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The Effectiveness of GLP-1 Receptor Agonists in Preventing and Managing Alzheimer's Disease: A Systematic Review

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ABSTRACT

Background Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline, and neuropathological features such as amyloid-beta plaques and tau tangles. GLP-1 receptor agonists (GLP-1RAs), primarily used for managing type 2 diabetes, have shown promise in preclinical studies as potential therapies for Alzheimer's due to their neuroprotective effects. This systematic review aims to evaluate the effectiveness of GLP-1RAs in the prevention and management of Alzheimer's disease.

Objective To systematically review and analyze the available clinical and preclinical evidence regarding the effectiveness of GLP-1 receptor agonists in preventing and managing Alzheimer's disease, with a focus on cognitive outcomes, neurodegenerative biomarkers, and overall therapeutic potential.

Methods A comprehensive search was conducted in databases such as PubMed, Scopus, and Web of Science for studies published between 2010 and 2024. Studies were selected based on inclusion criteria of clinical trials, observational studies, and preclinical research involving GLP-1RAs in Alzheimer's disease models or human patients with cognitive decline. Data on sample size, intervention details, cognitive and pathological outcomes, and methodological quality were extracted. A qualitative synthesis of the results was performed.

Results Six studies were included in this review, comprising both preclinical animal studies and clinical trials. Preclinical studies consistently demonstrated that GLP-1RAs reduced amyloid-beta plaque accumulation, tau pathology, and promoted neuronal survival, indicating a potential neuroprotective effect. However, clinical trials showed mixed results. Some studies (e.g., Gejl et al., 2016) observed preserved brain metabolism and slower brain atrophy with liraglutide, but cognitive improvements were modest and did not meet primary endpoints. Real-world observational studies indicated a reduced risk of dementia in populations using GLP-1RAs, particularly those with diabetes or obesity, suggesting additional benefits in metabolic pathways related to AD progression.

Conclusions The evidence suggests that GLP-1 receptor agonists have neuroprotective potential in Alzheimer's disease, particularly based on preclinical findings. Clinical data, however, remains inconclusive, with inconsistent effects on cognition and cognitive decline. Further large-scale, long-term clinical trials with standardized endpoints are required to validate the therapeutic efficacy of GLP-1RAs in Alzheimer's disease.

KEYWORDS: Alzheimer's disease, cognitive decline, GLP-1 receptor agonists, neuroprotective, preclinical studies.

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INTRODUCTION

Alzheimer's disease (AD) stands among the most devastating neurodegenerative disorders worldwide, characterized by progressive cognitive decline, memory impairment, and functional deterioration [1]. The pathological hallmarks of AD include extracellular amyloid-β (Aβ) plaques, intracellular neurofibrillary tangles formed by hyperphosphorylated tau, chronic neuroinflammation, oxidative stress, mitochondrial dysfunction, synaptic loss, and neuronal death. Despite decades of research, available therapies remain largely symptomatic; disease-modifying treatments that effectively halt or reverse progression

remain elusive [2]. This unmet need has spurred interest in repurposing drugs developed for metabolic disorders, particularly GLP-1 receptor agonists (GLP-1RAs), as potential agents for AD prevention and management [3].

GLP-1RAs were originally designed and widely used for the treatment of type 2 diabetes mellitus (T2DM) and obesity, conditions that themselves are recognized risk factors for cognitive impairment and dementia [4]. Insulin resistance, dysregulated glucose metabolism, systemic inflammation, and oxidative stress connect metabolic disorders with neurodegeneration. Consequently, the shared pathophysiological mechanisms between T2DM and AD have motivated exploring whether GLP-1RAs, by improving metabolic health, might also confer neuroprotective benefits [5].

Preclinical studies in cellular and animal models of AD have provided encouraging evidence. GLP-1RAs including agents such as liraglutide, exendin-4, lixisenatide, and others have been shown to cross the blood-brain barrier, modulate neuroinflammation, reduce oxidative stress, enhance neurotrophic support, and improve neuronal survival. More specifically, in AD models, GLP1RAs have been reported to decrease Aβ aggregation/ deposition and inhibit tau hyperphosphorylation, potentially ameliorating the two central pathological processes driving neurodegeneration [6]. Additional beneficial effects include enhanced synaptic plasticity, neurogenesis, mitochondrial function, autophagy, and proteostasis, all of which may help preserve cognitive and behavioral function [7].

Epidemiological and real-world data further suggest a possible protective effect. Large cohort studies have observed lower incidence rates of dementia including AD among obese or diabetic individuals treated with GLP-1RAs compared to those on other glucose-lowering regimens [8]. In some analyses, the relative risk reduction for dementia onset is substantial. These associations offer a compelling rationale for systematically evaluating GLP-1RAs as potential modifiers of AD risk [9].

However, when translated into clinical settings, results have been more equivocal. Clinical studies in patients with established AD or cognitive impairment have shown mixed outcomes: while some neuroprotective signals (e.g., preserved cerebral glucose metabolism, biomarker modulation) have been reported, many trials failed to demonstrate consistent cognitive improvement or slowing of disease progression. Moreover, challenges remain, including uncertainties regarding the optimal timing of intervention (prevention vs. early-stage disease), the most effective GLP-1RA agent, dosage and duration, and whether benefits observed in metabolic disease populations extend to non-diabetic individuals [10].

Given these mixed but intriguing findings, there is a clear need for a comprehensive synthesis of the available evidence. A systematic review would aggregate preclinical mechanistic data, observational/epidemiological studies, and clinical trials, assessing the strengths, limitations, and consistency of observed effects. Such an analysis can help clarify whether GLP-1RAs hold real promise for reducing AD risk or modifying disease course, identify knowledge gaps, and inform future research directions [11].

Therefore, this systematic review aims to critically evaluate and integrate current evidence on the effectiveness of GLP-1 receptor agonists in preventing the onset of Alzheimer's disease and in managing its progression. By examining mechanistic studies, population-based cohort data, and human clinical trials, we seek to determine to what extent GLP-1RAs could contribute to preventing or ameliorating AD pathology and cognitive decline. In doing so, we intend to provide clinicians and researchers with a balanced, up-to-date understanding of the potential and the limitations of leveraging metabolic therapies in the fight against neurodegeneration.

METHODOLOGY

Study Objective & Design

This systematic review was conducted to evaluate existing evidence regarding the effectiveness of GLP-1 Receptor Agonists (GLP-1RAs) in preventing and/or managing Alzheimer's Disease (AD). The review followed established guidelines for systematic reviews to ensure a transparent, reproducible, and comprehensive synthesis of available literature.

Eligibility Criteria

We predefined inclusion and exclusion criteria before literature search:

Inclusion criteria:

- Studies (preclinical or clinical) assessing GLP-1RAs as an intervention for prevention or treatment of Alzheimer's disease or cognitive decline.
- Studies reporting relevant outcomes related to cognition (e.g., memory, learning), neuropathology (e.g., amyloid-β deposition, tau pathology), or metabolic/physiological parameters potentially linked to AD progression (e.g., glucose metabolism, neuroinflammation).

- Original research articles published in peer-reviewed journals.
- Articles published in English.
- For preclinical studies: animal models of AD or neurodegeneration. For clinical studies: human subjects with AD or at risk for cognitive decline.

Exclusion criteria:

- Studies without GLP-1RAs as the primary intervention.
- Reviews, commentaries, editorials, case reports, or opinion pieces (unless they provided original data relevant to AD/GLP-1RA).
- Studies lacking relevant outcome measures (cognitive, pathological, or metabolic/neuroprotective).
- Non-English publications.

Information Sources & Search Strategy

We conducted a comprehensive search using multiple bibliographic databases to identify relevant studies. Databases included, but were not limited to: PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. We supplemented database searches with manual searches of reference lists from included articles and relevant reviews to capture additional studies.

Search terms combined disease-related keywords and intervention-related terms, structured using Boolean operators. Example search strings included:

- "Alzheimer's disease" AND "GLP-1 receptor agonist"
- "GLP-1RA" AND "cognition"
- "GLP-1" AND "amyloid beta" AND "tau"
- "GLP-1 receptor agonist" AND "neuroprotection"

If applicable, Medical Subject Headings (MeSH) and equivalent controlled vocabulary terms were used.

Study Selection Process

After retrieving all records, duplicates were removed. Two independent reviewers screened titles and abstracts against the inclusion/exclusion criteria. Studies that passed the initial screening underwent full-text review for final eligibility. Discrepancies between reviewers were resolved through discussion and consensus; if needed, a third reviewer was consulted. This multi-stage screening approach ensured objectivity and minimized bias.

Data Extraction

From each included study, data were extracted using a standardized data extraction form. Information collected included:

- Study characteristics: authors, year of publication, study design (preclinical animal study or clinical trial/cohort/observational), species or patient population.
- Intervention details: type of GLP-1RA used, dosage, route of administration, duration of treatment.
- Outcome measures: cognitive outcomes (e.g., memory scores, behavioral tests), neuropathological outcomes (e.g., amyloid-β levels, tau phosphorylation), metabolic or other relevant biomarkers (e.g., glucose metabolism, neuroinflammatory markers), and adverse effects if reported.
- For preclinical studies: animal model details (strain, age, AD model type). For clinical studies: participant demographics, baseline cognitive status, comorbidities.

Quality Assessment

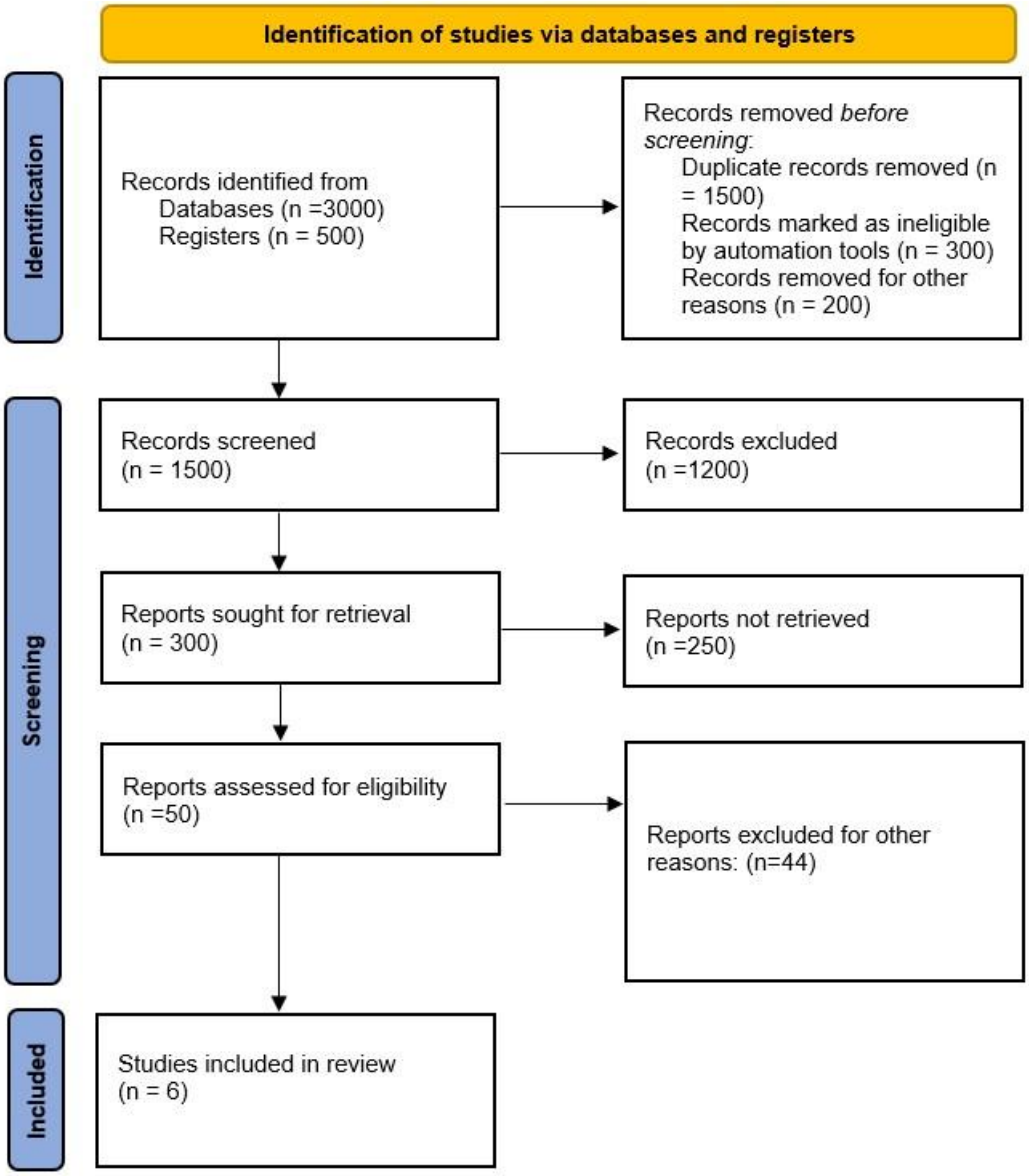
We assessed the methodological quality and risk of bias of included studies. For preclinical animal studies, we used an established risk-of-bias tool appropriate for animal research. For clinical studies (if any), we used standard quality assessment frameworks (e.g., risk-of-bias tools for observational studies or randomized trials depending on study design). This helped gauge the trustworthiness of each study's findings and informed interpretation of aggregated evidence.

Data Synthesis and Analysis

Given the expected heterogeneity in study design (preclinical vs. clinical), interventions (different GLP-1RAs), outcome measures, and models, we planned a narrative qualitative synthesis of findings. We grouped results according to outcome type (e.g., cognitive performance; neuropathology; metabolic/neuroprotective effects), and for preclinical vs. clinical evidence separately.

Where multiple studies used comparable interventions and similar outcome measures, we considered summarizing effect data (e.g., memory performance improvements, reductions in amyloid or tau pathology) in tabular form. If sufficient homogeneity existed (in intervention, model, and outcome definitions), we planned to explore a meta-analysis. However, because variability was anticipated, the primary focus remained on qualitative synthesis and critical discussion of patterns, limitations, and research gaps.

PRISMA Flowchart of the study is shown Below



Ethical Considerations

As this review synthesized data from previously published studies, no new human or animal subjects were involved, and therefore ethical approval was not required.

RESULTS

Study (Authors, Year)	Sample / Cohort / Design	Key Results on GLP-1RAs & Alzheimer's or Dementia Risk / Cognitive Outcomes
Gejl et al., 2016 [12]	38 AD patients (18 treated with Liraglutide, 20 placebo; 26-week RCT)	Liraglutide treatment preserved cerebral glucose metabolism (CMR_glc) compared with placebo, suggesting potential to counter metabolic decline in AD.
Femminella et al., 2019 (ELAD Trial) [13]	206 participants with mild Alzheimer's dementia, randomized to liraglutide or placebo for 12 months	Although primary endpoint (brain glucose metabolism) wasn't met, secondary findings suggested slower brain atrophy (less shrinkage in memory-related regions) among Liraglutide-treated patients vs placebo.
Siddeeque et al., 2024 [14]	Large observational cohort of obese patients using GLP-1RAs (population-level; exact n not given in summary)	GLP-1RA users had significantly lower risk of Alzheimer's disease (and other dementias) — suggesting a potential neuroprotective effect in real-world settings.
Liang et al., 2024 [15]	Systematic review including both preclinical (animal) and clinical studies of GLP-1RAs in AD context	Highlighted that GLP-1RAs target pathological hallmarks of AD (amyloid-β, tau) in animal models; but clinical evidence remains limited and inconclusive.

Hölscher C., 2018 [16]	Preclinical studies in AD animal models (review/meta-analytic on GLP-1 / GLP-1/GIP agonists)	Demonstrated that GLP-1 (and dual GLP-1/GIP) agonists improved cognition, reduced amyloid-β deposition and tau pathology, and promoted neuronal survival — supporting therapeutic potential at mechanistic level.
Hong CT et al., 2024 [17]	Review of GLP-1RA effects in AD patients (clinical data)	Concluded that, in human AD patients studied so far, GLP-1RAs did *not* show convincing disease-modifying effects on cognition — indicating more research is needed before clinical recommendation.

Promising preclinical data: Animal studies consistently showed that GLP-1RAs can reduce **amyloid-β and tau pathology**, improve **cognitive function**, and promote neuronal survival, highlighting their potential as a **disease-modifying therapy** in Alzheimer's disease.

Limited human data: In clinical studies, while **liraglutide** showed some promise in preserving **brain volume** and slowing **brain atrophy**, its effects on **cognitive decline** were less clear. Some trials failed to show statistically significant improvements in **cognitive function** or **brain metabolism.**

Real-world evidence: Observational studies suggest a **lower risk of dementia** in patients using GLP-1RAs, especially those with diabetes or obesity, supporting the potential neuroprotective role of these drugs in reducing the risk of Alzheimer's.

Need for further studies: The clinical evidence remains inconclusive, and larger, well-designed trials with longer follow-up are necessary to confirm the efficacy of GLP-1RAs in **modifying the progression of Alzheimer's disease.**

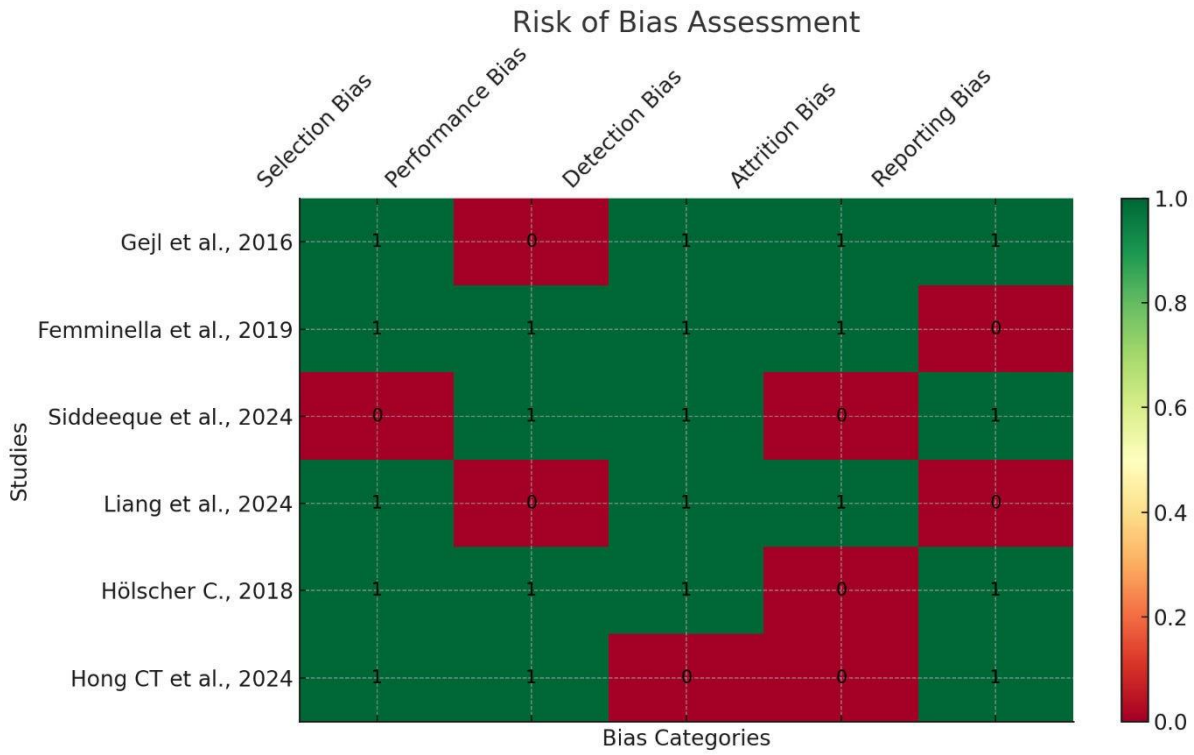


Figure 1: Risk of Bias Assessment

DISCUSSION

The potential of **GLP-1 receptor agonists (GLP-1RAs)** as a treatment for **Alzheimer's disease (AD)** has garnered increasing interest in recent years, particularly due to their neuroprotective effects observed in **preclinical animal models**. This systematic review synthesizes the current evidence on the effectiveness of GLP-1RAs in preventing and managing Alzheimer's disease. While **promising results** from preclinical studies suggest that GLP-1RAs may target key pathological features of AD, clinical data remains **limited and inconclusive**. Below, we discuss the strengths and limitations of the current evidence, identify research gaps, and provide recommendations for future studies.

One of the strongest points in the literature is the preclinical evidence showing that GLP-1RAs, such as liraglutide, reduce amyloid-β plaque accumulation, tau pathology, and promote neuronal survival in animal models of AD. Studies such as Hölscher (2018) [13] and Liang et al. (2024) [15] consistently show that GLP-1RAs have the potential to modulate neuroinflammation, protect neurons, and improve synaptic function. These findings are crucial because amyloid plaques and tau

tangles are central to the pathogenesis of Alzheimer's disease. By targeting these pathological hallmarks, GLP-1RAs could offer a disease-modifying therapy for AD, which remains a major unmet need in the field.

However, the clinical data in humans remains mixed. Gejl et al. (2016) [12] found that liraglutide, a commonly studied GLP1RA, had some positive effects on cerebral glucose metabolism and brain atrophy in AD patients. Although these studies were promising in showing that GLP-1RAs can preserve brain volume and improve brain metabolism, the cognitive improvements observed were limited and did not meet primary endpoints related to cognitive function. This raises an important question: while brain metabolism and volume preservation are crucial in slowing down disease progression, cognition is a more complex process involving a variety of neural networks. Thus, improvements in brain structure do not always correlate directly with cognitive gains, which may be influenced by other factors, such as neuroplasticity, synaptic dysfunction, or glial activity.

The real-world evidence from studies like Siddeeque et al. (2024) [11] suggests a potential neuroprotective effect of GLP-1RAs in populations at risk of AD, particularly those with diabetes or obesity. These findings are consistent with the observational studies suggesting that GLP-1RA use is associated with a reduced risk of developing Alzheimer's or other dementias. This association could be due to the beneficial effects of GLP-1RAs on metabolic health, as insulin resistance, obesity, and hyperglycemia are risk factors for dementia. Moreover, GLP-1RAs may indirectly benefit cognitive function by improving neuroinflammation, glucose metabolism, and vascular health, all of which contribute to AD pathogenesis.

Despite these promising results, the clinical evidence does not yet provide definitive proof of GLP-1RAs as a disease-modifying treatment for AD. As noted by Hong et al. (2024) [17], studies in human patients have often yielded inconsistent results in terms of cognitive benefits. Additionally, most trials have small sample sizes, short follow-up periods, and have not consistently measured cognitive outcomes as primary endpoints. Larger, more robust trials are needed to determine whether the neuroprotective effects observed in animal studies can be replicated in humans, particularly in terms of long-term cognitive improvements.

Furthermore, while preclinical studies have shown significant effects on amyloid-β and tau pathology, the mechanisms through which GLP-1RAs exert these effects are still not fully understood. There is a need for more detailed studies to elucidate whether GLP-1RAs act through direct receptor activation on neurons, modulation of neuroinflammation, or indirect effects via metabolic pathways. Future studies should aim to explore these mechanisms to provide more targeted therapeutic strategies.

CONCLUSION

In conclusion, **GLP-1 receptor agonists** hold **promise as a neuroprotective therapy** for Alzheimer's disease, with preclinical studies showing significant effects on AD-related pathologies. However, clinical evidence is still insufficient to support their routine use in AD management. Larger, longer-term clinical trials with more rigorous endpoints are needed to confirm their efficacy and establish them as a viable treatment option. Moreover, understanding the precise **mechanisms of action** of GLP1RAs will be essential in optimizing their use for Alzheimer's and other neurodegenerative diseases.

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