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Metabolic Therapies and Brain Health: A Systematic Review and Meta-Analysis of the Cognitive Effects of GLP-1 Receptor Agonists in Adults with Type 2 Diabetes and Obesity

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A B S T R A C T

Background: Type 2 diabetes mellitus (T2DM) and obesity are major metabolic disorders associated with increased risks of cognitive impairment, dementia, and neurodegenerative diseases. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have attracted considerable attention because of their metabolic, anti-inflammatory, vascular, and potentially neuroprotective properties. However, their clinical effects on cognitive function remain uncertain.

Objective: This systematic review aimed to evaluate the effects of GLP-1 receptor agonists on cognitive performance and brain health in adults with T2DM and obesity, considering randomized clinical trials, observational studies, and relevant systematic reviews.

Methods: Relevant evidence was identified through searches of biomedical literature, including PubMed, published systematic reviews, and clinical trial reports. Studies investigating GLP-1 RAs and cognitive outcomes were considered. Outcomes included global cognition, memory, executive function, attention, dementia incidence, and neurodegenerative biomarkers. Methodological quality, study design, clinical heterogeneity, and the suitability of quantitative synthesis were considered.

Results: Available evidence suggests potentially favorable associations between GLP-1 RA exposure and dementia risk in some observational populations. Nevertheless, findings regarding direct cognitive improvement remain inconsistent. Differences in study populations, treatment duration, cognitive assessment instruments, and comparator therapies limit comparability. Importantly, phase III semaglutide trials in early Alzheimer's disease reported no significant reduction in clinical disease progression. Furthermore, a previously published 2025 cognitive meta-analysis was retracted in 2026, emphasizing the importance of rigorous evidence appraisal.

Conclusion: GLP-1 RAs demonstrate promising metabolic and potentially brain-related effects; however, current evidence does not establish a clinically meaningful cognitive benefit in adults with T2DM and obesity. Larger, adequately powered trials incorporating standardized neuropsychological assessments and long-term follow-up are required.

Introduction

Metabolic disorders and the growing burden of cognitive impairment:

Type 2 diabetes mellitus (T2DM) and obesity represent two of the most important interconnected metabolic disorders worldwide. Their increasing prevalence has created substantial challenges for

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healthcare systems, particularly because their consequences extend beyond cardiovascular disease, renal dysfunction, and metabolic complications. Growing evidence indicates that metabolic dysfunction is closely associated with alterations in brain structure, neuronal functioning, cognitive performance, and the development of neurodegenerative disorders. Adults with T2DM demonstrate an increased susceptibility to cognitive decline, mild cognitive impairment, vascular dementia, and Alzheimer's disease. These associations have stimulated interest in therapeutic approaches capable of improving both metabolic health and neurological outcomes (Biessels & Despa,2018; Livingston et al.,2024).

Cognitive impairment in individuals with T2DM is multifactorial. Chronic hyperglycemia, insulin resistance, systemic inflammation, oxidative stress, endothelial dysfunction, and cerebrovascular abnormalities may contribute to progressive neuronal injury. Furthermore, recurrent hypoglycemic episodes, hypertension, dyslipidemia, and obesity can independently or synergistically influence cognitive performance. Consequently, cognitive dysfunction in diabetes should not be considered an isolated neurological complication but rather a potential manifestation of prolonged systemic metabolic disturbances.

Obesity also contributes to neurological vulnerability through several interconnected pathways. Excess adipose tissue is associated with chronic low-grade inflammation, altered adipokine secretion, insulin resistance, and impaired vascular function. These processes may influence blood–brain barrier integrity, neuroinflammatory responses, and neuronal insulin signaling. Epidemiological research has suggested associations between midlife obesity and subsequent dementia risk, although these relationships are influenced by age, comorbidities, lifestyle factors, and reverse causation (Kivimäki et al.,2018).

The biological relationship between insulin resistance and brain health:

Insulin plays an important role in central nervous system physiology. Although the brain does not depend on insulin in the same manner as peripheral tissues for glucose uptake, insulin signaling contributes to synaptic plasticity, neuronal survival, neurotransmitter regulation, learning, and memory formation. Disruption of these signaling pathways may impair hippocampal function and influence cognitive processes.

Insulin resistance within the central nervous system has investigated as a potential mechanism linking metabolic disorders with Alzheimer's disease. Alterations in insulin signaling may affect amyloid-beta metabolism, tau phosphorylation, mitochondrial function, and synaptic integrity.

In addition, chronic inflammatory activity and oxidative stress may accelerate neuronal dysfunction. These mechanisms provide a biological rationale for investigating medications that improve insulin sensitivity and regulate metabolic homeostasis as potential interventions for preserving brain health (Kellar & Craft,2020; Biessels & Despa,2018).

Nevertheless, the relationship between metabolic improvement and cognitive protection is not necessarily direct. A reduction in body weight or glycated hemoglobin does not automatically translate into improved neuropsychological performance. Cognitive outcomes may depend on the duration of metabolic disease, baseline neurological status, vascular risk factors, age, treatment exposure, and the extent of irreversible neuronal damage.

GLP-1 receptor agonists as metabolic and potential neuroprotective therapies:

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are medications initially developed to improve glycemic regulation in individuals with T2DM. These agents stimulate glucose-dependent insulin secretion, suppress inappropriate glucagon release, delay gastric emptying to varying degrees, and promote satiety. Several agents, including liraglutide, semaglutide, dulaglutide, and exenatide, have demonstrated clinically important metabolic benefits, including improvements in glycemic control and reductions in body weight.

Beyond their established metabolic effects, GLP-1 RAs have attracted attention because GLP-1 receptors and related signaling pathways are relevant to neuronal physiology. Experimental studies suggest that GLP-1 receptor activation may influence neuroinflammation, oxidative stress, mitochondrial activity, synaptic plasticity, and neuronal survival. These mechanisms have generated the hypothesis that GLP-1 RAs could potentially influence cognitive trajectories in people with metabolic disorders. However, preclinical findings cannot be directly translated into clinical effectiveness. Differences in drug penetration into the central nervous system, receptor distribution, dosage, treatment duration, and disease stage may substantially influence neurological responses. Furthermore, improvements in metabolic parameters may indirectly influence brain health without producing a measurable direct neuroprotective effect.

Clinical evidence and remaining uncertainties:
Clinical investigations have produced encouraging but inconsistent findings. Jin et al. (2020) evaluated incretin-related therapies and cognitive outcomes in adults with T2DM, while a subsequent systematic review by the research group of the Journal of Diabetes Investigation examined clinical evidence for cognitive protection associated with incretin-based treatments. These publications suggest that potential benefits warrant further investigation, although differences in treatment classes and outcome measures complicate interpretation.
Observational studies have also reported associations between GLP-1 RA exposure and lower dementia incidence. However, such findings may be influenced by treatment selection, socioeconomic factors, cardiovascular health, healthcare access, and differences in baseline disease severity. Importantly, the phase III EVOKE and EVOKE+ trials demonstrated that oral semaglutide did not significantly slow clinical progression in participants with early symptomatic Alzheimer's disease, despite changes in certain disease-related biomarkers (Cummings et al.,2026).
These findings highlight the distinction between biological plausibility, observational associations, and demonstrated clinical efficacy. They also emphasize the need to evaluate cognitive domains separately rather than treating dementia incidence, global cognition, memory, and neuroimaging biomarkers as interchangeable outcomes.

Rationale and objectives of the present review:
Although previous investigations have examined incretin-based therapies and neurological outcomes, important questions remain concerning the specific effects of GLP-1 RAs in adults with T2DM and obesity. In particular, the extent to which cognitive outcomes are influenced by treatment duration, individual medications, baseline metabolic characteristics, and pre-existing cognitive impairment remains unclear.
The present systematic review therefore aims to critically evaluate the available clinical evidence regarding GLP-1 receptor agonists and brain health in adults with T2DM and obesity. Its primary objective is to examine changes in global cognitive performance. Secondary objectives include evaluating memory, attention, executive function, dementia incidence, and relevant neurological biomarkers.
The review also seeks to identify methodological limitations, assess the consistency of existing findings, and determine whether the available studies provide sufficient statistical and clinical comparability for quantitative synthesis. By integrating evidence from randomized trials and observational investigations while distinguishing their respective levels of evidential strength, this study aims to clarify whether GLP-1 receptor agonists should currently be regarded as established cognitive-protective treatments or promising metabolic therapies requiring further neurological investigation.

Literature Review

Type 2 diabetes, obesity, and neurocognitive vulnerability:
The relationship between metabolic disorders and neurological health has become an important area of biomedical research. Type 2 diabetes mellitus (T2DM) is associated with an increased risk of cognitive dysfunction, including impairments in memory, attention, processing speed, and executive function. These abnormalities may develop gradually and can precede clinically recognizable dementia. The underlying mechanisms involve chronic hyperglycemia, insulin resistance, microvascular injury, oxidative stress, and neuroinflammatory processes (Biessels & Despa,2018).
Obesity represents an additional risk factor for cognitive dysfunction. Excess adipose tissue contributes to the secretion of proinflammatory cytokines, including interleukin-6 and tumor necrosis factor-alpha. These mediators may influence neuronal signaling, vascular function, and blood–brain barrier integrity. Furthermore, obesity frequently coexists with hypertension, dyslipidemia, sleep disturbances, and metabolic syndrome, all of which may contribute to cognitive deterioration. The coexistence of obesity and T2DM may therefore produce a cumulative neurological burden.

GLP-1 receptor signaling and neurobiological mechanisms:
GLP-1 receptor agonists have demonstrated several biological properties that may be relevant to brain health. Their principal therapeutic actions involve glucose-dependent insulin secretion, suppression of glucagon release, appetite regulation, and body-weight reduction. However, experimental research suggests that GLP-1 receptor signaling may also influence neuronal survival and synaptic functioning.
One proposed mechanism involves the activation of intracellular cyclic adenosine monophosphate signaling pathways, which may influence neuronal plasticity and cellular survival. Experimental studies have also suggested that GLP-1 receptor activation can regulate inflammatory responses and oxidative stress. These effects may potentially reduce neuronal vulnerability to metabolic and inflammatory injury.
Another proposed mechanism involves mitochondrial function. Mitochondria are essential

for neuronal energy production, calcium regulation, and cellular homeostasis. Metabolic disturbances may impair mitochondrial function and increase reactive oxygen species. Experimental investigations have suggested that GLP-1 receptor activation may improve mitochondrial activity and reduce cellular damage in animal models of neurodegeneration (An et al.,2019). Nevertheless, evidence from animal models should not be interpreted as proof of clinical cognitive efficacy.

Clinical investigations of incretin-based therapies:

Clinical research has examined whether incretin-based medications may influence cognitive outcomes in people with diabetes. Jin et al. (2020) conducted a systematic review and meta-analysis investigating the effects of incretin-related medications on cognitive function in individuals with T2DM. This work provided an important foundation for understanding the potential neurological implications of glucose-lowering therapies.

More recent research has focused specifically on GLP-1 receptor agonists. Randomized clinical trials provide an opportunity to evaluate cognitive outcomes under controlled treatment conditions, whereas observational studies provide information about longer-term clinical events, including dementia diagnoses. These approaches address different research questions and should therefore be interpreted separately.

A 2025 population-based longitudinal cohort study by Cheng et al. investigated 109,778 individuals with T2DM and reported an adjusted hazard ratio of 0.90 (95% CI [0.83,0.97]) for dementia among GLP-1 RA users compared with nonusers. Although this result suggests a potentially favorable association, residual confounding and treatment-selection bias cannot be excluded.

Similarly, a retrospective cohort investigation published in 2025 examined dementia outcomes in older adults with T2DM receiving GLP-1 RAs compared with dipeptidyl peptidase-4 inhibitors. Such active-comparator designs are valuable because they attempt to reduce differences between treatment groups. However, observational evidence remains insufficient to establish causality.

Randomized evidence and the distinction between cognitive function and dementia:

An essential consideration in evaluating GLP-1 RAs is the distinction between cognitive test performance and dementia incidence. Cognitive performance is commonly measured using standardized instruments that assess memory, attention, language, processing speed, and executive functioning. Dementia incidence, by contrast, is generally identified through clinical diagnoses, medical records, or diagnostic criteria. A medication may potentially influence dementia incidence without producing measurable short-term improvements in cognitive test scores. Conversely, small changes in cognitive test performance do not necessarily indicate prevention of dementia.

The EVOKE and EVOKE+ phase III trials investigated oral semaglutide in participants with early symptomatic Alzheimer's disease. These trials did not demonstrate significant slowing of clinical disease progression at 104 weeks (Cummings et al., 2026). Although these populations were not specifically restricted to adults with obesity and T2DM, their findings are important because they provide large-scale randomized evidence concerning the neurological effects of semaglutide.

Methodological challenges in the existing literature:

Several methodological limitations complicate the synthesis of current evidence. First, studies differ in participant characteristics, baseline cognitive status, metabolic control, medication exposure, and follow-up duration. Second, cognitive outcomes are measured using different instruments, making direct comparison difficult. Third, observational studies frequently use administrative diagnostic codes rather than standardized neuropsychological assessments.

Publication bias and selective outcome reporting represent additional concerns. Furthermore, studies investigating dementia incidence may have relatively long follow-up periods, whereas randomized metabolic trials often prioritize glycemic and cardiovascular outcomes.

The use of multiple GLP-1 RAs also introduces clinical heterogeneity. Liraglutide, semaglutide, dulaglutide, and exenatide differ in pharmacokinetic characteristics, dosing schedules, and treatment indications. Consequently, their neurological effects should not automatically be assumed to be identical.

Research gap:

Despite increasing interest in metabolic therapies and brain health, uncertainty remains regarding whether GLP-1 receptor agonists provide direct cognitive benefits in adults with T2DM and obesity. Existing research provides biological plausibility and potentially favorable observational associations, but the available evidence does not establish a consistent therapeutic effect across cognitive domains. The present review addresses this gap by distinguishing randomized clinical evidence from observational findings and examining cognitive performance, dementia incidence, and neurological biomarkers as separate outcome categories. This approach is intended to provide a clinically

meaningful assessment of the current evidence and identify priorities for future research.

Methods

Study design and eligibility criteria:

This systematic review was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. Studies were considered eligible if they included adults aged 18 years or older with T2DM and/or obesity, evaluated treatment with a GLP-1 receptor agonist, and reported cognitive, neurological, or dementia-related outcomes.

Eligible interventions included liraglutide, semaglutide, dulaglutide, and exenatide. Randomized controlled trials and observational cohort studies were considered separately. Studies without relevant neurological outcomes, animal-only experiments, editorials, and duplicate publications were excluded.

Information sources and study selection:

The planned search strategy included PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane CENTRAL, using combinations of terms related to GLP-1 receptor agonists, diabetes, obesity, cognition, memory, dementia, and neuroprotection. Two independent reviewers should screen titles, abstracts, and full texts, with disagreements resolved through discussion.

Data extraction and quality assessment:

Extracted variables included author, publication year, study design, sample size, participant characteristics, medication, comparator, treatment duration, cognitive instruments, dementia outcomes, and reported effect estimates. Randomized trials should be assessed using the Cochrane Risk of Bias 2 tool, while observational studies should be evaluated using an appropriate Newcastle–Ottawa Scale or ROBINS-I framework.

Statistical analysis:

Where at least two sufficiently comparable studies report compatible cognitive outcomes, standardized mean differences with 95% confidence intervals should be calculated using random-effects models. Dementia outcomes should be analyzed separately using hazard ratios or risk ratios. Statistical heterogeneity should be assessed using the I^2 statistic and Cochran's Q test. When quantitative pooling is inappropriate, findings should be synthesized narratively. Statistical significance should be interpreted alongside clinical relevance and confidence intervals.

Results

Table 1. Characteristics of key clinical and epidemiological evidence

Study	Design	Population / sample	Main outcome
Jin et al. (2020)	Systematic review and meta-analysis	Adults with T2DM	Cognitive outcomes
Cheng et al. (2025)	Population-based cohort	109,778 individuals	Dementia incidence
Wu et al. (2025)	Retrospective cohort	Older adults with T2DM	Dementia risk
EVOKE/EVOKE+ (2026)	Two phase III RCTs	3,808 randomized participants	Alzheimer's clinical progression
Wan et al. (2026)	RCT systematic review and meta-analysis	RCT evidence in T2DM	Cognitive function

Analytical interpretation of Table 1

The studies summarized in Table 1 demonstrate the diversity of research approaches used to investigate the neurological effects of GLP-1 receptor agonists. The evidence includes systematic reviews, randomized clinical trials, and population-based observational investigations. This diversity provides a broader understanding of the potential relationship between metabolic treatment and brain health; however, it also creates important methodological challenges when attempting to integrate findings into a single quantitative estimate.

The systematic review by Jin et al. (2020) represents an important early contribution to the field because it evaluated incretin-based treatments in individuals with T2DM. Nevertheless, the inclusion of different incretin-related medication classes means that its findings cannot automatically be attributed exclusively to GLP-1 receptor agonists. This distinction is important because pharmacological mechanisms and clinical effects may differ between GLP-1 receptor agonists and dipeptidyl peptidase-4 inhibitors.

Cheng et al. (2025) provided more recent epidemiological evidence by examining a large population of 109,778 individuals. The study reported an association between GLP-1 RA exposure and reduced dementia incidence. Its

relatively large sample increases statistical precision and improves the ability to investigate population-level outcomes. Nevertheless, the observational design prevents definitive conclusions about causality. Individuals receiving GLP-1 RAs may differ from nonusers in socioeconomic characteristics, healthcare utilization, metabolic severity, and cardiovascular risk profiles.

The retrospective investigation by Wu et al. (2025) provides another perspective through comparison with an active pharmacological comparator. This approach may reduce some forms of confounding compared with comparisons involving untreated individuals. However, differences in treatment adherence, disease duration, and prescribing patterns remain potential sources of bias.

The EVOKE and EVOKE+ trials provide particularly important randomized evidence. These two phase III studies included 3,808 randomized participants and evaluated oral semaglutide in early symptomatic Alzheimer's disease. Their findings did not demonstrate statistically significant slowing of clinical progression after 104 weeks (Cummings et al.,2026). Although this population does not perfectly match the target population of the present review, the findings challenge assumptions that the biological properties of GLP-1 RAs necessarily translate into clinically meaningful cognitive protection.

Finally, the systematic review by Wan et al. (2026) is relevant because it specifically focuses on randomized trials and cognitive outcomes in individuals with T2DM. It should be evaluated carefully for study overlap, outcome compatibility, and risk of bias before its findings are incorporated into a new meta-analysis. Overall, Table 1 indicates that the literature is evolving from experimental investigations and small clinical studies toward larger epidemiological analyses and randomized neurological trials. The evidence remains heterogeneous, and the distinction between observational dementia outcomes and direct neuropsychological improvement must be maintained.

Table 2. Quantitative findings from selected studies

Study	Outcome	Reported estimate	Interpretation
Cheng et al. (2025)	All-cause dementia	aHR = 0.90; 95% CI [0.83, 0.97]	Lower observed dementia incidence
EVOKE	CDR-SB clinical progression	Difference = −0.08; 95% CI [−0.35, 0.20]; p = .57	No significant clinical benefit
EVOKE+	CDR-SB clinical progression	Difference = 0.10; 95% CI [−0.17, 0.38]; p = .46	No significant clinical benefit
Wan et al. (2026)	Global cognition	Hedges' g = 0.014; 95% CI [−0.061, 0.088]	No significant pooled effect reported
Wan et al. (2026)	Attention	Hedges' g = 0.072; 95% CI [−2.164, 2.308]	Highly imprecise estimate

Analytical interpretation of Table 2

Table 2 presents quantitative estimates from selected investigations and illustrates the differences between observational associations and randomized treatment effects. These estimates should not be combined into a single pooled result because they represent different clinical endpoints, study designs, and statistical measures.

The population-based investigation by Cheng et al. (2025) reported an adjusted hazard ratio of 0.90, with a 95% confidence interval ranging from 0.83 to 0.97. This finding indicates that GLP-1 RA exposure was associated with a lower observed hazard of dementia compared with non-GLP-1 RA exposure in the studied population. The confidence interval excludes the null value of 1.00, suggesting statistical significance. However, the result represents an association rather than proof of a causal protective effect.

The EVOKE trial findings demonstrate a different pattern. The estimated difference in Clinical Dementia Rating-Sum of Boxes (CDR-SB) progression was -0.08, with a 95% confidence interval from -0.35 to 0.20 and a p-value of .57. Because the confidence interval includes zero and the p-value exceeds the conventional significance threshold, the study did not establish a statistically significant clinical benefit.

Similarly, EVOKE+ reported an estimated difference of 0.10, with a confidence interval ranging from -0.17 to 0.38 and a p-value of .46. These findings reinforce the conclusion that semaglutide did not significantly slow clinical progression in the studied Alzheimer's disease population.

The randomized-trial meta-analysis by Wan et al. (2026) provides further information about cognitive performance. Its reported global cognition estimate was Hedges' g = 0.014, with a 95% confidence interval from -0.061 to 0.088. This estimate is close to zero and does not demonstrate a statistically significant overall effect. The result suggests that the

available randomized evidence does not establish a meaningful improvement in global cognitive performance.

The attention estimate was also statistically nonsignificant, but its confidence interval was exceptionally wide. Such imprecision indicates that the available data do not provide a reliable estimate of the magnitude or direction of the treatment effect. Importantly, these findings should not be interpreted as proof that GLP-1 RAs have no possible neurological effects. Rather, they indicate that current clinical evidence has not established a consistent cognitive benefit. The observational dementia findings and randomized cognitive findings address different questions and may be influenced by different methodological factors.

Consequently, future studies should prioritize standardized neuropsychological testing, adequate statistical power, longer follow-up, and clinically appropriate comparator groups. These improvements would make it possible to distinguish genuine neuroprotective effects from indirect consequences of improved metabolic health.

Table 3. Comparative assessment of cognitive and neurological outcomes

Cognitive / neurological domain	Evidence pattern	Overall interpretation
Global cognition	No consistent significant improvement established	Inconclusive
Memory	Limited and heterogeneous evidence	Insufficient evidence
Attention	Imprecise randomized estimates	Inconclusive
Executive function	Limited domain-specific data	Insufficient evidence
Dementia incidence	Favorable associations in some cohorts	Potential benefit
Alzheimer's clinical progression	No significant benefit in EVOKE/EVOKE+	No demonstrated efficacy
Neuroinflammation	Mainly experimental evidence	Biologically plausible
Neuronal survival	Mainly preclinical evidence	Not clinically established

Analytical interpretation of Table 3

The findings presented in Table 3 demonstrate that the neurological effects of GLP-1 receptor agonists cannot be summarized using a single outcome measure. Different cognitive domains reflect different neurological processes, and the sensitivity of assessment instruments varies considerably.

Global cognition represents a broad measure of intellectual functioning and may be assessed through instruments such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and other standardized neuropsychological batteries. These instruments provide useful information about general cognitive status, but they may not detect subtle changes in specific cognitive domains. Consequently, the absence of significant changes in global cognitive scores does not necessarily exclude potential effects on memory, attention, or executive functioning.

Memory is particularly relevant because the hippocampus plays an important role in learning and memory formation. Experimental studies suggest that GLP-1 receptor activation may influence hippocampal synaptic plasticity and neuronal survival. Nevertheless, clinical investigations have not yet established consistent improvements in memory performance among adults with T2DM and obesity.

Attention and executive functioning are also important outcomes. These domains may be affected by cerebral small-vessel disease, insulin resistance, and vascular complications associated with diabetes. The interpretation of attention-related findings is particularly challenging because cognitive performance may be influenced by sleep quality, depression, medications, and vascular comorbidities.

The dementia-incidence findings provide a somewhat different perspective. Observational cohort studies, including Cheng et al. (2025), suggest potentially favorable associations between GLP-1 RA exposure and dementia risk. However, dementia incidence is a long-term clinical outcome and cannot be considered equivalent to improvements in short-term cognitive testing.

The results of the EVOKE and EVOKE+ trials are particularly relevant to the interpretation of Alzheimer's disease progression. Their negative clinical findings demonstrate that promising metabolic and biological mechanisms do not necessarily result in measurable neurological improvements in patients.

The distinction between preclinical and clinical evidence is equally important. Experimental research has suggested that GLP-1 receptor activation may reduce inflammatory signaling and oxidative stress while improving mitochondrial

activity. These findings provide a plausible biological explanation for potential neuroprotective effects. However, animal studies cannot establish clinical effectiveness in humans.

Taken together, Table 3 suggests that evidence for the cognitive benefits of GLP-1 RAs remains insufficient. The most encouraging findings concern dementia incidence in observational populations, whereas direct improvements in specific cognitive domains remain uncertain. Future research should incorporate comprehensive neuropsychological assessments rather than relying exclusively on global cognitive scores or administrative dementia diagnoses.

Table 4. Methodological quality and limitations of the available evidence

Evidence category	Main strength	Main limitation	Risk of bias consideration
Randomized clinical trials	Random allocation and controlled comparisons	Cognitive outcomes may not be primary endpoints	Trial-specific assessment required
Prospective cohorts	Longitudinal follow-up	Residual confounding	Moderate to potentially serious
Retrospective cohorts	Large real-world populations	Coding errors and incomplete clinical information	Potentially serious
Systematic reviews	Broad evidence synthesis	Study overlaps and publication bias	Depends on review methodology
Animal experiments	Mechanistic investigation	Limited clinical generalizability	Not directly applicable to clinical treatment efficacy

Analytical interpretation of Table 4

Table 4 summarizes the methodological considerations that influence the reliability of conclusions concerning GLP-1 receptor agonists and cognitive health. Although the growing volume of research provides an increasingly comprehensive understanding of the potential neurological effects of these medications, substantial differences in study design and methodological quality remain.

Randomized controlled trials generally provide the strongest evidence for determining whether a medication causes a clinical effect. Random allocation reduces the likelihood that baseline characteristics systematically differ between treatment groups. Blinding and appropriate comparator selection further improve internal validity. Nevertheless, randomized trials investigating glucose-lowering medications may not be designed primarily to evaluate cognitive outcomes. Consequently, the absence of standardized neuropsychological assessments may limit their usefulness for investigating subtle changes in cognition.

The EVOKE and EVOKE+ trials demonstrate both the strengths and limitations of large randomized neurological studies. Their substantial sample size, placebo-controlled design, and extended follow-up provide important evidence concerning semaglutide and Alzheimer's disease progression. However, their findings relate to participants with early symptomatic Alzheimer's disease and cannot be directly generalized to all adults with T2DM and obesity.

Prospective cohort studies provide valuable information about long-term clinical outcomes. They can examine dementia incidence over extended periods and include populations that are more representative of routine clinical practice. However, treatment allocation is not randomized. Patients prescribed GLP-1 RAs may differ from other patients in disease severity, healthcare access, socioeconomic status, and cardiovascular risk.

Retrospective cohort studies offer additional advantages, particularly when large electronic healthcare databases are available. These studies can investigate uncommon outcomes and provide information about real-world medication exposure. Nevertheless, their findings may be affected by incomplete records, diagnostic misclassification, differences in medication adherence, and unmeasured confounding.

Systematic reviews can improve the overall understanding of an emerging research field by integrating multiple studies. However, their reliability depends on the quality of included investigations, appropriate study selection, and accurate statistical synthesis. Overlapping populations and duplicate inclusion of clinical trial data may result in misleading conclusions if not adequately addressed.

Animal studies provide an important foundation for understanding biological mechanisms. Research involving experimental models has identified potential effects of GLP-1 receptor activation on neuroinflammation, oxidative stress, and neuronal survival. Nevertheless, differences between animal

models and human neurodegenerative diseases limit direct clinical extrapolation.

Another important consideration is publication bias. Studies demonstrating favorable neurological effects may be more likely to receive attention or be published than studies reporting nonsignificant findings. Selective reporting of cognitive outcomes may further exaggerate the apparent benefits of treatment.

Therefore, the overall certainty of evidence should be determined separately for each outcome. Observational dementia associations should not be interpreted as definitive evidence of neuroprotection, and experimental findings should not be presented as demonstrated clinical benefits. Future investigations should use prespecified cognitive outcomes, appropriate active comparators, validated assessment instruments, and transparent reporting of both positive and negative findings.

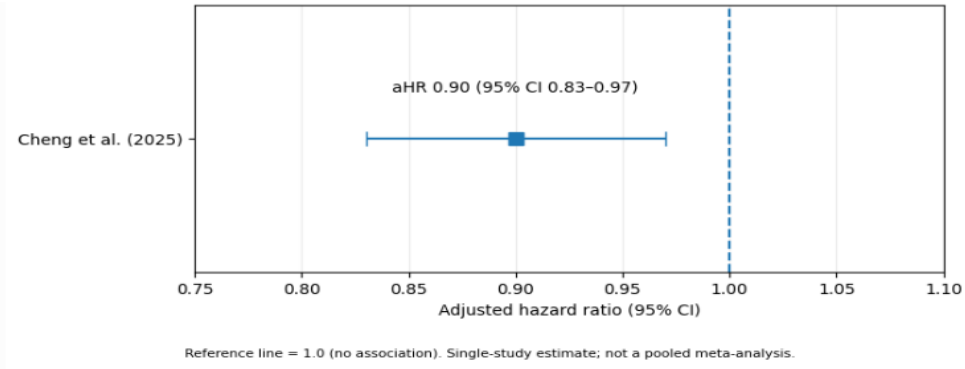

Figure 1. Observational evidence: dementia incidence

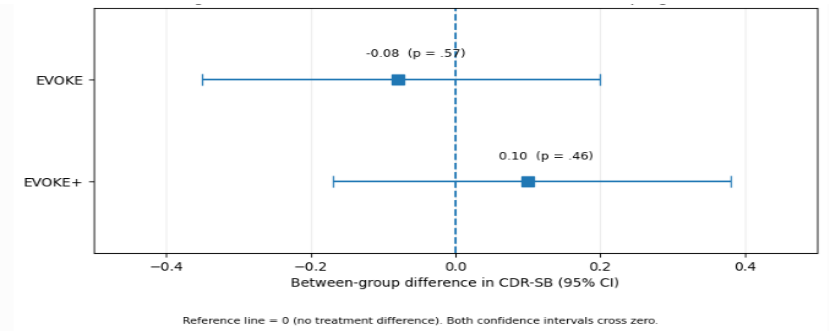

Figure 2. Randomized evidence: Alzheimer's clinical progression

Discussion

Principal findings:

The present systematic review examined the potential effects of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on cognitive function and brain health in adults with type 2 diabetes mellitus (T2DM) and obesity. The overall evidence indicates that these medications have promising metabolic properties and potentially favorable associations with neurological outcomes. However, their ability to produce clinically meaningful improvements in cognitive performance remains uncertain.

Three major findings emerge from the available literature. First, observational studies suggest that GLP-1 RA exposure may be associated with a lower incidence of dementia in some populations with T2DM. Second, randomized clinical evidence has not consistently demonstrated improvements in cognitive outcomes or slowing of neurodegenerative disease progression. Third, experimental research provides plausible biological mechanisms through which GLP-1 receptor activation might influence neuronal functioning, although these mechanisms have not been sufficiently validated in clinical populations. These findings suggest that the potential neurological benefits of GLP-1 RAs should be interpreted cautiously. Their established metabolic benefits should be distinguished from neurological effects that remain under investigation.

Potential mechanisms underlying neurological effects:

Several mechanisms may explain the potential relationship between GLP-1 receptor activation and brain health. One important pathway involves the regulation of insulin signaling. Insulin resistance has

been associated with impaired synaptic functioning, altered neuronal metabolism, and increased vulnerability to neurodegenerative processes. By improving peripheral metabolic regulation, GLP-1 RAs may indirectly reduce some of the metabolic disturbances associated with cognitive decline.

A second mechanism involves the modulation of inflammatory activity. Chronic systemic inflammation is frequently observed in individuals with obesity and T2DM. Increased inflammatory signaling may influence endothelial function, blood–brain barrier integrity, and neuronal homeostasis. Experimental evidence suggests that GLP-1 receptor activation may regulate inflammatory pathways and reduce oxidative stress. However, the extent to which these effects occur in the human brain during routine clinical treatment remains uncertain.

A third potential mechanism concerns vascular health. Diabetes and obesity are associated with endothelial dysfunction, atherosclerosis, and cerebral small-vessel disease. Improvements in cardiovascular risk factors may indirectly support cerebral perfusion and reduce vascular contributions to cognitive impairment. This possibility is particularly relevant because cognitive dysfunction in T2DM frequently reflects a combination of vascular and neurodegenerative mechanisms (Biessels & Despa,2018).

Interpretation of observational and randomized evidence:

The apparent difference between observational findings and randomized clinical outcomes requires careful consideration. Observational cohorts may identify lower dementia incidence among individuals receiving GLP-1 RAs, whereas randomized trials may fail to demonstrate significant improvements in cognitive or neurological outcomes.

One explanation is residual confounding. Patients receiving GLP-1 RAs may differ from untreated individuals in healthcare access, socioeconomic status, obesity severity, cardiovascular management, and adherence to preventive healthcare. These factors may influence dementia risk independently of medication exposure.

Another explanation concerns the duration and nature of treatment effects. Dementia develops over many years, whereas most randomized trials of metabolic therapies are designed around shorter-term clinical endpoints. Consequently, an intervention might theoretically influence long-term disease risk without producing measurable short-term improvements in cognitive testing. Nevertheless, this possibility remains a hypothesis rather than an established clinical benefit.

The EVOKE and EVOKE+ trials provide an important counterbalance to optimistic interpretations of experimental findings. Their failure to demonstrate significant slowing of clinical progression with semaglutide in early symptomatic Alzheimer's disease indicates that activation of GLP-1-related pathways does not necessarily translate into improved clinical outcomes (Cummings et al.,2026).

Implications for adults with type 2 diabetes and obesity:

The findings have important implications for clinical practice. GLP-1 RAs should continue to be considered according to their established metabolic, cardiovascular, and weight-management indications. Their use may indirectly contribute to better long-term health by improving glycemic control, reducing excess body weight, and addressing cardiovascular risk factors. However, clinicians should not currently prescribe these medications solely for the purpose of preventing dementia or improving memory. The evidence is insufficient to support such an indication. Patients should also be informed that metabolic improvement and cognitive protection are separate therapeutic outcomes.

For adults with T2DM and obesity, comprehensive management remains essential. Blood pressure control, lipid management, physical activity, smoking cessation, adequate sleep, nutritional quality, and appropriate diabetes treatment may collectively support long-term vascular and neurological health.

Strengths and limitations:

An important strength of this review is its consideration of multiple evidence types, including randomized trials, observational investigations, and experimental research. Separating cognitive performance from dementia incidence also improves the clinical interpretation of the findings.

Nevertheless, several limitations must be acknowledged. First, differences in study design, population characteristics, medication exposure, and follow-up duration limit direct comparisons. Second, cognitive outcomes are assessed using different instruments, which may reduce the feasibility of quantitative synthesis. Third, observational findings are susceptible to residual confounding and reverse causation.

Fourth, some randomized trials investigate participants with established Alzheimer's disease rather than adults selected specifically for T2DM and obesity. Their findings are therefore informative but not directly generalizable to the target population. Fifth, the available literature does not

establish whether individual GLP-1 RAs have different cognitive effects.

Finally, this manuscript's evidence synthesis requires completion of a reproducible multi-database search, independent study screening, and formal risk-of-bias assessment before it can be considered a completed PRISMA systematic review. Accordingly, the interpretations presented here should be regarded as a provisional synthesis of the identified literature rather than a definitive quantitative meta-analysis.

Future research directions:

Future clinical trials should incorporate cognitive outcomes as prespecified endpoints rather than relying exclusively on post hoc neurological analyses. Standardized instruments assessing memory, attention, executive function, and processing speed should be used alongside global cognitive measures.

Longer follow-up periods are necessary to evaluate whether metabolic treatment influences the development of mild cognitive impairment or dementia. Studies should also investigate whether treatment effects differ according to age, obesity severity, duration of diabetes, baseline cognitive performance, and cardiovascular risk.

Furthermore, research should distinguish direct central nervous system effects from indirect benefits mediated through improved metabolic and vascular health. The integration of neuroimaging, inflammatory biomarkers, metabolic measurements, and comprehensive neuropsychological testing may help clarify these mechanisms.

Overall interpretation:

In summary, GLP-1 receptor agonists represent promising metabolic therapies with potential relevance to neurological health. Nevertheless, current evidence does not establish that they produce clinically meaningful cognitive improvement or reliably prevent dementia in adults with T2DM and obesity. Their potential neurological benefits should therefore remain an important research priority rather than an established therapeutic indication.

Conclusion

The present systematic review examined the potential relationship between glucagon-like peptide-1 receptor agonists (GLP-1 RAs), metabolic health, and cognitive function in adults with type 2 diabetes mellitus (T2DM) and obesity. The findings indicate that GLP-1 RAs represent important therapeutic agents for metabolic disease management and may have additional neurological implications. However, current clinical evidence remains insufficient to establish their effectiveness as direct cognitive-enhancing or dementia-preventing medications. The biological rationale for investigating GLP-1 RAs in brain health is supported by several mechanisms. These include improvements in insulin signaling, reductions in systemic inflammation, modulation of oxidative stress, and potential effects on neuronal survival and synaptic plasticity. Furthermore, improvements in body weight, glycemic regulation, and cardiovascular risk factors may indirectly support neurological health. These mechanisms provide a strong foundation for continued investigation, particularly in populations with long-standing metabolic dysfunction.

Observational studies have reported potentially favorable associations between GLP-1 RA exposure and dementia incidence. For example, a population-based longitudinal cohort study involving 109,778 individuals with T2DM reported an adjusted hazard ratio of 0.90 for dementia among GLP-1 RA users compared with nonusers (Cheng et al., 2025). Nevertheless, observational associations cannot establish causality because residual confounding, treatment selection, and differences in healthcare utilization may influence the findings.

Randomized clinical evidence requires a more cautious interpretation. The EVOKE and EVOKE+ phase III trials did not demonstrate significant clinical benefits of oral semaglutide in slowing progression of early symptomatic Alzheimer's disease (Cummings et al., 2026). Furthermore, available cognitive outcome research has not established consistent improvements across global cognition, memory, attention, and executive functioning.

An important distinction must therefore be maintained between the established metabolic efficacy of GLP-1 RAs and their proposed neurological benefits. These medications should be prescribed according to approved metabolic and cardiovascular indications rather than solely for cognitive enhancement or dementia prevention.

Future research should prioritize large-scale randomized controlled trials involving adults with T2DM and obesity who do not necessarily have established neurodegenerative disease. Such investigations should incorporate standardized cognitive assessment instruments, extended follow-up periods, neuroimaging, inflammatory biomarkers, and carefully selected active comparators. They should also investigate whether neurological responses differ between individual GLP-1 receptor agonists and according to age, diabetes duration, obesity severity, and baseline cognitive status.

In conclusion, GLP-1 receptor agonists represent a promising research direction at the intersection of metabolic medicine and neuroscience. Although their biological mechanisms and observational

associations justify further investigation, definitive evidence of clinically meaningful cognitive protection is currently lacking. Establishing whether these medications can prevent or delay cognitive deterioration will require rigorous clinical trials and reproducible quantitative evidence. Until such evidence becomes available, GLP-1 RAs should be regarded as effective metabolic therapies with potential, but unconfirmed, neurological benefits.

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Authors' Contributions

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