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Uncovering the genetic underpinnings for different psychiatric disorder combinations

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Original Article

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Abstract

Background. Psychiatric disorders are highly heterogeneous. It is clinically valuable to distinguish psychiatric disorders by the presence or absence of a specific comorbid condition.
Methods. We employed a novel algorithm (CombGWAS) to decipher the genetic basis of psychiatric disorder combinations using genome-wide association studies summary statistics. We focused on comorbidities and combinations of diseases, such as schizophrenia (SCZ) with and without depression, which can be considered as two 'subtypes' of SCZ. We also studied psychiatric disorders comorbid with obesity as disease subtypes.
Results. We compared the genetic architectures of psychiatric disorders with and without specific comorbidities, identifying both shared and unique susceptibility genes/variants across 8 subtype pairs (16 entities). Despite high genetic correlations between subtypes, most subtype pairs exhibited distinct genetic correlations with the same cardiovascular disease (CVD). Some pairs even displayed opposite genetic correlations, especially those involving obesity. For instance, the genetic correlation (rg) between SCZ with obesity and type 2 diabetes (T2DM) was 0.248 (p = 4.42E−28), while the rg between SCZ without obesity and T2DM was −0.154 (p = 6.79E−12). Mendelian randomization analyses revealed that comorbid psychiatric disorders often have stronger causal effects on cardiovascular risks compared to single disorders, but the effects vary across psychiatric subtypes. Notably, obese and nonobese major depressive disorder/SCZ showed opposite causal effects on the risks of T2DM.
Conclusions. Our study provides novel insights into the genetic basis of psychiatric disorder heterogeneity, revealing unique genetic signatures across various disorder combinations. Notably, comorbid psychiatric disorders often showed different causal relationships with CVD compared to single disorders.

Introduction

Psychiatric disorders constitute significant health and societal burdens on a global scale, consistently ranked among the most debilitating medical conditions across diverse age groups (GBD 2019 Diseases and Injuries Collaborators. (2020)). While diagnostic classification systems define disorders based on symptomatology, psychiatric comorbidity is common, with patients frequently presenting with multiple concurrent conditions. For example, a considerable proportion of patients with schizophrenia (SCZ) have comorbid depression, obsessive-compulsive disorder (OCD), and other psychiatric disorders (Gorman, 1996). Similarly, around 75% of patients with depression have comorbid anxiety disorders.

This comorbidity highlights the vast heterogeneity in psychiatry, as subtypes of a primary disorder with different psychiatric comorbidities may have distinct neurobiological underpinnings. Clarifying the genetic basis for these different psychiatric comorbidities can unveil biological mechanisms and promote individualized care.

Genome-wide association studies (GWASs) have achieved success in revealing the genetic basis of complex disorders (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Trubetskoy et al., 2022; Uffelmann et al., 2021), including psychiatric disorders. However, prior research on GWASs mainly focused on exploring the genetic basis of a *single* psychiatric entity, and largely ignored psychiatric comorbidity, with notable exceptions, such as the seminal cross-disorder GWASs by the Cross-Disorder Group of the Psychiatric Genomics Consortium (2013).

Our team has recently developed an innovative statistical framework, CombGWAS (Yin et al., 2021), to uncover the genetic architecture of disease combinations. In this study, we applied

CombGWAS to decipher the genetic signatures distinguishing 16 psychiatric disorder combinations, such as SCZ and major depressive disorder (MDD) with and without various comorbidities. We also considered psychiatric disorders with/without comorbid obesity as disease subtypes, highlighting the intricate relationships between these conditions and their implications for cardiovascular health. Emerging evidence suggests bidirectional relationships between metabolic dysregulation (such as obesity) and psychiatric disorders (Gao et al., 2024; Goldfarb et al., 2022; Hiles, Révész, Lamers, Giltay, & Penninx, 2016; Pan et al., 2012).

Unlike other conventional methods, such as polygenic risk scores (Choi, Mak, & O'Reilly, 2020) or linkage disequilibrium (LD) score regression (LDSR) (Bulik-Sullivan, Loh, Finucane, Ripke, & Yang, 2015) that only reveal *overall* genetic overlap, our approach can identify specific susceptibility variants responsible for the presence or absence of a particular comorbidity. This provides deeper insights into the complex genetic underpinnings of psychiatric disorder heterogeneity. Our method can also estimate the effect size (e.g. odds ratio [OR]) of the variants contributing to the comorbidities, which cannot be achieved by other existing approaches. Furthermore, we employed additional analyses, including genetic correlation, Mendelian randomization (MR), and functional enrichment, to comprehensively characterize the shared and unique genetic architectures across psychiatric subtypes and their relationships with cardiovascular diseases (CVDs).

We summarize the key contributions and novelties of this study below:

1. We applied a novel statistical framework, CombGWAS, to decipher the genetic signatures that distinguish 16 psychiatric disorder combinations, including subtypes with and without specific comorbidities. We identified numerous susceptibility genes/variants across different psychiatric disease subtypes, providing insights into the genetic heterogeneity underlying these conditions.
2. We investigated MDD and SCZ with/without obesity as disease subtypes and revealed their genetic underpinnings. To our knowledge, this is the first GWAS-based study to uncover genetic variants underlying these comorbid conditions.
3. We revealed distinct genetic correlations between psychiatric disorder subtypes and CVDs, shedding light on the complex links between psychiatric and cardiometabolic traits. For example, we uncovered that MDD and SCZ with or without obesity exhibit very different, and often opposite, genetic correlations with cardiometabolic disorders.
4. Our MR analyses revealed that comorbid psychiatric disorders often have more profound causal effects on cardiovascular risks compared to single psychiatric disorders, but the causal effect estimates also vary across different psychiatric subtypes. Notably, obese and nonobese MDD/SCZ showed opposite causal effects on the risks of T2DM.
5. We provided comprehensive genetic and biological insights (through pathway, cell type, and drug enrichment analyses) that may inform the development of personalized treatment and prevention strategies for psychiatric disorder combinations.

Overall, our work represents a significant advancement in understanding the complex genetic underpinnings of psychiatric disorder heterogeneity and comorbidities, which is crucial for improving clinical management and patient outcomes in the long term.

Methods

In this study, we employed CombGWAS (Yin et al., 2021) to estimate the genetic architecture of the combinations of psychiatric disorders. CombGWAS is a statistical framework specially designed to mimic case–control GWASs of combinations of diseases (or comorbid conditions) by using summary statistics taken from case–control GWASs of the corresponding diseases only. The mathematical formulation is as follows.

Consider $S \sim bin(n=2,q)$ as a random biallelic single-nucleotide polymorphism (SNP) with q denoting the effect allele frequency. We considered two binary psychiatric-related traits P_1 and P_2, and generated a multivariate linear model on N subjects as follows:

$$\begin{bmatrix} P_{11} & P_{21} \\ P_{11} & P_{22} \\ \vdots & \vdots \\ P_{1N} & P_{2N} \end{bmatrix} = \begin{bmatrix} 1 & S_1 \\ 1 & S_2 \\ \vdots & \vdots \\ 1 & S_N \end{bmatrix} \begin{bmatrix} \beta_{01} & \beta_{02} \\ \beta_{11} & \beta_{12} \end{bmatrix} + \epsilon \tag{1}$$

The left-hand side P is an $N \times 2$ phenotype matrix, and the matrices on the right-hand side are, respectively, an $N \times 2$ SNP matrix, 2×2 association estimates, and an $N \times 2$ error matrix. The error matrix ($\epsilon \sim N(0, \sum)$) is assumed to follow a multivariate normal distribution. β_{11} and β_{12} represent the regression coefficients for traits P_1 and P_2 for SNP S, which are directly obtained from the summary statistics of traits P_1 and P_2. β_{01} and β_{02} are the intercept terms estimated from the same summary statistics using the following equations: $\beta_{01} = \overline{P_1} - \beta_{11} * \overline{S} = k_1 - \beta_{11} * 2 * eaf_{P_1}$ and $\beta_{02} = \overline{P_2} - \beta_{12} * \overline{S} = k_2 - \beta_{12} * 2 * eaf_{P_2}$, where k_1 and k_2 denote the population prevalence of traits P_1 and P_2, and eaf_{P_1} and eaf_{P_2} denote the effect allele frequencies for the SNP in each trait's GWAS.

The psychiatric comorbidity of two disorders (P_1 and P_2) can be defined as a function of these two traits:

$$Comor = f(P_1, P_2) = P_1 \times P_2 \tag{2}$$

Similarly, the 'single' psychiatric disorder (with the particular comorbid disorder excluded) can be defined as follows:

$$Single = f(P_1, P_2) = P_1 \times (1 - P_2) \tag{3}$$

Our goal here is to infer the association estimates for genome-wide SNPs for the target traits (i.e. the comorbid psychiatric disorders or the single psychiatric disorder without the specific comorbid disorder).

$$f(P_1, P_2) =: T = \gamma_0 + \gamma_1 S + e \tag{4}$$

Here, e is assumed to follow a normal distribution with zero mean. γ_0 and γ_1 are the intercept and regression coefficient, respectively, for the target phenotype (comorbidity or a disorder without a comorbidity). For downstream analysis, γ_1 serves as the primary effect size measure (equivalent to β in standard GWASs), representing the association strength with the target phenotype. According to Yin et al. (2021), the association estimates for the combined psychiatric disorders can be estimated as follows:

$$Comor(\widehat{\gamma_0}) = \widehat{\beta_{01}} \times \widehat{\beta_{02}} + Cov(P_1, P_2) \tag{5}$$

$$\begin{aligned} Comor(\widehat{\gamma_1}) = {} & \frac{2q(1-q)}{2q(1-q)+q^2}\left[\left(\left(\widehat{\beta_{01}} + \widehat{\beta_{11}}\right) \times \left(\widehat{\beta_{02}} + \widehat{\beta_{12}}\right) - \widehat{\beta_{01}} \times \widehat{\beta_{02}}\right)\right] + \frac{q^2}{2q(1-q)+q^2} \\ & \frac{\left[\left(\left(\widehat{\beta_{01}} + 2\widehat{\beta_{11}}\right) \times \left(\widehat{\beta_{02}} + 2\widehat{\beta_{12}}\right) - \widehat{\beta_{01}} \times \widehat{\beta_{02}}\right)\right]}{2} \end{aligned} \tag{6}$$

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Here, $Cov(P_1,P_2)$ denotes the covariance between the two binary traits. Along the same line, the association estimates for the single psychiatric disorder without the particular comorbid disorder can be computed as follows:

$$Single(\widehat{\gamma_0}) = \widehat{\beta_{01}} \times \left(1 - \widehat{\beta_{02}}\right) - Cov(P_1,P_2) \tag{7}$$

$$Single(\widehat{\gamma_1}) = \frac{2q(1-q)}{2q(1-q)+q^2}\left[\left(\left(\widehat{\beta_{01}} + \widehat{\beta_{11}}\right) \times \left(1 - \widehat{\beta_{02}} - \widehat{\beta_{12}}\right) - \widehat{\beta_{01}} \times \left(1 - \widehat{\beta_{02}}\right)\right)\right] + \frac{q^2}{2q(1-q)+q^2} \frac{\left[\left(\left(\widehat{\beta_{01}} + 2\widehat{\beta_{11}}\right) \times \left(1 - \widehat{\beta_{02}} - 2\widehat{\beta_{12}}\right) - \widehat{\beta_{01}} \times \left(1 - \widehat{\beta_{02}}\right)\right)\right]}{2} \tag{8}$$

The estimates used in the above equations are presumably derived from a linear regression model. However, for binary traits, the association estimates are usually calculated from logistic regression models. Therefore, we need to transform the estimates (ORs) derived from logistic regression to those of linear regression, using the following equation:

$$(\alpha k - k)(1-k) = \beta_1^2[p(1-p) + \alpha p(1-p)] + \beta_1[\alpha k(1-p) + \alpha p - \alpha pk + kp + (1-p)(1-k)] \tag{9}$$

where p indicates the effect allele frequency of the SNP under study S, k represents the proportion of cases, β_1 represents the coefficient under a linear model, and α defines the OR of SNP S regressed on the same binary trait. We solve the above equation for β_1. We choose the solution whose absolute value is smaller than the coefficient under a logistic model, i.e., abs(β_1)<abs (log(α)). Then we convert the coefficients back to ORs. The variances for $\widehat{\gamma_0}$ and $\widehat{\gamma_1}$ for the target disease combination can be estimated by the delta method, which employs a first-order Taylor expansion to estimate the variance of a function. Also, it is noteworthy that our proposed analytic framework assumes the absence of significant interactions between the comorbid trait (s) and the genetic variants under study, as explained elsewhere (Yin et al., 2021). In our previous study, we verified the validity of CombGWAS using both extensive simulations and applications to UK-Biobank data. Briefly, we reperformed a GWAS in the UK Biobank (UKBB) using the actual phenotype data of disease combinations as the outcome, and the results were highly similar to those computed from CombGWAS.

Enrichment analyses

We utilized several methods to clarify the putative functional and biological mechanisms of the identified susceptibility variants for the 'psychiatric phenotypes/subtypes' of interest (i.e. the comorbid psychiatric disorders, and the 'single' psychiatric disorders without the particular comorbid disorder). First, the MAGMA tool within FUMA (Watanabe, Taskesen, Van Bochoven, & Posthuma, 2017; Watanabe, Umićević Mirkov, de Leeuw, van den Heuvel, & Posthuma, 2019) was used to map the identified genetic variants to their corresponding genes. This established the gene-level associations with the psychiatric phenotypes/subtypes. The definitions for independent significant SNPs and genomic risk loci in our study were also based on the criteria established by FUMA (https://fuma.ctglab.nl/tutorial#riskloci).

Second, we performed tissue specificity analysis to examine if the susceptibility genes were enriched in specific tissues. Furthermore, we carried out a cell type enrichment analysis to uncover specific cell types or cell populations that may play crucial roles in the etiology of the subtypes. We also conducted pathway analysis using the program 'ConsensusPathDB' (Herwig, Hardt, Lienhard, & Kamburov, 2016; Kamburov, Stelzl, Lehrach, & Herwig, 2013). Moreover, we performed drug enrichment analyses on the identified susceptibility gene sets using 'enrichr' (Kuleshov et al., 2016; Xie et al., 2021). This analysis identified potential therapeutic agents or drug targets that may be relevant to the treatment of the investigated psychiatric conditions. Notably, we also conducted tissue, pathway, cell type, and drug enrichment analyses based on subtype-specific genes.

Genetic correlation among psychiatric disease subtypes and CVDs

We employed LDSR (Bulik-Sullivan et al., 2015) to calculate the genetic correlation (rg) between different psychiatric entities to see if they represent genetically distinct disease subtypes with unique genetic architectures. We tested if rg ≠ 0 (assessing genetic overlap) and rg ≠ 1 (assessing subtype distinctiveness) to comprehensively characterize genetic relationships. Furthermore, we explored the genetic correlations between different psychiatric disorder subtypes and CVDs, including coronary artery disease (CAD), type 2 diabetes (T2DM), and stroke, highlighting possible links between these conditions.

MR analysis

MR is a method that leverages genetic variants as 'instruments' to represent the exposure for inferring causal relationships between risk factors and outcomes. We performed MR to estimate the causal effects of the studied psychiatric entities on various CVDs, testing the hypothesis that comorbidity amplifies cardiovascular risk. This analysis was included to provide clinical and translational insights into the comorbidities. A two-sample MR design was employed, using both inverse-variance weighted (MR-IVW) (Bowden, Davey Smith, Haycock, & Burgess, 2016) and Egger regression (MR-Egger) (Burgess & Thompson, 2017) approaches. The number of genetic variants included in the MR analysis may influence the causal estimates. To ensure the robustness of our findings, we performed MR at multiple r^2 thresholds (0.001, 0.01, 0.05, and 0.1), taking SNP correlations into account.

Psychiatric disorders studied

We applied CombGWAS to examine seven different psychiatric disorders and obesity, namely: Alzheimer's disease (AD), attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), anxiety disorders, insomnia, MDD, obesity, and SCZ. The datasets used are shown in Supplementary Table S1. Using CombGWAS, we estimated the effect sizes (ORs), standard errors (SEs), and corresponding p-values for each disease combination for genome-wide SNPs.

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Our selection of disorders was guided by a deliberate strategy focusing on three key criteria, chosen to maximize the clinical and scientific relevance of our findings (as shown below).

Disorder selection criteria:

1. **High rates of clinical co-occurrence**. We prioritized disorders that frequently co-occur in clinical practice (Bard et al., 2023; Hirschfeld, 2001; Hours, Recasens, & Baleyte, 2022; Staner, 2010). The National Comorbidity Survey Replication (NCS-R) has consistently demonstrated that a substantial proportion of individuals with one psychiatric disorder will meet the criteria for at least one other disorder in their lifetime (Kessler & Merikangas, 2004). For example, MDD and anxiety disorders were selected for exceptionally high comorbidity rates (Hirschfeld, 2001; Kessler & Merikangas, 2004).
2. **Significant impact on patient outcomes and treatment**. We chose pairings where the comorbidity is known to exacerbate illness severity and complicate clinical management (e.g. see Kraus et al., 2023; McWhinney et al., 2022). The presence of comorbidity between the selected disorders may be associated with poorer clinical outcomes, increased functional impairment, and greater healthcare utilization (GBD 2019; Mental Disorders Collaborators, 2022). For example, examining MDD/SCZ with and without obesity is crucial for understanding factors that can lengthen psychiatric hospitalizations and worsen long-term physical outcomes (Kraus et al., 2023; McWhinney et al., 2022).
3. **Representation of distinct but overlapping domains of psychopathology**. The selected pairs serve as critical case studies for understanding the interplay between different, yet often intersecting, biological and psychological domains (Doherty & Owen, 2014; dos Santos Durães, Yokomizo, Saffi, & de Almeida Rocca, 2022; Fisher, Dunn, & Dong, 2024). For instance, studying comorbid MDD and SCZ provides a model for exploring the shared genetics and neural circuits underlying both affective and psychotic disorders.

We analyzed the genetic basis for 16 (or 8 pairs) psychiatric entities, with a primary focus on MDD and SCZ. The psychiatric entities include ADHD with and without comorbid ASD, MDD with and without AD, MDD with and without anxiety disorders, MDD with and without ASD, MDD with and without insomnia, MDD with and without obesity, MDD with and without SCZ, and SCZ with and without obesity.

Results

Overview

Table 1 demonstrates the independent significant SNPs (p <5e−08, r^2 < 0.6) and genomic risk loci for the eight comorbid psychiatric disorders and eight single psychiatric entities (single psychiatric disorder without a particular comorbid disorder). Our analysis revealed a total of 954 independent significant SNPs, mapped to 325 genomic risk loci, for the 8 *comorbid* psychiatric disorders (Figures 1 and 2, Table 1, and Supplementary Table S2). In addition, we identified 934 independent significant SNPs mapped to 328 genomic risk loci for the 8 *single* psychiatric entities without a comorbidity.

The identified susceptibility genetic variants were mapped to genes by MAGMA. We identified both subtype-specific and shared susceptibility genes, loci, and pathways across psychiatric disorder subtypes. Supplementary Table S3 provides additional details of the shared and nonshared genes associated with the psychiatric entities studied.

Tissue enrichment analysis

We conducted a tissue enrichment analysis using the FUMA tool, leveraging a precomputed list of differentially expressed genes (DEGs) across various tissues obtained from GTEx. The input consisted of significant genes identified in GWASs (via MAGMA), which were then tested for enrichment among these DEGs. We view this analysis as hypothesis-generating, as differential expression does not necessarily imply a causal role for the tissue.

Supplementary Figures S1 and S2 show the tissue enrichment analysis results for all 16 psychiatric entities studied. We observed that all the entities showed enrichment predominantly in the brain tissues. Interestingly, the basal ganglia emerged as the top-enriched tissue for all psychiatric entities involving ADHD or ASD. Abundant evidence supports its critical role in maintaining normal motor actions and cognitive functions (Damasio & Maurer, 1978; Graybiel, 2008; Jin & Costa, 2015). In a study by Curtin et al. (2018), ADHD was associated with a 2.4-fold increased risk of basal ganglia diseases. Notably, subtype-specific tissue enrichment was observed across different subtype pairs. For instance, significant enrichment of brain amygdala was only observed in ADHD with ASD (Supplementary Figures S1 and S2).

Another intriguing finding is that the cerebellum was the top-enriched tissue for all disease combinations involving MDD. A growing body of research has demonstrated its involvement in impaired cognitive function and emotion dysregulation (Depping, Schmitgen, Kubera, & Wolf, 2018; Depping et al., 2020; Hoche, Guell, Vangel, Sherman, & Schmahmann, 2018). Compared to other psychiatric entities involving MDD, the two entities involving obesity

Table 1. Number of identified independent significant SNPs and genomic risk loci for different combinations of psychiatric disorders

First trait	No. of ind. sig. SNPs	Second trait	No. of ind. sig. SNPs	Loci (first trait only | second trait only | shared	Gene (first trait only | second trait only | shared	Pathways (first trait only | second trait only| shared
ADHD with ASD	20	ADHD without ASD	23	18|11|1	22|49|20	1|9|0
MDD with AD	148	MDD without AD	153	31|47|6	189|411|307	26|3|98
MDD with anxiety	209	MDD without anxiety	139	48|27|25	346|63|643	6|9|97
MDD with ASD	3	MDD without ASD	149	3|54|0	25|74|19	0|104|0
MDD with insomnia	111	MDD without insomnia	111	46|37|2	517/307/263	25|22|81
MDD with obesity	50	MDD without obesity	44	21|21|0	126|271|23	6|87|0
MDD with SCZ	330	MDD without SCZ	146	95|52|0	2054|337|423	48|13|39
SCZ with obesity	83	SCZ without obesity	169	29|48|0	320|1239|517	9|21|100

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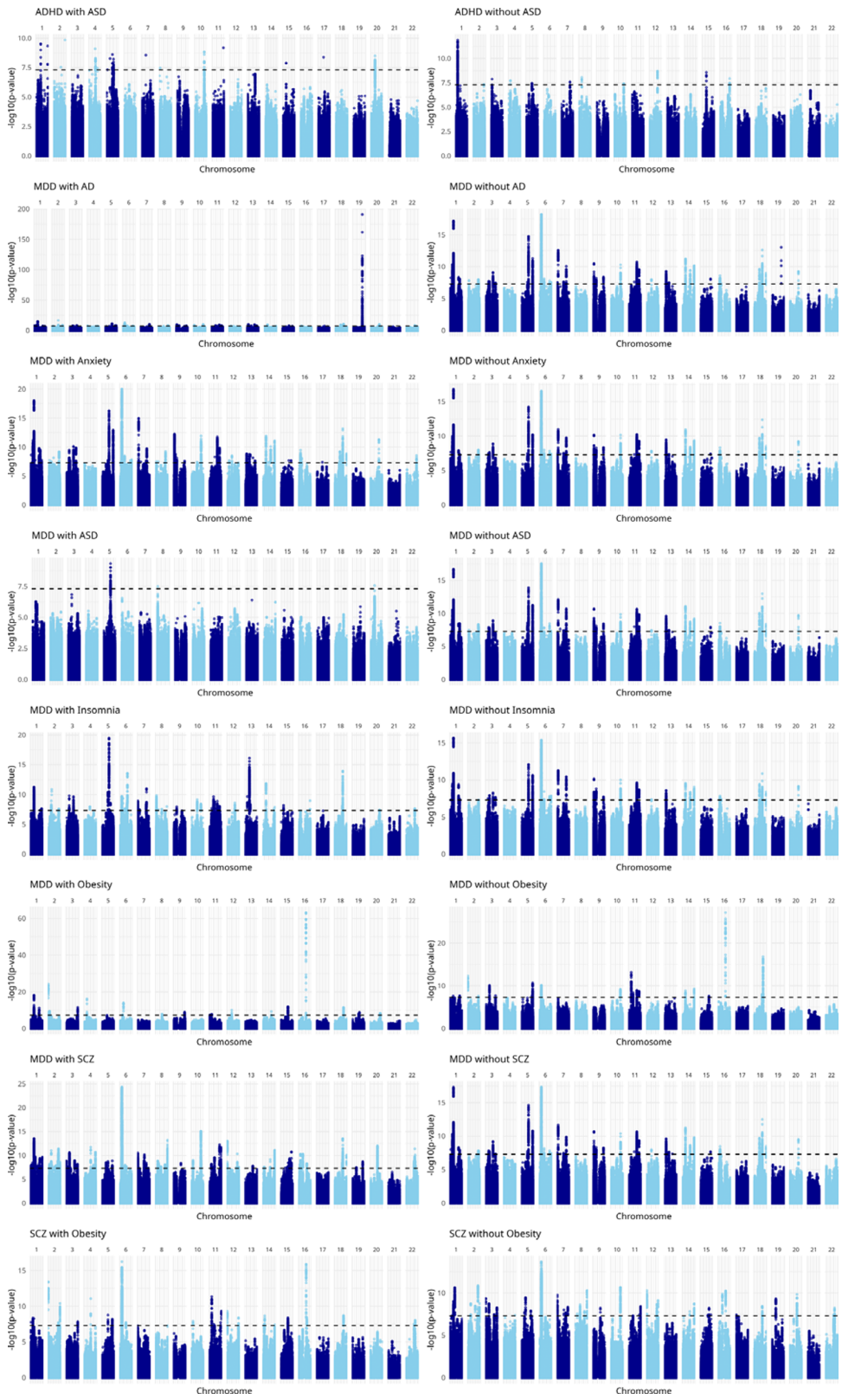

Figure 1. Manhattan plots of GWAS results for 16 psychiatric entities.
Note: ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; MDD, major depressive disorder; SCZ, schizophrenia.

(i.e. MDD with obesity and MDD without obesity) exhibited a lower number of enriched brain tissues, with the cerebellar hemisphere ranked as the top-enriched tissue.

Pathway enrichment analysis

We conducted pathway enrichment analysis using the web tool ConsensusPathDB (Supplementary Table S4). We observed a

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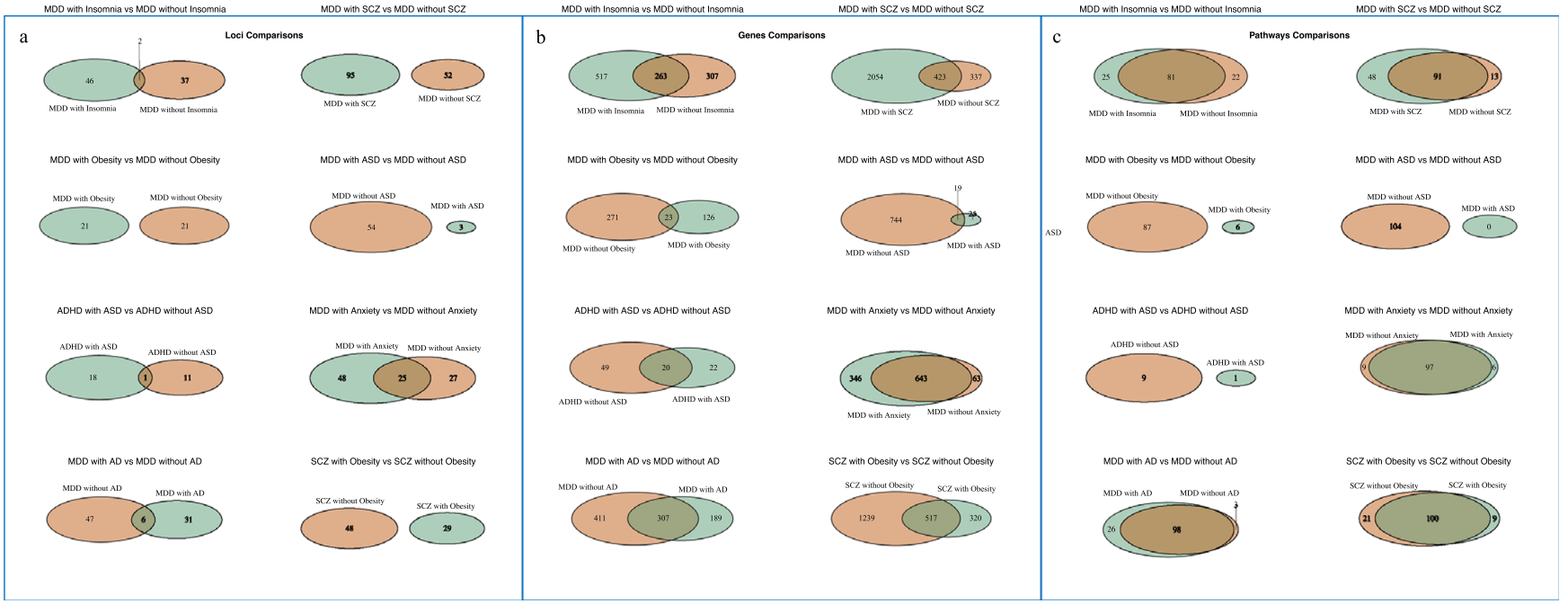

Figure 2. Number of shared genomic risk loci, genes, and pathways across eight pairs of subtypes.

mixture of shared and condition-specific enriched pathways across different psychiatric entities. For instance, 'Signaling by Nuclear Receptors' was one of the top-enriched pathways shared between MDD with AD and MDD without AD. In a previous study, Fries, Saldana, Finnstein, and Rein (2023) have highlighted the critical role of this pathway in coordinating an organism's response to stress, a major risk factor for MDD. Additionally, Mandrekar-Colucci and Landreth (2011) identified nuclear receptors as a promising therapeutic target for AD, as they could regulate microglial activation and mitigate the brain's inflammatory responses.

The cardiolipin biosynthesis pathway was specifically enriched in MDD with AD. Alterations in cardiolipin content, structure, and localization have been reported to be associated with impaired neurogenesis and neuronal dysfunction (Falabella, Vernon, Hanna, Claypool, & Pitceathly, 2021), contributing to neurodegenerative diseases.

Notably, we did not find any common pathways between ADHD with and without ASD, as well as between MDD with and without ASD.

We also conducted enrichment analyses based on *subtype-specific* genes to elucidate subtype-specific biology (Supplementary Table S5). For example, neuronal system, nervous system development, dopaminergic synapse, and brain-derived neurotrophic factor signaling pathway are the top-enriched pathways specific to MDD with SCZ. This finding aligns well with established knowledge that both disorders are linked to disruptions in neuroplasticity (Angelucci, Brene, & Mathe, 2005; Delva & Stanwood, 2021).

Cell type enrichment analysis

Cell type enrichment analyses were also performed to uncover the involved cell types for each studied disease combination (Figure 3). However, since not all cell types were available for analysis in FUMA, our results should be considered exploratory. We found that GABAergic neurons were the most enriched cell type most psychiatric entities. Fogaça and Duman (2019) reported decreased expression of GABAergic interneuron markers in the frontal cortex could result in depressive-like behaviors. Moreover, impaired GABAergic neurotransmission has been implicated in patients with depression, prompting the development of therapeutic strategies targeting this deficit (Duman, Sanacora, & Krystal, 2019). Notably, the top-enriched cell types identified for the psychiatric disease combinations were located in brain tissues. Psychiatric disorder combinations showed significant immune cell type enrichments (Supplementary Table S6), consistent with established immune dysregulation in these disorders (Gibney & Drexhage, 2013; Iakunchykova, Leonardsen, & Wang, 2024).

Drug enrichment analysis

To further explore the homogeneity and heterogeneity underlying the studied psychiatric entities, we performed drug enrichment analysis on the susceptibility gene sets identified for each disease combination (Supplementary Tables S7 and S8). This analysis is considered exploratory or hypothesis-generating, as further experimental validations are required. Some enriched drugs were unique to particular psychiatric entities, while others were shared across different psychiatric entities. For example, chlorprothixene (a typical antipsychotic) was one of the top-enriched drugs specific to ADHD and ASD. Antipsychotics are often prescribed in ASD (Posey, Stigler, Erickson, & McDougle, 2008) for irritability and associated behaviors including aggression and self-injury. Antipsychotics are also sometimes prescribed in ADHD due to other comorbid conditions, especially behavior problems (Lee, Zhang, & Rose, 2022). Romidepsin was another top-enriched drug specific to ADHD with ASD based on subtype-specific genes. Qin et al. (2018) showed its potential in alleviating social deficits in mouse models. Among all disease combinations involving MDD, except for MDD with ASD, fendiline was among the top-enriched drugs. Interestingly, a previous study (So, Chau, Lau, Wong, & Zhao, 2019) suggested fendiline as a promising repurposing drug for patients with MDD.

Genetic correlation among psychiatric disorder subtypes and CVDs

We calculated genetic correlations between pairs of psychiatric entities with and without particular comorbid conditions (Table 2). The results (rg ranging from 0.1664 to 1.0271) revealed moderate- tohigh genetic correlations in most pairs, suggesting shared genetic architecture. For instance, MDD with anxiety disorder exhibited a high genetic correlation with MDD without anxiety disorder (rg = 0.9964). Similarly, a high genetic correlation was also observed between SCZ with and without obesity (rg = 0.9016). Interestingly, MDD with obesity only displayed a weak genetic correlation with MDD without obesity, implying that they may represent *distinct biological subtypes* of MDD (rg = 0.1663).

To further investigate the genetic overlap between psychiatric entities and CVDs, we analyzed their genetic correlations by LDSR (Table 3 and Supplementary Table S9). We prioritize subtype pairs with distinct genetic architectures. As shown in Table 3, most 'pairs' of psychiatric subtypes (i.e. a disorder with and without a comorbidity) exhibited significantly different genetic correlations with CVDs, indicating distinct genetic relationships.

Interestingly, some psychiatric subtypes displayed opposite genetic correlations with the same CVD. For example, while SCZ with obesity exhibited a positive genetic correlation with T2DM (rg = 0.2481), SCZ without obesity demonstrated a negative genetic correlation with T2DM (rg = −0.1539). Similarly, SCZ with and without obesity displayed opposing genetic correlations with CAD. Notably, the genetic correlations between 'unsubtyped' (originally defined) psychiatric disorders and CVDs generally lie between those for 'subtyped' (comorbid or only single) disorders. These findings highlight the complex interactions between genetic factors associated with psychiatric entities and CVDs, indicating potential distinct genetic signatures for different psychiatric subtypes.

Results of MR analysis

MR analysis was conducted to investigate whether a certain psychiatric disease combination is causally linked to a significantly higher or lower risk of cardiovascular outcomes. Most results were consistent across different r^2 cutoffs. For simplicity, we primarily report analysis results at $r^2 = 0.001, p = 5E-08$, which are standard settings in TwoSampleMR. Table 4 summarizes the results (Supplementary Table S10 for full results). It is noteworthy that with a binary exposure, the causal estimate (OR) reflects the average effect on the outcome associated with a 2.72-fold increase in the prevalence of the exposure (e.g. an increase in exposure prevalence from 1 to 2.72%) (Burgess & Labrecque, 2018).

Many studied psychiatric disorder combinations exhibited a significant causal relationship with increased risks of CVDs. Importantly, the magnitude of effect sizes varies across different psychiatric disorder subtypes. For example, both MDD with and without anxiety were found to be causally linked to significantly increased CAD risks. The OR of MDD with anxiety on CAD is

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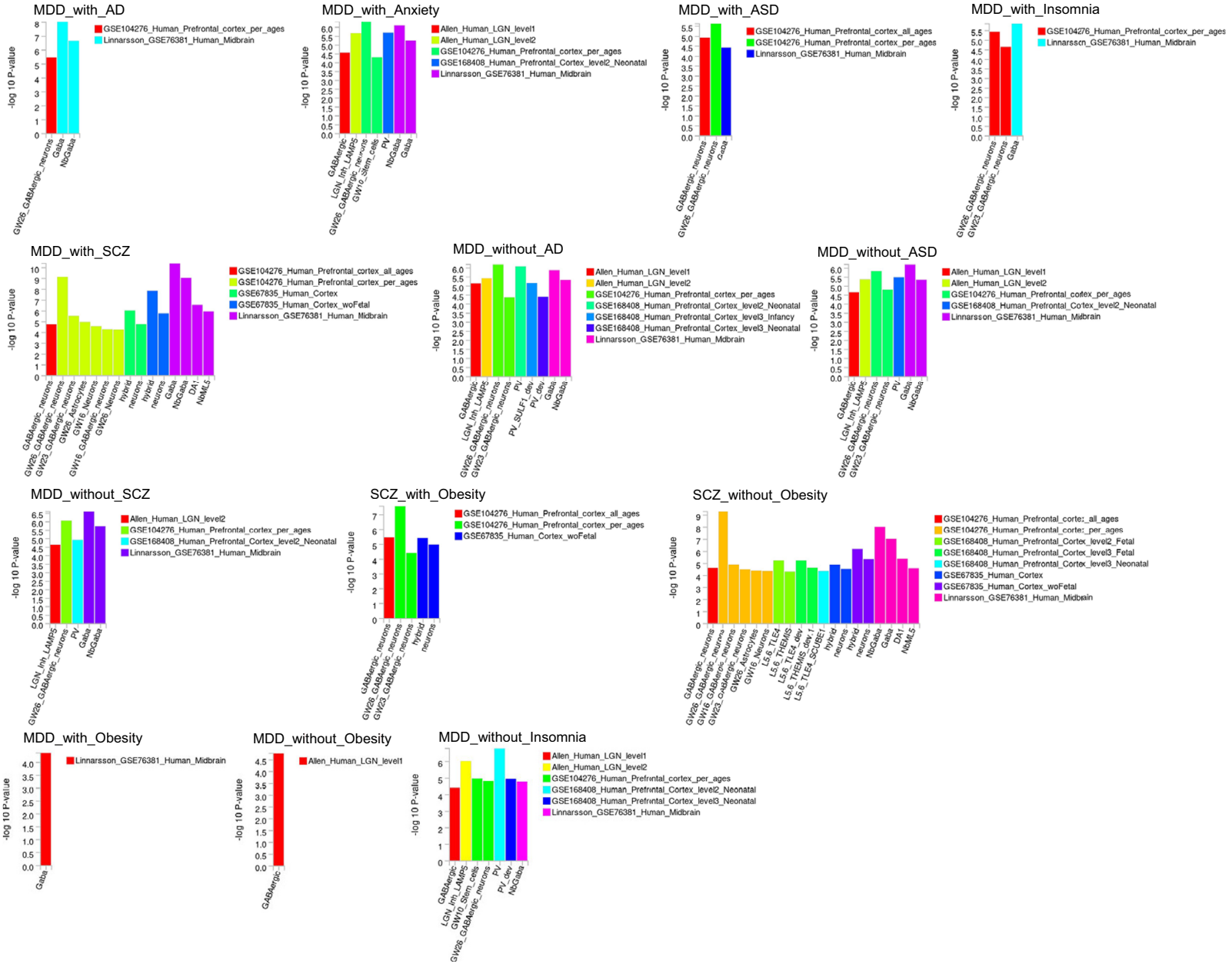

Figure 3. Cell type enrichment analysis results for each studied psychiatric disease combination.

Table 2. Genetic correlation between different psychiatric entities

First trait	Heritability	Second trait	Heritability	rg	p (rg = 0)	p (rg = 1)
MDD with AD	0.0813 (0.0047)	MDD without AD	0.0959 (0.0038)	1.0255 (0.0265)	0	3.36E−01
MDD with anxiety	0.2273 (0.0092)	MDD without anxiety	0.2044 (0.0082)	0.9964 (0.001)	0	3.18E−04
SCZ with obesity	0.1718 (0.0058)	SCZ without obesity	0.2693 (0.0088)	0.9016 (0.0133)	0	1.38E−13
ADHD with ASD	0.2230 (0.0154)	ADHD without ASD	0.2507 (0.0160)	0.8167 (0.0163)	0	0
MDD with insomnia	0.1216 (0.0044)	MDD without insomnia	0.0993 (0.004)	0.7915 (0.0117)	0	0
MDD with ASD	0.1210 (0.0069)	MDD without ASD	0.2704 (0.0113)	0.6830 (0.0214)	6.50E−224	0
MDD with SCZ	0.2296 (0.0074)	MDD without SCZ	0.058 (0.0041)	0.5713 (0.0172)	9.05E−243	0
MDD with obesity	0.1936 (0.0083)	MDD without obesity	0.2183 (0.0091)	0.1663 (0.0309)	7.08E−08	0

Note: rg indicates the calculated genetic correlation between two disease 'subtypes'. p (rg = 0) refers to the p-value by testing whether the rg differs from zero; p (rg = 1) refers to the p-value by testing whether the rg differs from 1.

$2.106\,(\mathrm{MR-IVW}, p = 2.35\mathrm{E}-05)$, while that of MDD without anxiety on CAD is $1.108\,(\mathrm{MR-Egger}, p = 3.78\mathrm{E}-05)$.

Additionally, we found that comorbid psychiatric disorders often had stronger causal effects on cardiovascular outcomes than single disorders. For example, MDD with insomnia was causally linked to a significantly increased risk of CAD with an OR of $3.721\,(\mathrm{MR-IVW}, p = 1.72\mathrm{E}-06)$, while MDD without insomnia had a much lower OR of $1.054\,(\mathrm{MR-IVW}, p = 2.71\mathrm{E}-03)$.

Both obese MDD and obese SCZ, but not nonobese MDD or SCZ, were found to be causally linked to increased T2DM risk, highlighting obesity's role in amplifying CVD liability. Specifically, obese MDD and obese SCZ were linked to T2DM risk with ORs of $5.418\,(\mathrm{MR-IVW}, p = 3.58\mathrm{E}-06)$ and $1.364\,(\mathrm{MR-Egger}, p = 2.81\mathrm{E}-03)$, respectively. In contrast, nonobese MDD ($\mathrm{MR-Egger}, \mathrm{OR} = 0.292, p = 9.87\mathrm{E}-04$) and nonobese SCZ ($\mathrm{MR-Egger}, \mathrm{OR} = 0.948, p = 2.58\mathrm{E}-02$) were associated with significantly *decreased* T2DM risk.

The above results underscore the complex causal relationships between specific psychiatric disease combinations and various cardiovascular outcomes.

Discussion

Overview

This study represents a conceptual and methodological advance in psychiatric genetics, moving beyond the identification of genetic risk factors of individual disorders to the direct delineation of clinical heterogeneity. While prior research established that psychiatric disorders share a polygenic architecture, the exact genetic basis of comorbid disorders has not been investigated systematically. Our work demonstrates that a specific comorbidity can fundamentally alter a disorder's genetic signature and its relationship with other health outcomes.

A key innovation of this approach is its ability to reveal clinically vital genetic relationships that are undetectable with standard methods. For instance, our analysis shows that the genetic risk for T2DM is positively correlated with SCZ with comorbid obesity, yet negatively correlated with SCZ without obesity. This novel finding provides proof of concept for a genetically informed nosology, suggesting that 'metabolically normal' and 'metabolically abnormal' SCZ may be distinct biological subtypes. The same also applies to MDD. This distinction has immediate implications for patient stratification and the clinical management of cardiovascular risk. By demonstrating this principle across multiple disorder pairs, we also revealed distinct loci, divergent health relationships, and unique pathway enrichments for various psychiatric disorder combinations. These findings are largely unreported in previous studies. This work provides a roadmap toward precision psychiatry, laying the foundation for subtype-specific biomarkers and personalized therapies.

Unique genetic underpinnings of psychiatric disorder subtypes

A key finding of this study is the demonstration of distinct genetic underpinnings of psychiatric disorder subtypes. The proportion of subtype-specific loci/SNPs varies across psychiatric entity pairs, with the smallest proportion exceeding 50%. We observed a slightly different pattern for subtype-specific genes, with proportions ranging between 8.9 and 97.5%, but most subtypes showed over 50% unique genes. These genes provide insights into the subtype-specific biological mechanisms and pathophysiology. For instance, *KDM4A* and *SEMA6D* emerged as top susceptibility genes only in ADHD without ASD, indicating the unique genetic underpinnings for ADHD subtypes. In a recent study, Guo et al. (2024) revealed KDM4A as a negative regulator of engram formation for memory separation. These subtype-specific susceptibility genes could be utilized in the differentiation between subtypes and inform targeted treatment strategies.

Furthermore, we performed a comprehensive analysis of enriched pathways, cell types, and drugs based on the GWAS results. These enrichment analyses shed light on the potential biological mechanisms and pathways involved in the development and manifestation of specific subtypes. We also revealed some interesting patterns. For example, although we observed high proportions of subtype-specific genes for MDD with insomnia and MDD without insomnia, the proportion of subtype-specific pathways was lower. These findings suggest that a high proportion of subtype-specific genes does not always translate to a similarly high proportion of unique pathways. For example, it can possibly be due to different combinations of genes corresponding to different pathways.

Genetic correlations among disease subtypes and CVDs

The majority of disease subtypes exhibited high ($\mathrm{rg} \geq 0.8$) or moderate ($0.4 \leq \mathrm{rg} < 0.8$) correlation with one another. Among the eight pairs of subtypes examined, only one pair, that is, MDD with obesity versus MDD without obesity, demonstrates a weak correlation. Despite their high genetic correlations, most subtypes exhibited distinct genetic correlations with the same CVD. Some

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Table 3. Genetic correlation between psychiatric entities and cardiovascular diseases

First trait	Second trait	rg	*p*
SCZ with obesity	CAD	0.1014 (0.0247)	**3.89E−05**
SCZ	CAD	−0.0239 (0.0229)	2.98E−01
SCZ without obesity	CAD	−0.0709 (0.0243)	**3.50E−03**
SCZ with obesity	Stroke	0.1189 (0.0369)	**1.2E−03**
SCZ	Stroke	0.0476 (0.0332)	1.52E−01
SCZ without obesity	Stroke	0.0549 (0.0382)	1.50E−01
SCZ with obesity	T2DM	0.2481 (0.0226)	**4.42E−28**
SCZ	T2DM	−0.0471 (0.0177)	**7.7E−03**
SCZ without obesity	T2DM	−0.1539 (0.0382)	**6.79E−12**
MDD with obesity	CAD	0.2795 (0.0302)	**2.40E−20**
MDD	CAD	0.1988 (0.025)	**1.92E−15**
MDD without obesity	CAD	0.0323 (0.0253)	2.02E−01
MDD with obesity	Stroke	0.1651 (0.0396)	**3.03E−05**
MDD	Stroke	0.0717 (0.0416)	*8.46E−02*
MDD without obesity	Stroke	−0.0279 (0.0419)	5.05E−01
MDD with obesity	T2DM	0.5041 (0.0273)	**4.48E−76**
MDD	T2DM	0.1395 (0.0212)	**4.72E−11**
MDD without obesity	T2DM	−0.1895 (0.0273)	**3.47E−12**
MDD without insomnia	CAD	0.1868 (0.0271)	**5.49E−12**
MDD	CAD	0.1988 (0.025)	**1.92E−15**
MDD with insomnia	CAD	0.2564 (0.0275)	**1.13E−20**
MDD without SCZ	CAD	0.2009 (0.0247)	**4.57E−16**
MDD	CAD	0.1988 (0.025)	**1.92E−15**
MDD with SCZ	CAD	0.0432 (0.0228)	*5.84E−02*
MDD without ASD	CAD	0.2065 (0.0269)	**1.49E−14**
MDD	CAD	0.1988 (0.025)	**1.92E−15**
MDD with ASD	CAD	0.0369 (0.0326)	2.57E−01
MDD without ASD	Stroke	0.0766 (0.0429)	**7.43E−02**
MDD	Stroke	0.0717 (0.0416)	**8.46E−02**
MDD with ASD	Stroke	−0.0587 (0.0515)	2.54E−01
ADHD without ASD	CAD	0.2815 (0.0344)	**2.67E−16**
ADHD	CAD	0.2793 (0.0342)	**2.99E−16**
ADHD with ASD	CAD	0.1508 (0.0355)	**2.19E−05**
ADHD without ASD	Stroke	0.2131 (0.0543)	**8.72E−05**
ADHD	Stroke	0.2098 (0.0543)	**1.00E−04**
ADHD with ASD	Stroke	0.0752 (0.0594)	2.06E−01
ADHD without ASD	DM	0.3220 (0.0277)	**2.90E−31**
ADHD	DM	0.3205 (0.0275)	**1.86E−31**
ADHD with ASD	DM	0.2326 (0.0281)	**1.11E−16**

Note: rg indicates the calculated genetic correlation between two psychiatric disorder subtypes and cardiovascular diseases. *Results for* MDD + AD and MDD + ANX are not included due to space limits. Bold values indicate a *p*-value of ≤ 0.05, while italic values represent a *p*-value between 0.05 and 0.1. We included full results in Supplementary Table S9a.

pairs even displayed entirely opposing genetic correlations, particularly those subtype pairs that involved obesity. These findings suggest that the psychiatric disorder combinations we studied may represent biologically distinct subtypes with both shared and unique genetic signatures.

Evidence indicates that normal weight may protect against CVDs (Powell-Wiley et al., 2021), potentially counteracting the elevated risks of CVD conferred by psychiatric disorders. This aligns with the observed opposing or weak genetic correlations between nonobese psychiatric disorders and CVD.

Varying causal effects of different psychiatric disorder subtypes on cardiovascular outcomes

While many psychiatric disorder combinations showed increased CVD risks, comorbid disorders typically demonstrated stronger causal effects than single disorders. This highlights the importance of considering the cumulative impact of comorbid disorders on cardiovascular health.

Of note, obese and nonobese MDD/SCZ showed opposite causal effects on T2DM risk. Obesity in MDD or SCZ enhances CVD risk, informing targeted interventions (e.g. weight management). These findings underscore the need for more comprehensive and personalized screening, prevention, and treatment strategies that address both psychiatric and cardiovascular conditions in individuals with comorbidities.

Integrated genetic insights from multiple levels of analysis

In this study, we employed a comprehensive series of complementary analyses to elucidate both shared and distinct genetic architectures across psychiatric disorder subtypes. Our multilevel approach, encompassing GWAS, gene, pathway, cell type, drug enrichment analyses, genetic correlation, and MR, provided an in-depth understanding by revealing both convergent and divergent biological mechanisms underlying psychiatric disorder combinations.

For instance, several lines of evidence converged to highlight specific biological mechanisms for subtypes of ADHD. Both gene-based analyses (implicating *KDM4A*) (Guo et al., 2024) and pathway analyses (implicating, e.g. synaptic vesicle cycle) (Wang et al., 2025) independently pointed toward memory-related mechanisms in ADHD without ASD. This convergence across different analytical levels strongly suggests that memory formation and related processes may represent a distinct etiological pathway for this subtype.

Notably, our multimethod approach also revealed instructive divergences between analytical findings, which are equally crucial for a comprehensive understanding. For example, while genetic correlation analysis indicated a high degree of genetic similarity between MDD with AD and MDD without AD ($rg = 1.0255, \mathrm{SE} = 0.0265$), the MR analysis revealed significantly different causal effects on diabetes mellitus ($\mathrm{OR} = 0.712, p = 2.14\mathrm{E}-05$ for MDD with AD versus $\mathrm{OR} = 1.224, p = 4.23\mathrm{E}-03$ for MDD without AD). This example illustrates that conditions sharing substantial underlying genetic risk factors (high rg) may nonetheless exert differential downstream causal effects on other health outcomes. It should be noted that even if rg is high, the actual effect sizes (beta) of SNPs for traits 1 and 2 can still differ, for example, when the LD structure and allele frequencies differ across the two cohorts, or when heritabilities differ between the two traits.

Furthermore, the contrasting causal effects observed in the MR analysis for obese versus nonobese MDD/SCZ on T2DM risk (e.g. obese MDD increasing T2DM risk while nonobese MDD decreasing it) provide another example of how the same psychiatric disorder may have substantially different clinical consequences depending on the comorbidity status, which can be fully appreciated by integrating genetic correlation and MR findings.

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Table 4. MR analysis results for cardiovascular outcomes

Exposure	Outcome	OR (2.72 times of exposure prevalence)	*p*	Exposure	Outcome	OR (2.72 times of exposure prevalence)	*p*
ADHD with ASD	CAD	1.350	2.04E−01	ADHD without ASD	CAD	1.047	2.71E−01
ADHD with ASD	DM	0.312	**8.05E−02**[a]	ADHD without ASD	DM	1.102	**1.58E−05**
ADHD with ASD	Stroke	1.680	**4.84E−02**	ADHD without ASD	Stroke	1.083	**4.76E−02**
MDD with AD	CAD	1.310	**1.97E−10**	MDD without AD	CAD	0.594	1.1.3E−01[a]
MDD with AD	DM	0.712	**2.14E−05**[a]	MDD without AD	DM	1.224	**4.23E−03**
MDD with AD	Stroke	1.059	3.87E−01	MDD without AD	Stroke	1.037	5.36E−01
MDD with anxiety	CAD	2.106	**2.35E−05**	MDD without anxiety	CAD	1.108	**3.78E−05**
MDD with anxiety	DM	1.917	**3.03E−03**	MDD without anxiety	DM	1.109	**3.76E−04**
MDD with anxiety	Stroke	1.537	***5.79E−02***	MDD without anxiety	Stroke	1.045	1.56E−01
MDD with ASD	CAD	1.088	1.69E−01	MDD without ASD	CAD	1.184	**3.60E−05**
MDD with ASD	DM	1.007	9.82E−01	MDD without ASD	DM	1.166	**1.99E−03**
MDD with ASD	Stroke	1.062	5.90E−01	MDD without ASD	Stroke	1.058	2.70E−01
MDD with insomnia	CAD	3.721	**1.72E−06**	MDD without insomnia	CAD	1.054	**2.71E−03**
MDD with insomnia	DM	2.115	**1.59E−02**	MDD without insomnia	DM	1.056	**7.31E−03**
MDD with insomnia	Stroke	1.340	2.67E−01	MDD without insomnia	Stroke	1.027	2.46E−01
MDD with obesity	CAD	1.365	**1.81E−07**	MDD without obesity	CAD	0.919	1.94E−01
MDD with obesity	DM	5.418	**3.58E−06**[a]	MDD without obesity	DM	0.292	**9.87E−04**[a]
MDD with obesity	Stroke	1.078	2.09E−01	MDD without obesity	Stroke	0.943	***8.52E−02***
MDD with SCZ	CAD	1.059	2.28E−01	MDD without SCZ	CAD	1.211	**4.64E−05**
MDD with SCZ	DM	0.964	3.63E−01	MDD without SCZ	DM	1.182	**3.52E−03**
MDD with SCZ	Stroke	1.031	4.92E−01	MDD without SCZ	Stroke	1.061	3.28E−01
SCZ with obesity	CAD	1.117	**1.83E−02**	SCZ without obesity	CAD	1.156	**2.91E−02**[a]
SCZ with obesity	DM	1.364	**2.81E−03**	SCZ without obesity	DM	0.948	**2.58E−02**
SCZ with obesity	Stroke	1.106	***6.94E−02***	SCZ without obesity	Stroke	1.009	5.43E−01

Note: MR analysis results were primarily based on MR-IVW.

[a]The causal analysis results were derived from MR-Egger instead of MR-IVW due to the presence of imbalanced horizontal pleiotropy, as indicated by a significant Egger intercept. Since the exposure is binary, the OR represents the average effect to the outcome if the exposure prevalence (prevalence) is increased by 2.72 times. Bold values indicate a *p*-value of ≤ 0.05, while italic values represent a *p*-value between 0.05 and 0.1.

Limitations

This study has several limitations. First, the GWAS summary statistics used were primarily derived from European samples. As such, some results may be population-specific and may not be generalizable to non-European groups. This limitation may be mitigated with the availability of summary statistics from other ethnic groups. While our analysis provides valuable insights into the genetic signatures underlying different psychiatric disease subtypes, further exploration is required to validate these findings. Replication studies using independent cohorts and individuals with comorbid conditions, as well as more diverse populations, would enhance the robustness and generalizability of the observed genetic associations. Besides, our study only included a limited number of psychiatric disease combinations. Also, the biological mechanisms underlying the psychiatric disorder subtypes will require further experimental studies.

Another limitation is that substantial differences in heritabilities and sample sizes between the trait pairs may influence the results. Large disparities between traits could disproportionately bias the contribution toward traits with higher heritabilities or sample sizes. For example, given two traits (A and B), if A is much more heritable and the sample size is larger, the genetic architecture of A + B (comorbidity) may be biased toward that of trait A itself. This concern may be particularly relevant for highly heritable disorders with large available sample sizes, such as SCZ.

Conclusions

To conclude, our study successfully identified the genetic basis and risk genes for eight pairs of psychiatric disease subtypes. Secondary analyses, including pathway, cell type, and drug enrichment analyses, provided further biological insights into the pathophysiology of these disorder subtypes. Genetic correlation and MR analyses shed light on the links of these subtypes with various CVDs, which may have important clinical implications. Furthermore, the identified nonshared susceptibility genes may provide a way to differentiate the different 'subtypes'.

Future research should incorporate data from diverse ethnic groups, conduct replication studies, and perform functional investigations to enhance the robustness and generalizability of the observed genetic associations. By elucidating the genetic basis of a wide variety of psychiatric disorder subtypes, our study paves the

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way for the development of personalized treatment and preventive strategies for individuals affected by these complex disorders.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291725101396.

Data availability statement. The GWAS summary statistics of the studied disorders were downloaded from publicly available databases.

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Competing interests. The authors declare none.

References

Angelucci, F., Brene, S., & Mathe, A. A. (2005). BDNF in schizophrenia, depression and corresponding animal models. *Molecular Psychiatry*, **10**(4), 345–352.

Bard, H. A., O'Driscoll, C., Miller, C. B., Henry, A. L., Cape, J., & Espie, C. A. (2023). Insomnia, depression, and anxiety symptoms interact and individually impact functioning: A network and relative importance analysis in the context of insomnia. *Sleep Medicine*, **101**, 505–514.

Bowden, J., Davey Smith, G., Haycock, P. C., & Burgess, S. (2016). Consistent estimation in mendelian randomization with some invalid instruments using a weighted median estimator. *Genetic Epidemiology*, **40**(4), 304–314.

Bulik-Sullivan, B. K., Loh, P., Finucane, H. K., Ripke, S., Yang, J., Schizophrenia Working Group of the Psychiatric Genomics Consortium, Patterson, N., Daly, M. J., Price, A. L., & Neale, B. M. (2015). LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature Genetics*, **47**(3), 291–295.

Burgess, S., & Labrecque, J. A. (2018). Mendelian randomization with a binary exposure variable: Interpretation and presentation of causal estimates. *European Journal of Epidemiology*, **33**, 947–952.

Burgess, S., & Thompson, S. G. (2017). Interpreting findings from mendelian randomization using the MR-egger method. *European Journal of Epidemiology*, **32**, 377–389.

Choi, S. W., Mak, T. S., & O'Reilly, P. F. (2020). Tutorial: A guide to performing polygenic risk score analyses. *Nature Protocols*, **15**(9), 2759–2772.

Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *The Lancet*, **381** (9875), 1371–1379.

Curtin, K., Fleckenstein, A. E., Keeshin, B. R., Yurgelun-Todd, D. A., Renshaw, P. F., Smith, K. R., & Hanson, G. R. (2018). Increased risk of diseases of the basal ganglia and cerebellum in patients with a history of attention-deficit/hyperactivity disorder. *Neuropsychopharmacology*, **43** (13), 2548–2555.

Damasio, A. R., & Maurer, R. G. (1978). A neurological model for childhood autism. *Archives of Neurology*, **35** (12), 777–786.

Delva, N. C., & Stanwood, G. D. (2021). Dysregulation of brain dopamine systems in major depressive disorder. *Experimental Biology and Medicine*, **246**(9), 1084–1093.

Depping, M. S., Schmitgen, M. M., Bach, C., Listunova, L., Kienzle, J., Kubera, K. M., Roesch-Ely, D., & Wolf, R. C. (2020). Abnormal cerebellar volume in patients with remitted major depression with persistent cognitive deficits. *The Cerebellum*, **19**, 762–770.

Depping, M. S., Schmitgen, M. M., Kubera, K. M., & Wolf, R. C. (2018). Cerebellar contributions to major depression. *Frontiers in Psychiatry*, **9**, 634.

Doherty, J. L., & Owen, M. J. (2014). Genomic insights into the overlap between psychiatric disorders: Implications for research and clinical practice. *Genome Medicine*, **6**, 1–13.

dos Santos Durães, R. S., Yokomizo, J. E., Saffi, F., & de Almeida Rocca, C. C. (2022). Differential diagnosis findings between Alzheimer's disease and major depressive disorder: A review. *Psychiatry and Clinical Psychopharmacology*, **32**(1), 80.

Duman, R. S., Sanacora, G., & Krystal, J. H. (2019). Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. *Neuron*, **102**(1), 75–90.

Falabella, M., Vernon, H. J., Hanna, M. G., Claypool, S. M., & Pitceathly, R. D. (2021). Cardiolipin, mitochondria, and neurological disease. *Trends in Endocrinology & Metabolism*, **32**(4), 224–237.

Fisher, D. W., Dunn, J. T., & Dong, H. (2024). Distinguishing features of depression in dementia from primary psychiatric disease. *Discover Mental Health*, **4**(1), 3.

Fogaça, M. V., & Duman, R. S. (2019). Cortical GABAergic dysfunction in stress and depression: New insights for therapeutic interventions. *Frontiers in Cellular Neuroscience*, **13**, 87.

Fries, G. R., Saldana, V. A., Finnstein, J., & Rein, T. (2023). Molecular pathways of major depressive disorder converge on the synapse. *Molecular Psychiatry*, **28**(1), 284–297.

Gao, X., Qin, Y., Jiao, S., Hao, J., Zhao, J., Wang, J., Wen, Y., & Wang, T. (2024). Genetic evidence for the causal relations between metabolic syndrome and psychiatric disorders: A mendelian randomization study. *Translational Psychiatry*, **14**(1), 46.

GBD 2019 Diseases and Injuries Collaborators. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the global burden of disease study 2019. *The Lancet*, **396**(10258), 1204–1222.

GBD 2019 Mental Disorders Collaborators. (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the global burden of disease study 2019. *The Lancet Psychiatry*, **9**(2), 137–150.

Gibney, S. M., & Drexhage, H. A. (2013). Evidence for a dysregulated immune system in the etiology of psychiatric disorders. *Journal of Neuroimmune Pharmacology*, **8**(4), 900–920.

Goldfarb, M., De Hert, M., Detraux, J., Di Palo, K., Munir, H., Music, S., Piña, I., & Ringen, P. A. (2022). Severe mental illness and cardiovascular disease: JACC state-of-the-art review. *Journal of the American College of Cardiology*, **80**(9), 918–933.

Gorman, J. M. (1996). Comorbid depression and anxiety spectrum disorders. *Depression and Anxiety*, **4**(4), 160–168.

Graybiel, A. M. (2008). Habits, rituals, and the evaluative brain. *Annual Review of Neuroscience*, **31**, 359–387.

Guo, X., Hong, P., Xiong, S., Yan, Y., Xie, H., & Guan, J. (2024). Kdm4a is an activity downregulated barrier to generate engrams for memory separation. *Nature Communications*, **15**(1), 5887.

Herwig, R., Hardt, C., Lienhard, M., & Kamburov, A. (2016). Analyzing and interpreting genome data at the network level with ConsensusPathDB. *Nature Protocols*, **11**(10), 1889–1907.

Hiles, S. A., Révész, D., Lamers, F., Giltay, E., & Penninx, B. W. (2016). Bidirectional prospective associations of metabolic syndrome components with depression, anxiety, and antidepressant use. *Depression and Anxiety*, **33**(8), 754–764.

Hirschfeld, R. M. (2001). The comorbidity of major depression and anxiety disorders: Recognition and management in primary care. *Primary Care Companion to the Journal of Clinical Psychiatry*, **3**(6), 244.

Hoche, F., Guell, X., Vangel, M. G., Sherman, J. C., & Schmahmann, J. D. (2018). The cerebellar cognitive affective/Schaumann syndrome scale. *Brain*, **141**(1), 248–270.

Hours, C., Recasens, C., & Baleyte, J. (2022). ASD and ADHD comorbidity: What are we talking about? *Frontiers in Psychiatry*, **13**, 837424.

Iakunchykova, O., Leonardsen, E. H., & Wang, Y. (2024). Genetic evidence for causal effects of immune dysfunction in psychiatric disorders: Where are we? *Translational Psychiatry*, **14**(1), 63.

Jin, X., & Costa, R. M. (2015). Shaping action sequences in basal ganglia circuits. *Current Opinion in Neurobiology*, **33**, 188–196.

Kamburov, A., Stelzl, U., Lehrach, H., & Herwig, R. (2013). The ConsensusPathDB interaction database: 2013 update. *Nucleic Acids Research*, **41**(D1), D793–D800.

Kessler, R. C., & Merikangas, K. R. (2004). The national comorbidity survey replication (NCS-R): Background and aims. *International Journal of Methods in Psychiatric Research*, **13**(2), 60–68.

Kraus, C., Kautzky, A., Watzal, V., Gramser, A., Kadriu, B., Deng, Z., Bartova, L., Zarate Jr., C. A., Lanzenberger, R., Souery, D., Montgomery, S., Mendlewicz, J., Zohar, J., Fanelli, G., Serretti, A., & Kasper, S. (2023). Body mass index and clinical outcomes in individuals with major depressive disorder: Findings from the GSRD European multicenter database. *Journal of Affective Disorders*, **335**, 349.

Kuleshov, M. V., Jones, M. R., Rouillard, A. D., Fernandez, N. F., Duan, Q., Wang, Z., Koplev, S., Jenkins, S. L., Jagodnik, K. M., Lachmann, A., McDermott, M. G., Monteiro, C. D., Gundersen, G. W., & Ma'ayan, A. (2016). Enrichr: A comprehensive gene set enrichment analysis web server 2016 update. *Nucleic Acids Research*, **44**(W1), W90–W97.

Lee, H., Zhang, C., & Rose, R. (2022). Pediatric off-label antipsychotic use for attention-deficit/hyperactivity disorder. *Clinical Therapeutics*, **44**(9), e83–e90.

Mandrekar-Colucci, S., & Landreth, G. E. (2011). Nuclear receptors as therapeutic targets for Alzheimer's disease. *Expert Opinion on Therapeutic Targets*, **15**(9), 1085–1097.

McWhinney, S.R., Brosch, K., Calhoun, V.D., Crespo-Facorro, B., Crossley, N. A., Dannlowski, U., Dickie, E., Dietze, L.M.F., Donohoe, G., Du Plessis, S., Ehrlich, S., Emsley, R., Furstova, P., Glahn, D.C., Gonzalez-Valderrama, A., Grotegerd, D., Holleran, L., Kircher, T.T.J., Knytl, P., Kolenic, M., Lencer, R., Nenadić, I., Opel, N., Pfarr, J.-K., Rodrigue, A.L., Rootes-Murdy, K., Ross, A. J., Sim, K., Škoch, A., Spaniel, F., Stein, F., Švancer, P., Tordesillas-Gutiérrez, D., Undurraga, J., Vázquez-Bourgon, J., Voineskos, A., Walton, E., Weickert, T.W., Weickert, C.S., Thompson, P.M., van Erp, T.G.M., Turner, J.A., Hajek, T. (2022). Obesity and brain structure in schizophrenia–ENIGMA study in 3021 individuals. *Molecular Psychiatry*, **27**(9), 3731–3737.

Pan, A., Keum, N., Okereke, O. I., Sun, Q., Kivimaki, M., Rubin, R. R., & Hu, F. B. (2012). Bidirectional association between depression and metabolic syndrome: A systematic review and meta-analysis of epidemiological studies. *Diabetes Care*, **35**(5), 1171–1180.

Posey, D. J., Stigler, K. A., Erickson, C. A., & McDougle, C. J. (2008). Antipsychotics in the treatment of autism. *The Journal of Clinical Investigation*, **118**(1), 6–14.

Powell-Wiley, T. M., Poirier, P., Burke, L. E., Després, J., Gordon-Larsen, P., Lavie, C. J., … Sanders, P. (2021). Obesity and cardiovascular disease: A scientific statement from the american heart association. *Circulation*, **143** (21), e984–e1010.

Qin, L., Ma, K., Wang, Z., Hu, Z., Matas, E., Wei, J., & Yan, Z. (2018). Social deficits in Shank3-deficient mouse models of autism are rescued by histone deacetylase (HDAC) inhibition. *Nature Neuroscience*, **21**(4), 564–575.

Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, **511** (7510), 421–427.

So, H., Chau, C. K., Lau, A., Wong, S., & Zhao, K. (2019). Translating GWAS findings into therapies for depression and anxiety disorders: Gene-set analyses reveal enrichment of psychiatric drug classes and implications for drug repositioning. *Psychological Medicine*, **49** (16), 2692–2708.

Staner, L. (2010). Comorbidity of insomnia and depression. *Sleep Medicine Reviews*, **14**(1), 35–46.

Trubetskoy, V., Pardiñas, A.F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T.B., Bryois, J., Chen, C.-Y., Dennison, C.A., Hall, L.S., Lam, M., Watanabe, K., Frei, O., Ge, T., Harwood, J.C., Koopmans, F., Magnusson, S., Richards, A.L., Sidorenko, J., Wu, Y., Zeng, J., Grove, J., Kim, M., Li, Z., Voloudakis, G., Zhang, W., Adams, M., Agartz, I., Atkinson, E.G., Agerbo, E., Al Eissa, M., Albus, M., Alexander, M., Alizadeh, B.Z., Alptekin, K., Als, T.D., Amin, F., Arolt, V., Arrojo, M., Athanasiu, L., Azevedo, M.H., Bacanu, S.A., Bass, N.J., Begemann, M., Belliveau, R.A., Bene, J., Benyamin, B., Bergen, S.E., Blasi, G., Bobes, J., Bonassi, S., Braun, A., Bressan, R.A., Bromet, E.J., Bruggeman, R., Buckley, P.F., Buckner, R.L., Bybjerg-Grauholm, J., Cahn, W., Cairns, M.J., Calkins, M. E., Carr, V.J., Castle, D.J., Catts, S.V., Chambert, K.D., Chan, R.C.K., Chaumette, B., Cheng, W., Cheung, E.F.C., Chong, S.A., Cohen, D., Consoli, A., Cordeiro, Q., Costas, J., Curtis, C., Davidson, M., Davis, K.L., de Haan, L., Degenhardt, F., DeLisi, L.E., Demontis, D., Dickerson, F., Dikeos, D., Dinan, T.G., Djurovic, S., Duan, J., Ducci, G., Dudbridge, F., Eriksson, J.G., Fañanás, L., Faraone, S.V., Fiorentino, A., Forstner, A. J., Frank, J., Freimer, N.B., Fromer, M., Frustaci, A., Gadelha, A., Genovese, G., Gershon, E.S., Giannitelli, M., Giegling, I., Giusti-Rodríguez, P., Godard, S., Goldstein, J.I., González Peñas, J., González-Pinto, A., Gopal, S., Gratten, J., Green, M.F., Greenwood, T.A., Guillin, O., Gülöksüz, S., Gur, R.E., Gur, R.C., Gutiérrez, B., Hahn, E., Hakonarson, H., Haroutunian, V., Hartmann, A.M., Harvey, C., Hayward, C., Henskens, F.A., Herms, S., Hoffmann, P., Howrigan, D.P., Ikeda, M., Iyegbe, C., Joa, I., Julià, A., Kähler, A.K., Kam-Thong, T., Kamatani, Y., Karachanak-Yankova, S., Kebir, O., Keller, M.C., Kelly, B.J., Khrunin, A., Kim, S.W., Klovins, J., Kondratiev, N., Konte, B., Kraft, J., Kubo, M., Kučinskas, V., Kučinskiene, Z.A., Kusumawardhani, A., Kuzelova-Ptackova, H., Landi, S., Lazzeroni, L.C., Lee, P.H., Legge, S.E., Lehrer, D.S., Lencer, R., Lerer, B., Li, M., Lieberman, J.A., Light, G.A., Limborska, S., Liu, C.-M., Lönnqvist, J., Loughland, C.M., Lubinski, J., Luykx, J.J., Lynham, A., Macek, M.J., Mackinnon, A., Magnusson, P.K.E., Maher, B.S., Maier, W., Malaspina, D., Mallet, J., Marder, S.R., Marsal, S., Martin, A.R., Martorell, L., Mattheisen, M., McCarley, R.W., McDonald, C., McGrath, J.J., Medeiros, H., Meier, S.M., Melegh, B., Melle, I., Mesholam-Gately, R.I., Metspalu, A., Michie, P.T., Milani, L., Milanova, V., Mitjans, M., Molden, E., Molina, E., Molto, M.D., Mondelli, V., Moreno, C., Morley, C.P., Muntané, G., Murphy, K.C., Myin-Germeys, I., Nenadić, I., Nestadt, G., Nikitina-Zake, L., Noto, C., Nuechterlein, K.H., O'Brien, N.L., O'Neill, F. A., Oh, S.-Y., Olincy, A., Ota, V.K., Pantelis, C., Papadimitriou, G.N., Parellada, M., Paunio, T., Pellegrino, R., Periyasamy, S., Perkins, D.O., Pfuhlmann, B., Pietiläinen, O., Pimm, J., Porteous, D., Powell, J., Quattrone, D., Quested, D., Radant, A.D., Rampino, A., Rapaport, M.H., Rautanen, A., Reichenberg, A., Roe, C., Roffman, J.L., Roth, J., Rothermundt, M., Rutten, B.P.F., Saker-Delye, S., Salomaa, V., Sanjuan, J., Santoro, M.L., Savitz, A., Schall, U., Scott, R.J., Seidman, L.J., Sharp, S. I., Shi, J., Siever, L.J., Sigurdsson, E., Skarabis, N., Slominsky, P., So, H.-C., Sobell, J.L., Söderman, E., Stain, H.J., Steen, N.E., Steixner-Kumar, A. A., Stögmann, E., Stone, W.S., Straub, R.E., Streit, F., Strengman, E., Stroup, T.S., Subramaniam, M., Sugar, C.A., Suvisaari, J., Svrakic, D.M., Swerdlow, N.R., Szatkiewicz, J.P., Tam Ta, T.M., Takahashi, A., Terao, C., Thibaut, F., Toncheva, D., Tooney, P.A., Torretta, S., Tosato, S., Tura, G.B., Turetsky, B.I., Üçok, A., Vaaler, A., van Amelsvoort, T., van Winkel, R., Veijola, J., Waddington, J., Walter, H., Webb, B.T., Weiser, M., Williams, N.M., Witt, S.H., Wormley, B.K., Wu, J.Q., Xu, Z., Yolken, R., Zai, C.C., Zhou, W., Zhu, F., Zimprich, F., Atbaşoğlu, E.Ç., Ayub, M., Benner, C., Bertolino, A., Black, D.W., Bray, N.J., Breen, G., Buccola, N. G., Byerley, W.F., Chen, W.J., Cloninger, C.R., Crespo-Facorro, B., Donohoe, G., Freedman, R., Galletly, C., Gandal, M.J., Gennarelli, M., Hougaard, D.M., Hwu, H.-G., Jablensky, A.V., McCarroll, S.A., Moran, J. L., Mors, O., Mortensen, P.B., Müller-Myhsok, B., Neil, A.L., Nordentoft, M., Pato, C.N., Pocklington, A.J., Roussos, P., Vassos, E., Verhage, M., Visscher, P.M., Yang, J., Posthuma, D., Andreassen, O.A., Kendler, K.S., Owen, M.J., Wray, N.R., Daly, M.J., Huang, H., Neale, B.M., Sullivan, P. F., Ripke, S., Walters, J.T.R., O'Donovan, M.C.; Schizophrenia Working Group of the Psychiatric Genomics Consortium (2022). Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature*, **604** (7906), 502–508.

Uffelmann, E., Huang, Q.Q., Munung, N.S., de Vries, J., Okada, Y., Martin, A.R., Martin, H.C., Lappalainen, T., Posthuma, D. (2021). Genome-wide association studies. *Nature Reviews Methods Primers*, **1**(1), 59.

Wang, M., Liang, X., Jin, K., Liu, Y., Luo, S., Zhang, Q., Wang, X., Dong, Z., Zhang, X. (2025). The involvement of the synaptic vesicle cycle in homocysteine induced neurotoxicity in vitro and in vivo. *Scientific Reports*, **15**(1), 1–14.

Watanabe, K., Taskesen, E., Van Bochoven, A., & Posthuma, D. (2017). Functional mapping and annotation of genetic associations with FUMA. *Nature Communications*, **8**(1), 1826.

Watanabe, K., Umićević Mirkov, M., de Leeuw, C. A., van den Heuvel, M. P., & Posthuma, D. (2019). Genetic mapping of cell type specificity for complex traits. *Nature Communications*, **10**(1), 3222.

Xie, Z., Bailey, A., Kuleshov, M.V., Clarke, D.J.B., Evangelista, J.E., Jenkins, S.L., Lachmann, A., Wojciechowicz, M.L., Kropiwnicki, E., Jagodnik, K.M., Jeon, M., Ma'ayan, A. (2021). Gene set knowledge discovery with enrichr. *Current Protocols*, **1**(3), e90.

Yin, L., Chau, C. K., Lin, Y., Rao, S., Xiang, Y., Sham, P., & So, H. (2021). A framework to decipher the genetic architecture of combinations of complex diseases: Applications in cardiovascular medicine. *Bioinformatics*, **37**(22), 4137–4147.

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