for inclusion in the meta-analysis (Figure 1).

Systematic Review

Of the studies included, six were conducted in China, three in Australia, one in Spain, two in the United States, two in Saudi Arabia, and one each in the Philippines, Poland, Mexico, the Netherlands, and Romania. Publication years ranged from 2008 to 2024. Methodological quality assessment using the NOS indicated that all included studies exhibited moderate to high methodological quality.

Collectively, the studies evaluated 36,094 older adults with T2DM, although the operational definitions of "older adults" differed across investigations. Sample size ranged from 68 participants in Reijmer et al (15) to 11,140 participants in Gong et al (16). Detailed demographic and methodological characteristics of all included studies are summarized in Table 1.

Univariate Analysis Findings

As presented in Table 2, univariate meta-analyses showed that all three investigated variables were positively associated with an elevated risk of MCI. Cardiovascular disease was assessed in eight studies, and the pooled analysis indicated that CVD increased the odds of MCI by nearly 1.5-fold ($OR = 1.48$; 95% CI: 1.106–1.993). Considerable heterogeneity was detected across the included studies ($I^2 = 89.37\%$; Figure 2), likely reflecting variations in study design, participant characteristics, diagnostic criteria for MCI, and covariate adjustment strategies. Nevertheless, leave-one-out sensitivity analyses confirmed that no single study disproportionately influenced the pooled estimate, supporting the reliability of this association.

Hypertension was evaluated in eight studies (Figure 3) and demonstrated a statistically significant positive relationship with MCI ($OR = 1.47$; 95% CI: 1.273–1.707), accompanied by comparatively lower heterogeneity ($I^2 = 38.24\%$).

Stroke, evaluated in seven studies, exhibited the strongest association among the three examined variables. Pooled analysis revealed that stroke increased the likelihood of MCI by approximately 1.6 times ($OR = 1.59$; 95% CI: 1.290–1.965; $I^2 = 69.88\%$). Assessment of publication bias using Egger's linear regression test revealed no evidence of bias for any of the three variables (Figure 4).

Multivariate Analysis Findings

Following adjustment for potential confounding variables, the pattern of findings shifted. Although CVD maintained

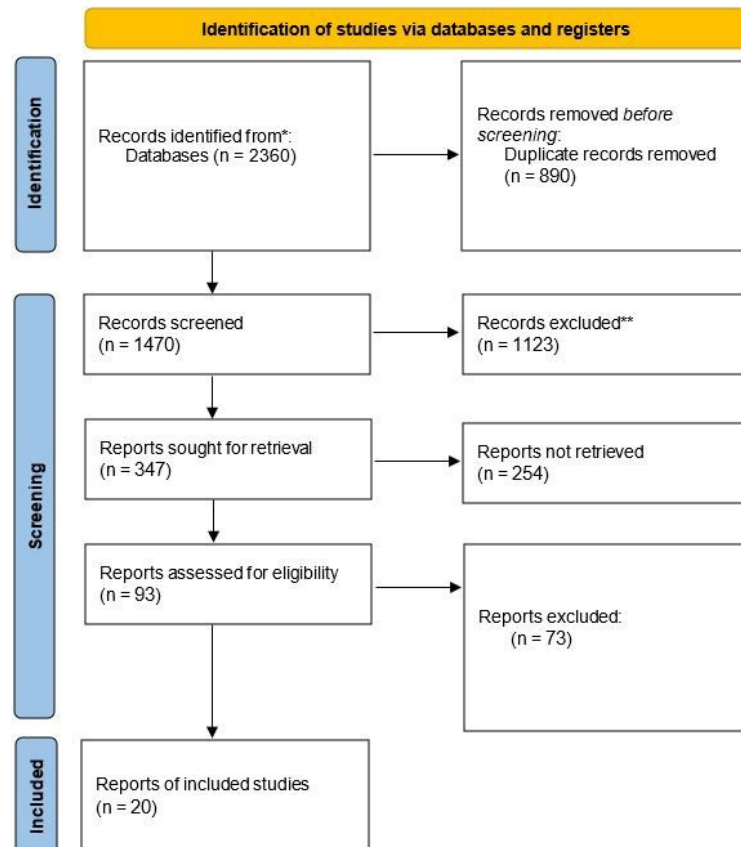


Figure 1. PRISMA Flow Diagram of Study Selection and Screening

Note. PRISMA: Preferred reporting items for systematic reviews and meta-analyses.

Table 1. Demographic Characteristics and Main Features of the Included Studies

First Author	Publication Year	Country	Diagnostic Tool	Sample Size (n)	Mean Age (Range or SD)
Albai (17)	2019	Romania	MMSE	207	58 (47-65.5)
AlHarkan (18)	2024	Saudi Arabia	SLUMS	343	65
Formiga (19)	2023	Europe	MMSE	335	79 (77-82)
Huang (20)	2021	China	MoCA	913	48.7 (14.6)
Huang (21)	2021	USA	BRFSS	5263	>65
Lavielle (22)	2015	Mexico	Quick MCI Scale	1712	51 (11)
Reijmer (23)	2011	Netherlands	NS	68	NS
Xiu (24)	2019	China	MMSE	10039	71.21 (7.41)
Althubaity (25)	2021	Saudi Arabia	MoCA-B	179	58.6 (9.6)
Blanquisco (26)	2017	Philippines	MoCA	133	67 (4.8)
Bozanic (27)	2023	Spain	MMSE	358	68.9 (4.8)
Bruce (28)	2008	Australia	MMSE	205	75 (4.01)
Bruce (29)	2014	Australia	MMSE	339	72
Ding (30)	2024	China	MoCA	1256	57.5 (11.2)
Gong (31)	2021	Australia	MMSE	11140	65.8 (6.4)
Gorska-Ciebiada (32)	2014	Poland	MoCA	276	NS
Gupta (33)	2023	USA	Mini Cog	198	78.13
Ma (34)	2023	China	MMSE	504	NS
Xiu (35)	2019	China	MMSE	2626	71.2 (7.4)
Zhao (36)	2020	China	MMSE	1519	72 (6.3)

Note. NS: Not specified; MMSE: Mini-mental state examination; SLUMS: Saint Louis university mental status examination; MoCA: Montreal cognitive assessment; BRFSS: Behavioral risk factor surveillance system; SD: Standard deviation.

Table 2. Results of Univariate Analysis for the Investigated Variables

Variable	Study (n)	Heterogeneity	Publication Bias	OR	Lower Limit	Upper Limit
CVD	8	89.37	0.503	1.485	1.106	1.993
Hypertension	8	38.24	0.815	1.474	1.273	1.707
Stroke	7	69.88	0.211	1.592	1.290	1.965

Note. CVD: Cardiovascular diseases; OR: Odds ratio; n: Number of studies; CI: Confidence interval.

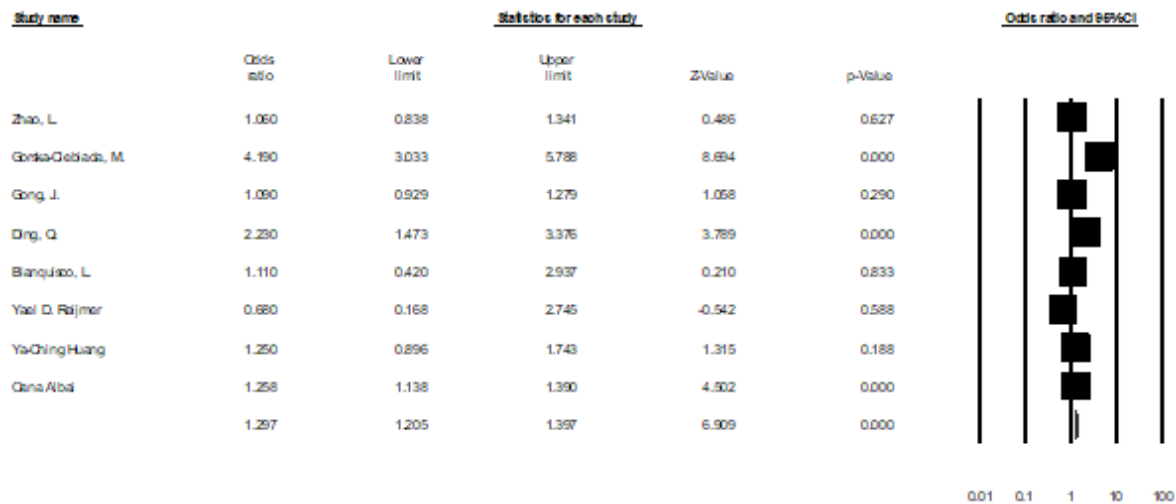


Figure 2. Forest Plot of Univariate Analysis of Cardiovascular Diseases

an elevated point estimate, the association was no longer statistically significant (OR= 1.57; 95% CI: 0.844–2.922; $I^2=72.10\%$), as depicted in Figure 5. A similar trend was observed for hypertension: despite an elevated pooled effect estimate across four adjusted studies, the relationship did not reach statistical significance (OR= 1.69; 95% CI: 0.926–

3.077; Figure 6).

In contrast, stroke remained a significant and consistent predictor of cognitive impairment even after adjustment. Based on five studies, stroke increased the risk of MCI by more than 1.7-fold (OR= 1.71; 95% CI: 1.305–2.244), with low between-study heterogeneity (Figure 7).

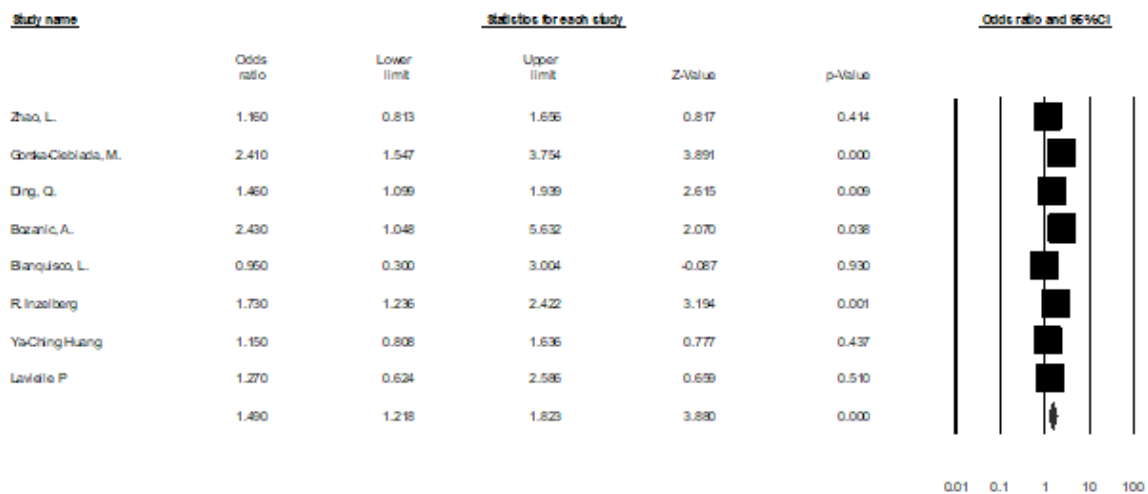


Figure 3. Forest Plot of the Univariate Analysis of Hypertension

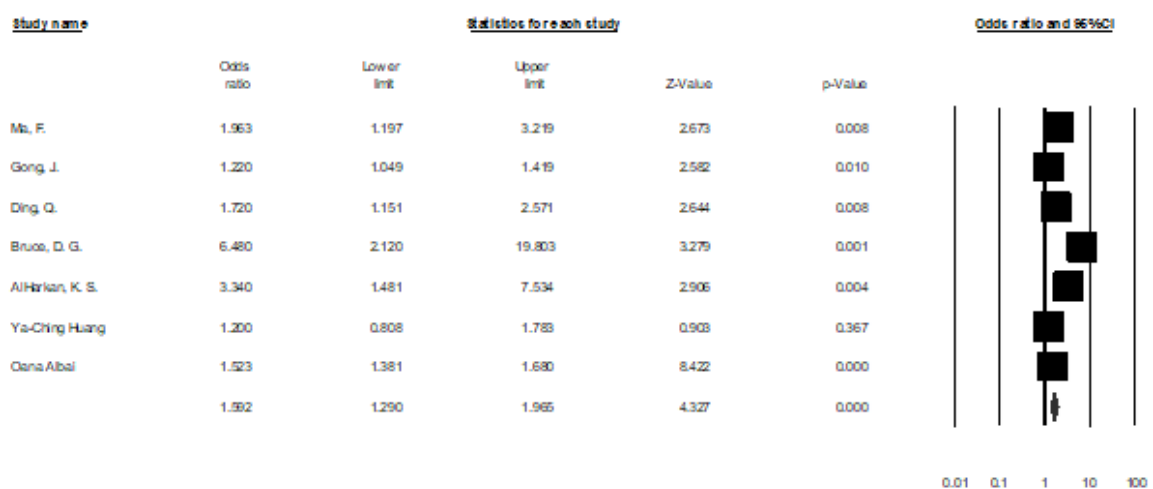


Figure 4. Forest Plot of the Univariate Analysis of Stroke

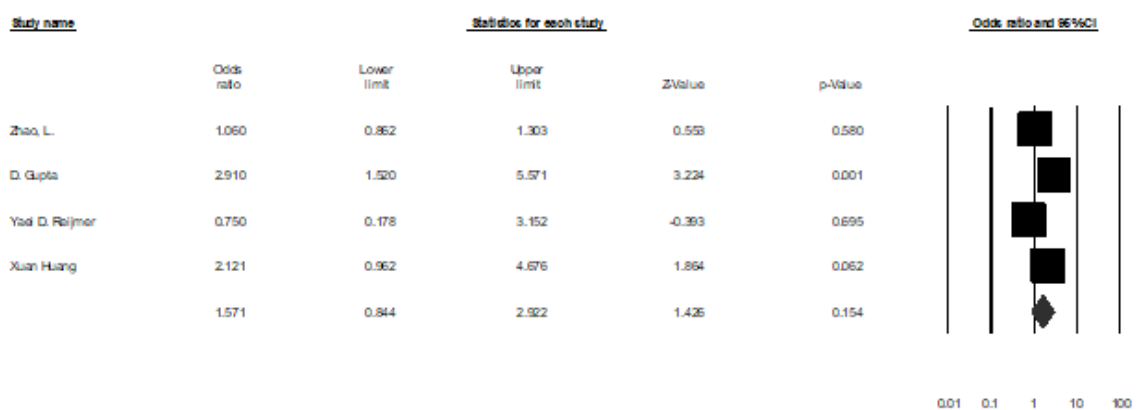


Figure 5. Forest Plot of the Multivariate Analysis of Cardiovascular Diseases

Sensitivity Analysis

Leave-one-out sensitivity analyses confirmed the stability of the pooled effect estimates. Sequential removal of individual studies did not materially affect the overall results, indicating that no single study exerted undue influence. These findings reinforce the robustness and credibility of the meta-analysis.

Discussion

This systematic review and meta-analysis quantified the

associations between various risk factors and MCI in older adults with T2DM. The results indicated that CVD, stroke, and hypertension were significantly associated with an increased likelihood of developing MCI. In the univariate meta-analysis, all examined variables were linked to higher odds of cognitive disorder. Specifically, the presence of CVD was associated with an approximate 50% increase in the odds of MCI (OR = 1.48; 95% CI: 1.106–1.993), although substantial heterogeneity was observed ($I^2 = 89.37\%$). This heterogeneity may stem from methodological differences

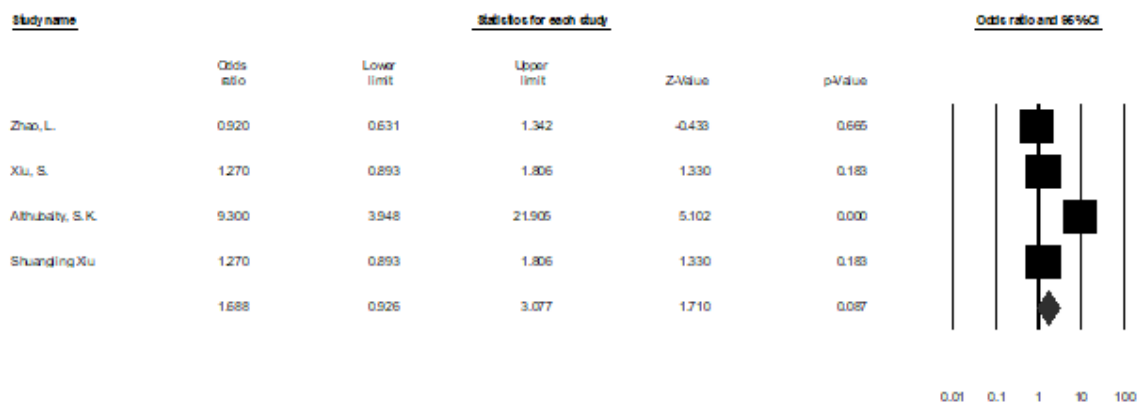


Figure 6. Forest Plot of the Multivariate Analysis of Hypertension

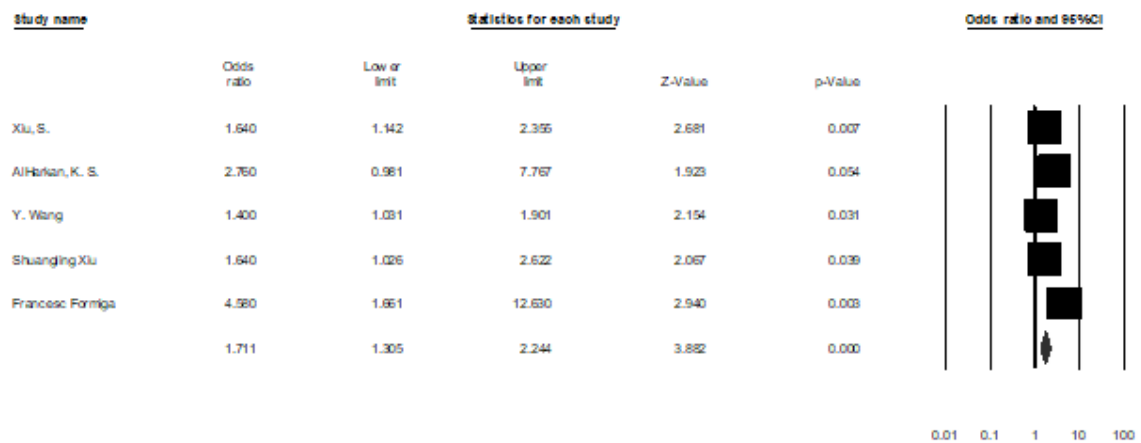


Figure 7. Forest Plot of the Multivariate Analysis of Stroke

across study designs, population characteristics, or outcome definitions, highlighting the need for sensitivity analyses to verify the true magnitude of this association. These findings are consistent with previous studies reporting that underlying cardiovascular conditions substantially elevate the risk of cognitive disorder in diabetic populations.

Prior literature demonstrates that cardiovascular risk factors (CVRFs) are associated with MCI and may influence its progression to dementia. Siuda et al (37) reported that patients with MCI and concurrent CVD exhibited more pronounced deficits in learning new information, recall, and short-term memory. These findings indicate that patients with diabetes and CVD may represent a subgroup at increased risk of further cognitive decline and may benefit from close clinical observation and periodic cognitive assessment to facilitate the early recognition of worsening cognitive status.

In a population-based prospective cohort study, Roberts et al (38) showed that heart disease was specifically associated with an increased risk of non-amnesic MCI (naMCI), a potential precursor to vascular and other non-Alzheimer’s dementias. This association was particularly strong among women (HR = 3.07; 95% CI: 1.58–5.99) but not statistically significant among men. Heart disease was not associated with amnesic MCI (aMCI), underscoring the importance of distinguishing between MCI subtypes and considering sex-specific differences when assessing risk. Overall, these findings suggest that CVRFs are

associated with the onset and severity of MCI and its possible progression to dementia. They also support the importance of preventive strategies and careful management of cardiovascular risk factors—including hypertension, diabetes, and heart disease—in populations at increased risk. Further longitudinal studies are needed to clarify the causal relationships and determine whether modifying these risk factors can effectively reduce cognitive decline.

Hypertension was also significantly associated with an increased risk of MCI (OR = 1.47; 95% CI: 1.27–1.71), with relatively low heterogeneity ($I^2 = 38.24\%$), suggesting a relatively robust and consistent association across studies. These findings align with previous epidemiological evidence identifying hypertension as a modifiable risk factor for cognitive decline and dementia. Community-based cohort studies have reported an increased risk of MCI by up to 40%, particularly non-amnesic MCI (naMCI). For instance, a northern Manhattan cohort study reported an increased risk of naMCI associated with hypertension (HR = 1.70; 95% CI: 1.13–2.42), with no significant association observed for aMCI. These converging findings underscore the potential role of hypertension as a modifiable risk factor for non-amnesic cognitive impairment and vascular-related dementia (39).

Recent reviews also support an association between midlife hypertension and later-life cognitive decline and dementia, although evidence among adults aged over 80

years and individuals with established MCI remains limited. While most antihypertensive medications may help reduce dementia risk, optimal blood pressure targets and the most effective therapeutic approaches for patients with MCI have not been fully established. Therefore, the present findings highlight the importance of monitoring and managing blood pressure in individuals at risk, particularly during the early or preclinical stages of cognitive impairment. However, causal conclusions cannot be drawn from the available observational evidence (40).

Regarding stroke, the pooled results indicated a stronger association with cognitive outcomes than those observed for CVD and hypertension, increasing the likelihood of MCI by approximately 60% (OR = 1.59; 95% CI: 1.29–1.97). Although moderate heterogeneity was observed ($I^2 = 69.88\%$), the positive association remained statistically significant. These findings identify stroke and related vascular pathology as important correlates of cognitive impairment and underscore the importance of effective secondary prevention in individuals with a history of stroke.

Despite the overall consistency of our findings with prior literature, some studies have reported null or inconsistent associations between cardiovascular risk factors and cognitive outcomes. For instance, certain population-based cohorts found no significant relationship between hypertension and cognitive decline after adjustment for age, education, and comorbidities, suggesting that the association may depend on study design, follow-up duration, and the extent to which confounding factors are addressed. Similarly, although much of the evidence supports a link between CVD and MCI, several longitudinal studies have not confirmed a causal relationship, indicating that shared risk factors—rather than direct vascular effects—may partly explain this relationship (41). In contrast, the evidence linking stroke to MCI appears more consistent; however, post-stroke cognitive trajectories can vary substantially depending on lesion location and recovery patterns. Therefore, alongside CVD, hypertension and stroke should be considered important components of the vascular-cognitive continuum. Future studies should systematically compare these factors and explore potential effect modification by age, sex, and glycemic control (42).

The absence of publication bias for all three examined variables suggests that the results may be less susceptible to selective reporting, allowing for a more reliable interpretation of the associations observed.

Limitations

This study has several limitations. Most included studies were cross-sectional, limiting the ability to account for confounding variables. The limited number of available studies also restricted the statistical analyses that could be performed for certain variables. Additionally, the small number of studies in some analyses limits the generalizability of the findings to all populations, underscoring the need for further research.

Conclusion

This study suggests that among older adults with diabetes, cardiovascular risk factors—particularly hypertension and stroke—are associated with an increased likelihood of MCI. However, after adjustment for potential confounders, the associations between CVD and hypertension and MCI were attenuated and were no longer statistically significant. These findings indicate that the observed relationships may be partly explained by shared underlying mechanisms. They underscore the potential relevance of cardiovascular health to cognitive aging among individuals with diabetes, although causal inferences should be made cautiously due to the observational nature of the included studies. Maintaining optimal blood pressure control and early management of cardiovascular risk factors may help preserve cognitive function. Further longitudinal and interventional research is warranted to clarify causal pathways and inform targeted prevention strategies.

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Consent for Publication

All authors contributed to the review and manuscript preparation and confirmed the final draft. This manuscript is not under review by any other journal.

Data Availability Statement

The datasets are available from the corresponding author upon reasonable request.

Ethical Approval

This study was designed in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Faculty of Midwifery and Nursing, Kermanshah University of Medical Sciences, Kermanshah, Iran.

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IRCT Code

Not applicable.

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