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Neuroprotective effects of GLP-1 receptor agonists in neurodegenerative Disorders: A Large-Scale Propensity-Matched cohort study

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ABSTRACT

Background: GLP-1 receptor agonists, traditionally used for treating type 2 diabetes mellitus and obesity, have demonstrated anti-inflammatory properties. However, their potential neuroprotective effects in neurodegenerative disorders remain unclear.

Objective: To evaluate the impact of GLP-1 receptor agonists on the risk of developing various neurodegenerative conditions in obese patients.

Methods: This comprehensive retrospective cohort study analyzed data from 5,307,845 obese adult patients across 73 healthcare organizations in 17 countries. Propensity score matching was performed, resulting in 102,935 patients in each cohort. We compared the risk of developing neurodegenerative disorders between obese patients receiving GLP-1 receptor agonist therapy and those who were not.

Results: Obese patients treated with GLP-1 receptor agonists showed significantly lower risks of developing Alzheimer's disease (RR = 0.627, 95 %CI = 0.481–0.817), Lewy body dementia (RR = 0.590, 95 %CI = 0.462–0.753), and vascular dementia (RR = 0.438, 95 %CI = 0.327–0.588). The risk reduction for Parkinson's disease was not statistically significant overall (RR = 0.784, 95 %CI = 0.580–1.058) but was significant for semaglutide users (RR = 0.574, 95 %CI = 0.369–0.893). Semaglutide consistently showed the most pronounced protective effects across all disorders. Additionally, a significant reduction in all-cause mortality was observed (HR = 0.525, 95 %CI = 0.493–0.558).

Conclusion: This study provides evidence that the effects of GLP-1 receptor agonists may extend beyond their known metabolic and cardioprotective benefits to include neuroprotection, associated with a decreased risk of developing various neurodegenerative disorders. These findings suggest the potential for expanding the therapeutic applications of GLP-1 receptor agonists to improve neurocognitive outcomes. Further research is warranted to elucidate the mechanisms underlying these neuroprotective effects and to explore their clinical applications in neurodegenerative disease prevention and treatment.

1. Introduction

Neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Lewy body dementia, and vascular dementia, represent a growing global health challenge as populations age [1]. These conditions are characterized by progressive loss of neurons, leading to cognitive decline, motor dysfunction, and a significant reduction in quality of life [2]. Despite intensive research efforts, effective treatments

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for these disorders remain elusive, emphasizing the need for novel therapeutic approaches and preventive strategies [3].

Recent evidence suggests a potential link between metabolic dysfunction and neurodegenerative processes [4,5]. Insulin resistance, oxidative stress, and chronic inflammation – all hallmarks of metabolic disorders such as obesity and type 2 diabetes – have been implicated in the pathogenesis of various neurodegenerative conditions [6,7]. This connection has led researchers to explore whether medications used to treat metabolic disorders might also confer neuroprotective benefits.

GLP-1 receptors are in the pancreas and release insulin when activated [8]. Glucagon-like peptide-1 (GLP-1) receptor agonists, a class of drugs primarily used for the treatment of type 2 diabetes and obesity, have emerged as potential candidates for neuroprotection [9]. GLP-1 receptors were first approved for type 2 diabetes treatment in 2005, and since their release, they have proven to have other potential benefits for a wide range of patient populations [10]. These drugs, including semaglutide, dulaglutide, and liraglutide, are known for their ability to improve glycemic control, promote weight loss, and reduce cardiovascular risk [11]. Importantly, preclinical studies have demonstrated that GLP-1 receptor agonists may also possess neuroprotective properties, including anti-inflammatory effects, reduction of oxidative stress, enhancement of mitochondrial function, and potential inhibition of pathological protein aggregation [11–15].

The neuroprotective potential of GLP-1 receptor agonists is particularly intriguing, given the shared pathological features of many neurodegenerative disorders [16]. These include abnormal protein aggregation (such as β-amyloid and tau in Alzheimer's disease, α-synuclein in Parkinson's disease and Lewy body dementia), neuroinflammation, oxidative damage, and mitochondrial dysfunction [17]. Additionally, the growing recognition of insulin resistance in the brain as a contributor to neurodegenerative processes – exemplified by Alzheimer's disease, sometimes being referred to as "type 3 diabetes" – further supports the investigation of anti-diabetic medications for neuroprotection [12].

Despite these promising preclinical findings, large-scale clinical evidence for the neuroprotective effects of GLP-1 receptor agonists in humans remains limited [18,19]. Small sample sizes, short follow-up periods, and a focus on single neurodegenerative conditions have constrained previous studies. Additionally, it has been previously found that treatment with GLP-1 receptor agonists can improve the impairment of synaptic plasticity observed in animal models of diabetes obesity [20]. There is a clear need for comprehensive, long-term studies examining the impact of GLP-1 receptor agonists on multiple neurodegenerative disorders in a real-world setting.

To address this gap in knowledge, we conducted a large-scale, retrospective cohort study using propensity score matching to investigate the association between GLP-1 receptor agonist use and the risk of developing various neurodegenerative disorders in obese patients. By leveraging a global collaborative network encompassing over 150 million patient records, we aimed to provide robust evidence regarding the potential neuroprotective effects of these drugs. Our study focused on four major neurodegenerative disorders – Alzheimer's disease, Parkinson's disease, Lewy body dementia, and vascular dementia – while also exploring the impact on overall mortality.

This research has significant implications for public health and clinical practice. If GLP-1 receptor agonists are found to have neuroprotective effects, it could open new avenues for the prevention and treatment of neurodegenerative disorders, potentially offering a dual benefit for patients with metabolic disorders who are at increased risk of cognitive decline. Furthermore, understanding the differential effects of various GLP-1 receptor agonists could inform more targeted therapeutic strategies and guide future drug development efforts in the field of neurodegeneration.

2. Methods

2.1. Study Design and data Source

This retrospective cohort study utilized data from a global collaborative network spanning 17 countries and 127 healthcare organizations. The database, accessed on July 31, 2024, contained electronic health records of 152,398,854 patients. This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board. The requirement for informed consent was waived due to the use of de-identified data.

2.2. Study population

We included adult patients (≥18 years) with a diagnosis of obesity (BMI ≥ 30 kg/m^2) between January 1, 2010, and December 31, 2023. Patients were excluded if they had a history of bariatric surgery, prior central nervous system disorders, or had previously used or discontinued other incretin therapies (exenatide, albiglutide, tirzepatide, or lixisenatide) (Supplementary Table S1 and S2).

2.3. Exposure

The exposure of interest was the use of GLP-1 receptor agonists (GLP1Ra), including semaglutide, dulaglutide, and liraglutide. Patients were classified as GLP1Ra users if they had at least one prescription for any of these medications during the study period. The date of the first prescription was considered the index date. Non-users were assigned a random index date within the same period.

2.4. Outcomes

The primary outcomes were the incidence of four neurodegenerative disorders: Alzheimer's disease, Parkinson's disease, Lewy body dementia, and vascular dementia. These were identified using the International Classification of Diseases, 10th Revision (ICD-10) codes (Supplementary Table S3). Secondary outcomes included all-cause mortality and the incidence of other neurodegenerative disorders (Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, spinocerebellar ataxia, Creutzfeldt-Jakob disease, multiple sclerosis, Niemann-Pick disease type C, Wilson's disease, and neuronal ceroid lipofuscinoses).

2.5. Propensity scores matching analysis

We collected data on demographic characteristics (age, sex, race), comorbidities (metabolic disorders, diabetes mellitus, hypertensive diseases, chronic kidney disease), and medication use. These variables were assessed at baseline and used for propensity score matching. Propensity score matching was performed to balance baseline characteristics between GLP1Ra users and non-users. We used a 1:1 nearest neighbor matching algorithm without replacement, with a caliper width of 0.2 standard deviations of the logit of the propensity score. Separate propensity score models were created for the overall GLP1Ra analysis and each drug (semaglutide, dulaglutide, and liraglutide).

2.6. Statistical analysis

We compared the incidence of neurodegenerative disorders between matched GLP1Ra users and non-users using chi-square tests. Relative risks (RRs) with 95 % confidence intervals (CIs) were calculated. Time-to-event analyses were performed using Cox proportional hazard models to estimate hazard ratios (HRs) for mortality risk. Follow-up time was calculated from the index date until the occurrence of the outcome of interest, death, or the end of the study period, whichever came first.

Subgroup analyses were performed for each GLP1Ra drug. All statistical analyses were performed using TriNetX built-in analytical tools [21]. A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1. Study population characteristics

Our study analyzed data from a global collaborative network spanning 17 countries and 127 healthcare organizations, encompassing 152,398,854 patients as of July 31, 2024. After applying inclusion and exclusion criteria (Fig. 1), we identified 2,231,163 eligible patients. The final cohorts consisted of 102,935 patients in the GLP-1 receptor agonist (GLP1Ra) group and 2,122,919 in the control group. Propensity score matching resulted in 102,935 patients in each group. Before matching, significant differences were observed between the cohorts in age, gender, race, and comorbidities. GLP1Ra cohort was slightly younger (50.6 vs. 48.2 years), had more females (61.7 % vs. 54.6 %), and had significantly higher rates of metabolic disorders (54.1 % vs. 18.1 %), diabetes mellitus (51.0 % vs. 9.0 %), hypertensive diseases (52.5 % vs. 20.9 %), and kidney diseases (9.6 % vs. 3.4 %). After matching, these differences were effectively balanced ($p > 0.05$ for all comparisons) Table 1.

3.2. Risk of neurodegenerative disorders

The GLP1Ra group was observed for an average of 17.5 months (SD 18.4 months), with a median follow-up of 11.8 months (IQR 19.7 months). In contrast, the control group had a longer average follow-up of 31.8 months (SD 31.4 months), with a median of 22.3 months (IQR 45.4 months).

Table 2 presents the incidence of neurodegenerative disorders. For Alzheimer's disease, there was a significantly lower incidence in the overall GLP1Ra group compared to the control group (0.09 % vs 0.14 %, $p < 0.001$). This trend is particularly pronounced for semaglutide users (0.05 % vs 0.12 %, $p < 0.001$). Dulaglutide shows a similar trend, though not statistically significant (p = 0.06), while liraglutide shows no significant difference. Parkinson's disease incidence, while lower in the overall GLP1Ra group, does not reach statistical significance (0.07 % vs 0.09 %, p = 0.11). However, semaglutide users show a significantly lower incidence (0.05 % vs 0.09 %, $p = 0.013$). Lewy body dementia shows a marked reduction in incidence for the overall GLP1Ra group (0.1 % vs. 0.17 %, $p < 0.001$), with semaglutide again showing the most pronounced effect (0.06 % vs. 0.14 %, $p < 0.001$). Vascular dementia follows a similar pattern, with significantly lower incidence in the overall GLP1Ra group (0.06 % vs. 0.14 %, $p < 0.001$) and an even more pronounced effect in semaglutide users (0.02 % vs. 0.12 %, $p < 0.001$).

In addition to Alzheimer's disease, Parkinson's disease, Lewy body dementia, and vascular dementia, our study investigated several other neurodegenerative disorders. These included Huntington's disease, amyotrophic lateral sclerosis (ALS), frontotemporal dementia, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, spinocerebellar ataxia, Creutzfeldt-Jakob disease, multiple sclerosis, Niemann-Pick disease type C, Wilson's disease, and neuronal ceroid lipofuscinoses. However, due to the low frequency of these conditions in our study population, especially when stratified by drug type, we focused our primary analysis on the four most common neurodegenerative disorders.

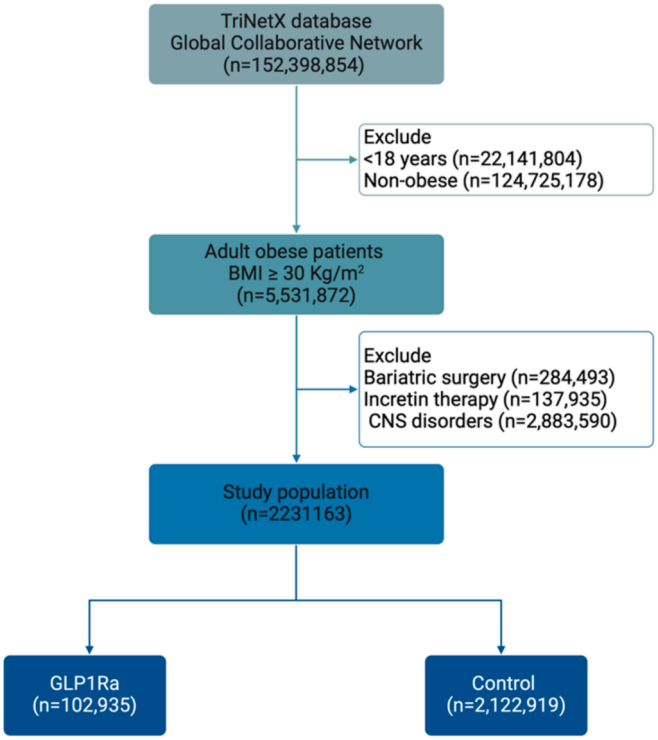

Fig. 1. Workflow for patient selection in TriNetX database.

3.3. Survival analysis

Table 3 presents the case fatality rates for the GLP1Ra and control cohorts. Overall, the GLP1Ra cohort had a significantly lower mortality rate compared to the control cohort (1.34 % vs 4.47 %, $p < 0.001$). Cox regression analysis showed that GLP1Ra use was associated with a significantly reduced risk of mortality overall (HR = 0.525, 95 %CI = 0.493–0.558, $p < 0.001$). Both semaglutide (HR = 0.336, 95 %CI = 0.297–0.381, p < 0.001) and dulaglutide (HR = 0.604, 95 %CI = 0.543–0.671, $p < 0.001$) showed significant reductions in mortality risk, while liraglutide showed no significant effect.

4. Discussion

This large-scale, propensity-matched cohort study provides compelling evidence for the potential neuroprotective effects of GLP-1 receptor agonists in obese patients. It has been shown over time that GLP-1-based anti-diabetics do not only regulate blood glucose but have a wide range of diverse effects, such as reducing apoptotic cell death of pancreatic beta cells in T2DM [16]. The effects of these drugs are further dissected in our study. Our findings demonstrate significantly reduced risks of developing Alzheimer's disease, Lewy body dementia, and vascular dementia among GLP1Ra users, with a trend towards reduced risk for Parkinson's disease. Moreover, we observed a substantial reduction in all-cause mortality associated with GLP-1 receptor agonists use.

The neuroprotective effects of GLP-1 receptor agonists appear to operate through several complementary pathways that collectively protect neural tissue (Fig. 2). At the cellular level, these agents modulate microglial activation and reduce pro-inflammatory cytokine production, creating an anti-inflammatory environment [22,23]. This immune modulation is coupled with enhanced mitochondrial function, including improved oxidative phosphorylation efficiency ATP production, which is particularly crucial in energy-demanding neural tissues [24,25]. The activation of the NRF2 pathway and upregulation of antioxidant enzymes provide additional protection against oxidative stress, while inhibition of pathological protein aggregation directly addresses a key feature of neurodegenerative disorders [26]. Preclinical studies have demonstrated that there have been improved synaptic numbers and synaptic activity, motor activity, dopaminergic neurons, cortical activity, and energy utilization in the brain [18,27]. The improvement in metabolic parameters and vascular health associated with GLP1Ra use may contribute to overall brain health and resilience against

Table 1
Characteristics of the study population before and after propensity score matching.

Variable	Before propensity matching			After propensity matching		
	GLP1Ra (n = 102935)	Control (n = 2122919)	*p*-value	GLP1Ra (n = 102935)	Control (n = 102935)	*p*-value
Demographics						
Age at Index	50.6 ± 14.4	48.2 ± 17.3	<0.001	50.6 ± 14.4	50.6 ± 14.4	0.95
Sex						
Female	63,460 (61.7 %)	1,158,086 (54.6 %)	<0.001	63,460 (61.7 %)	63,471 (61.7 %)	0.96
Male	32,448 (31.5 %)	742,904 (34.9 %)		32,448 (31.5 %)	33,956 (33 %)	
Race						
White	63,511 (61.7 %)	1,248,988 (58.8 %)	<0.001	63,511 (61.7 %)	63,558 (61.7 %)	0.83
Black	19,344 (18.8 %)	336,206 (15.8 %)		19,344 (18.8 %)	19,330 (18.8 %)	
Asian	2577 (2.5 %)	43,441 (2.05 %)		2577 (2.5 %)	2594 (2.5 %)	
Comorbidity						
Metabolic disorders	55,688 (54.1 %)	384,553 (18.1 %)	<0.001	55,688 (54.1 %)	55,690 (54.1 %)	0.99
Diabetes mellitus	52,492 (51 %)	191,046 (9.0 %)	<0.001	52,492 (51 %)	52,483 (51 %)	0.97
Hypertensive disease	54,075 (52.5 %)	444,379 (20.9 %)	<0.001	54,075 (52.5 %)	54,105 (52.6 %)	0.90
Chronic kidney disease	9899 (9.6 %)	71,500 (3.4 %)	<0.001	9899 (9.6 %)	9876 (9.6 %)	0.86

Data are presented as mean ± standard deviation or n (%). P-values were calculated using t-tests for continuous variables and chi-square tests for categorical variables. GLP1Ra: GLP-1 receptor agonist.

Table 2
Risk of neurodegenerative disorders in GLP1Ra users and non-users.

Disease	Drug	GLP1Ra	Control	*p*-value	RR	95 %CI
Alzheimer's disease	GLP1Ra vs none	89 (0.09 %)	142 (0.14 %)	**<0.001**	**0.627**	**(0.481, 0.817)**
	Semaglutide vs none	27 (0.05 %)	68 (0.12 %)	**<0.001**	**0.397**	**(0.254, 0.620)**
	Dulaglutide vs none	28 (0.15 %)	44 (0.23 %)	0.06	0.636	(0.396, 1.022)
	Liraglutide vs none	14 (0.14 %)	11 (0.11 %)	0.55	1.273	(0.578, 2.802)
Parkinson's disease	GLP1Ra vs none	76 (0.07 %)	97 (0.09 %)	0.11	0.784	(0.580, 1.058)
	Semaglutide vs none	31 (0.05 %)	54 (0.09 %)	**0.013**	**0.574**	**(0.369, 0.893)**
	Dulaglutide vs none	18 (0.09 %)	24 (0.13 %)	0.35	0.75	(0.407, 1.381)
	Liraglutide vs none	11 (0.11 %)	10 (0.1 %)	0.827	1.1	(0.467, 2.589)
Lewy body dementia	GLP1Ra vs none	102 (0.1 %)	173 (0.17 %)	**<0.001**	**0.59**	**(0.462, 0.753)**
	Semaglutide vs none	32 (0.06 %)	78 (0.14 %)	**<0.001**	**0.41**	**(0.272, 0.619)**
	Dulaglutide vs none	37 (0.19 %)	52 (0.27 %)	0.11	0.712	(0.467, 1.084)
	Liraglutide vs none	13 (0.13 %)	14 (0.14 %)	0.85	0.929	(0.437, 1.974)
Vascular dementia	GLP1Ra vs none	64 (0.06 %)	146 (0.14 %)	**<0.001**	**0.438**	**(0.327, 0.588)**
	Semaglutide vs none	12 (0.02 %)	66 (0.12 %)	**<0.001**	**0.182**	**(0.098, 0.336)**
	Dulaglutide vs none	28 (0.15 %)	40 (0.21 %)	0.15	0.7	(0.432, 1.134)
	Liraglutide vs none	15 (0.15 %)	14 (0.14 %)	0.85	1.071	(0.517, 2.218)

Data are presented as n (%). P-values were calculated using chi-square tests. GLP1Ra: GLP-1 receptor agonist; Cohorts were matched for each analysis: Overall (n = 102,935 per group), Semaglutide (n = 57,043 per group), Dulaglutide (n = 19,165 per group), Liraglutide (n = 9,724 per group). Relative risk (RR) and 95 % confidence intervals (CI) for overall and stratified analysis. Bold values indicate significance at *p*-values < 0.05.

Table 3
Case fatality rates in GLP1Ra users and non-users.

Drug	GLP1Ra	Control	*p*-value	HR	95 %CI
GLP1Ra vs none	1380 (1.34 %)	4604 (4.47 %)	**<0.001**	**0.525**	**(0.493, 0.558)**
Semaglutide vs none	309 (0.54 %)	2155 (3.78 %)	**<0.001**	**0.336**	**(0.297, 0.381)**
Dulaglutide vs none	514 (2.68 %)	1255 (6.55 %)	**<0.001**	**0.604**	**(0.543, 0.671)**
Liraglutide vs none	335 (3.45 %)	377 (3.88 %)	0.11	1.032	(0.889, 1.197)

Data are presented as n (%). P-values were calculated using chi-square tests. GLP1Ra: GLP-1 receptor agonist. Hazard ratios (HR) and 95 % confidence intervals (CI) are reported for mortality risk. Bold values indicate significance at *p*-values < 0.05.

neurodegenerative processes [28] (Table 4).

The observed risk reductions were most pronounced for Alzheimer's disease and vascular dementia, with relative risk reductions of 37.3 % and 56.2 %, respectively. These findings strongly support the growing body of evidence suggesting a link between metabolic dysfunction and neurodegenerative processes. Our results provide the first large-scale epidemiological evidence supporting this connection, particularly in Alzheimer's disease, due to the observed brain insulin resistance [29]. The substantial risk reduction in vascular dementia is particularly noteworthy and may be attributed to the known cardiovascular benefits of GLP-1 receptor agonists, including improved glycemic control, weight loss, and positive effects on lipid profiles [30].

Drug-specific effects emerged as a crucial finding, challenging the assumption of a pure class effect. While the overall risk reduction for Parkinson's disease did not reach statistical significance, subgroup analysis revealed a significant protective effect among semaglutide users. This differential effect across GLP1Ra drugs was consistent across all outcomes, with semaglutide consistently showing the most substantial risk reductions. The superior performance of semaglutide across all outcomes appears related to its enhanced blood–brain barrier penetration, extended half-life (168 h versus 13 h for liraglutide), and potentially unique receptor binding characteristics. This observation raises

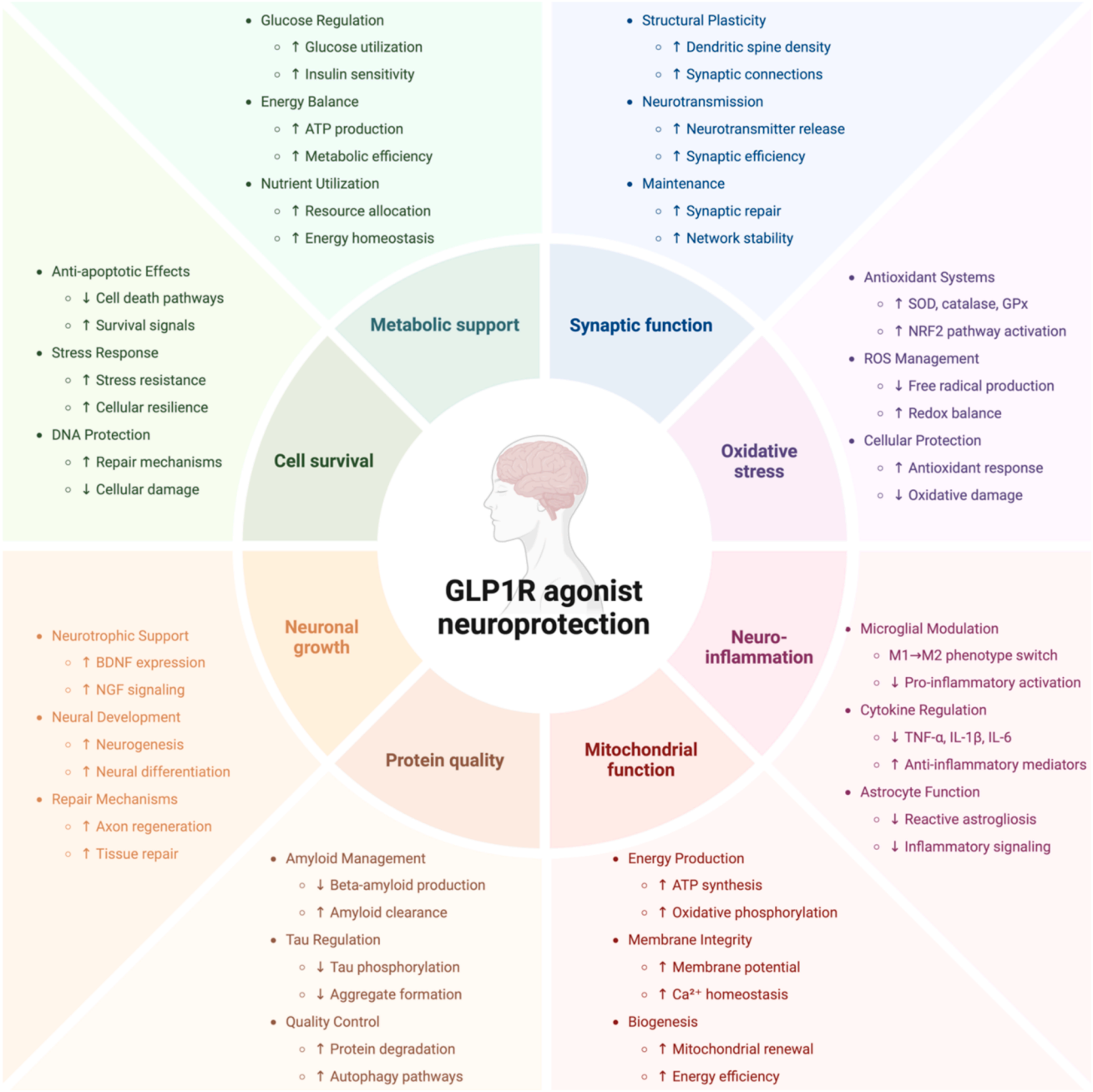

Fig. 2. Neuroprotective Mechanisms of GLP-1 Receptor Agonists in Neurodegenerative Disorders. The figure depicts the five major neuroprotective pathways activated by GLP-1 receptor signaling in neural tissue.

intriguing questions about the potential mechanisms underlying the neuroprotective effects of GLP-1 receptor agonists and suggests that these effects may be drug-specific rather than a class effect [31].

The significant reduction in all-cause mortality observed in our study adds to the growing evidence of the multifaceted benefits of GLP-1 receptor agonists beyond glycemic control. This comprehensive effect likely stems from multiple mechanisms: improved cardiovascular function, enhanced metabolic parameters, reduced systemic inflammation, and better endothelial function [23,24,32,33]. The convergence of these benefits may explain the robust neuroprotective effects observed in our study.

Our study has several strengths, including its large sample size, long follow-up period, and the use of propensity score matching to minimize confounding. Our study has several strengths, including its large sample size, long follow-up period, and the use of propensity score matching to minimize confounding. The analysis of individual GLP-1 receptor agonists provides crucial insights into drug-specific effects, particularly relevant for clinical decision-making.

However, several limitations should be considered when interpreting our results. First, as an observational study, we cannot establish causality, and residual confounding may exist despite our rigorous matching process. Second, the use of electronic health records may introduce misclassification bias, although this is likely to be non-differential between the exposed and unexposed groups. Third, we were unable to account for lifestyle factors such as diet and exercise, which may influence both GLP-1 receptor agonists use and neurodegenerative risk. Finally, the follow-up time was shorter in the GLP-1 receptor agonists group, which may have led to an underestimation of the protective effect.

Table 4
Comprehensive Overview of GLP-1 Receptor Agonist Neuroprotective Mechanisms.

Mechanism	Description	Ref
1. Neuroinflammation reduction		
Microglial Modulation	Switch from pro-inflammatory M1 to anti-inflammatory M2 phenotype; reduces inflammatory response	[35]
Pro-inflammatory Cytokines	Decreased production of TNF-α, IL-1β, IL-6 in neural tissue	[36]
Anti-inflammatory Mediators	Enhanced expression of IL-10, TGF-β; promotes anti-inflammatory state	[37]
Astrocyte Reactivity	Reduced astrocyte activation and inflammatory signaling	[35]
2. Mitochondrial function enhancement		
Oxidative Phosphorylation	Improved efficiency of electron transport chain and ATP synthesis	[24]
ATP Production	Enhanced energy metabolism and cellular bioenergetics	[24]
Calcium Homeostasis	Better regulation of intracellular calcium levels	[38]
Membrane Potential	Strengthened mitochondrial membrane integrity	[24]
3. Oxidative stress management		
Antioxidant Enzymes	Upregulation of SOD, catalase, GPx activities	[26]
ROS Production	Reduced generation of harmful reactive oxygen species	[39]
NRF2 Pathway	Enhanced activation of antioxidant response elements	[26]
Redox Balance	Improved cellular oxidative/antioxidative equilibrium	[40]
4. Protein aggregation prevention		
β-amyloid Regulation	Direct reduction of β-amyloid production and accumulation	[41]
Tau Phosphorylation	Reduced hyperphosphorylation and aggregation of tau protein	[42]
Protein Quality Control	Enhanced protein degradation and autophagy pathways	[43]
Aggregate Clearance	Improved clearance of toxic protein aggregates	[41]
5. Synaptic function enhancement		
Synaptic Plasticity	Enhanced ability for synaptic modification and adaptation	[44]
Dendritic Spine Density	Increased number and stability of dendritic spines	[38]
Neurotransmitter Release	Improved synaptic transmission and signaling	[24]
Synaptic Maintenance	Better long-term stability and repair of synaptic connections	[38]

4.1. Clinical implications and future Perspectives

This study's findings have significant implications for clinical practice, suggesting several strategic changes. We recommend implementing systematic risk stratification for neurodegenerative disorders, particularly focusing on patients with obesity and metabolic disorders. Treatment optimization should prioritize semaglutide, given its superior neuroprotective profile, with regular cognitive monitoring protocols integrated into routine care. Implementation strategies should include standardized guidelines for patient selection, monitoring protocols, and quality-of-life assessments.

Future research should focus on elucidating the mechanisms underlying the neuroprotective effects of GLP-1 receptor agonists, particularly the apparent superiority of semaglutide. Semaglutide is available as a monotherapy for T2DM and is overall well tolerated, with no risk of hypoglycemia [34]. Prospective clinical trials should address specific questions about the optimal timing of intervention, dose-dependent effects, and potential combination therapies. Additionally, biomarker development for early intervention and cognitive monitoring will be crucial for translating these findings into clinical practice. Studies investigating the effects of GLP-1 receptor agonists on cognitive function and brain structure in non-demented individuals could provide valuable insights into their potential for early intervention.

5. Conclusion

In conclusion, our study provides strong evidence for the neuroprotective potential of GLP-1 receptor agonists, particularly semaglutide, in obese patients. These findings suggest that the benefits of these drugs may extend beyond their established metabolic and cardiovascular effects to include protection against neurodegenerative disorders. As the global burden of both obesity and neurodegenerative diseases continues to rise, the potential for GLP-1 receptor agonists to address both conditions simultaneously represents an exciting opportunity for improving public health.

CRediT authorship contribution statement

Nabeela Siddeeque: Methodology, Investigation, Data curation. **Mohammad H. Hussein:** Resources, Methodology, Investigation, Data curation. **Ahmed Abdelmaksoud:** Software, Resources, Investigation, Formal analysis. **Julia Bishop:** Validation, Software, Resources, Data curation. **Abdallah S. Attia:** Writing – original draft, Visualization, Software, Methodology, Formal analysis. **Rami M. Elshazli:** Writing – original draft, Software, Resources, Methodology, Data curation. **Manal S. Fawzy:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis. **Eman A. Toraih:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2024.113537.

Data availability

Data will be made available on request.

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