nature communications

Article

https://doi.org/10.1038/s41467-025-60487-w

Shared genetic architecture of posttraumatic stress disorder with cardiovascular imaging, risk, and diagnoses

Received: 24 August 2024

Accepted: 21 May 2025

Published online: 01 July 2025

Check for updates

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Patients with post-traumatic stress disorder face increased cardiovascular risk. This study examines shared genetic regions between post-traumatic stress disorder and 246 cardiovascular conditions across electronic health records, 82 cardiac imaging, and health behaviors defined by Life's Essential 8. Post-traumatic stress disorder is genetically correlated with cardiovascular diagnoses in 33 regions, imaging traits in 4 regions, and health behaviors in 44 regions. Potentially shared causal variants between post-traumatic stress disorder and 17 cardiovascular conditions were observed in 11 regions. Subsequent observational analysis in AllofUS cohort showed post-traumatic stress disorder is associated with 13 diagnoses even after accounting for socioeconomic factors and depression. Genetically regulated proteome expression in brain and blood tissues identified 33 blood and 122 brain genes shared between the two conditions, revealing neuronal, immune, metabolic, and calcium-related mechanisms, with several genes as targets for existing drugs. These findings exhibit shared risk loci and genes are involved in tissue-specific mechanisms.

Given that cardiovascular (CV)-related outcomes, including diseases and risk factors, are the leading cause of morbidity and mortality worldwide[1], it is imperative to extend our understanding of associations beyond traditionally known CV risk factors. Recently, the American Heart Association (AHA) recognized the influence of psychological stress on adverse CV health[2]. Posttraumatic stress disorder (PTSD) is considered a stress-related mental disorder with a lifetime prevalence ranging from 2% to 25%[3]. PTSD and CV diseases are highly comorbid. Specifically, PTSD has been associated with CVD[4], hypertension[5], diabetes[6], ischemic heart disease[7], stroke[8],

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https://doi.org/10.1038/s41467-025-60487-w

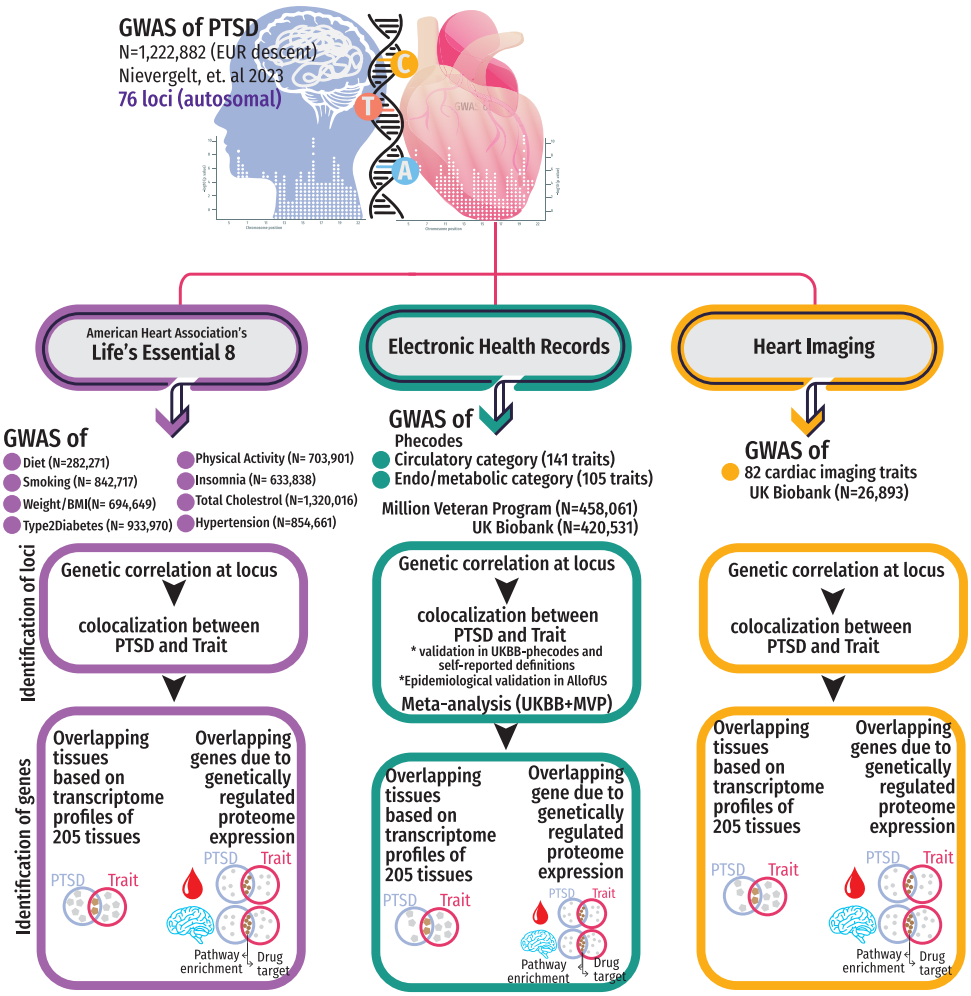

Fig. 1 | Study design. We investigated loci shared between posttraumatic stress disorder (PTSD) and cardiovascular (CV)-related traits, including the American Heart Association's Life Essential 8 factors, CV diagnoses derived from electronic health records (EHR), and cardiac imaging phenotypes. After identifying genetically correlated loci between PTSD and CV conditions, we investigated shared causal variants. For the EHR-based CV diagnoses, we performed replication of shared causal variants in the UK Biobank and a follow-up analysis in the All of US Research Program. The traits with evidence of PTSD-CV shared causal variants were tested with respect to tissue-specific transcriptomic and proteomic profiles. The overlapping genes were investigated for overrepresented pathways and drug targets.

carotid intima-media thickness[9], and coronary artery disease[10]. PTSD and CVD have been reported to share several pathophysiological features. For instance, patients with PTSD have higher adrenergic activity both at baseline and after being subjected to stress-inducing situations[11], imposing a chronically increased burden on both the heart and the circulatory system. High adrenergic states are also associated with CVD symptoms, including increased heart rate and acutely increased blood pressure[12]. Additionally, PTSD can increase the risk of CVDs by increasing the risk of dyslipidemia and diabetes, although the biology of this association is not yet fully understood[13,14].

Both PTSD and CVD have substantial genetic components, with heritability estimates of 30–40% for PTSD[13,15] and 15–57% for hypertension, 26% for heart failure (HF), and 40-60% for coronary artery disease[16–20]. Recently, our group showed PTSD polygenic risk being associated with several cardiovascular symptoms and disorders[21] and showed potential genetic causality towards cardiac arrhythmias[21], ischemic stroke[22], coronary artery disease, and hypertension[23]. Previous studies reporting overlap between PTSD and cardiovascular disease (CVD) either relied solely on epidemiological[13] or genetic data, examined only a limited range of CVD outcomes[23–25] often from a single source, or lacked a comprehensive exploration of mechanistic insights[26,27]. Additionally, these studies often did not adequately address potential confounders, such as socioeconomic and behavioral factors. Therefore, several critical gaps remain in understanding the shared genetic architecture between PTSD and CVD which were highlighted by the experts from AHA and the National Heart, Lung, and Blood Institute[28], including exploring genomic regions linked to both PTSD and cardiovascular disease, identifying specific disruptions in brain circuitry, and utilizing cell-specific methods to investigate how PTSD-related neural pathways may causally contribute to cardiovascular dysfunction. In this study, we address these knowledge gaps by leveraging the latest and largest GWAS (genome-wide association study) data to study genetic overlap between the PTSD[29] and CV outcomes from three different domains including EHR diagnoses, heart imaging[30] and Life's Essential 8 (LE8) key measures for improving and maintaining – evidence-based cardiovascular health as factors and behaviors recently outlined by the American Heart Association[2]. Specifically, we aimed to (i) identify loci that are shared between PTSD and CV conditions, (ii) test the specificity of PTSD-CVD comorbidity accounting for socioeconomic factors (BMI, smoking, deprivation index) and diagnosis of depression, and (iii) infer biological mechanisms underlying PTSD and CV outcomes based on tissue-specific transcriptomic regulation and proteomic gene-associations that overlap between PTSD and CVD traits (Fig. 1).

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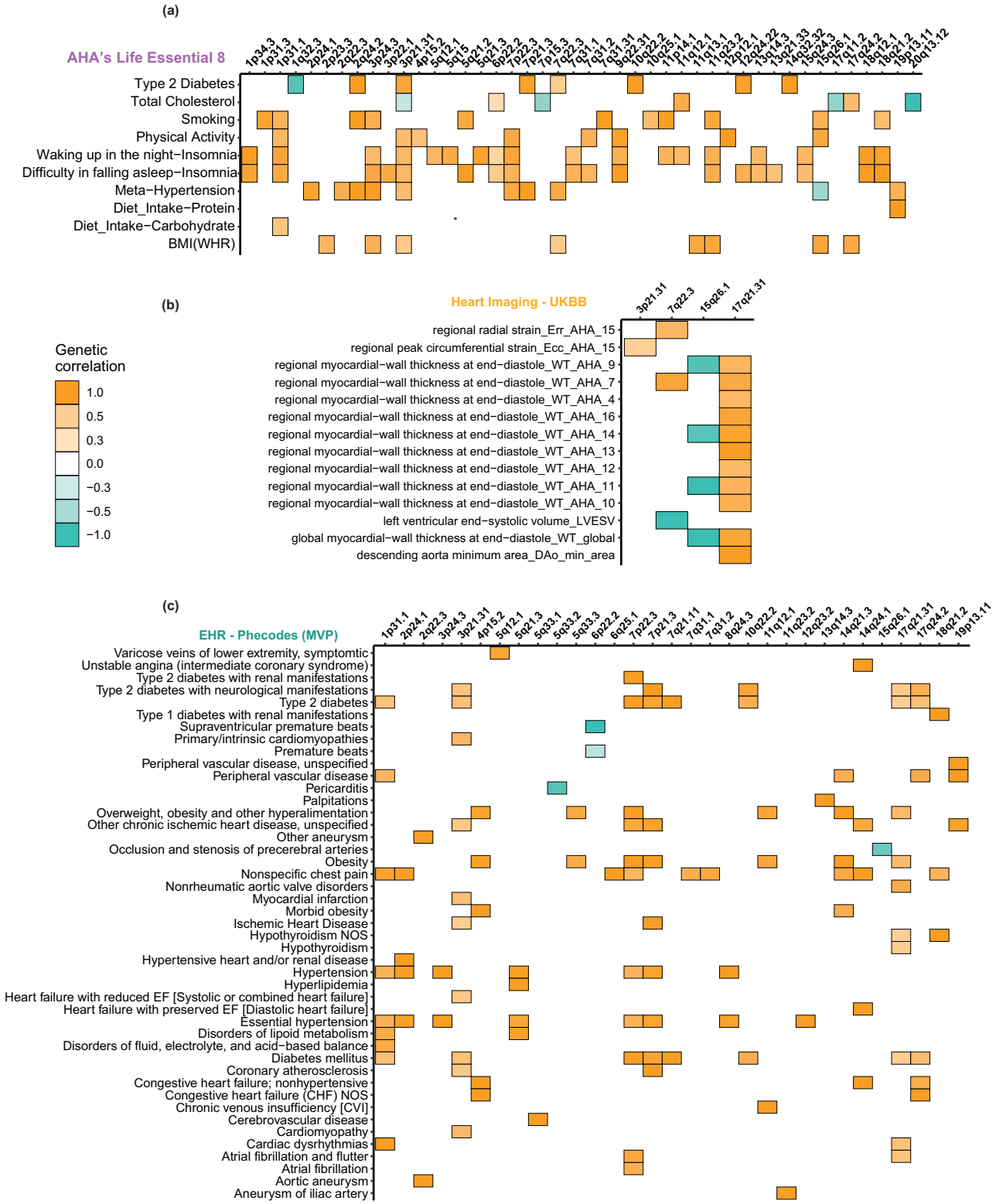

Fig. 2 | Local genetic correlation between PTSD and CV conditions. Matrix plot of local genetic correlation between PTSD and conditions grouped by their CV category (**a**) Life's Essential 8 from different sources (**b**) heart imaging from UKBB and **c** the EHR-based CV definitions (i.e., phecodes) are from Million Veteran Program. The x-axis shows loci as cytoband positions. The positive correlation is denoted in orange, cyan indicates negative correlation, and the size of the squares corresponds to the magnitude of the genetic correlation.

Results

Genetically correlated loci between PTSD and CVD Traits

We investigated 76 genome-wide significant (GWS) risk loci associated with the PTSD GWAS ($P < 5 \times 10^{-8}$, Supplementary Data S1–3) for local genetic correlation with GWAS of 246 CV-related phecodes from MVP, 82 cardiac imaging traits from UKBB, and LE8-related phenotypes from various studies. We observed statistically significant SNP-based heritability at 73 loci for all the phenotypes investigated (Supplementary

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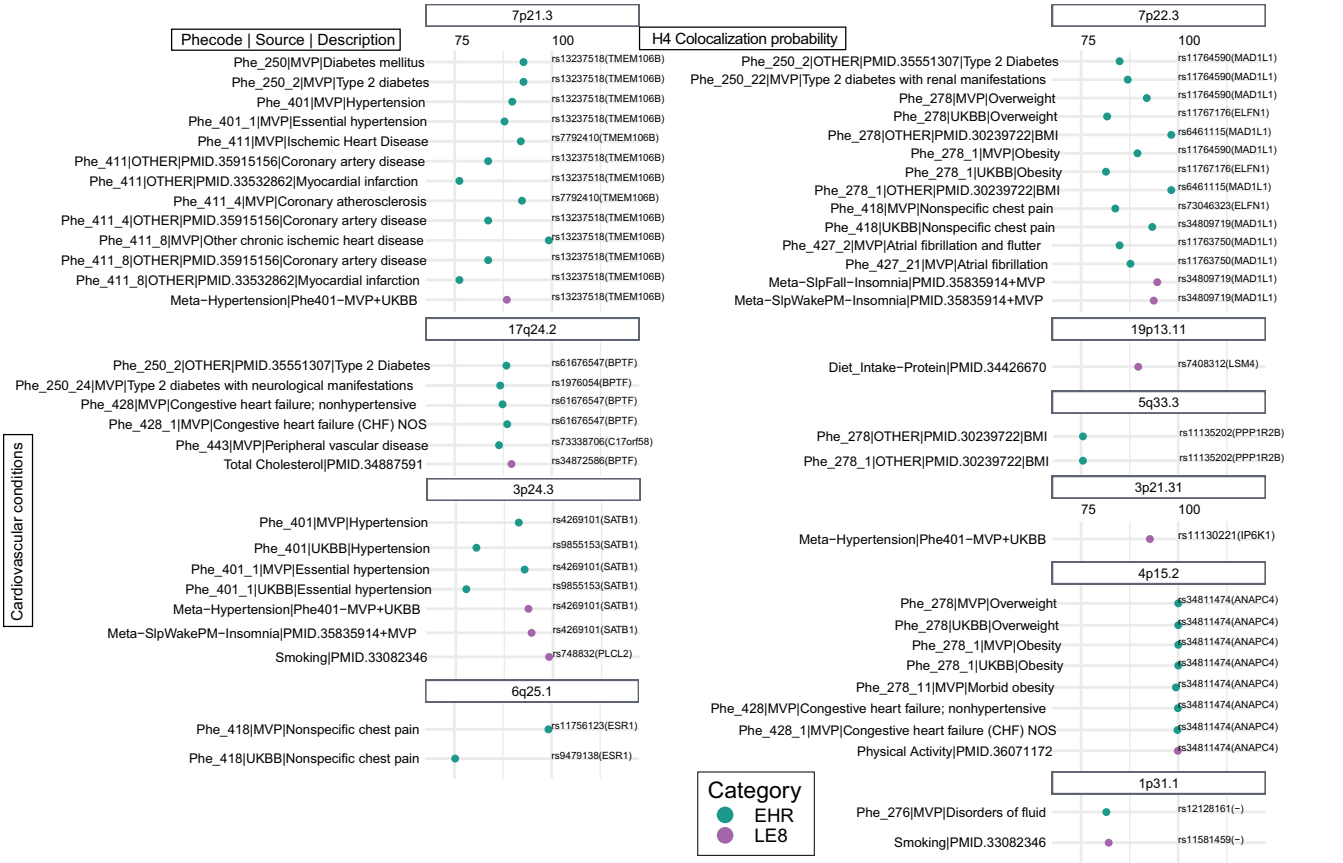

Fig. 3 | Shared causal variants between PTSD and CV conditions. The x-axis shows on top shows H4 colocalization probability i.e., same causal variant between traits (gene closest to the variant), between PTSD and CV traits. The y-axis is CV conditions, grouped by EHR (green) and AHA's Life's essential 8 traits (purple).

Data S4). For CV- phecodes, we identified 112 local genetic correlations with PTSD across 33 loci (FDR $q < 0.05$; Fig. 2, Supplementary Data S5). Among these, 67 were related to circulatory system, and 45 to endocrine/metabolic phecodes. Additionally, four PTSD-associated loci presented local genetic correlations between PTSD and 14 heart imaging traits (FDR $q < 0.05$; Fig. 2, Supplementary Data S5). For LE8-factors, 92 local genetic correlations with PTSD were identified across 44 loci (Fig. 2, Supplementary Data S5). Notably, fat dietary intake was the only LE8- trait that was not genetically correlated with PTSD at any of the investigated loci. Overall, most local genetic correlations were positive. Among the few negative local genetic correlations, four were between PTSD and total cholesterol across different loci and six at 15q26.1 between PTSD and multiple phenotypes (Fig. 2, Supplementary Data S5).

Considering locus-specific results, the 17q21.31 region exhibited the highest number of genetically correlated traits ($N = 21$; Fig. 2, Supplementary Data S5), including 10 CV-related phecodes (e.g., cardiac dysrhythmias, nonrheumatic aortic valve disorders, diabetes mellitus, overweight, and hypothyroidism) and 11 heart imaging traits (e.g., various sections of myocardial-wall thickness at end-diastole and descending aorta minimum area).

Shared causal variants between PTSD and CV conditions within genetically correlated loci

We investigated whether the local genetic correlation between PTSD and CV-related phenotypes is due to a shared causal variant or both traits are associated but with distinct causal variants (colocalization hypotheses H4—shared causal variant, or H3—regional colocalization, respectively)[31].

EHR: Using colocalization approach, we identified 20 CV-related phecodes that shared the same causal SNP with PTSD across 11 loci (H4-PP ≥ 80%, Fig. 3; Supplementary Data S6). Under the H3 hypothesis (H3-PP ≥ 80%), 19 CV diagnoses shared potentially causal but distinct PTSD variants (Fig. 3; Supplementary Data S6). To replicate the colocalization findings observed using MVP phecodes, we repeated the analysis using UKBB phecodes and other cohorts that incorporate a combination of EHR and self-report definitions. Specifically, we matched 24 CV phecodes in UK Biobank ($N = 420{,}531$)[32] and 11 GWASs from major consortia comprising of self-reported and/or clinical data ($N = \sim 1{,}320{,}016$)[33–39]. In UKBB, 13 out of the 24 examined traits displayed replications (H4/H3-PP ≥ 70%), revealing consistent colocalization patterns with PTSD across 8 loci (Supplementary Data S6; Supplementary Fig. S1&2). In the other cohorts, validation was achieved for 5 phenotypes (i.e., myocardial infarction, coronary artery disease, atrial fibrillation, type 2 diabetes, and BMI) across 8 distinct loci (H4/H3-PP ≥ 70%; Supplementary Data S6; Supplementary Fig. S1&2). Across discovery (in MVP) and replication (in UKBB and other cohorts), obesity and being overweight demonstrated the highest posterior probability of sharing the same causal variant with PTSD in locus 4p15.2 (H4-PP = 1, a shared causal SNP - rs34811474 - *ANAPC4*).

Imaging traits: Among the heart imaging traits, there was colocalization on two loci for 8 traits. Within locus 17q21.31, variants were associated with PTSD and seven different levels of measurements of regional myocardial-wall thickness at end-diastole, and the global myocardial-wall thickness at end-diastole (H3-PP ≥ 80.0%). In locus 15q21.31, PTSD and the global myocardial-wall thickness at end-diastole share the same causal trait (H4-PP = 92.5%, causal SNP - rs17514846- *FURIN*).

LE8 traits: Considering LE8 checklist, we observed statistically significant PTSD colocalization (H4/H3 ≥ 80%) in 31 loci (Fig. 3; Supplementary Data S6; Supplementary Fig. S1&S2). While no colocalization was observed between PTSD and dietary carbohydrate intake, the other LE8-related phenotypes shared the same PTSD casual SNP in 20 loci collectively (H4-PP ≥ 80%; closest gene (shared causal variant), *ANAPC4* (rs34811474), *ARHGAP15* (rs10191758), *BPTF* (rs34872586), *CDH2* (rs7243332), *FOXP2* (rs1476535, rs8180817), *IP6K1* (rs11130221), *KMT2E* (rs2470937), *LSM4* (rs7408312), *MAD1L1* (rs34809719), *NCAM1* (rs7106434), *NCOA5* (rs6032660), *PDE4B* (rs2310819), *PLCL2* (rs748832), *PROX1* (rs340874), *SATB1* (rs4269101), *TANK* (rs197261), *TMEM106B* (rs13237518), non-coding regions (rs11581459, rs325500, rs4275621)) Supplementary Data S6; Supplementary Fig. S1&2). Interestingly, physical activity shared the same causal variant with PTSD in locus 4p15.2 (H4-PP = 99%) that we observed with respect to obesity and being overweight (shared causal SNP - rs34811474 - *ANAPC4*). Both total cholesterol and BMI–adjusted-waist-to-hip ratio had the H3 highest posterior probability with PTSD in 6p22.2 and 3p21.31, respectively (H3-PP = 100%, Supplementary Data S6; Supplementary Fig. S1-S3).

Overall, 7p21.3, 7p22.3, 4p15.2, and 17q24.2 regions exhibited the highest number of H4 probability-based colocalized CV-related phenotypes (Fig. 3). While 17q21.31 and 3p21 showed colocalization between PTSD and CV phecodes, heart imaging phenotypes, and LE8 checklist, mostly due to H3 hypothesis. (Supplementary Fig. S4).

To prioritize genes within the colocalized regions, we first identified 506 genes physically located in the 38 loci that showed evidence of colocalization between PTSD and CV conditions. We leveraged multi-tissue molecular profiles (gene, proteome, and splicing expression) and CV traits available from OpenTargets platform[40,41]. We identified 270 genes that had H4 or H3 hypothesis probability ≥0.6 of colocalizing with 201 different CV conditions across 124 tissues. Among the highest H4 associations (H4-PP = 100%), there were multiple phenotypes related to the body electrical impedance, BMI, blood lipids, blood pressure, hemoglobin A1c in multiple tissues (gene/splicing/proteome expression in various tissues), smoking, sleep duration, and hypothyroidism. (Supplementary Data S7).

Observational association of PTSD with CV-related diagnoses in the All of US cohort

To further investigate the comorbidity between PTSD, and 13 CV diagnoses (lifetime prevalence) observed in our genetically informed analysis, we conducted an observational analysis using EHR data for circulatory and metabolic diagnoses from AoU cohort (as per phecodes: 244-hypothyroidism, 244.4-hypothyroidism NOS, 250-diabetes mellitus, 250.2-Type 2 diabetes, 278-Overweight, obesity, and hyperalimentation, 278.1-obesity, 401-hypertension, 401.1-essential hypertension, 411.8-other chronic ischemic heart disease, 418-nonspecific chest pain, 427-Cardiac dysrhythmias, 427.2 atrial fibrillation and flutter, and 411.4-coronary atherosclerosis).

Specifically, we tested the association of PTSD (13,877 cases) with 13 CV diagnoses (Supplementary Data S8) considering three adjustment models: i) base-model (covariates:- age, sex, and self-reported race); ii) SES-model (base-model covariates and deprivation index, smoking, and BMI), iii) depression-model (SES-model and depression diagnosis-[phecode 296.2]). PTSD was significantly associated with all 13 CV phecodes across all three models ($p < 5.15 \times 10^{-6}$; Supplementary Data S8). However, while there was no difference between the estimates obtained from base and SES-models, we observed a reduction in effect sizes observed in the depression model compared to the base model ranging from 84% for chronic ischemic heart disease (odds ratio, OR = 2.61 vs 1.41, p-difference = 5.44×10^{-19}) to 48% for hypothyroidism (OR = 1.78 vs 1.2, p-difference = 5.7×10^{-25}). Nevertheless, the effect sizes observed accounting for depression comorbidity confirm the relationship linking PTSD to CV-related traits.

Partitioned heritability to identify tissues overlapping between PTSD, CV diagnoses, heart imaging, and LE8 traits

To gain biological insights into PTSD and CV conditions, we further employed in-silico genetic approaches to identify tissues that might overlap due to similar gene expression profiles. We limited our analyses to CV traits that showed multiple levels of evidence for genetic overlap: 13 CV diagnoses (meta-analyzed between UKBB and MVP; Supplementary Data S9), 8 heart imaging traits and eight LE8 traits.

We conducted a partitioned-heritability analysis, which systematically models tissue-specific gene expression data from 205 cell-type and gene expression annotations. This approach integrates GWAS data for the trait of interest to prioritize disease-specific causal tissues. We identified 6 tissues that are enriched based on gene expression in PTSD: the limbic system ($p = 4 \times 10^{-6}$), the cerebral cortex ($p = 6 \times 10^{-5}$), the brain ($p = 4 \times 10^{-6}$), the entorhinal cortex ($p = 4 \times 10^{-4}$), the hippocampus ($p = 10^{-3}$), and the brain cortex ($p = 9 \times 10^{-4}$). These tissues were not FDR significant in other traits, but were nominally significant for nonspecific chest pain, overweight, 'overweight, obesity and other hyperalimentation', physical activity, smoking, diet intake proportion of protein, and insomnia (SlpFall- difficulty in falling asleep, and SlpWakePM-difficulty in falling asleep after waking up in the middle of the night) ($p < 0.05$; Supplementary Data S10; Supplementary Fig. S5). No heart imaging trait remained significant in the multi-tissue enrichment analysis.

Proteome-Wide Association Study (PWAS): integrating genetic variants from GWAS and proteome expression in brain and blood tissues

PWAS studies combine effect-estimate of genetic variants on diseases, and abundance or expression of proteins, thereby prioritizing genes that may be associated with disease/traits via altered proteome expression. We tested GWAS of PTSD, and CV phenotypes with genetically regulated proteome expression in dlPFC and blood. The CV phenotypes included 13 phecodes, seven heart imaging traits, and LE8 factors. To maximize statistical power, we meta-analyzed GWAS of each of the 13 CV diagnoses from MVP and UKBB to improve statistical power for gaining insights into overlapping mechanistic pathways [N total = 865,527]. Details regarding each meta-analyzed CV diagnosis are available in Supplementary Data S9. Leveraging weights derived from dlPFC-specific pQTLs, we identified 122 genes associated with both PTSD and CVD phenotypes (FDR $q < 0.05$; Fig. 4, Supplementary Data S11). The majority of these PTSD associations were shared with LE8 factors ($N = 109$). Several genes demonstrated proteomic associations across CV phecodes, heart imaging phenotypes, and LE8 factors (e.g., *ATG7*, *CCDC92*, *CNNM2*, *DNM1*, *FAM134 A*, *SIRPA*, *SNX32*, and *TROIM47*). Other pleiotropic genes included *CCDC92*, *SIRPA* and *LRRC37A2* that were associated with PTSD and 20 or more CV-related phenotypes (Supplementary Data S11). The strongest proteome-wide association with PTSD was observed with *ICA1L* ($Z = 6.89$, $p = 5 \times 10^{-12}$) that was also associated with several CV phecodes such as atrial fibrillation ($Z = 2.9$, $p = 4 \times 10^{-59}$), coronary atherosclerosis ($Z = 16.2$, $p = 5 \times 10^{-50}$), and T2D [EHR-MVP + UKBB] ($Z = 3.87$, $p = 1.07 \times 10^{-4}$). While these associations were positively related to increased *ICA1L* proteomic expression, we also observed an inverse relationship with total cholesterol ($Z = -18.86$, $p = 2 \times 10^{-79}$), insomnia ($Z = -6.03$, $p = 2 \times 10^{-9}$), physical activity ($Z = -3.41$, $p = 6 \times 10^{-4}$), and smoking ($Z = -4.85$, $p = 10^{-6}$). The strongest inverse association with PTSD was *KHK* ($Z = -6.86$, $p = 7 \times 10^{-12}$), which was also negatively associated with several other phenotypes, such as T2D ($Z = -5.22$, $p = 2 \times 10^{-7}$), hypertension ($Z = -4.59$, $p = 4 \times 10^{-6}$), unspecified chronic ischemic heart disease ($Z = -4.04$, $p = 5 \times 10^{-5}$), hypothyroidism ($Z = -3.94$, $p = 8 \times 10^{-5}$) protein intake ($Z = -3.84$, $p = 10^{-4}$), coronary atherosclerosis ($Z = -3.82$, $p = 10^{-4}$), and nonspecific chest pain ($Z = -3.32$, $p = 9 \times 10^{-4}$). *KHK* was positively associated with BMI ($Z = 3.49$, $p = 5 \times 10^{-4}$) and LE8-T2D ($Z = 3.56$, $p = 4 \times 10^{-4}$). Total cholesterol demonstrated the highest

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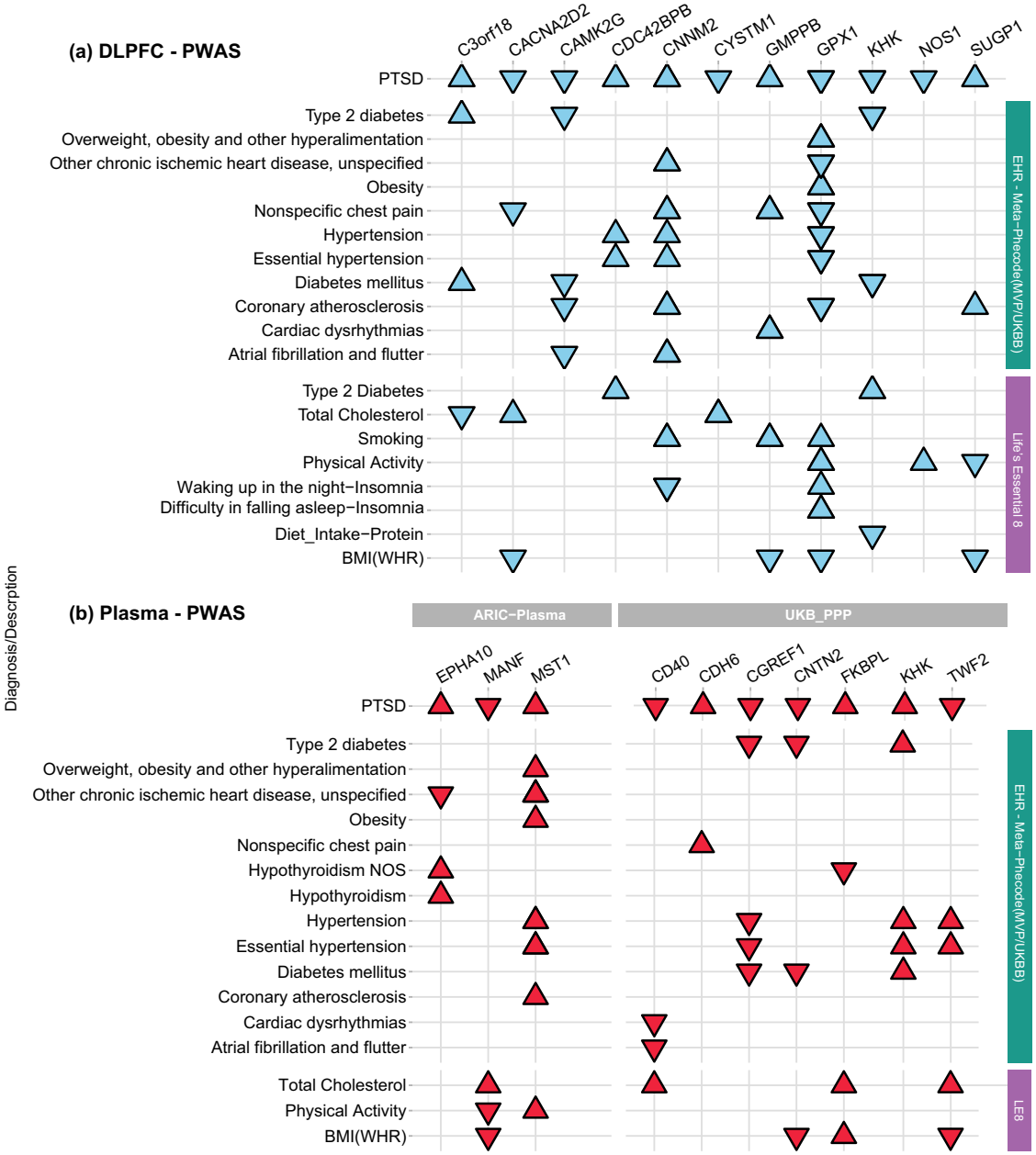

Fig. 4 | Shared genes between PTSD and CV conditions based on proteome-wide associations. Distribution of z-scores across significant PWAS genes between PTSD and CV conditions using A) brain proteome in blue and B) blood proteome in red. Genes are grouped based on two blood-based proteome panels/brain-based panel (y-axis) and respective CV conditions (x-axis). Significant genes are shown as red (blood) or blue (brain) triangles, wherein triangles facing up and down represent positive and negative z-scores (two-sided), respectively.

number of overlapping genes with PTSD, with 56 genes overlapping in the brain proteome including genes with the highest effect estimate such as *PLCG1* ($Z = -18.349$, $p = 3.37 \times 10^{-75}$). Among the significant genes, we applied FOCUS to prioritize causal genes that mediate risk to the trait via proteome abundance. We found 11 genes in credible set that were causal for PTSD and at least one CV trait (Supplementary Data S12, Fig. 4A).

Leveraging blood-proteome expression from two different studies, ARIC (using FUSION), and UKBB-PPP(using SMR), we identified 33 genes associated with both PTSD and at least one or more of the 13 CV diagnoses, 8 heart imaging traits, and LE8 factors investigated (Supplementary Data S11). The strongest positive association with PTSD was *FES* ($Z = 6.15$, $p = 8 \times 10^{-10}$), which was also positively associated with smoking ($Z = 5.95$, $p = 3 \times 10^{-9}$) and physical activity ($Z = 4.19$, $p = 3 \times 10^{-5}$). *FES* proteomic expression exhibited negative associations with essential hypertension ($Z = -9.92$, $p = 3 \times 10^{-23}$), unspecified chronic ischemic myocardial disease ($Z = -8.51$, $p = 2 \times 10^{-17}$), and global myocardial wall-thickness at end-diastole ($Z = -4.08$, $p = 5 \times 10^{-5}$). The strongest negative association with PTSD was observed with *CD40* ($Z = -5.27$, $p = 10^{-7}$), which was also negatively associated with atrial fibrillation and flutter ($Z = -3.73$, $p = 2 \times 10^{-4}$) and positively associated with total cholesterol ($Z = 7.17$, $p = 8 \times 10^{-13}$). Considering both blood and dlPFC, *SIRPA*, *MANF*, and *POR* exhibited cross-tissue proteome-wide associations with PTSD and CVD traits (Supplementary Data S11). To prioritize genes statistically causal genes, we applied FOCUS and HEIDI tests on ARIC, and UKBB-PPP respectively. We observed 10 genes that were causal for PTSD and CV traits (Supplementary Data S12 Fig. 4B).

By comparing genes prioritized from colocalized regions and genes identified from PWAS, we identified 403 distinct genes with 17

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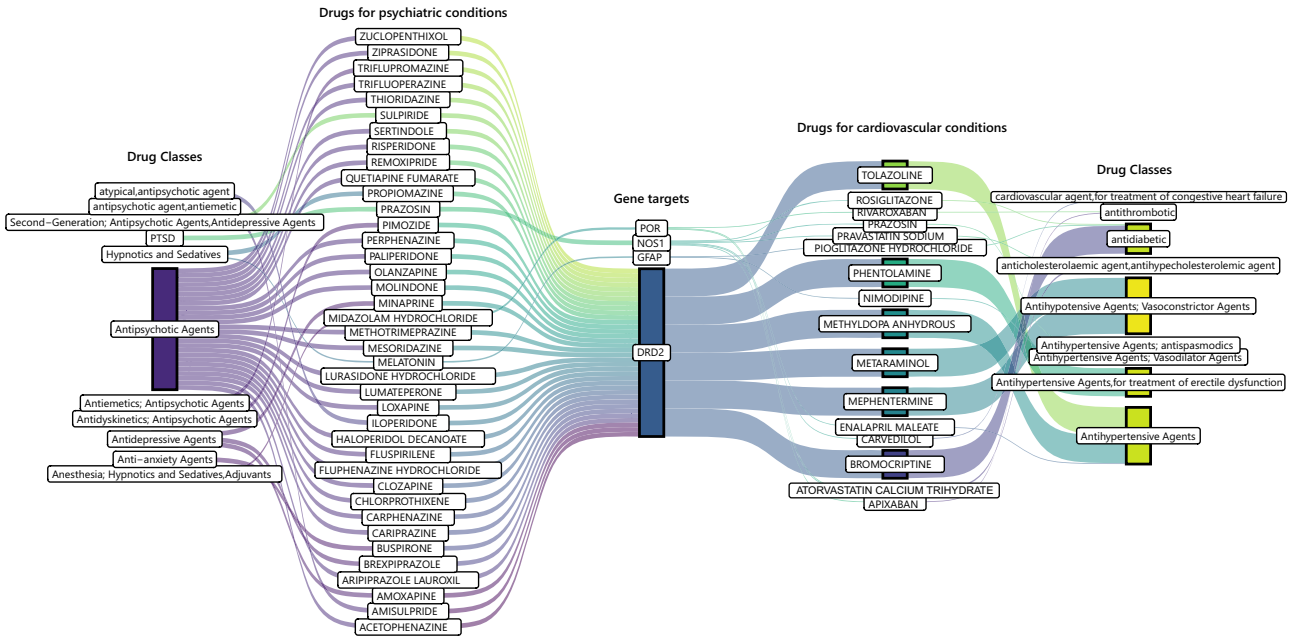

Fig. 5 | Comparing common drugs and their gene-targets between PTSD and CV conditions. This Sankey plot shows the psychiatric drugs and their classes (first & second panel) that target genes – *DRD2*, *GFAP*, *POR* and *NOS1* (third panel), which are also targeted by CV drugs (third panel) and their corresponding CV categories (fourth & fifth panel) (see Supplementary Data for more details).

overlapping between the two methods: *BTN2A1*, *BTN3A2*, *C3orf18*, *CACNA2D2*, *CD40*, *DAG1*, *FES*, *FURIN*, *GMPPB*, *GPX1*, *HYAL1*, *LRRC37A2*, *MST1*, *NCAM1*, *SEMA3F*, *SERPING1*, *UBE2L6*.

Pathway enrichment

Considering genes identified by the tissue-specific PWAS, we identified 25 pathways overrepresented by the PTSD&CV proteome-wide significant genes in the dlPFC, and 36 pathways in the blood (Supplementary Data S13). Among the dlPFC PWAS genes, in addition to basic cellular functions (Supplementary Fig. S6; Supplementary Data S13), we observed metabolic and calcium modulating pathways: "oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor" (FDR P-value = 3.92×10^{-2}), "Calmodulin-induced events" (FDR P-value = 3.97×10^{-2}), the "CaM pathway" (FDR P-value = 3.97×10^{-2}), and "Ca-dependent events" (FDR P-value = 4.95×10^{-2}). We also performed pathway enrichment on 11 statistically causal genes identified, and observed seven pathways, including "Pathways of neurodegeneration-multiple diseases", "Adrenergic signaling in cardiomyocytes", "Oxytocin signaling pathway", "Metabolic pathways", and "Calcium signaling pathway" (FDR P-value < 0.05) (Supplementary Data S14).

Among the pathways overrepresented by the blood PWAS genes, in addition to biological and cellular processes (Supplementary Fig. S7; Supplementary Data S13), we observed several immune and neuronal processes Such as "response to stimulus" (FDR P-value = 5.84×10^{-4}), "regulation of immune response" (FDR P-value = 4.98×10^{-3}), "regulation of immune system process" (FDR P-value = 7.33×10^{-3}), "regulation of response to stimulus" (FDR P-value = 0.011), neuron projection development (FDR P-value = 0.014). None of the significant pathways enriched in blood and brain tissues were overlapping. The pathway enrichment for genes with a single causal variant for PTSD and CV traits did not identify any significant pathways.

Drug repurposing in research context

To contextualize the role of reported shared genes between PTSD and CV conditions, we aimed (i) to identify which of these shared genes/proteins are known therapeutic targets, (ii) determine if any of these shared genes are targeted by medications known to treat either condition, and/or (iii) if they exhibit opposing side effects. This analysis helps clarify why the observed genes may not be specific to a single disease but instead contribute to both conditions and the potential risks and benefits of the drugs involved.

We identified 74 approved drugs targeting 30 genes that were either designated for psychiatric (as a range of psychiatric drugs can be used for treating PTSD and associated symptoms) or cardiovascular conditions (Supplementary Data S15, Fig. 5). Looking at gene targets that overlap between psychiatric and CV conditions, we found *DRD2*, *GFAP*, *POR* and *NOS1* to be targets of several CV medications that address conditions including hypo/hypertension, diabetes, cholesterol and heart failure. Only Prazosin, an alpha-1 adrenergic receptor antagonist was the only drug that is known to treat hypertension, and has off-label benefit for PTSD-associated nightmares[42,43]. Among genes, *DRD2* had the highest number of interactions with both psychiatric and CV drugs. While interaction type between each drug and gene target is not available, we observed that 87.5% of drugs are inhibitors, and 21.5% are agonists to *DRD2*.

We also investigated adverse effects of these drugs, and among the 45 psychiatric drugs, most cardiovascular-system-related adverse effects included increased weight or weight fluctuations, tachycardia, and QT prolongation, which indicates a disturbance in the heart ventricle chamber signal transmission[44]. Other CV adverse effects of psychiatric drugs include blood glucose increase, diabetes, orthostatic hypotension, and dyslipidemia.

Conversely, among the 30 CVD drugs, adverse psychiatric effects were less observed, and included depression, suicide attempt, cognitive disorder, and hallucination. (Supplementary Data S16).

Discussion

To our knowledge, this is the first work that includes a comprehensive evaluation of CV measurements from diverse sources, such as imaging, diagnoses, and risk factors. By leveraging additional GWAS data of EHR-based phecodes for CV diagnoses from the MVP, the study generates statistically well-powered GWAS results, addressing phenotypes that previously lacked sufficient power or were analyzed using data from a single source, such as the UKBB. Additionally, the study validates genetic associations between PTSD and CV conditions using

observational data and dissects shared genes to explore the biological mechanisms underlying PTSD-CV comorbidity. We report causal variants for CV diagnoses and imaging traits that are shared with PTSD, while CV health behaviors, as per AHA's LE8 show a broader genetic overlap across several loci. Among the EHR CV traits, colocalization analyses of discovery and replication cohorts indicated loci 3p21.31, 17q21.31, 7p22.3, and 7p21.3 as potential PTSD-CVD pleiotropy hotspots. Specifically, loci 3p21.31 and 17q21.31 exhibited different LD-linked causal variants, while loci 7p22.3 (*MADIL1*, *ELFN1*) and 7p21.3 (*TMEM106B*, *VWDE*, *THSD7A*) had the greatest number of causal variants shared between PTSD and multiple CV conditions (e.g., hypertension, diabetes, coronary artery disease, obesity/overweight, atrial fibrillation, and non-specific chest pain). Although some of these loci have been identified in the context of psychiatric disorders[45–47], we additionally observed genes at these loci also colocalize between multi-tissue molecular profiles of several cardiovascular traits, highlighting their significant role as a potential common denominator to PTSD and CV conditions. Often, genetic data is a proxy for diagnostic risk, and mirrors association, but is limited in adjusting for additional confounders without losing statistical power. We confirmed the specificity of PTSD-CV genetic relationships using epidemiological observation from EHR data of 249,906 AllofUS participants. We observed that PTSD diagnosis is associated with 13 CV diagnoses (identified using genetic data from MVP EHR data and replicated in UKBB EHRs), even after accounting for smoking, BMI, deprivation index, and depression diagnosis. Interestingly, 4 of the 13 diagnoses overlap with CV health factors from the LE8 traits – type 2 diabetes, obesity, overweight, and hypertension, which is parallel to the genetic study of ideal cardiovascular health based on LE 7[48].

To comprehensively identify regions and genes, we recognized that LD-defined regions may not precisely align with genes based on their length or proximity. To address this, we implemented a multi-tiered analytical approach that examined both disease-related effects and quantitative trait loci effects. Specifically, we used colocalization analysis to investigate variants with disease-related effects (annotated based on their closest gene), and genes identified via PWAS, indicate a collective set of variants as protein quantitative trait loci (pQTLs) for each gene. By leveraging the cumulative effect of genetic variants on protein expression, also aids in identifying potentially actionable gene targets that overlap between PTSD and cardiovascular conditions. We identified twice as many genes using brain-based proteome expression weights than with blood. We also observed interesting relationships, such as total cholesterol demonstrating negative genetic correlation with PTSD at multiple loci, and almost half of the gene associations have opposite effect estimates between PTSD and total cholesterol. These observations may contribute to the abnormal total cholesterol reported in individuals with PTSD[49]. Additionally, we report many shared proteomic associations of PTSD and CVD to further identify underlying common disease mechanisms and therapeutic targets. Among them, *LRRC37A2* was related to the most CVD traits ($N = 20$), followed by *MST1* ($N = 18$). *LRRC37A2* has been associated with coronary artery disease[50], cardiorespiratory fitness[51], and thyroid function[52]. *MST1* activation has been linked to the pathogenesis of cardiovascular and metabolic diseases[53] while its downregulation in the hippocampus appears to be protective in the context of stress-related mental health conditions (e.g., PTSD)[54]. *NCAM1* showed the most statistically significant proteomic association with smoking. This is in line with previous evidence linking this locus to smoking[55]. Other PTSD-CV shared genes with supporting evidence from previous CV studies included *TMEM106B*[56–58], *MAD1L1*[59,60], *SATB1*[61], *PLCL2*[62], *FURIN*[63,64], *FOXP2*[65], *ESR1*[66], and *CNNM2*[67]. Pathway enrichment analyses highlighted different blood vs. brain patterns. Specifically, genes identified by the blood-based PWAS were enriched for mostly immunological and neuronal processes, while the brain-based PWAS genes were related to carbohydrate metabolism and calcium-modulating functions. The pathway enrichment of genes that are statistically causal for brain proteome expression further highlighted the role of metabolism of oxytocin, calcium signaling, adrenergic signaling in cardiomyocytes, and circadian rhythm. These findings converge with previous hypotheses related to the role of immune-metabolic signaling[68,69] and calcium dysregulation[70–74] in PTSD and CV pathogeneses. This tissue-specific pathway identification is likely due to the differential gene expression between blood and brain samples. Additionally, a caveat that should be considered is substantial differences in sample sizes across proteome studies: the brain-proteome reference includes only 528 samples, compared to over 7,000 and 50,000 samples in the blood-proteome studies. These sample size disparities significantly impact statistical power and our ability to detect associations, wherein the blood proteome has better power over the brain proteome as of current data available.

The drug repurposing analyses contextualized the role of shared genes between PTSD and cardiovascular conditions as potential targets of both psychiatric and CV drugs, or exhibit opposing side effects, suggesting these genes may influence both conditions rather than being disease-specific. We identified *DRD2*, *GFAP*, *NOS1* and *POR* as common gene targets of several PTSD and CV drugs. Prazosin was common to PTSD and CV conditions, although with mixed results for alleviation of PTSD and related symptoms. Altered levels of *GFAP* expression are associated with PTSD[75], and thrombotic injury to the vascular muscle leads to secretion of GFAP[76]. Furthermore, the drugs used for PTSD treatment that we identified in our drug-gene-interaction analysis have reported adverse CV effects such as weight gain, weight changes, cardiac arrhythmia, abnormal blood pressure, and diabetes[77,78]. *NCAM1*, which colocalizes with BMI, is on the same locus as *DRD2* at 11q23.2, with both genes having molecular colocalization with insulin-like growth factor, blood pressure, and BMI. On the other hand, CVD drugs that exhibit psychiatric adverse effects such as depression and cognitive dysfunction have been associated with serotonergic[79], and antidepressant response[80–82] respectively. These findings suggest a common role of the drugs in the two different diseases, where multiple mechanisms may be involved, either protective or detrimental.

While we provide a comprehensive assessment of the biology shared between PTSD and several CV conditions, our study has some limitations. Due to the well-known disparities in genetic research[83], our analyses were limited to European ancestries, which do not allow generalization in all continental populations. We used MVP as the discovery cohort for EHR-based CV diagnoses due to its relatively low sample overlap with PTSD GWAS [~29%], this may have filtered out some loci that could have been identified with other cohorts as discovery. Additionally, veteran participants may not be representative of genetic profile identified from other (civilian) populations due to underlying demographic differences, such as recruitment design, varied healthcare administration patterns, type and burden of trauma exposure, higher male prevalence, and MVP being slightly older cohort (average age is 61.9 yrs) than AoU (average age is 57.3 yrs), and UKBB (average age is 56.52 yrs). Since we prioritized large and diverse measurements of CV conditions, this would lead to phenotype differences, a potential caveat to consider while interpreting results. We leveraged all the recent proteome studies to dissect molecular pathways, which led to using two different TWAS approaches, FUSION and SMR, as the weights were only available for the specific approach. While we were comprehensive in assessing all cohorts, these methodological differences could have led to capturing different sets of gene associations. Furthermore, though all the methods[84–87] we implemented do account for sample overlap, there is possibility that some gene-trait associations might be cohort specific, such as those from UKBB. Therefore, these genes should be tested further when large-scale cohorts for molecular phenotypes become available in the future. While our observational analysis in the AllofUs cohort confirmed the PTSD-CV

comorbidities in the civilian cohort, further studies will be needed to verify the same for PTSD-CV shared loci identified in our molecular analyses. The observational analysis was cross-sectional using the lifetime prevalence of PTSD and CV conditions. This did not permit us to investigate the temporal relationships between the two traits. The drug-gene targets and subsequent mapping to PTSD and CV conditions is explained as an example to learn about the role of gene drugs in therapeutic and adverse effects of drugs. The drugs mentioned were identified from research studies and may not reflect actual prescription practices and need further validation before we can make hypotheses regarding their impact on patients' implications. Pharmacovigilance data for gene-drug targets was extracted from a single source and may not be updated from research data or ongoing trials.

In conclusion, this study examines the shared biology of PTSD and CV health, leveraging large-scale molecular data and multi-modal information. Specifically, considering EHR diagnoses, cardiac imaging phenotypes, and cardiac health-related habits, we highlighted the local genetic correlations, proteomic and transcriptomic associations, and the potential pharmacological targets for molecular mechanisms underlying PTSD-CVD comorbidity. These findings converge on overlap in several domains across PTSD and CVD and within the context of the broader PTSD-CVD literature highlight important mechanisms relevant to potential pharmacological intervention, warranting additional research.

Methods

Study populations

We conducted the study to explore the genetic overlap between PTSD and cardiovascular outcomes, as defined by electronic health records (EHR) and heart imaging (Fig. 1). Because we used previously collected, deidentified, data, this study did not require institutional review board approval. Ethics approval and participants' consent were obtained by the original studies[2,30,33–39,88–92].

Summary statistics for GWAS of PTSD utilized in this study originated from a comprehensive meta-analysis led by Nievergelt et al.[29] that identified 76 autosomal loci (Supplementary Data S1) using FUMA and the 1000G LD reference panel. This meta-analysis encompasses findings from 88 studies gathered through the PGC-PTSD Freeze 3 data collection from three primary sources: PTSD studies employing clinician-administered or self-reported instruments (Freeze 2.5 plus subsequently collected studies, 77 studies), Million Veteran Program (MVP) release 3 GWAS utilizing the Posttraumatic Stress Disorder Checklist (PCL for DSM-IV) [N = 186,689 individuals][93], and 10 biobank studies incorporating EHR-derived PTSD status. In total, the study incorporated 95 GWASs, with a sample size of 1,222,882 individuals of European descent (effective sample size (Neff) = 641,533).

GWAS of cardiovascular and metabolic diagnoses using EHR

Million Veteran Program. The CVD phenotype datasets utilized in this study were sourced from the MVP[94] (see data availability), a nationwide initiative sponsored by the Department of Veterans Affairs Office of Research and Development[95]. In our investigation of the genetic overlap between PTSD and cardiovascular clinical outcomes, we leveraged summary statistics from GWAS of EHR-based phecodes. Phecodes are manually curated groups of International Classification of Diseases (ICD) codes-9/10, designed to capture clinically meaningful concepts for research purposes using the PheMap, which classifies diagnoses into 17 categories (available at https://phewascatalog.org/)[96]. We tested 141 diagnoses from circulatory and 105 from endocrine/metabolic categories. A detailed description of GWAS of these traits in 458,203 individuals of European genetic ancestry in MVP is available elsewhere[94]. (Supplementary Data S2).

UK Biobank. To replicate MVP findings, we leveraged GWAS of EHR-based phecodes data available from the UK Biobank (UKBB)[97]. Specifically, we analyzed summary statistics of GWAS of phecodes in 420,531 participants of European descent performed by the Pan-UKBB initiative[32]. Each MVP trait was matched with a corresponding UKBB phenotype based on their phecode concordance. Because MVP phecodes 278.11, 427.21, 428.3 were not available in the UK Biobank, we used the numbering to find the exact matches, some codes were unavailable, so we used the closest decimal available: Phecode 278.11 (Morbid Obesity, MVP) to Phecode 278.1 (Obesity, UKBB), Phecode 427.21 (Atrial Fibrillation, MVP) to Phecode 427.2 (Atrial Fibrillation and flutter, UKBB), and Phecode 428.3 (Heart failure with reduced EF [Systolic or combined heart failure], MVP) to Phecode 428.2 (Heart failure NOS, UKBB), and Venous thromboembolism with chronic venous insufficiency, since both conditions relate to damage in the leg veins, as that was closest proxy available. The details of the replication datasets are presented in Supplementary Data S3 with a comprehensive overview of clinical diagnoses, corresponding phecodes, study resources, and sample sizes.

Other GWAS cohorts. In addition to the UKBB data, we replicated MVP findings also using 11 GWAS performed from major consortia that may include a combination of self-reported or clinical studies[33–39]. The sample sizes of these datasets ranged from 119,715 to 1,020,441, and their diagnoses were paired with corresponding phecodes (Supplementary Data S3)[34,39]. For Type 2 Diabetes adjusted by BMI, we used summary statistics by the Diabetes Meta-Analysis of Trans-Ethnic association studies (DIAMANTE) Consortium[38], which are genetically correlated (rg) with Phecode 250.2 (Type 2 Diabetes: rg = 0.992, SE = 0.008; $p < 1 \times 10^{-300}$) and Phecode 250 (Diabetes Mellitus rg=0.991, SE = 0.008; $p < 1 \times 10^{-300}$).

GWAS of heart imaging phenotypes from the UK Biobank. To also explore PTSD relationship with the structure and function of the heart and aorta, we incorporated summary-level data from a cardiac imaging GWAS[30]. This study used information from UKBB participants who underwent comprehensive cardiovascular magnetic resonance (CMR) imaging and employed a machine learning regenerating and analyzing pipeline that resulted in 82 quantitative imaging phenotypes from 26,893 participants of European descent[30]. These phenotypes (e.g., short-axis, long-axis, and aortic cine images) provide a detailed characterization of cardiac and aortic structure and function (Supplementary Data S2)[30].

GWAS of CV risk factors as defined by Life's Essential 8. To investigate the role of other factors in the genetic overlap with CV health and PTSD, we considered the LE8 checklist defined by AHA, 2022[2], which underscores eight key health factors and health behaviors related to CV well-being: eat better, be more active, quit tobacco, get healthy sleep, manage weight, control cholesterol, manage blood sugar, manage blood pressure. For our study, we identified 11 GWAS related to LE8 factors (N = 282,271 ~ 1,320,016), including GWAS for diet (i.e., energy intake proportion of fat, carbohydrate, protein, each adjusted by body mass index, BMI)[91], physical activity[90], smoking[89], insomnia[92], BMI-adjusted waist-hip-ratio (BMI(whr))[39], total cholesterol[88], diabetes[38], and hypertension [MVP + UKBB]. To maximize the sample size available, we meta-analyzed hypertension GWAS (phecode 401) available from MVP and UKBB, resulting in a sample size of 433,585 cases and 421,076 controls. We used GWAS of BMI(whr), because it helps distinguish between different types of adiposity. While BMI measures overall body mass, it doesn't differentiate between peripheral fat and central/abdominal fat, which have different metabolic implications[98]. Central adiposity is more strongly associated with metabolic disorders and cardiovascular risk than overall adiposity. By adjusting BMI for WHR, we aim to better isolate genetic variants specifically associated with metabolic health related to central

adiposity[99]. Additionally, we do use the GWAS of BMI as part of the replication cohorts listed in other GWAS cohorts. For insomnia, we generated two GWAS datasets, one meta-analyzing GWAS of insomnia from Watanabe and colleagues[92] with MVP GWAS of "unable to fall asleep" (SlpFall – 188,830 cases) and the other meta-analyzing Watanabe insomnia GWAS[92] with MVP GWAS of "waking up in the night and not be able to fall back asleep" (SlpWakePM – 216,711 cases). To maximize the sample size available, when needed, GWAS datasets were meta-analyzed using a fixed-effects inverse variance-weighted model available in METAL[100]. A detailed description of all cohorts is presented in Supplementary Data S2.

Proteomic cohorts

A Proteome-Wide Association Study (PWAS) identifies whether the relationship between genetic variants and disease outcomes is mediated by changes in protein levels. It uses effect estimates (known as weights) derived from protein quantitative trait loci (pQTLs) and integrates them with disease/trait GWAS to determine if genetic variants contribute to disease risk through their effects on protein abundance. Here we describe the sources of each of the cohorts that have data available on genotypes and protein abundance from blood and brain tissues.

Brain proteomic datasets. The Religious Orders Study and Rush Memory and Aging Project (ROS/MAP) proteome expression weights (effect estimates of pQTLs) were generated by Wingo et al.[101], using dorsolateral prefrontal cortex (dlPFC) tissues available from 376 individuals of European ancestry[101]. Briefly, 1,475 proteins exhibited significant cis associations with genetic variation. The weights/effect estimates assigned to pQTLs were used in our PWAS. Additionally, their study utilized dlPFC genetic-proteomic data from the Banner Sun Health Research Institute (BANNER). This dataset comprises brain dlPFC samples from 152 individuals of European descent, with 8,168 proteins included in proteomic profiles following quality control[101]. Through the integration of proteomic expression data and SNP genotypes, 1,139 proteins exhibited significant pQTLs. (See Data Availability and Links).

Atherosclerosis Risk in Communities (ARIC) Study. To study the plasma proteome, we utilized data from Zhang and colleagues[102]. Proteomic data were derived from summary-level information obtained from The Atherosclerosis Risk in Communities (ARIC) Study, focusing on 7213 individuals of European descent[102]. The study measures plasma proteome levels using the SOMAmer-V4 platform. After quality control, 1348 plasma proteins exhibiting associations with common variants in cis regions were investigated in our PWAS study (See Data Availability).

UKBB-Plasma Proteome Project (UKB-PPP). In addition to the ARIC Study, we tested data from the UK Biobank Pharma Proteomics Project (UKB-PPP). This project provides the plasma proteomic profiles of 54,219 participants. UKB-PPP used Olink proteomics assay for proteome assessment and reported expression weights for protein quantitative trait loci (pQTLs) for 2923 unique proteins[103].

Risk loci from PTSD GWAS

To identify genomic loci of interest in PTSD GWAS summary statistics, as per original study we used Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA)[104]. Considering LD weights from the European reference populations of the 1000 Genomes Project, resulting in 76 independent genomic risk loci ($P < 5 \times 10^{-8}$, $r^2 < 0.6$, MAF ≥ 0.01, LD distance <250 kb) (Supplementary Data S1) as reported by Nievergelt et al. 2024.

Shared regions and variants between PTSD and the CVD traits

Local Analysis of [co]Variant Association (LAVA). LAVA[84] was employed to identify loci exhibiting local genetic correlation between PTSD and a total of 328 CV traits across three categories. We applied univariate LAVA models at the 76 PTSD risk loci to estimate heritability. Loci that reached false discovery rate significance at 5% (FDR $q < 0.05$) for the heritability (univariate model) were selected for local genetic correlation (bivariate) between PTSD and each one of the CV/LE8 traits. Local RG results were filtered to include only those cases where both traits exhibited significant heritability on the locus, as determined by an FDR $q < 0.05$. Sample overlap was estimated with LD score regression (LDSC)[85] with the European LD scores calculated from the 1000 Genomes as reference (https://github.com/bulik/ldsc). Variants that were not SNPs (e.g., indels) and SNPs that were strand-ambiguous, multi-allelic, and had a minor allele frequency (MAF) < 0.01 were excluded.

Colocalization analysis. Colocalization is a statistical approach used to assess whether pairs of traits share a putative causal variant within the same genomic region. COLOC employs a Bayesian approach, considering various variant-level hypotheses and calculating Bayes factors from SNP effect estimates and standard errors[40]. The variant-level hypotheses correspond to: H0 (no association to either trait), H1 (association to only trait 1), H2 (association to only trait 2), H3 (associations to both traits with different causal variants), and H4 (associations to both traits with shared causal variants)[31]. In our study, each genomic region was expanded by 500 kb on either side of the position. COLOC[40] was applied to assess colocalization between PTSD and the significantly correlated trait. Results with H4 or H3 hypothesis probabilities ≥80% were considered as shared with default priors of 1×10^{-4}. For replication, we used data from UKBB and other cohorts considering H4 or H3 hypothesis probabilities ≥70% as strong evidence of shared variants.

Tissue and molecular-profile-based prioritization of genes within colocalized regions. To identify genes within each locus (i.e., colocalized regions between PTSD and CVD traits) based on physical location, we used the UCSC Genome Browser (see Data Availability and Links). To prioritize genes based on their regulatory roles, we evaluated colocalization probabilities (H3 and H4) for molecular profiles, including gene, protein, and splicing expression across various tissues. These probabilities were obtained for the identified genes and all reported psychiatric/CV phenotypes from published GWAS studies using OpenTargets[41]. By manually examining the traits, we labeled the traits as psychiatric and/or CVDs.

Observational analysis in All of US Research Program

Started in 2018, the National Institutes of Health's All of US (AoU) Research Program has enrolled over 700,000 diverse participants, emphasizing health equity in the context of precision medicine. Leveraging EHR data available for 254,700 AoU participants[105], phecodes were mapped from International Classification of Disease ICD9/ICD10(CM) codes using Phecode Map (see data availability and links). Logistic regression (two-sided p-value) using the PheWAS R package was employed to assess the association of PTSD (13,877 cases) with CV phecodes identified in MVP and UKBB analyses, considering three models (i) base-model (sex, age, self-reported race), (ii) socioeconomic (SES)-model (bases model covariates plus BMI, smoking, deprivation index), and (iii) depression-model (SES-model covariates plus depression diagnosis: phecode 296.2-Ncases:72,143). The self-reported demographic characteristics of AoU are as follows: females (61.8%), average age in years = 54 ± 17 (mean ± SD), 57.17% White, 19.4% (self-identified race), Black or African American, 3.54% Asian, 0.62% Middle Eastern/North African, 1.92% More than one population, 0.11% Native

Hawaiian/Pacific Islander, and 17.1% None of the above), while 44.1% were smokers (past and current).

Partitioned heritability for tissue-specific enrichment

To identify disease-relevant tissues for PTSD and CV traits, we applied stratified LD score regression[106] to the GWAS summary statistics of each trait. LDSC-seg leverages gene expression data from diverse tissues to quantify the heritability enrichment for specific tissues. We analyzed 205 gene expression- tissue/cell-type annotations from GTEx and Franke lab[106].

Proteome-wide association study

Proteome-wide associations of PTSD and its colocalized traits were estimated. We integrated GWAS data with tissue-specific pQTLs. For the colocalized phecodes, PWAS was conducted using the meta-analysed GWAS combining MVP and UKBB as described above, using the FUnctional Summary-based ImputatiON (FUSION) (available at http://gusevlab.org/projects/fusion/)[86] for ROSMAP/Banner (brain), and ARIC (plasma). The subsequent genes were tested in FOCUS for prioritization of statistically causal genes. PWAS using weights from UKB-PPP plasma proteome was performed using Summary-based Mendelian Randomization (SMR)[87]. The analysis was performed using SMR[87]. The results were adjusted for multiple testing with FDR correction (FDR $q < 0.05$). Significant FDR genes were prioritized using the HEIDI test to identify causality (p_HEIDI > 0.05).

In-silico functional analysis

Pathway enrichment. To gain insight into the shared mechanisms between PTSD and CVD traits, we conducted pathway enrichment analysis based on the genes detected in brain and blood proteome-wide analyses. Pathway enrichments for each tissue-based PWAS genes were sought using a web-based tool, g:Profiler (https://biit.cs.ut.ee/gprofiler/gost) among three libraries: Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG), and Reactome Pathway Database (REAC)[107]. GO Database contains three functional domains: cellular component (CC), molecular function (MF), and biological process (BP). A significance threshold of FDR q < 0.05 was used to identify significant pathways.

Drug repurposing in the research context. Significant genes from the brain and plasma PWAS and the prioritized genes from the colocalization analysis were used for identifying drugs from the drug-gene interaction database (DGidb)[108]. Secondly, we obtained information including drug ID, clinical uses, and adverse effects from stored at OpenTargets (https://www.opentargets.org/), which are originally sourced from the FDA database. The OpenTarget results were compared with current CVD and PTSD treatments to identify drugs with overlapping functions and suggest new potential therapies.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The meta-analyzed MVP-UKBB GWAS summary statistics of 14 traits that generated in this study have been deposited in the zenodo database under accession code [https://doi.org/10.5281/zenodo.15243069]. The MVP summary statistics data are available under https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001672.v11.p1. The raw UKBB data are protected and are not available due to data privacy laws. The processed UKBB data are available at Pan-UKBB: https://pan.ukbb.broadinstitute.org/. The data generated in this study are provided in the Supplementary Information/Source Data file. The access to AllofUS was made through data use agreement at https://www.researchallofus.org/data-tools/data-access/. The DLPFC proteome weights are available at https://doi.org/10.7303/syn23627957, blood proteome weight are available at http://nilanjanchatterjeelab.org/pwas/; and UK Biobank Plasma Proteome at https://metabolomips.org/ukbbpgwas/. Software/web resources links include, UCSC Genome Browser: https://genome.ucsc.edu/cgi-bin/hgTables, Open Targets: https://genetics.opentargets.org/, LAVA: https://github.com/josefin-werme/LAVA, SMR: https://yanglab.westlake.edu.cn/software/smr/, and Phecode Map: https://phewascatalog.org/. We did not use any custom code for the analysis performed in this study.

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Acknowledgements

This study was supported by grants from the National Institutes of Health (RF1 MH132337-RP, R33 DA047527-R.P., and K99 AG078503-G.A.P.), One Mind-RP, the Alzheimer's Association (Research Fellowship AARF-22-967171-G.A.P.), Horizon 2020 (Marie Sklodowska-Curie Individual Fellowship 101028810-D.K.), Yale Women's Faculty Forum-GAP, and Suzhou Municipal Health Commission (LCZX202207)-J.S., L.S., H.L. We also acknowledge the contribution of the participants, and the investigators involved in the UK Biobank, the Million Veteran Program, the All of Us Research Program, and the Psychiatric Genomics Consortium. Major financial support for the PTSD-PGC was provided by the Cohen Veterans Bioscience, Stanley Center for Psychiatric Research at the Broad Institute, and the National Institute of Mental Health (NIMH; R01MH106595, R01MH124847, R01MH124851-PGC-PTSD). The All of Us Research Program is supported by the National Institutes of Health, Office of the Director: Regional Medical Centers: 1 OT2 OD026549; 1 OT2 OD026554; 1 OT2 OD026557; 1 OT2 OD026556; 1 OT2 OD026550; 1 OT2 OD 026552; 1 OT2 OD026553; 1 OT2 OD026548; 1 OT2 OD026551; 1 OT2 OD026555; IAA #: AOD 16037; Federally Qualified Health Centers: HHSN 263201600085U; Data and Research Center: 5 U2C OD023196; Biobank: 1 U24 OD023121; The Participant Center: U24 OD023176; Participant Technology Systems Center: 1 U24 OD023163; Communications and Engagement: 3 OT2 OD023205; 3 OT2 OD023206; and Community Partners: 1 OT2 OD025277; 3 OT2 OD025315; 1 OT2 OD025337; 1 OT2 OD025276.

Author contributions

G.A.P. and R.P. supervised the study. J.S., G.A.P., R.P., and G.J.F. contributed to the study design. J.S. led the analysis, W.V., E.F., C.O., and D.K. contributed to the analysis and data collection. K.W.C., C.J.O., M.B.S., H.L., L.S., and J.G. contributed to the result interpretations. The Posttraumatic Stress Disorder Working Group of the Psychiatric Genomics Consortium provided data. All authors contributed to the manuscript drafting and revisions.

Competing interests

R.P. reports a research grant from Alkermes outside the scope of this study. R.P. and J.G. are paid for their editorial work on the journal Complex Psychiatry. J.G. is named as an inventor on PCT patent application no. 15/878,640 entitled "Genotype-guided dosing of opioid agonists", filed January 24, 2018. M.B.S. has in the past 3 years received consulting income from Actelion, Acadia Pharmaceuticals, Aptinyx, atai Life Sciences, Boehringer Ingelheim, Bionomics, BioXcel Therapeutics, Clexio, Delix Pharmaceuticals, EmpowerPharm, Engrail Therapeutics, GW Pharmaceuticals, Janssen, Jazz Pharmaceuticals, and Roche/Genentech; has stock options in Oxeia Biopharmaceuticals and EpiVario; and has been paid for editorial work on Depression and Anxiety (Editor-in-Chief), Biological Psychiatry (Deputy Editor), and UpToDate (Co-Editor-in-Chief for Psychiatry). C.J.O an employee of Novartis Pharmaceuticals). D.K. is the founder and CEO of EndoCare Therapeutics, but the company conducts research unrelated to the present study. The other authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-025-60487-w.

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Peer review information *Nature Communications* thanks William Reay and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. A peer review file is available.

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