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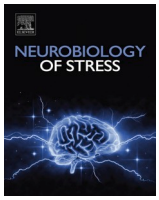

Shared genetic risk and causal associations between Post-traumatic stress disorder and migraine with antithrombotic agents and other medications

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ABSTRACT

Post-traumatic stress disorder (PTSD) is a psychiatric disorder that frequently co-occurs with pain disorders including migraine. There are proposed biological, genetic and environmental factors associated with both PTSD and migraine suggesting shared etiology. Genome-Wide Association Studies (GWAS) have been used to identify genomic risk loci associated with various disorders and to investigate genetic overlap between traits. There is a significant genetic correlation between PTSD and migraine with no evidence of a causal relationship that could be attributed to pleiotropy. Cross-disorder genetic analyses were applied to investigate the genetic overlap and causal associations using GWAS summary statistics of PTSD (n = 214408), migraine (n = 873341) and 23 medication use traits (n = 78808–305913) including anti-depressants, anti-migraine preparations and beta-blocking agents.

Across the entire genome, anti-thrombotic agents had a significant and negative genetic correlation with PTSD (rG = −0.2, P_{FDR} = 0.032) and a positive genetic correlation with migraine (rG = 0.26, P_{FDR} = 2.23 x 10^{-8}). PTSD showed significant genetic correlation with 11 other medication use traits including beta blocking agents (rG = −0.11, P_{FDR} = 0.034). Of the 2495 genomic regions tested, PTSD showed significant local genetic correlation with 12 medication use traits at 43 loci; while migraine showed significant genetic correlation with only anti-inflammatory agents and anti-rheumatic products at locus 12:57522282–57607142 (*DAB1*) ($P < 2 \times 10^{-5}$). The genetic liability to PTSD had a causal effect on increased risk of using pain medication such as opioids (β_{ivw} = 0.59, $P = 5.21 \times 10^{-5}$) while the genetic liability to migraine had a causal effect on the increased risk of using anti-thrombotic agents (β_{ivw} = 0.59, $P = 1.69 \times 10^{-7}$). The genes in the genomic regions shared between PTSD and medication use traits were enriched in neural-related pathways such as neuron development, neurogenesis and protein kinase activity. These results provide further insight into the genetically controlled biological and environmental factors underlying the shared etiology between PTSD and migraine. The identified biomarkers can be used as a basis for investigation as potential drug targets for both disorders. These findings are significant for drug re-purposing and treatment of PTSD and migraine using monotherapy.

1. Introduction

Post-traumatic Stress Disorder (PTSD) is a psychiatric disorder that occurs after exposure to extreme traumatic life events (APA, 2013). The lifetime prevalence of PTSD is estimated at 6%, and is higher in women (8%) than in men (4%) (Goldstein et al., 2016). PTSD has a genetic component with estimated heritability of 43% (95%CI: 15–63%) from twin studies and SNP-based heritability of 6.4% (Gasperi et al., 2021; Stein et al., 2021). PTSD has significant overlap with other psychiatric and personality disorders including major depressive disorder and generalized anxiety disorders such as anxiety and mood; and this complicates its treatment (Rytwinski et al., 2013; Herrera-Escobar et al.,

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2021). PTSD symptoms are heterogenous, and its treatment is targeted towards anxiety, hyperarousal and abnormal fear circuitry such as trauma-related cognitions (Burback et al., 2024). Medications commonly used for PTSD, for example sertraline, which is an anti-depressant, are used in the treatment of other disorders. Prazosin is an alpha1-adrenergic antagonist effectively used in PTSD patients with adrenergic dysfunction and for high blood pressure (Reist et al., 2021). PTSD does not occur in isolation and is often co-morbid with pain disorders including migraine (Polimanti et al., 2022; Blacker et al., 2019; Kind and Otis, 2019; Sareen, 2014).

Migraine is a neurovascular disorder characterized by severe unilateral throbbing headache attacks lasting 4−72 h (Goadsby et al., 2017a). The occurrence of migraine involves mechanical excitation of sensory fibres that innervate the intracranial blood vessels (Noseda and Burstein, 2013; Bernstein and Burstein, 2012). The lifetime prevalence of migraine is estimated at 15–20% and like PTSD, it is more common in females (19%) than males (11%) (Vos et al., 2020). The medications commonly used for migraine acute attacks include abortive drugs like triptans, anti-histamines, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and anti-emetics (Eigenbrodt et al., 2021; Brooks et al., 2023). These may be supplemented by prophylactic therapy for preventing attacks, such medications include gepants and monoclonal antibodies to CGRP (Eigenbrodt et al., 2021). The others include tricyclic anti-depressants, beta-blockers, calcium channel blockers, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and anti-epileptic medication. (Brooks et al., 2023; Minen et al., 2016). Studies show varied impact of psychiatric disorders on the outcome of migraine treatment with some reporting failure or no impact on improvement, additionally they have been associated with increased frequency of migraine attacks and drug intake (Radat, 2021; Oh et al., 2014).

There are drugs that have been found to be effective for treatment of both migraine and psychiatric disorders. Anti-convulsants and beta-blocking agents such as propranolol which are used for treatment of high blood pressure and arrhythmia, and prevention of heart attack and stroke; are effective for prevention of migraine and help with anxiety symptoms but can aggravate depression (Minen et al., 2016). Tricyclic anti-depressants (TCAs) such as amitriptyline and serotonin reuptake inhibitor (SSRI) have strong efficacy evidence in migraine at low doses and with minimal side effects (Minen et al., 2016; Silberstein et al., 2007). Such medications could be considered for use in people with migraine as well as anxiety and depression, however TCAs are effective for depression at high doses with side effects such as hypotension, sedation, weight gain and constipation (Jackson et al., 2010; Arroll et al., 2005). Like PTSD, there are several co-morbidities of migraine which affect the cardiovascular system (myocardial infarction, hypertension, hypotension), the central nervous (essential tremor) and the gastrointestinal body system (ulcer disease, colitis and irritable bowel syndrome) (Silberstein et al., 2007). The other disorders that may commonly co-occur with migraine include allergy/asthma and sleep, psychiatric and chronic pain disorders. Co-morbidities may impact the choice of treatment and therefore assessment and consideration of medications used for other disorders is essential (Valderas et al., 2009). Monitoring other co-morbidities in the diagnosis and treatment of PTSD and migraine is important to gain control of all associated illnesses and for improvement of general well-being, reducing pain and disability (Yang et al., 2016; Buse et al., 2013).

It has been suggested that several systems are likely to be involved in the intrinsic PTSD-migraine relationship (Peterlin et al., 2011). Biological, environmental and/or genetic risk factors may converge to produce a brain state which predisposes an individual to both PTSD and migraine (Antonaci et al., 2011). The proposed neurobiological mechanisms underlying PTSD - Migraine co-morbidity include dysfunction of the autonomic nervous system, hypothalamic pituitary adrenal (HPA) axis and brain serotonergic activity which might be affected by polymorphism in the serotonin transporter gene (5-HTTLPR) (Minen et al., 2016; Smitherman et al., 2009). The other biological and environmental factors that play a role in the pathophysiology of both PTSD and migraine include stress, trauma, inflammation, immune dysregulation, medication overuse, ovarian hormone fluctuations and central sensitization (Juang and Yang, 2014). Medical conditions may be co-morbid due to shared genetic factors that increase the risk of both conditions, for example the MTHFR C677T variant is associated with increased risk of both migraine with aura and MDD (Scher et al., 2006; Samaan et al., 2011; Liu et al., 2014).

Genome-Wide Association Studies (GWAS) have been used to investigate genetic overlap between PTSD, migraine and other disorders including MDD, ADHD, bipolar disorder, epilepsy, stroke and cardiac heart disease (Polimanti et al., 2022; Sutherland et al., 2019; Yang et al., 2018; Oedegaard et al., 2010; Winsvold et al., 2015). There are contrasting findings on the genetic correlation between PTSD and migraine from previous studies that used relatively small samples and one was conducted among men only (Gasperi et al., 2021; Anttila et al., 2018; Smeland et al., 2023). We have previously found a modest but significant genetic correlation between PTSD and migraine, and no evidence of a causal association (Bainomugisa, 2024) (under review). This implies that the shared genetic risk between these disorders can be attributed mediating factors that may influence both PTSD and migraine. Based on prior analyses between these disorders, the hypothesized pathways include phosphatidylinositol signalling system which is therapeutic target for migraine, MDD and SCZ, and cortical actin cytoskeleton which is related to neurodevelopment and fear memory. Further, this study hypothesis that there are additional aetiological environmental factors and biological mechanisms such as stress and trauma-related pathways that influence PTSD and migraine. Genetic overlap between traits in absence of a causal relationship can be explained by either horizontal or vertical pleiotropy where risk variants affect both traits independently, or affect a trait indirectly through another trait respectively (Gratten and Visscher, 2016). We hypothesized that genetic variants associated with medication use for other co-morbidities may have pleiotropic effects on PTSD and migraine.

GWAS summary statistics for medication use have previously been used to show that genetic predisposition to common disease predicts likelihood of taking relevant medications (Wu et al., 2019). Therefore, medication use traits were used as proxies for the respective disorders they are used to treat and to investigate the genetically controlled biological or environmental etiological factors underlying PTSD and migraine. This study investigated the shared genetic risk between the medication use traits with PTSD and migraine, and from local genetic correlation analyses the genes in the genomic loci with significant shared genetic risk were identified. The roles of these genes in relation to PTSD and migraine were evaluated to highlight their potential influence in the genetic relationship between these disorders. Lastly, the causal associations between medication use with PTSD and migraine were assessed to further highlight plausible mediating factors between PTSD and migraine. These findings are important as they explore further into the pleiotropic relationship between these disorders and potential drug targets were identified. The common medications implicated in this study can be further investigated for drug repurposing and in the improvement of treatment of patients with PTSD and migraine using monotherapy.

2. Materials and methods

Ethical approval and informed consent were obtained as indicated in the respective original publications of the GWAS. This study involved secondary data analyses and no individual data was used.

2.1. GWAS summary statistics for migraine

We obtained the largest and most recent migraine GWAS meta-analysis of several studies from the International Headache Genetics

Consortium (IHGC2021) with 102,084 cases and 771,257 controls of European ancestry. IHGC2021 comprises association results for 10,843,197 SNPs; details of the cohorts, genotyping and phenotyping procedure are described in the original publication (Hautakangas et al., 2022).

2.2. GWAS summary statistics for PTSD

GWAS of case-control PTSD in American veterans of European ancestry from the Million Veterans' Program were used in this study; this comprised 36,301 cases, 178,107 controls and association results of 8,839,304 SNPs (MVP2021) (Stein et al., 2021). PTSD diagnosis was based on the Electronic Health Record Algorithm (Stein et al., 2021; Harrington et al., 2019). Details on genotyping are available dbGaP/-database of Genotypes and Phenotypes/National Center for Biotechnology Information, National Library of Medicine (NCBI/NLM)/https://www.ncbi.nlm.nih.gov/gap.

2.3. GWAS summary statistics for medication use

The publicly available GWAS summary statistics for 23 categories of medication-use traits were obtained from https://cnsgenomics.com/data/wu_et_al_2019_nc/23_medication-taking_GWAS_summary_statistics, (Wu et al., 2019). These traits were categorized by UK Biobank http://www.ukbiobank.ac.uk/about-biobank-uk/based on active ingredients that could be linked to the Anatomical Therapeutic Chemical Classification System (Santos et al., 2017). The case control GWAS comprised UK Biobank individuals of European ancestry (N = 318,177) with a total of 7,288,504 SNPs per medication use category except for anti-thrombotic agents with 4,787,703 SNPs (Table 1). Demographics of the participants, phenotyping and genotyping are detailed in the original publication (Wu et al., 2019).

2.4. Quality control

All cohorts included in this study were of European ancestry. To ensure consistency of alleles and variants across GWAS summary statistics, data was formatted using munge_sumstats.py in plink 1.9 b (Chang et al., 2015). The hapmap SNPs that were used for the pre-calculated LD scores were extracted from the GWAS summary statistics using the provided list of SNPs (w_hm3. snplist) (https://github.com/bulik/ldsc/wiki). Variants (SNPs) with missing beta values, low imputation quality <0.9), low minor allele frequency (MAF <0.01) and deviating from Hardy-Weinberg equilibrium (*P*-values $<1 \times 10^{-6}$) were excluded from the analysis. In addition, duplicated SNPs, variants that were not SNPs and strand-ambiguous SNPs were also excluded. The data in *sumstats* format were used in subsequent analyses for genome-wide and local genetic correlation and causal analysis using latent causality variable.

2.5. Genetic correlation analyses

2.5.1. Linkage disequilibrium score regression (LDSC)

Univariate linkage disequilibrium score regression (LDSC) was used to examine the SNP-based heritability of each trait included in this study, this is important as a strong genetic signal is required to perform genetic correlation for genetically-related traits (Bulik-Sullivan et al., 2015). The analysis of genetic correlation between the medication use traits with PTSD and migraine was performed using bivariate LDSC to identify medication use traits with shared genetic risk for both disorders. Pre-calculated estimates of LD scores from the HapMap3 European refence panel of approximately 1.2 million SNPs were utilized. The LDSC method estimates the average genome-wide genetic correlation through quantifying the contribution of each SNP by regressing marginal z-scores in GWAS summary statistics of two traits with a shared genetic basis on LD (Linkage Disequilibrium) (Bulik-Sullivan et al., 2015). LDSC can estimate the genetic correlation (rG) in the presence of sample overlap which only affects the LDSC intercept and not the slope that determines the rG estimate. However, LDSC may not detect signals that are confined to specific regions or in opposite directions.

Table 1
Summary of GWAS datasets.

Phenotype ID	Phenotype	Cases	Controls	n
PTSD	Post-traumatic stress disorder	36301	178107	214408
MIGRAINE	Migraine	102084	771257	873341
ULCER	Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)	53137	79230	132367
DIABETES	Drugs used in diabetes	15272	290641	305913
ANTITHROMBOTICS	Anti-thrombotic agents	67653	85986	153639
VASODILATORS	Vasodilators used in cardiac diseases	5546	237113	242659
ANTIHYPERTENSIVES	Anti-hypertensives	6431	145949	152380
DIURETICS	Diuretics	34453	194633	229086
BETA BLOCKERS	Beta blocking agents	31700	192324	224024
CALCIUM	Calcium channel blockers	31904	172474	204378
RENIN	Agents acting on the renin-angiotensin system	62752	174778	237530
REDUCTASE	HMG CoA reductase inhibitors	73475	216910	290385
THYROID	Thyroid preparations	24832	280750	305582
IMMUNOSUP	Immunosuppressants	3954	268648	272602
ANTIINF/ANTIRHEU	Anti-inflammatory and anti-rheumatic products, non-steroids	74150	90370	164520
BONE	Drugs affecting bone structure and mineralization	7870	207798	215668
OPIOIDS	Opioids	22982	55826	78808
SALIC	Salicylic acid and derivatives	61583	50427	112010
ANILIDES	Anilides	83218	96592	179810
ANTIM	Anti-migraine preparations	5521	114323	119844
ANTID	Anti-depressants	33757	270405	304162
ADRENERGICS	Adrenergics, inhalants	28880	147565	176445
GLUCO	Glucocorticoids	17352	188348	205700
ANTIHIST	Anti-histamines for systemic use	13984	137652	151636
ANTIGLAU	Anti-glaucoma preparations and miotics	5215	95653	100868

Overview of the GWAS summary statistics for PTSD, migraine and the medication use traits, abbreviations as used throughout the manuscript, sample size (n) for each set of summary statistics, number of cases, number of controls.

2.5.2. Local Analysis of [Co]variant association

Local genetic correlation (rG) analyses complemented global genetic correlation between PTSD, migraine and each medication use trait, this was implemented using R-package Local Analysis of [Co]variant Association (Werme et al., 2022). This method identifies the specific genomic loci with significant genetic signals ($P < 1 \times 10^{-4}$) and then performs pairwise local genetic correlation across 2495 loci which have been defined by partitioning the genome into blocks of ~1 Mb while minimising LD between them. The analyses consisted of two steps: 1) univariate association analyses to detect the local h^2_{SNP} signal of each phenotype within each genomic locus; and 2) bivariate association analyses to estimate the pair-wise genetic correlation between two phenotypes of interest at the chosen locus. Bivariate association analyses were restricted to the genomic loci showing a significant h^2_{SNP} signal for both phenotypes. The *p*-values of local rG were corrected using false discovery rate considering the intercorrelations and co-heritability of the traits tested in the bivariate association analyses.

The genomic loci revealing significant genetic correlation were subsequently used to determine the genes and pathways shared between PTSD, migraine and the medication use traits. We identified genes included in each locus based on annotation to Genome Reference Consortium Human (GRCh37) positions and associated biological mechanisms using the *g:GOSt* function of the 'g:profiler' webpage (Raudvere et al., 2019).

2.6. Causal association between PTSD, migraine and medication use traits

2.6.1. Two-sample mendelian randomization (2SMR)

Two-sample MR (2SMR) was applied to test for causal relationships (vertical pleiotropy) between the genetic liability of PTSD and migraine to medication use, and the reverse of causal effect of the genetic liability to medication use on PTSD and migraine. 2SMR provides important information about the direction and strength of the causal effects (Zhu et al., 2018; Hemani et al., 2017). This analysis was conducted using the "TwoSampleMR" R package, the primary analysis is conducted using the random-effects inverse variance weighted (IVW) method which has high statistical power (Burgess et al., 2019). LD-independent Genome-wide Significant SNPs were used in the exposure GWAS were used as instrumental variants (IVs). The MR sensitivity models were applied to test for IVW validity considering that a single invalid IV may cause bias in the overall estimate (Burgess and Thompson, 2017; Burgess et al., 2013). These methods are based on different MR assumptions including the validity and strength of the variants, the weighted median provides a reliable causal estimate even when half of the IVs do not meet the MR assumptions (Bowden et al., 2016). Although the MR Egger model has lower statistical power than IVW, it tests for horizontal pleiotropy (Bowden et al., 2015). The other MR sensitivity models include simple mode and weighted mode.

2.6.2. Latent causal variable (LCV) model

The latent causal variable (LCV) model examines whether significant genetic correlation demonstrates a potential causal relationship. LCV was used to estimate the genetic causality proportion (GCP) between PTSD and migraine with medication use traits. Latent Causality Variable analysis was implemented using RunLCV.R software available in the Github repository (https://github.com/lukejoconnor/LCV) (O'Connor and Price, 2018). To ensure consistency of alleles and variants across GWAS summary statistics, data was formatted using munge_sumstats.py, which is available by the LD-score software and extracted hapmap SNPs using the provided list of SNPs (w_hm3. snplist) (https://github.com/bulik/ldsc/wiki).

LCV estimates the genetic correlation using GWAS summary statistics and relies on a latent variable *l*, to estimate the genetic causality proportion (GCP). *l* is assumed to be the causal constituent mediating the genetic correlation (rG) between two traits. LCV uses a modified LDSC approach to estimate the rG, which may differ from the rG estimated by LDSC (Bulik-Sullivan et al., 2015). A weak GCP value near zero for genetically correlated traits implies no genetic causality, association is likely influenced by horizontal pleiotropic effects between the phenotypes and an intervention on any of them would not affect the other due to absence of genetic causality between them. In contrast, an absolute GCP value of 1 indicates the detection of causal association that could be explained by vertical pleiotropic effects among a pair of genetically correlated phenotypes. This implies that the effect of a genetic variant on a trait is mediated by its effect on another trait. Simulations show that GCP >0.60 indicates partial genetic causality and adequately guards against false positives, GCP <0.60 is considered low and shows limited partial genetic causality (O'Connor and Price, 2018). Multiple comparison was corrected for using Benjamini-Hochberg's False Discovery Rate (FDR <5 %), and medication use traits with evidence of a potential causal relationship with PTSD and migraine were identified based on their GCP estimate.

3. Results

3.1. Global genetic correlation between PTSD, migraine and medication use

First, SNP-based heritability was estimated using univariate LDSC, all the medication use traits showed significant genetic signal with median heritability 0.059 and range (0.006–0.146). The highest heritability was found for opioids 0.146 (s.e 0.008) while anti-histamines for systemic use showed the lowest heritability 0.006 (s.e 0.002) (Table 2). Bivariate LDSC analysis showed that anti-thrombotic agents use had a significant and negative genetic correlation with PTSD (rG = −0.20, P_{FDR} = 0.032); and a significant and positive genetic correlation with migraine (rG = 0.26, P_{FDR} = 2.23 x 10^{-8}). This indicates that the SNPs associated with use of anti-thrombotic agents reduce the risk of PTSD and increase the risk of migraine. PTSD had low to moderate significant negative genetic correlation with 9 other medication use traits including salicylic acid and derivatives (rG = −0.19, P_{FDR} = 0.002), calcium channel blockers (rG = −0.12, P_{FDR} = 0.002) and beta-blocking agents (rG = −0.11, P_{FDR} = 0.034). Migraine had a low negative genetic correlation with anti-depressants (rG = −0.06, p = 2.94 x 10^{-2}) and salicylic derivatives (rG = −0.08, p = 0.0032), however they did not survive multiple testing correction. All results are shown in Table 2.

3.2. Local genetic correlation between PTSD, migraine and medication use

A total of 2495 loci were assessed for genetic signals for each trait included in this study and the SNP-based heritability (h^2_{SNP}) was significantly different from zero at all loci for PTSD and at least one medication use phenotype, and migraine at 502 loci (p < 1x10^{-4}) (Supplementary Table 1).

Fig. 1 shows pair-wise locus-specific genetic correlation at the genomic loci with significant h^2_{SNP}. PTSD showed significant local genetic correlation with 12 medication use traits at 43 loci [38 (88%) positive rG; 5 (12%) negative rG] (P < 2 x 10^{-5} = May 0, 2495) (Supplementary Table 2). At 5% FDR, PTSD showed significant local genetic correlation with 15 medication use traits at 1162 loci [878 (76%) positive rG; 284 (24%) negative rG]; only 120 loci were distinctively associated with PTSD and one medication use trait (Supplementary Table 3). The genes in the top loci associated with PTSD and the medication use traits included *TNFRSF14* (calcium channel blockers, renin and diuretics), *R3HDM1, ZRANB3, C1orf109, DLEC1* and *EIF2B3* (reductase), *LRP1B* and *ALK* (anti-inflammatory/anti-rheumatic products), *GADL1* and *LCLAT1* (diuretics), *HIPK1* and *ZBTB20* (thyroid preparations), *RASGRP3, ZNF362, SLC9A9* (immunosuppressants). The genes in the loci associated with PTSD and anti-thrombotic agents include *CNTN4, PRDM16*, *PTPRF*, *KAZN* and *SORCS3; PRDM16* gene was associated with PTSD and various other medication use traits such as hypertensives, anti-inflammatory and anti-rheumatoid products, beta blocking agents, diuretics, renin, immunosuppressants, reductase and thyroid preparations.

In contrast, migraine showed significant genetic correlation only at locus chr12:57522282–57607142 (*DAB1*) with anti-inflammatory agents and anti-rheumatic products (P < 2 x 10^{-5}). This locus was significantly associated with PTSD, anti-migraine and anti-inflammatory/anti-rheumatic preparations (FDR 5%). Migraine showed significant genetic correlation with 8 medication use traits including anti-hypertensives, calcium blocking agents, renin and opioids at 31 loci (FDR 5%) (Supplementary Table 4). Some of the other loci that showed significant genetic correlation between migraine and non-steroid anti-inflammatory and anti-rheumatic products include locus chr12:57422301–57444549 (*DNAH12, C8B*) and chr6:97010406–97067806 (*EPHA6*, *NCAPH*) which was associated with 9 additional medication use traits. and associated with migraine, anti-migraine preparations and anti-inflammatory products. Locus chr11:47269851–47290584 (*TTC7A, CYP4B1)* was associated with

Table 2
Linkage Disequilibrium score regression.

Phenotype ID	H^2_{SNP} (s.e)	rG_PTSD	PTSD_*P*	PTSD_P_{FDR}	rG_MIG	MIG_*P*	MIG_P_{FDR}
ULCER	0.0926 (0.0051)	0.49	0.00217	0.0716	−0.04	0.0657	1
DIABETES	0.0455 (0.0031)	−0.16	0.0013	0.0455	−0.002	0.9438	1
ANTITHROMBOTICS	0.0510 (0.0050)	−0.20	8.00×10^{-4}	0.0320	0.26	9.70×10^{-10}	2.23×10^{-8}
VASODILATORS	0.0138 (0.0022)	−0.18	0.0023	0.0736	−0.06	0.1518	1
ANTIHYPERTENSIVES	0.0210 (0.0037)	−0.13	0.0362	0.7602	−0.07	0.1121	1
DIURETICS	0.0986 (0.0060)	−0.10	4.0×10^{-4}	0.0168	−0.03	0.1596	1
BETABLOCKERS	0.0659 (0.0044)	−0.11	9.0×10^{-4}	0.0342	−0.02	0.2857	1
CALCIUM	0.1065 (0.0057)	−0.12	5.14×10^{-5}	0.0022	−0.02	0.371	1
RENIN	0.1304 (0.0060)	−0.08	0.0015	0.0510	−0.02	0.1464	1
REDUCTASE	0.0733 (0.0055)	−0.13	0.0012	0.0432	−0.04	0.0839	1
THYROID	0.0655 (0.0059)	−0.07	0.0115	0.2875	−0.009	0.6297	1
IMMUNOSUP	0.0057 (0.0018)	−0.24	0.0101	0.2673	−0.05	0.4101	1
ANTIINF/ANTIRHEU	0.0591 (0.0043)	−0.10	0.0099	0.2673	−0.02	0.4424	1
BONE	0.0213 (0.0028)	−0.18	7.00×10^{-4}	0.0287	−0.07	0.0535	1
OPIOIDS	0.1458 (0.0083)	−0.08	0.014	0.3220	−0.04	0.1496	1
SALIC	0.0557 (0.0054)	−0.19	5.48×10^{-5}	0.0023	−0.08	0.0032	0.0704
ANILIDES	0.0623 (0.0039)	−0.07	0.0774	0.3560	−0.03	0.3070	1
ANTIM	0.0452 (0.0053)	−0.13	0.0072	0.2088	−0.01	0.8229	1
ANTID	0.0260 (0.0020)	−0.11	0.0065	0.1950	−0.06	0.0294	0.6174
ADRENERGICS	0.0789 (0.0060)	−0.10	0.0011	0.0407	−0.03	0.1520	1
GLUCO	0.0342 (0.0037)	−0.13	0.009	0.2520	−0.03	0.3958	1
ANTIHIST	0.0322 (0.0036)	−0.12	0.0129	0.3096	−0.05	0.1124	1
ANTIGLAU	0.0521 (0.0064)	−0.16	8.00×10^{-4}	0.0320	−0.06	0.0915	1

The table shows abbreviations of the medication use traits used in this study, h^2_{SNP}: SNP-based heritability estimated using LDSC, SNP-based heritability and standard error, rG: Genetic correlation between PTSD and migraine with medication use using LDSC, P_{FDR} *P*-value of genetic correlation after adjustment using false discovery rate.

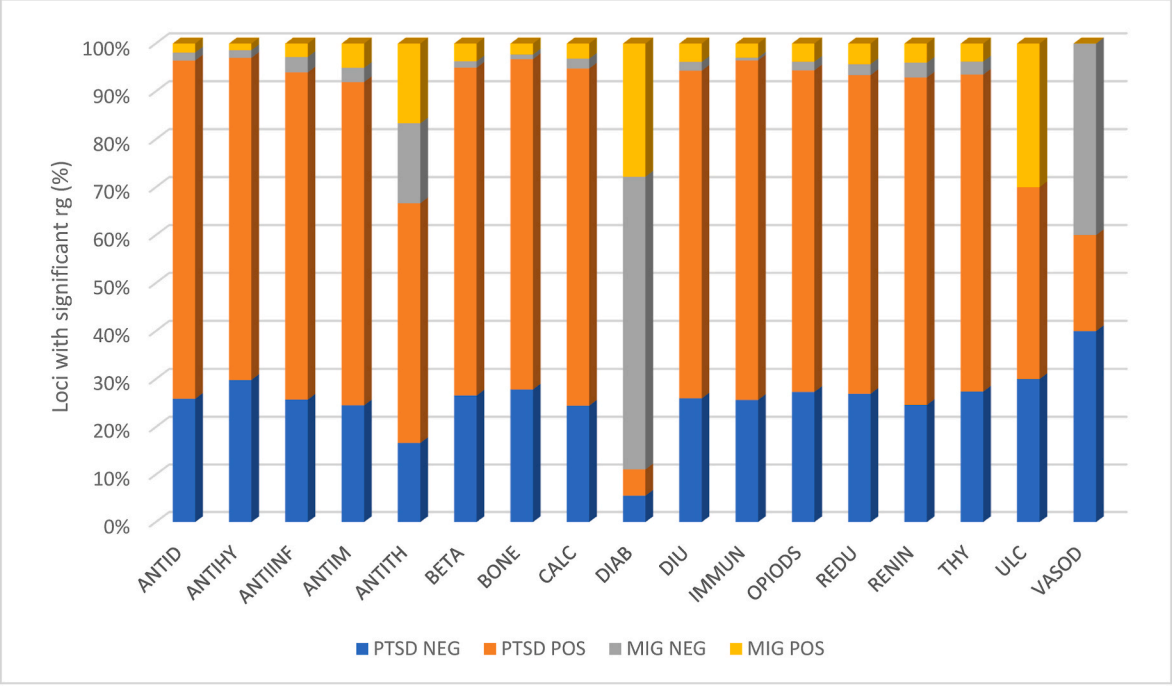

Fig. 1. Loci with significant local genetic correlation between PTSD, migraine and medication use traits (*PFDR* < 0.05). Y-axis shows number of loci associated with each medication use trait with PTSD and migraine, with positive rg in orange and negative rg in blue for PTSD; and positive rg in yellow and negative rg in grey for migraine. Abbreviations of medication use: ANTID, anti-depressants; ANTIHYP, antihypertensives; ANTIINF, anti-inflammatory and anti-rheumatic products; ANTIM, anti-migraine preparations; ANTITH, anti-thrombotic agents; BETA, beta-blocking agents; BONE, drugs for bone structure and mineralization; CALC, calcium blockers; DIAB, diabetes; DIU, diuretics; IMMUN, immunosuppressants; REDU, reductase; THY, thyroid preparations; ULCER, drugs for peptic ulcers and GORD; VASOD, vasodilators used in cardiac disease.

migraine, calcium blockers, renin and diuretics (FDR 5%). Some of the other genes in loci with significant genetic correlation between migraine and anti-migraine preparations included: *NCAPH, SNRNP200*, *TRPM8* and *IRF2BP2*.

The genes in genomic regions shared between PTSD and medication use traits such as anti-migraine and thyroid preparations, diuretics, renin and beta blocking agents were enriched in neuronal-related pathways such as neuron differentiation, neuron projection, neuron development, and generation of neurons (Supplementary Table 5). The genes encoded in the loci associated with PTSD and anti-inflammatory/anti-rheumatic use were enriched in other pathways such as hydrolase activity, acting on carbon-nitrogen (but not peptide) bonds, linear

amidines, sodium ion transmembrane transporter activity, cell projection and synaptic vesicle cycle. The other pathways associated with PTSD, anti-migraine and thyroid preparations included plasma membrane, pre-synaptic, post-synaptic and synaptic membrane, transmembrane receptor protein kinase activity, transmembrane receptor protein tyrosine kinase activity, protein kinase activity and plasma membrane bounded cell projection. The genes in the loci associated with migraine and anti-thrombotic agents were enriched in negative regulation of arachidonic acid secretion which produces inflammatory mediators.

3.3. Causal associations between PTSD, migraine and medication use traits

With evidence of SNP-level genetic overlap between PTSD, migraine and the medication use traits, bi-directional 2-Sample Mendelian Randomization (2SMR) models were applied to infer causal relationships. The results are shown in (Tables 3 and 4; Figs. 2 and 3). The primary IVW analyses found that the genetic liability to PTSD had a causal effect on increased risk of using opioids ($\beta_{ivw} = 0.59$, $P = 5.21 \times 10^{-5}$) and salicylic acid and derivatives ($\beta_{ivw} = 0.12$, $P = 1.69 \times 10^{-7}$) at 5% FDR, and a similar pattern was observed for the weighted median. There was no evidence of global or unbalanced pleiotropy in all the causal associations observed as shown by the MR-Egger intercepts which were not significantly different from zero. This implies that any observed heterogeneity of instruments was not a result of horizontal pleiotropy. Consistent causal relationships for all MR models except MR Egger may be due to sample variations or violation of MR assumptions (Burgess and Thompson, 2017). Reverse MR analysis showed that the genetic liability to medication use of opioids ($\beta_{ivw} = 0.25$, $P = 2.51 \times 10^{-3}$), drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD) ($\beta_{ivw} = 0.20$, $P = 0.02$) and adrenergics ($\beta_{ivw} = 0.04$, $P = 0.01$) had a causal effect on increased risk of PTSD at a nominal *P*-value threshold of 0.05. Additionally, there was a significant causal effect between the genetic liability of using HMG CoA reductase inhibitors ($\beta_{ivw} = -0.04$, $P = 0.04$) with decreased risk of PTSD. A similar pattern was observed for the weighted median model. The precision of the weighted median model with much lower standard errors in comparison to MR-Egger shows validity of most of the instrument variants used in MR analysis (Table 4).

From the IVW model, the genetic liability to migraine had a significant causal effect on 8 medication use traits after adjusting for multiple testing; these included: increased risk of medication use for peptic ulcer and gastro-oesophageal reflux disease (GORD) ($\beta_{ivw} = 0.10$, $P = 9.29 \times 10^{-7}$), anti-inflammatory, anti-rheumatic products and non-steroids ($\beta_{ivw} = 0.28$, $P = 1.25 \times 10^{-44}$), anilides ($\beta_{ivw} = 0.34$, $P = 6.10 \times 10^{-76}$), anti-migraine preparations ($\beta_{ivw} = 0.17$, $P = 1.4 \times 10^{-24}$), opioids ($\beta_{ivw} = 0.27$, $P = 1.7 \times 10^{-24}$) and decreased risk of using HMG CoA reductase inhibitors ($\beta_{ivw} = -0.06$, $P = 1.01 \times 10^{-3}$). These observations were consistent for the weighted median and MR Egger 2SMR models. MR Egger intercept that is significantly different from zero shows evidence of horizontal pleiotropy. At the nominal *P*-value threshold of 0.05, similar results were observed between the genetic liability to migraine and reduced risk of using glucocorticoids ($\beta_{ivw} = -0.06$, $P = 0.038$). Additionally, we observed that the genetic liability to migraine had a significant causal effect on increased risk of using salicylic acid and derivatives ($\beta_{ivw} = 0.12$, $P = 3.49 \times 10^{-9}$), and anti-glaucoma preparations and miotics ($\beta_{ivw} = 0.25$, $P = 9.08 \times 10^{-7}$) at 5% FDR. This was consistent for weighted median, with no evidence of significant horizontal pleiotropy from the MR Egger model. Similar results were observed for anti-thrombotic agents ($\beta_{ivw} = 0.37$, $P = 1.80 \times 10^{-2}$) and thyroid preparations ($\beta_{ivw} = -0.08$, $P = 3.70 \times 10^{-3}$) at a nominal *P*-value threshold of 0.05. From reverse MR, the genetic liability to use of diuretics ($\beta_{ivw} = 0.05$, $P = 8.02 \times 10^{-4}$) and anti-migraine preparations ($\beta_{ivw} = 0.44$, $P = 3.51 \times 10^{-22}$) had a significant causal effect on increased risk of migraine, this was consistent for the weighted median model, with no evidence of horizontal pleiotropy from MR Egger model. At the nominal *P*-value threshold of 0.05, similar results were observed between the genetic liability to use of calcium channel ($\beta_{ivw} = 0.03$, $P = 0.043$), immunosuppresants ($\beta_{ivw} = 0.020$, $P = 0.014$), anilides ($\beta_{ivw} = 0.167$, $P = 0.005$) and increased risk of migraine.

The LCV model found some interesting non-zero genetic causality proportions between the medication use traits with PTSD and migraine (Table 5). Medication for peptic ulcer and gastro-oesophageal reflux disease (GORD) (rG = 0.44, GCP = −0.29, $GCP_{pvalue} = 1.46 \times 10^{-8}$) and use of vasodilators (rG = 0.24, GCP = −0.23, $GCP_{pvalue} = 8.36 \times 10^{-16}$) were found to potentially increase the risk of PTSD (FDR <5%). GCP <0.60 shows limited partial genetic causality. At the nominal *P*-value threshold of 0.05, use of anti-depressants (rG = −0.09, GCP = −0.13, $GCP_{pvalue} = 5.5 \times 10^{-2}$) potentially increased the risk of PTSD. In contrast, PTSD potentially increased the risk of using salicylic acid derivatives (rG = −0.12, GCP = 0.14, $GCP_{pvalue} = 0.014$). Migraine potentially increased the risk of using anti-thrombotic agents (rG = 0.22, GCP = 0.48, $P = 0.032$).

4. Discussion

This study investigated the role of medication use as a potential source of pleiotropy in PTSD and migraine. First, the global and local genetic correlations between PTSD, migraine and 23 medication use categories were assessed. The GWAS summary statistics for medication use included treatment for disorders related to pain and stress, and various body systems including the immune, cardiovascular, respiratory and others. We observed a significant genome-wide genetic correlation (rG) between anti-thrombotic agents with both PTSD (negative rG) and migraine (positive rG). Heart-related medication (Calcium channel and beta blocking agents) had significant positive local genetic correlation with both PTSD and migraine. PTSD showed significant global genetic correlation with 10 other medication use traits including drugs used for the treatment of cardiovascular and pain related disorders. PTSD often co-occurs and overlaps with cardiovascular, respiratory, other psychiatric and behavioural conditions such as substance abuse and sleep disorders; trauma is a risk factor for all these disorders. (Burg and Soufer, 2016; Smoller, 2016; Richards et al., 2020). The other medications that had a significant genome-wide genetic correlation with migraine included anti-depressants and salicylic derivatives ($P < 0.05$). Subsequently the genes and pathways in the loci significantly associated with PTSD, migraine and medication use were identified and causal associations assessed.

Collectively, some findings suggest that the cardiovascular system may mediate the occurrence of both PTSD and migraine. Our results showed shared genetic risk for PTSD, migraine and anti-thrombotic agents; the SNPs associated with use of anti-thrombotic agents have a protective effect on PTSD and increased risk effect on migraine. Anti-thrombotic agents are used in secondary prevention of stroke and adverse events after ischemic stroke (IS). The absolute risk of ischemic stroke in migraine is relatively low and primary prevention with anti-thrombotic agents is not indicated (de Falco and de Falco, 2015). However, epidemiological studies and meta-analyses show that the risk of IS is twice as high in migraine with aura (MA) due to particular brain susceptibility to cortical spread depression (de Falco and de Falco, 2015; Tietjen and Collins, 2018). Deep venous thrombosis and medications for cardiovascular disorders such as hypertension, blood clots (platelet aggregation) and thromboembolism have previously been found to increase the risk of migraine (Zhao et al., 2016). Elevated diastolic blood pressure has been reported to aggravate migraine/headache while some migraine/headache medications lower blood pressure (Silberstein et al., 2007). In contrast, other migraine/headache medications such as triptans and the ergotamine tartrate that reduce the amplitude of temporal artery pulsation, increase the risk for IS, vascular malformations and genetic disorders (Goadsby et al., 2017b). Similar to this study, the causal association between migraine risk with hypertension and blood

Table 3
Mendelian Randomization for causal associations of PTSD and migraine (exposures) on medication use traits (outcomes).

Outcome	nSNPs	PTSD – 3 SNPs						Migraine – 148 SNPs					
		Inverse variance weighted		Weighted median		MR Egger		Inverse variance weighted		Weighted median		MR Egger	
		beta	***P*-value**	**Beta**	***P*-value**	**Beta**	***P*-value**	**Beta**	***P*-value**	**Beta**	***P*-value**	**Beta**	***P*-value**
ULCER	3	0.3078	0.1271	0.1201	0.3650	0.2558	0.8370	0.0993	9.29×10^{-7} **	0.0975	3.71×10^{-4} **	0.1234	0.0278 *
DIABETES	3	0.1885	0.1788	0.2163	0.1998	0.0524	0.9309	−0.0614	0.0736	−0.0514	0.2061	−0.1616	0.0870
ANTITHROMBOTICS	2	0.2921	0.2334	–		–		0.11804	1.69×10^{-7} **	0.1054	4.70×10^{-4} **	0.0234	0.6972
VASODILATORS	3	0.5601	0.0345 *	0.4761	0.1380	0.0529	0.9712	−0.1011	0.0590	−0.0674	0.3117	−0.3831	0.0091 *
ANTIHYPERTENSIVES	3	−0.0023	0.9934	0.1261	0.6689	0.9047	0.5346	0.0466	0.2713	−0.0102	0.8627	0.1573	0.1763
DIURETICS	3	0.0862	0.5089	0.0744	0.5887	−0.2083	0.7709	0.0030	0.9175	−0.0494	0.1353	−0.05073	0.5257
BETABLOCKERS	3	0.1823	0.1242	0.0945	0.4776	0.0921	0.8974	−0.0396	0.6061	0.0265	0.4101	0.0446	0.1118
CALCIUM	3	−0.0058	0.9743	−0.0676	0.6422	−0.2988	0.7778	−0.0377	0.2092	−0.0894	0.0044 *	−0.1425	0.0842
RENIN	3	0.2126	0.1521	0.0746	0.4695	0.2551	0.7823	−0.0346	0.1591	−0.0450	0.0721	−0.0794	0.2401
REDUCTASE	3	0.2335	0.1093	0.1048	0.2880	0.3084	0.7364	−0.0607	0.0010 **	−0.0726	0.0007 **	−0.1752	0.0006 **
THYROID	3	−0.1717	0.2245	−0.0470	0.7537	−0.7622	0.4458	−0.0848	0.0037 *	−0.0797	0.0169 *	−0.1102	0.1719
IMMUNOSUP	3	−0.1123	0.6814	0.1087	0.3463	−1.1118	0.9370	−0.0383	0.4385	−0.0625	0.4051	0.0130	0.9237
ANTIINF/ANTIRHEU	3	0.1400	0.0936	0.1358	0.2052	−0.0272	0.9423	0.2836	1.2×10^{-44} **	0.28838	9.9×10^{-32} **	0.3631	7.4×10^{-10} **
BONE	3	−0.1587	0.4094	−0.2083	0.3745	0.3983	0.6539	−0.0062	0.8814	−0.0328	0.5444	−0.0273	0.8119
OPIOIDS	3	0.5927	5.2×10^{-5} **	0.5648	3.59×10^{-3} *	−0.0877	0.8761	0.2656	1.7×10^{-24} **	0.18626	4.87×10^{-7} **	0.2083	4.02×10^{-3} *
SALIC	3	0.3701	0.0180 *	0.3571	0.0087 *	−0.0692	0.9278	0.1225	3.48×10^{-9} **	0.14361	1.10×10^{-6} **	0.0729	0.2012
ANILIDES	3	0.1198	0.2700	0.1431	0.184374	0.444987	0.467637	0.335911	6.1×10^{-76} **	0.334232	2.1×10^{-41} **	0.363973	1.8×10^{-11} **
ANTIM	3	0.2497	0.4000	0.1382	0.684664	−0.23719	0.888975	0.171282	1.4×10^{-24} **	0.134036	7.2×10^{-69} **	0.134204	3×10^{-148} **
ANTID	3	0.1706	0.3854	0.0934	0.514324	−0.18330	0.868943	0.042520	0.417451	0.068737	0.011871 *	0.064042	0.000775 **
ADRENERGICS	3	0.1175	0.2794	0.1233	0.364202	0.250619	0.623243	−0.03073	0.305604	−0.02981	0.383628	−0.12810	0.120046
GLUCO	3	0.1208	0.3706	0.0801	0.633079	−0.23716	0.698480	−0.06185	0.038159 *	−0.11462	0.003661 *	−0.17997	0.028346 *
ANTIHIST	3	0.1014	0.5551	−0.0285	0.885383	−0.00943	0.992721	0.000586	0.983135	0.003798	0.925343	−0.09059	0.233923
ANTIGLAU	3	0.2655	0.3376	−0.0727	0.823992	0.944185	0.457073	0.248714	9.08×10^{-7} **	0.178631	0.011622 *	0.011372	0.93414

2SMR: 2 Sample Mendelian Randomization; MR Egger: Egger regression approach; nSNPs: Total number of SNPs used as instruments; test *p*-value; $^{**}p < 2.17 \times 10^{-3}$, $^{*}p < 0.05$.

Table 4
Mendelian Randomization for causal associations of medication use traits (exposure) on PTSD and migraine.

Outcomes		PTSD							Migraine					
		Inverse variance weighted		Weighted median		MR Egger			Inverse variance weighted		Weighted median		MR Egger	
Exposure	**NSNPs**	**BETA (SE)**	***P***	**BETA (SE)**	***P***	**BETA (SE)**	***P***	**nSNPs**	**BETA (SE)**	***P***	**BETA (SE)**	***P***	**BETA (SE)**	***P***
ULCER	6	0.20251	**0.0232** *	0.2107 (0.1096)	**0.0545** *	0.7174 (0.8710)	0.4564	7	0.0200 (0.0819)	0.8081	−0.0122 (0.0719)	0.8652	−0.6093 (0.7342)	0.4444
DIABETES	101	0.00093	0.9399	−0.0189 (0.0201)	0.3467	−0.0199 (0.0309)	0.5212	104	-1.9×10^{-3} (0.0120)	0.8706	0.0163 (0.0120)	0.1738	8.91×10^{-5} (0.0306)	0.9976
ANTITHROMBOTICS	12	−0.0468	0.5234	−0.0133 (0.0849)	0.8759	−0.3349 (0.1879)	0.1051	12	0.0558 (0.0734)	0.4470	−0.0465 (0.0700)	0.5071	0.0148 (0.2138)	0.9461
VASODILATORS	3	−0.0139	0.7430	−0.0181 (0.0458)	0.6925	−0.0068 (0.0866)	0.9503	3	−0.0427 (0.0258)	0.0989	−0.0403 (0.0309)	0.1924	−0.0780 (0.0529)	0.3794
ANTIHYPERTENSIVES	4	0.00759	0.9236	−0.0652 (0.0539)	0.2273	−0.02904 (0.1657)	0.1303	4	0.0165 (0.0543)	0.7614	0.0522 (0.0358)	0.1447	−0.1853 (0.9308)	0.1848
DIURETICS	119	0.00599	0.7460	−0.0133 (0.0247)	0.5903	−0.0609 (0.0657)	0.3556	126	0.0492 (0.0147)	0.0008 **	0.0385 (0.0167)	0.0211 *	0.0228 (0.0535)	0.6705
BETABLOCKERS	61	−0.0058	0.8077	0.0143 (0.0334)	0.6695	−0.0953 (0.1022)	0.3550	1	−0.1901 (0.0229)	0.1233	0.0308 (0.0227)	0.1743	0.0047 (0.0985)	0.9624
CALCIUM	133	−0.0266	0.1413	−0.0294 (0.0229)	0.2002	−0.0380 (0.0625)	0.5437	139	0.0342 (0.0169)	0.0429 *	0.0243 (0.0154)	0.1156	0.0110 (0.0584)	0.8515
RENIN	232	−0.0097	0.5779	−0.0068 (0.0237)	0.7750	−0.0434 (0.0642)	0.5002	246	0.0281 (0.0168)	0.0949	0.0460 (0.0155)	0.0029 *	−0.0030 (0.0617)	0.9614
REDUCTASE	197	−0.0363	0.0421 *	−0.0650 (0.0260)	0.0125 *	−0.0218 (0.0389)	0.5770	210	−0.0057 (0.0125)	0.6519	−0.0119 (0.0163)	0.4649	0.0137 (0.0276)	0.6195
THYROID	323	0.00180	0.8125	0.0002 (0.0114)	0.9838	0.0255 (0.0190)	0.1814	348	0.0081 (0.0065)	0.2145	0.0072 (0.0077)	0.3515	0.0292 (0.0166)	0.0800
IMMUNOSUP	38	−0.0060	0.5741	0.0002 (0.0147)	0.9884	−0.0193 (0.0319)	0.5474	41	0.0203 (0.0083)	0.0144 *	0.0010 (0.0093)	0.2831	0.0065 (0.0254)	0.7999
ANTIINF/ANTIRHEU	8	0.1540	0.3924	−0.0102 (0.1542)	0.9472	−0.6662 (0.8615)	0.4687	8	0.3094 (0.2179)	0.1555	−0.0124 (0.0964)	0.8973	−0.1381 (0.1817)	0.9108
BONE	9	0.0153	0.6103	0.03590 (0.0382)	0.3473	0.1141 (0.1668)	0.5162	10	0.0035 (0.0288)	0.9029	−0.0163 (0.0261)	0.5328	−0.0432 (0.1998)	0.8341
OPIOIDS	3	0.2541	0.0025 *	0.2118 (0.1090)	0.0520 *	−0.2178 (0.1598)	0.5855	3	0.0802 (0.1030)	0.4365	0.0326 (0.0736)	0.6578	0.1332 (0.2711)	0.9687
SALIC	11	−0.1029	0.0807	−0.1093	0.1526	−0.1444	0.4681	11	0.0611 (0.0675)	0.3652	−0.0144 (0.0560)	0.7976	−0.2062 (0.2155)	0.3636
ANILIDES	17	0.07466	0.4015	0.0414	0.6475	0.3512 0.4045	0.3990	18	0.4669 (0.1674)	0.0053 *	0.0993 (0.0691)	0.1505 (0.0185)	0.23638 (0.8546)	0.7856
ANTIM	13	−0.0357	0.1184	−0.0225	0.4488	−0.0543 (0.2054)	0.7963	14	0.4407 (0.0455)	3.51×10^{-22} **	0.3338 (0.0381)	1.74×10^{-18} **	0.5228 (0.2901)	0.0967
ANTID	1	0.0514	0.7738	–	–	–	–	14	0.5228 (0.2901)	0.0967	0.3338 (0.0381)	1.74×10^{-18} **	0.4407 (0.0455)	3.51×10^{-22} **
ADRENERGICS	129	0.03617	0.0129 *	0.0566	0.0065 *	0.0481 (0.0414)	0.2476	134	0.0207 (0.0143)	0.1490	0.0268 (0.0140)	0.0560	0.0661 (0.0419)	0.1172
GLUCO	53	0.0125	0.4736	0.0089	0.7293	−0.0295 (0.0574)	0.6088	53	0.0133 (0.0164)	0.4178	−0.0111 (0.0163)	0.4965	0.0208 (0.0565)	0.7135
ANTIHIST	10	−0.0293	0.4409	−0.0111	0.8330	−0.0120 (0.1551)	0.9402	10	−0.0149 (0.0357)	0.6777	0.00415 (0.0343)	0.9035	0.0617 (0.1504)	0.6925
ANTIGLAU	14	−0.0095	0.7051	−0.0135	0.6248	−0.0930	0.2088	16	0.0062	0.7237	0.0171	0.2945	0.0152	0.7826

2SMR: 2 Sample Mendelian Randomization; MR Egger: Egger regression approach; nSNPs: Total number of SNPs used as instruments; SE: standard error; *P*: *P*-value for causal analysis test, $^{**}p < 2.17 \times 10^{-3}$, $p < 0.05$.

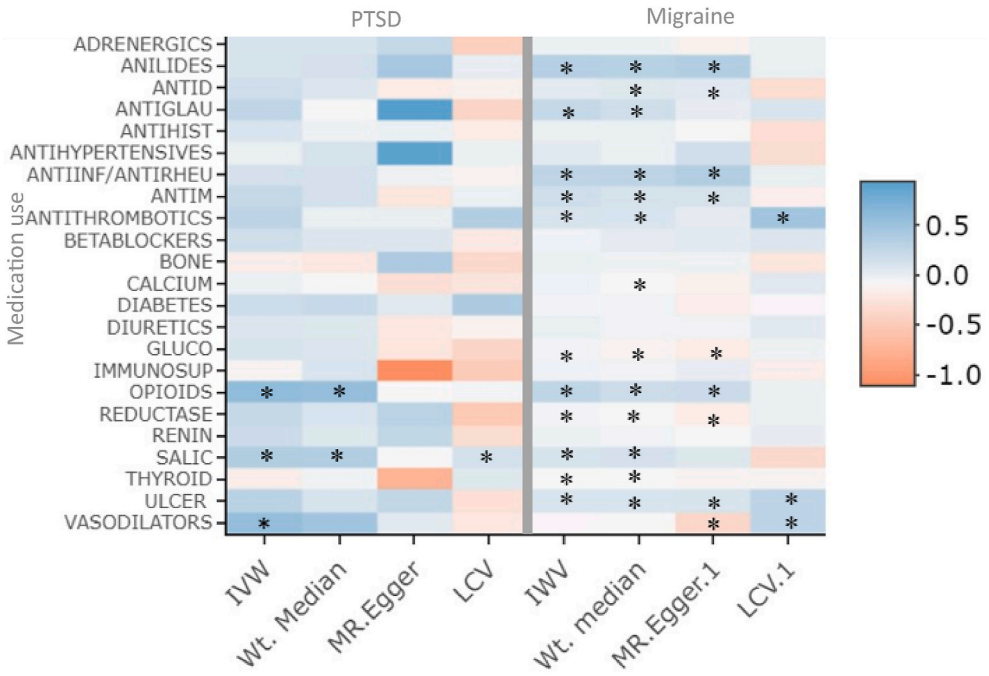

Fig. 2. Heatmap of causal associations of PTSD and migraine (exposure) on medication use traits (outcomes). The colour of each cell represents causal effect as estimated by the various MR and LCV models with the right-side colour bar as the reference indicating variation in strength and direction of causal effect as shown in Table 5. 3 with positive in blue and negative in pink. The asterisks (*) denote statistical significance of causal effect at $P < 0.05$ based on the primary model (IWV). IVW: Inverse variance weighted, Wt. Median: Weighted median, MR Egger: Mendelian Randomization, LCV: Latent Causality Variable.

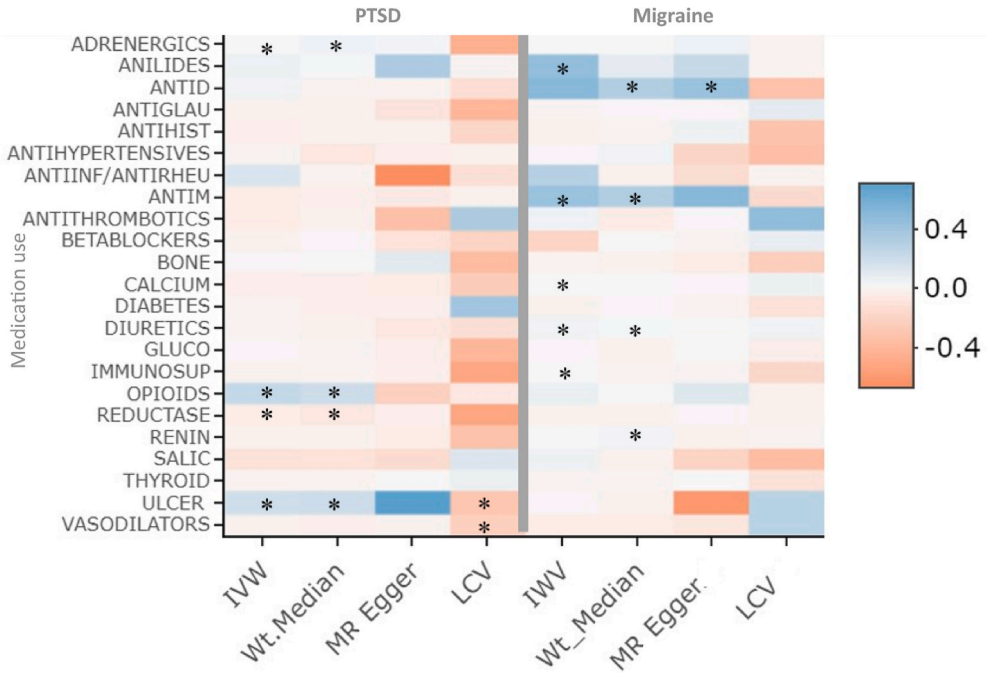

Fig. 3. Heatmap plot of causal associations of genetic predisposition to medication use traits (exposure) on PTSD and migraine (outcomes). The colour of each cell represents causal effect as estimated by the various MR and LCV models with the right-side colour bar as the reference indicating variation in strength and direction of causal effect as shown in Table 5.4 with positive in blue and negative in pink. The asterisks (*) denote statistical significance of causal effect at $P < 0.05$ based on the primary model (IWV). IVW: Inverse variance weighted, Wt. Median: Weighted median, MR: Mendelian Randomization, LCV: Latent Causality Variable.

clot formations have been found to be inconsistent, these relationships are attributed to vasoconstriction and platelet clumping (Guo et al., 2020).

Some of the genes in the loci associated with PTSD and anti-thrombotic agents include *CNTN4* and *PRDM16*. *CNTN4* has been implicated in other neuropsychiatric disorders including autism spectrum disorder (ASD) and schizophrenia (Oguro-Ando et al., 2021). CNTN4 is associated with dysregulation of the hypothalamus which can increase levels of cortisol, a hormone that has been linked to panic disorder (Zhao et al., 2021). On the other hand, altered function of genes related to hematopoiesis such as *PRDM16* has been reported to play a role in the differences in platelet and erythrocyte counts reported in

Table 5
Genetic causality proportion of PTSD and migraine on medication use.

Trait 1	PTSD			Migraine		
Trait 2	**rG (se)**	**GCP (se)**	***P*-value**	**rG (se)**	**GCP (se)**	***P*-value**
ANTIDEPRESSANTS	−0.09 (0.05)	−0.13 (0.56)	0.055	−0.04 (0.04)	−0.32 (0.40)	0.316
ANTITHROMBOTICS	0.34 (0.02)	0.36 (0.34)	0.093	0.22 (0.07)	0.48 (0.23)	*0.032
GLUCOCORTICOIDES	−0.12 (0.04)	−0.40 (0.39)	0.690	0.01 (0.04)	−0.03 (0.57)	0.417
BONES	−0.14 (0.05)	−0.37 (0.40)	0.730	−0.04 (0.05)	−0.24 (0.45)	0.794
SALIC	−0.12 (0.05)	0.14 (0.54)	0.014*	−0.08 (0.04)	−0.36 (0.40)	0.382
ADRENERGICS	−0.10 (0.03)	−0.45 (0.39)	0.676	–	–	–
ANILIDES	−0.05 (0.04)	0.01 (0.58)	0.546	–	–	–
ANTIHYPERTENSIVES	−0.10 (0.07)	−0.01 (0.31)	1	−0.03 (0.05)	−0.34 (0.40)	0.501
ANTIINFLAMMATORY	−0.09 (0.04)	−0.12 (0.57)	0.6421	–	–	–
ANTIMIGRAINE	−0.10 (0.05)	−0.01 (0.58)	0.521	0.05 (0.07)	−0.15 (0.47)	0.631
BETABLOCKERS	−0.07 (0.04)	−0.20 (0.46)	1	−0.01 (0.03)	0.09 (0.54)	0.904
DIABETES	0.17 (0.05)	0.40 (0.38)	0.694	0.01(0.04)	−0.10 (0.52)	0.794
BONES	−0.15 (0.06)	−0.37 (0.41)	0.730	−0.04 (0.05)	−0.24(0.45)	0.501
CALCIUM	−0.09 (0.03)	−0.25 (0.53)	0.754	0.01 (0.03)	0.06 (0.55)	0.794
DIURETICS	−0.08 (0.03)	−0.12 (0.57)	0.676	0.00 (0.03)	0.05 (0.56)	0.794
ANTIGLAUCOMA	−0.15 (0.05)	−0.40 (0.39)	0.790	−0.02 (0.04)	0.10 (0.54)	0.794
ANTIHISTAMINES	−0.09 (0.05)	−0.18 (0.36)	1	−0.04 (0.05)	−0.31(0.43)	0.398
IMMUNOSUP	−0.21 (0.10)	−0.51 (0.28)	0.962	0.00 (0.07)	−0.17 (0.45)	1
OPIOIDS	−0.05 (0.04)	−0.06 (0.58)	0.541	−0.01 (0.04)	−0.01 (0.56)	0.794
REDUCTASE	−0.10 (0.04)	−0.52 (0.33)	0.312	−0.01 (0.03)	−0.01(0.58)	0.794
RENIN	−0.04 (0.03)	−0.33 (0.46)	0.531	0.00 (0.03)	0.01 (0.55)	1
SALICYLIC	−0.15 (0.04)	0.28 (0.47)	0.387	−0.08 (0.04)	−0.38 (0.40)	0.316
THYROID	−0.06 (0.03)	0.07 (0.56)	0.633	0.04 (0.03)	−0.11 (0.50)	0.501
ULCERS	0.44 (0.05)	−0.29 (0.15)	$**1.46 \times 10^{-8}$	0.34 (0.04)	0.30 (0.14)	*0.050
VASODILATORS	0.24 (0.06)	−0.23 (0.16)	$**8.36 \times 10^{-16}$	0.06 (0.06)	0.30 (0.14)	*0.050

LCV: Latent Causality Variable; se: standard error; rG: genetic correlation using LC; se: standard error; GCP: genetic causality proportion; **P*-value $p < 0.05$ threshold; ***P*-value $<2.17 \times 10^{-3}$ (0.05/23).

migraine patients and contribute to hypercoagulability (Aguilo et al., 2011; Zhao et al., 2016; Gormley et al., 2016). Additionally, locus 9q34.2 (*ABO*) was associated with migraine and anti-thrombotic agents. Variation in the *ABO* gene is the basis of the ABO blood group which has been associated with venous thrombosis, alkaline phosphate and pulmonary embolism (Spiezia et al., 2013).

We found evidence of shared genetic risk between heart-related medications and both disorders. Calcium channel blockers are used in treatment of migraine and hypertension, they block entry of calcium ions into the cell and regulate vascular smooth muscle contraction (Guo et al., 2020). These medications are indicated in atrial fibrillation (AF) which is an irregular and often very rapid heart rhythm (arrhythmia) that can lead to blood clots in the heart. AF increases the risk of stroke, heart failure and other heart-related complications (Anter et al., 2009). Psychological stress and negative emotions are associated with the initiation and progression of AF, moreover PTSD was associated with increased risk for early incident AF after adjustment for established AF risk factors and depression (Rosman et al., 2019). Previous studies reported a bi-directional relationship between PTSD and coronary artery disease (CAD). This association has been attributed to psychiatric-somatic co-morbidities of PTSD (Polimanti et al., 2022) including cardiovascular disease outcomes such as angina pectoris, tachycardia, and hypertension immune dysfunction, and metabolic syndrome (Mellon et al., 2018).

Secondly, there was an indication that stress may influence both PTSD and migraine. Medication use for anti-depressants was significantly associated with both PTSD and migraine from pair-wise locus-specific genetic correlation analyses. Tricyclic anti-depressants such as amitriptyline are used in the treatment of both PTSD and migraine. It has been suggested that anti-depressants may be associated with both PTSD and migraine directly or through other factors such as stress (Minen et al., 2016; Dresler et al., 2019). Stress may mediate the association between migraine and psychiatric comorbidities, however there is no specific mediation of serotonin in these co-morbidities (Dresler et al., 2019; Zhang et al., 2019; Radat and Swendsen, 2005). Stress and migraine have a direct or indirect bi-directional relationship with serotonin as a plausible mediator (Noseda et al., 2014). Stressors are triggers for migraine and migraine is considered a stressor, it impacts social and occupational functioning (Peroutka, 2014; Rains, 2009). Migraine patients report higher stress levels than healthy controls, prolonged stress triggers activation of the trigeminovascular system through the action of the HPA axis (Dresler et al., 2019; Burstein and Jakubowski, 2009).

Further in relation to stress, there was evidence that the pain regulation system may play a role in both PTSD and migraine. This was indicated by the significant local genetic correlation between the pain medications with both PTSD and migraine. Additionally, use of salicylic acids/derivatives and anilides had a bi-directional causal effect with increased risk of PTSD and migraine, respectively. Chronic stress activates prolonged inflammation that leads to damage and significant alterations in brain regions implicated in pain (Rome and Rome, 2000; Miller et al., 2018). Higher prevalence of migraine in PTSD has been attributed to abnormal endocrine response and limbically augmented pain syndrome where normal arousal induced by pain becomes chronic and the brain fails to adjust adequately (Rome and Rome, 2000). Opioids such as butorphanol, codeine, tramadol and meperidine (Demerol) have moderate evidence of effectiveness for migraine (Diener et al., 2018). Routine use is not recommended due to high potential abuse, furthermore, brain cells with opioid receptors gradually change and this decreases response to opioid stimulation (D'Amico et al., 2018; Volkow and McLellan, 2016). Several epidemiological studies have reported co-morbidity of PTSD and opioid use disorder, for example a study found greater opioid use among individuals with comorbid PTSD and chronic pain (Kind and Otis, 2019).

The other mechanism that was implicated in both disorders was inflammation. Our study showed shared loci between anti-inflammatory/anti-rheumatic products with both PTSD and migraine. In addition, the genetic liability to migraine had a causal effect on increased risk of using anti-inflammatory/anti-rheumatoid, glucocorticoids, and drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD). Abdominal abnormalities such as pain or discomfort have been reported to increase the risk of migraine through inflammation and vascular mediators (Arzani et al., 2020; Cá et al., 2016). Gene expression changes in the HPA axis, including glucocorticoid receptors (GRs), GR

response elements and inflammatory genes have been implicated following trauma (Burback et al., 2024; Mehta et al., 2020). There is increasing evidence supporting the role of inflammation in the occurrence of migraine (Malhotra, 2016). The pituitary adenylate cyclase-activating polypeptide (PACAP) that is implicated in neuro-inflammation of migraine, has been targeted in the likely prevention of migraine (Sundrum and Walker, 2018). Previous studies have demonstrated alteration of specific pro- and anti-inflammatory cytokine markers across trauma types for example elevated serum Interleukin-6 (IL-6) levels via the blood-brain barrier due to psychosocial stress (Kim et al., 2020). Additionally, a genetic study showed that SNP rs1130864 was significantly associated with plasma C-reactive protein (CRP) levels and PTSD symptom severity (Michopoulos et al., 2015). However, there is no evidence of a causal relationship between PTSD symptom severity and plasma CPR levels (Miller et al., 2018). Altered inflammatory markers have been associated with structural and functional alterations in brain regions responsible for the stress and emotion regulation including the hippocampus and frontal cortex (Kim et al., 2020).

Strengths of this study include multiple analytical methods applied to well-powered GWAS summary statistics of PTSD and the largest known GWAS dataset for migraine to assess pleiotropic associations using medication use traits. Various models were used to detect mediating biological factors underlying the shared genetic risk between PTSD and migraine. For instance, loci-specific genetic correlation analysis was applied to capture small effects and effects in opposite directions that may not be captured at the genome-wide level. For causal associations, multiple MR models which use LD-independent genome-wide significant SNPs and the LCV model that uses genome-wide SNPs were used in this study. However, there are some potential limitations in this study. First, the medication use traits were used as proxies for the disorders they are indicated for. However, the majority of our findings are consistent with previous investigations and generate various testable hypotheses. Secondly, it is important to consider the potential sources of bias in this study, such as self-reported medication use data and the prescriptions were not verified. Additionally, GWAS ($n_{cases} > 10{,}000$) are considered well-powered to identify common risk variants associated with a disease/trait (Visscher et al., 2017). However, there was considerable variation in the size and power across of datasets for PTSD, migraine and the individual medication use traits. Although both PTSD and migraine are more prevalent among females than males, the MVP PTSD GWAS is predominantly male. The only known European sex-stratified migraine GWAS is underpowered (Anttila et al., 2013) and therefore sex-stratified analyses were not performed. Lastly, only cohorts of European ancestry were included in this study hence findings may not be generalisable to other ancestries.

4.1. Conclusion

This study provides evidence suggesting genetically-controlled biological factors underlying PTSD and migraine. Results indicated that the significant genetic relationship between PTSD and migraine may be partly mediated by stress and pain pathways as well as the cardiovascular and immune systems. These factors have previously been independently associated with PTSD and migraine. Findings showed significant genetic overlap and causal associations between PTSD and migraine with medication related to blood and heart disorders, stress, pain, and inflammation. Significant genetic correlation suggests shared etiology underlying PTSD, migraine and some of the assessed disorders. Heart and blood-related medications including anti-thrombotic agents, calcium channel blockers, beta blocking agents and anilides all shared loci with both PTSD and migraine; this supports previous studies showing evidence of co-morbidity between PTSD and migraine with cardiovascular diseases and abdominal disorders. The shared loci between anti-inflammatory/anti-rheumatic products and anti-migraine preparations with both PTSD and migraine highlight the role of the immune system through inflammation. This is further supported by significant causal associations between migraine and anti-inflammatory/anti-rheumatic products, glucocorticoids and peptic ulcers/GORD. This study gives more insight into the genetically-controlled biological and environmental aetiological factors that may account for the significant genetic correlation with absence of a causal relationship in the pathophysiology of PTSD and migraine. Most importantly the medications associated with both disorders can be further investigated for potential drug repurposing and for use in treatment of both disorders (monotherapy). Monotherapy is cost effective, simplifies management of these co-morbidities, minimizes potential side effects and eliminates potential drug interactions (Silberstein et al., 2007). The shared loci and genes can be used as basis for further investigation as potential drug targets for both disorders.

CRediT authorship contribution statement

Charlotte K. Bainomugisa: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Dagmar Bruenig:** Writing – review & editing. **Heidi G. Sutherland:** Writing – review & editing. **Lyn R. Griffiths:** Writing – review & editing, Supervision. **Dale R. Nyholt:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Divya Mehta:** Writing – review & editing, Supervision, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2024.100703.

Data availability

The migraine GWAS summary statistics are obtained from the

23andMe and IHGC. The full GWAS summary statistics for the 23andMe discovery dataset will be available made available through 23andMe to qualified researchers under an agreement with 23andMe that protects the privacy of the 23andMe participants. For further details and to access the data, please visit https://research.23andme.com/collaborate/#dataset-access/. Researchers can perform a meta-analysis of 23andMe migraine summary statistics and IHGC migraine GWAS summary statistics to get the full summary statistics of the migraine dataset. MVP PTSD data are available on request from the dbGaP website under phs001672. v1. p1 (dbGaP: https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001672.v1.p1). The summary statistics on medication use are available on https://cnsgenomics.com/data/wu_et_al_2019_nc/website.

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