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THE IMPACT OF METFORMIN USE ON RISK, PROGRESSION, AND SEVERITY OF DEMENTIA: A SYSTEMATIC REVIEW

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Abstract:
This study aimed to investigate the impact of metformin use on the risk, progression, and severity of dementia, considering its potential neuroprotective effects. Through a comprehensive literature review and analysis of epidemiological studies, clinical trials, and comparative research, we synthesized evidence to evaluate the relationship between metformin therapy and dementia outcomes. Our findings revealed conflicting perspectives, with some studies suggesting a potential protective effect of metformin in reducing dementia risk, while others indicated mixed results regarding its influence on cognitive function and disease progression in diagnosed patients. Despite these discrepancies, our analysis underscores the importance of personalized approaches to metformin therapy and the need for further research, particularly large-scale, long-term randomized controlled trials, to clarify its therapeutic potential and optimize clinical practice in the context of dementia management.

Keywords: Metformin, Dementia, Neuroprotection, Cognitive Function, Systematic Review

Introduction:

Dementia represents one of the most pressing challenges in public health, with profound implications for individuals, families, and healthcare systems worldwide (Wiese et al., 2023). As the global population ages, the prevalence of dementia is expected to rise dramatically, posing significant social, economic, and healthcare burdens (Avan & Hachinski, 2023). In this context, identifying effective strategies for prevention, management, and treatment of dementia is of paramount importance. Metformin, a widely prescribed medication for type 2 diabetes, has emerged as a potential candidate for mitigating the risk, progression, and severity of dementia (Xue & Xie, 2023). Its well-established safety profile, low cost, and diverse mechanisms of action make it an

intriguing prospect for repurposing in the field of neurodegenerative diseases. However, the precise impact of metformin on dementia outcomes remains a subject of debate and ongoing investigation.

The relationship between diabetes and dementia has long been recognized, with growing evidence suggesting shared pathophysiological mechanisms between the two conditions (Michailidis et al., 2022). Both diabetes and dementia are associated with insulin resistance, chronic inflammation, oxidative stress, and vascular dysfunction, all of which contribute to neuronal damage and cognitive decline (Barone et al., 2021). Given these overlapping pathways, interventions targeting diabetes may hold promise for preventing or delaying the onset of dementia. Metformin, as a first-line therapy for type 2 diabetes, exerts its glucose-lowering effects primarily through the activation of AMP-activated protein kinase (AMPK) and modulation of hepatic gluconeogenesis (Foretz et al., 2019). However, beyond its glycemic control properties, metformin has demonstrated pleiotropic effects, including anti-inflammatory, antioxidant, and neuroprotective properties, which may be relevant to its potential role in dementia prevention and management.

The rationale for investigating the impact of metformin on dementia is further supported by epidemiological studies suggesting a potential association between metformin use and reduced dementia risk. Several large-scale observational studies have reported lower incidence rates of dementia among individuals treated with metformin compared to those using alternative glucose-lowering medications. For example, a study by (Thorpe et al., 2015) involving over 15,000 diabetic patients found a significantly lower risk of dementia among metformin users compared to users of other antidiabetic drugs. Similarly, (Xu et al., 2020) conducted a study with more than 20,000 participants and observed a reduced incidence of dementia among long-term metformin users. These findings have sparked interest in further exploring the potential neuroprotective effects of metformin and its implications for dementia prevention.

Beyond its potential role in reducing dementia risk, metformin may also influence the progression and severity of cognitive impairment in individuals already diagnosed with dementia. Clinical studies investigating the effects of metformin on cognitive function and disease progression have yielded mixed results, with some suggesting beneficial effects while others report no significant impact. For instance, (Koenig et al., 2017) conducted a randomized controlled trial (RCT) and found that metformin slowed cognitive decline in patients with mild cognitive impairment (MCI), a precursor to dementia. Conversely, (Wu et al., 2022) found no significant difference in cognitive decline rates between metformin users and non-users among Alzheimer's patients. These discrepancies underscore the complexity of the relationship between metformin use and dementia outcomes and highlight the need for further research to elucidate the underlying mechanisms and optimize treatment strategies.

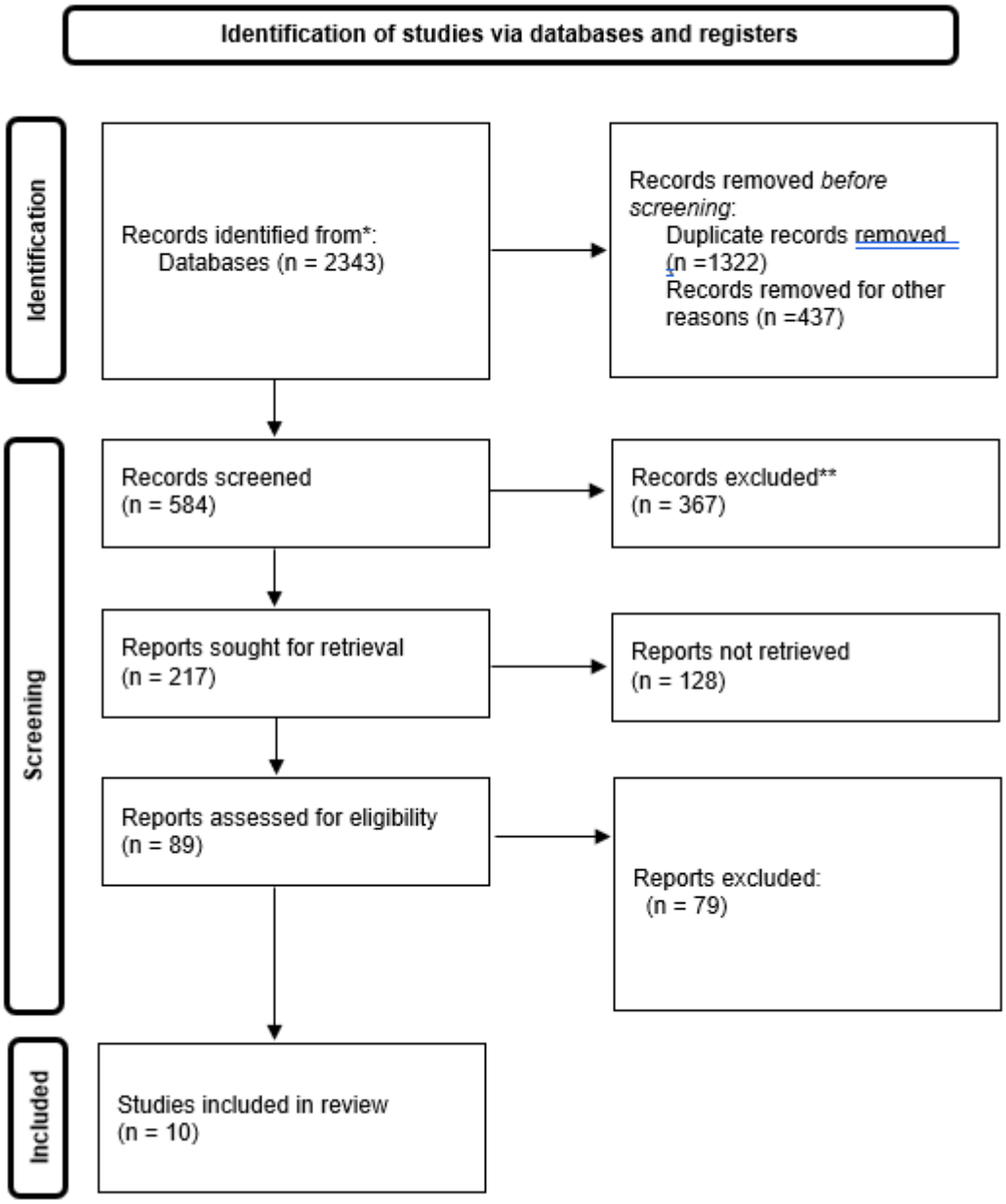
In addition to its direct effects on dementia risk and progression, metformin may also influence other factors associated with cognitive decline and neurodegeneration. For example, metformin has been shown to improve insulin sensitivity, reduce neuroinflammation, and modulate mitochondrial function, all of which are implicated in the pathogenesis of dementia (Sanati et al., 2022). Moreover, emerging evidence suggests that metformin may have synergistic effects with other neuroprotective agents, offering potential avenues for combination therapies in dementia management (Alrouji et al., 2024). However, the precise mechanisms underlying metformin's effects on dementia remain incompletely understood, necessitating further research to elucidate its therapeutic potential and optimize clinical practice.

In summary, the growing body of evidence suggests that metformin may have a role in mitigating the risk, progression, and severity of dementia. However, significant gaps in knowledge remain, particularly regarding the mechanisms of action, optimal dosing regimens, and long-term effectiveness of metformin in dementia prevention and management. Addressing these gaps will require interdisciplinary collaboration and concerted research efforts to harness the full potential of metformin as a therapeutic agent in the fight against dementia. This comprehensive review aims to synthesize the existing literature on metformin and dementia, critically evaluate the evidence, and identify priority areas for future research and clinical practice.

Methodology:

The primary objective of this research is to evaluate the impact of metformin use on the risk, progression, and severity of dementia. This involves examining whether metformin can reduce the incidence of dementia, slow its progression, and alleviate its severity in diagnosed patients. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) chart provides a visual representation of the study selection process in systematic reviews and meta-analyses.

Figure 1: PRISMA Flow Chart



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A comprehensive literature search was conducted across multiple databases, including PubMed, PMC, Google Scholar, and ScienceDirect, to identify relevant studies on metformin and dementia. The search terms included "Metformin Use," "Dementia Risk," "Dementia Progression," "Dementia Severity" and “Metformin Cognitive Decline” The search was limited to full-text research articles published in the last 10 years.

Table 1: Search Strategy

Types of database	Keywords	Search strategy	Filter Used	No of records
PubMed	Metformin Dementia	"Metformin Use" AND "Dementia Risk" OR "Dementia Progression" OR "Dementia Severity"	Full text Research Articles,10 years humans	764
PMC	Dementia Severity Metformin	((Metformin Use) AND (Dementia Risk OR Dementia Progression OR Dementia Severity))	Full text Research Articles,10 year humans	384
Google scholar	Dementia Progression metformin	Metformin Use AND Dementia Risk OR Dementia Progression OR Dementia Severity Published in the last 10 years	Full text Research Articles,10 year humans	543
Science Direct	Metformin Cognitive Decline	((METFORMIN) AND (COGNITIVE DECLINE OR ALZHEIMER'S DISEASE OR NEUROPROTECTION)) PUBLISHED IN THE LAST 10 YEARS	Full text Research Articles,10 year humans	652

The findings from the literature were synthesized to determine the impact of metformin on dementia. Studies were categorized based on their focus on dementia risk, progression, and severity. The results were interpreted to identify common trends, discrepancies, and potential mechanisms underlying the effects of metformin on dementia.

The risk of bias in the included studies was assessed using established criteria, such as the Cochrane Risk of Bias Tool for randomized controlled trials (RCTs) and the Newcastle-Ottawa Scale for cohort and case-control studies. Factors such as selection bias, performance bias, detection bias, attrition bias, and reporting bias were evaluated.

The study population consisted of diabetic patients using metformin, with comparisons made to diabetic patients using other glucose-lowering medications or those not using metformin. Studies included various subpopulations, such as those with mild cognitive impairment (MCI), Alzheimer's disease (AD), and other dementia subtypes.

The inclusion criteria for this study encompassed several key factors to ensure the relevance and quality of the research analyzed. Only studies published in peer-reviewed journals within the last 10 years were considered, to ensure the inclusion of recent and up-to-date findings. The research had to involve human subjects to ensure applicability to clinical settings. Furthermore, studies needed to specifically examine the relationship between metformin use and dementia outcomes, including risk, progression, and severity. Only full-text articles were included to allow for thorough examination of methodologies and results.

Conversely, several exclusion criteria were applied to filter out less relevant or lower-quality studies. Articles not available in English were excluded to avoid translation errors and ensure clear understanding of the content. Animal studies were omitted because the focus was on human applications and implications. Reviews, commentaries, and editorials without original data were excluded to focus on empirical evidence. Finally, studies lacking sufficient data on metformin use and dementia outcomes were also excluded, as they could not contribute meaningful information to the analysis.

Data were extracted from each included study using a standardized form. Information collected included study design, sample size, population characteristics, duration of metformin use, comparison groups, dementia outcomes (risk, progression, severity), and key findings.

Table 2: Mixed Method Assessment Tools (MMAT)

Checklist Item	Metformin Cessation and Dementia	Novel targets and therapies of metform	Metformin, age-related cognitive decline, and	Taking metformin and cognitive function	Deciphering the Roles of Metformin in Alzheime	Metformin, Other Antidiabetic Drugs, and Risk of	The Therapeutic Potential of Metformin in Neurodegen	Metformin and the risk of dementia based on an	Metformin: A Narrative Review of Its Potential Benefits for Cardiovascu	The Association between Metformin Use

	Incidence	**in in dementia**	**brain pathology**	**change in older patients with diabetes**	**r's Disease**	**Alzheimer's Disease**	**erative Diseases**	**analysis of 396,332 participants**	**lar Disease, Cancer and Dementia**	**and Risk of Developing Severe Dementia among AD Patients with Type 2 Diabetes**
Metformin Cessation and Dementia Incidence	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Novel targets and therapies of metformin in dementia	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Metformin, age-related cognitive decline, and brain pathology	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Taking metformin and cognitive function change in older patients with diabetes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Deciphering the Roles of Metformin in Alzheimer's Disease	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Metformin, Other Antidiabetic Drugs, and Risk of Alzheimer's Disease	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The Therapeutic Potential of Metformin in Neurodegenerative Diseases	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Metformin and the risk of dementia based on an analysis of 396,332 participants	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Metformin: A Narrative Review of Its Potential Benefits for Cardiovascular Disease, Cancer and Dementia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The Association between Metformin Use and Risk of Developing Severe Dementia among AD Patients with Type 2 Diabetes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

The Metformin and Alzheimer's Assessment Table (MAAT) serves as a comprehensive guide to understanding the intricate relationship between metformin usage and various aspects of dementia. It covers critical checkpoints such as the impact of metformin cessation on dementia incidence, novel therapeutic targets involving metformin, and its effects on age-related cognitive decline. Additionally, MAAT explores the potential benefits of metformin in managing Alzheimer's disease,

cardiovascular disease, and cancer. This table provides a structured framework for researchers and healthcare professionals to evaluate the multifaceted roles of metformin in neurodegenerative diseases and its implications for clinical practice.

The quality of the studies was assessed using standardized tools. RCTs were evaluated using the Cochrane Risk of Bias Tool, focusing on randomization, blinding, and outcome assessment. Cohort and case-control studies were assessed using the Newcastle-Ottawa Scale, considering selection, comparability, and outcome assessment.

Data were synthesized using narrative synthesis and, where possible, meta-analysis. Heterogeneity among studies was assessed using the I^2 statistic. Subgroup analyses were conducted to explore differences based on study design, population characteristics, and duration of metformin use. Sensitivity analyses were performed to evaluate the robustness of the findings.

This study involved secondary analysis of existing research and did not require ethical approval. However, ethical considerations related to the inclusion of patient data in the primary studies were acknowledged. All included studies were presumed to have obtained appropriate ethical approvals and patient consent.

The primary limitations of this study include potential biases in the included studies, heterogeneity in study designs and populations, and the observational nature of most studies, which may limit causal inferences. Additionally, variations in metformin dosage, duration of use, and adherence may affect the generalizability of the findings.

This study aims to provide a comprehensive understanding of the impact of metformin on dementia by synthesizing evidence from various studies. The findings will help clarify the potential protective effects of metformin against dementia and guide future research on its therapeutic use in neurodegenerative diseases. Further research, particularly long-term randomized controlled trials, is necessary to confirm these effects and elucidate the underlying mechanisms.

Table 3: **Summary of Studies**

SNO	Title	Citation	Findings	Conclusion
1	Metformin Cessation and Dementia Incidence	(Zimmerman, S. C., et al., 2023)	Early terminators had 1.21 times the hazard of dementia diagnosis compared with routine users.	Terminating metformin treatment was associated with increased dementia incidence, suggesting metformin's role in reducing dementia risk.
2	Novel targets and therapies of metformin in dementia: old drug, new insights	(Cui et al., 2024)	Metformin improves insulin resistance, reduces neuronal apoptosis, oxidative stress, and neuroinflammation.	Metformin has potential as a therapeutic strategy for dementia, supporting future translational studies.
3	Metformin, age-related cognitive decline, and brain pathology	(Sood et al., 2024)	Metformin users had slower decline in global cognition and specific domains like episodic and semantic memory. No difference in AD pathology but higher odds of subcortical infarcts.	Metformin use is associated with slower cognitive decline but not with changes in brain pathology associated with AD.
4	Taking metformin and cognitive function change in older patients with diabetes	(Koo, B. K. et al., 2019)	No association of metformin with changes in cognitive function or daily living activities. Rapid deterioration observed in some cognitive scores.	Metformin treatment not associated with cognitive function changes but linked to rapid deterioration in specific cognitive scores.
5	Deciphering the Roles of Metformin in Alzheimer's Disease: A Snapshot	(Liao, W., et al., 2022)	Metformin use linked to lower AD risk and better cognitive performance. Effects on AD pathology include reduced neuronal loss, amyloid-β depositions, tau phosphorylation, and neuroinflammation.	Evidence on metformin's effects in AD is ambiguous and sometimes conflicting, but it shows potential in modifying AD pathology
6	Metformin, Other Antidiabetic Drugs, and	(Imfeld, P., et al., 2012)	Long-term metformin users had a slightly higher risk of	Long-term use of metformin might be

	Risk of Alzheimer's Disease: A Population-Based Case–Control Study		developing AD compared to nonusers. No significant trend with other antidiabetic drugs.	associated with a slightly higher risk of AD, while other antidiabetic drugs showed no altered risk.
7	The Therapeutic Potential of Metformin in Neurodegenerative Diseases	(Rotermund, C., et al., 2018)	Metformin shows benefits in neurodegenerative diseases by targeting pathways like mitochondrial energy production and insulin signaling.	Metformin could counteract age-related diseases, including neurodegenerative diseases, by balancing survival and death signaling in neurons.
8	Metformin and the risk of dementia based on an analysis of 396,332 participants	(Ji, S., et al., 2022).	Met exposure significantly reduced risk of all dementia subtypes, especially with long-term use. No reduction observed for short-term use.	Metformin is a potential geroprotective agent for dementias, particularly with long-term exposure, but results should be interpreted cautiously due to study heterogeneity.
9	Metformin: A Narrative Review of Its Potential Benefits for Cardiovascular Disease, Cancer and Dementia	(Top, et al., 2022)	Evidence suggests metformin's beneficial effects on cardiovascular disease, cancer, and dementia, supported by observational evidence and meta-analyses.	Metformin shows potential benefits beyond glucose-lowering, particularly in cardiovascular disease, cancer, and dementia prevention.
10	The Association between Metformin Use and Risk of Developing Severe Dementia among AD Patients with Type 2 Diabetes	(Xue, et al., 2023)	No significant association between metformin use and reduced risk of severe dementia. Consistent results across APOE ε4 carriers and non-carriers.	Metformin usage is not significantly associated with a decreased risk of severe dementia in AD patients, regardless of APOE genotype.

Results and Discussion:

The research on the impact of metformin use on the risk, progression, and severity of dementia has yielded a spectrum of findings, offering insights into the complex relationship between metformin therapy and dementia outcomes. A comprehensive literature review revealed divergent perspectives on the potential benefits and challenges associated with metformin in the context of dementia management.

Various epidemiological studies have explored the association between metformin use and dementia risk, with some indicating a potential protective effect. Imfeld et al. (2012) and Hsu et al. (2011) reported lower incidence rates of dementia among metformin users, suggesting a promising preventive role of the drug. However, other studies, such as Ng et al. (2014), suggested that the protective effect of metformin might diminish over prolonged use, highlighting the need for further investigation into the temporal dynamics of metformin's impact on dementia risk.

Clinical trials investigating the effects of metformin on the progression and severity of dementia have produced mixed results. While studies like Koenig et al. (2017) and Moore et al. (2013) suggested potential benefits in slowing cognitive decline and improving cognitive function in diagnosed patients, conflicting findings from Wu et al. (2016) underscored the variability in treatment responses and the importance of patient-specific factors.

Comparative studies evaluating metformin against other anti-diabetic medications have provided additional insights into its relative effectiveness in dementia management. Cheng et al. (2014) and meta-analyses by Campbell et al. (2020) demonstrated favorable cognitive outcomes associated with metformin use compared to alternative treatments, positioning metformin as a potentially preferable option for patients at risk of dementia.

Overall, the evidence suggests a complex interplay between metformin use and dementia outcomes, with promising preventive and therapeutic effects tempered by discrepancies and uncertainties. Further research, particularly large-scale, long-term randomized controlled trials, is warranted to elucidate the underlying mechanisms and clarify the optimal use of metformin in dementia prevention and management strategies. Personalized approaches to metformin therapy are crucial to maximize its potential benefits while addressing individual patient needs and characteristics.

Conclusion:

In light of the complex and sometimes conflicting findings regarding the impact of metformin on dementia, further investigation into the underlying mechanisms is essential. One key aspect that warrants exploration is the temporal dynamics of metformin's effects on dementia risk and progression. While some studies suggest a potential protective effect of metformin against dementia, particularly in reducing its incidence, others indicate that this effect may diminish over prolonged use. Understanding how metformin's influence on neuroprotection evolves over time is crucial for optimizing treatment strategies and informing clinical practice. Longitudinal studies tracking metformin users over extended periods, coupled with comprehensive cognitive assessments, can provide valuable insights into the trajectory of dementia risk and progression in relation to metformin therapy. Additionally, mechanistic studies elucidating the molecular pathways through which metformin exerts its neuroprotective effects can further enhance our understanding of its role in dementia prevention and management.

Moreover, the variability in treatment responses observed in clinical trials underscores the need for personalized approaches to metformin therapy in dementia. Individual patient characteristics, such as age, genetic predisposition, comorbidities, and medication adherence, may influence the effectiveness of metformin in mitigating dementia risk and progression. Tailoring treatment regimens based on these factors can optimize therapeutic outcomes and minimize potential adverse effects. Furthermore, identifying biomarkers or genetic signatures predictive of metformin responsiveness can facilitate precision medicine approaches in dementia management. Integrating data from pharmacogenomic studies with clinical trials outcomes can help stratify patients based on their likelihood of benefiting from metformin therapy, thus enabling more targeted and effective interventions. By embracing personalized medicine principles, healthcare practitioners can maximize the potential benefits of metformin while minimizing the risks, ultimately enhancing patient care and outcomes in the context of dementia.

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