Shared genetic architecture and bidirectional clinical risks within the psycho-metabolic nexus

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Summary

Background Increasing evidence suggests a complex interplay between psychiatric disorders and metabolic dysregulations. However, most research has been limited to specific disorder pairs, leaving a significant gap in our understanding of the broader psycho-metabolic nexus.

Methods This study leveraged large-scale cohort data and genome-wide association study (GWAS) summary statistics, covering 8 common psychiatric disorders and 43 metabolic traits. We introduced a comprehensive analytical strategy to identify shared genetic bases sequentially, from key genetic correlation regions to local pleiotropy and pleiotropic genes. Finally, we developed polygenic risk score (PRS) models to translate these findings into clinical applications.

Findings We identified significant bidirectional clinical risks between psychiatric disorders and metabolic dysregulations among 310,848 participants from the UK Biobank. Genetic correlation analysis confirmed 104 robust trait pairs, revealing 1088 key genomic regions, including critical hotspots such as chr3: 47588462-50387742. Cross-trait meta-analysis uncovered 388 pleiotropic single nucleotide variants (SNVs) and 126 shared causal variants. Among variants, 45 novel SNVs were associated with psychiatric disorders and 75 novel SNVs were associated with metabolic traits, shedding light on new targets to unravel the mechanism of comorbidity. Notably, *RBM6*, a gene involved in alternative splicing and cellular stress response regulation, emerged as a key pleiotropic gene. When psychiatric and metabolic genetic information were integrated, PRS models demonstrated enhanced predictive power.

Interpretation The study highlights the intertwined genetic and clinical relationships between psychiatric disorders and metabolic dysregulations, emphasising the need for integrated approaches in diagnosis and treatment.

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Research in context

Evidence before this study

The incidence of metabolic syndrome among the patients with psychiatric disorders frequently coexists, becoming one of the greatest challenges in the clinical practice of psychiatry. Previous studies have revealed connections between specific psychiatric and metabolic conditions; however, the comprehensive genetic architecture linking a broader spectrum of psychiatric disorders and metabolic traits remains largely unexplored. We searched PubMed and Google Scholar for genetic and epidemiological studies published in English that examined the relationship between psychiatric disorders and metabolic conditions (updated to July 29, 2024). Search terms included ['genetics' or 'genome-wide association study' or 'GWAS' or 'Mendelian randomisation' or 'MR' or 'genetic correlation' or 'genetic overlap'] and ['epidemiology' or 'cohort study' or 'UK Biobank' or 'correlation'] and ['psychiatric disorders' or 'mental disorders' or 'psychological disorders'] and ['metabolic' or 'metabolic syndrome' or 'cardiometabolic' or 'metabolic dysregulation' or 'metabolic traits'].

Previous research has identified modest genetic and clinical correlations between specific psychiatric disorders and metabolic traits, such as major depressive disorder, schizophrenia, and bipolar disorder with metabolic syndrome, body mass index, and others. However, comprehensive and in-depth studies on this shared genetic architecture are still lacking. Some studies suggest that the interaction between these conditions may exacerbate the severity and duration of psychiatric disorders, though the shared mechanisms remain underexplored.

Added value of this study

This study leveraged the latest and most comprehensive data to conduct an in-depth analysis of the genetic and clinical connections between psychiatric disorders and metabolic dysregulations. Through a comprehensive local analysis strategy, we identified 388 pleiotropic single nucleotide variants (SNVs) and 126 shared causal variants that link psychiatric disorders with metabolic traits. Of interest, we identified 45 novel SNVs associated with psychiatric disorders and 75 novel SNVs associated with metabolic traits. Additionally, we uncovered key pleiotropic genes, such as *RBM6*, which play critical roles in gene regulation and metabolic processes. Our approach also highlighted new therapeutic targets, including HDAC and mTOR inhibitors, for managing the comorbidity of psychiatric disorders with metabolic disorders. The study not only elucidated the genetic overlap between these conditions but also demonstrated the potential of polygenic risk scores in enhancing the prediction of psychiatric/metabolic comorbidities.

Implications of all the available evidence

The findings from this study provided critical insights into the shared genetic and clinical mechanisms underlying the comorbidities between psychiatric disorders and metabolic dysregulations. By identifying key genetic loci and pleiotropic genes involved in both mental health and metabolic processes, this research highlighted the interconnected nature of these conditions.

Introduction

The psycho-metabolic nexus garners a surging concern, as it links the severity and duration of symptoms to the bidirectional and longitudinal interactions between psychiatric disorders and metabolic dysregulations.[1] Of note, most of the mortality in individuals with psychiatric disorders can be attributed to physical comorbidities, particularly metabolic disorders, and cardiometabolic disorders.[2,3] Thus, the shared mechanism underlying high comorbidities of psycho-metabolic disorders is of great importance.

The last decade has witnessed an increasing interest in understanding the comorbidities of psycho-metabolic disorders through the lens of large-scale genome-wide association studies (GWAS). Investigations into genetic liability through causal inference or polygenic risk scores (PRSs) have highlighted the partial genetic contribution to the psycho-metabolic nexus.[4,5] Meanwhile, genetic variants associated with specific psychiatric and metabolic disorders have been preliminarily identified at the genome-wide genetic correlation level, revealing genetic factors that transcend individual disease boundaries.[6–8] However, little research has focused on the genetic associations of a broad scope of psychiatric or metabolic disorders and the integrated local genetic correlations remain largely unexplored.

To address these issues, we estimated the bidirectional clinical risks between major psychiatric disorders and metabolic dysregulations in a longitudinal cohort of UK Biobank (UKBB). Then, we comprehensively leveraged large GWAS data of 8 psychiatric disorders, 19 metabolic traits, 9 metabolic disorders, and 15 cardiometabolic disorders. To decrease the multiple corrections, we employed a comprehensive local analysis strategy, incorporating regional genetic correlations and comprehensive pleiotropic analyses to overcome constricted depth and integrity in previous GWAS research. Targeting clarified genetic factors in the psycho-metabolic nexus,

computational drugs were featured. We then explored the causal relationships between psychiatric disorders and metabolic dysregulations and investigated the mediating role of 1400 metabolite traits. Finally, we examined the potential of PRSs in precision diagnosis to translate these findings into clinical applications.

Methods

Data selection

To investigate the clinical risk associations within the psycho-metabolic nexus, we obtained 502,462 samples from UKBB with diagnoses based on the *International Statistical Classification of Diseases, 10th revision* in 2010–2022 (Application Number 144904).[9] After excluding participants with missing data, sex chromosome aneuploidy, genetic kinship, and non-European ancestry, we retained 310,848 samples of European ancestry for analysis (Supplementary Table S1).

In the genetic pleiotropy analysis, this study included 16 GWAS summary datasets for 8 psychiatric disorders that are comprised of the main scope of psychiatric disorders including major depressive disorder (MDD), bipolar disorder (BD), schizophrenia (SCZ), anxiety disorder (ANX), post-traumatic stress disorder (PTSD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and obsessive-compulsive disorder (OCD)[10] and 46 GWAS summary datasets for 43 metabolic profiles. The latest meta-analyses of GWAS results from the Psychiatric Genomics Consortium (PGC) for each psychiatric disorder,[11–17] were combined with data from the FinnGen (version R11) database for analysis,[18] except ASD due to its limited size (Ncase = 767) in FinnGen.[19] For MDD, we incorporated three GWAS datasets, including iPSYCH,[11] FinnGen,[18] and 23andMe.[20] For metabolic profiles including 19 metabolic traits (8 glucose traits, 5 lipid traits, 3 blood pressure traits, and 3 adiposity traits), 9 metabolic disorders, and 15 cardiometabolic disorders, data were sourced from the UKBB,[21,22] FinnGen,[18] and several large consortia.[23–34]

All cohort statistics and GWAS resources were approved by relevant ethics committees, and written informed consent was obtained from all participants, with details provided in the Supplementary Tables S2 and S3.

Clinical risk assessment

To investigate the bidirectional clinical risks, psychiatric or metabolic profiles in UKBB were focused on. We analysed 6 available psychiatric disorders (ASD was excluded due to limited sample size, Ncase = 3) and 24 metabolic profiles, treating them as either exposures or outcomes. Logistic and linear regression models with False Discovery Rate (FDR) correction were employed to estimate these clinical risks. Confounders including the top 10 genetic principal components (PCs), age, sex, and average total household income before tax were adjusted. FDR correction ($q < 0.05$) was used for multiple corrections. Interaction analyses of metabolic profiles on psychiatric disorders were also conducted.

Genetic pleiotropy analysis

In the genetic section, except for the local genetic correlation analysis, all other analyses excluded the major histocompatibility complex (MHC) region (chromosome 6: 25-35 Mb) due to complexity. The workflow of methods was provided in Fig. 1.

Meta-analysis of genome-wide association studies

To ensure the data quality, rigorous quality control measures, including checks for genomic control value and exclusion of shared single nucleotide variants (SNVs) with minor allele frequency <1%, were applied to the GWAS summary data. Data constructed in GRCh38 were converted to GRCh37 using the liftOver tool for consistency.[35]

After quality control, meta-analyses were performed to gain convincing results in larger sample sizes. For MDD, given that the data from iPSYCH included data from FinnGen (version R6), which would significantly overlap with FinnGen (version R11), we noted a high genetic correlation between the two datasets (iPSYCH vs. FinnGen) ($rg = 0.8$, $P < 1.00 \times 10^{-300}$). To address the sample overlap in GWAS results, we conducted a meta-analysis using MTAG software with the -equal_h2 option to derive MTAG MDD.[36] When performing a meta-analysis of MTAG MDD with 23andMe or other GWAS data for the same trait, we ensured minimal sample overlap between participating studies and homogeneity of effect sizes by calculating λ_{meta}. A λ_{meta} value significantly greater than 1 would indicate potential heterogeneity, while a λ_{meta} value substantially less than 1 suggests possible sample overlap. We ensured all study pairs had λ_{meta} values close to 1.[37,38]

For meta-analyses without sample overlap, we used the inverse variance weighted (IVW) fixed-effects method of the METAL software. In cases where sample overlap was present, we used Metasoft to calculate the heterogeneity (I^2) and the P value according to Cochran's Q test (P_het). When heterogeneity was observed ($I^2 \geq 50$ or P_het < 0.05), we prioritised the P value from the random effects model calculated using RE2C.[39–41]

For GWAS meta-analysis, we used MungeSumstats (an R package available at Bioconductor) for rapid standardisation and quality control.[42] The GWAS obtained from all meta-analyses in this study were evaluated for λ, LDSC intercept, and effective sample size ($4/[1/n_{case} + 1/n_{control}]$).

Genome-wide genetic correlation

Genome-wide genetic correlations between psychiatric disorders and metabolic dysregulations were examined using linkage disequilibrium score regression (LDSC)[43] and the Genetic Covariance Analyzer (GNOVA).[44] LDSC analyses were performed using the 1000

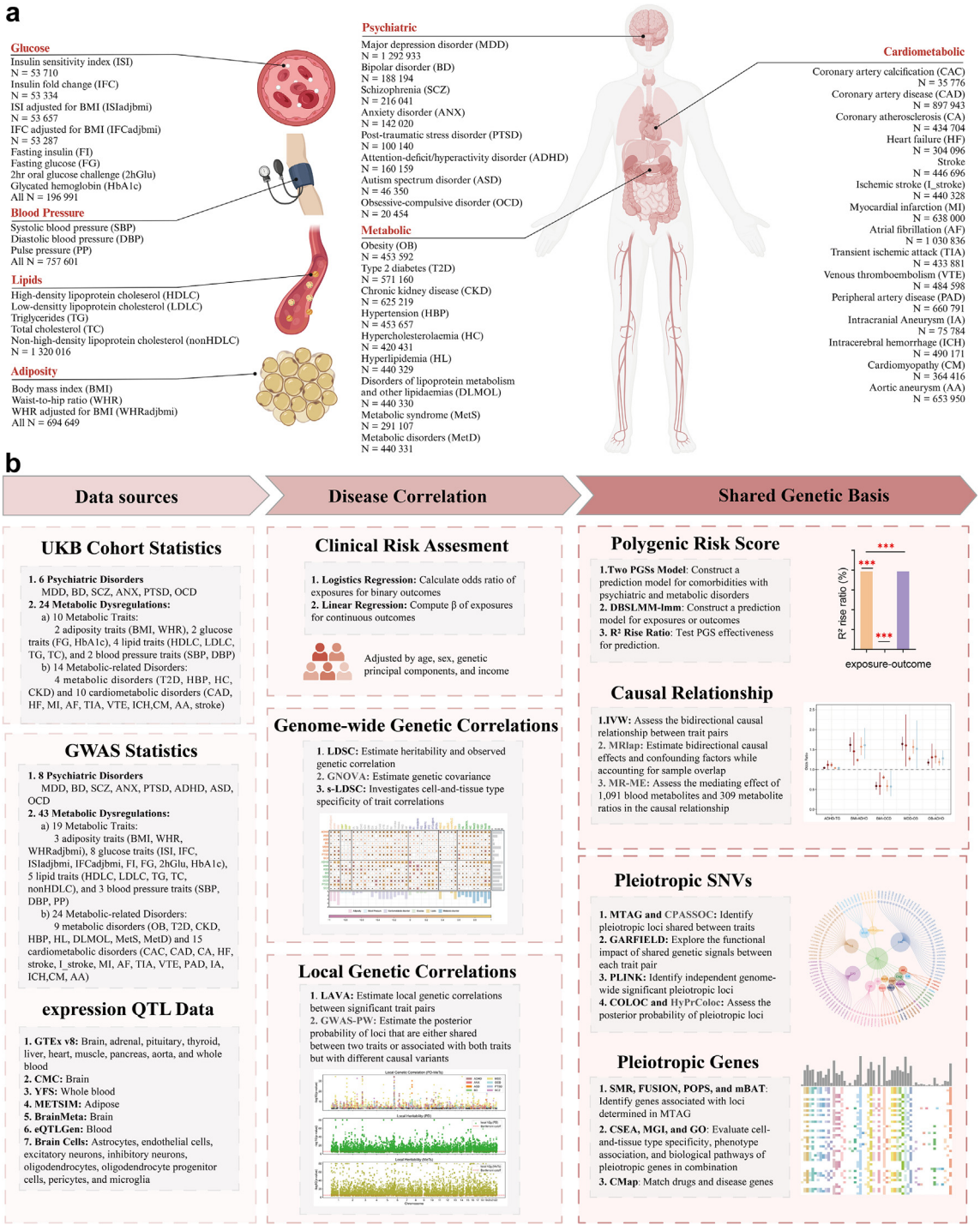

***Fig. 1:* Study workflow**. a, We listed the trait categories, aberrations and sample size of 8 psychiatric disorders, 19 metabolic traits (8 glucose traits, 3 blood pressure traits, 5 lipid traits, and 3 adiposity traits), 9 metabolic disorders, and 15 cardiometabolic disorders GWAS results used in the genetic pleiotropy analysis. b, Study overview. For data sources, we obtained prospective cohort data from 6 psychiatric disorders and 24 metabolic profiles in UKBB, large European GWAS data from 8 psychiatric disorders and 43 metabolic profiles, and several eQTL sources. Then, we estimated the mutual clinical risks through regression analyses, global genetic correlations through LDSC and GNOVA, and local genetic correlations through LAVA and GWAS-PW, between psychiatric disorders and metabolic dysregulations. Last, we explored the genetic liability in causal relationships in MR and prediction performance in PRSs, with pleiotropic variants and genes derived under the framework of local genetic correlations.

Genomes Project-based LD score for European ancestry with intercept not restricted.[45] Benjamini-Hochberg FDR ($q < 0.05$) for multiple testing corrections were employed. Subsequent analyses were based on trait pairs with significant genome-wide genetic correlations in LDSC and GNOVA analyses.

To explore the correlation across various cell-and-tissue types, stratified LD score regression (s-LDSC) was performed.[46] This analysis included data from 5 datasets: 39 brain tissue cells from Zeisel et al., 292 immune cells from ImmGen, 152 cell types and tissue types from Franke et al., and 53 cell types from GTEx V8.[46,47] Following the methodology of Bryois et al., we filtered out non-protein-coding genes, genes with duplicative names, genes within the MHC region, and genes with no expression in any of the examined cell and tissue types.[48] Gene expression was scaled to 1 million unique molecular identifiers per cell type, and the total proportion of each gene expressed in all specific cell types was computed. The significance of the heritability-enrichment estimates for each SNV was then assessed using the P value of the regression coefficient z-score with FDR correction.

For local genetic correlation among 2495 regions, Local Analysis of Variance Annotation (LAVA) was used to define the regions with significant heritability in both trait and correlation.[49] Bivariate analyses were performed only for loci that showed univariate signals at $P < 0.05/2495$ for both phenotypes.[49] Pairwise GWAS (GWAS-PW) was used to validate LAVA results, applying a threshold of posterior probability of A3/4 ($PP.A3/4) > 0.8$.[50] Subsequent analyses were based on trait pairs with significant genome-wide genetic correlations and focused only on genomic regions with significant local genetic correlations within these pairs. This targeted approach reduced multiple comparisons.

Cross-trait meta-analysis

To identify pleiotropic loci shared between paired traits, Multi-Trait Analysis of GWAS (MTAG) was performed, complemented by Cross-Phenotype Association (CPASSOC) for sensitivity analysis.[36,51] Independent genome-wide significant pleiotropic loci were identified using PLINK1.9 ($r^2 < 0.02$ and 500-kb window).[52] Significant pleiotropic SNVs were defined as $P < 1 \times 10^{-4}$ in GWAS studies and $P < 5 \times 10^{-8}$ in the meta-analysis, ensuring the meta-analysis P value was smaller than the original value. Functional annotation was conducted using ANNOVAR, annotation-dependent depletion (CADD) scores, loss-of-function observed/expected upper bound fraction (LOEUF) score, and snpXplorer,[53,54] providing a detailed understanding of the functional impact of identified variants. CADD scores were calculated by FUMA. SNVs with a CADD score larger than 12.37 were considered a potentially deleterious variant.[55] For these potential pleiotropic loci (markers in the ±100 kb range), bayesian colocalisation (COLOC), SuSiE, and HyPrColoc determined the probability of shared causal variants, enhancing the credibility of our findings.[56–58] For COLOC, we used the default settings of the coloc.abf function ($p1 = p2 = 1 \times 10^{-4}$, $p12 = 1 \times 10^{-5}$; where p1 and p2 represent the prior probabilities of SNVs being associated with trait 1 and trait 2, respectively, and p12 represents the prior probability of SNVs being associated with both traits), and considered a posterior probability of H4 ($PP.H4) \geq 0.8$ as the criterion for colocalised loci.[59] For SuSiE, we analysed loci with $PP.H4 \geq 0.8$ to enhance the accuracy of colocalisation analysis when multiple causal variants were present.[58] For HyPrColoc, posterior probability ≥ 0.8 was recognised as colocalised loci.[56]

The functional impact of shared genetic signalling was investigated using GARFIELD, focussing on SNPs identified in MTAG.[60] GARFIELD compared annotated markers from specific cell types and adjusted for various genetic factors. Under Bonferroni correction based on the number of annotations from each tissue, relevant tissues were grouped into 26 categories. Proportions of significant annotations in each category were examined with Pearson correlation test.

Identification of pleiotropic genes

To identify the association at loci identified in cross-trait meta-analyses for each trait pair, we conducted Summary-data-based Mendelian Randomization (SMR), functional Summary-Based Imputation (FUSION), Polygenic Priority Score (PoPS), and mBAT-combo (mBAT) analyses.[61–65] The first two methods linked genetic variants to gene expression leveraging eQTL data, while PoPS prioritised genes based on polygenic scores incorporating biological pathways and protein interactions and mBAT enhanced detection of gene-trait associations.

FUSION analyses were performed in FUSION software, with SNV weights downloaded from the FUSION website. The included SNV weights covered all available brain, adrenal, pituitary, thyroid, liver, heart, muscle, pancreas, aorta, and whole blood from GTEx v8, as well as SNV weights for brain tissue from CMC, whole blood from YFS, and adipose from METSIM.[64,66] For SMR, we included brain tissue data from BrainMeta, blood data from the eQTLGen consortium, 9 brain cell types from two studies, other eQTL data from GTEx (consistent with FUSION), pQTL data from the UKBB, and 4907 proteins in plasma measured in 35,559 Icelandic participants.[67–73] For PoPS, MAGMA was used to calculate gene-level association statistics and gene–gene correlations, and the enrichment of 79 gene features was calculated.[74] The final PoPS for each gene was determined by fitting a joint model that considered all resulting feature enrichments. mBAT, a multivariate technique, excelled in identifying gene-trait associations amidst masking effects using GWAS summary data.[63]

Inclusion criteria for the final credible pleiotropic genes required: 1) Bonferroni-adjusted $P < 0.05$ in SMR,

FUSION, and mBAT; 2) *P* HEIDI >0.01 in SMR; 3) PoPS Score > 1.

For the identified pleiotropic genes, we conducted cell/tissue type-specific enrichment, phenotype enrichment, and pathway enrichment analyses using tools such as WebCSEA, Mouse Genome Informatics platform (MGI), FUMA, and Gene Ontology (GO). These analyses provided deeper insights into the associations between specific cell types, phenotypes, and pathways.

WebCSEA provided a gene set query against tissue-cell-type (TCs) expression signatures of 11 single-cell gene expression datasets. Specifically, Dai et al. collected more than 5.5 million cells from 111 tissues and 1355 TCs, and filtered out the low-expression genes.[75] Genes with the top 5% t-statistic scores in focal cell type were defined as cell type-specific genes. We conducted Fisher's exact test to assess whether the shared genes for each trait pair were overrepresented with the cell type-specific genes. The significance threshold was set at a Bonferroni-corrected P-value < 0.05.

For tissue-specific analysis, we utilised the GENE2FUNC function in FUMA, selecting two datasets from GTEx that cover 30 or 53 different tissues. Differentially expressed gene (DEG) sets were pre-calculated by performing two-sided t-tests for each label against all other labels. Expression values were log2-transformed and normalised. Genes with a Bonferroni-corrected P-value ≤ 0.05 and an absolute log fold change ≥ 0.58 were defined as differentially expressed. In addition to DEG identification, upregulated and downregulated DEGs were also pre-calculated by considering the sign of the t-statistic.

MGI was performed to conduct phenotypic enrichment analysis.[76] Fisher's exact test was applied to examine the difference in the proportion of genes associated with certain phenotypes in the pleiotropic genome compared with non-pleiotropic genes to highlight the phenotypic specificity. The significance threshold was set at a P-value < 0.05.

For gene set functional enrichment analysis, we accessed the KEGG REST API (https://www.kegg.jp/kegg/rest/keggapi.html) for the latest gene annotations and used GO annotations from org.Hs.eg.db as background information. Enrichment analysis employed clusterProfiler.[77] Enrichment significance was determined using a false discovery rate (FDR) corrected P-value (q-value) <0.05.

Computational drug repurposing

Based on genetic associations, the Connectivity Map (CMap) algorithm identified potential therapeutic drugs associated with pleiotropic genes by comparing gene expression signatures with drug profiles.[78] To identify drugs for treating psychiatric disorders with comorbidities, we used these shared genes in more than 10 pairs. We extracted FUSION Z-values for the credible genes and utilised these values as proxies for traits. Specifically, we referenced the FUSION association signals of our target genes against the reference maps in the CMap touchstone database. We assessed the connectivity between a genome and a drug based on the consistency of the drug in reversing the expression levels of all associated genes. The CMap algorithm quantified this relationship using the τ-score, where a negative τ-score suggested that the drug normalised the gene expression linked to the trait. We posited that more negative τ-scores provide robust evidence for the potential repurposing of a drug to treat.[37,79] Drugs with strong connectivity scores (<–75) were considered candidates for therapeutic relevance.

Causal inference and polygenic risk score validation

To infer causality between psychiatric disorders and metabolic profiles, Mendelian Randomization (MR) was performed. IVW with FDR correction was employed as the primary method. As the sensitive tests, MR-Egger, weighted median, weighted mode, and MRlap were applied to validate the results.[80–83] MRlap was adopted to address bias in sample overlap.[80]

We first selected genome-wide significant SNVs with $P < 5 \times 10^{-8}$, and used the 1000 Genomes Project Phase 3 European populations as the LD reference panel to obtain independent instrumental variants with $r^2 < 0.001$ and distance > 10,000 kb. If there were not at least 3 independent SNVs, the threshold was relaxed to $P < 5 \times 10^{-6}$. We then used the phenotypic variance explained by genetic variation and the F-statistic to assess the strength of the genetic association of instrumental SNVs and the instrumental bias. For IVW, FDR was used with a significance threshold of $P < 0.05$.

To examine the mediating effect of 1091 blood metabolites and 309 metabolite ratios in the association of robust pairs in all examinations in bidirectional MR, an MR for mediation (MR-ME) analysis was performed.[84] We calculated the mediation P-value, the mediation effect, and the proportion mediated. The mediation P-value was calculated using the formula:

$$mediated = \beta_{exposure\_to\_mediator} \times \beta_{mediator\_to\_outcome}$$

$$S = \sqrt{\beta^2_{exposure\_to\_mediator} \times se^2_{mediator\_to\_outcome} + \beta^2_{mediator\_to\_outcome} \times se^2_{exposure\_to\_mediator}},\ Z = \frac{mediated}{S}$$

$P = 2 \times pnorm(|Z|)$

The mediation effect, or mean indirect effect, was calculated as $mean\_indirect = \beta_{exposure\_to\_mediator} \times \beta_{mediator\_to\_outcome}$.

The proportion mediated was determined by $pro\_m = \frac{mean\_indirect}{exp\_out}$.

To validate the genetic role in comorbidity, PRS was constructed using Deterministic Bayesian Sparse Linear Mixed Model (DBSLMM) based on GWAS statistics for psychiatric disorders and metabolic profiles.[85] Continuous traits were modelled with Gaussian linear models and binary traits with generalised logistic regression, testing PRS effectiveness for each trait. Adjustments were made for age, sex, the top 10 genetic PCs, and income. Models with two PRSs were assessed for improved predictive performance beyond outcome-specific PRS.[86] Pearson's R^2 and McFadden's pseudo-R^2 evaluated model performance with FDR correction. Bootstrap calculated 95% confidence intervals (CI) for Pearson's R^2 and area under the curve for binary traits.

Role of funders

Funders had no role in study design, data collection, data analyses, interpretation, or writing of report.

Results

Mutual clinical risks

Metabolic traits, including higher body mass index (BMI), waist-to-hip ratio (WHR), glycated haemoglobin, and triglycerides (TG), were found to be bidirectionally associated with increased risks of psychiatric disorders. Conversely, higher levels of high-density lipoprotein cholesterol were negatively associated with psychiatric conditions, suggesting a protective role. Our analysis also demonstrated that psychiatric and metabolic disorders mutually increase each other's risk. Specifically, type 2 diabetes (T2D) showed a significant increase in the risk for all psychiatric disorders, with ORs ranging from 3.45 to 17.09 (e.g., T2D-MDD, OR = 5.80, 95% CI: 3.78–8.91, P = 3.12×10^{-14}). The reverse associations were similarly robust, with ORs ranging from 3.44 to 17.81 (e.g., MDD-T2D, OR = 5.79, 95% CI: 3.77–8.89, P = 3.40×10^{-13}). We observed similar bidirectional relationships for other conditions, such as coronary artery disease (CAD), stroke, transient ischaemic stroke, and heart failure. Altogether, we identified 65 metabolic exposures were associated with psychiatric outcomes, 58 psychiatric exposures were associated with metabolic outcomes, and 50 psycho-metabolic pairs shared mutual clinical associations.

Furthermore, we investigated interactions of metabolic dysregulations, identifying 30 trait pairs with significant interactions. Notably, both T2D (OR = 5.68, 95% CI: 2.81–11.50, P = 1.40×10^{-6}) and transient ischaemic attack (OR = 2.32, 95% CI: 1.09–4.91, P = 0.028) individually increased the likelihood of BD diagnosis, and their combined effect resulted in an extra risk for BD (OR = 4.92, 95% CI: 1.02–23.70, P = 0.047) (Supplementary Tables S4–S7).

Genome-wide genetic correlation

We first conducted a meta-analysis on GWAS summary data for the same traits (Supplementary Results and Supplementary Fig. S1). Approaching LDSC and GNOVA respectively, we identified 118 and 228 genome-wide genetic correlations between psycho-metabolic traits, respectively, with 104 of these correlations remaining robustly significant. Many of these significant correlations aligned with the observed high-risk trait pairs (Fig. 2a and Supplementary Table S8). Among these, ADHD shared the highest number of traits with metabolic profiles (27/43, 63%), while BMI was significantly correlated with most psychiatric disorders, excluding BD (7/8, 88%). Notably, PTSD exhibited the strongest genetic correlation with obesity (OB) (rg.LDSC = 0.38, P = 1.47×10^{-16}), followed by ADHD-OB, ADHD-metabolic syndrome, and MDD-high lipid (HL) (rg.LDSC $\geq$ 0.35, P < 1×10^{-7}).

The s-LDSC analysis of these 104 paired traits revealed cell and tissue type specificity within the psycho-metabolic profiles (Supplementary Table S9). Psychiatric disorders showed overlapping genetic associations with adiposity across various tissue types, including lung, epithelial system, leukocytes, entorhinal cortex, enteric glia, and vascular system, indicating shared pathological mechanisms at the cellular level (Fig. 2b). This shared genetic architecture demonstrated that common biological pathways, such as inflammation and vascular function, might underlie psychiatric and metabolic conditions, providing potential targets for integrated therapeutic approaches. In contrast, dysregulation of lipids, glucose, and cardiometabolic disorders appeared to involve different mechanisms across distinct cell-and-tissue types compared to psychiatric disorders. These findings underscored the importance of considering the specificity of genetic influences when developing personalised interventions.

Local genetic correlations

To identify local loci with significant genetic correlations that might be overlooked in genome-wide analyses, we applied LAVA to 104 paired traits. This analysis revealed 1650 regions with localised genetic loci with psycho-metabolic profiles (Fig. 2c and Supplementary Table S10). Following a sensitivity test using GWAS-PW, 91 paired traits with 1088 regions were retained, forming a final union set for further analysis (Supplementary Table S11). Notably, regions 464 (chr3: 47588462-50387742) and 953 (chr6: 28666365-29529755) showed the most significant localised genetic correlations, spanning 25 phenotype pairs.

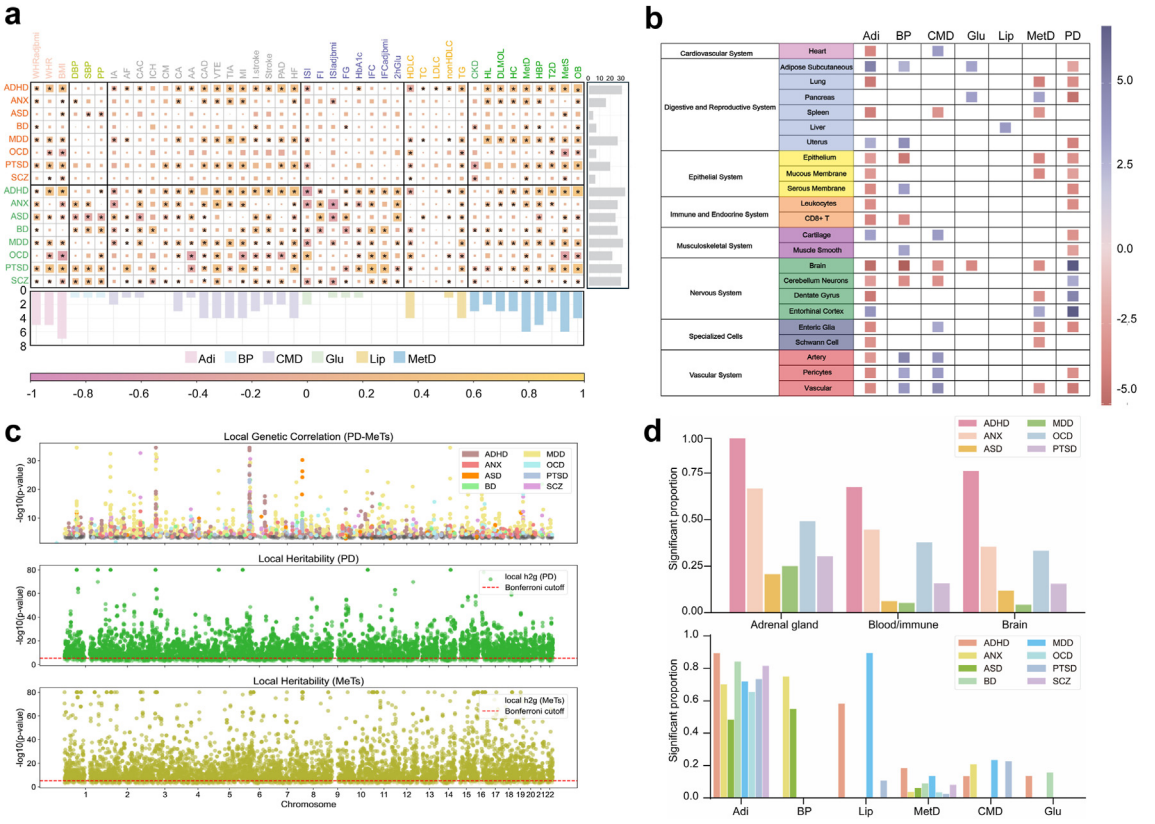

Fig. 2: **Genetic correlations and tissue-specific functional impact between psychiatric and metabolic disorders**. a, Genome-wide genetic correlations between psycho-metabolic traits were identified by LDSC (top) and GNOVA (bottom). The right grey bar represented the summation number of significantly correlated trait pairs for each psychiatric disorder. The bottom colour bar represented the summation number of significantly correlated trait pairs in both LDSC and GNOVA for each metabolic dysregulation. b, Functional impact of the 104 paired traits (discerned from robustness in both LDSC and GNOVA) revealed tissue type specificity in the psycho-metabolic profiles. The colour plot represented functional enrichment degrees (Z value) in each tissue type. Adi, Adipposity; BP, Blood pressure; Lip, Lipids; MetD, Metabolic disorder; CMD, Cardiometabolic disorder; Glu, Glucose. c, Manhattan plots from top to bottom displayed LAVA results of PD-MeTs, PD, and MetS. The red line indicated the significance threshold (P = 0.05/2495). PD, Psychiatric disorder; MeTs, Metabolic traits. d, Functional impacts of 91 trait pairs on genetic signalling across various tissue types were explored via GARFIELD, with a focus on SNVs more significant in MTAG than in any individual trait.

Localised pleiotropies and enrichment analysis

Through cross-trait meta-analysis using MTAG and CPASSOC, we identified 388 SNVs as potential pleiotropic variants across 33 paired traits (Supplementary Table S12). By querying the GWAS Catalogue, we identified 45 novel SNVs associated with psychiatric disorders and 75 novel SNVs associated with metabolic traits among these variants (defined as loci located more than one million base pairs away from reported GWAS loci).[87] Significant associations were observed between these SNVs and psycho-metabolic profiles. Pearson correlation analysis of the effect sizes revealed that 7 trait pairs had correlation values exceeding 0.9, with 3 pairs showing correlations close to 1 (Supplementary Table S13). Furthermore, we identified 37 SNVs that influence multiple trait pairs simultaneously (Supplementary Table S14). Notably, rs11209952 and rs12128707 were individually found to be associated with three different trait pairs, highlighting their potential pleiotropic effects. These findings suggested that these specific variants may play a crucial role in the shared genetic architecture underlying these conditions, warranting further investigation into their biological mechanisms.

Colocalisation analysis identified 125 (32%) independent genomic risk loci as candidate causal variants with PP.H4 ≥ 0.8, spanning 54 distinct chromosomal regions (Fig. 3, Supplementary Fig. S2, and Supplementary Table S12). Additionally, we identified 45 independent genomic risk loci that passed the coloc-SuSiE sensitivity analysis (SuSiE.PP.H4 ≥ 0.8) (Supplementary Table S15). BMI shared the most causal variants with MDD, represented by 38 SNVs. A total of 4 shared causal SNVs were identified in more than

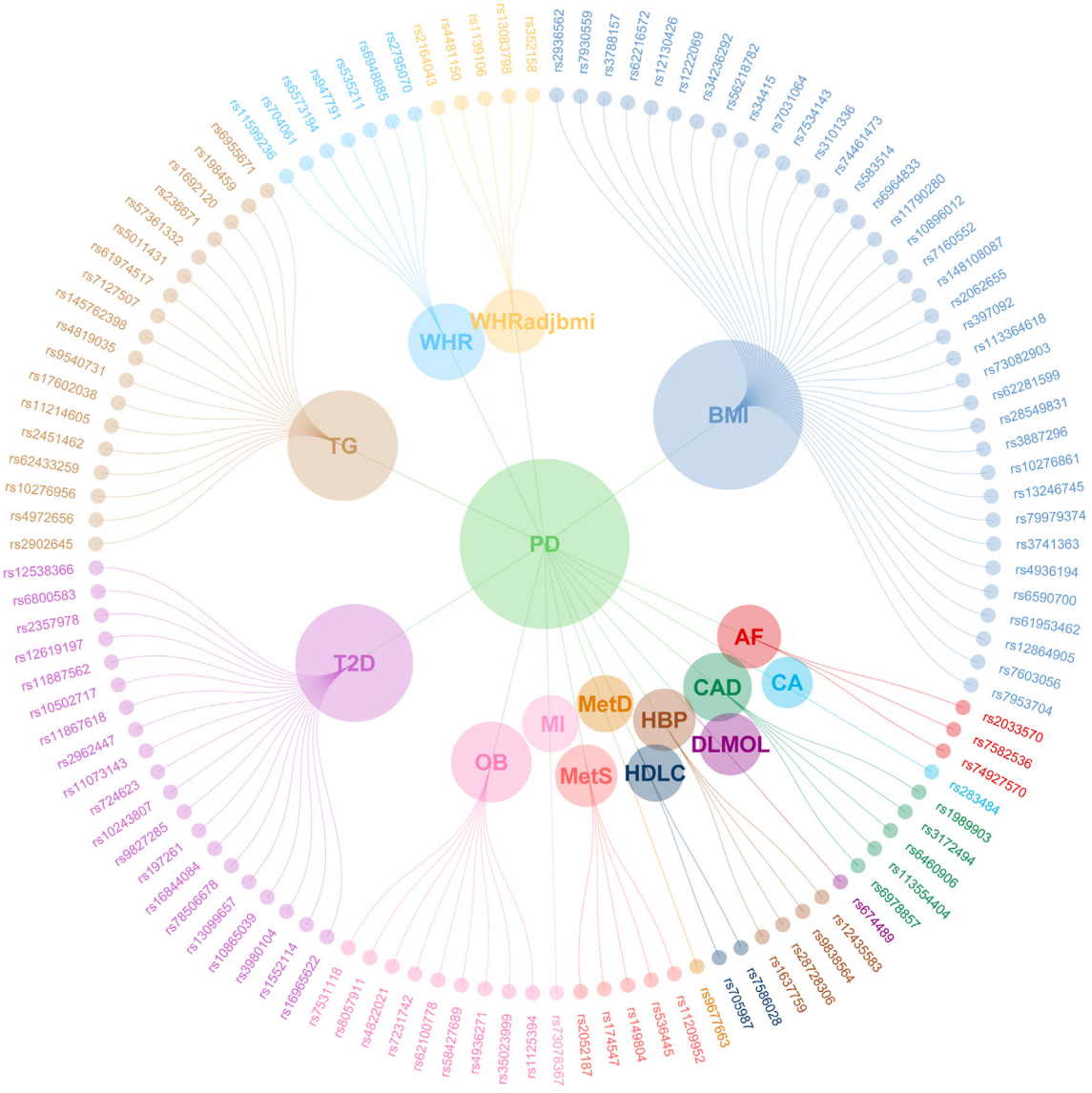

Fig. 3: **Potential pleiotropic variants between psychiatric and metabolic disorders**. A network diagram of 126 causal shared SNVs with colocalisation (PP.H4 ≥ 0.8) using COLOC analysis categorised by metabolic traits. A network diagram of 126 causal shared SNVs categorised by psychiatric disorders can be seen in Supplementary Fig. S2. PD, Psychiatric disorder.

1 trait pair. These notable shared causal variants included rs3172494 in ADHD/MDD-CAD, rs11599236 in MDD-BMI/WHR, rs28728306 in MDD-high blood pressure/T2D, and rs13083798 in BD-WHRadjbmi and SCZ-WHR. The robustness of these findings was supported by HyPrColoc analysis (Fig. 4a–d and Supplementary Table S16).

Among the shared pleiotropic genes that nearest to these SNVs, *TMEM106B*, involved in endosomes/lysosomes and dendrite morphogenesis,[88] revealed 10 potential pleiotropic variants across 4 trait pairs (MDD-TG/T2D/BMI/CAD), with rs5011431 and rs57361332 identified as causal in MDD-TG, rs10243807 in MDD-T2D, and rs6460906 in MDD-CAD (Supplementary Table S12).

Functional annotation using ANNOVAR showed that 60 of the 126 SNVs (48%) were intronic variants, 40 (32%) were intergenic variants, and only 2 (2%) were exonic variants (Supplementary Table S12). Notably, 8 of the 126 (6%) shared causal variants were predicted to have deleterious effects based on combined CADD scores greater than 12.37. These included rs3172494 (MDD/ADHD-CAD; CADD score: 21.5; nearest gene: *IP6K2* [OMIM 606992]) and rs16844084 (MDD-T2D;

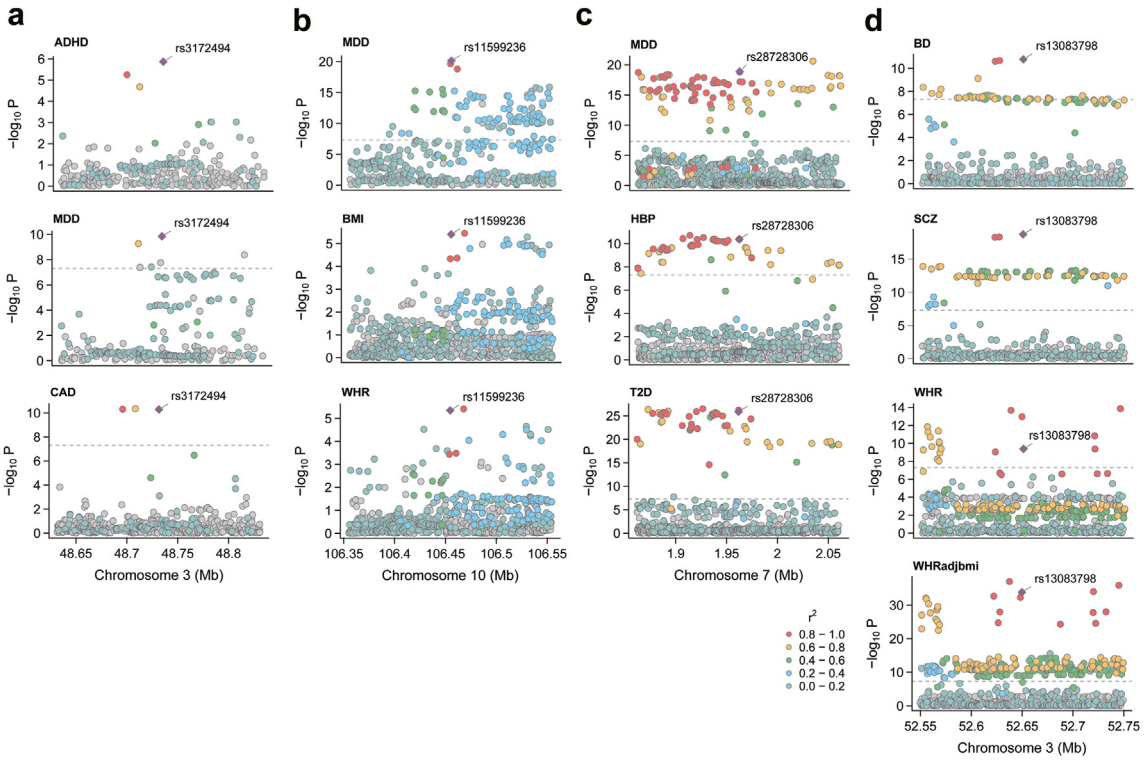

Fig. 4: **Potential pleiotropic variants in trait pairs and shared genes**. a–d, The x-axis showed position within the genome and the y-axis denoted the $-\log_{10}$P for the association. Colour denoted the LD between different variants. 4 SNVs indicated by purple colour were colocalised across more than one trait pair and validated by HyPrColoc. Panels a–d represented rs3172494 in ADHD/MDD-CAD, rs11599236 in MDD-BMI/WHR, rs28728306 in MDD-high blood pressure/T2D, and rs13083798 in BD-WHRadjbmi and SCZ-WHR, respectively. The grey line indicated the significance threshold ($P = 5 \times 10^{-8}$). e, 132 robust pleiotropic genes were identified across all SMR, FUSION, PoPS, and mBAT approaches. Inclusion criteria for the final credible pleiotropic genes required: 1) Bonferroni-adjusted $P < 0.05$ in SMR, FUSION, and mBAT; 2) *P* HEIDI >0.01 in SMR; 3) PoPS Score > 1. The grey bar represented the summation number of genes found within each trait pair.

CADD score: 18.78; nearest gene: *BAZ2B* [OMIM 605683]), implicating them in mitochondrial function and neurological development.[89–91]

According to the LOEUF analysis, we identified a total of 40 highly intolerant SNVs (LOEUF < 0.2) (Supplementary Table S12).[92] Among them, rs9898605 in the ADHD-nonHDLC trait pair had the lowest LOEUF value (0.048), suggesting the most gene intolerance to loss-of-function variation. Additionally, 3 highly intolerant SNVs (rs2052187, rs13083798, and rs10789931) were observed across multiple groups, underscoring their pleiotropic effects and suggesting a shared genetic architecture underlying these complex traits. These shared SNVs highlighted important pathways that may simultaneously influence both psychiatric disorders and metabolic dysregulation.

Focussing on SNPs more significant in MTAG than in any individual trait, we employed GARFIELD to assess the functional impact of 91 trait pairs on genetic signalling (Fig. 2d). The analysis revealed that psychiatric disorders were predominantly associated with significant proportions of adiposity across various tissue types. Notably, MDD and ADHD exhibited stronger functional correlations with lipids metabolism, while ANX and ASD were more closely linked to blood pressure regulation (Supplementary Tables S17–S19). Among tissue types, the adrenal gland showed the highest proportion of significant associations across psychiatric disorders in each metabolic category, with blood/immune tissues ranked second in all classes except adiposity.

Furthermore, for the 388 shared SNVs, we utilised snpXplorer for eQTL tissue annotation (Supplementary Table S12). The results indicated that these SNVs were active across various tissues, including adipose tissue (subcutaneous and visceral), brain regions (such as the caudate nucleus, anterior cingulate cortex, and cerebellum), and endocrine glands (such as the thyroid and pituitary). These tissues play crucial roles in metabolic regulation and neurological function, suggesting a shared genetic architecture underlying the intersection of metabolic traits (e.g., OB, T2D) and psychiatric disorders (e.g., MDD, ANX). This highlighted potential pathways through which metabolic dysregulation may impact brain function and contribute to the development of psychiatric conditions.

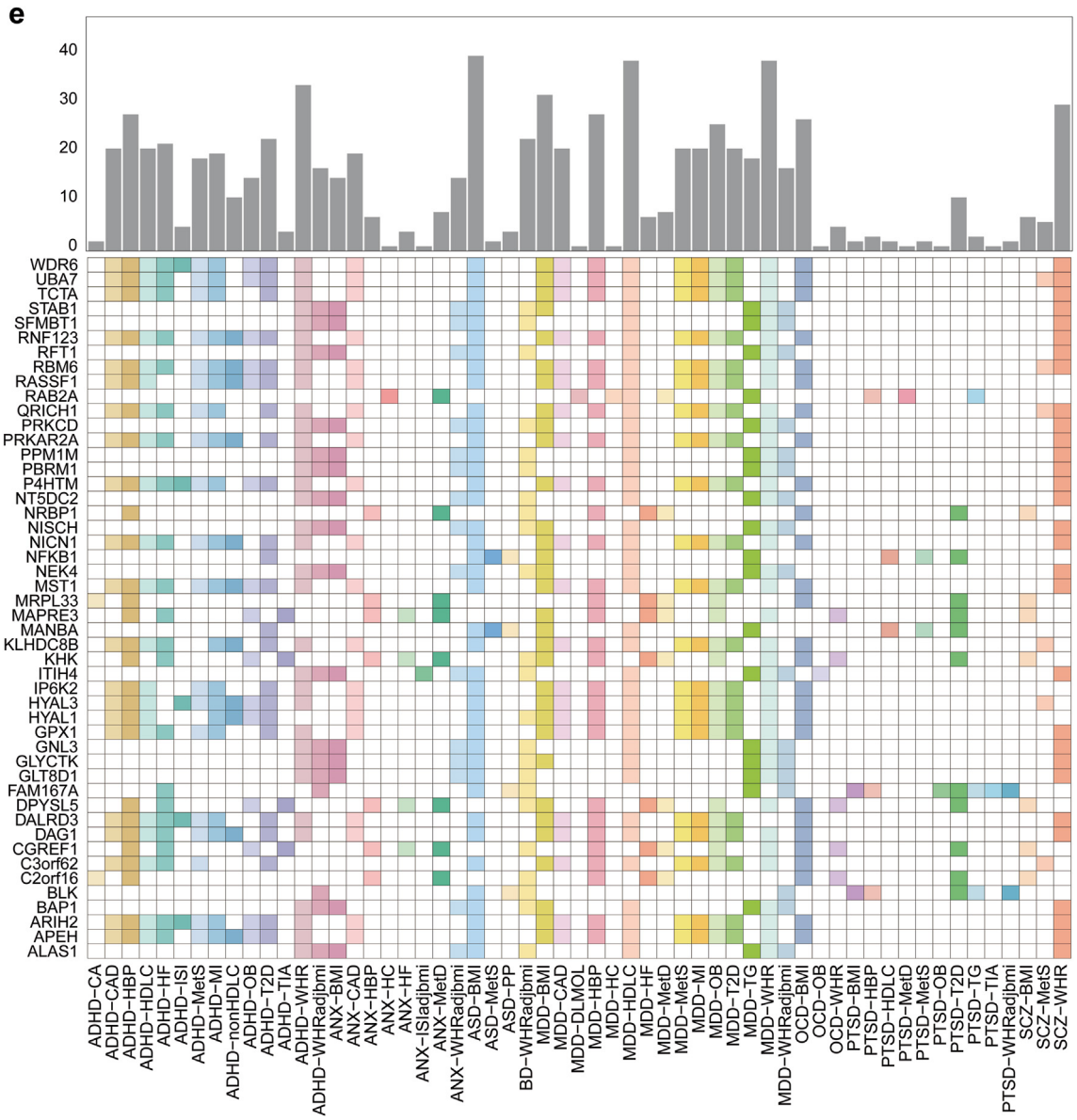

Fig. 4: Continued.

Localised pleiotropic genes

Annotating GWAS variants to genes solely based on proximity can be overly simplistic and may overlook pleiotropic effects. To address this, we employed four methods, SMR, FUSION, PoPS, and mBAT, to identify pleiotropic genes (Supplementary Tables S20–S23). Depending on these approaches, we identified 1055, 430, 577, and 2272 genes, respectively. Altogether, we identified 132 pleiotropic genes consistently recognised across all methods for subsequent analysis (Supplementary Table S24).

In our genetic investigation, we found a significant overlap, with 19 genes consistently showing significance across 20 or more trait pairs (Fig. 4e). Notably, *RBM6* emerged as a central pleiotropic gene within the psycho-metabolic nexus, demonstrating significance in 24 examined pairs. This was followed by genes such as *APEH, ARIH2, HYAL3, MST1, P4HTM, RNF123, UBA7*, and *WDR6*, each significant in 23 pairs. These genes are primarily associated with the hyaluronan metabolic process and cellular stress response pathways (Supplementary Table S25 and Supplementary Fig. S3).

Using GENE2FUNC function in FUMA, we identified 99 genes previously reported to be associated with psychiatric disorders or metabolic traits (Supplementary Table S26). In addition, we found that up to 48 genes

were enriched for traits related to brain morphology, such as cortical surface area and subcortical volume, which were among the most significantly associated traits. Other notable traits included HDLC levels, triglyceride levels, and body fat distribution indicators. Further analyses on complex traits, such as inflammatory bowel disease and cognitive function, highlighted the pleiotropic effects of these shared genes, emphasising their potential roles in influencing both psychiatric and metabolic traits.

Cell and tissue-specific enrichment analysis of the 132 pleiotropic genes revealed the highest enrichment in the eye and glial cells (Supplementary Figs. S4 and S5 and Supplementary Table S27).[55] Significant downregulation of these genes was observed in tissues such as the pancreas, heart, liver, muscle, kidney, brain, and blood, indicating these tissues as central hubs for comorbidity. The downregulation was particularly pronounced in cell types of the pancreas and specific brain regions, including the hippocampus, amygdala, basal ganglia, substantia nigra, and hypothalamus, aligning with the s-LDSC findings (Supplementary Figs. S6 and S7).

These genes were associated with a wide range of phenotypes, including brain morphology, psychiatric disorders, metabolic profiles, autoimmune conditions (e.g., inflammatory bowel disease), and behavioural traits (e.g., cognition, sleep, and alcohol consumption) (Supplementary Fig. S8).[87] MGI analyses further confirmed associations of these genes across various metabolic-related phenotypes, including digestive, liver, cardiovascular, and respiratory systems, as well as embryonic development and mortality (Supplementary Table S28).

Localised pleiotropic drug

As metabolic dysregulations often coexist with psychiatric disorders, we used these shared genes in more than 10 pairs to identify drugs for treating comorbidities. We utilised the CMap platform to match drugs and disease genes. In total, we analysed FUSION z-values for 48 plausible pleiotropic genes, and 54 relevant drugs in 36 classes were revealed (Supplementary Table S29). These drug classes contained histone deacetylase (HDAC) inhibitors, mechanistic target of rapamycin (mTOR) inhibitors, and cyclin-dependent kinase (CDK) inhibitors.

Causal relationship

MR analysis confirmed causal relationships between psychiatric disorders and metabolic profiles across 52 pairs, with consistent effect directions in IVW, MR-Egger, weighted median, and weighted mode (Supplementary Table S30). MRlap validated 50 of these pairs, with MDD and ADHD showing the most significant causal links to metabolic outcomes (Supplementary Results and Supplementary Table S31). Notably, 5 pairs demonstrated consistent significant causality across all methods, aligning with UKBB cohort findings (Supplementary Fig. S9). These robust causal associations underscored the potential clinical impact of addressing metabolic dysregulation in psychiatric populations.

In MR-ME analysis, we identified metabolic pathways that may influence psychiatric conditions. For instance, the causal effect of BMI on ADHD was shown to be mediated by alterations in the alpha-ketoglutarate to succinate ratio and the threonine to alpha-ketobutyrate ratio (Supplementary Table S32). These findings suggested that metabolic imbalances could play a role in the development of psychiatric conditions, providing potential targets for early intervention and treatment strategies aimed at correcting these metabolic pathways to improve psychiatric outcomes.

Prediction model with PRS

By integrating clinical risk results with genetic associations, we focused on psychiatric disorders (MDD, BD, SCZ, and ANX) and 3 metabolic dysregulations (BMI, T2D, and CAD) as either exposure or outcome to construct 24 PRS model profiles. All the outcomes of PRSs achieved higher prediction efficacy, and 58% (14/24) exposures of PRSs did so. Considering the combined genetic associations in exposure and outcome, 33% (8/24) of 2 model PRSs demonstrated significantly improved prediction over the only outcome of PRSs (Fig. 5 and Supplementary Tables S33 and S34).

In these 8 pairs, all showed significant clinical risks, highlighting their relevance for clinical application. Furthermore, 63% (5/8) of these pairs also exhibited robust genetic correlations in both LDSC and GNOVA analyses, reinforcing the genetic basis of these associations. These findings underscored the potential of utilising PRS models not only for risk stratification but also for early identification of individuals at heightened risk for developing comorbid psychiatric and metabolic disorders. This approach may guide personalised interventions and preventive strategies aimed at mitigating the clinical burden associated with these complex conditions.

Discussion

Our study identified mutual clinical risks, shared genetic architecture, and causal relationships between psychiatric disorders and metabolic dysregulations within the psycho-metabolic nexus (Graphical Abstract and Supplementary Discussion). Clinically, bidirectional risks, particularly between MDD and T2D, suggested a documented mutually exacerbating relationship.[93] Genetically, significant correlations indicated shared susceptibility across disease boundaries, with tissue-specific influences identified in the brain, adipose tissue, and cardiovascular system.

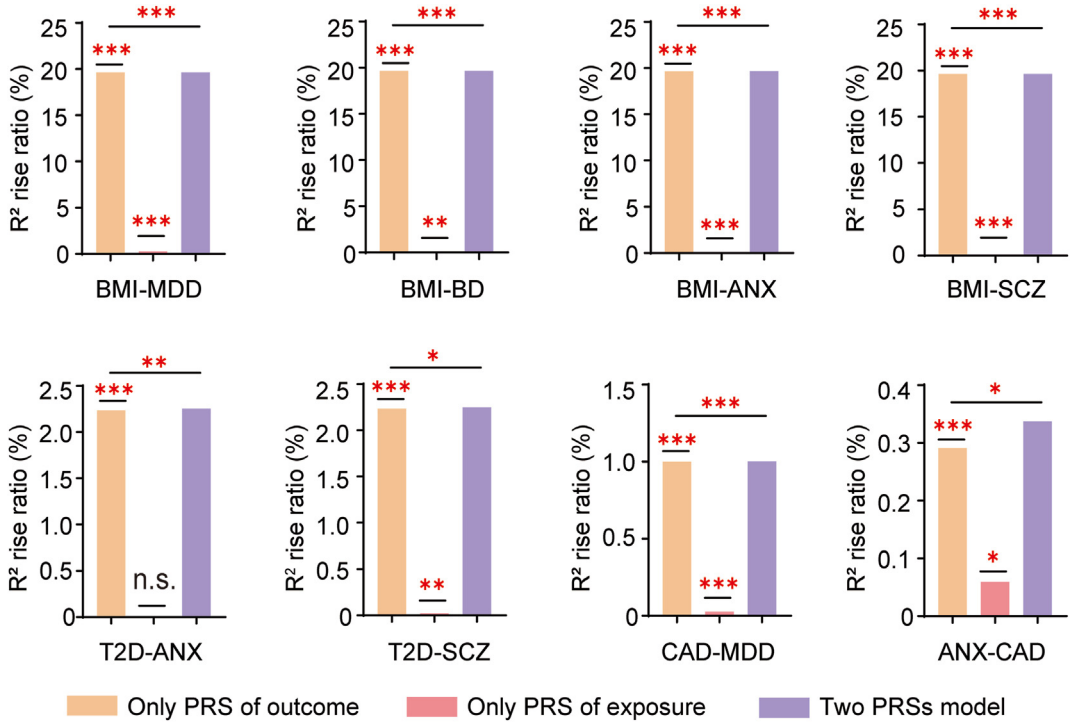

Fig. 5: **PRSs with both metabolic and psychiatric traits improved the prediction efficacy**. 8 of 24 groups demonstrated improved prediction performance in two model PRSs significantly over the only outcome of PRSs. Trait pairs were organised as exposure-outcome. We constructed 3 types of PRSs (only PRS of outcome, only PRS of exposure, and two PRSs model) to test the prediction efficacy of outcome. All PRSs were constructed using DBSLMM based on GWAS statistics for psychiatric disorders and metabolic profiles. Continuous traits were modelled with Gaussian linear models and binary traits with generalised logistic regression, testing PRSs effectiveness for each exposure trait. Adjustments were made for age, sex, the top 10 genetic PCs, and income. Prediction efficacy of different PRSs evidenced by R^2 rise ratio. Models with two PRSs were assessed for improved predictive performance beyond outcome-specific PRS. Pearson's R^2 and McFadden's pseudo-R^2 evaluated model performance with FDR correction. We labelled the significance of prediction efficacy of only PRS of exposure, two PRSs model, and the difference between two PRSs model two PRSs model and only PRS of outcome. *P < 0.05, **P < 0.01, and ***P < 0.001.

Using a local analysis strategy, we combined local genetic correlations and pleiotropic analyses to minimise bias. This approach revealed a genetic hotspot at chr3: 47588462-50387742, linking psychiatric and metabolic disorders through key genes like *CTNNB1, INKA1*, and *EOMES*, which are involved in neural and metabolic functions.[94,95] Additionally, the region within the MHC locus, specifically chr6: 28666365-29529755, also demonstrated a connection between psychiatric disorders and metabolic traits. The MHC region contains numerous immune-related genes including the HLA gene family. Thus, it is supposed to impact mental health by influencing immune function, gene-immune interactions, and the regulatory/non-immune role of neurodevelopment and neuronal plasticity.[96–101] Likewise, the genetic variations in MHC could also contribute to inflammation and immune responses, promoting the pathophysiology of metabolic disorders.[102,103] As reported, the HLA-DRB1*03 allele potentially caused the co-occurrence of SCZ and T2D.[104] Altogether, the genetic complexity, high diversity, and involvement in gene-environment interactions make the MHC region a key genetic hub where shared variants may influence both psychiatric and metabolic trait types, underscoring its importance in understanding the genetic architecture of the psycho-metabolic nexus. However, the MHC region was excluded due to complexity in our subsequent analysis, awaiting explorations in future clinical studies.

Further analyses identified 388 pleiotropic SNVs and 126 shared causal variants, with significant associations in psycho-metabolic traits. Of interest, we identified 45 novel SNVs associated with psychiatric disorders and 75 novel SNVs associated with metabolic traits, shedding light on new targets to unravel the mechanism of comorbidity. Notably, BMI shared the most causal variants with MDD, highlighting the genetic overlap between psychiatric disorders and adiposity. Such correlated trait pairs were also reported in a previous study.[8] Functional annotation and colocalisation identified 4 key causal variants. For instance, rs13083798 was identified as a key causal variant near the *PBRM1* gene,

part of the PBAF complex, which is crucial for chromatin structure and gene regulation.[105] Dysregulation of *PBRM1*-related genes has been linked to psychiatric disorders like SCZ and BD, as well as metabolic abnormalities including angiogenesis and AMPK/fatty acid oxidation, underscoring the critical role of *PBRM1* in mental health and metabolic stability.[106–109] Additionally, *PBRM1* was also identified as one of the pleiotropic genes in our subsequent analyses within 11 psycho-metabolic trait pairs.

Then, we identified 132 pleiotropic genes, with *RBM6* playing a central role in nearly 30% of trait pairs, possibly influencing neural development, neurotransmission, and metabolic regulation.[110–112] Many of these genes encode enzymes in metabolic processes, particularly in the brain and heart, driving psychiatric and metabolic disorders.[113,114] For instance, *ARIH2* and *RNF123* regulate protein degradation and inflammation,[115,116] while *HYAL3* and *MST1* impact cell signalling, neuroinflammation, and metabolic balance.[113,114,117,118]

The high comorbidity between psychiatric and metabolic disorders poses clinical challenges, especially regarding pharmacological treatments that often exacerbate metabolic issues.[119] We identified translational drug targets, including HDAC, mTOR, and CDK inhibitors, which affect metabolic and psychiatric processes.[120–122] HDAC inhibitors, such as valproic acid, have shown promise across various psychiatric disorders,[123] while mTOR inhibitors like rapamycin demonstrate potential for conditions like MDD and PTSD.[124,125] Although CDK inhibitors are less studied, they have been proposed as potential antidepressants due to neurogenesis.[120] Unlike conventional treatments that address comorbidities by targeting separate mechanisms, our approach introduced innovative pharmacological strategies that address distinct disorders through convergent therapeutic mechanisms, which potentially benefits precise treatment for comorbid endotypes.

MR analyses provided evidence for reciprocal causal relationships between psychotic disorders and metabolic phenotypes, with genetic predispositions linking BMI with ADHD and MDD.[4] These findings suggested the importance of monitoring metabolic factors like obesity in psychiatric care. We also observed robust evidence demonstrating genetic predisposition for ADHD contributed to increased TG levels, offering a genetic explanation for the positive association between ADHD and TG observed in prospective cohorts.[126] *RBM6,* a key gene involved in lipid dysregulation in ADHD, awaits investigations in the ADHD-TG association.[111] Further, MR-ME analyses focused on the intermediate roles of metabolites in these associations, identifying potential metabolic targets for intervention. For instance, the ratio of alpha-ketoglutarate to succinate, which may influence cerebral energy metabolism, could play a role in the link between BMI and ADHD.[127]

PRSs have become crucial in understanding complex genetic phenotypes and advancing precision medicine. Our use of two PRS models demonstrated a significant improvement in predicting psychiatric/metabolic comorbidity by incorporating additional metabolic or psychiatric information. Although the accuracy gains were modest, these results suggested that integrating supplementary PRSs can enhance predictive performance to some extent.[5] Altogether, the shared genetic architecture and bidirectional relationship between psychiatric and metabolic disorders highlighted the importance of addressing both mental and physical health. Early identification of individuals with a high genetic burden in the psycho-metabolic nexus is essential for targeted interventions, and PRS shows promise in risk stratification and guiding future treatment strategies.

Limitations

There are some limitations inherent to our study: 1) our study was restricted to European ancestry, which might not generalise to other ancestries; 2) we did not have an independent replication cohort due to combining available GWAS datasets for the same phenotype through meta-analysis; 3) potential bias due to variations in sample sizes across different traits may influence the detection of genetic correlations and causal relationships; 4) our study relies on tools like LDSC, MTAG, COLOC, and HyPrColoc, each with inherent assumptions that may impact our findings. For instance, MTAG presumes shared heritability and a consistent genetic correlation structure, which might not capture non-linear relationships among psychiatric and metabolic traits, even though CPASSOC was supplemented as a sensitivity analysis.

Conclusions

Our study identified mutual clinical risks, shared genetic architecture, and causal relationships between psychiatric disorders and metabolic dysregulations within the psycho-metabolic nexus, emphasising the need for integrated approaches in diagnosis and treatment.

Contributors

XNG, YF, XLJ, and NNJ designed the study, analysed data, and wrote the manuscript draft and revised manuscript. AM and JBL reviewed and edited the manuscript. SHH, SY, and ZW conceived the study, supervised the study, and reviewed the manuscript. SHH and SY had full access to data. All authors read and approved the final version. XNG, YF, XLJ, and NNJ contributed equally.

Data sharing statement

All original data in this study are available online or upon request from the committee including UKBB and 23andMe. The code in this study has been uploaded to https://github.com/Whyyu98/Psycho-Metabolic-Nexus.

Declaration of interests

No conflicts of interest, financial or otherwise, are declared by the authors. All authors were not paid to write this article by a pharmaceutical company or other agency.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2024.105530.

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