Psychiatry Research 333 (2024) 115758

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Genetic contribution to the comorbidity between attention-deficit/hyperactivity disorder and substance use disorders

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ARTICLE INFO

Keywords:
Attention-deficit hyperactivity disorder
Substance use disorders
Pleiotropy
Mendelian randomization
Polygenic risk scoring

ABSTRACT

We characterized the genetic architecture of the attention-deficit hyperactivity disorder-substance use disorder (ADHD-SUD) relationship by investigating genetic correlation, causality, pleiotropy, and common polygenic risk. Summary statistics from genome-wide association studies (GWAS) were used to investigate ADHD (N_{eff} = 51,568), cannabis use disorder (CanUD, N_{eff} = 161,053), opioid use disorder (OUD, N_{eff} = 57,120), problematic alcohol use (PAU, N_{eff} = 502,272), and problematic tobacco use (PTU, N_{eff} = 97,836). ADHD, CanUD, and OUD GWAS meta-analyses included cohorts with case definitions based on different diagnostic criteria. PAU GWAS combined information related to alcohol use disorder, alcohol dependence, and the items related to alcohol

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https://doi.org/10.1016/j.psychres.2024.115758
Received 27 September 2023; Received in revised form 17 January 2024; Accepted 23 January 2024
Available online 3 February 2024

problematic consequences assessed by the alcohol use disorders identification test. PTU GWAS was generated a multi-trait analysis including information regarding Fagerström Test for Nicotine Dependence and cigarettes per day. Linkage disequilibrium score regression analyses indicated positive genetic correlation with CanUD, OUD, PAU, and PTU. Genomic structural equation modeling showed that these genetic correlations were related to two latent factors: one including ADHD, CanUD, and PTU and the other with OUD and PAU. The evidence of a causal effect of PAU and PTU on ADHD was stronger than the reverse in the two-sample Mendelian randomization analysis. Conversely, similar strength of evidence was found between ADHD and CanUD. *CADM2* rs62250713 was a pleiotropic SNP between ADHD and all SUDs. We found seven, one, and twenty-eight pleiotropic variants between ADHD and CanUD, PAU, and PTU, respectively. Finally, OUD, CanUD, and PAU PRS were associated with increased odds of ADHD. Our findings demonstrated the contribution of multiple pleiotropic mechanisms to the comorbidity between ADHD and SUDs.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by inattentive, hyperactive, and impulsive behaviors (Ribases et al., 2023) and occurs in about 5 % of children (Faraone and Larsson, 2019) and 2.8 % of adults (Ribases et al., 2023), with a twin-based heritability (h^2) of 74 % (Faraone and Larsson, 2019). Being a complex disorder, the effect of individual genetic variants on the disease is very small, but the aggregate effect of single nucleotide polymorphisms (SNPs) is estimated to be 14 % in the most recent genome-wide association study (GWAS) on ADHD which identified 27 risk loci (Demontis et al., 2023). Up to 70–80 % of individuals with ADHD have several comorbidities (Ribases et al., 2023), including other neurodevelopmental disorders (Gnanavel et al., 2019), internalizing disorders (Gnanavel et al., 2019), and substance use disorders (SUDs) (Capusan et al., 2019). The risk of developing SUDs increases during their adolescence, with a faster progression rate compared to the general population (Wimberley et al., 2020). Moreover, ADHD is present in one out of four patients with SUD (van Emmerik-van Oortmerssen et al., 2012). Both ADHD and SUDs are important public health burdens, especially so when they occur concurrently (Karlsdotter et al., 2016). ADHD economic impact is estimated to be $13.2 billion (Sciberras et al., 2022), while SUDs cost $13.2 billion to hospitals annually only in the United States (Peterson et al., 2021). Beyond the economic burden, these conditions reduce life expectancy with individuals affected by ADHD-SUD comorbidity having an even higher mortality rate (Dalsgaard et al., 2015). Individuals with ADHD who receive treatment earlier in adolescence are less likely to develop SUDs than individuals who receive treatment later, or those who do not receive any (Zulauf et al., 2014).

SUDs are characterized by impaired control over the use of psychoactive substances despite problems that arise from their use (Jahan and Burgess, 2023). SUDs are heritable (twin-based $h^2 \sim 50$ % (Deak and Johnson, 2021)) complex disorders, with both genetic and environmental factors contributing to their development (Deak and Johnson, 2021). Recent GWASs identified many risk loci for cannabis use disorder (CanUD), opioid use disorder (OUD), problematic alcohol use (PAU), and problematic tobacco use (PTU) (Table 1) (Hatoum et al., 2023; Kember et al., 2022; Levey et al., 2023; Zhou et al., 2023). Because of the higher statistical power, GWAS of other ADHD comorbid disorders found even more genome-wide significant loci: 287 for schizophrenia (Trubetskoy et al., 2022), 64 for bipolar disorder (Mullins et al., 2021), and 178 for depression (Levey et al., 2021). Additionally, several studies already explored different pleiotropic mechanisms contributing to ADHD comorbidity with psychiatric conditions studied by more powerful GWAS (Du Rietz et al., 2021; Grotzinger et al., 2022; Powell et al., 2021; Wendt et al., 2023). Conversely, with respect to ADHD-SUD pleiotropy, studies reported positive genetic correlations of ADHD with CanUD (Pasman et al., 2018), lifetime cannabis use (Soler Artigas et al., 2020), alcohol dependence (Walters et al., 2018), OUD (Kember et al., 2022), and nicotine dependence (Vink et al., 2021). Furthermore, an ADHD polygenic risk score (PRS) was associated with any SUD diagnosis (Wimberley et al., 2020), smoking (Du Rietz et al., 2018), alcohol dependence (Du Rietz et al., 2018), and lifetime cannabis use (Vilar-Ribo et al., 2021). The genetic liability to ADHD also increases the risk of smoking initiation (Treur et al., 2021), alcohol dependence (Treur et al., 2021), lifetime cannabis use (Soler Artigas et al., 2020; Vilar-Ribo et al., 2021), and liability to smoking initiation and lifetime cannabis use increased ADHD risk (Treur et al., 2021; Vilar-Ribo et al., 2021). Furthermore, 40 loci were pleiotropic between ADHD and ever smoking, and 22 loci were pleiotropic between ADHD and smoking initiation (Jang et al., 2022). However, inconsistent findings were also observed, with some studies reporting no association between ADHD-PRS and any SUD (Carey et al., 2016; Gurriaran et al., 2019), including cannabis dependence (Rabinowitz et al., 2018). Another study reported no causal relationship between the genetic liability to ADHD and alcohol dependence or addiction to any illicit drugs in either direction (Vilar-Ribo et al., 2021). While these previous studies support the potential role of pleiotropy in contributing to ADHD-SUD comorbidity, no studies applied multiple analytic approaches to investigate different pleiotropic mechanisms linking ADHD to different SUDs. To fill this gap, we characterized the genetic architecture of the ADHD-SUD relationship using large-scale genome-wide datasets with adequate power to detect reliable associations. Specifically, we investigated genetic correlations, shared latent factors, bidirectional causality, horizontal pleiotropy, and polygenic risk for SUDs in patients with ADHD. The results highlight the complex relationship between ADHD and SUDs, pointing to dynamics that may be targeted to develop better preventive and therapeutic strategies.

Table 1
Genome-wide association studies included in the present study. Additional details for each trait are reported in Supplemental Table 1.

Trait	Abbreviation	Ncases	Ncontrols	Neff	Data source	GWS loci
Attention-deficit hyperactivity disorder	ADHD	38,691	186,843	52,568	iPSYCH, deCODE, PGC	27
Cannabis use disorder	CanUD	32,436	563,331	161,053	MVP, iPSYCH, PGC, deCODE, Yale-Penn, Partners	22
Opioid use disorder	OUD	15,040	282,607	57,120	MVP, PGC, Yale-Penn, Partners	4
Problematic alcohol use	PAU	113,325	639,923	502,272	MVP, FinnGen, UKB, PGC, iPSYCH, QIMR, Yale-Penn	85
Problematic tobacco use	PTU	–	–	97,836	(Hatoum et al., 2023; Liu et al., 2019; Quach et al., 2020)	12

SNP-h^2: SNP-heritability on the liability scale (see sample and population prevalence in Supplemental Table 1), iPSYCH: Integrative Psychiatric Research Consortium (Denmark), deCODE: deCODE Genetics (Iceland), PGC: Psychiatric Genomics Consortium, MVP: Million Veteran Program (United States), Yale-Penn 3: Yale-Penn cohort (United States), Partners: Partners Healthcare Biobank (Mass General Brigham, United States), FinnGen: a nation-wide network of Finnish biobanks, UKB: United Kingdom Biobank, QIMR: Queensland Institute of Medical Research, GWS: genome-wide significant.

2. Methods

2.1. Genome-wide datasets

Table 1 provides details regarding the GWAS investigated in the present study. ADHD GWAS included data from iPSYCH, deCODE genetics, and ten ADHD cohorts collected by the Psychiatric Genomics Consortium (PGC) (Demontis et al., 2023). In total, 38,691 cases and 186,843 controls of European ancestry were included. The meta-analysis included samples with different ADHD case definitions based on DSM (Diagnostic and Statistical Manual of Mental Disorders) and ICD (International Classification of Diseases) criteria and self-reported information. For CanUD GWAS, 41,281 cases and 843,744 controls were obtained by meta-analysing previous PGC data (32,436 cases and 563,331 controls) with novel information from the Million Veteran Program (MVP), iPSYCH, deCODE, Yale-Penn 3, and Partners Healthcare Biobank (Levey et al., 2023). In the MVP cohort, CanUD cases were individuals with inpatient or outpatient ICD codes for CanUD, and controls were individuals without ICD codes for cannabis dependence, cannabis abuse, or cannabis use in their electronic health records. Cohorts from the MVP, Yale-Penn 3, the Partners Healthcare Biobank, and PGC were meta-analyzed for the GWAS of OUD stringent definition, yielding 15,040 cases and 282,607 controls (Kember et al., 2022). For PAU, a GWAS meta-analysis (113,325 cases and 639,923 controls) was carried out by combining cohorts assessed for alcohol use disorder, alcohol dependence, and the items related to alcohol problematic consequences assessed by the alcohol use disorders identification test (Zhou et al., 2023). PTU GWAS was generated a multi-trait analysis including information regarding Fagerström Test for Nicotine Dependence and cigarettes per day (Hatoum et al., 2023). Due to the lack of data available for other ancestries for ADHD, only individuals of European ancestry were analyzed in the present study.

In the PRS analysis, the target sample consisted of 5899 unrelated individuals with European ancestry: 1775 ADHD cases (33.2 % females; mean age=27.9 years (SD=13.3)) and 4124 healthy controls (45.7 % females; mean age=50.1 years (SD=15.6)). Patients were recruited at the outpatient facility of the Adult ADHD Program in the Hospital Universitari Vall d'Hebron (HUVH), Barcelona, Spain. The diagnosis of ADHD was evaluated with the Structured Clinical Interview for DSM-IV (SCID-I) and the Conners Adult ADHD Diagnostic Interview for DSM-IV (CAADID-II). Healthy controls were from the same recruitment area as the ADHD patients. All participants provided written informed consent, and the study was approved by the ethical committee at the hospital. Samples were genotyped in five genotyping waves using different Illumina arrays: Omni1 (n = 982), Omni2.5 (n = 256), Psychchip (n = 1699), Infinium™ Global Screening Array-24 v2.0 (n = 2743), and Infinium™ Global Screening Array-24 v3.0 (n = 219). Pre-imputation quality control was done with the PLINK 2.0 (Chang et al., 2015) and included individual and variant filtering based on the following parameters: variant call rate >0.95 (before individual filtering), individual call rate >0.98, autosomal heterozygosity deviation (| Fhet | <0.2), variant call rate >0.98 (after individual filtering), the difference in variant missingness between cases and controls <0.02, Hardy-Weinberg equilibrium (HWE) (P >1e−06 in controls or P >1e−10 in cases) and minor allele frequency (MAF) > 0.01. Ancestry outliers were identified by principal component analysis (PCA) using PLINK 2.0 and the 1000 Genomes Project reference panel (Auton et al., 2015). Imputation was conducted through the Michigan Imputation Server (Das et al., 2016), using the Haplotype Reference Consortium (HRC Version r1.1 2016) reference panel (GRCh37/hg19). After imputation, the genotype waves were merged and SNPs that were common across all waves, with imputation INFO score >0.8 and MAF >0.01 were considered. Related and duplicated samples across waves were identified by the "KING--robust kinship estimator" analysis with PLINK 2.0 (Manichaikul et al., 2010) and one individual was excluded from each pair of subjects with kinship coefficient > 0.0442. For the sex-stratified analyses, PCs were recalculated in the respective groups.

2.2. SNP-based heritability and global genetic correlation

SNP-based heritability (SNP-h^2) on the liability scale and global genetic correlation were calculated for ADHD, CanUD, OUD, PAU, and PTU using Linkage Disequilibrium Score Regression (LDSC) (Bulik-Sullivan et al., 2015). We used the estimates of sample and population prevalence reported in the original GWAS of ADHD, CanUD, and PAU (Demontis et al., 2023; Hatoum et al., 2023; Levey et al., 2023). For OUD, the number of cases and controls were used to calculate sample prevalence, and population prevalence was calculated based on data from the Center for Disease Control (CDC) (2.7 million cases/333 million United States population) (Supplemental Table 1). The Phase 3 European populations from the 1000 Genomes Project were used as the linkage disequilibrium (LD) reference panel (Auton et al., 2015). LDSC analysis was restricted to SNPs included in the HapMap 3 reference panel (International HapMap et al., 2010) to use a set of well-imputed and common variants.

2.3. Genomic structural equation modeling

Genomic structural equation modeling (gSEM) (Grotzinger et al., 2019) was used to assess the shared genetic architecture of ADHD, CanUD, OUD, PAU, and PTU. Similar to LDSC, we restricted the analysis to Hapmap 3 variants. We performed exploratory factor analyses (EFA) examining single and two-factor models. To assess model convergence and factor loadings, we applied confirmatory factor analysis (CFA). EFA and CFA model fit were evaluated using standard model fit indices (Grotzinger et al., 2019). The Phase 3 European populations from the 1000 Genomes Project were used as the LD reference panel (Auton et al., 2015).

2.4. Genetically informed causal inference analysis

To assess possible causal effects between ADHD and CanUD, OUD, PAU, and PTU, we conducted bi-directional two-sample MR analyses with the TwoSampleMR R package (v0.5.6, https://mrcieu.github.io/TwoSampleMR/index.html) (Hemani et al., 2018b). ADHD was tested as both exposure and outcome. LD-independent (r^2=0.001 within a 10,000-kb window) genome-wide significant variants ($P < 5 \times 10^{-8}$) were selected as genetic instruments. For OUD, we used the $P < 5 \times 10^{-6}$ threshold due to the low number of genome-wide significant variants. Variants were only included if they were present in both the exposure and outcome GWAS. We used variant IDs, effect allele, other allele, effect allele frequency, effect size, standard error, and p-value for the analyses. We applied five Mendelian Randomization (MR) methods, inverse variance weighted (IVW), MR-Egger, weighted median, simple mode, and weighted mode (Hemani et al., 2018b). We considered the outcome of the IVW method as the primary results due to its higher statistical power compared to the others (Hemani et al., 2018a). The other four methods were used to assess the concordance in the direction of effects. Pleiotropy with MR-Egger regression intercept and MR heterogeneity tests were used to assess the sensitivity of the results.

2.5. Pleiotropy analysis

We used the PolarMorphism R package (von Berg et al., 2022) to investigate single loci partly responsible for the horizontal pleiotropy between ADHD and CanUD, OUD, PAU, and PTU. Variants with a theta q-value < 0.05 were considered pleiotropic, and were clumped using the following parameters in PLINK 2.0 (Purcell et al., 2007): –clump-kb 5000, –clump-p1 0.05, –clump-p2 0.05 and –clump-r2 0.2. Pleiotropy was estimated between all five traits (ADHD, CanUD, OUD, PAU, and PTU), and also between ADHD and each trait separately.

2.6. Characterization of pleiotropic loci

We conducted a gene-based analysis with the "best-SNP test" of the Versatile Gene-based Association Study 2 tool (Mishra and Macgregor, 2015) with the list of variants with nominally significant pleiotropy between the traits as input. Using these gene sets, a pathway enrichment analysis was performed to study gene ontology, biological pathways, and molecular functions. We applied False Discovery Rate (FDR) ($q < 0.05$) to account for multiple testing correction.

We also conducted a multi-trait colocalization analysis with the shared SNP between all traits, *CADM2* rs62250713 and gene expression in different tissues with the hypercoloc R package (Foley et al., 2021). This tool uses a Bayesian clustering algorithm to identify colocalized traits and candidate causal SNPs. As recommended by the developers, posterior probability >70 % was considered as evidence of colocalization (Foley et al., 2021). The following tissues were tested due to rs62250713 being significant eQTLs for them previously (https://gtexportal.org/home/snp/rs62250713): subcutaneous and visceral adipose tissue, brain - substantia nigra, and brain-spinal cord from the Genotype-Tissue Expression (GTEx) (GTEx Consortium, 2020). Additionally, eight different brain cell types were tested to investigate if this SNP was an eQTL for them: astrocytes, endothelial cells, excitatory neurons, inhibitory neurons, microglia, oligodendrocytes, oligodendrocyte progenitor cells, and pericytes using a dataset generated by Bryois et al. (2022).

2.7. Polygenic risk scoring

PRSs were calculated from best-guess genotypes after imputation using PLINK 2.0 based on the following GWAS summary statistics: CanUD (Johnson et al., 2020), OUD (Kember et al., 2022), PAU (Zhou et al., 2023) and PTU (Hatoum et al., 2023). PRS-CS tool was used to infer posterior SNP effect sizes under continuous shrinkage priors and to estimate the global shrinkage parameter (φ) using a Bayesian approach (Ge et al., 2019) using the 1000 Genomes European LD panel (Auton et al., 2015). Logistic regression models were used to associate ADHD diagnosis with CanUD-PRS, OUD-PRS, PAU-PRS and PTU-PRS including sex, age, batch and the first ten PCs as covariates (sex was excluded in sex-stratified analyses). Bonferroni correction was applied to correct for multiple testing. The criterion for significance was set at $p < 0.0125$ (0.05/4).

3. Results

3.1. Global genetic correlation

We observed positive global genetic correlation between ADHD and all SUDs, ranging from 0.34 (SE = 0.08) for OUD to 0.61 for CanUD (SE = 0.03) (Fig. 1, Supplemental Table 1). The global genetic correlation between ADHD and CanUD was statistically higher compared to all the others (OUD: z-score=10.11, p-value=2.66×10^{-23}, PAU: z-score = 10.11, p-value=2.66×10^{-23}, PTU: z-score=6.56, p-value=1.75×10^{-10}; Supplemental Table 1).

3.2. Genomic structural equation modeling

We performed single- and two-factor EFAs using gSEM to analyze different models for the shared genetic architecture of the five studied traits. There were not enough variables to fit a three-factor EFA. The cumulative variance accounted for by the single-factor EFA was 0.54 (Supplemental Table 2). The two-factor EFA model explained a cumulative variance of 0.73 (0.47 for factor 1, and 0.26 for factor 2, with the sum of squared (SS) loadings of 2.23 and 1.29, respectively, Supplemental Table 2). Given the greater proportion of variance explained by the two-factor model and SS loadings suggesting that both factors were contributing valuable information, the two-factor model was evaluated further using CFA. Two different CFA models were fit, one allowing each variable to load on a single factor, and another allowing CanUD to co-load on both factors as specified by the EFA results (Supplemental Table 2). The model allowing CanUD to co-load on both factors fit the data best (comparative fit index [CFI], 1; $\chi 2 = 7.36$; Aikake information criterion [AIC], 31.36; standardized root mean square residual [SRMR], 0.03, Fig. 2, Supplemental Table 2). OUD and PAU loaded on factor 1 (loading=0.90, SE = 0.07); loading=0.85, SE = 0.05, respectively), while PTU and ADHD loaded on factor 2 (loading=0.49, SE0.03; loading=0.91, SE = 0.05, respectively). CanUD loaded on both factor 1 (loading=0.76, SE = 0.07), and factor 2 (loading=0.27, SE = 0.06). There was a correlation of 0.49 between the two factors. Comparative model fit is reported in Supplemental Table 3. Overall, gSEM results suggest stronger pleiotropic mechanisms linking ADHD to PTU and CanUD than ADHD genetic factors shared with OUD and PAU.

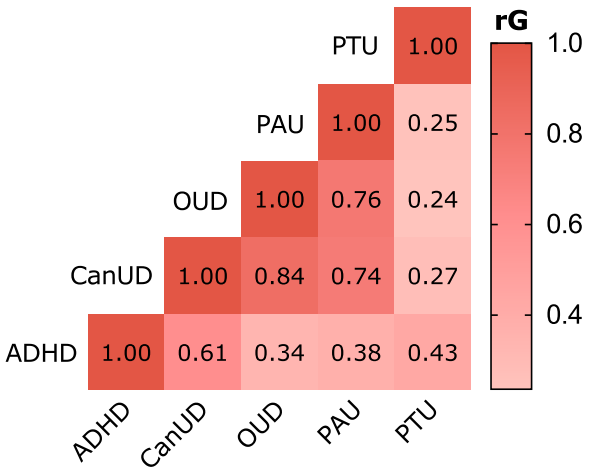

Fig. 1. Genetic correlations between attention-deficit hyperactivity disorder (ADHD) and cannabis use disorder (CanUD), opioid use disorder (OUD), problematic alcohol use (PAU), and problematic tobacco use (PTU).

3.3. Genetically informed causal inference analysis

The two-sample MR analyses showed a positive, bi-directional relationship of ADHD with CanUD, PAU, and PTU (Fig. 3, Supplemental Table 3). No causal relationship was found between ADHD and OUD. The IVW method showed bi-directional effects linking ADHD and CanUD (ADHD → CanUD: beta=0.33, 95 % CI=0.23–0.42; CanUD → ADHD: beta=0.38, 95 % CI=0.27–0.48). Conversely, evidence of the effect of the genetic liabilities to PTU and PAU appear to stronger on ADHD than the reverse (ADHD → PTU: beta=0.07, 95 % CI= 0.04–0.10, PTU → ADHD: beta=0.28, 95 % CI=0.16–0.40; ADHD → PAU: beta=0.03, 95 % CI=0.004–0.05; PAU → ADHD: beta=0.56, 95 % CI=0.35–0.78). The results using MR Egger, weighted median, simple mode, and weighted mode tests were in the same positive direction in all but one case – the MR Egger estimate was null for ADHD → PTU. The results of MR-Egger regression intercept and MR heterogeneity tests support that the effects detected should not be due to possible violations in the MR assumptions (Supplemental Table 3).

3.4. Pleiotropy analysis

The genome-wide pleiotropy analysis of the five traits simultaneously revealed nine LD-independent SNPs with significant evidence of horizontal pleiotropy (theta q-value<0.05). Among them, one intronic SNP, *CADM2* rs62250713 (3:85464643, Z_{ADHD}=3.3, Z_{CanUD}=5, Z_{OUD}=3.7, Z_{PAU}=5, Z_{PTU}=4.4, $q_{theta}=5.8 \times 10^{-3}$) remained significant after applying a *post-hoc* Bonferroni multiple testing correction to the effect of each trait (p-value<5.6×10^{-3}, z-score>|2.8|) (Supplemental

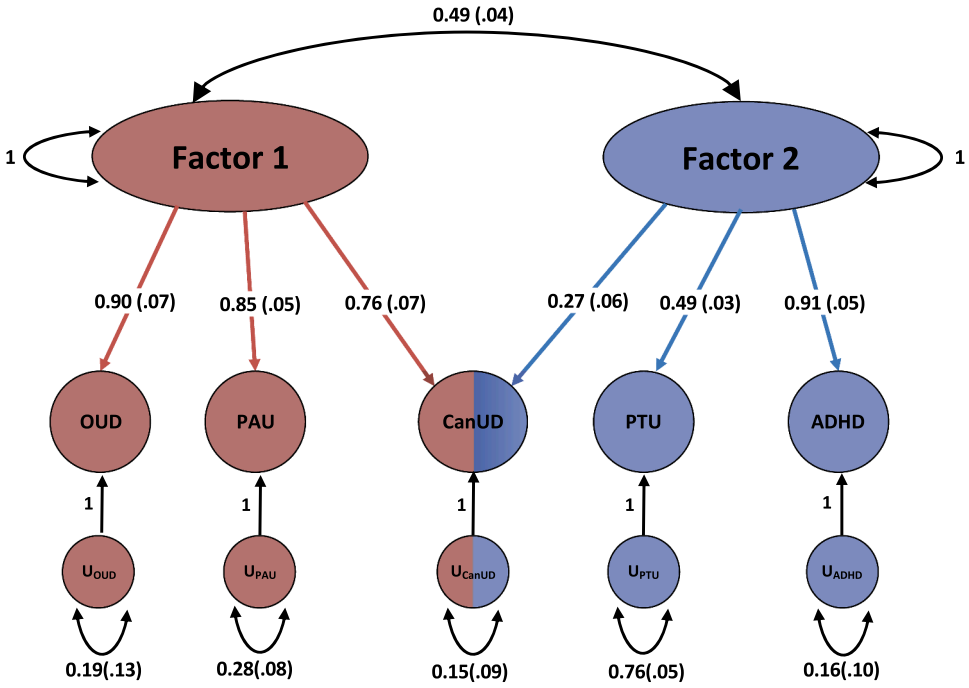

Fig. 2. Genomic structural equation modeling of attention-deficit hyperactivity disorder (ADHD) and cannabis use disorder (CanUD), opioid use disorder (OUD), problematic alcohol use (PAU), and problematic tobacco use (PTU). Values correspond to loadings with standard error.

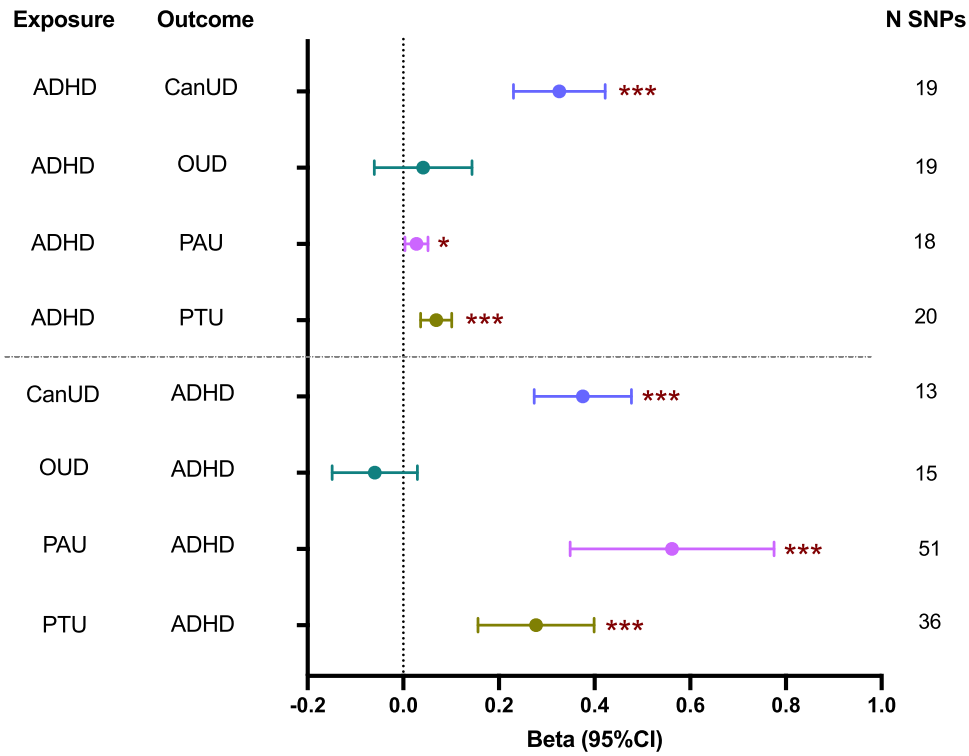

Fig. 3. Bi-directional two-sample Mendelian randomization analysis using attention-deficit hyperactivity disorder (ADHD) as both exposure and outcome. Effect size and 95 % confidence intervals are reported for the inverse variance-weighted effect estimates. ADHD: attention-deficit hyperactivity disorder, CanUD: cannabis use disorder, OUD: opioid use disorder, PAU: problematic alcohol use, PTU: problematic tobacco use, CI: confidence interval, SNP: single nucleotide polymorphism. $p < 0.05$*; $p < 0.001$***.

Table 4). ADHD Analysis with respect to each of the other traits separately yielded seven, one, and twenty-eight loci with genome-wide significant evidence of horizontal pleiotropy (theta q-value<0.05). Specifically, after applying a post hoc Bonferroni correction, pleiotropy with ADHD was significant for CanUD (p-value$<1.1 \times 10^{-3}$, z-score>|3.3|), PAU (p-value$<1.2 \times 10^{-6}$, z-score>|3.2|), and PTU (p-value$<1.3 \times 10^{-3}$, z-score>|3.2|) (Table 2, Supplemental Tables 5–7). No pleiotropic locus was found between ADHD and OUD.

Table 2
Variants with genome-wide significant evidence (theta q-value<0.05) of horizontal pleiotropy between attention-deficit hyperactivity disorder (ADHD) and cannabis use disorder (CanUD), problematic alcohol use (PAU), and problematic tobacco use (PTU).

Marker name	Chr	Position	Z-score$_{ADHD}$	Z-score$_{SUD}$	q$_{theta}$	Closest gene
ADHD – CanUD						
rs17400325	2	177,701,185	3.419	3.484	0.047	*PDE11A-AS1*
rs1554266	2	22,207,923	−4.124	−3.569	0.047	non-coding RNA gene
rs10953765	7	114,651,380	−4.592	−3.514	0.047	*FOXP2*
rs850278	14	56,905,818	3.317	3.598	0.047	*OTX2-AS1*
rs2364111	11	113,740,213	−3.283	−4.225	0.047	*ZW10*
rs10143566	14	98,251,591	4.043	3.302	0.047	intergenic
rs10789929	11	112,959,940	−3.317	−4.603	0.047	non-coding RNA gene
ADHD – PAU						
rs28707439	8	92,057,974	3.149	3.149	0.017	*RUNX1T1*
ADHD – PTU						
rs1484144	4	79,296,443	3.614	−3.614	4.75×10^{-4}	*LINC01088*
rs17642632	1	197,839,648	−3.536	3.609	0.045	regulatory region variant
rs2947411	2	614,168	−3.363	4.101	0.045	intergenic
rs1554266	2	22,207,923	−4.225	3.356	0.045	non-coding transcript variant
rs4974084	3	48,901,647	3.086	−3.366	0.045	regulatory region variant
rs2163971	3	85,379,576	3.519	3.644	0.045	*CADM2*
rs62250718	3	85,474,633	3.524	3.257	0.045	*CADM2*
rs4678361	3	136,114,163	−3.306	3.440	0.045	*PPP2R3A*
rs7624303	3	158,133,434	3.213	−3.520	0.045	*RSRC1*
rs228619	4	102,648,126	−3.775	3.759	0.045	*MANBA*
rs76761914	4	111,384,619	4.462	−3.557	0.045	non-coding transcript variant
rs28618243	5	145,143,520	−4.218	3.359	0.045	non-coding transcript variant
rs77962221	6	20,439,397	−3.077	−3.339	0.045	*E2F3*
rs78648104	6	50,715,296	4.283	−3.423	0.045	*TFAP2D*
rs9767122	6	149,783,553	3.293	−3.662	0.045	*PCMT1*
rs7791299	7	1,895,962	3.565	−3.487	0.045	*MAD1L1*
rs10258495	7	135,563,810	−3.282	3.616	0.045	*NUP205*
rs12572777	10	8,737,499	−3.388	3.088	0.045	intergenic
rs1516263	12	73,014,371	−3.469	−3.479	0.045	intergenic
rs79965177	14	98,028,223	−3.756	3.766	0.045	regulatory region variant
rs2008259	14	98,180,602	−3.340	4.088	0.045	non-coding transcript variant
rs28480089	15	56,664,058	3.611	3.552	0.045	*ZNF280D*
rs4784359	16	51,550,785	3.400	3.387	0.045	intergenic
rs258336	16	89,654,423	3.498	3.973	0.045	non-coding transcript variant
rs6508210	18	53,220,821	−3.387	3.612	0.045	*DCC*
rs8105984	19	19,263,259	−3.283	3.633	0.045	non-coding transcript variant
rs72720396	1	90,726,025	3.262	−3.775	0.045	intergenic
rs13164188	5	104,578,822	4.969	−3.325	0.045	non-coding transcript variant

To characterize these pleiotropic loci, we performed gene-based (Supplemental Tables 8–12) and pathway (Supplemental Tables 13–17) analyses. These analyses did not reveal associations that survived FDR multiple testing correction. The ADHD-SUD pleiotropic locus, *CADM2* rs62250713, when tested for colocalization with gene expression from various brain and cell tissues showed no significant results. Among the pleiotropic variants identified, there was weak evidence of colocalization for rs1368742 between ADHD and PAU (posterior probability=0.5, regional association probability=0.9, posterior probability explained by the causal variant=0.4; posterior probability>0.7 would be clear evidence (Foley et al., 2021)).

3.5. Polygenic risk scores

ADHD was statistically associated with all SUD polygenic risk scores (PRSs) except for PTU (Table 3). OUD-PRS showed the strongest association with ADHD (OR = 1.24, $p < 1 \times 10^{-7}$), followed by CanUD-PRS (OR = 1.19, $p < 3.83 \times 10^{-5}$) and PAU-PRS (OR = 1.12, $p = 4.09 \times 10^{-3}$). Sex-stratified analyses showed no differences between males and females (sex difference $p > 0.05$). The results did not change when we restricted the analysis to only adults (age≥17 years; 1381 cases and 4124 controls).

4. Discussion

This study used multiple analytic approaches and found evidence of multiple pleiotropic mechanisms contributing to the comorbidity between ADHD and SUDs.

Table 3
Association of CanUD-PRS, OUD-PRS, PAU-PRS and PTU-PRS with ADHD in sex-combined and sex-stratified models.

	Sex-combined^ (1775 cases and 4124 controls)	Males# (1215 cases and 2188 controls)	Females# (560 cases and 1936 controls)
CanUD-PRS, OR (95 %CI)	**1.19 (1.29–1.09)**	**1.17 (1.30–1.05)**	**1.21 (1.38–1.06)**
OUD-PRS, OR (95 %CI)	**1.24 (1.35–1.15)**	**1.27 (1.41–1.14)**	**1.23 (1.39–1.08)**
PAU-PRS, OR (95 %CI)	**1.12 (1.22–1.04)**	1.11 (1.23–1.00)	1.11 (1.26–0.98)
PTU-PRS, OR (95 %CI)	1.04 (1.13–0.96)	1.07 (1.19–0.97)	1.01 (1.15–0.88)

^Age, sex, batch & 10 PCs as covariates; # Age, batch & 10 PCs as covariates. PRS associations surviving Bonferroni multiple testing correction ($p < 0.0125$) are presented in bold. CanUD: Cannabis Use Disorder; OUD: Opioid Use Disorder; PAU: Problematic Alcohol Use; PTU: Problematic Tobacco Use.

By leveraging large-scale genomic datasets, our results extended previous evidence of genetic overlap of ADHD with traits related to the misuse of psychoactive substances (Soler Artigas et al., 2020; Treur et al., 2021; Vilar-Ribo et al., 2021). In line with the recent ADHD GWAS (Demontis et al., 2023), we observed a higher positive genetic correlation of ADHD with CanUD (rg = 0.61 ± 0.03) than that shown in previous studies with lifetime cannabis use (rg = 0.15 ± 0.04; rg = 0.29 ± 0.07) (Soler Artigas et al., 2020; Vilar-Ribo et al., 2021). Conversely,

ADHD genetic correlation with PTU was similar to one observed for smoking initiation (rg = 0.48 ± 0.07) (Demontis et al., 2023) and nicotine dependence (rg = 0.53 ± 0.07) (Vink et al., 2021). In line with a recent report (Zhou et al., 2023), the genetic correlation of ADHD with PAU (rg = 0.33 ± 0.03) was consistent with previous estimates between ADHD and alcohol use disorder (rg = 0.37 ± 0.05) (Kranzler et al., 2019) and alcohol dependence (rg = 0.47 ± 0.12) (Vilar-Ribo et al., 2021). In a previous study, ADHD was genetically correlated with problematic opioid use. A different pattern was present for opioid-related phenotypes, where problematic opioid use (defined as "Have you ever in your life used prescription painkillers (taken not as prescribed)" appears to have a higher genetic correlation with ADHD (rg = 0.54 ± 0.17) (Sanchez-Roige et al., 2021) than OUD (rg = 0.34 ± 0.08). There is consistent and growing literature regarding the genetic differences between substance use and substance use disorders (Gelernter and Polimanti, 2021; Ribases et al., 2023). With respect to their genetic overlap with ADHD, our findings show that there may be substance-specific patterns. Specifically, shared psychopathology between ADHD and CanUD may be responsible for the higher genetic correlation observed when compared to lifetime cannabis use. This difference does not seem to be present when comparing the genetic correlations of ADHD with PTU and nicotine dependence with the one observed for smoking initiation. With respect to ADHD relationship with CanUD and PTU, it is important to remember the comorbidity between these SUDs with up to 90 % of cannabis users are also tobacco smokers (Rabin and George, 2015). Accordingly, ADHD-CanUD genetic correlation may be partially due to pleiotropic effects also shared with PTU. Analgesic misuse was more highly genetically correlated with ADHD than OUD. This suggests that the ADHD pleiotropy with opioid-related phenotypes may be partially due to mechanisms not directly related to the psychopathology shared with OUD.

The genomic SEM analysis provided additional evidence that the genetic similarities between ADHD and SUDs appear to be substance-specific. Namely, two factors seem to underlie the genetic correlations observed. In line with the possible close relationship between ADHD and tobacco/nicotine phenotypes (i.e., no difference between the genetic correlation of ADHD with PTU and smoking initiation), PTU and ADHD loaded fully on the same factor. Conversely, OUD loaded fully and CanUD loaded partially on a different factor that was only moderately genetically correlated with the ADHD-PTU factor (rg = 0.49 ± 0.04). Epidemiological studies show differences among ADHD adult patients in the use of certain substances in some cohorts but not in others (Biederman et al., 1998; Estevez et al., 2016; King et al., 1999; Pomerleau et al., 1995; Torgersen et al., 2006). Beyond genetic overlap, other factors likely contribute to substance-specific patterns in ADHD-SUD comorbidities. For example, the misuse of alcohol in ADHD patients is partially due to its legal status and easy access (Gray-Phillip et al., 2018). Tobacco smoking seems to reduce some ADHD symptoms, including inattention, prolonged reaction time, and negative moods (Levin et al., 1996). In a recent study, students with greater ADHD symptoms were more likely to smoke more than 10 cigarettes/day (Galera et al., 2017).

The MR analysis enabled us to investigate whether the genetic correlations observed were due to possible cause-effect relationships. Previous MR analyses investigated the association of ADHD with the use and misuse of substances, reporting possible causal effects related to alcohol, cannabis, and nicotine (Treur et al., 2021; Vilar-Ribo et al., 2021). Leveraging more powerful GWASs, we expanded these results, showing that preferential patterns across substances may also play a role in the ADHD-SUD relationship. Indeed, CanUD and ADHD showed bidirectional associations with ADHD that are comparable in magnitude, suggesting that shared psychopathology is mainly responsible for this comorbidity. Conversely, the genetic liabilities to PAU and PTU on ADHD showed stronger evidence than the reverse direction. Specifically, some sensitivity analyses for the reverse direction showed reduced effect sizes and non-significant results, suggesting a possible causal effect of addiction-related traits on ADHD. This may contradict the expectation that ADHD should have an earlier age of onset than SUDs. While there is evidence supporting the presence of adult-onset ADHD in certain individuals, diagnosis still relies on the presence of childhood ADHD symptoms (Asherson and Agnew-Blais, 2019; Taylor et al., 2022). Hence, other mechanisms could explain PAU and PTU results of our genetically informed causal inference analysis. The genetic liabilities to alcohol and tobacco use have been previously associated with psychiatric and behavioral traits in children and young adults who did not endorse any substance use (De Angelis et al., 2021). This may support that the genetically informed pleiotropic effects identified in our study could indicate the possible neurobiological effects of PAU and PTU on ADHD rather than the effect of alcohol and tobacco misuse. Because the ADHD GWAS included ADHD cases independently of their age of onset (Demontis et al., 2023), PAU and PTU effects on ADHD may be related to the persistence of ADHD in adulthood. A previous study showed that late-diagnosed ADHD has a higher genetic correlation with alcohol use disorder than childhood ADHD (Rajagopal et al., 2022). Another explanation could be that PAU and PTU contribute to having childhood ADHD persisting into adulthood. Furthermore, tobacco smoking during adolescence has been associated with attention problems later in life (Treur et al., 2015). Similarly, alcohol appears to affect inattentiveness, impaired decision-making, and impulsivity more strongly in adult ADHD cases than in adult controls (Weafer et al., 2009). The effect of other factors such as dynastic effects may also influence these results. With respect to OUD, our MR analysis showed null effects in both directions. This is likely due to a lack of power in the OUD GWAS. Indeed, our PRS analysis identified a slightly stronger effect of OUD polygenic risk on ADHD than the ones observed for PAU and PTU PRS. Because of ADHD prevalence among OUD cases (18–21 %) (Gupta et al., 2020; Rohner et al., 2023), further studies of OUD-ADHD pleiotropy are warranted when more statistically powerful OUD GWAS are available.

To assess the contribution of shared genetic effects to ADHD-SUD comorbidities, we performed a genome-wide analysis of horizontal pleiotropy. One locus, *CADM2* rs62250713, showed evidence of pleiotropic effects with ADHD and the other four traits of interest. Variants in LD (r2>0.6) with rs62250713 were associated with several psychiatric and behavioral phenotypes: irritable mood (Nagel et al., 2018), coffee consumption (Yin et al., 2022), cannabis use (Pasman et al., 2018; Yin et al., 2022), anxiety (Hill et al., 2020), externalizing behavior (Karlsson Linner et al., 2021), and lifetime smoking (Pasman et al., 2022). Genome-wide significant associations of other *CADM2* variants with many traits have been reported, e.g. general risk tolerance (Karlsson Linner et al., 2019), risk-taking behavior (Strawbridge et al., 2018), smoking initiation (Liu et al., 2019), alcohol consumption (Clarke et al., 2017), risky sexual behavior (Karlsson Linner et al., 2019), and opioid dependence (Gaddis et al., 2022). Consequently, *CADM2* likely plays an important role in the molecular mechanisms shared between ADHD and SUDs. This gene encodes an adhesion molecule involved in cell aggregation and synapse organization. There is convergent evidence from animal models and humans that *CADM2* is associated with impulsivity and cognition (Sanchez-Roige et al., 2023) with particular involvement in executive function and processing speed (Ibrahim-Verbaas et al., 2016).

Analyzing ADHD with respect to each addiction-related phenotype separately, we identified additional loci with evidence of horizontal pleiotropy. Among the SNPs pleiotropic between ADHD and CanUD, several were previously associated with behavioral traits, such as insomnia (Watanabe et al., 2022), smoking initiation (Liu et al., 2019), and neuroticism (Nagel et al., 2018). The only variant identified with respect to ADHD-PAU horizontal pleiotropy (rs28707439) was previously identified as shared between ADHD and general intelligence (O'Connell et al., 2020). Several ADHD-PTU pleiotropic variants showed associations with cognitive performance (Lee et al., 2018), autism spectrum disorder (Wu et al., 2020), and depressive symptoms (Wu et al., 2020). Due to the limited statistical power of OUD GWAS, we did not identify any genome-wide significant locus with ADHD-OUD

pleiotropic effects. Additionally, we also did not observe any statistical enrichment for biological pathways and molecular processes among the pleiotropic loci identified. This may be due to the need for more powerful GWAS to characterize further the molecular basis of ADHD-SUD comorbidity.

Considering the findings generated by different analytic approaches applied in the present study, we hypothesize that horizontal and vertical pleiotropy (shared genetic mechanisms and possible causal effects, respectively) both contribute to ADHD-SUD comorbidities with differences among substances. Specifically, ADHD-CanUD comorbidity could be mainly due to shared genetic mechanisms (horizontal pleiotropy supported by the bidirectional relationship observed in MR analysis and the multiple pleiotropic loci identified by PolarMorphism approach), while ADHD-PAU comorbidity is primarily driven by possible causal effects (vertical pleiotropy supported by PAU→ADHD effect identified by MR and only one locus identified by PolarMorphism approach). The ADHD-PTU relationship seems to be related to a combination of different pleiotropic pathways (supported by results from gSEM, MR, and PolarMorphism analyses). While these patterns in ADHD-SUD pleiotropy have to be confirmed by further studies, understanding the genetic factors contributing to ADHD-SUD comorbidity could enhance preventive strategies that alter possible causal relationships and yield more effective treatments based on specific ADHD-SUD molecular targets.

Our study has several limitations. First, the difference in the statistical power among the GWAS datasets may have contributed to some of the substance-specific patterns observed. In particular, OUD GWAS is less powered than the other SUD GWAS. Accordingly, OUD results will need to be confirmed by larger studies. Second, because of the lack of large-scale datasets for non-European ancestry, we investigated only GWAS data from individuals of European ancestry. Hence, our results may not be generalizable to other ancestry groups. Third, because sex-stratified GWAS are not available for SUD phenotypes, we did not systematically investigate the possible sex differences in ADHD-SUD pleiotropy. Additionally, the lack of sex differences in our PRS analyses may be due to the fact we used sex-combined SUD GWASs as training datasets. Unfortunately, sex-stratified SUD GWAS are not currently available. Similarly, age-of-onset ADHD GWAS is not available to understand possible childhood vs. adulthood differences in the causal relationships between ADHD and SUDs. We used positional mapping to explore genes and pathways related to the pleiotropic variants identified by the PolarMorphism analysis. This may have limited our ability to characterize loci linked to ADHD-SUD pleiotropy through complex regulatory mechanisms.

CRediT authorship contribution statement

Dora Koller: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Marina Mitjans:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **Manuela Kouakou:** Investigation, Methodology. **Eleni Friligkou:** Data curation, Formal analysis. **Brenda Cabrera-Mendoza:** Formal analysis. **Joseph D. Deak:** Formal analysis. **Natalia Llonga:** Formal analysis, Writing – original draft. **Gita A. Pathak:** Investigation, Validation. **Brendan Stiltner:** Investigation, Validation. **Solveig Løkhammer:** Formal analysis. **Daniel F. Levey:** Data curation. **Hang Zhou:** Data curation. **Alexander S. Hatoum:** Data curation. **Rachel L. Kember:** Data curation. **Henry R. Kranzler:** Data curation. **Murray B. Stein:** Data curation. **Roser Corominas:** Investigation. **Ditte Demontis:** Investigation, Methodology. **María Soler Artigas:** Data curation. **Josep Antoni Ramos-Quiroga:** Data curation. **Joel Gelernter:** Data curation. **Marta Ribasés:** Data curation, Writing – original draft. **Bru Cormand:** Funding acquisition, Methodology, Conceptualization. **Renato Polimanti:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Dr. Polimanti reports a research grant from Alkermes. Drs. Polimanti and Gelernter are paid for their editorial work in the journal Complex Psychiatry. Drs. Gelernter and Kranzler hold US patent 10,900,082 titled: "Genotype-guided dosing of opioid agonists," issued January 26, 2021. Dr. Kranzler is a member of advisory boards for Clearmind Medicine, Dicerna Pharmaceuticals, Enthion Pharmaceuticals, and Sophrosyne Pharmaceuticals, and Enthion Pharmaceuticals; a consultant to Sobrera Pharmaceuticals; the recipient of research funding and medication supplies for an investigator-initiated study from Alkermes; and a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was supported in the past 3 years by Alkermes, Dicerna, Ethypharm, Lundbeck, Mitsubishi, Otsuka, and Pear Therapeutics. Drs. Gelernter and Kranzler hold U.S. patent 10,900,082 titled: "Genotype-guided dosing of opioid agonists," issued 26 January 2021. Dr. Demontis has received speaker fees from Medice Nordic. The other authors declare no competing interests.

Acknowledgements

The authors acknowledge support from the Horizon 2020 Marie Sklodowska-Curie Individual Fellowship from the European Commission (101028810), the National Institutes of Health (R33 DA047527, R21 DC018098, RF1 MH132337, K99 AG078503, T32 MH014276, T32 AA02825, K01 DA051759), Veterans Affairs Office of Research & Development (5IK2BX005058 and CX001849-01), Alzheimer's Association Research Fellowship (AARF-22-967171), American Foundation for Suicide Prevention (PDF-1-022-21), the Agència de Gestió d'Ajuts Universitaris i de Recerca (AGAUR, 2021-SGR-01093), grants RYC-2017-21636 and RYC2021-033573-I funded by MCIN/AEI/10.13039/501100011033 and by the European Union "NextGenerationEU"/PRTR" Ramón y Cajal contract (RYC-2017-21636) and One Mind.

BC received financial support from the Spanish 'Ministerio de Ciencia, Innovación y Universidades' (PID2021-1277760B-I100), 'Generalitat de Catalunya/AGAUR' (2021-SGR-01093), ICREA Academia 2021, 'Fundació La Marató de TV3' (202218-31), and the European Union H2020 Program [H2020/2014-2020] under grant agreements n° 667302 (CoCA), 728018 (Eat2beNICE), and 841899 (GRASAD). We thank the participants and the investigators involved in the UK Biobank, Million Veteran Program, and the Psychiatric Genomics Consortium for making their data publicly available. This publication does not represent the views of the Department of Veterans Affairs or the United States Government.

Materials & Correspondence

Drs Koller and Polimanti had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Any queries should be directed to either of these authors.

Data and code availability

All data generated are available in the article and its supplemental material. This study did not develop new code. Each software used in the analyses described is publicly available in the corresponding repository. Genome-wide data used in this article are publicly available (ADHD: https://ipsych.dk/en/research/downloads, SUDs: dbGaP phs001672.v1.p1, https://www.ncbi.nlm.nih.gov/gap/).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2024.115758.

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