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Exploring glucagon-like peptide-1 receptor agonists as potential disease-modifying agent in psychiatric and neurodevelopmental conditions: evidence from a drug target Mendelian randomization

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Abstract

Background Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have recently received Food and Drug Administration (FDA) approval for obesity management. However, the causal relationship between GLP-1RAs and psychiatric and neurodevelopmental conditions remains unclear.

Methods We used Mendelian randomization (MR) to investigate the association between genetically proxied GLP-1RA exposure and 12 psychiatric and neurodevelopmental conditions. Genetic instruments were derived from cis-eQTLs for GLP-1R, and analyses were conducted using large-scale GWAS datasets. Type 2 diabetes was included as a positive control (107,133 cases, 656,672 controls). Findings were assessed across multiple independent datasets, including FinnGen, Psychiatric Genomics Consortium (PGC), and UK Biobank, and were synthesized through meta-analysis.

Result Genetically proxied GLP-1RA exposure was associated with a lower risk of schizophrenia (OR = 0.72, 95% CI [0.61–0.86]), bipolar disorder (OR = 0.91, 95% CI [0.88–0.94]), bulimia nervosa (OR = 0.34, 95% CI [0.23–0.52]), post-traumatic stress disorder (PTSD) (OR = 0.45, 95% CI [0.31–0.67]), and autism (OR = 0.55, 95% CI [0.32–0.93]), all $P < 0.001$. Conversely, higher GLP-1R expression was associated with an increased risk of obsessive-compulsive disorder (OCD) (OR = 2.30, 95% CI [1.26–4.22], $P < 0.001$). No significant associations were observed for anorexia nervosa, broad depression, major depressive disorder (MDD), or suicide and intentional self-harm. Sensitivity analyses and heterogeneity assessments supported the robustness of these findings across multiple cohorts.

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Limitations GLP-1RAs reduced some psychiatric and neurodevelopmental conditions but lacked extensive evidence. Bulimia nervosa and PTSD evidence was limited to one database. Bipolar disorder and OCD results varied, with significant OCD findings in one database. The study's European ancestry focus limits generalizability. Rare disorders and disease progression were not examined. Future research needs diverse populations, long-term follow-ups, and treatment exploration.

Conclusions Our study suggests that GLP-1RAs may decrease the risk of schizophrenia, anxiety disorders, bipolar disorder, bulimia nervosa, PTSD, and autism, but may increase the risk of OCD. Larger randomized controlled trials with long-term follow-up are necessary to confirm these associations and evaluate the risk-benefit ratios.

Clinical trial number Not applicable.

Keywords GLP-1R agonists, Psychiatric and neurodevelopmental conditions, Drug target, Mendelian randomization

Introduction

Semaglutide, a glucagon-like peptide-1 receptor (GLP-1R) agonist, received supplemental FDA approval on June 4, 2021, for treating obesity and overweight in adults [1]. Glucagon-like peptide-1 (GLP-1), a key incretin in the gut-insulin axis, is primarily secreted by intestinal L cells and plays a critical role in regulating glucose metabolism and other physiological functions [2]. Beyond its intestinal origin, GLP-1 is also produced in different tissues, including the central nervous system (CNS), where GLP-1R is highly expressed in regions such as the hypothalamus, hindbrain, and amygdala [3–5]. GLP-1R agonists mimic the natural hormone's action to regulate glucose metabolism and other physiological processes [6].

In July 2023, concerns about the psychiatric effects of GLP-1RAs were raised after the European Medicines Agency began reviewing approximately 150 reports of self-injury and suicidal ideation in individuals using liraglutide or semaglutide [7, 8]. However, some studies suggest that semaglutide may not increase the risk of suicidal behavior and could potentially reduce suicide risk in certain patients [9–11]. These conflicting findings underscore the urgent need for further research to clarify the relationship between GLP-1RAs and psychiatric and neurodevelopmental conditions.

To investigate this relationship, we employed Mendelian randomization (MR), a robust genetic epidemiology method that uses genetic variants as instrumental variables (IVs) to infer causal relationships between exposures and disease outcomes. MR minimizes bias from confounding factors and reverse causation, providing evidence for potential causal effects. Leveraging large-scale genome-wide association study (GWAS) datasets, MR offers a cost-effective and rigorous alternative to randomized controlled trials (RCTs), making it an ideal approach for exploring the effects of GLP-1RAs across multiple health outcomes.

This study investigates the associations between GLP-1RAs and 12 psychiatric and neurodevelopmental outcomes, including schizophrenia, anxiety disorders, bipolar disorder, bulimia nervosa, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), autism spectrum disorder (ASD), anorexia nervosa, major depressive disorder (MDD), broad depression, and suicide or self-harm. These conditions were selected based on evidence linking their underlying biological pathways—such as neuroinflammation, glucose metabolism, and reward processing—to GLP-1 signaling. Among these outcomes, ASD was included due to its relevance to pathways potentially influenced by GLP-1RAs. Preclinical studies suggest that GLP-1RAs possess neuroprotective, anti-inflammatory, and antioxidative properties, which could address specific symptoms or comorbidities of ASD, such as mood dysregulation, anxiety, or metabolic challenges. Importantly, this study does not seek to pathologize or "treat" ASD but rather aims to explore whether GLP-1RAs might offer symptom management benefits that could enhance the quality of life.

By applying MR to assess the causal relationships between GLP-1RAs and these outcomes, this study provides a comprehensive framework for understanding the broader therapeutic potential of GLP-1RAs beyond metabolic diseases. These findings aim to contribute to the growing body of research on GLP-1 signaling and its implications for mental health and neurodevelopmental conditions.

Methods

Study design

The study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) guidelines. Figure 1 provides a comprehensive overview of the study design.

We selected genetic instruments for GLP-1R using summary-level data from the eQTLGen Consortium. These instruments were used to perform Mendelian randomization (MR) analyses, assessing the potential causal relationship between GLP-1R gene expression and 12 psychiatric and neurodevelopmental conditions. To ensure the reliability of the genetic instruments, we conducted a positive control analysis by examining their

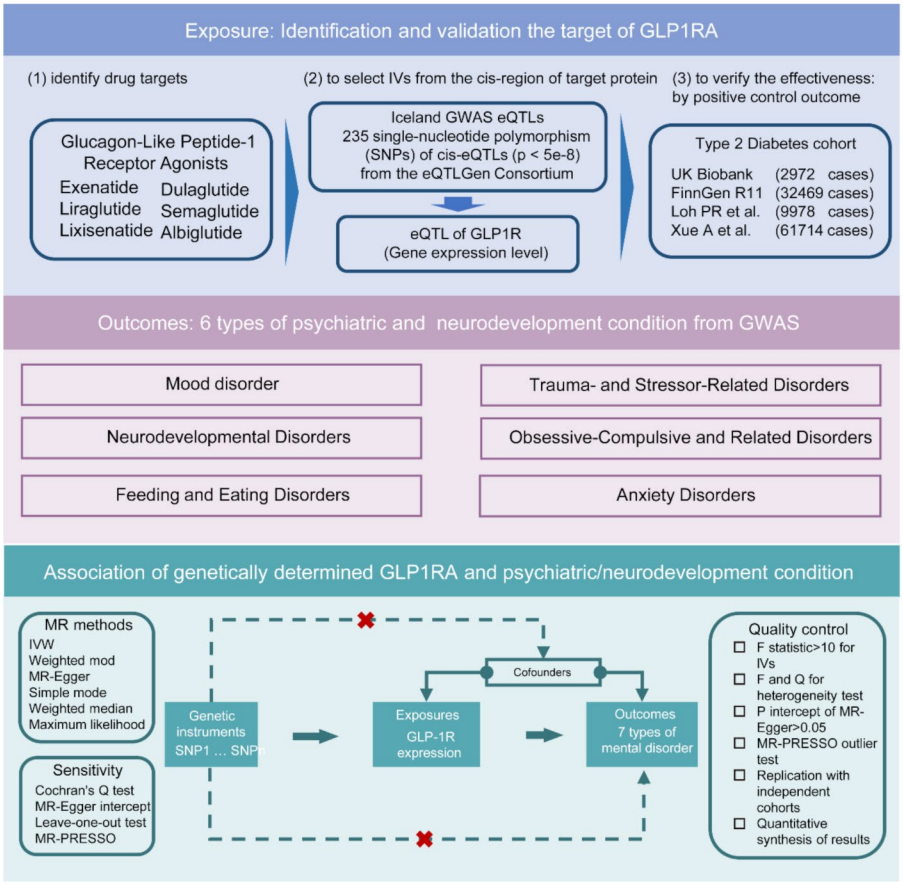

Fig. 1 Overview of the study design

association with type 2 diabetes, a condition known to be influenced by GLP-1R activation.

To assess the consistency of our findings across multiple independent datasets, we conducted MR analyses in FinnGen, PGC, and UK Biobank. The results from these cohorts were then meta-analyzed to integrate evidence from diverse populations and enhance statistical power. UK Biobank was included in multiple analyses due to its large sample size and broad phenotypic coverage, allowing for a more comprehensive evaluation of effect consistency across different datasets.

All studies included in our analysis were approved by the relevant institutional review boards, and informed consent was obtained from all participants.

Mendelian randomization analysis

Selection of genetic instruments

In this study, we included GLP-1RAs, approved by the FDA for blood glucose and weight regulation, as an exposure. As shown in Fig. 1, cis-eQTLs for the target gene (GLP-1R) served as proxies for exposure to GLP-1RAs. We obtained summary-level data for these cis-eQTLs, which included 235 single-nucleotide polymorphisms (SNPs), from the eQTLGen Consortium. Details are provided in Supplementary Table S1. Common cis-eQTL SNPs (minor allele frequency [MAF] > 1%) significantly ($p < 5.0 \times 10^{-8}$) associated with GLP-1R expression in blood were selected as instrumental variables. To minimize the influence of linkage disequilibrium (LD), we included SNPs with low weak LD ($r^2 < 0.001$). Besides, SNPs within the human major histocompatibility complex (MHC) region (chr6: from 26 Mb to 34 Mb) were removed, as the LD patterns of SNPs in the MHC region are complex. Subsequently, LD analysis was conducted within a 10,000 kb window to remove SNPs with an $r^2 > 0.001$. Strength of each SNP as an instrument was assessed using the F-statistic, calculated as mean β^2/σ^2, where β represents the effect size of SNP on the exposure (i.e., the allelic difference in exposure) and σ is the standard error of β. A high F-statistic (> 10) indicates minimal risk of weak instrument bias, which is crucial in MR studies [12–14]. Thus, only SNPs with F-statistics exceeding 10 were retained for further analysis. Additionally, the proportion of exposure variance explained by instrumental variables was evaluated using R^2, computed as $R^2 = 2$ EAF (1 – EAF) β^2, where EAF denotes the effect allele

frequency of the exposure. We also assessed the association between these genetic instruments and type 2 diabetes as a proxy for GLP-1R agonist exposure. Finally, to address potential pleiotropic effects, we excluded SNPs associated with other potential confounders identified through PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/).

Outcome sources

To minimize potential bias due to population diversity, we restricted our drug target MR analysis to participants of European ancestry. Type 2 diabetes data were extracted based on 4 cohorts, which in total included 107,133 cases and 656,672 controls (Supplementary Table S2). We gathered GWAS summary-level data for 12 common types of psychiatric disorder, including schizophrenia, anxiety disorders, bipolar disorder, bulimia nervosa, PTSD, autism, OCD, anorexia nervosa, broad depression, MDD, and suicide or other intentional self-harm, from large-scale consortia. Detailed information on each outcome is provided in Supplementary Table S2.

Assessment of consistency across finngen, PGC, UKB, and other GWAS datasets with meta-analysis

To evaluate the consistency of our findings across multiple independent datasets, we conducted Mendelian randomization (MR) analyses using summary genetic data from the FinnGen consortium (R9) (https://www.finngen.fi/en), Psychiatric Genomics Consortium (PGC, http://www.med.unc.edu/pgc), and UK Biobank (http://www.ukbiobank.ac.uk/about-biobank-uk/). The number of individuals included in these analyses ranged from 133,164 to 306,119, as detailed in Supplementary Table S2.

To integrate evidence across datasets, we performed a meta-analysis combining MR estimates from all cohorts, which allowed us to strengthen statistical power, assess effect consistency, and ensure the robustness of the observed associations across diverse populations.

Statistical analysis

We performed MR analysis using the "TwoSampleMR" R package (version 0.5.8). The associations between cis-eQTLs and outcomes were calculated as odds ratios (ORs) with corresponding confidence intervals (CIs) using the random-effects inverse-variance weighted (IVW) method. A positive control analysis was conducted to validate the genetic instruments for GLP-1R by verifying the association of genetic instruments from eQTLs with type 2 diabetes, given that GLP-1R agonists are FDA-approved for blood glucose and weight control.

To ensure the robustness of our MR findings, we conducted a series of sensitivity analyses designed to comprehensively assess the underlying MR assumptions. We employed MR-Egger regression, weighted median, and mode-based estimators (including both weighted and simple mode) to obtain robust causal effect estimates even if a subset of the instruments were invalid. We note that MR-Egger regression has lower statistical power compared to other methods (e.g., IVW) due to its reliance on the Instrument Strength Independent of Direct Effect (InSIDE) assumption and its sensitivity to weak instruments. Consequently, MR-Egger may yield wider CIs, particularly in smaller cohorts. In addition, we applied maximum likelihood estimation and the Robust Adjusted Profile Score (RAPS) method to account for potential measurement error and weak instrument bias. Furthermore, we used MR-PRESSO (via the MR-PRESSO R package, version 1.0) to detect and correct for outlier SNPs that might distort the causal estimates. Heterogeneity among SNP-specific estimates was evaluated using Cochran's Q test and quantified by the I^2 statistic. Notably, the MR-Egger regression results indicated no significant horizontal pleiotropy. Detailed results for these sensitivity analyses are provided in Supplementary Tables S4, S5, and S6.

Meta-analysis

To synthesize evidence across datasets, we conducted a meta-analysis to evaluate the associations between GLP-1RAs and psychiatric outcomes. For each outcome, we combined results from multiple GWAS using both fixed-effects and random-effects models. Fixed-effects models were applied under the assumption of a shared underlying effect size across datasets, while random-effects models accounted for potential heterogeneity among studies. Heterogeneity was assessed using Cochran's Q test and the I^2 statistic.

Effect estimates were reported as ORs with 95% CIs. For datasets with overlapping populations, we ensured that only the non-overlapping subset was included in the meta-analysis to avoid duplication bias. All analyses were performed using the meta and metafor packages in R (version 4.3.0). The precision of effect estimates was assessed using 95% CIs, with a focus on whether the intervals excluded the null value of 1. This meta-analysis approach ensured a robust integration of evidence while addressing potential variability across datasets.

Results

Genetic instruments selection

We selected 4 significant cis-eQTL SNPs from eQTLGen as genetic instruments for the GLP-1R target gene. The F statistic for all instrument variants was over 74, indicating no bias from weak instruments (Supplementary Table S3). In addition, the result of positive control proved that the intervention significantly decreased the risk of type 2 diabetes (OR [95% CI] = 0.90 [0.88–0.92]). This finding was consistent across different studies,

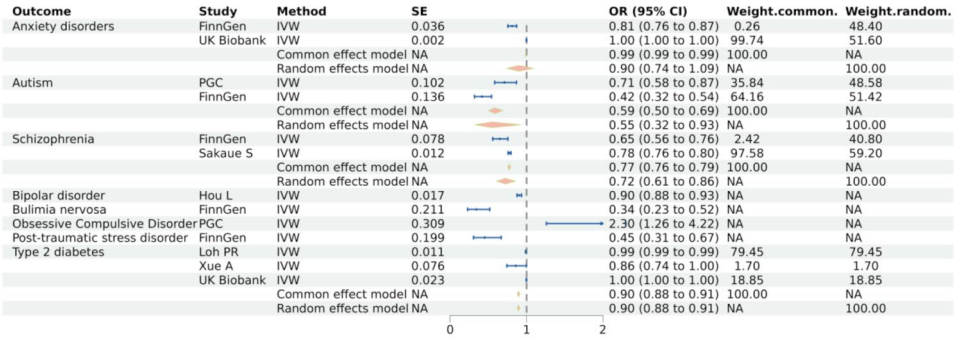

Fig. 2 Significant MR results of GLP-1R expression in psychiatric and neurodevelopmental conditions

including FinnGen (OR [95% CI] = 0.95 [0.88–1.03]), Cai L (OR [95% CI] = 0.89 [0.87–0.91]), UK Biobank (OR [95% CI] = 0.90 [0.87–0.95]), and Xue A (OR [95% CI] = 0.86 [0.74–1.00]).

Mendelian randomization analysis on GLP-1RA with 12 psychiatric and neurodevelopmental conditions

Mendelian randomization (MR) analysis across multiple independent GWAS datasets, including FinnGen, PGC, UK Biobank, and other large consortia, revealed a consistent protective association between higher GLP-1R gene expression and several psychiatric and neurodevelopmental conditions. In Fig. 2, the meta-analysis of all available cohorts showed a significant reduction in risk for schizophrenia (OR = 0.72, 95% CI [0.61–0.86]), bipolar disorder (OR = 0.91, 95% CI [0.88–0.94]), bulimia nervosa (OR = 0.34, 95% CI [0.23–0.52]), PTSD (OR = 0.45, 95% CI [0.31–0.67]), and autism (OR = 0.55, 95% CI [0.32–0.93]). And a approximately significant risk factor is anxiety disorders (OR = 0.90, 95% CI [0.74–1.09]). In contrast, higher GLP-1R expression was associated with an increased risk of OCD (OR = 2.30, 95% CI [1.26–4.22]). No significant associations were observed for anorexia nervosa, broad depression, major depressive disorder, or suicide and intentional self-harm.

Specifically, consistent effect estimates were observed across multiple independent cohorts, as demonstrated for schizophrenia (FinnGen: OR = 0.65, 95% CI [0.56–0.76]; Sakaue S: OR = 0.78, 95% CI [0.76–0.80]; meta-analysis: OR = 0.72, 95% CI [0.61–0.86]), anxiety disorders (FinnGen: OR = 0.81, 95% CI [0.76–0.87]; UKB: OR = 1.00, 95% CI [0.99–0.99]; meta-analysis: OR = 0.90, 95% CI [0.74–1.09]), and autism (FinnGen: OR = 0.42, 95% CI [0.32–0.54]; PGC: OR = 0.71, 95% CI [0.58–0.87]; meta-analysis: OR = 0.55, 95% CI [0.32–0.93]). For bipolar disorder, estimates varied across studies (Hou L: OR = 0.90, 95% CI [0.88–0.93]; Stahl E: OR = 0.93, 95% CI [0.81–1.05]), but meta-analysis still supported a protective association (OR = 0.91, 95% CI [0.88–0.94]).

Sensitivity analyses using MR-Egger, weighted median, weighted mode, simple mode, maximum likelihood, and RAPS (Supplementary Table S4) showed consistent directionality of effects for schizophrenia, anxiety disorders, and autism. However, CIs for many sensitivity analyses crossed the null (OR = 1), particularly in MR-Egger, which is known to have lower statistical power due to its reliance on stronger assumptions (e.g., Instrument Strength Independent of Direct Effect). For example, MR-Egger estimates for anxiety disorders (OR = 0.81, 95% CI: 0.59–1.11) and autism (OR = 0.62, 95% CI: 0.32–1.20) included the null value. MR-PRESSO identified outliers for autism and major depression, but no global pleiotropy was detected for other outcomes (Supplementary Table S5). MR-Egger regression indicated no significant horizontal pleiotropy (Supplementary Table S6), supporting the validity of our primary findings.

Heterogeneity tests using Cochran's Q revealed moderate heterogeneity for anxiety disorders ($P = 0.009$), suggesting some variability in effects across datasets. However, for most conditions, results remained consistent across independent cohorts, with meta-analysis reinforcing the robustness of observed associations. Collectively, these findings suggest that GLP-1R activation may have a protective role in schizophrenia, anxiety disorders, autism, and bipolar disorder, though further validation through non-genetic epidemiological studies and clinical trials is warranted.

Discussion

GLP-1RAs, primarily developed for metabolic conditions, have demonstrated promising effects on brain pathways involved in emotional regulation and reward processing. This study systematically explored the associations between GLP-1RAs and 12 common psychiatric and neurodevelopmental conditions using large-scale GWAS datasets, revealing protective effects against schizophrenia, anxiety disorders, bipolar disorder, bulimia nervosa, PTSD, and autism, with consistent findings

across multiple databases for anxiety disorders, autism, and schizophrenia. However, a slight increase in OCD risk was observed, and no significant associations were identified for broad depression, major depressive disorder, anorexia nervosa, or self-harm.

Building upon these primary results, we further assessed the robustness of these associations through a comprehensive series of sensitivity analyses and meta-analysis. To address potential confounding inherent in observational studies, we employed a drug-target Mendelian randomization framework. Sensitivity analyses including MR Egger regression, weighted median, weighted mode (both weighted and simple), maximum likelihood, and RAPS yielded consistent results, thereby reinforcing our causal inferences. Our meta-analysis integrating data from FinnGen, PGC, and UK Biobank cohorts enhanced statistical power by mitigating cohort-specific biases.

While our meta-analysis demonstrated robust protective associations between GLP-1R activation and psychiatric conditions such as schizophrenia and anxiety disorders, sensitivity analyses revealed broader CIs that occasionally crossed the null. This uncertainty may reflect limitations in statistical power, particularly for MR-Egger, which requires stronger assumptions and larger sample sizes to detect causal effects. However, the consistency of effect directions across all sensitivity methods (e.g., weighted median, RAPS) and the integration of evidence through meta-analysis strengthen confidence in our primary findings. For example, the meta-OR for schizophrenia (0.72, 95% CI: 0.61–0.86) remained stable despite heterogeneity in individual cohort estimates. Potential pleiotropy, though not detected in MR-Egger or MR-PRESSO, cannot be fully excluded. Future studies with larger datasets may clarify whether specific SNPs disproportionately drive observed effects or if subtle pleiotropic pathways exist.

The observed clinical associations align with established neurobiological effects of GLP-1RAs. Research has extensively explored the effects of endogenous and exogenous GLP-1 on brain activity related to homeostasis and reward systems, particularly in the context of obesity and type 2 diabetes mellitus (T2DM). Studies using functional MRI (fMRI) with food pictures have shown that dietary intake and the consequent increase in endogenous GLP-1 levels reduce the activation of the insula region in diabetic subjects compared to lean subjects [15]. Exenatide, an exogenous GLP-1RA, has been shown to enhance hypothalamic connectivity in obese individuals who respond to its anorexigenic effects, while also decreasing food reward-related brain activation. This is evident from studies where exenatide blunted the fMRI signal in brain areas such as the amygdala, insula, hippocampus, and frontal cortex in obese individuals but not in lean individuals [16, 17]. Additionally, exenatide increased cerebral glucose metabolism in regions associated with glucose homeostasis, appetite, and food reward, as observed through [(18)F]2-fluoro-2-deoxy-d-glucose PET/CT scans [17–19].

Acute and chronic administration of GLP-1RAs exhibit distinct effects on emotional behavior. Acute administration, such as with Exendin-4, induces anxiety-like behaviors in rodent models, accompanied by altered serotonin signaling in the amygdala. Conversely, chronic administration significantly alleviates depression-like symptoms, independent of weight loss or food intake, highlighting its direct impact on mood regulation [20, 21]. These findings suggest that chronic GLP-1RA treatment may exert anxiolytic and antidepressant effects through modulation of serotonergic pathways and long-term neuroadaptive processes. In bipolar disorder, GLP-1RAs like liraglutide demonstrate mood-stabilizing properties. For instance, liraglutide alone mitigates amphetamine-induced mania-like symptoms and cognitive deficits, while its combination with lithium enhances neuroprotection, which may involve mechanisms such as improved mitochondrial function and reduced neuroinflammation [22]. GLP-1RAs also show potential in addressing bulimia nervosa, a disorder characterized by impaired satiety signaling and heightened sensitivity to food rewards. Acting on hypothalamic and reward pathways, GLP-1RAs promote satiety and reduce anticipatory food rewards [19, 23]. Furthermore, their influence on brain regions such as the medial prefrontal cortex and ventral hippocampus highlights a mechanism that integrates appetite control with reward regulation [24–26]. In autism, GLP-1RAs may exert therapeutic effects through anti-inflammatory, antioxidant, and neuroprotective mechanisms. Experimental models show that Exenatide reduces hippocampal gliosis, improves serotonergic and GABAergic signaling, and alleviates behavioral disturbances, suggesting a pathway targeting inflammation, oxidative stress, and neurotransmitter imbalances [27]. The pathways linking GLP-1RAs to psychiatric and neurodevelopmental conditions remain underexplored for conditions such as PTSD and OCD. However, the potential modulation of neuroinflammatory and serotonergic systems by GLP-1RAs warrants further investigation in these areas.

Overall, beyond their established metabolic effects, GLP-1RAs may orchestrate a network of neurophysiological and biochemical processes that intersect with mood and behavior regulation. Central to these effects is the modulation of glucose metabolism in brain regions associated with emotional and cognitive functions, suggesting a potential role for energy homeostasis in mental health. In addition to directly influencing satiety and appetite control via hypothalamic and hindbrain pathways, GLP-1RAs appear to engage higher-order networks involved

in reward processing and emotional regulation, such as the insula, amygdala, and medial prefrontal cortex. These regions not only govern immediate behavioral responses but also mediate long-term neuroadaptive changes that may protect against mood dysregulation and impulsivity. Recent experimental and clinical observations [15, 19, 23] hint at GLP-1RAs acting as modulators of neuroinflammation, oxidative stress, and neurogenesis, providing a broader framework for their potential impact on psychiatric conditions. This mechanistic diversity suggests that GLP-1RAs could be repurposed to target complex, multifactorial disorders like schizophrenia, bipolar disorder, and bulimia nervosa, where current treatment options are limited or suboptimal. The convergence of metabolic, neuroimmune, and reward pathways positions GLP-1RAs as a promising focus for future translational studies to bridge gaps in our understanding of psychiatric pathophysiology and therapeutics.

This study possesses several notable strengths that underscore its contribution to the field. First, it provides a comprehensive investigation of the associations between GLP-1RAs and 12 common psychiatric and neurodevelopmental conditions, utilizing large-scale GWAS summary statistics. By systematically examining this wide array of disorders, the study sheds light on the potential therapeutic roles of GLP-1RAs beyond their established metabolic applications. Key findings, including the potential protective effects of GLP-1RAs on schizophrenia, anxiety disorders, and autism, were consistently observed across multiple independent datasets, reinforcing the robustness and reproducibility of the results. Another major strength of this study is its novel exploration of under-researched conditions, including PTSD and OCD. To our knowledge, this is the first Mendelian randomization study to assess the associations between GLP-1RAs and these psychiatric conditions. By identifying these potential links, the study opens avenues for future research into the therapeutic applications of GLP-1RAs in these disorders, which currently lack robust clinical evidence. Additionally, the study moves beyond simple statistical associations to propose plausible mechanistic pathways through which GLP-1RAs may influence psychiatric outcomes. These pathways include modulation of neuroinflammation, glucose metabolism, and reward system activity, offering a framework for understanding how GLP-1RAs might exert their effects on mood, cognition, and behavior. By integrating findings from preclinical and clinical studies, this work provides a translational perspective that bridges genetic evidence with potential therapeutic mechanisms. Finally, the innovative application of drug-target Mendelian randomization underscores the utility of this approach in evaluating the causal effects of pharmacological interventions on disease outcomes. This method not only strengthens the evidence for the observed associations but also highlights GLP-1RAs as promising candidates for repurposing in the treatment of psychiatric and neurodevelopmental conditions. Collectively, these strengths position this study as a significant contribution to the growing field of psychiatric genetics and therapeutic development.

When interpreting our results, it is important to highlight that GLP-1RAs were associated with a reduced incidence of anxiety disorders, autism, bulimia nervosa, PTSD, and schizophrenia. However, the associations between GLP-1RAs and bulimia nervosa or PTSD were based solely on evidence from Mendelian randomization analysis. There are currently no clinical trials investigating the use of GLP-1RAs in patients with PTSD or OCD, leaving the clinical validation of these findings unexplored. Future studies should aim to bridge this gap by providing direct evidence through well-designed clinical trials. Secondly, the findings of this study demonstrated variable levels of consistency across datasets for the association between GLP-1RAs and psychiatric and neurodevelopmental conditions. Specifically, robust and consistent protective effects were observed for schizophrenia and anxiety disorders, as evidenced by significant associations across all datasets analyzed. For instance, both the FinnGen and UK Biobank datasets yielded consistent inverse associations for anxiety disorders (FinnGen: OR = 0.81, 95% CI [0.76, 0.87]; UK Biobank: OR = 0.99, 95% CI [0.99, 0.99]). In contrast, results for bipolar disorder and OCD exhibited marked heterogeneity. The association for bipolar disorder was significant in Hou L's study (OR = 0.90, 95% CI [0.88, 0.93]) but lacked statistical significance in Stahl E's analysis. Similarly, the association for OCD was significant in the PGC dataset (OR = 2.30, 95% CI [1.26, 4.22]) but not in FinnGen. These discrepancies may arise from differences in sample sizes, study designs, and the power of individual datasets to detect genetic associations. For rarer disorders such as PTSD and bulimia nervosa, significant findings were limited to a single database (FinnGen), emphasizing the need for validation in independent cohorts to confirm these preliminary associations. For example, the protective association with PTSD (FinnGen: OR = 0.45, 95% CI [0.31, 0.67]) is compelling but requires further validation. Overall, these differences underscore the importance of dataset harmonization and the inclusion of larger, more diverse cohorts in future studies. Thirdly, this study is its restriction to individuals of European ancestry. While this approach minimizes population stratification biases, it may limit the generalizability of our findings to other ancestral groups. Genetic variants associated with GLP-1 receptor expression and their effects on psychiatric and neurodevelopmental conditions may vary across populations due to differences in allele frequencies, linkage disequilibrium patterns, and environmental exposures.

Lastly, our study focused solely on the risk of psychiatric disorder onset, not on disease progression. Future research should examine the potential role of GLP-1RAs in the treatment and prognosis of psychiatric and neurodevelopmental conditions.

Abbreviations

BCAAs	Branched-chain amino acids
CIs	Confidence intervals
DR	Dorsal raphe
fMRI	Functional MRI
GLP-1RAs	Glucagon-like peptide-1 receptor agonists
GWAS	Genome-wide association studies
IGF	Insulin-like growth factors
IR	Insulin receptor
IVW	Inverse-variance weighted
LD	Linkage disequilibrium
LIRA	Liraglutide
LPS	Lipopolysaccharide
MDD	Major depressive disorder
MHC	Histocompatibility complex
MR	Mendelian randomization
OCD	Obsessive-compulsive disorder
ORs	Odds ratios
PGC	Psychiatric genomics consortium
RCTs	Randomized controlled trials
T2DM	Type 2 diabetes mellitus
UKB	UK biobank

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-025-06914-0.

Supplementary Material 1

Supplementary Material 2

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Author contributions
LZ: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. YX: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. XC: Supervision, Conceptualization, JL: Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization, ZL: Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

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Data availability
No datasets were generated or analysed during the current study.

Data and code availability
All data sourced from the FinnGen consortium (R9) (https://www.finngen.fi/en), Psychiatric Genomics Consortium (PGC, http://www.med.unc.edu/pgc), and UK Biobank (http://www.ukbiobank.ac.uk/about-biobank-uk/).
All codes are available from the corresponding author through reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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