Supplementary Methods

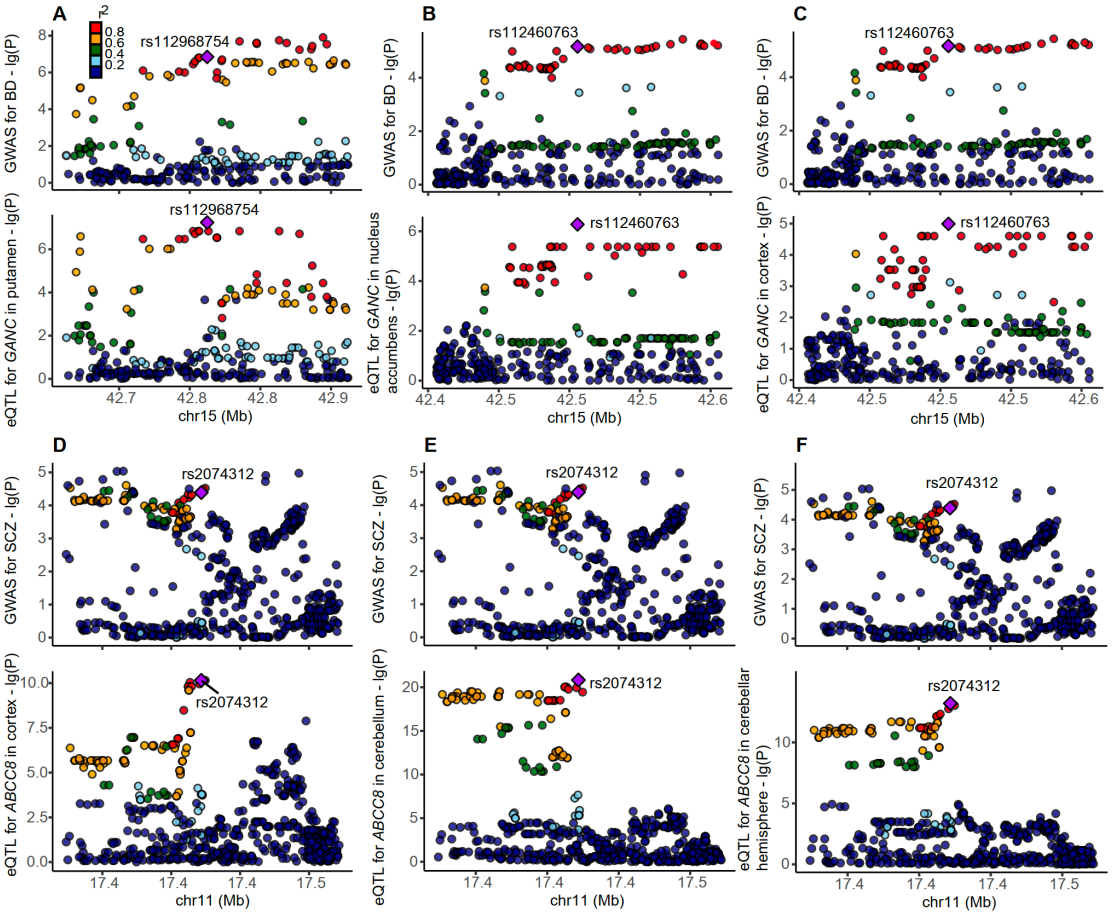
Colocalization analysis

Based on evidence from Mendelian Randomization (MR) results, we also performed Bayesian colocalization analyses using the R package coloc (version 5.2.1) for validation[1]. Colocalization analyses help verify if two traits with genetic links in the same genomic region share the same causal variant, serving as a complement to MR by minimizing linkage disequilibrium bias and confirming if a causal effect stems from the same variant[2,3]. This methodology is predicated on several key assumptions: 1) Each trait is influenced by no more than one causal genetic variant. 2) The potential of a genetic variant to be causal is independent across all variants analyzed. 3) The colocalization analysis encompasses all causal genetic variants, both genotyped and imputed. Based on these assumptions, the analysis considers five hypotheses: H0 posits no causal genetic variants for either trait; H1 identifies one causal variant for trait 1; H2 identifies one for trait 2; H3 posits separate causal variants for each trait within the same region; and H4 indicates a single causal variant affecting both traits[1].

We used default prior probability: $p_1 = 1 \times 10^{-4}$; $p_2 = 1 \times 10^{-4}$; $p_{12} = 1 \times 10^{-5}$. p_1, p_2, and p_{12} represent the prior probabilities that a SNP within the tested region significantly associates with the expression of the tested gene, the tested outcome, or both, respectively. In our analysis, variants ± 100 kb of the top SNP were included. Default priors were used for analysis. We evaluated the evidence of colocalization by posterior probability for hypothesis 4 (PP.H4), which indicated the presence of associations for both drug targets and psychiatric disorders, driven by the same causal variant(s).

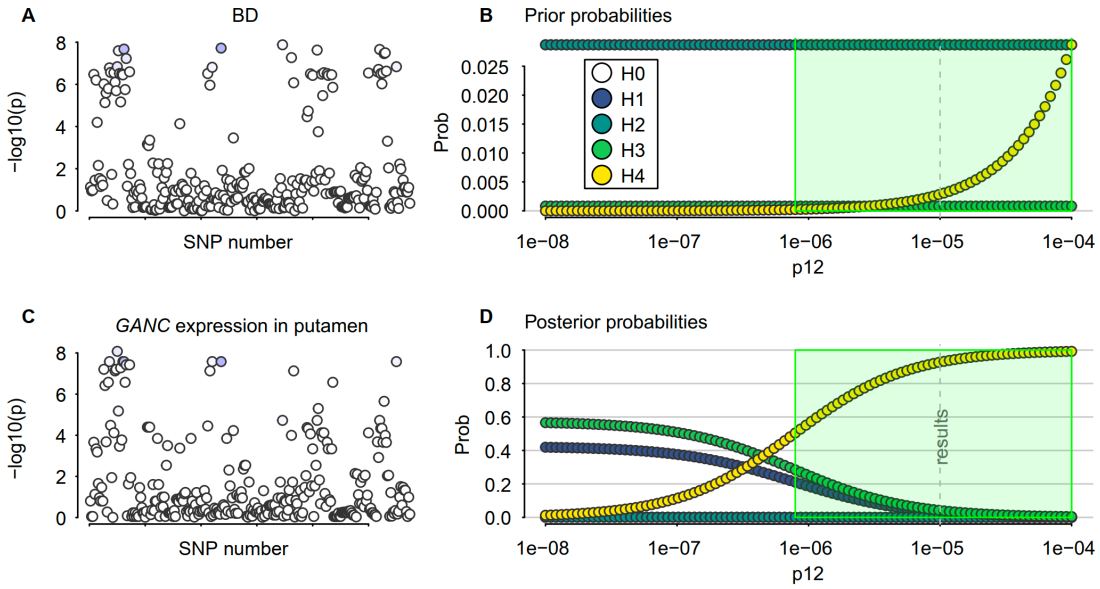
Sensitivity analyses were employed to assess the range of prior probabilities supporting conclusions[4], with associations exhibiting a PP.H4 greater than 0.5 considered indicative of likely colocalization[5]. The R package LocusCompare was used to visualize colocalization results.

Supplementary Figures

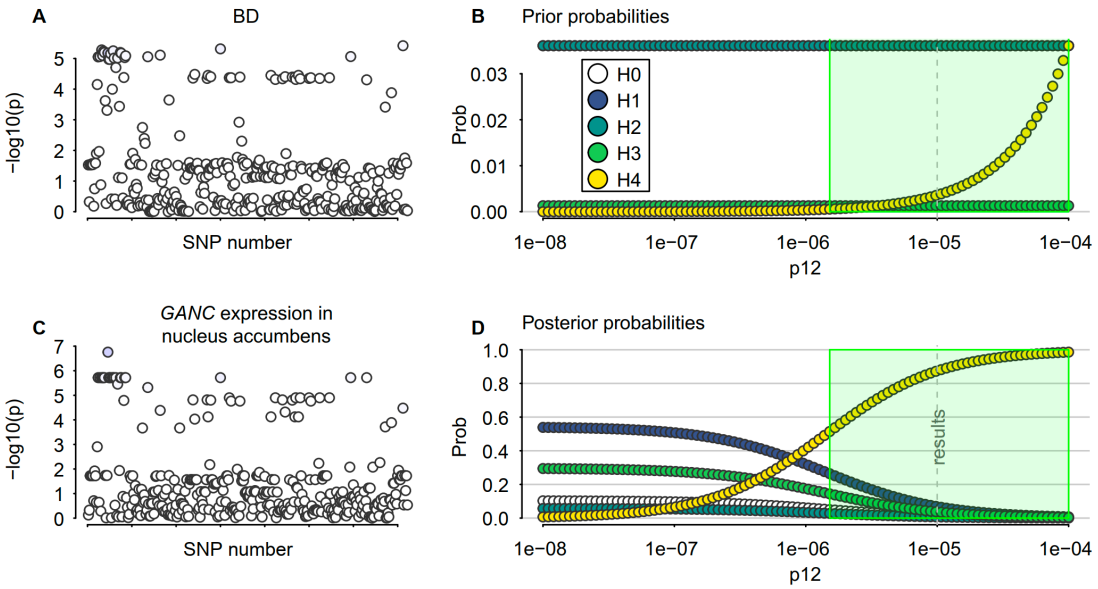


Supplementary Figure S1. LocusCompare plots comparing eQTL results for *GANC* or *ABCC8* and GWAS for BD or SCZ. (A) The plots display the lead SNP, which has the highest posterior probability for H4 in the colocalization analysis between *GANC* expression in the putamen basal ganglia and BD risk, with other SNPs colored according to their LD r² with the lead SNP. **(B)** The plots display the lead SNP, which has the highest posterior probability for H4 in the colocalization analysis between *GANC* expression in the nucleus accumbens basal ganglia and BD risk, with other SNPs colored according to their LD r² with the lead SNP. **(C)** The plots display the lead SNP, which has the highest posterior probability for H4 in the colocalization analysis between *GANC* expression in the cortex and BD risk, with other SNPs colored according to their LD r² with the lead SNP. **(D)** The plots display the lead SNP, which has the highest posterior probability for H4 in the colocalization analysis between *ABCC8* expression in the cortex and SCZ risk, with other SNPs colored according to their LD r² with the lead SNP. **(E)** The plots display the lead SNP, which has the highest posterior probability for H4 in the colocalization analysis between *ABCC8* expression in the cerebellum and SCZ risk, with other SNPs colored according to their LD r² with the lead SNP. **(F)** The plots display the lead SNP, which has the highest posterior probability for H4 in the colocalization analysis between *ABCC8* expression in the

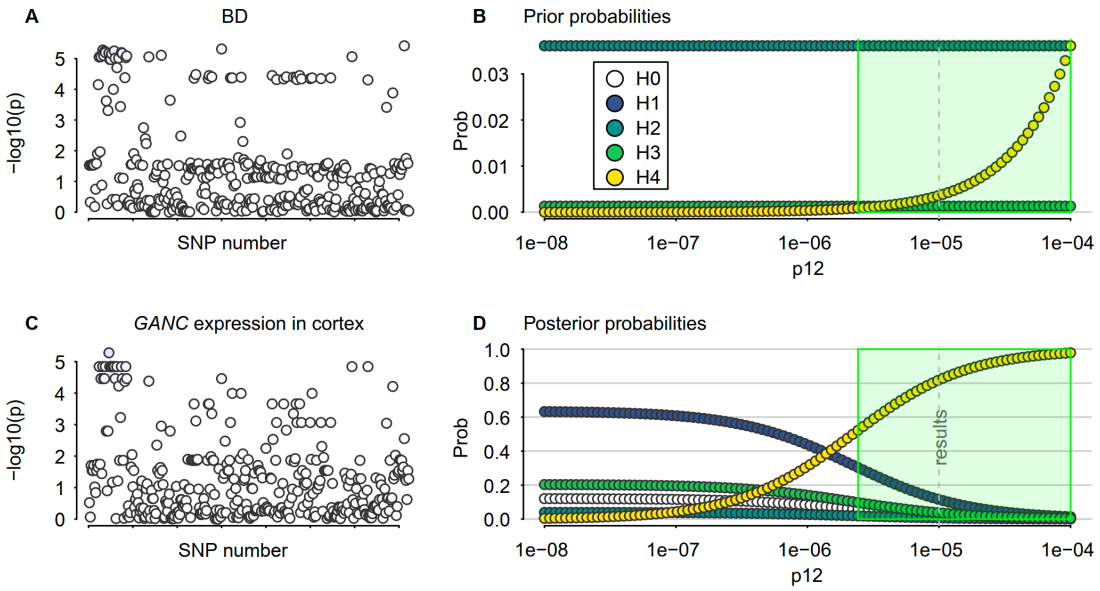
cerebellar hemisphere and SCZ risk, with other SNPs colored according to their LD r^2 with the lead SNP. GWAS, genome-wide association study; BD, bipolar disorder; eQTL, expression quantitative trait loci; GANC, Glucosidase Alpha Neutral C; SCZ, schizophrenia; ABCC8, ATP Binding Cassette Subfamily C Member 8.



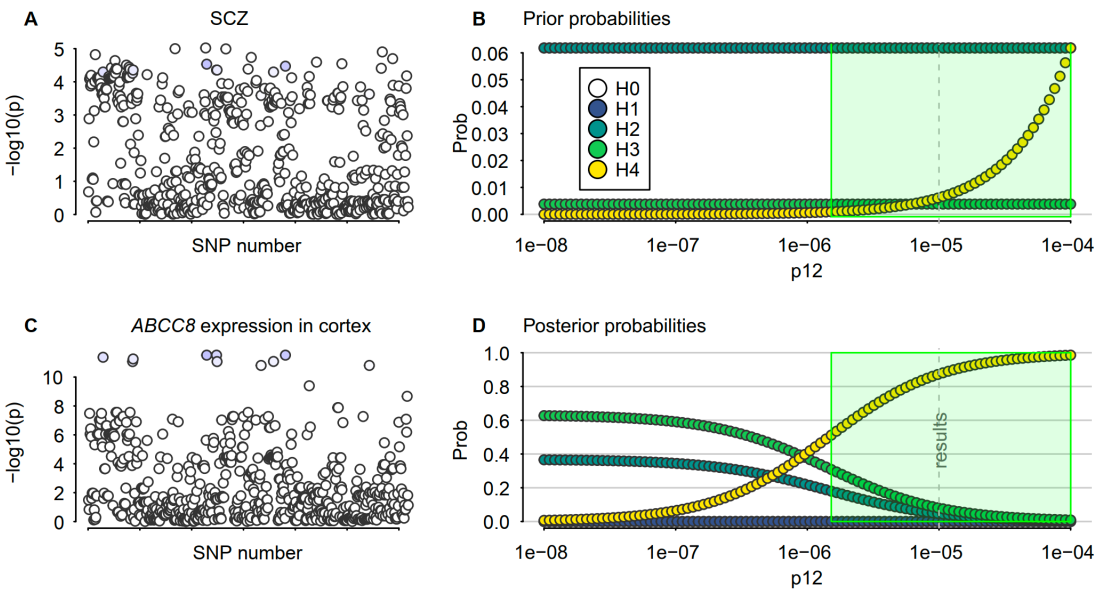
Supplementary Figure S2. Sensitivity analysis for colocalization of *GANC* expression in the putamen basal ganglia and BD in the rule of H4 > 0.5. (A) The panel displays the Manhattan plot for BD. **(B)** The panel displays the Manhattan plot for *GANC* expression in the putamen basal ganglia. **(C)** The panel illustrates prior probabilities for H0-H4 as a function of p12. **(D)** The panel illustrates posterior probabilities for H0-H4 as a function of p12. The dashed vertical line represents the value of p12 used in the initial analysis. In the green region, the conclusion of colocalization looks quite robust. SNP, single nucleotide polymorphism; GANC, Glucosidase Alpha Neutral C; BD, bipolar disorder; p12, the prior probabilities that a SNP within the tested region significantly associates with the expression of the tested gene and outcome.



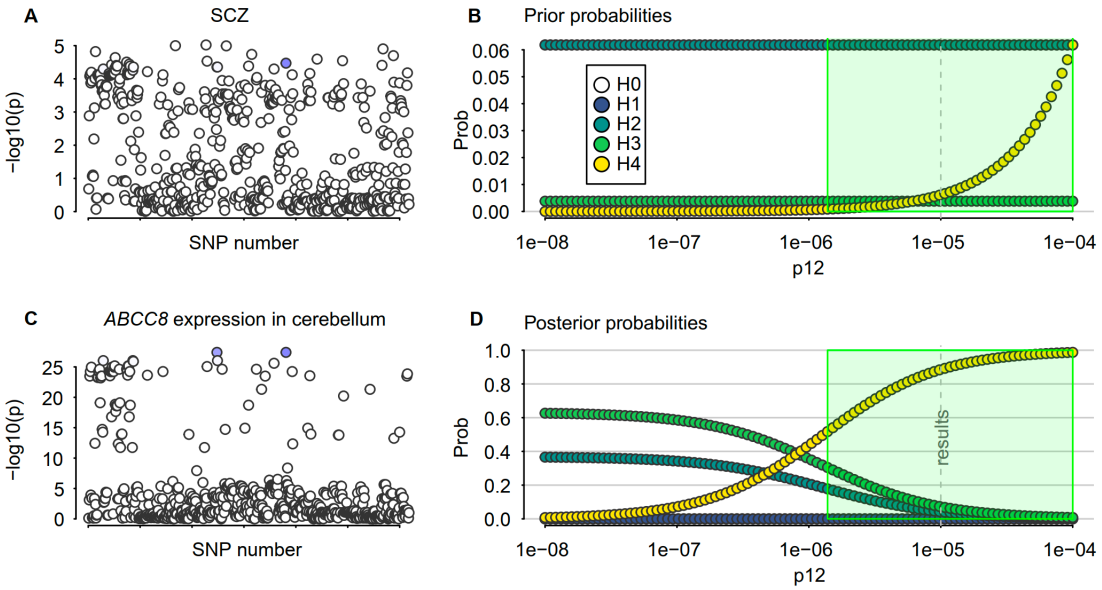
Supplementary Figure S3. Sensitivity analysis for colocalization of *GANC* expression in the nucleus accumbens basal ganglia and BD in the rule of H4 > 0.5. **(A)** The panel displays the Manhattan plot for BD. **(B)** The panel displays the Manhattan plot for *GANC* expression in the nucleus accumbens basal ganglia. **(C)** The panel illustrates prior probabilities for H0-H4 as a function of p12. **(D)** The panel illustrates posterior probabilities for H0-H4 as a function of p12. The dashed vertical line represents the value of p12 used in the initial analysis. In the green region, the conclusion of colocalization looks quite robust. SNP, single nucleotide polymorphism; GANC, Glucosidase Alpha Neutral C; BD, bipolar disorder; p12, the prior probabilities that a SNP within the tested region significantly associates with the expression of the tested gene and outcome.



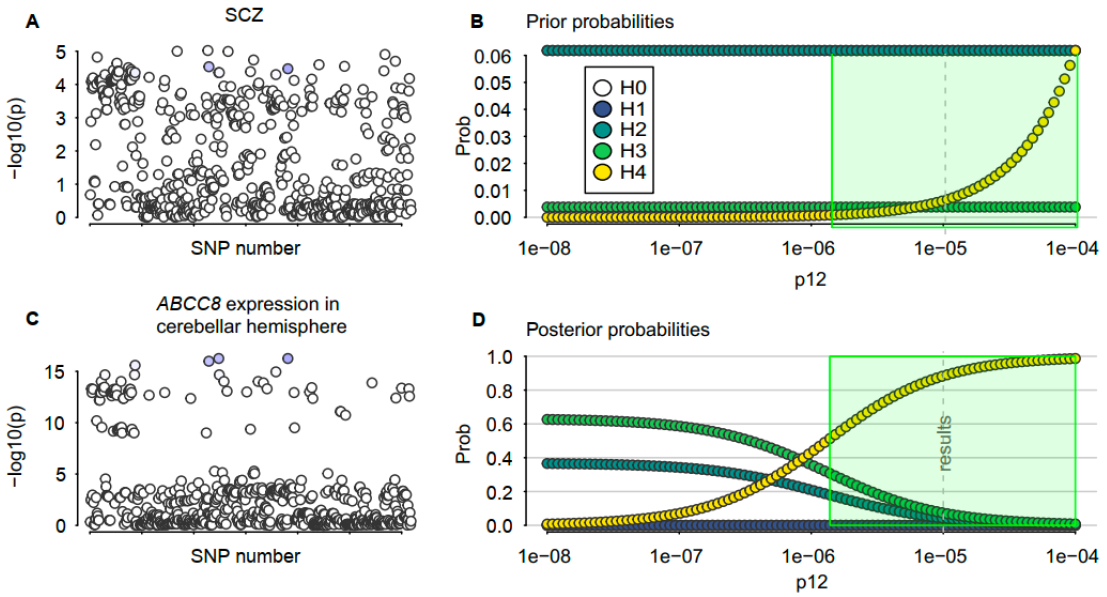
Supplementary Figure S4. Sensitivity analysis for colocalization of *GANC* expression in the cortex and BD in the rule of H4 > 0.5. (A) The panel displays the Manhattan plot for BD. **(B)** The panel displays the Manhattan plot for *GANC* expression in the cortex. **(C)** The panel illustrates prior probabilities for H0-H4 as a function of p12. **(D)** The panel illustrates posterior probabilities for H0-H4 as a function of p12. The dashed vertical line represents the value of p12 used in the initial analysis. In the green region, the conclusion of colocalization looks quite robust. SNP, single nucleotide polymorphism; GANC, Glucosidase Alpha Neutral C; BD, bipolar disorder; p12, the prior probabilities that a SNP within the tested region significantly associates with the expression of the tested gene and outcome.



Supplementary Figure S5. Sensitivity analysis for colocalization of *ABCC8* expression in the cortex and SCZ in the rule of H4 > 0.5. (A) The panel displays the Manhattan plot for SCZ. **(B)** The panel displays the Manhattan plot for *ABCC8* expression in the cortex. **(C)** The panel illustrates prior probabilities for H0-H4 as a function of p12. **(D)** The panel illustrates posterior probabilities for H0-H4 as a function of p12. The dashed vertical line represents the value of p12 used in the initial analysis. In the green region, the conclusion of colocalization looks quite robust. SNP, single nucleotide polymorphism; ABCC8, ATP Binding Cassette Subfamily C Member 8; SCZ, schizophrenia; p12, the prior probabilities that a SNP within the tested region significantly associates with the expression of the tested gene and outcome.



Supplementary Figure S6. Sensitivity analysis for colocalization of *ABCC8* expression in the cerebellum and SCZ in the rule of H4 > 0.5. (A) The panel displays the Manhattan plot for SCZ. **(B)** The panel displays the Manhattan plot for *ABCC8* expression in the cerebellum. **(C)** The panel illustrates prior probabilities for H0-H4 as a function of p12. **(D)** The panel illustrates posterior probabilities for H0-H4 as a function of p12. The dashed vertical line represents the value of p12 used in the initial analysis. In the green region, the conclusion of colocalization looks quite robust. SNP, single nucleotide polymorphism; ABCC8, ATP Binding Cassette Subfamily C Member 8; SCZ, schizophrenia; p12, the prior probabilities that a SNP within the tested region significantly associates with the expression of the tested gene and outcome.



Supplementary Figure S7. Sensitivity analysis for colocalization of *ABCC8* expression in the cerebellar hemisphere and SCZ in the rule of H4 > 0.5. (A) The panel displays the Manhattan plot for SCZ. **(B)** The panel displays the Manhattan plot for *ABCC8* expression in the cerebellar hemisphere. **(C)** The panel illustrates prior probabilities for H0-H4 as a function of p12. **(D)** The panel illustrates posterior probabilities for H0-H4 as a function of p12. The dashed vertical line represents the value of p12 used in the initial analysis. In the green region, the conclusion of colocalization looks quite robust. SNP, single nucleotide polymorphism; ABCC8, ATP Binding Cassette Subfamily C Member 8; SCZ, schizophrenia; p12, the prior probabilities that a SNP within the tested region significantly associates with the expression of the tested gene and outcome.

128 **STROBE-MR checklist of recommended items to address in reports of Mendelian randomization studies** [6,7]

Item No.	Section	Checklist item	Page No.	Relevant text from manuscript
1	**TITLE and ABSTRACT**	Indicate Mendelian randomization (MR) as the study's design in the title and/or the abstract if that is a main purpose of the study	1, 2	We identified 32 target genes of 60 antidiabetics and performed Mendelian randomization analyses using expression and protein quantitative trait loci data from brain tissues alongside summary data for seven psychiatric disorders.
	INTRODUCTION			
2	**Background**	Explain the scientific background and rationale for the reported study. What is the exposure? Is a potential causal relationship between exposure and outcome plausible? Justify why MR is a helpful method to address the study question	5	Mendelian randomization (MR) is a promising tool for identifying new uses for approved drugs, enabling cost-effective testing of costly or time-consuming interventions. Drug target MR analysis utilizes quantitative trait loci (QTL) data of drug target genes as instrumental variables (IVs) for exposures and summary data from genome-wide association studies (GWAS) of psychiatric disorders for outcomes to investigate whether genetic variants causally affect diseases through changes in gene expression, thereby aiding drug repurposing efforts

3	**Objectives**	State specific objectives clearly, including pre-specified causal hypotheses (if any). State that MR is a method that, under specific assumptions, intends to estimate causal effects	6	We hypothesize that antidiabetic drugs targets could provide promising novel targets for psychiatric disorders.
	METHODS			
4	**Study design and data sources**	Present key elements of the study design early in the article. Consider including a table listing sources of data for all phases of the study. For each data source contributing to the analysis, describe the following:		
	a)	Setting: Describe the study design and the underlying population, if possible. Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection, when available.	6	This study utilized Mendelian randomization analysis, colocalization analysis, and various functional analyses, leveraging publicly available summary data from expression quantitative trait loci (eQTL), protein quantitative trait loci (pQTL), and GWAS for exposures and outcomes (Additional file 2: Table S1).
	b)	Participants: Give the eligibility criteria, and the sources and methods of selection of participants. Report the sample size, and whether any power or sample size calculations were carried out prior to the main analysis	6,9	Prior to the primary analyses, power for each MR test was calculated using the mRnd web tool (https://sb452.shinyapps.io/power/), based on study-specific sample size, case/control ratio, and instrument R^2 (Additional file 2: Table S1 and S4). Assuming a two-sided $\alpha = 0.05$ and the default causal effect (odds ratio (OR) = 1.20), 93.6% of the MR analyses

			achieved >80% power (minimum = 0.612), supporting the adequacy of the study design.
	c) Describe measurement, quality control and selection of genetic variants	8	To minimize horizontal pleiotropy brought by *trans*-eQTLs, we only utilized *cis*-eQTLs as IVs. We identified antidiabetic drug target genes with significant eQTLs (eQTL $P < 1 \times 10^{-4}$) in the brain, and the top eQTL of each target in each brain tissue was used as an IV (Additional file 2: Table S4). We also extracted pQTL summary data from the Religious Orders Study and Rush Memory and Aging Project (ROSMAP) to select IVs for drug target proteins. We selected SNPs significantly associated with target proteins as IVs (pQTL $P < 0.05$). To avoid weak IV bias, we calculated the *F*-statistic for each IV using the SNP-exposure association (*beta*) and the standard error (*SE*) of the SNP-exposure association for each SNP by the formula: $F = (beta^2/SE^2)$.
	d) For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases	NA	

		e)	Provide details of ethics committee approval and participant informed consent, if relevant	7	Only publicly available data were used in this study. Ethical approval and consent to participation were available in the original studies.
5	**Assumptions**		Explicitly state the three core IV assumptions for the main analysis (relevance, independence and exclusion restriction) as well assumptions for any additional or sensitivity analysis	6	For accurate causal estimation in MR analysis, three critical assumptions must be met: (1) a strong association between the IVs and the drug target genes (relevance), (2) independence of IVs on confounders (exchangeability), and (3) no direct effects of IVs on psychiatric risk except via the drug target genes (exclusion restriction). The framework of our study design and diagram of the MR analysis is presented in Fig. 1.
6	**Statistical methods: main analysis**		Describe statistical methods and statistics used		
		a)	Describe how quantitative variables were handled in the analyses (i.e., scale, units, model)	NA	
		b)	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	9	In the MR analysis for antidiabetic drug targets, the Wald ratio method was employed for targets with one top SNP as an IV, while the inverse-variance weighted (IVW) regression method was utilized for those with multiple top SNPs as IVs

		c) Describe the MR estimator (e.g. two-stage least squares, Wald ratio) and related statistics. Detail the included covariates and, in case of two-sample MR, whether the same covariate set was used for adjustment in the two samples	9	In the MR analysis for antidiabetic drug targets, the Wald ratio method was employed for targets with one top SNP as an IV, while the inverse-variance weighted (IVW) regression method was utilized for those with multiple top SNPs as IVs
		d) Explain how missing data were addressed	NA	
		e) If applicable, indicate how multiple testing was addressed	9	In this study, we applied the Bonferroni correction to determine the statistical significance of the MR effect estimations.
7	**Assessment of assumptions**	Describe any methods or prior knowledge used to assess the assumptions or justify their validity	NA	
8	**Sensitivity analyses and additional analyses**	Describe any sensitivity analyses or additional analyses performed (e.g. comparison of effect estimates from different approaches, independent replication, bias analytic techniques, validation of instruments, simulations)	9, 10	For MR results that achieved Bonferroni-corrected significance, we re-conducted the analysis with an instrument variable threshold of 5×10^{-8} as a sensitivity analysis. 2.7 Colocalization analysis 2.8 Replication MR analysis
9	**Software and pre-registration**			

	a)	Name statistical software and package(s), including version and settings used	9, 13	All MR analyses were conducted using the R package *TwoSampleMR*. All analyses were performed using R version 4.3.1.
	b)	State whether the study protocol and details were pre-registered (as well as when and where)	NA	
	RESULTS			
10	**Descriptive data**			
	a)	Report the numbers of individuals at each stage of included studies and reasons for exclusion. Consider use of a flow diagram	Additional file 2: Table S1	Additional file 2: Table S1
	b)	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	Additional file 2: Table S4	Additional file 2: Table S4
	c)	If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies	NA	
	d)	For two-sample MR: i. Provide justification of the similarity of the genetic variant-exposure associations between the exposure and outcome samples	14	There is no overlap between the exposure and outcome datasets.

		ii. Provide information on the number of individuals who overlap between the exposure and outcome studies		
11	**Main results**			
	a)	Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale	Additional file 2: Table S5-S11	Additional file 2: Table S5-S11
	b)	Report MR estimates of the relationship between exposure and outcome, and the measures of uncertainty from the MR analysis, on an interpretable scale, such as odds ratio or relative risk per SD difference	13, 14	In Additional file 2: Table S5-S11, results from MR analyses found suggestive evidence for the association between antidiabetic drug target genes and ADHD, ASD, AN, BD, MDD, OCD, and SCZ, respectively. Among these results, higher expression levels of *Glucosidase Alpha Neutral C* (*GANC*) across nine brain regions (amygdala, cerebellar hemisphere, cerebellum, cortex, frontal cortex, hippocampus, nucleus accumbens basal ganglia, putamen basal ganglia, and substantia nigra) were significantly associated with a lower risk of BD after Bonferroni correction (OR, 0.764 to 0.877; *P*, 4.04×10^{-5} to 1.45×10^{-7}), while higher expression levels of *ATP Binding Cassette Subfamily C Member 8* (*ABCC8*) across three brain regions (cerebellar hemisphere, cerebellum, and cortex) were significantly associated with a higher risk of SCZ after Bonferroni

				correction (OR, 1.069 to 1.119; $P = 4.42 \times 10^{-5}$; Additional file 2: Table S12 and Fig. 2).
		c)	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	
		d)	Consider plots to visualize results (e.g. forest plot, scatterplot of associations between genetic variants and outcome versus between genetic variants and exposure)	Figure 2	Figure 2
12	**Assessment of assumptions**				
		a)	Report the assessment of the validity of the assumptions	NA	
		b)	Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I^2, Q statistic or E-value)	NA	We employed the Wald ratio method.
13	**Sensitivity analyses and additional analyses**				
		a)	Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	14, 15	Limiting instruments to genome-wide significant variants ($P < 5 \times 10^{-8}$) left suitable proxies only for *GANC* expression in the cerebellar hemisphere and for *ABCC8* expression in the cerebellar hemisphere, cerebellum, and cortex. MR analyses based on these

			variants remained Bonferroni-significant for bipolar disorder and schizophrenia, respectively (Additional file 2: Table S12). No genome-wide significant instruments were available for the other tissue-trait combinations. To ensure the stability of the primary analysis, we repeated the MR analyses using the GTEx dataset restricted to the European population, yielding results consistent with the primary findings.
	b) Report results from other sensitivity analyses or additional analyses	14-18	3.2 Colocalization analysis 3.4 Single-Cell Gene Expression Annotation 3.5 Developmental trajectories for identified target genes 3.6 Phenome-wide association study 3.7 GO/KEGG enrichment 3.8 Drug-gene interaction
	c) Report any assessment of direction of causal relationship (e.g., bidirectional MR)	NA	
	d) When relevant, report and compare with estimates from non-MR analyses	NA	
	e) Consider additional plots to visualize results (e.g., leave-one-out analyses)	Figure 3-5	Figure 3-5

	DISCUSSION			
14	**Key results**	Summarize key results with reference to study objectives	18,19	We investigated the effects of genetic variants in antidiabetic drug targets on psychiatric disorders using public QTL and GWAS summary data. Our findings indicate that elevated *GANC* expression (a target gene of miglitol) in the putamen basal ganglia, nucleus accumbens basal ganglia, cortex, and blood is associated with a reduced risk of BD. Additionally, increased *ABCC8* expression (a target gene of sulfonylurea and glinide drugs) in the cortex, cerebellum, cerebellar hemisphere, and in VIP-expressing and LAMP5-expressing inhibitory neurons is linked to an elevated risk of SCZ. Colocalization analysis further validated the associations between *GANC* and *ABCC8* expression with BD and SCZ risk, respectively.
15	**Limitations**	Discuss limitations of the study, taking into account the validity of the IV assumptions, other sources of potential bias, and imprecision. Discuss both direction and magnitude of any potential bias and any efforts to address them	25	Our study has several limitations. First, our study can only predict the on-target effects of antidiabetic drugs and cannot infer effects that are not mediated by these targets. Second, all datasets were drawn from participants of European ancestry, and the QTL cohorts are modest in size relative to typical GWAS, which may restrict the sensitivity of our analyses and the

				generalizability of the findings, particularly to non-European populations. Replication in larger cohorts with greater ethnic and age diversity is therefore warranted. Third, using only top SNPs as IVs may reduce the efficiency of MR. Therefore, we employed strong IVs, colocalization validation, and replication MR analyses. Lastly, given the limited blood-brain barrier permeability of commonly used oral sulfonylurea formulations and the absence of large-scale clinical trials providing direct evidence, caution is warranted in repurposing existing sulfonylurea and glinide drugs for SCZ.
16	**Interpretation**			
	a)	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies	25	Overall, our study suggests that *GANC* may serve as a protective gene for bipolar disorder, while *ABCC8* may be a risk gene for schizophrenia. These findings identify novel targets for the treatment of psychiatric disorders and propose the use of sulfonylurea and glinide drugs as potential adjunct therapies for managing schizophrenia. Further clinical studies are required to explore the impact of antidiabetic drugs on psychiatric disorders prospectively, focusing on their mechanisms, efficacy, and safety.

		b) Mechanism: Discuss underlying biological mechanisms that could drive a potential causal relationship between the investigated exposure and the outcome, and whether the gene-environment equivalence assumption is reasonable. Use causal language carefully, clarifying that IV estimates may provide causal effects only under certain assumptions	19-22	Gene expression trajectory analysis revealed that *GANC* expression... The protein encoded by *ABCC8*, a member of the multidrug resistance-associated proteins subfamily within the ATP-binding cassette transporters...
		c) Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	23	Given the causal association between increased *ABCC8* expression and elevated SCZ risk, sulfonylureas and glinides that inhibit the ABCC8 subunit of K-ATP channels, especially in brain tissues, may represent promising candidates for managing SCZ...
17	**Generalizability**	Discuss the generalizability of the study results (a) to other populations, (b) across other exposure periods/timings, and (c) across other levels of exposure	25	Second, all datasets were drawn from participants of European ancestry, and the QTL cohorts are modest in size relative to typical GWAS, which may restrict the sensitivity of our analyses and the generalizability of the findings, particularly to non-European populations. Replication in larger cohorts with greater ethnic and age diversity is therefore warranted.
	OTHER INFORMATION			

18	**Funding**	Describe sources of funding and the role of funders in the present study and, if applicable, sources of funding for the databases and original study or studies on which the present study is based	26	This work was supported by the National Natural Science Foundation of China (82330042); National Key R&D Program of China (2023YFE0119400, 2021YFF1201100); Capital's Funds for Health Improvement and Research (2024-1-4111); Fundamental Research Funds for the Central Universities (Peking University Medicine Fund for world's leading discipline and discipline cluster development, BMU2022DJXK007); Beijing Municipal Health Commission Research Ward Programme (3rd batch); Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2023-PT320-08). This work was also supported by Grant BX20240029 from the National Postdoctoral Program for Innovative Talents (Zhe Lu). The funders did not have any role in the design of the study, and collection, analysis, and interpretation of data and in writing the manuscript.
19	**Data and data sharing**	Provide the data used to perform all analyses or report where and how the data can be accessed, and reference these sources in the article. Provide the statistical code needed to reproduce the results in the article, or report whether the code is publicly accessible and if so, where	27	The GWAS data, eQTL data, and pQTL data sources are listed in Additional file 2: Table S2. All other data and codes in this study are available upon reasonable request to the corresponding author.

20	**Conflicts of Interest**	All authors should declare all potential conflicts of interest	27	The authors have nothing to disclose.

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References

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