Cross-ancestry meta-analysis of opioid use disorder uncovers novel loci with predominant effects in brain regions associated with addiction

Rachel L. Kember,[1,2] Rachel Vickers-Smith,[1,3,4] Heng Xu,[2] Sylvanus Toikumo,[2] Maria Niarchou,[5] Hang Zhou,[6,7] Emily E. Hartwell,[1,2] Richard C. Crist,[1,2] Christopher T. Rentsch,[6,7,8] VA Million Veteran Program, Lea K. Davis,[5] Amy C. Justice,[6,7,9] Sandra Sanchez-Roige,[5,10] Kyle M. Kampman,[1,2] Joel Gelernter,[6,7] Henry R. Kranzler[1,2*]

[1] Mental Illness Research, Education and Clinical Center, Veterans Integrated Service Network 4, Crescenz Veterans Affairs Medical Center, Philadelphia, PA 19104
[2] Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104
[3] Department of Epidemiology, University of Kentucky College of Public Health, Lexington, KY 40536
[4] Center on Drug and Alcohol Research, Department of Behavioral Science, University of Kentucky College of Medicine, Lexington, KY 40536
[5] Department of Medicine, Division of Genetic Medicine, Vanderbilt University Medical Center, Nashville, TN 37232
[6] Veterans Affairs Connecticut Healthcare System, West Haven, CT 06516
[7] Yale University School of Medicine, New Haven, CT 06511
[8] Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK, WC1E 7HT
[9] Yale School of Public Health, New Haven, CT 06511
[10] Department of Psychiatry, University of California San Diego, San Diego, CA 92110

*Correspondence to Henry R. Kranzler at kranzler@pennmedicine.upenn.edu

Abstract

Despite an estimated heritability of ~50%, genome-wide association studies of opioid use disorder (OUD) have revealed few genome-wide significant loci. We conducted a cross-ancestry meta-analysis of OUD in the Million Veteran Program (N=425,944). In addition to known exonic variants in *OPRM1* and *FURIN*, we identified intronic variants in *RABEPK, FBXW4*, *NCAM1*, and *KCNN1*. A meta-analysis including other datasets identified a locus in *TSNARE1*. In total, we identified 14 loci for OUD, 12 of which are novel. Significant genetic correlations were identified for 127 traits, including psychiatric disorders and other substance use-related traits. The only significantly enriched cell type group was central nervous system, with gene-expression enrichment in brain regions previously associated with substance use disorders. These findings increase our understanding of the biological basis of OUD and provide further evidence that it is a brain disease, which may help to reduce stigma and inform efforts to address the opioid epidemic.

Introduction

Opioid use disorder (OUD) is a problematic pattern of opioid use that leads to significant impairment or distress[1]. In the United States, a 10-fold increase in opioid analgesic prescriptions between 1990 and 2010 contributed to an epidemic of opioid misuse, abuse, and overdose deaths[2–4]. By 2019, 3.7% of U.S. adults reported past-year opioid misuse and 0.6% met criteria for an OUD[5]. Overdose deaths, which continue to increase annually, have reached crisis proportions[6], reflecting the limitations of available preventive and treatment efforts.

Genetic studies can help inform our understanding of the biology underlying OUD. However, although the estimated heritability (h^2) of OUD based on twin and family studies is ~50%[7], few genetic associations have been identified. Genome-wide association studies (GWAS) of OUD, opioid dependence (OD) or related phenotypes have yielded inconsistent results, likely due to the limited sample size of the discovery datasets and different case and control definitions[8–11].

The use of data from electronic health records (EHRs) linked to biobanks has permitted increasingly large GWAS samples. An EHR-based study of 1,039 OUD cases identified two genome-wide significant (GWS) loci, with SNP-based heritability of 6.0%[12]. A meta-analysis of African Americans (AAs; 5,212 OUD cases) and European Americans (EAs; 10,544 OUD cases) based largely on data from the Million Veteran Program (MVP), identified a single GWS SNP, rs1799971 in *OPRM1*, in EAs only, with SNP-based heritability of 11.3%[13]. There were no GWS findings in AAs or in a cross-ancestry meta-analysis. A study that combined data from multiple cohorts (20,858 OUD cases), including an earlier release of MVP data, identified 2 GWS loci – a variant within *OPRM1* in a cross-ancestry analysis, and an additional variant in *FURIN* in a European-ancestry (EUR) meta-analysis[14].

Two recent GWAS have increased sample sizes for genetic discovery by examining opioid-related phenotypes other than OUD. A GWAS of prescription opioid misuse in a EUR sample from 23andMe (27,805 cases) identified 2 novel GWS loci[15]. A meta-analysis of EUR

individuals including 23,367 cases ascertained using either Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnoses or frequency of opioid use[16] identified GWS SNPs in *OPRM1* and, in gene-based analyses, *PPP6C* and *FURIN*.

These studies also identified significant genetic correlations (r_gs) with traits well known to co-occur with OUD, suggesting widespread pleiotropy. The strongest positive r_gs were with substance-related traits[12,13,15,16] and psychiatric disorders[13,15,16]. Negative r_gs were seen for educational attainment[13,15,16] and subjective wellbeing[16]. Causal effects on OUD for some of these traits were identified via Mendelian randomization (MR) analysis[13]. Positive causal effects on OUD were found for regular tobacco smoking, major depressive disorder, and neuroticism. A negative causal effect on OUD was seen for educational attainment. The causal effect of OUD on these traits was unable to be examined due to the limited number of GWS variants.

The different phenotypes used in these studies reflect the difficulty of ascertaining a large, multi-ancestry, well-characterized sample for use in GWAS of opioid-related phenotypes. EHR-based traits generally use International Classification of Disease (ICD) diagnostic codes for phenotyping OUD (e.g.,[12,13]). Cohorts recruited from some non-clinical biobanks rely on single-item, self-report questionnaires (e.g.,[15]) or have combined multiple case and control definitions derived as latent variables in genomic structural equation modelling (SEM)[16]. A key consideration in selecting OUD cases, particularly given the high prevalence of opioid use in the United States, is the stringency of the definition. More stringent case definitions increase confidence in the specificity of the diagnosis and, by reducing heterogeneity, may increase statistical power. However, they also reduce the sample size and have the potential to reduce generalizability by not capturing a disorder's full range of presentations (e.g., by misclassifying cases as subthreshold).

Here, we conducted a cross-ancestry meta-analysis of OUD that included AA, EA, and Hispanic American (HA) subjects recruited from the MVP that maximized OUD cases by using a less stringent definition (requiring the presence of a single OUD diagnostic code) and compared

them to opioid-exposed controls (N_{cases}=31,473, $N_{controls}$=394,471). In supplementary analyses, we compared our results to those using a stringent OUD phenotype in MVP (N_{cases}=23,459, $N_{controls}$=394,471), and performed a meta-analysis that combined data from the MVP, Yale-Penn (unpublished data), the Partners HealthCare Biobank[12], and the Psychiatric Genomics Consortium (PGC)[11] (N_{cases}=37,761, $N_{controls}$=409,760).

Results

Sample Description

Our MVP sample comprised 425,944 individuals (AA: 88,498; EA: 302,585; HA: 34,861), of whom 90.6% were male (Supplementary Table 1). The less stringent OUD definition yielded 28.8%-38.9% more cases across the ancestral groups (AA=8,968, EA=19,978, HA=2,527) than the stringent definition (AA=6,457; EA=15,040; HA=1,962). 2,525 (8%) of the less stringent cases and 1,926 (8%) of the stringent cases had no opioid prescription fills. Among the individuals with a single OUD code (N=8,014), 599 (7%) had no opioid prescription fills. Of the remaining individuals with an opioid prescription, less stringent cases had 77.2 (SD=96.9) opioid prescription fills, stringent cases had 76.5 (SD=97.6) fills, and controls had 25.0 fills (SD=48.3). Thus, most individuals with an OUD diagnosis had documented prescriptions for opioids. Further, individuals with a single diagnosis code for OUD (i.e., less stringent) had a similar number of opioid fills as those with the stringent diagnosis. Finally, the documented exposure to prescription opioids was similar for OUD cases defined using the less stringent diagnosis and those defined using the stringent diagnosis.

Identification of Novel Loci Associated with Opioid Use Disorder

The cross-ancestry meta-analysis of the less stringent OUD diagnosis within the MVP sample yielded 12 GWS variants, 10 of which were independent after conditioning on the lead variant within each locus (Figure 1, Supplementary Table 3). The protein-coding genes nearest these variants are *CDKAL1*, *BTNL2*, and *OPRM1* (all on chr. 6), *RABEPK* (chr. 9), *FBXW4* (chr. 10; a second locus on chr. 10 had no protein-coding gene within 500 kb), *NCAM1* (chr. 11), *FURIN* (chr. 15), *KCNN1* (chr. 19), and *RNF114* (chr. 20). The most robust signal was in *OPRM1* (lead SNP rs1799971, $p=6.78 \times 10^{-10}$), which replicates the main finding of the previous MVP OUD GWAS[13]. The variant in *FURIN* is supported by prior findings at the variant[14] and

gene-based[16] levels. In addition, there were 3 ancestry-specific loci (Supplementary Table 4): 1 each in AAs (*NNT*, chr. 5), EAs (*CDH8*, chr. 16), and HAs (*MRS2*, chr. 8).

(Figure 1 About Here)

Replication of Loci Associated with Opioid Use Disorder

The cross-ancestry meta-analysis of the stringent OUD diagnosis in the MVP sample also identified the variants in *OPRM1* and *FURIN* and one additional locus (*TSNARE1*, chr. 8) (Supplementary Table 5). The cross-ancestry meta-analysis of all datasets (MVP, Partners HealthCare Biobank, PGC and YP3) identified no additional loci (Supplementary Table 8). GWS loci from all analyses are presented in Supplementary Tables 3-8. Based on all analyses, we identified a total of 14 GWS loci, 12 novel (Table 1).

(Table 1 About Here)

SNP Heritability and Genetic Correlations Across GWAS Datasets

In MVP, similar estimates of SNP heritability (h^2_{SNP} ± standard error) were obtained for the less stringent phenotype in AAs (0.11 ± 0.03) and EAs (0.12 ± 0.01). Estimates of h^2_{SNP} for the stringent OUD phenotype were slightly higher (AA: 0.20 ± 0.05; EA: 0.15 ± 0.01), and estimates were slightly lower for the ancestry-specific meta-analyses across datasets (AA: 0.08 ± 0.03; EA: 0.11 ± 0.01). Variation in these estimates appears to be driven by changes in effective sample size, as estimates using actual sample size show little variation (Supplementary Table 9). Using a two-sample t-test, we found no significant difference in h^2_{snp} across the ancestral groups (MVP less stringent phenotype: p-value = 0.69; MVP stringent phenotype: p-value = 0.35; and ancestry-specific meta-analysis: p-value = 0.4).

The cross- ancestry r_g between MVP AA and EA populations is 0.43 (SE=0.21, $p=6.83x10^{-3}$) for the less stringent diagnosis, and r_g=0.48, (SE=0.23, $p=2.58x10^{-2}$) for the stringent diagnosis. The within-ancestry r_g (± standard error) between datasets is high, ranging from 0.66 (± 0.3) between the less stringent OUD MVP and Partners HealthCare Biobank datasets in EAs, to 1.2 (± 0.2) between the less stringent OUD MVP and the previous OUD

MVP GWAS[13] in EAs (which used the same diagnosis definition as the present stringent analysis) (Supplementary Table 10). Because the SNP heritability of the PGC and Yale-Penn datasets was low, we did not calculate r_gs between MVP and either of these datasets. A sign test showed that the majority of SNPs with $p<1x10^{-5}$ (N SNPs AFR=400, EUR=954) had the same direction of effect in both MVP and other datasets, with the exception of MVP AA and PGC AFR (AFR: MVP-PGC 21.7%, $p=2.2\times10^{-16}$; MVP-YP3 60.1%, $p=3.1\times10^{-3}$; EUR: MVP-PGC 61.1%, $p=1.07\times10^{-9}$; MVP-YP3 65.1%, $p=2.2x10^{-16}$; MVP-Partner 74.5%, $p=2.2\times10^{-16}$).

Considering the similarity in h^2_{SNP} between the different OUD GWAS and the greater number of loci captured by the less stringent diagnosis in MVP, all downstream analyses are based on the GWAS for the less stringent OUD case definition in EAs within the MVP sample.

Partitioning Heritability Enrichment

We performed partitioning heritability enrichment analyses in LDSC[17] and examined heritability enrichment for gene expression using GTEx data[18]. In the baseline model, Genomic Evolutionary Rate Profiling (GERP)[19] functional annotation was significantly enriched ($p=6.7x10^{-4}$), suggesting that SNPs included in the analyses are under stronger negative selection (Supplementary Table 11). The only significantly enriched cell type group was central nervous system (CNS; $p=3.34\times10^{-3}$, Figure 2A, Supplementary Table 12). We observed significant enrichment for OUD in brain tissues only, including the anterior cingulate cortex ($p=4.71\times10^{-6}$), limbic system ($p=3.25\times10^{-5}$), prefrontal cortex ($p=5.73\times10^{-5}$), cerebral cortex ($p=9.81\times10^{-5}$), cortex ($p=1.11\times10^{-4}$), hypothalamus ($p=1.23\times10^{-4}$), amygdala ($p=1.41\times10^{-4}$), and hippocampus ($p=2.04\times10^{-4}$) (Figure 2B, Supplementary Table 13). There were no significant enrichments for epigenetic annotations after correction for multiple testing (Supplementary Table 14).

(Figure 2 About Here)

Transcriptome-wide Analysis

We used S-PrediXcan[20] to predict the effect of genetic variation on gene expression. Significant within-tissue gene expression regulation was identified for 43 tissues, including brain, adipose, gastrointestinal, thyroid, and liver (Supplementary Figure 2, Supplementary Tables 15 and 16). Significant associations with expression in brain tissues were detected for *FURIN*, *FES*, *LRP8*, *LINC01556*, *ZNF660* and *RP1-153G14.4* (Figure 2C). Some of these genes (*FURIN*, *LINC01556*, *ZNF660*, and *RP1-153G14.4*) were also expressed in non-brain tissues, such as adipose, gastrointestinal, and thyroid tissues (Supplementary Figure 2), suggesting that OUD-related genetic variation may exert significant transcriptomic changes in the periphery as well as the CNS.

Considering the sharing of eQTLs across multiple tissues, we tested the joint effects of variation in gene expression across tissues using S-MultiXcan[21]. Significant transcriptomic effects for OUD were detected in 8 genes, 5 of which overlapped with genes detected by S-PrediXcan (*FURIN*, *FES*, *RP1-153G14.4*, *LRP8*, and *RABEPK*) and 3 which were novel (*ZNF391*, *ZKSCAN4*, and *MAGOH*) (Supplementary Table 17). We also observed that the lead SNP in *RABEPK* is in high LD with *PPP6C* variants (r^2>0.8) that are significantly associated with gene expression and chromatin interaction, especially in the prefrontal cortex (Supplementary Figure 3).

Using summary-based MR (SMR) and Brain-eMeta data[22], we found that *FURIN* (beta=-0.13) and *PPP6C* (beta=0.09) passed the SMR (FDR q<0.05) and HEIDI (HEIDI p>0.05) causality tests, consistent with the genes being associated with OUD via their regulation of brain mRNA expression levels (Supplementary Table 18). We also found that *OPRM1* expression is causal for OUD when the variant rs3778151 is used as an instrument (beta=-0.21, FDR q=0.03, HEIDI p=0.06). In the cerebellum (which has high levels of *OPRM1* expression in GTEx), expression is causal for OUD using either variant as an instrument (FDR q<0.05). However, the most significant variant (rs1799971) fails the heterogeneity test (HEIDI $p=1.75\times10^{-4}$). This suggests that the effect of rs1799971 is functional rather than mediated by gene expression,

consistent with it being a non-synonymous substitution. This contrasts with rs3778151, which appears to exert its causal effect via gene expression (HEIDI p=0.07).

Gene Set, Functional Enrichment, and Drug Repurposing Analyses

MAGMA gene-based analyses identified one GWS gene in AAs (*CHRM2*, $p=9.52\times10^{-7}$) and three GWS genes in EAs (*OPRM1*, $p=2.17\times10^{-7}$; *FTO*, $p=9.52\times10^{-7}$; *DRD2*, $p=1.67\times10^{-6}$) (Supplementary Figure 4), but none in HAs. GCTA-fastBAT gene-based analyses identified two GWS genes in EAs (*OPRM1,* $p=3.14\times10^{-8}$; *BTRC*, $p=3.21\times10^{-7}$), but none in AAs or HAs. Following Bonferroni correction, no biological processes or pathways were significantly enriched, although nominal associations in EAs highlighted pathways of potential relevance, including "dopamine receptors" ($p=1.87\times10^{-5}$) and "regulation of adenylate cyclase activating G-protein coupled receptor signaling pathway" ($p=4.39\times10^{-5}$) (Supplementary Table 19).

Genes identified in the variant-level, gene-based, or transcriptome (brain region) analyses (N=24) are summarized in Supplementary Table 20. Examination of these genes for drug-gene interactions via the Drug Gene Interaction database identified 761 interactions between 8 genes (*CHRM2, DRD2, FES, FURIN, KCNN1, NCAM1, OPRM1, PRL*) and 340 unique medications (Supplementary Table 21, Supplementary Figure 5). *OPRM1* had 193 interactions, mainly with classes of analgesics, anesthetics, and drugs for constipation. *DRD2* had 376 interactions, most of which were with psycholeptics.

Genetic Correlations

We estimated pairwise r_g with OUD for 40 published phenotypes using LDSC[23]. OUD showed significant r_g with 21 traits. As expected, the strongest positive correlations were with substance use traits (e.g., problematic alcohol use: $r_g=0.70$, cannabis use disorder: $r_g=0.65$, ever smoked regularly: $r_g=0.44$), and psychiatric disorders (e.g., bipolar disorder: $r_g=0.32$, major depressive disorder: $r_g=0.29$). The strongest negative correlation ($r_g=-0.27$) was with educational

attainment (Figure 3A, Supplementary Table 22). We also assessed r_g of OUD with 1,270 complex traits from the UKBB using CTG-VL[24]. After multiple testing correction ($p=3.94\times10^{-5}$), OUD was significantly associated with 106 traits (Supplementary Figure 6, Supplementary Table 23). These included positive correlations with substance use-related traits (e.g., current smoking: r_g=0.44; ever addicted to any substance or behavior: r_g=0.67), psychiatric traits (e.g. anxiety treatment: r_g=0.41, self-reported depression: r_g=0.35) and pain-related traits (e.g. low back pain: r_g=0.44, multisite chronic pain: r_g=0.26), and negative correlations with having secondary education qualifications (r_g=-0.34) and the presence of social support (r_g=-0.36). Thus, overall, we found that increased risk of OUD is genetically correlated with increased liability for use of substances, psychiatric disorders, and experiencing pain, and lower likelihood of educational attainment and social support.

(Figure 3 About Here)

Mendelian Randomization

Using MR, we tested for bidirectional causal effects between OUD and the 21 traits identified as significantly genetically correlated with OUD (Figure 3A, Supplementary Figure 7). There was a causal effect of OUD on 6 traits: problematic alcohol use, drinks per week, cannabis use disorder, general risk tolerance, MDD, and cross disorder. Among the 21 traits, 9 had a causal effect on OUD, of which 2 showed a negative causal effect on OUD (cognitive performance and educational level) and 7 a positive causal effect on OUD (in descending order of magnitude: drinks per week, worry subcluster, neuroticism, the number of sexual partners, major depressive disorder, cigarettes per day and schizophrenia).

Polygenic Risk Scores and Phenome-wide Association Studies

PRS were calculated in 2 independent datasets to identify phenotypic associations of genetic liability for OUD. In the Yale-Penn sample, PRS were calculated for 4,918 African ancestry and 5,692 European ancestry individuals. No significant associations were identified

for AAs (Supplementary Figure 8, Supplementary Table 24). In EAs, PheWAS identified 43 phenotypes in the opiate domain and 78 phenotypes in other phenotypic domains that were significantly associated with OUD PRS (Figure 3C, Supplementary Table 25). The most significantly associated phenotypes were “ever used opioid” and “time spent obtaining/using opioids”. In BioVU, PRS were calculated for 12,384 AAs and 66,903 EAs. No significant associations were found for OUD PRS in AAs (Supplementary Figure 9, Supplementary Table 26). In EAs, the OUD PRS was associated with 27 phenotypes, including “substance addiction and disorders” and “mood disorders” (Figure 3B, Supplementary Table 27).

Genomic Structural Equation Modeling

We conducted genomic SEM to evaluate how OUD relates to the three other substance use traits and the seven psychiatric disorders identified as the most significantly associated with OUD in genetic correlation analyses. Exploratory factor analysis involving all 11 traits supported a 4-factor model with cumulative variance of 0.639. We retained paths with a loading factor $\geq$0.2 and conducted confirmatory factor analysis. In this analysis, the 4-factor model fit the data well (comparative fit index = 0.948, Akaike information criterion = 340.840, χ^2 = 276.840, degrees of freedom = 34, standard root mean root square error = 0.073). The 4 substance use traits all loaded on Factor 1, with a major contribution from OUD (0.84 ± 0.05) and problematic alcohol use (0.91 ± 0.3), and lower contributions from cannabis use disorder (0.58 ± 0.06) and ever smoked regularly (0.40 ± 0.03). Cannabis use disorder (0.37 ± 0.06) and ever smoked regularly (0.42 ± 0.03), together with other psychiatric disorders, also loaded on Factor 3. Major psychiatric disorders, including bipolar disorder (0.86 ± 0.04), schizophrenia (0.76 ± 0.03), and MDD (0.43 ± 0.03) loaded on Factor 2. Tourette’s syndrome (0.33 ± 0.07) and obsessive-compulsive disorder (1.03 ± 0.21) loaded on Factor 4 (Figure 4, Supplementary Table 28).

(Figure 4 About Here)

Discussion

This study, the largest single-sample GWAS of OUD to date, identified 14 loci associated with the disorder, 12 of which are novel findings. 3 of these loci were significant in ancestry-specific analyses only, demonstrating that inclusion of diverse ancestral samples in genetic studies of OUD permits the identification of novel genetic variants. Post-GWAS analyses in EAs revealed enrichment for OUD in the CNS, particularly the brain, and an extensive phenotypic spectrum associated with genetic liability for OUD.

Because the effect sizes of common variants contributing to highly polygenic phenotypes such as OUD are small, large sample sizes are required to identify GWS loci. The largest OUD GWAS prior to the current study greatly increased the effective sample size ($N_{effective}$=88,115) by meta-analyzing the results of studies that used a range of case and control definitions[16]. Here, we performed GWAS using the stringent definition of OUD used by Zhou et al.[13] ($N_{effective}$=88,569) and a less stringent definition requiring the presence of only 1 ICD-9/10 diagnostic code for opioid abuse or dependence ($N_{effective}$=116,590). Although the less stringent definition lowers the specificity of the case phenotyping (i.e., individuals are more likely to be mislabeled as having OUD), it increases the number of cases by more than 8,000, reveals 8 more GWS variants than the stringent definition, and as denoted by the high genetic correlation between the two definitions, has a similar polygenic architecture. These results support prior conclusions that the potential variability introduced by broadening phenotypic definitions in genetic studies of OUD is outweighed by substantial increases in sample size[16]. In contrast, our meta-analysis of the MVP data with other datasets reduced the number of GWS loci identified, potentially because the smaller additional datasets increased the variability in the effect size of variants.

The most significant locus, *OPRM1*, encodes the mu-opioid receptor, which binds morphine and other opioids and has been the focus of many functional and candidate gene studies of opioid-related phenotypes[25–27]. In a previous GWAS comprised principally of subjects

from MVP, OUD was significantly associated only with *OPRM1* in EAs[13], with the lead SNP being the non-synonymous, exon 1 variant rs1799971 (A118G). In neither that study, nor the present study, was the SNP associated with OUD in AAs, presumably because the minor (G) allele frequency in this population group is considerably lower than in EAs[28]. Even so, it is difficult to explain why meta-analysis with AAs does not increase the statistical strength of the association of OUD with this variant if it is truly the lead functional variant, even if based on introgressed EA alleles alone.

We identified a second peak in *OPRM1*, with the lead SNP rs3778151, a variant in intron 1 that is in high LD with rs9478500 (r^2=0.56-0.90)[29], the variant associated with opioid addiction in a recent meta-analysis[16]. A prior study in EA alcohol- or drug-dependent cases and controls also identified two independent LD blocks in *OPRM1*[30]. Our SMR analyses suggest a plausible role for both variants in OUD: a functional effect for the non-synonymous substitution rs1799971 and an effect on gene expression by rs3778151.

Our cross-ancestry analysis identified a SNP in *FURIN*, with transcriptome-wide analyses showing significant downregulation of gene-expression in brain-related tissues. These findings support the reported associations of OUD with *FURIN* both in gene-based analyses[14,16] and in a variant-level meta-analysis[14]. Although *FURIN* encodes a protease that cleaves some endogenous opioids[31], the enzyme has not previously been linked to the effects of exogenous opioids or mu-opioid receptor signaling. Given these findings, further research on the mechanism underlying the gene's effects on risk of OUD is warranted.

Our analysis also identified 12 novel GWS loci. Two of these, in *RABEPK* and *NCAM1*, were GWS in a multi-trait analysis using MTAG of OUD with cannabis use disorder and alcohol use disorder[14]. Here, we show associations directly with OUD. *RABEPK* is adjacent to *PPP6C*, a gene previously implicated in a gene-level analysis of OUD[16] that has also been linked to reward-related phenotypes like obesity and smoking[32,33]. Our analysis shows that the lead SNP in *RABEPK* is tagging *PPP6C* variants that affect gene expression and chromatin interaction.

Furthermore, SMR analyses show that expression changes in *PPP6C* are causal for OUD. These lines of evidence suggest that *PPP6C* is likely the causal gene in this locus. *NCAM1* and *KCNN1* have been implicated in the neuropharmacology of opioid-related phenotypes. The mouse homolog of *KCNN1* is differentially expressed in the nucleus accumbens following chronic morphine exposure[34], and downregulated in the rodent prelimbic cortex after exposure to cues associated with morphine withdrawal[35]. *NCAM1* also appears to be involved in the response to morphine exposure. Tolerance in rodents due to repeated morphine injection can be prevented by treatment with an antisense oligodeoxynucleotide that targets *Ncam1*[36]. *NCAM1* variants have also been significantly associated with other substance use traits[33,37–39].

Several other loci contain GWAS hits for other traits, suggesting widespread pleiotropy of loci associated with OUD. *CDKAL1* and *BTNL2* have been associated with metabolic traits such as type 2 diabetes, body mass index[40] and obesity-related phenotypes[32]. *FBXW4* and *CDH8* have prior associations with cognitive traits such as educational attainment and mathematical ability[41], and *TSNARE1* has a prior association with schizophrenia[42].

Partitioning heritability enrichment analyses showed that CNS cells were the only significantly enriched group. We found significant enrichment for OUD in brain tissues only, including regions previously associated with the underlying neurobiology of the disorder[43]. These findings underscore the neural basis of OUD and reinforce the conceptualization of substance use disorders, which are often chronic and relapsing, as brain diseases. This notion was novel when proposed nearly 25 years ago[44] and although today it is a view widely held by neuroscientists and clinicians, it is not universally understood by politicians or the general public. Improving our understanding of the biological basis of OUD could promote a science-based response to the opioid epidemic.

Consistent with prior findings, OUD showed strong genetic correlations with multiple substance use disorders, psychiatric disorders, cognitive traits, and risk behavior[13,15,16,45]. MR analyses demonstrated causal effects of OUD on problematic alcohol use and cannabis use

disorder, and a bidirectional causal effect of drinks per week. These findings have both theoretical and clinical implications for the “gateway hypothesis” of addiction liability, which posits that substance use starts with a legal substance and progresses on to the use of hard drugs, such as opioids. A more compelling explanation for the high rate of comorbidity of OUD with other substance-related traits is common genetic liability or pleiotropic effects[46], which is supported here both by the robust genetic correlations between OUD and other substance-related traits, the causal effects of OUD on other substance use, and the latent addiction factor identified through genomic SEM.

Genetic liability for psychiatric traits, including neuroticism and schizophrenia, was also causally associated with OUD, with a bidirectional causal effect of MDD on OUD. Our findings, along with those of others[13], suggest that OUD has a common biological pathway with schizophrenia and MDD. Despite the significant genetic correlations and causal associations between OUD and psychiatric disorders, genomic SEM indicated a common genetic factor representing broad genetic liability for substance use disorders that is distinct from those underlying the psychiatric disorders. The factor structure among psychiatric disorders seen here is consistent with previous findings[47] and shows that cannabis use disorder and smoking, unlike OUD, load onto both the substance use disorder factor and the factor underlying MDD, ADHD, autism spectrum disorder, and Tourette’s syndrome.

PheWAS of the genetic liability for OUD in the Yale-Penn sample, which was ascertained for substance use disorders, reproduced the broad association with other substance use. In a clinical dataset using EHR data, the genetic liability for OUD was associated with multiple traits in every phenotypic domain tested, demonstrating the widespread effects of OUD liability on bodily systems. Some of the associations may be due to phenotypic correlation. For instance, associations were found with viral hepatitis and human immunodeficiency virus (HIV), potential proxies of injection drug use, and with chronic pain and back pain, potential proxies for the use of analgesic medications. The lack of association with

obesity, type 1 diabetes, and skin cancer could reflect under reporting or under diagnosis in individuals with OUD, or they could reflect true biological relationships. The lack of genetic correlation between obesity and OUD (Supplementary Table 22) argues against a biological relationship between the two.

Limitations to the present study should be noted. Although it includes AA, EA, and HA individuals, participants of European ancestry comprise more than 60% of the total sample, which in large part drove the results of the cross-ancestry analysis. This disparity in sample size is also reflected in analyses of the individual ancestral groups, in which the smaller AA and HA groups provided less statistical power and yielded fewer significant loci. The lower power of the AA GWAS is also reflected in the lack of associations in PRS analysis in AAs. Future GWAS of OUD should focus on expanding sample sizes for non-European-ancestral populations to capture loci that are relevant to specific population groups. The sample for this study is >90% male, reflecting the sex distribution of Veterans in the United States. Risk variants relevant only to women may thus have been overlooked due to the lower statistical power. Because the MVP dataset lacks information on the initiation of opioid use among patients diagnosed with OUD, we could not differentiate patients who developed the disorder only after being prescribed opioid analgesics from those whose first opioid use involved recreational use of analgesics or heroin. Differences in the initiation of opioid use could reflect different genetic risk factors contributing to non-overlapping intermediate phenotypes (e.g., pain threshold/susceptibility in analgesic use vs. risk taking in recreational use). Finally, a study of the validity of incident OUD diagnoses in the VA EHR showed that 26% of diagnoses were erroneous, attributable to administrative errors (77%) or clinical ones (23%)[48]. Such false positive errors, however, are likely to bias the findings to the null, rather than contribute to false positive findings.

In summary, we have identified 14 genetic loci associated with OUD, the majority novel. Many of the loci contain genes with prior associations with substance use or psychiatric disorders, suggesting widespread pleiotropy. The use of a less stringent definition of OUD

allowed a 25% larger number of OUD cases than a stringent definition in the MVP sample. Downstream analyses validate this approach by demonstrating plausible enrichment of OUD in brain regions, genetic correlations with other substance use disorders and psychiatric disorders, and association between OUD PRS and opioid dependence in an independent sample. Our findings provide insight into the biological underpinnings of OUD, which could inform preventive, diagnostic, and therapeutic efforts and thereby help to address the opioid epidemic.

Acknowledgments

This work was supported by Merit Review Awards from the U.S. Department of Veterans Affairs Biomedical Laboratory Research and Development Service [# I01 BX003341 (A.J., H.R.K.)] and Clinical Science Research and Development Service [# I01 CX001734 (K.M.K.)]; the VISN 4 Mental Illness Research, Education, and Clinical Center (H.R.K.); NIAAA grant K01 AA028292 (R.L.K.); and NIDA grant DA046345 (H.R.K.). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The views expressed in this article are those of the authors and do not necessarily represent the position or policy of the Department of Veterans Affairs or the United States Government.

Author Contributions

R.L.K, H.X., and H.R.K., conceived analyses. R.L.K. and H.R.K. wrote the first draft and prepared all drafts for submission; R.L.K accomplished primary analyses; H.X., S.T., M.N., and H.Z. conducted additional analyses; R.L.K. L.K.D., S.S-R, and J.G. supervised additional analyses; R.V.S., E.E.H., C.T.R., M.N., L.K.D., and S.S-R. provided critical support regarding phenotypes and data in individual datasets; and K.M.K, A.C.J., and H.R.K. provided resource support. All authors reviewed the manuscript and approved it for submission.

Competing Interests

Dr. Kranzler is a member of advisory boards for Dicerna Pharmaceuticals, 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 last three years by Alkermes, Dicerna, Ethypharm, Lundbeck, Mitsubishi, and Otsuka. Drs. Gelernter and Kranzler are holders of U.S. patent 10,900,082 titled: "Genotype-guided dosing of opioid agonists," issued 26 January 2021. The remaining authors declare no competing interests.

Table 1: Summary of the 14 GWS loci identified in GWAS analyses of OUD			
Chr	**Position (GRCh37/hg19) of lead SNPs**	**Nearest genes**	**GWAS analysis**
5	43846681	*NNT*	AA (Less stringent)
6	21362610, 21478361	*CDKAL1, SOX4*	Cross-ancestry (Less stringent), HA (Less stringent), Cross-ancestry (Meta)
6	32383573	*BTNL2*	Cross-ancestry (Less stringent)
6	154360797, 154380719, 154382139, 154393680, 154396472	*OPRM1*	Cross-ancestry (Less stringent), EA (Less Stringent), Cross-ancestry (Stringent), EA (Stringent), Cross-ancestry (Meta), EA (Meta)
6	24394925	*MRS2*	HA (Less stringent)
8	143312933, 143316970	*TSNARE1*	Cross-ancestry (Stringent), EA (Stringent), EA (Meta)
9	127873473, 127959540, 127980426	*SCAI, RABEPK*	Cross-ancestry (Less stringent), Cross-ancestry (Meta), EA (Meta)
10	103414885	*FBXW4*	Cross-ancestry (Less stringent), EA (Less Stringent), EA (Meta)
10	110504365	*[]*	Cross-ancestry (Less stringent)
11	112869404	*NCAM1*	Cross-ancestry (Less stringent)
15	91410009, 91406146, 91426560	*FURIN*	Cross-ancestry (Less stringent), EA (Less Stringent), Cross-ancestry (Stringent), EA (Stringent), Cross-ancestry (Meta), EA (Meta)
16	61631362	*CDH8*	EA (Less stringent), EA (Stringent)
19	18093588	*KCNN1*	Cross-ancestry (Less stringent), AA (Less stringent), Cross-ancestry (Meta), AA (Meta)
20	48540277, 48583726	*RNF114*	Cross-ancestry (Less stringent), Cross-ancestry (Meta)

GWS=genome-wide significant; GWAS=genome-wide association study; OUD=opioid use disorder; Chr=chromosome number; SNPs=single nucleotide polymorphisms

Figure Legends

Figure 1: Manhattan and quantile-quantile plot for cross-ancestry meta-analysis of OUD (N case=31,480, N control=394,484). Effective sample size weighted meta-analyses were performed in METAL. The nearest protein-coding gene (<1Mb) in each locus is labelled. [ ] represents an intergenic locus. Dashed line indicates GWS after correction for multiple testing ($p < 5 \times 10^{-8}$).

Figure 2: Enrichment of OUD in the brain. A. Partitioning heritability enrichment analyses using LDSC show enrichment for OUD in the central nervous system (CNS). The dashed black line indicates Bonferroni-corrected significance ($p < 0.005$). B. Heritability enrichment for gene expression using GTEx data show enrichment for OUD in brain regions previously associated with addiction. C. Predicted gene expression using S-PrediXcan identify genes with differential expression in brain regions. Color of circle indicates downregulation (blue) or upregulation (red). Size of circle indicates –log10 p-value. Bonferroni correction was applied within each tissue conditioned on the number of genes tested.

Figure 3: Phenotypic spectrum associated with OUD. A. Genetic correlation analyses show multiple traits significantly genetically correlated with OUD following Bonferroni correction ($p < 1.25 \times 10^{-3}$; red bar – positively correlated, blue bar – negatively correlated). Mendelian randomization analyses identify causal associations between OUD and other traits (arrows, red – positive causal association, blue – negative causal association). B and C. PheWAS results in BioVU (B) and Yale-Penn (C) datasets. All phenotypes significant at FDR $p<0.05$ are plotted. In B, all phenotypes which pass Bonferroni correction ($p < 3.7 \times 10^{-5}$) are labelled. For readability, in C, only the top 3 traits within each group which pass Bonferroni correction ($p < 7.9 \times 10^{-5}$) are labelled. Circle size denotes effect size.

Figure 4: Genomic SEM analysis of OUD with other substance use traits (OUD: opioid use disorder; PAU: problematic alcohol use; CUD: cannabis use disorder; SMK: ever smoked regularly) and psychiatric disorders (SCZ: schizophrenia; BIP: bipolar disorder; MDD: major depressive disorder; ASD: autism spectrum disorder; ADHD: attention deficit hyperactivity disorder; TS: Tourette's syndrome; OCD: obsessive compulsive disorder). Four factors were identified. Factor loadings for each trait are depicted by arrows between the trait and the factor. Correlation between factors is indicated by arrows between the factors. Residual variance for each trait is indicated by the U-circles. Standard errors are depicted in parentheses.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. (American Psychiatric Association, 2013). doi:10.1176/appi.books.9780890425596.
2. Strang, J. *et al.* Opioid use disorder. *Nat. Rev. Dis. Primer* **6**, 3 (2020).
3. Vowles, K. E. *et al.* Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *PAIN* **156**, 569–576 (2015).
4. Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers and other drugs among women--United States, 1999-2010. *MMWR Morb. Mortal. Wkly. Rep.* **62**, 537–542 (2013).
5. Key Substance Use and Mental Health Indicators in the United States: Results from the 2019 National Survey on Drug Use and Health. https://www.samhsa.gov/data/sites/default/files/reports/rpt29393/2019NSDUHFFRPDFWHTML/2019NSDUHFFR090120.htm.
6. Wilson, N. Drug and Opioid-Involved Overdose Deaths — United States, 2017–2018. *MMWR Morb. Mortal. Wkly. Rep.* **69**, (2020).
7. Kendler, K. S., Jacobson, K. C., Prescott, C. A. & Neale, M. C. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *Am. J. Psychiatry* **160**, 687–695 (2003).
8. Gelernter, J. *et al.* Genome-wide association study of opioid dependence: multiple associations mapped to calcium and potassium pathways. *Biol. Psychiatry* **76**, 66–74 (2014).
9. Cheng, Z. *et al.* Genome-wide Association Study Identifies a Regulatory Variant of RGMA Associated With Opioid Dependence in European Americans. *Biol. Psychiatry* **84**, 762–770 (2018).
10. Nelson, E. C. *et al.* Evidence of CNIH3 involvement in opioid dependence. *Mol. Psychiatry* **21**, 608–614 (2016).

11. Polimanti, R. *et al.* Leveraging genome-wide data to investigate differences between opioid use vs. opioid dependence in 41,176 individuals from the Psychiatric Genomics Consortium. *Mol. Psychiatry* **25**, 1673–1687 (2020).
12. Song, W. *et al.* Genome-wide association analysis of opioid use disorder: A novel approach using clinical data. *Drug Alcohol Depend.* **217**, 108276 (2020).
13. Zhou, H. *et al.* Association of OPRM1 Functional Coding Variant With Opioid Use Disorder: A Genome-Wide Association Study. *JAMA Psychiatry* **77**, 1072–1080 (2020).
14. Deak, J. D. *et al. Genome-wide association study and multi-trait analysis of opioid use disorder identifies novel associations in 639,709 individuals of European and African ancestry.* 2021.12.04.21267094 https://www.medrxiv.org/content/10.1101/2021.12.04.21267094v1 (2021) doi:10.1101/2021.12.04.21267094.
15. Sanchez-Roige, S. *et al.* Genome-wide association study of problematic opioid prescription use in 132,113 23andMe research participants of European ancestry. *Mol. Psychiatry* 1–9 (2021) doi:10.1038/s41380-021-01335-3.
16. Gaddis, N. *et al. Multi-trait genome-wide association study of opioid addiction: OPRM1 and Beyond*. 2021.09.13.21263503 https://www.medrxiv.org/content/10.1101/2021.09.13.21263503v1 (2021) doi:10.1101/2021.09.13.21263503.
17. Finucane, H. K. *et al.* Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nat. Genet.* **47**, 1228–1235 (2015).
18. The GTEx Consortium. The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Science* **369**, 1318–1330 (2020).
19. Davydov, E. V. *et al.* Identifying a high fraction of the human genome to be under selective constraint using GERP++. *PLoS Comput. Biol.* **6**, e1001025 (2010).

20. Barbeira, A. N. *et al.* Exploring the phenotypic consequences of tissue specific gene expression variation inferred from GWAS summary statistics. *Nat. Commun.* **9**, 1825 (2018).

21. Barbeira, A. N. *et al.* Integrating predicted transcriptome from multiple tissues improves association detection. *PLOS Genet.* **15**, e1007889 (2019).

22. Qi, T. *et al.* Identifying gene targets for brain-related traits using transcriptomic and methylomic data from blood. *Nat. Commun.* **9**, 2282 (2018).

23. Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47**, 291–295 (2015).

24. Cuellar-Partida, G. *et al. Complex-Traits Genetics Virtual Lab: A community-driven web platform for post-GWAS analyses*. http://biorxiv.org/lookup/doi/10.1101/518027 (2019) doi:10.1101/518027.

25. Crist, R. C. & Berrettini, W. H. Pharmacogenetics of OPRM1. *Pharmacol. Biochem. Behav.* **123**, 25–33 (2014).

26. Crist, R. C., Reiner, B. C. & Berrettini, W. H. A review of opioid addiction genetics. *Curr. Opin. Psychol.* **27**, 31–35 (2019).

27. Moningka, H., Lichenstein, S. & Yip, S. W. Current Understanding of the Neurobiology of Opioid Use Disorder: an Overview. *Curr. Behav. Neurosci. Rep.* **6**, 1–11 (2019).

28. Gelernter, J., Kranzler, H. & Cubells, J. Genetics of two mu opioid receptor gene (OPRM1) exon I polymorphisms: population studies, and allele frequencies in alcohol- and drug-dependent subjects. *Mol. Psychiatry* **4**, 476–483 (1999).

29. Howe, K. L. *et al.* Ensembl 2021. *Nucleic Acids Res.* **49**, D884–D891 (2021).

30. Zhang, H. *et al.* Association between two μ-opioid receptor gene (OPRM1) haplotype blocks and drug or alcohol dependence. *Hum. Mol. Genet.* **15**, 807–819 (2006).

31. Breslin, M. B. *et al.* Differential processing of proenkephalin by prohormone convertases 1(3) and 2 and furin. *J. Biol. Chem.* **268**, 27084–27093 (1993).

595 32. Christakoudi, S., Evangelou, E., Riboli, E. & Tsilidis, K. K. GWAS of allometric body-
596 shape indices in UK Biobank identifies loci suggesting associations with morphogenesis,
597 organogenesis, adrenal cell renewal and cancer. *Sci. Rep.* **11**, 10688 (2021).
598 33. Liu, M. *et al.* Association studies of up to 1.2 million individuals yield new insights into
599 the genetic etiology of tobacco and alcohol use. *Nat. Genet.* **51**, 237–244 (2019).
600 34. Grice, D. E. *et al.* Transcriptional profiling of C57 and DBA strains of mice in the absence
601 and presence of morphine. *BMC Genomics* **8**, 76 (2007).
602 35. Yu, L. *et al.* Activity in projection neurons from prelimbic cortex to the PVT is necessary
603 for retrieval of morphine withdrawal memory. *Cell Rep.* **35**, 108958 (2021).
604 36. Fujita-Hamabe, W., Nakamoto, K. & Tokuyama, S. Involvement of NCAM and FGF
605 receptor signaling in the development of analgesic tolerance to morphine. *Eur. J. Pharmacol.*
606 **672**, 77–82 (2011).
607 37. Yang, B.-Z. *et al.* Association of haplotypic variants in DRD2, ANKK1, TTC12 and
608 NCAM1 to alcohol dependence in independent case control and family samples. *Hum. Mol.*
609 *Genet.* **16**, 2844–2853 (2007).
610 38. Yang, B.-Z. *et al.* Haplotypic variants in DRD2, ANKK1, TTC12, and NCAM1 are
611 associated with comorbid alcohol and drug dependence. *Alcohol. Clin. Exp. Res.* **32**, 2117–
612 2127 (2008).
613 39. Pasman, J. A. *et al.* GWAS of lifetime cannabis use reveals new risk loci, genetic
614 overlap with psychiatric traits, and a causal influence of schizophrenia. *Nat. Neurosci.* **21**,
615 1161–1170 (2018).
616 40. Vujkovic, M. *et al.* Discovery of 318 new risk loci for type 2 diabetes and related vascular
617 outcomes among 1.4 million participants in a multi-ancestry meta-analysis. *Nat. Genet.* **52**,
618 680–691 (2020).

41. Lee, J. J. *et al.* Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat. Genet.* **50**, 1112–1121 (2018).

42. Amare, A. T. *et al.* Bivariate genome-wide association analyses of the broad depression phenotype combined with major depressive disorder, bipolar disorder or schizophrenia reveal eight novel genetic loci for depression. *Mol. Psychiatry* **25**, 1420–1429 (2020).

43. Koob, G. F. Neurobiology of Opioid Addiction: Opponent Process, Hyperkatifeia, and Negative Reinforcement. *Biol. Psychiatry* **87**, 44–53 (2020).

44. Leshner, A. I. Addiction is a brain disease, and it matters. *Science* **278**, 45–47 (1997).

45. Karlsson Linnér, R. *et al.* Multivariate analysis of 1.5 million people identifies genetic associations with traits related to self-regulation and addiction. *Nat. Neurosci.* **24**, 1367–1376 (2021).

46. Vanyukov, M. M. *et al.* Common liability to addiction and “gateway hypothesis”: Theoretical, empirical and evolutionary perspective. *Drug Alcohol Depend.* **123**, S3-17 (2012).

47. Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. *Cell* **179**, 1469-1482.e11 (2019).

48. Howell, B. A. *et al.* Validity of Incident Opioid Use Disorder (OUD) Diagnoses in Administrative Data: a Chart Verification Study. *J. Gen. Intern. Med.* **36**, 1264–1270 (2021).

Methods

Overview of Analyses

We conducted an ancestry-specific GWAS using a less stringent OUD case definition in AAs, EAs, and HAs from the MVP, followed by a cross-ancestry meta-analysis. Cases had received at least one lifetime ICD Ninth Revision (ICD-9) or Tenth Revision (ICD-10) diagnosis of OUD and control subjects were opioid exposed. Further details on phenotyping are described below.

In a supplementary analysis, we performed within-ancestry meta-analyses for AAs and EAs from the MVP, Yale-Penn (unpublished data), the Partners HealthCare Biobank[12], and the PGC[11], followed by a cross-ancestry meta-analysis which included all samples. In a second supplementary analysis, we repeated the GWAS in MVP with the more stringent case definition used in the prior MVP OUD GWAS[13]. Most subsequent downstream analyses are based on the GWAS for the less stringent OUD case definition in EAs within the MVP sample, with the exception being the use of the stringent definition in the same population group to estimate its heritability and to calculate genetic correlations between the less stringent and stringent traits. An overview of the analyses is provided in Supplementary Figure 1.

Million Veteran Program Cohort

As of September 2021, the MVP[49] had recruited approximately 850,000 veterans at 63 VA medical centers nationwide. All participants provide written informed consent and a blood sample for DNA extraction and genotyping and give permission to access their EHR for research purposes. The MVP was approved by the Central Veterans Affairs Institutional Review Board (IRB) and all site-specific IRBs. All relevant ethical regulations for work with human subjects were followed in the conduct of the study.

Phenotypes

OUD diagnostic codes based on ICD-9/10 were obtained from the VA EHR. The main GWAS used a less stringent definition of OUD (N = 31,473), which required the presence of 1 inpatient or outpatient ICD-9/10 diagnostic code for OUD (304.0, 304.7, 305.5, F11.1, F11.2) in the EHR. The stringent definition (N = 23,459), used in the supplementary GWAS, required at least 1 inpatient or 2 outpatient ICD-9/10 OUD diagnostic codes in the EHR. Controls (N = 394,471) for all GWAS were defined as individuals with at least 1 outpatient opioid analgesic prescription fill [excluding prescriptions for OUD treatment (e.g., buprenorphine or methadone)] and no ICD-9/10 diagnosis code for OUD documented in the EHR (i.e., opioid-exposed). Demographics are presented in Supplementary Table 1.

Genotyping and Imputation

The genotyping of samples in the MVP is ongoing and, in this analysis, we used Release 4 imputed data. MVP samples were genotyped with a custom Affymetrix Axiom Biobank Array. Quality control of genotype data and subsequent imputation were performed by the MVP Genomics working group. Duplicate samples were removed, as were those with a sex mismatch, 7 or more relatives in MVP (kinship>0.08), excessive heterozygosity or a genotype call rate <98.5%. Variants were removed if they were monomorphic, had a missing call rate <0.8, or a Hardy-Weinberg equilibrium $p<1x10^{-6}$ both in the entire sample using a PCA-adjusted method and within 1 of the 3 major ancestry groups (AA, EA, HA). Genotypes were phased with SHAPEIT4 (v.4.1.3)[50] and imputed using Minimac4[51], with biallelic SNPs imputed using the African Genome Resources (AGR) reference panel by the Sanger Institute (which includes all samples from 1000 Genomes Project phase 3, version 5[52] plus 1500 unrelated pan-African samples), and non-biallelic SNPs and indels imputed in a secondary imputation using the 1000 Genomes Project phase 3, version 5[52] reference panel. Indels and complex variants from the second imputation were merged into the AGR imputation.

We removed 1 individual from each pair of related individuals at random (kinship>0.08, N=31,010). Genetic ancestry was unified with self-identified race/ethnicity using the HARE (Harmonizing Genetic Ancestry and Self-Identified Race/Ethnicity) method[54]. Quality control of imputed variants was performed within each ancestral group. Genetic variants were excluded based on minor allele frequency (MAF: AA<0.005; EA<0.001; HA<0.01), genotype call rate<0.95, and Hardy-Weinberg equilibrium $p<1x10^{-6}$ or a population-specific imputation quality (INFO) score <0.7. Genome-wide association analyses were performed using PLINK 2.0[53] and a logistic regression model. Covariates included sex, age at enrollment, and the first 10 genetic principal components (PCs) within each ancestry.

Datasets for Meta-analysis

Supplementary Table 2 summarizes the datasets used for meta-analysis. Summary statistics for GWAS of OUD were obtained from two previously published datasets: 1) Partners HealthCare Biobank, which used the same less stringent case definition and opioid-exposed controls in European ancestry individuals[12] 2) PGC, which used a DSM-IV OD diagnosis and opioid-exposed controls in African and European ancestry individuals[11]. We also included the Yale-Penn 3 (YP3) unpublished dataset (Yale-Penn 1 and 2 were included in PGC analyses). In YP3, we conducted a GWAS using cases with a DSM-IV OD diagnosis and opioid-exposed controls. For AAs, there were 168 cases and 153 controls; for EAs, there were 578 cases and 219 controls. We used GEMMA to conduct association analysis to account for relatedness between the individuals. Sex, age at enrollment, and the first 10 PCs were included as covariates. We used a sign test to compare the direction of effects for SNPs in MVP and the other three datasets. SNPs with $p<1x10^{-5}$ from MVP AFR results (400 SNPs) or from MVP EUR results (954 SNPs) were evaluated for the direction of their signs in PGC, Partners, and Yale-Penn 3 results. We used a binomial test to evaluate the null hypothesis that 50% of SNPs have the same effect direction in independent datasets.

Meta-analysis and Independent Variants

Meta-analyses were conducted using a sample-size-weighted method in METAL[55] due to substantial differences in sample sizes. To compensate for the imbalance in the ratio of cases to controls, effective sample sizes were calculated using the formula: 4/[1/n_case + 1/n_control]. Effective sample sizes were used in all meta-analyses and all downstream analyses. Meta-analyses were conducted across the following datasets: 1) cross-ancestry (AA, EA, and HA) meta-analysis within MVP, comprising 31,473 less stringent OUD cases and 394,471 controls and 23,459 stringent cases and 394,471 controls; 2) within-ancestry meta-analysis across datasets (AA: MVP [8,968 less stringent cases and 79,530 controls], PGC [1,297 less stringent cases and 1,291 controls], YP3 [168 less stringent cases and 153 controls]; EA: MVP [19,978 less stringent cases and 282,607 controls], Partners HealthCare Biobank [Partners: 1,038 less stringent cases and 10,744 controls], PGC [3,272 less stringent cases and 2,876 controls], YP3 [578 less stringent cases and 219 controls]); 3) cross-ancestry meta-analysis across all datasets (AA [MVP, PGC, YP3; 10,433 less stringent cases and 80,974 controls]; EA [MVP, Partners HealthCare Biobank, PGC, YP3; 24,866 less stringent cases and 296,446 controls]; HA [MVP; 2,527 less stringent cases and 32,334 controls]).

To identify independent variants, we performed LD-clumping within each ancestry using a range of 3000 kb, $r^2 > 0.1$, and the matched 1000 Genomes[52] reference panel. Following clumping, variants that were located <1Mb apart were merged into a single locus. For loci that contained multiple variants, we conducted conditional analyses using COJO in GCTA[56]. Within each locus, we conditioned on the most significant variant. Upon conditioning, variants within the locus that remained significant ($p < 5 \times 10^{-8}$) were considered independent.

SNP-based Heritability Analyses and Partitioning Heritability Enrichment

We used LD score regression[23] (LDSC) to estimate OUD (less stringent and stringent case definitions) SNP-based heritability (h^2_{SNP}) in AAs and EAs for common SNPs mapped to HapMap3[57]. To ensure matching of population linkage disequilibrium (LD) structure, we used pre-computed LD scores based on African and European 1000 Genomes Project Phase 3[52]. SNPs in the major histocompatibility complex (MHC) region were excluded. Because of the high degree of genetic admixture in HAs and the smaller size of the sample, we did not estimate h^2_{SNP} in that population group.

We used LDSC to partition h^2_{SNP} in the OUD EA dataset and examined the enrichment of the partitioned h^2_{SNP} based on different functional genomic annotation models[17,58]. In the baseline model, we examined 75 overlapping functional annotations comprising genomic, epigenomic, and regulatory features (see ref [17] for details). Next, we analyzed 10 overlapping cell-type groups derived from 220 cell-type specific annotations in four histone marks: H3K4me1, H3K4me3, H3K4ac and H3K27ac (see ref [17] for details). Finally, enriched cell-type categories were analyzed based on annotations obtained from H3K4me1 imputed, gapped peak data generated by the Roadmap Epigenomics Mapping Consortium[59] (see ref [58] for details). For each h^2_{SNP} partitioning model, multi-allelic and MHC region variants were excluded, and Bonferroni-correction was applied to identify significant enrichment.

Gene-based, Functional Enrichment and Pathway Analyses

We performed gene-based association testing for OUD in FUMA v1.3.6a[60], using MAGMA v1.08[61], which employs multiple regression models to detect multiple marker effects that account for SNP p-values and LD between markers, using the matched-ancestry 1000 Genomes Project phase 3[52] panel as LD reference. We used a total of 18,707 protein-coding genes, with $p < 2.67 \times 10^{-6}$ (0.05/18,707) considered GWS. We also conducted a separate gene-based analysis using GCTA-fastBAT, which included 26,292 genes[62]. We tested the

genetic architecture of selected lead SNPs by integrating our GWAS results with brain-related GTEx v7 and chromatin interaction data in FUMA.

To identify gene sets enriched for OUD, we used MAGMA[61] to curate gene sets; Gene Ontology terms (obtained from MsigDB c2); and GWAS-catalog enrichment, correcting for gene size, variant density, and LD within and between genes. We also used MAGMA to test the association between gene-set properties and tissue-specific gene expression profiles using GTEx (v.7) data from 53 tissues (Bonferroni-corrected p-value threshold = 9.43×10^{-4}).

Transcriptome-wide Association Analyses

We performed transcriptome-wide association analyses using the MetaXcan framework[20] and the GTEx release v.8 eQTL MASHR-M models[63]. Forty-nine tissues from GTEx v.8 were analyzed comprising 12,951 samples. First, GWAS summary statistics were harmonized for the EA population based on the human genome assembly GRCh38 (hg38) and linked to the 1000 Genomes reference panel using GWAS tools, as previously described[20]. A transcriptome-wide association analysis of 49 tissues was run using S-PrediXcan[20]. A Bonferroni correction for statistical significance was applied within each tissue conditioned on the number of genes tested (Supplementary Table 15).

Because expression quantitative trait loci (eQTL) were correlated across tissues, we integrated gene expression signals for 49 tissue panels using S-MultiXcan[21] and tested 10,552 genes in total. Resulting p-values were Bonferroni corrected to identify significant gene associations (p-value threshold = 4.74×10^{-6}).

To examine whether the effects of GWS variants associated with OUD are mediated by changes in gene expression patterns, we performed summary-based Mendelian randomization (SMR) analyses[64] using brain cis-eQTL summary data (Brain-eMeta[22]) obtained from a meta-analysis of 10 brain regions in GTEx v6[65], and dorsolateral prefrontal cortex in CMC[66] and ROSMAP[67]. We also conducted SMR analyses for individual brain tissues generated from GTEx

v8[63]. We considered causal genes those with a p-value below an FDR threshold of 5% and no evidence of pleiotropy (HEIDI P value > 0.05).

Drug Interactions

To identify drugs that could potentially be repurposed to treat OUD, we examined genes identified in the variant or gene-level analyses using the Drug Gene Interaction Database[68] (https://www.dgidb.org). Medications were categorized using the Anatomical Therapeutic Chemical (ATC) classification system, retrieved from the Kyoto Encyclopedia of Genes and Genomics Kyoto Encyclopedia of Genes and Genomics (KEGG; https://www.genome.jp/kegg/drug/).

Genetic Correlation

We used LD score regression[23] to calculate the r_g between a) OUD or OD datasets used for meta-analysis (AA [MVP, PGC, YP3]; EA [MVP, Partners HealthCare Biobank, PGC, YP3]) and b) OUD (MVP EA) and 40 other published psychiatric, substance use, cognitive, and anthropometric traits selected based on a priori hypotheses (See Supplementary Table 20 for a full list), using pre-computed LD scores for HapMap3[57] SNPs based on the matched-ancestry 1000 Genomes Project Phase 3[52] reference panel. To explore additional traits in a hypothesis-free manner, we also estimated the r_g between OUD and 1,270 traits (comprising published and unpublished traits from the UK Biobank (UKBB) using the Complex-Trait Genetics Virtual Lab (CTG-VL) (https://genoma.io). CTG-VL integrates publicly available GWAS summary statistics and utilizes the LDSC framework to calculate r_g between complex traits and diseases of interest[24]. A Bonferroni correction was applied within each LDSC and CTG-VL analysis, and traits with a corrected p-value < 0.05 were regarded as significantly correlated.

We also estimated the trans-ancestry r_gs for OUD in the MVP between the AA and EA populations using the Popcorn package, a computationally efficient method that uses summary-

level data from GWAS while accounting for LD[69]. We used African and European 1000 Genomes Project Phase 3[52] data as the LD references.

Mendelian Randomization

We performed Mendelian randomization (MR) analysis using the *MendelianRandomization* package in R. Causal relationships between OUD and other traits were tested bidirectionally using three methods: Weighted Median, Inverse Variance Weighted and MR-Egger. We tested for pleiotropy using the MR-Egger intercept test. Instrumental variants were those associated with the exposure at $p < 1 \times 10^{-5}$. When the instrumental variants were not present in the outcome data, we identified the best-proxy variant (LD > 0.8). Variants with MAF < 0.01 or with no proxy with LD > 0.8 within 200 kb were removed. Each trait included more than 20 instrumental variables, which provides a robust estimate of causal effects. We considered causal effects as those for which at least 2 MR tests were significant after Bonferroni correction and that showed no evidence of violation of the horizontal pleiotropy test (MR-Egger intercept p > 0.05).

Polygenic Risk Scores and Phenome-wide Association Studies

We calculated PRS for OUD in two independent datasets (Yale-Penn and BioVU) using PRS-continuous shrinkage (PRS-CS)[70], followed by phenome-wide association analyses (PheWAS). In each dataset, OUD summary statistics from the matched ancestry were used to calculate PRS. Details for the analysis in each dataset are below.

Yale-Penn: We removed SNPs with INFO score < 0.7, MAF < 0.01 genotype call rate < 0.95, or an allele frequency difference between genotyping batches > 0.4, which left a total of 8,811,422 SNPs. We removed one individual from each pair of related individuals with pi-hat > 0.25. To estimate genetic ancestry, we calculated PCs on common SNPs between Yale-Penn and 1000 Genomes Project Phase 3[52] using the -pca flag in PLINK 1.9[53]. Subjects were

assigned to an ancestry based on the distance of 10 PCs from the 1000 Genomes reference populations. The resulting data set included 4,918 AAs and 5,692 EAs. We excluded binary phenotypes with fewer than either 100 cases or 100 controls, and continuous phenotypes with fewer than 100 individuals. We conducted PheWAS by fitting logistic regression models for binary traits and linear regression models for continuous traits. We used sex, age at enrollment, and the top 10 genetic PCs as covariates. We applied a Bonferroni correction to control for multiple comparisons.

BioVU: We used de-identified clinical data from Vanderbilt University Medical Center's (VUMC) Biobank (BioVU). Details on the quality control process have been described elsewhere[71]. The genotyping information that we used was from the Illumina MEGA^{EX} array. Genotypes were filtered for SNP and individual call rates, sex discrepancies, and excessive heterozygosity using PLINK v1.9[53]. Imputation of the autosomes was conducted using the Michigan Imputation Server[51] based on the Haplotype Reference Consortium reference panel. PCA using FlashPCA2 combined with CEU, YRI and CHB reference sets from 1000 Genomes Project Phase 3[52] was conducted to determine participants of African and European Ancestry. The sample was then filtered for cryptic relatedness by removing one individual of each pair for which pi-hat>0.2. This resulted in 12,384 individuals of African ancestry and 66,903 individuals of European ancestry samples for analysis. We conducted PheWAS by fitting a logistic regression for each of the 1,335 disease phenotypes available in BioVU to estimate the odds of a diagnosis of that phenotype given the OUD PRS. Each disease phenotype (commonly referred to as "phecode"; https://phewascatalog.org/phecodes, Phecode Map 1.2) was classified using ICD 9 and 10 diagnostic codes to establish "case" status. For an individual to be considered a case, they were required to have two ICD codes for the index phenotype, and each phenotype needed at least 100 cases to be included in the analysis. The covariates included in the analyses were sex, median age of the longitudinal EHR measurements, and the

top 10 genetic PCs. The project was approved by the VUMC Institutional Review Board (IRB #s 160302, 172020, 190418).

Genomic Structural Equation Modeling

To establish whether there is a shared genetic structure between OUD, other substance use disorders, and psychiatric disorders, we performed Genomic SEM[72] for OUD, 3 other substance use traits (problematic alcohol use[73], cannabis use disorder[74], ever smoked regularly[33]), and 7 psychiatric disorders (schizophrenia[75], bipolar disorder[76], major depressive disorder[77], autism spectrum disorder[78], attention deficit hyperactivity disorder[79], Tourette's syndrome[80], and obsessive-compulsive disorder[81]). We calculated a genetic covariance matrix using multivariable LDSC and the 1000 Genomes Project phase 3 European samples[52] as reference. An exploratory factor analysis was conducted using the genetic covariance matrix and a four latent-factor structure with varimax rotation. We used the determined structure containing paths with loading factor >0.2 to perform a confirmatory factor analysis implemented in the *GenomicsSEM* package in R. To prevent negative residual variance after estimation, we restricted the residual variance of OCD and ADHD to be greater than 0.

Data Availability

The full summary-level association data from the meta-analysis are available through dbGaP at: https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001672

Code Availability

Imputation was performed using Minimac3 (https://genome.sph.umich.edu/wiki/Minimac3). GWAS was performed using PLINK2 (https://www.cog-genomics.org/plink2). Meta-analyses were performed using METAL (https://genome.sph.umich.edu/wiki/METAL_Documentation). GCTA

(https://cnsgenomics.com/software/gcta/#Overview) was used for identification of independent loci (GCTA-COJO) and gene-based analysis (GCTA-fastBAT). FUMA (https://fuma.ctglab.nl/) was used for gene association, functional enrichment and gene set enrichment analyses. Transcriptomic analyses were performed using S-PrediXcan and S-MultiXcan (https://github.com/hakyimlab/MetaXcan). LDSC (https://github.com/bulik/ldsc) was used for heritability estimation, genetic correlation analysis (also using the Complex-Trait Genetics Virtual Lab (CTG-VL) (https://genoma.io)) and heritability enrichment analyses. Trans-ancestry genetic correlation was estimated using Popcorn (https://github.com/brielin/Popcorn). Polygenic risk score analyses were performed using PRS-CS (https://github.com/getian107/PRScs). PheWAS analyses were run using the PheWAS R package (https://github.com/PheWAS/PheWAS). The Mendelian Randomization R Package (https://cran.r-project.org/web/packages/MendelianRandomization/index.html) was used for MR analyses. Genomic Structural Equation Modeling was conducted using the GenomicsSEM R package (https://github.com/GenomicSEM/GenomicSEM).

Methods-only References

49. Gaziano, J. M. *et al.* Million Veteran Program: A mega-biobank to study genetic influences on health and disease. *J. Clin. Epidemiol.* **70**, 214–223 (2016).

50. Delaneau, O., Zagury, J.-F., Robinson, M. R., Marchini, J. L. & Dermitzakis, E. T. Accurate, scalable and integrative haplotype estimation. *Nat. Commun.* **10**, 5436 (2019).

51. Das, S. *et al.* Next-generation genotype imputation service and methods. *Nat. Genet.* **48**, 1284–1287 (2016).

52. Auton, A. *et al.* A global reference for human genetic variation. *Nature* **526**, 68–74 (2015).

53. Chang, C. C. *et al.* Second-generation PLINK: rising to the challenge of larger and richer datasets. *GigaScience* **4**, (2015).

54. Fang, H. *et al.* Harmonizing Genetic Ancestry and Self-identified Race/Ethnicity in Genome-wide Association Studies. *Am. J. Hum. Genet.* **105**, 763–772 (2019).

55. Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinforma. Oxf. Engl.* **26**, 2190–2191 (2010).

56. Yang, J., Lee, S. H., Goddard, M. E. & Visscher, P. M. GCTA: a tool for genome-wide complex trait analysis. *Am. J. Hum. Genet.* **88**, 76–82 (2011).

57. Altshuler, D. M. *et al.* Integrating common and rare genetic variation in diverse human populations. *Nature* **467**, 52–58 (2010).

58. Finucane, H. K. *et al.* Heritability enrichment of specifically expressed genes identifies disease-relevant tissues and cell types. *Nat. Genet.* **50**, 621–629 (2018).

59. Bernstein, B. E. *et al.* The NIH Roadmap Epigenomics Mapping Consortium. *Nat. Biotechnol.* **28**, 1045–1048 (2010).

60. Watanabe, K., Taskesen, E., van Bochoven, A. & Posthuma, D. Functional mapping and annotation of genetic associations with FUMA. *Nat. Commun.* **8**, 1826 (2017).

61. de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput. Biol.* **11**, e1004219 (2015).

62. Bakshi, A. *et al.* Fast set-based association analysis using summary data from GWAS identifies novel gene loci for human complex traits. *Sci. Rep.* **6**, 32894 (2016).

63. Barbeira, A. N. *et al.* Exploiting the GTEx resources to decipher the mechanisms at GWAS loci. *Genome Biol.* **22**, 49 (2021).

64. Zhu, Z. *et al.* Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nat. Genet.* **48**, 481–487 (2016).

65. Aguet, F. *et al.* Genetic effects on gene expression across human tissues. *Nature* **550**, 204–213 (2017).

66. Fromer, M. *et al.* Gene expression elucidates functional impact of polygenic risk for schizophrenia. *Nat. Neurosci.* **19**, 1442–1453 (2016).

67. Ng, B. *et al.* An xQTL map integrates the genetic architecture of the human brain's transcriptome and epigenome. *Nat. Neurosci.* **20**, 1418–1426 (2017).

68. Freshour, S. L. *et al.* Integration of the Drug–Gene Interaction Database (DGIdb 4.0) with open crowdsource efforts. *Nucleic Acids Res.* **49**, D1144–D1151 (2021).

69. Brown, B. C., Asian Genetic Epidemiology Network Type 2 Diabetes Consortium, Ye, C. J., Price, A. L. & Zaitlen, N. Transethnic Genetic-Correlation Estimates from Summary Statistics. *Am. J. Hum. Genet.* **99**, 76–88 (2016).

70. Ge, T., Chen, C.-Y., Ni, Y., Feng, Y.-C. A. & Smoller, J. W. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat. Commun.* **10**, 1776 (2019).

71. Dennis, J. K. *et al.* Clinical laboratory test-wide association scan of polygenic scores identifies biomarkers of complex disease. *Genome Med.* **13**, 6 (2021).

72. Grotzinger, A. D. *et al.* Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. *Nat. Hum. Behav.* **3**, 513–525 (2019).

73. Zhou, H. *et al.* Genome-wide meta-analysis of problematic alcohol use in 435,563 individuals yields insights into biology and relationships with other traits. *Nat. Neurosci.* **23**, 809–818 (2020).

74. Johnson, E. C. *et al.* A large-scale genome-wide association study meta-analysis of cannabis use disorder. *Lancet Psychiatry* **7**, 1032–1045 (2020).

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

76. Mullins, N. *et al.* Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat. Genet.* **53**, 817–829 (2021).

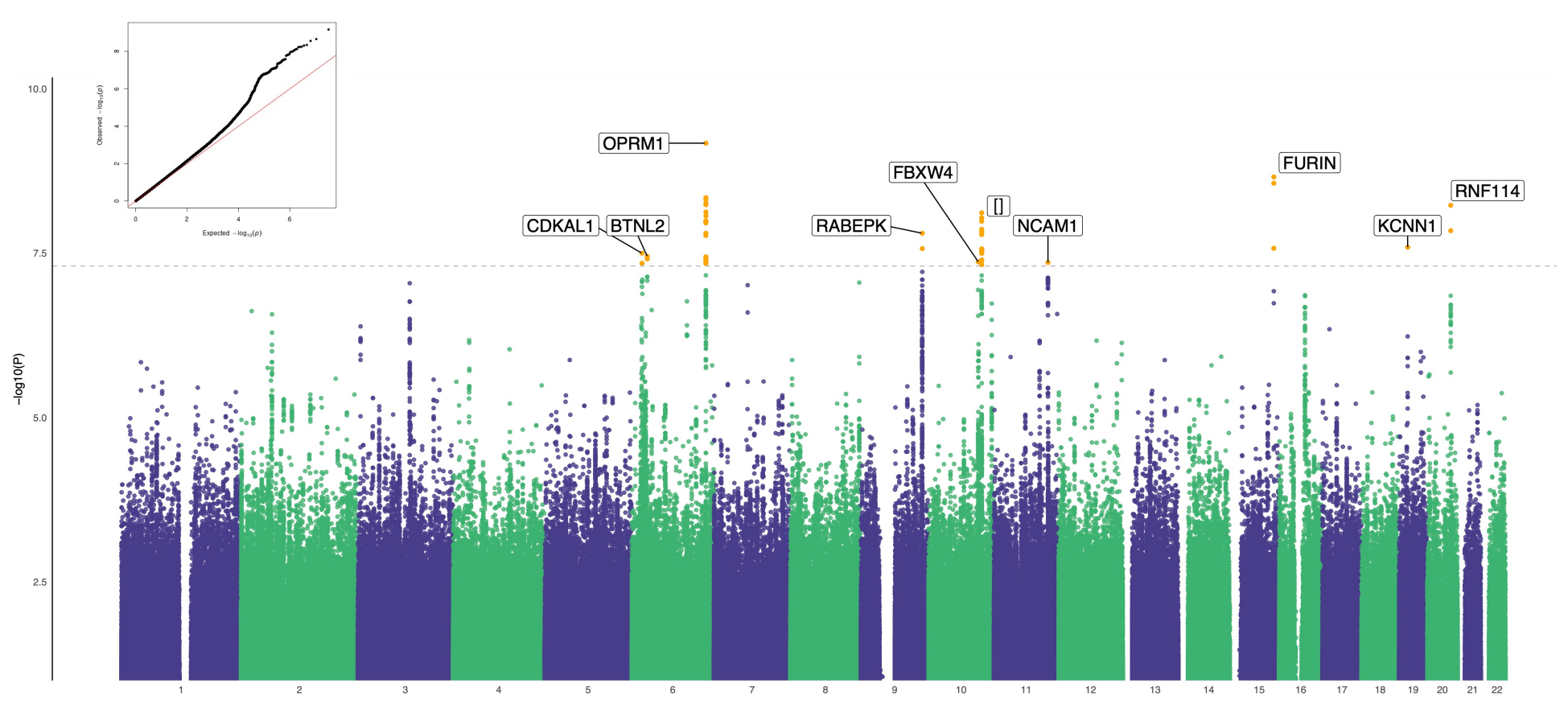
77. Howard, D. M. *et al.* Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat. Neurosci.* **22**, 343–352 (2019).

78. Grove, J. *et al.* Identification of common genetic risk variants for autism spectrum disorder. *Nat. Genet.* **51**, 431–444 (2019).

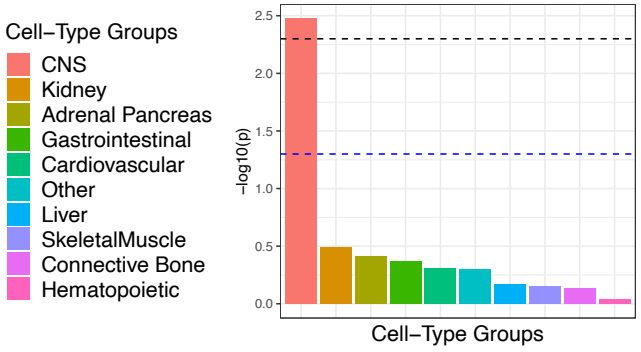
79. Demontis, D. *et al.* Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat. Genet.* **51**, 63–75 (2019).

80. Yu, D. *et al.* Interrogating the Genetic Determinants of Tourette's Syndrome and Other Tic Disorders Through Genome-Wide Association Studies. *Am. J. Psychiatry* **176**, 217–227 (2019).

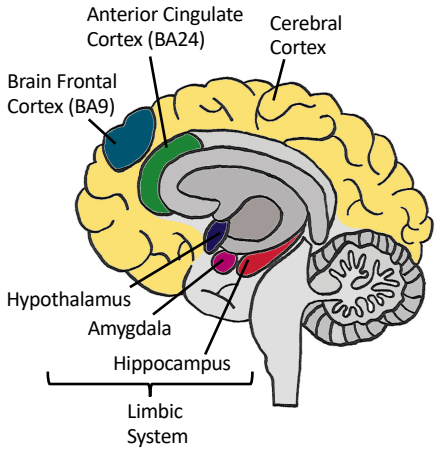
81. International Obsessive Compulsive Disorder Foundation Genetics Collaborative (IOCDF-GC) and OCD Collaborative Genetics Association Studies (OCGAS). Revealing the complex genetic architecture of obsessive-compulsive disorder using meta-analysis. *Mol. Psychiatry* **23**, 1181–1188 (2018)


OPRM1
CDKAL1
BTNL2
RABEPK
FBXW4
[]
NCAM1
FURIN
RNF114
KCNN1
−log10(P)
10.0
7.5
5.0
2.5
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Observed −log10(p)
Expected −log10(p)

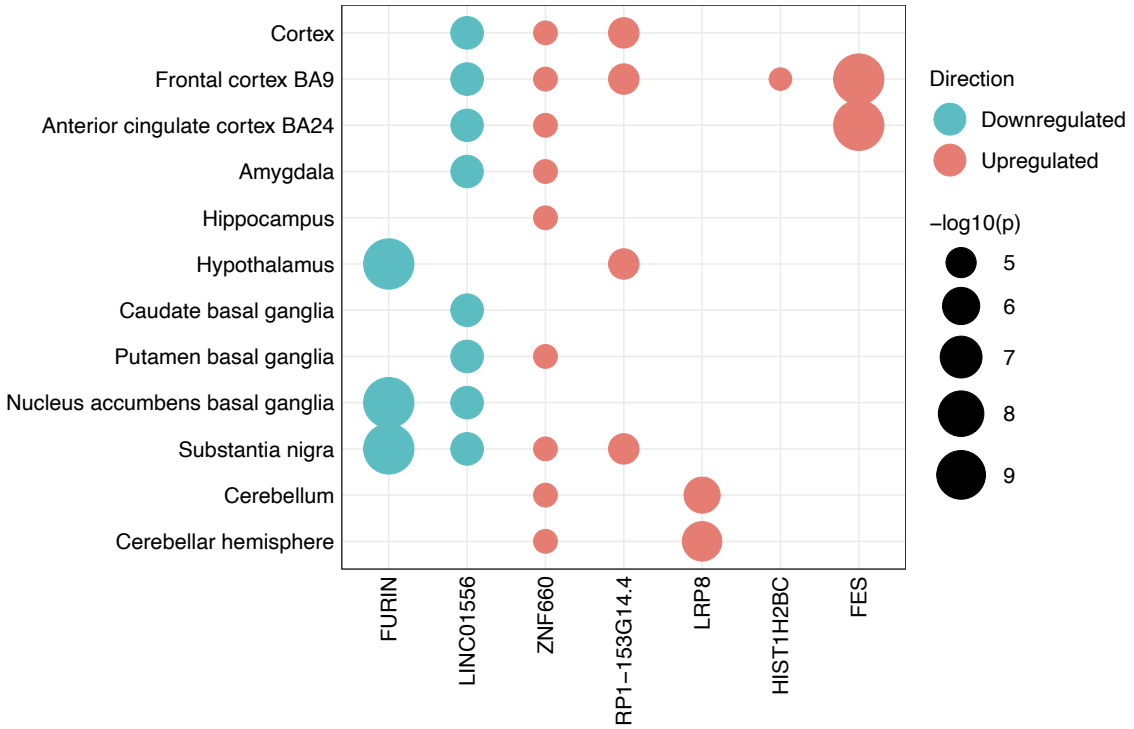
A


Cell–Type Groups
CNS
Kidney
Adrenal Pancreas
Gastrointestinal
Cardiovascular
Other
Liver
SkeletalMuscle
Connective Bone
Hematopoietic
−log10(p)
2.5
2.0
1.5
1.0
0.5
0.0
Cell–Type Groups

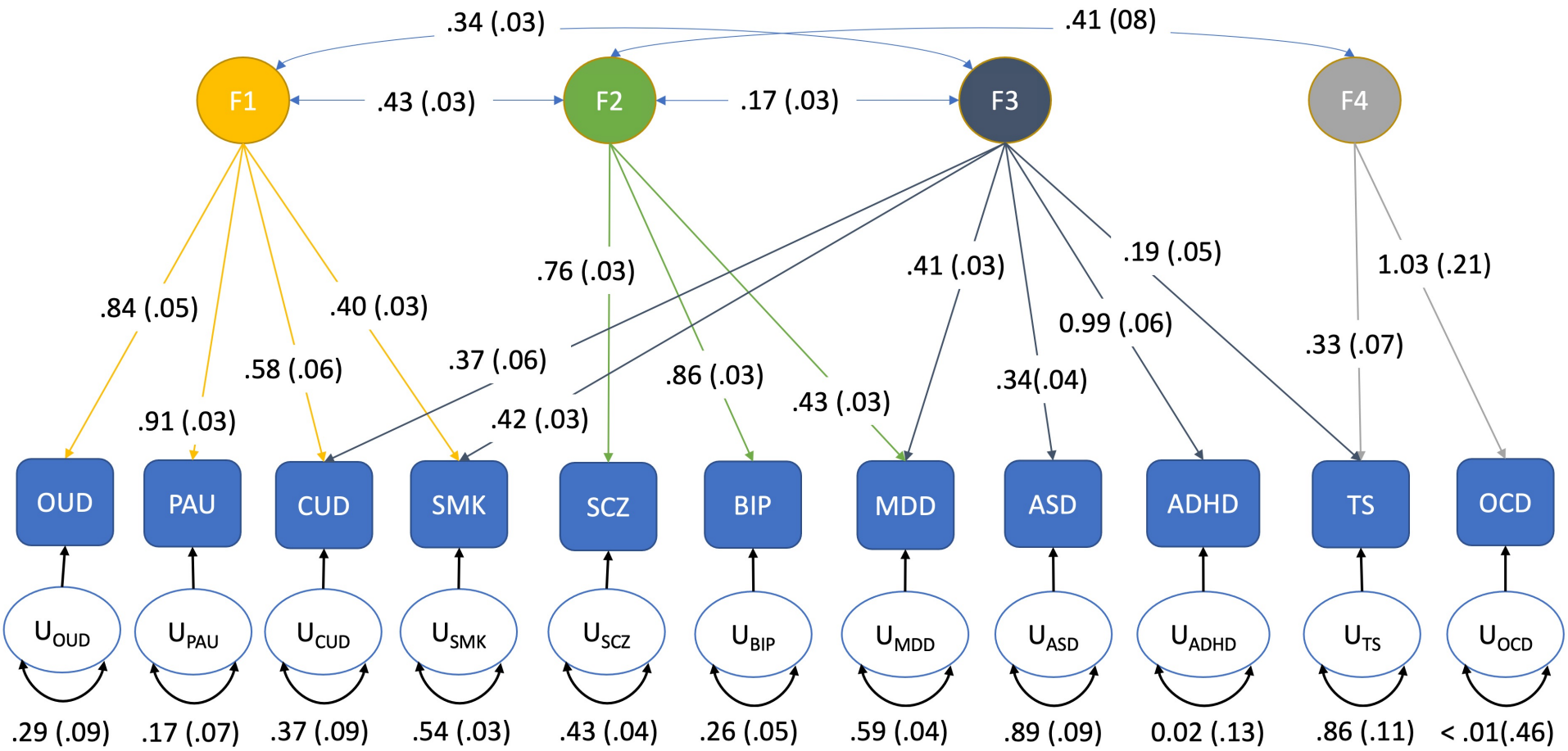
B


Anterior Cingulate Cortex (BA24)
Cerebral Cortex
Brain Frontal Cortex (BA9)
Hypothalamus
Amygdala
Hippocampus
Limbic System

C


Cortex
Frontal cortex BA9
Anterior cingulate cortex BA24
Amygdala
Hippocampus
Hypothalamus
Caudate basal ganglia
Putamen basal ganglia
Nucleus accumbens basal ganglia
Substantia nigra
Cerebellum
Cerebellar hemisphere
FURIN
LINC01556
ZNF660
RP1−153G14.4
LRP8
HIST1H2BC
FES
Direction
Downregulated
Upregulated
−log10(p)
5
6
7
8
9


A
Substance Use
Cognitive
Sleep
Psychiatric
Risk Behavior
OUD
Cannabis use disorder
Current vs former smoker
Age of initiating smoking
NO2A: Opioids
Drinks per week
Ever smoked regularly
Problematic alcohol use
Insomnia
Number of sexual partners
General risk tolerance
Worry subcluster
Depressed affect subcluster
ADHD
Neuroticism
MDD
Schizophrenia
Cross disorder
Bipolar disorder
Intelligence
Cognitive performance
Educational attainment
B
Seborrheic keratosis
Celiac disease
Type 1 diabetes
Blood in stool
Viral hepatitis C
Viral hepatitis
Anxiety, phobic and dissociative disorders
Tobacco use disorder
Substance addiction and disorders
Skin cancer
Neoplasm of uncertain behavior of skin
Chronic pain
Chronic pain syndrome
Chronic airway obstruction
Myopia
Back Pain
Dermatologic
Digestive
Endocrine/Metabolic
Infectious Diseases
Injuries & Poisonings
Mental Disorders
Neoplasms
Neurological
Respiratory
Sense Organs
Symptoms
−10
0
10
20
30
−log10(p−value) × Direction(Effect)
C
Education
Household income
Number of children
Hospital: hernia
Years: Alcohol to intoxication
Ever received outpatient psychiatric treatment
Caregiver: Parent
Household members cigarette smokers
Aware of household members using drug and alcohol
Age of first use
Sought treatment
DSM-5 criterion count
Regularly use
Ever used: Cocaine
Age of first use
Criteria: Reduction in other activities
Regularly use
Ever used: Opiate
Criteria: Time spent obtaining/using
Ever used: Sedatives
Ever injected
Age of first use
Ever used: Stimulants
Regularly use
Tobacco Dependence (DSM-IV)
Fagerström Test for Nicotine Dependence
Age of first use
Ever used: Combination
Regularly use
Criteria: Hyperactivity-impulsivity
Criteria: Inattention
Criteria: Shoplifting
Criteria: Unlawful behaviors
Symptom : Sum of physical reactions
Symptom : Restlessness
Criteria: Truancy
Truancy, suspended or expelled from school
Incapacitated
Age at diagnosis
Trouble functioning
Criteria: Loss of interest
Symptom: Trembling
Symptom: Dizziness
Criteria: Increased arousal
Sought treatment
Criteria: Hallucinations
Medical treatment following attempt
Hospitalization following attempt
Criteria: Unsuccessful effort to decrease
Demographics
Medical
Environment
Alcohol
Cocaine
Marijuana
Opiate
Sedatives
Stimulants
Tobacco
Other drug
ADHD
ASPD
Anxiety
Conduct Disorder
Depression
Panic Disorder
PTSD
Schizophrenia
Suicide
Gambling
−20
−10
0
10
20
30
−log10(p−value) × Direction(Effect)


.34 (.03)
.41 (08)
F1
.43 (.03)
F2
.17 (.03)
F3
F4
.84 (.05)
.40 (.03)
.58 (.06)
.91 (.03)
.37 (.06)
.42 (.03)
.76 (.03)
.86 (.03)
.43 (.03)
.41 (.03)
.34(.04)
0.99 (.06)
.19 (.05)
.33 (.07)
1.03 (.21)
OUD
PAU
CUD
SMK
SCZ
BIP
MDD
ASD
ADHD
TS
OCD
U_OUD
U_PAU
U_CUD
U_SMK
U_SCZ
U_BIP
U_MDD
U_ASD
U_ADHD
U_TS
U_OCD
.29 (.09)
.17 (.07)
.37 (.09)
.54 (.03)
.43 (.04)
.26 (.05)
.59 (.04)
.89 (.09)
0.02 (.13)
.86 (.11)
< .01(.46)

Supplementary Information for: “Cross-ancestry meta-analysis of opioid use disorder uncovers novel loci with predominant effects on brain”

Rachel L. Kember, Rachel Vickers-Smith, Heng Xu, Sylvanus Toikumo, Maria Niarchou, Hang Zhou, Emily E. Hartwell, Richard C. Crist, Christopher T. Rentsch, VA Million Veteran Program, Lea K. Davis, Amy C. Justice, Sandra Sanchez-Roige, Kyle M. Kampman, Joel Gelernter, Henry R. Kranzler

Supplementary Material

- Million Veteran Program: Consortium Acknowledgement for Manuscripts MVP Executive Committee:
  - Co-Chair: J. Michael Gaziano, M.D., M.P.H.
  - Co-Chair: Rachel Ramoni, D.M.D., Sc.D.
  - Jim Breeling, M.D. (ex-officio)
  - Kyong-Mi Chang, M.D.
  - Grant Huang, Ph.D.
  - Sumitra Muralidhar, Ph.D.
  - Christopher J. O'Donnell, M.D., M.P.H.
  - Philip S. Tsao, Ph.D.

- MVP Program Office
  - Sumitra Muralidhar, Ph.D.
  - Jennifer Moser, Ph.D.

- MVP Recruitment/Enrollment
  - Recruitment/Enrollment Director/Deputy Director, Boston – Stacey B. Whitbourne, Ph.D.; Jessica V. Brewer, M.P.H.
  - MVP Coordinating Centers
    - Clinical Epidemiology Research Center (CERC), West Haven – John Concato, M.D., M.P.H.
    - Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque - Stuart Warren, J.D., Pharm D.; Dean P. Argyres, M.S.
    - Genomics Coordinating Center, Palo Alto – Philip S. Tsao, Ph.D.
    - Massachusetts Veterans Epidemiology Research Information Center (MAVERIC), Boston - J. Michael Gaziano, M.D., M.P.H.
    - MVP Information Center, Canandaigua – Brady Stephens, M.S.
  - Core Biorepository, Boston – Mary T. Brophy M.D., M.P.H.; Donald E. Humphries, Ph.D.
  - MVP Informatics, Boston – Nhan Do, M.D.; Shahpoor Shayan
  - Data Operations/Analytics, Boston – Xuan-Mai T. Nguyen, Ph.D.

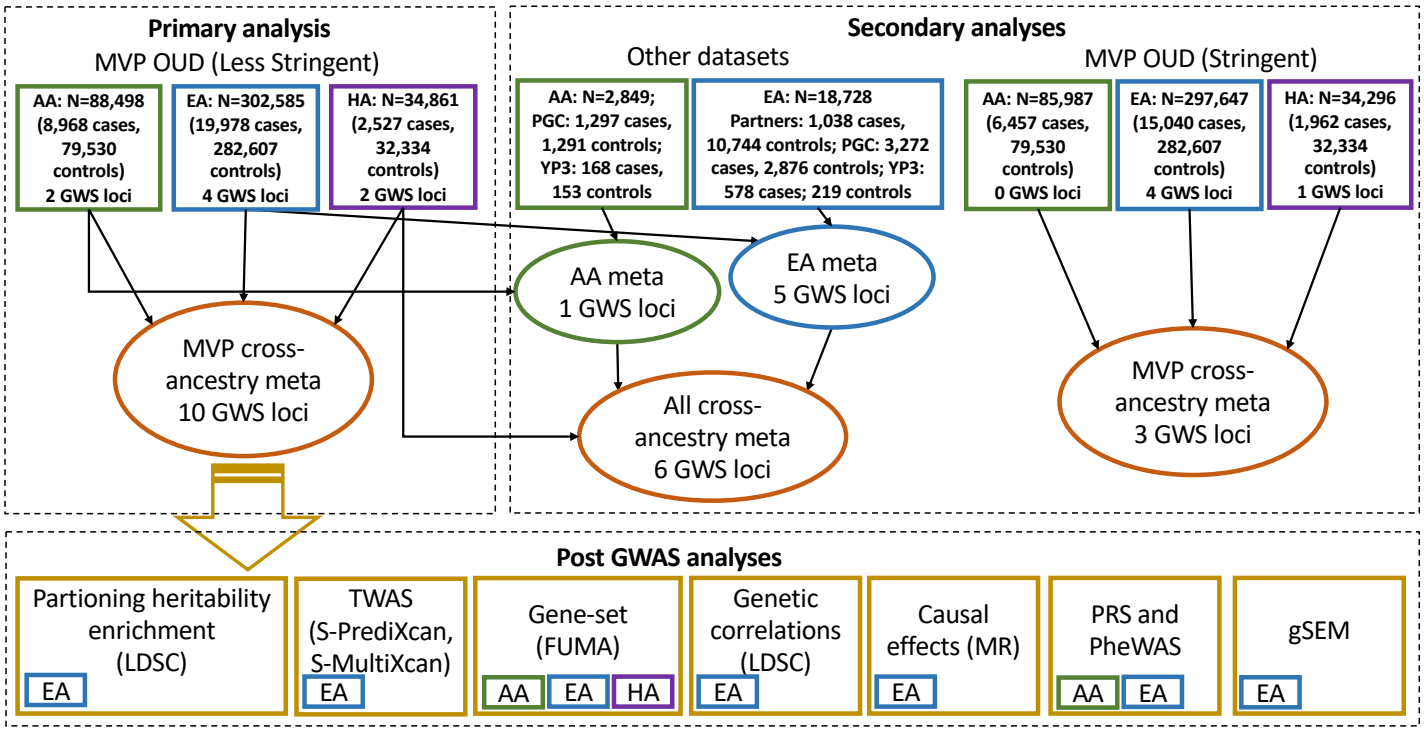
- MVP Science
  - Genomics - Christopher J. O'Donnell, M.D., M.P.H.; Saiju Pyarajan Ph.D.; Philip S. Tsao, Ph.D.
  - Phenomics - Kelly Cho, M.P.H, Ph.D.
  - Data and Computational Sciences – Saiju Pyarajan, Ph.D.
  - Statistical Genetics – Elizabeth Hauser, Ph.D.; Yan Sun, Ph.D.; Hongyu Zhao, Ph.D.

- MVP Local Site Investigators
  - Atlanta VA Medical Center (Peter Wilson)
  - Bay Pines VA Healthcare System (Rachel McArdle)
  - Birmingham VA Medical Center (Louis Dellitalia)
  - Cincinnati VA Medical Center (John Harley)
  - Clement J. Zablocki VA Medical Center (Jeffrey Whittle)
  - Durham VA Medical Center (Jean Beckham)
  - Edith Nourse Rogers Memorial Veterans Hospital (John Wells)
  - Edward Hines, Jr. VA Medical Center (Salvador Gutierrez)

- Fayetteville VA Medical Center (Gretchen Gibson)
- VA Health Care Upstate New York (Laurence Kaminsky)
- New Mexico VA Health Care System (Gerardo Villareal)
- VA Boston Healthcare System (Scott Kinlay)
- VA Western New York Healthcare System (Junzhe Xu)
- Ralph H. Johnson VA Medical Center (Mark Hamner)
- Wm. Jennings Bryan Dorn VA Medical Center (Kathlyn Sue Haddock)
- VA North Texas Health Care System (Sujata Bhushan)
- Hampton VA Medical Center (Pran Iruvanti)
- Hunter Holmes McGuire VA Medical Center (Michael Godschalk)
- Iowa City VA Health Care System (Zuhair Ballas)
- Jack C. Montgomery VA Medical Center (Malcolm Buford)
- James A. Haley Veterans' Hospital (Stephen Mastorides)
- Louisville VA Medical Center (Jon Klein)
- Manchester VA Medical Center (Nora Ratcliffe)
- Miami VA Health Care System (Hermes Florez)
- Michael E. DeBakey VA Medical Center (Alan Swann)
- Minneapolis VA Health Care System (Maureen Murdoch)
- N. FL/S. GA Veterans Health System (Peruvemba Sriram)
- Northport VA Medical Center (Shing Shing Yeh)
- Overton Brooks VA Medical Center (Ronald Washburn)
- Philadelphia VA Medical Center (Darshana Jhala)
- Phoenix VA Health Care System (Samuel Aguayo)
- Portland VA Medical Center (David Cohen)
- Providence VA Medical Center (Satish Sharma)
- Richard Roudebush VA Medical Center (John Callaghan)
- Salem VA Medical Center (Kris Ann Oursler)
- San Francisco VA Health Care System (Mary Whooley)
- South Texas Veterans Health Care System (Sunil Ahuja)
- Southeast Louisiana Veterans Health Care System (Amparo Gutierrez)
- Southern Arizona VA Health Care System (Ronald Schifman)
- Sioux Falls VA Health Care System (Jennifer Greco)
- St. Louis VA Health Care System (Michael Rauchman)
- Syracuse VA Medical Center (Richard Servatius)
- VA Eastern Kansas Health Care System (Mary Oehlert)
- VA Greater Los Angeles Health Care System (Agnes Wallbom)
- VA Loma Linda Healthcare System (Ronald Fernando)
- VA Long Beach Healthcare System (Timothy Morgan)
- VA Maine Healthcare System (Todd Stapley)
- VA New York Harbor Healthcare System (Scott Sherman)
- VA Pacific Islands Health Care System (Gwenevere Anderson)
- VA Palo Alto Health Care System (Philip Tsao)
- VA Pittsburgh Health Care System (Elif Sonel)
- VA Puget Sound Health Care System (Edward Boyko)
- VA Salt Lake City Health Care System (Laurence Meyer)
- VA San Diego Healthcare System (Samir Gupta)
- VA Southern Nevada Healthcare System (Joseph Fayad)
- VA Tennessee Valley Healthcare System (Adriana Hung)
- Washington DC VA Medical Center (Jack Lichy)
- W.G. (Bill) Hefner VA Medical Center (Robin Hurley)

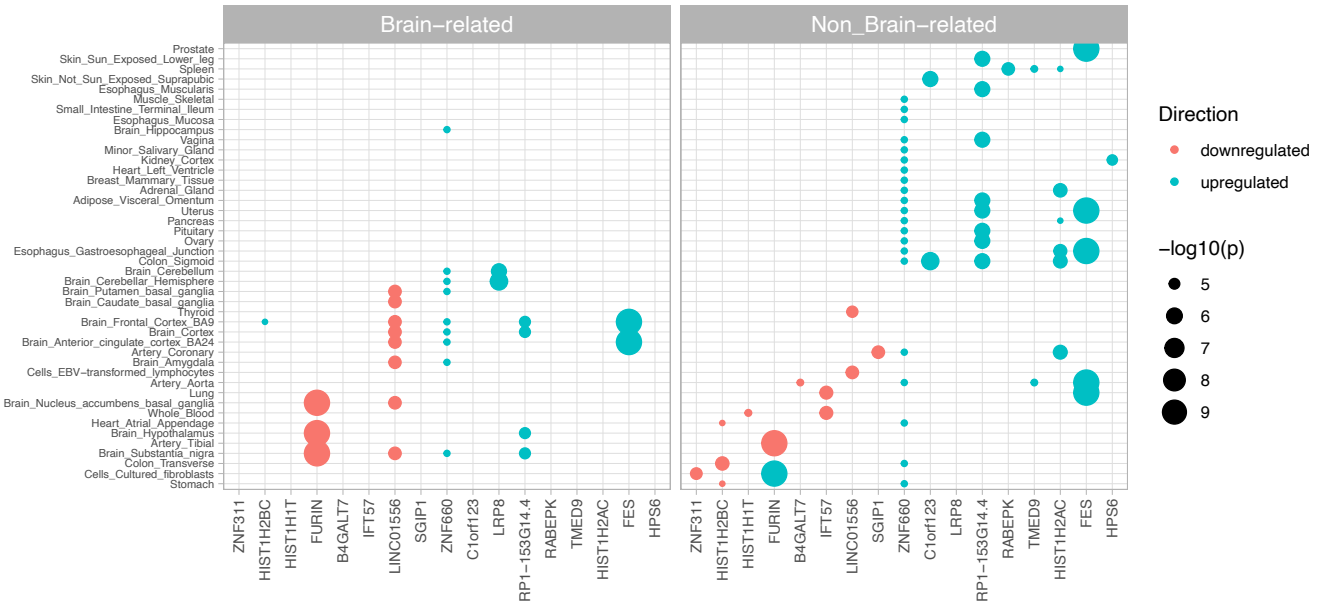
- White River Junction VA Medical Center (Brooks Robey)
- William S. Middleton Memorial Veterans Hospital (Robert Striker)

Supplementary Figure 1: Overview of analyses



Summary of all analyses. Top left: Primary analysis for OUD (less stringent) in MVP dataset. Within ancestry GWAS for African American (AA), European American (EA) and Hispanic American (HA) followed by cross-ancestry meta-analysis. These results were used for all downstream analyses. Top right: Supplementary analyses. 1. Within ancestry meta-analysis was conducted for AA between MVP, PGC, YP3 and for EA between MVP, Partners, PGC, YP3, followed by cross-ancestry meta-analysis. 2. Within ancestry OUD (stringent) GWAS for African American (AA), European American (EA) and Hispanic American (HA) followed by cross-ancestry meta-analysis. Bottom: Post GWAS analyses were conducted in Aas, EAs and HAs as indicated.

Supplementary Figure 2: Within-tissue gene expression (S-PrediXcan)

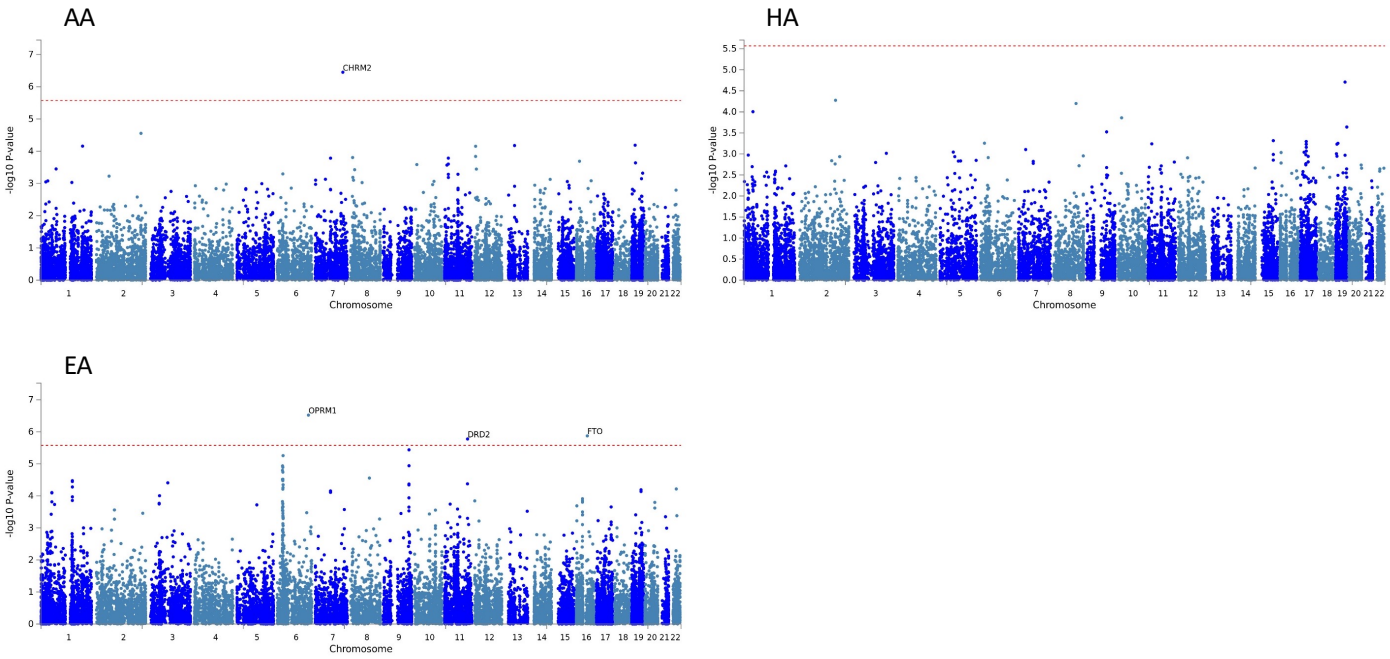


Within-tissue gene expression conducted using S-PrediXcan. Genes with predicted differential expression in brain-related tissues (left) and non-brain related tissues (right). Color of circle indicates downregulation (red) or upregulation (blue). Size of circle indicates –log10 p-value. Bonferroni correction was applied within each tissue based on the number of genes tested.

Supplementary Figure 3: Variants in *RABEPK* and *PPP6C*

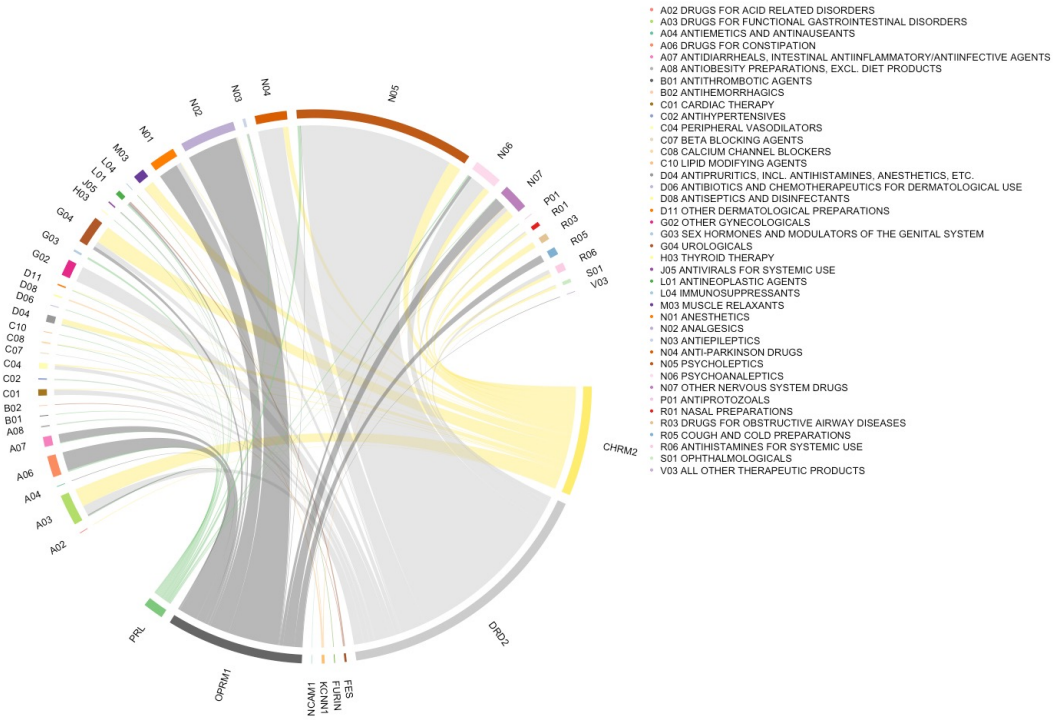
GWAS results were integrated with brain-related GTEx v7 and chromatin interaction data in FUMA. The lead SNP in *RABEPK* is in high LD with *PPP6C* variants (r2 > 0.8) that are significantly associated with gene expression and chromatin interaction, especially in the prefrontal cortex.

Supplementary Figure 4: Gene-based analyses



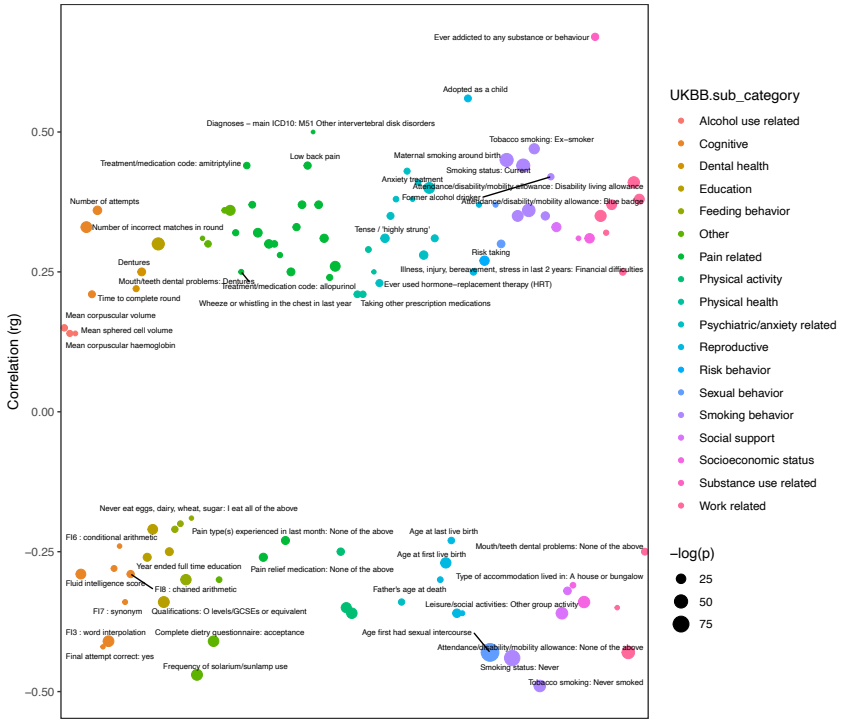
Gene-based Manhattan plots for AA, EA and HA. Gene-based association analyses were conducted using FUMA. Bonferroni correction threshold (represented by the red dashed line) = 2.67 × 10-6 (0.05/18,707).

Supplementary Figure 5: Drug-gene interactions



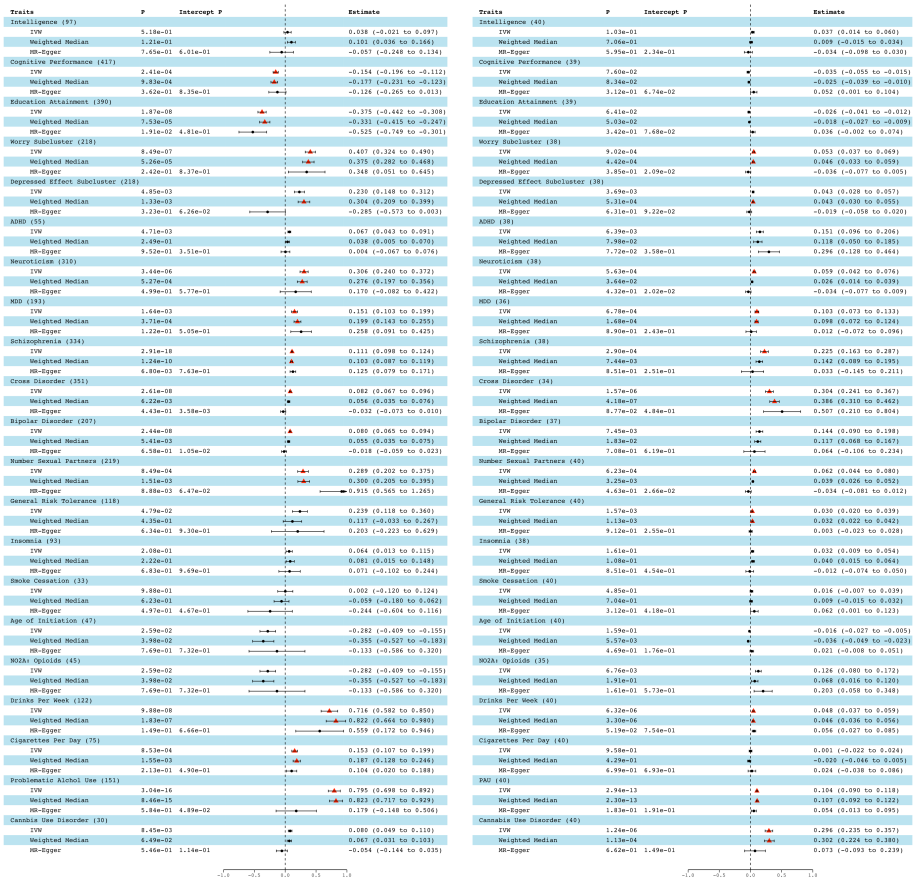
Drug-gene interactions for 8 genes associated with OUD. The width of the line between each gene and drug class indicates the number of interactions.

Supplementary Figure 6: Genetic correlation between OUD and UKBB complex traits



Genetic correlations for OUD in the UK Biobank dataset. All points passing Bonferroni correction (Bonferroni correction threshold = 3.94E-5 (0.05/1270) are plotted. The color of the circle indicates the phenotypic category. The size of the circle indicates the –log10 p-value.

Supplementary Figure 7: Mendelian randomization

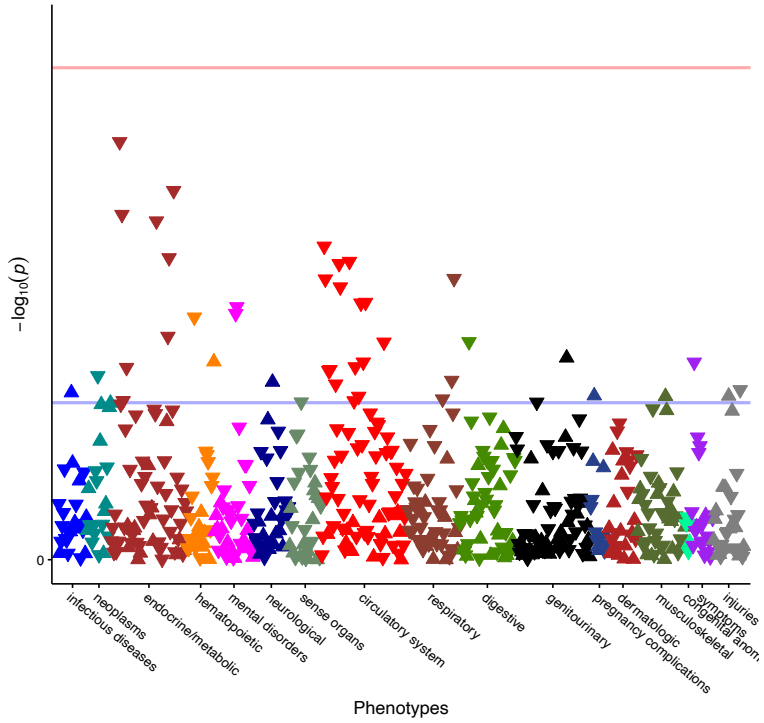


Causal association for traits genetically correlated with OUD. Left: Traits as the exposure, OUD as the outcome. Right: OUD as the exposure, traits as the outcome. Estimates (+/- 95% CI) and p-values for each MR analysis [Inverse variance weighted (IVW), Weighted median, and MR-Egger] are shown. Intercept p-value: MR-Egger horizontal pleiotropy test. Error bars: estimate +/- 95% CI.

Supplementary Figure 8: PheWAS in Yale-Penn AA individuals

PheWAS plot for OUD PRS in AA individuals from Yale-Penn. No phenotypes pass Bonferroni correction (Bonferroni correction threshold = 8.695652e-05 (0.05/575).

Supplementary Figure 9: PheWAS in BioVU AA individuals



PheWAS plot for OUD PRS in AA individuals from BioVU. No phenotypes pass Bonferroni correction (Bonferroni correction threshold = 7.936508e-05 (0.05/630).

Supplementary Table 25. Phenome-wide association results for OUD PRS in the EA Yal

phenotype	Simple_description
g1_opiev	Ever used: Opiates
g_OpDepBox1	Criteria: Time spent obtaining/using
g_DSM5_Dia	Opiate use disorder (DSM-5)
g_OPDependence	Opiate Dependence (DSM-IV)
g_OpDepBox5	Criteria: Tolerance
a_edu_attained	Education
g_OpDepBox6	Criteria: Withdrawal
g_DSM5_SxCT	DSM-5 criterion count
f1_cocev	Ever used: Cocaine
g1d_opiu	Regularly use
g_OpDepBox7	Criteria: Reduction in other activties
g_OpDepBox3	Criteria: Unsuccessful effort to decrease use
g22	Sought treatment
d_TobDep	Tobacco Dependence (DSM-IV)
g_OpDepBox4	Criteria: Used more than intended
g_OpDepBox2	Criteria: Continued use despite physical/psychological problems
g3_opidl	Frequent use
g_OPAbuse	Opiate Abuse
d_FTND	Fagerstrˆm Test for Nicotine Dependence
g11g_pro	Withdrawal symptom: Intefere with functioining
f1d_cocw	Regularly use
g11_3_st	Withdrawal symptom: Chills
g11	Withdrawal symptom: Sum
g5_opide	Craving
g11b	Two withdrawal symptoms occurred together
g11_5_st	Withdrawal symptom: Sweating
g11_9_mu	Withdrawal symptom: Craving
g11_13_s	Withdrawal symptom: Nose running
f_DSM5_Dia	Cocaine use disorder (DSM-5)
g11_1_fl	Withdrawal symptom: Depressed mood
g11_15_n	Withdrawal symptom: Muscle pain
g11_4_di	Withdrawal symptom: Increased heart rate
f_CocDependence	Cocaine Dependence (DSM-IV)
g7_1_opi	Symptom of use: Depression
g7_6_opi	Symptom of use: Decreased social contact
g_OP_Var4	Abuse criteria: Continued use despite social/interpersonal problems
f_CocDepBox3	Criteria: Unsuccessful effort to decrease use
g11_11_g	Withdrawal symptom: Stomach ache
f24	Sought treatment
g11_2_tr	Withdrawal symptom: Pupil dilation

g11_14_f	Withdrawal symptom: Yawning
g_OP_Var1	Abuse criteria: Failure to fulfill obligations
g11_8_ya	Withdrawal symptom: Insomnia
f_CocDepBox1	Criteria: Time spent obtaining/using
d3_cig10	>100 cigarettes lifetime
i_1_2	Truancy, suspended or expelled from school
f_CocDepBox4	Criteria: Used more than intended
f_DSM5_SxCT	DSM-5 criterion count
d_TobDep_Box3	Criteria: Used more than intended
f_CocAbuse	Cocaine Abuse
g7	Symptom of use: Number of these problems
g11_7_no	Withdrawal symptom: Nausea
d_TobDep_Box5	Criteria: Withdrawal
d_TobDep_Box4	Criteria: Unsuccessful effort to decrease use
f_CocDepBox7	Criteria: Reduction in other activties
f_Coc_Var2	Abuse criteria: Use in hazardous situations
b10_outp	Ever received outpatient psychiatric treatment
g7_2_opi	Symptom of use: Trouble concentrating
d4e_pack	Frequent use
f_CocDepBox2	Criteria: Continued use despite physical/psychological problems
f3_cocda	Frequent use
e31	Sought treatment
f_Coc_Var4	Abuse criteria: Continued use despite social/interpersonal problems
d16_2_nervsx	Withdrawal symptom: Anxiety
d16_a	Four withdrawal symptoms occurred together
d16_1_irrsx	Withdrawal symptom: Irritablility
g_OP_Var2	Abuse criteria: Use in hazardous situations
g11_10_p	Withdrawal symptom: Diarrhea
d_TobDep_Box7	Criteria: Tolerance
g11_6_ey	Withdrawal symptom: Fever
e_DSM5_SxCT	DSM-5 criterion count
f5_cocde	Craving
g11_12_h	Withdrawal symptom: Eyes running
e_AlcDep_Var4	Criteria: Reduction in other activties
a17b_hhi	Household income
e_AlcAb_Var1	Abuse criteria: Failure to fulfill obligations
d16_3_rstsx	Withdrawal symptom: Restlessness
f_Coc_Var1	Abuse criteria: Failure to fulfill obligations
d15	Sought treatment
f12	Withdrawal symptom: Sum
f12_8_st	Withdrawal symptom: Increased appetite
f12_6_st	Withdrawal symptom: Craving
h1_sed	Ever used: Sedatives

d1a_tob	Ever used: tobacco
f_CocDepBox5	Criteria: Tolerance
d16_6_deprsx	Withdrawal symptom: Depressed mood
e_AlcDep_Var2	Criteria: Unsuccessful effort to decrease use
a17_jobn	Employed
f_CocDepBox6	Criteria: Withdrawal
e_AlcDependence	Alcohol Dependence (DSM-IV)
e_AlcAb_Var2	Abuse criteria: Use in hazardous situations
e_AlcAb_Var4	Abuse criteria: Continued use despite social/interpersonal problems
f12_1_st	Withdrawal symptom: Depressed mood
h2a_mjwk	Regularly use
e_DSM5_Dia	Alcohol use disorder (DSM-5)
d_TobDep_Box6	Criteria: Continued use despite problems
e_AlcoholAbuse	Alcohol Abuse
h2a_othw	Regularly use
f12c	Two withdrawal symptoms occurred together
h1d_sedi	Ever injected
f12_9_st	Withdrawal symptom: Nightmares
d16_7_descigsx	Withdrawal symptom: Craving
f12g_pro	Withdrawal symptom: Intefere with functioining
f12_4_st	Withdrawal symptom: Insomnia
b7b_drn1	Years: Alcohol to intoxication
e14_drnk	Craving
f12_2_st	Withdrawal symptom: Restlessness
a14c_chi	Number of children
d16_8_appsx	Withdrawal symptom: Increased appetite
d_TobDep_Box1	Criteria: Time spent obtaining/using
e_AlcDep_Var7	Criteria: Withdrawal
d16_4_concnsx	Withdrawal symptom: Difficulty concentrating
b_Antipsychotics	Ever used: Antipsychotics
e_AlcDep_Var5	Criteria: Time spent obtaining/using
h_se_DepBox1	Criteria: Time spent obtaining/using
g_OP_Var3	Abuse criteria: Legal problems
e26c	Two withdrawal symptoms occurred together
h_mj_DepBox4	Criteria: Reduction in other activties
b7h_cocy	Years: Cocaine
e26_5_wdhrt1	Withdrawal symptom: Increased heart rate
e25_depr	Symptom of use: Depression
e26_4_wddepr1	Withdrawal symptom: Depressed mood
h1_mj	Ever used: Marijuana
h1_com	Ever used: Combination
e_AlcDep_Var3	Criteria: Used more than intended
d16_9_slpsx	Withdrawal symptom: Insomnia

h10a_20_	Withdrawal symptom: Hands shake
j33_mse_	Trouble functioning
e25	Symptom of use: Number psychological problems
h_ot_DSM5_Dia	Other drug use disorder (DSM-5)
f12_3_st	Withdrawal symptom: Sleepy
h_se_DepBox5	Criteria: Used more than intended
e_AlcDep_Var6	Criteria: Continued use despite physical/psychological problems
h2a_stim	Regularly use
h_se_DSM5_Dia	Sedatives use disorder (DSM-5)
h1b_mjag	Age of first use
h2a_sedw	Regularly use
h_ot_DepBox1	Criteria: Time spent obtaining/using
e26_3_wdanx1	Withdrawal symptom: Anxiety
e5_evryd	Frequent use
h_seDependence	Sedative Dependence (DSM-IV)
h1_stim	Ever used: Stimulants
j_boxb	Criteria: Loss of interest
b7i_amp1	Years: Amphtamines
f_Coc_Var3	Abuse criteria: Legal problems
h1d_stim	Ever injected
h_se_DSM5_SxCT	DSM-5 criterion count
j_diagnosis	Major Depressive Disorder
h10a_5_o	Withdrawal symptom: Oversleeping
b9_inpn	Number of inpatient psychiatric treatment times
h_se_DepBox2	Criteria: Unsuccessful effort to decrease use
f12_7_st	Withdrawal symptom: Slowed down
j_boxg	Criteria: Worthlessness/excessive guilt
g7_3_opi	Symptom of use: Paranoia
b7c_hery	Years: Heroin
h1_hal	Ever used: Hallucinogens
h_mj_DSM5_Dia	Marijuana use disorder (DSM-5)
j_boxa	Criteria: Depressed mood
p2_count	Symptom: Sum of physical reactions
g7_5_opi	Symptom of use: Nervousness
h_mjDependence	Marijuana Dependence (DSM-IV)
p2_3_anx	Symptom: Restlessness
p2_18_an	Symptom: Irritability
e26_6_wdnaus1	Withdrawal symptom: Nausea
h_mj_DepBox1	Criteria: Time spent obtaining/using
h10a_1_1	Withdrawal symptom: Depressed mood
h10a_3_1	Withdrawal symptom: Sleepy
p2_7_anx	Symptom: Sweating
e2a_4_na	Reaction: Nausea

b1_healt	Health rating
e26_7_wdweak1	Withdrawal symptom: Weakness
h_ot_DepBox2	Criteria: Unsuccessful effort to decrease use
j_box_count	Criterion count
p2_17_an	Symptom: Difficulty sleeping
h_se_Var4	Abuse criteria: Continued use despite social/interpersonal problems
i_ASPD_criterion_A1_2	Criteria: Shoplifting
h_st_DepBox2	Criteria: Unsuccessful effort to decrease use
e26_1_wdshk1	Withdrawal symptom: Shaking
p1_anxio	Ever anxious
h10a_sedd	Withdrawal symptom: Sum
h_ot_DepBox4	Criteria: Reduction in other activties
n5_suicm	Medical treatment following attempt
p_criterion_C	Criteria: Physical reaction
e_AlcAb_Var3	Abuse criteria: Legal problems
j1	Ever depressed
i_ASPD_criterion_A1	Criteria: Unlawful behaviors
i_CD_criterion_B15	Criteria: Truancy
h10d_sed	Withdrawal symptom: Intefere with functioining
z_1_parents	Caregiver: Parent
h10a_151	Withdrawal symptom: Sweating
h_seAbuse	Sedative Abuse
h_ot_DSM5_SxCT	DSM-5 criterion count
i_ASPD_criterion_A7	Criteria: Lack of remorse
h1d_otha	Ever injected
z6_smkrs	Household members cigarette smokers
i_ASPD_criterion_A1_9	Criteria: Been arrested (for any reason)
o_treatment	Sought treatment
h_otDependence	Other drug Dependence (DSM-IV)
h1a_mjn	Number of times used
j_boxh	Criteria: Difficulty concentrating
e_AlcDep_Var1	Criteria: Tolerance
p2_15_an	Symptom: Easily startled
p_criterion_B	Criteria: Difficult to control worry
h1_oth	Ever used: Other drugs
h10a_2_o	Withdrawal symptom: Restlessness
b_Antidepressants	Ever used: Antidepressants
M_A_II	Criteria: Hyperactivity-impulsivity
h_mj_DSM5_SxCT	DSM-5 criterion count
h_st_DepBox4	Criteria: Reduction in other activties
b_hos_hernia	Hospital: hernia
h_st_DSM5_Dia	Stimulants use disorder (DSM-5)
h1b_sola	Age of first use

h_se_DepBox7	Criteria: Continued use despite physical/psychological problems
o_CritD	Criteria: Increased arousal
t4_3_pan	Symptom: Dizziness
u_A3	Criteria: Unsuccessful effort to decrease
i_ASPD_criterion_A1_7	Criteria: Fraud, drug dealing, prostitution
p2_10_an	Symptom: Nausea
p_criterion_count	Criterion count
e25_para	Symptom of use: Paranoia
M_A_I	Criteria: Inattention
h_ot_DepBox6	Criteria: Withdrawal
h_st_DSM5_SxCT	DSM-5 criterion count
M_D	Criteria: Significant impairment
e25_thin	Symptom of use: Clouded thinking
b7a_alcy	Years: Alcohol
h_ot_Var4	Abuse criteria: Continued use despite social/interpersonal problems
n6_suich	Hospitalization following attempt
h4_othde	Craving
p2_4_anx	Symptom: Tired
l_A2	Criteria: Hallucinations
h1b_stim	Age of first use
p2_5_anx	Symptom: Shortness of breath
p5_anxtk	Cause substance use
b_Anxiolytics	Ever used: Anxiolytics
i_ASPD_criterion_A	Criterion count
b7j_cany	Years: Cannabis
M_B	Criteria: Duration
e13_blko	Blackout
b7e_opi1	Years: Opiates
h_se_Var2	Abuse criteria: Use in hazardous situations
t4_8_pan	Symptom: Trembling
h10a_2_1	Withdrawal symptom: Restlessness
j33bx_ra	Incapacitated
h10b_oth	Two withdrawal symptoms occurred together
h10a_211	Withdrawal symptom: Twitching
p2_6_anx	Symptom: Heart racing
h_stDependence	Stimulant Dependence (DSM-IV)
h10a_14_	Withdrawal symptom: Increased heart rate
h_mj_Var1	Abuse criteria: Failure to fulfill obligations
h_se_DepBox6	Criteria: Withdrawal
h4_stimd	Craving
h_otAbuse	Other drug Abuse
j36a_epi	Age at diagnosis
j_boxf	Criteria: Fatigue

p2_16_an	Symptom: Difficulty concentrating
M_diago	Attention Deficit Hyperactivity Disorder
M_ADHD_HadTx	Sought treatment
h_st_Var4	Abuse criteria: Continued use despite social/interpersonal problems
p_criterion_A	Criteria: Excessive worry
h10a_1_s	Withdrawal symptom: Depressed mood
e26_10_wdfidg1	Withdrawal symptom: Restlessness
h_ot_Var2	Abuse criteria: Use in hazardous situations
i_ASPD_criterion_A2	Criteria: Deceitfulness
M_CritSum	Criterion count
h10a_1_o	Withdrawal symptom: Depressed mood
j_boxe	Criteria: Psychomotor agitation/retardation
h_mj_DepBox5	Criteria: Used more than intended
h10a_2_s	Withdrawal symptom: Restlessness
b3_9_liv	Liver disease
f12_5_st	Withdrawal symptom: Oversleeping
h10a_18_	Withdrawal symptom: Headaches
h_se_Var1	Abuse criteria: Failure to fulfill obligations
e26_8_wdache1	Withdrawal symptom: Headaches
e25_jump	Symptom of use: Nervousness
t4_1_pan	Symptom: Shortness of breath
t4_7_pan	Symptom: Sweating
h_mjAbuse	Marijuana Abuse
h10a_4_s	Withdrawal symptom: Insomnia
e1_alcev	Ever used: Alcohol
t_diago	Panic disorder
p2_11_an	Symptom: Flushes/chills
h_st_DepBox1	Criteria: Time spent obtaining/using
h_mj_DepBox7	Criteria: Continued use despite physical/psychological problems
h_se_DepBox4	Criteria: Reduction in other activties
h_ot_Var1	Abuse criteria: Failure to fulfill obligations
t4_5_pan	Symptom: Numbness/tingling
h10a_191	Withdrawal symptom: Anxiety
e26_2_wdinsom1	Withdrawal symptom: Insomnia
f18a_cocod	Symptom of use: Overdose
h10b_sed	Two withdrawal symptoms occurred together
p_criterion_E	Criteria: Significant distress
e1a_alca	Age of first use
z5_subst	Aware of household members using drugs and alcohol
b4b_ernu	Number of emergency room visits
h_st_DepBox5	Criteria: Used more than intended
z5_hmttt	Frequent drug/alcohol use in household
h4_sedde	Craving

t4_count	Symptom: Sum of reactions
h_ot_DepBox3	Criteria: Tolerance
i_ASPD_criterion_A2_1	Criteria: Deceitful
h_mj_Var2	Abuse criteria: Use in hazardous situations
s1_agpho	Ever agoraphobic
h_st_Var1	Abuse criteria: Failure to fulfill obligations
b7f_bar1	Years: Barbituates
h10a_171	Withdrawal symptom: Nausea
h10a_stim	Withdrawal symptom: Sum
o_CritCt	Criterion count
d17_jit	Symptom of use: Psychological problems
h_ot_DepBox7	Criteria: Continued use despite physical/psychological problems
h_se_DepBox3	Criteria: Tolerance
u_A10	Criteria: Relies on others for money
h10a_8_s	Withdrawal symptom: Change in appetite
h19b_sti	Age at diagnosis
e2a_5_ha	Reaction: Headache
z_1_others	Caregiver: Other
i_ASPD_criterion_A1_1	Crtiera: Stealing
M_C	Criteria: Impairment in two or more settings
j31_mse_	Hospitalization
h10a_4_o	Withdrawal symptom: Insomnia
b3_15_st	STD
h_st_DepBox6	Criteria: Withdrawal
h10a_7_o	Withdrawal symptom: Slowed down
h10a_3_o	Withdrawal symptom: Sleepy
g20b_opi	Age at diagnosis
d18_hprob	Symptom of use: Health problems
h4a_mjde	Age at desire
t4_9_pan	Symptom: Flushes/chills
t_criterion_B	Criteria: Concern about panic attacks
p2_14_on	Symptom: On edge
h10a_161	Withdrawal symptom: Fever
h10b_sti	Two withdrawal symptoms occurred together
t4_4_pan	Symptom: Chest tightness
j_boxd	Criteria: Insomnia/hypersomnia
h10d_sti	Withdrawal symptom: Intefere with functioining
u_Gamble_CritASum	Criterion count
h10a_othe	Withdrawal symptom: Sum
e_AlcAbWODep	Alcohol Abuse without Dependence
i_ASPD_criterion_A2_4	Criteria: Lied to get out of trouble
h10a_3_s	Withdrawal symptom: Sleepy
h10a_4_1	Withdrawal symptom: Insomnia

n2_suict	Suicide attempt
b3_10_th	Thyroid disease
h_mj_Var4	Abuse criteria: Continued use despite social/interpersonal problems
t4_13_pa	Symptom: Nausea
e25_hear	Symptom of use: Auditory hallucination
u_A1	Criteria: Preoccupation
n7_wantd	High suicidal intent
t4_2_pan	Symptom: Heart racing
d5_smkwo_conti	Smoke after waking
z_1_relatives	Caregiver: Other relative
t_criterion_count	Criterion count
h1b_hala	Age of first use
h1d_coma	Ever injected
d16_5_hsdsx	Withdrawal symptom: Decreased heart rate
t2	Frequent episodes
h10d_oth	Withdrawal symptom: Intefere with functioining
b3_8_hea	Heart disease
h4_mjdes	Craving
o_CritC	Criteria: Avoidance
s5_agphb	Age at diagnosis
o_CritE	Criteria: Duration
b_hos_hysterectomy	Hospital: hysterectomy
h10a_6_o	Withdrawal symptom: Craving
u_A5	Criteria: Gamble to escape from problems
u1a_gamm	Frequency of gambling
f12e_coc	Withdrawal symptom: Number times multiple symptoms
b4a_hosp	Hospital: overnight stay
h_st_DepBox7	Criteria: Continued use despite physical/psychological problems
h10a_141	Withdrawal symptom: Increased heart rate
h10a_121	Withdrawal symptom: Stomach ache
o_diago	Post Traumatic Stress Disorder
i_CD_criterion_B14	Criteria: Ran away
h_mj_DepBox3	Criteria: Tolerance
u_A4	Criteria: Irritability
a9_mstat_married	Ever married
h_ot_DepBox5	Criteria: Used more than intended
t4_12_pa	Symptom: Fear of going crazy
i_CD_criterion_B1	Criteria: Bullies/threatens others
i22a_vl	Age at diagnosis
h1a_sedn	Number of times used
b7g_sedy	Years: Sedatives
o_CritA	Criteria: Exposure to traumatic event
o_CritB	Criteria: Reexperiencing

b3_5_epi	Epilepsy/seizure
i_CD_criterion_A	Criteria: Persistant pattern of behavior
h1_pcp	Ever used: PCP
p2_8_anx	Symptom: Dry mouth
t1_pancd	Ever have panic attack
k29b_mas	Frequent episodes
o_CritF	Criteria: Significant distress
h4a_stim	Age at desire
h1b_coma	Age of first use
h_stAbuse	Stimulant Abuse
p2_1_anx	Symptom: Trembling
t_criterion_A	Criteria: Panic attacks
i_ASPD_criterion_A3	Criteria: Impulsivity
b_hos_infection	Hospital: infection
n1b_suic	Suicidal plan
h2b_mjpm	Days of use per month
i_ASPD_criterion_A2_2	Criteria: Assumed an alias
M_A	Criteria: Inattentive/Impulsive
j_boxi	Criteria: Suicidal ideation
e2a_sum	Number of reactions
t11_pand	Cause substance use
h10a_172	Withdrawal symptom: Nausea
k_I_B7	Criteria: Excessive pleasurable activities
h1b_otha	Age of first use
h10a_192	Withdrawal symptom: Anxiety
q_AgeOnsetOCD_O	Age at obession diagnosis
h10a_6_s	Withdrawal symptom: Craving
h10a_101	Withdrawal symptom: Paranoia
b7k_hal1	Years: Hallucinogens
q_O_C	Criteria: Significant distress
h19b_mj1	Age at diagnosis
h10a_221	Withdrawal symptom: Dizziness
i_ASPD_criterion_A4	Criteria: Irritability/aggression
h10a_162	Withdrawal symptom: Fever
h1a_stim	Number of times used
h_st_Var2	Abuse criteria: Use in hazardous situations
t4_10_pa	Symptom: Feeling that things are unreal
i_ASPD_criterion_A2_3	Criteria: Cheated on tasks
s6_agphb	Cause substance use
h10a_8_o	Withdrawal symptom: Change in appetite
h21	Sought treatment
h10a_7_s	Withdrawal symptom: Slowed down
i_CD_diago	Conduct Disorder

p2_2_anx	Symptom: Tense muscles
h10a_19_	Withdrawal symptom: Anxiety
h10a_9_o	Withdrawal symptom: Nightmares
i_ASPD_criterion_A6	Criteria: Irresponsibility
t9_panan	Anxiety between attacks
k_I_B5	Criteria: Distractable
p2_9_anx	Symptom: Dizziness
h_otAbWODep	Other drug Abuse without Dependence
i_ASPD_diago	Anti-Social Personality Disorder
q_diago	Obessessive Compulsive Disorder
b_hos_kidney	Hospital: kidney
u_A6	Criteria: Chase losses
q_C_B	Criteria: Recognize compulsions are excessive
l_A	Criteria: Characteristic symptoms
u_Gamble_CritA	Criteria: Persistant maladaptive behavior
k_I_B	Criteria: At least 3 symptoms
j_boxc	Criteria: Change in appetite/weight
M_ageonset	Age at diagnosis
h10a_13_	Withdrawal symptom: Pupil dilation
p6_anxag	Age at diagnosis
j29_mse_	Prescribed medication
i_CD_criterion_B3	Criteria: Used weapon
u_A2	Criteria: Increased money to achieve desired excitement
e25_smel	Symptom of use: Olfactory hallucination
h10a_6_m	Withdrawal symptom: Craving
q_OCD_O_Sum	Obession criterion count
f12f_coc	Withdrawal symptom: Length time multiple symptoms
l_ct	Criterion count
r_A	Criteria: Fear of social situations
g1a_opiu	Number of times used
h10a_22_	Withdrawal symptom: Dizziness
h1b_seda	Age of first use
h_ot_Var3	Abuse criteria: Legal problems
b_hos_childbirth	Hospital: childbirth
a8a_rac1_W_nH	Race: White
h10a_241	Withdrawal symptom: Hallucinations
t7d	Panic attack for no definable reason
l_B	Criteria: Social/occupational dysfunction
b4b_surg	Hospital: outpatient surgery
z2_moven	Frequency of moving
b3_14_hi	HIV/AIDS
h_st_DepBox3	Criteria: Tolerance
i_CD_criterion_B11	Criteria: Lying

i_CD_criterion_B2	Criteria: Initiates fights
i_CD_criterion_B	Criteria: Significant impairment
n8_think	Suicidal intent
b3_3_bra	Brain injury/concussion
q_O_B	Criteria: Recognize obsessions are excessive
s_diago	Agoraphobia
q_C_A	Criteria: Compulsions & repetitive behaviors
i_ASPD_criterion_A5	Criteria: Reckless disregard for safety
d21a_smk	Age at diagnosis
q_OCD_C_Sum	Compulsion criterion count
b3_4_unc	Unconscious > 5 min
k_I_B4	Criteria: Racing thoughts
h2b_3_mj	Age of frequent use
q_AgeOnsetOCD_C	Age at compulsion diagnosis
s_criterion_B	Criteria: Avoidance/distress
k29_mass	Rapid cycling
d4d_ciga	Age of frequent use
q_O_A	Criteria: Obsessional thoughts
g11e_pro	Withdrawal symptom: Number times multiple symptoms
f2_cocus	Age of first use
u_A8	Criteria: Illegal acts
e26_9_wdhear1	Withdrawal symptom: Hallucinations
b8_eprob	Emotional problems
i_ASPD_criterion_A1_3	Criteria: Forge signature
z3_witne	Witness/experience violent crime before age 13
u3_gampr	Cause problems
i_CD_criterion_B10	Criteria: Breaking/entering
i_CD_criterion_B9	Criteria: Vandalism
t4_11_pa	Symptom: Fear you might die
q_C_diago	OCD compulsion
h1a_haln	Number of times used
g2_opi1s	Age of first use
s_criterion_A	Criteria: Agoraphobic fears
h2b_3_st	Age of frequent use
a9_mstat_divorced	Divorced
h10a_8_m	Withdrawal symptom: Change in appetite
k_B_I_D	Bipolar I Disorder
d1d_toba	Age of first use
h4a_sedd	Age at desire
r_age	Age at diagnosis
e13a	Number of blackouts
d_TobDep_Box2	Criteria: Reduction in other activties
n2a_suic	Number of suicide attempts

h2b_stim	Days of use per month
h_mj_DepBox6	Criteria: Withdrawal
h1_sol	Ever used: Solvents
a8a_rac1_Other	Race: Other
b7l_inh1	IYears: nhalants
i_ASPD_criterion_A1_4	Criteria: Breaking/entering
g7_4_opi	Symptom of use: Hallucinations
f22b_exp	Age at diagnosis
e24_feet	Symptom of use: Feet numbness
h10a_4_m	Withdrawal symptom: Insomnia
a9_mstat_windowed	Widowed
a9_mstat_never_married	Never married
b3_11_as	Asthma
b_No_MedicalProbs	Number of medical problems
h10a_21_	Withdrawal symptom: Twitching
e24_memo	Symptom of use: Memory problems
b_Mood_stabilizer	Ever used: Mood stabilizers
a8a_rac1_W_H	Race: White Hispanic
h10d_mji	Withdrawal symptom: Intefere with functioining
b7d_met1	Years: Methadone
b3_1_hbp	High blood pressure
q_C_C	Criteria: Interference
h10a_212	Withdrawal symptom: Twitching
e3a_firs	Age of first intoxication
k_I_B2	Criteria: Decreased need for sleep
h1a_comn	Number of times used
z_child_adver	Childhood Adversity
h10a_111	Withdrawal symptom: Diarrhea
h2b_othp	Days of use per month
h2b_3_se	Age of frequent use
k2b_mani	Age at diagnosis
e25_seei	Symptom of use: Visual hallucination
u_A9	Criteria: Jeopardized relationships
h1a_othn	Number of times used
i_CD_criterion_B13	Criteria: Staying out at night
b_hos_pregnancy	Hospital: pregnancy
u1c_gama	Age of onset
u_A7	Criteria: Lies
b3_12_di	Diabetes
e24	Symptom of use: Number health problems
k_I_B6	Criteria: Increase in goal-directed activity
u_diago	Pathological Gambling
e24_live	Symptom of use: Liver Disease

h10a_181	Withdrawal symptom: Headaches
r_C	Criteria: Recognize fear is excessive
k_I_B3	Criteria: Talkative/pressured speech
e2a_6_pa	Reaction: Heart palpitations
h_mjAbWODep	Marijuana Abuse without Dependence
h10a_2_m	Withdrawal symptom: Restlessness
h10b_mj2	Two withdrawal symptoms occurred together
i_CD_criterion_B5	Criteria: Physically cruel to animals
t8_panag	Age at diagnosis
t4_6_pan	Symptom: Choking sensation
h10a_15_	Withdrawal symptom: Sweating
h19b_oth	Age at diagnosis
o_AgeOfCritAEvent	Age at diagnosis
k_I_ct	Criterion count
h10a_5_s	Withdrawal symptom: Oversleeping
l_C	Criteria: Duration
h10a_mj	Withdrawal symptom: Sum
r_D	Criteria: Avoidance/distress
j3a_mse_	Age at most severe episode
z_1_a4	Number of caregivers
u1_gambl	Ever gambled
i_ASPD_criterion_A2_5	Criteria: Enjoyment from deceit
z_lt	Lifetime Trauma Assessment
a9_mstat_separated	Separated
k_I_A	Criteria: Elevated/irritable mood
f1d_1_co	Age of regularly use
b_Any_MedicalProbs	Any medical problem
f3b_cocd	Days of use per month
j36_epis	Number of episodes
l15_psye	Age at diagnosis
r_B	Criteria: Situation provokes anxiety
g11f_pro	Withdrawal symptom: Length time multiple symptoms
r_E	Criteria: Significant impairment
h2b_sedp	Days of use per month
e2a_1_bl	Reaction: Flush
b3_13_ca	Cancer
b_Asthma_medications	Ever used: Asthma meds
e24_vomi	Symptom of use: Vomit blood
n12a_hrm	Self harm
k_I_D	Criteria: Impairment
e24_othe	Symptom of use: Other problems
b_hos_surgery	Hospital: surgery
b_hos_accident	Hospital: accident

f1a_cocl	Number of times used
h1a_pcpn	Number of times used
n12b_hrm	Age at self harm
a14b_sti	Number of miscarriages
j3b_mse_	Length of severe episode
h19b_sed	Age at diagnosis
e2a_3_sl	Reaction: Sleepy
a_BMI	BMI
z1b_prnt	Parental death before age 6
d5_smkwo_cate	Smoke after waking: categorical
n1a_suic	Suicidal ideation
i_CD_criterion_B12	Crtiera: Stealing (without confrontation)
h4a_othd	Age at desire
h1a_soln	Number of times used
n2b_suic	Age at first attempt
k29a_mas	Frequency of rapid cycling
a18_mili	Military service
i_ASPD_criterion_A1_6	Criteria: Vandalism
j28_mse_	Sought treatment
k_I_B1	Criteria: Grandiosity
h2b_3_ot	Age of frequent use
h_mj_DepBox2	Criteria: Unsuccessful effort to decrease use
b_hos_heart	Hospital: heart
h_mj_Var3	Abuse criteria: Legal problems
b3_16_il	Any other illness
e3_regag	Age of regular use
j19e_mse	Length of episode
b_hos_pneumonia	Hospital: pneumonia
r_count	Criterion count
s3a_count	Criterion count
b3_2_mig	Migraine
r_diago	Social phobia
k2c_mani	Length of episode
h1b_pcpa	Age of first use
a8a_rac1_NA_AI	Race: Native American
a8a_rac1_Asian	Race: Asian
a8a_rac1_PI	Race: Pacific Islander
a8a_rac1_AB_nH	Race: Black
a8a_rac1_AB_H	Race: Black Hispanic
b3_6_men	Meningitis/encephalitis
b3_7_str	Stroke
b_hos_asthma	Hospital: asthma
b_Hormone_replacement	Ever used: Hormone replacement

b_Lipid_lowering_drug	Ever used: Lipid lowering meds
b_Diabetes_treatment	Ever used: Diabates meds
e2a_2_hi	Reaction: Hives
e24_panc	Symptom of use: Pancreatitis
e24_yelj	Symptom of use: Yellow jaundice
e24_stdi	Symptom of use: Stomach Disease
e24_dmgh	Symptom of use: Heart damage
f18b_cochlthprobsp	Symptom of use: Other health problems
f_CocAbWODep	Cocaine Abuse without Dependence
g_OPAbWODep	Opiate Abuse without Dependence
h10a_9_s	Withdrawal symptom: Nightmares
h10a_10s	Withdrawal symptom: Paranoia
h10a_23_	Withdrawal symptom: Seizures
h10a_24_	Withdrawal symptom: Hallucinations
h10a_231	Withdrawal symptom: Seizures
h_st_Var3	Abuse criteria: Legal problems
h_se_Var3	Abuse criteria: Legal problems
h10a_10_	Withdrawal symptom: Paranoia
h10a_11_	Withdrawal symptom: Diarrhea
h10a_12_	Withdrawal symptom: Stomach ache
h_stAbWODep	Stimulant Abuse without Dependence
h10a_16_	Withdrawal symptom: Fever
h10a_17_	Withdrawal symptom: Nausea
h_seAbWODep	Sedative Abuse without Dependence
l_A1	Criteria: Delusions
l_A3	Criteria: Disorganized speech
l_A4	Criteria: Catatonic/disorganized behavior
l_A5	Criteria: Negative symptoms
l_diago	Schizophrenia
j20_mse_	Experienced hallucinations
j23	Episode caused by event
j30_mse_	Receive ECT
k_I_diago	Mania
k20_mncm	Prescribed medication
k_B_II_D	Bipolar II Disorder
i_CD_criterion_B4	Criteria: Physically cruel to people
i_CD_criterion_B6	Criteria: Stealing with confrontation
i_CD_criterion_B7	Criteria: Forced sexual activity
i_CD_criterion_B8	Criteria: Set fires
i_ASPD_criterion_A1_5	Criteria: Set fires
i_ASPD_criterion_A1_8	Criteria: Arrested for other reasons
M_ADHD_GotMeds	Prescribed medication
p2_12_an	Symptom: Frequent urination

p2_13_an	Symptom: Trouble swallowing
p_diago	Generalized Anxiety Disorder
q_O_diago	OCD obsession

e-Penn sample. Bonferroni correction threshold = 7.936508e-05 (0.05/630)

Group	beta	SE	OR	p	type
Opiate	0.27310459	0.03097444	1.31403767	1.17E-18	logistic
Opiate	0.26545549	0.03089455	1.30402481	8.52E-18	logistic
Opiate	0.26495933	0.03085909	1.30337796	9.00E-18	logistic
Opiate	0.26334917	0.03114314	1.301281	2.76E-17	logistic
Opiate	0.25951241	0.03080825	1.29629787	3.65E-17	logistic
Demographic	-0.1793882	0.02148481	NA	8.53E-17	linear
Opiate	0.25397973	0.03067199	1.28914567	1.23E-16	logistic
Opiate	0.51637485	0.06259493	NA	1.96E-16	linear
Cocaine	0.26532333	0.03254687	1.30385248	3.58E-16	logistic
Opiate	0.24753416	0.03047745	1.28086311	4.59E-16	logistic
Opiate	0.24734536	0.03124537	1.28062131	2.45E-15	logistic
Opiate	0.24211637	0.03068164	1.27394243	2.99E-15	logistic
Opiate	0.24152032	0.03086739	1.27318332	5.10E-15	logistic
Tobacco	0.25468914	0.03256888	1.29006053	5.28E-15	logistic
Opiate	0.24016422	0.03075829	1.27145793	5.81E-15	logistic
Opiate	0.2384896	0.03064136	1.2693305	7.07E-15	logistic
Opiate	0.23682158	0.03052445	1.267215	8.60E-15	logistic
Opiate	0.23580086	0.03053582	1.2659222	1.14E-14	logistic
Tobacco	0.29043816	0.03754023	NA	1.20E-14	linear
Opiate	0.23572331	0.03088413	1.26582402	2.30E-14	logistic
Cocaine	0.22965433	0.03014703	1.25816503	2.58E-14	logistic
Opiate	0.23483406	0.03082704	1.26469889	2.58E-14	logistic
Opiate	0.62030348	0.08123803	NA	2.62E-14	linear
Opiate	0.23329404	0.03083608	1.26275272	3.86E-14	logistic
Opiate	0.23406077	0.03095377	1.26372128	3.98E-14	logistic
Opiate	0.2348023	0.03115588	1.26465872	4.83E-14	logistic
Opiate	0.23317321	0.03106232	1.26260015	6.07E-14	logistic
Opiate	0.22850833	0.03096356	1.25672399	1.58E-13	logistic
Cocaine	0.22477984	0.03048988	1.25204703	1.68E-13	logistic
Opiate	0.22999949	0.03126325	1.25859937	1.88E-13	logistic
Opiate	0.23230202	0.03159362	1.26150067	1.94E-13	logistic
Opiate	0.23266327	0.03167469	1.26195647	2.05E-13	logistic
Cocaine	0.22622897	0.03088376	1.25386273	2.39E-13	logistic
Opiate	0.22861113	0.03154089	1.2568532	4.23E-13	logistic
Opiate	0.22353614	0.03096199	1.25049083	5.21E-13	logistic
Opiate	0.22269361	0.03087087	1.24943769	5.44E-13	logistic
Cocaine	0.21488174	0.02982117	1.23971527	5.78E-13	logistic
Opiate	0.22346279	0.03107349	1.25039911	6.41E-13	logistic
Cocaine	0.2156645	0.03010189	1.24068606	7.81E-13	logistic
Opiate	0.22074092	0.03087021	1.24700032	8.64E-13	logistic

Opiate	0.2475459	0.03477544	1.28087816	1.09E-12	logistic
Opiate	0.2245243	0.03154166	1.25172713	1.09E-12	logistic
Opiate	0.22181538	0.03124119	1.24834089	1.25E-12	logistic
Cocaine	0.20827564	0.02980685	1.23155258	2.80E-12	logistic
Tobacco	0.22076849	0.03160167	1.24703469	2.83E-12	logistic
Conduct Diso	0.22304237	0.0321492	1.24987353	3.98E-12	logistic
Cocaine	0.20431528	0.02961847	1.22668484	5.27E-12	logistic
Cocaine	0.42028385	0.06089633	NA	5.70E-12	linear
Tobacco	0.19963831	0.02920104	1.22096107	8.10E-12	logistic
Cocaine	0.20132504	0.02985137	1.22302224	1.54E-11	logistic
Opiate	0.14699697	0.02223523	NA	4.17E-11	linear
Opiate	0.20433175	0.03108359	1.22670504	4.91E-11	logistic
Tobacco	0.19011004	0.02900558	1.20938268	5.59E-11	logistic
Tobacco	0.19284146	0.0294665	1.21269052	5.97E-11	logistic
Cocaine	0.19473235	0.02988866	1.21498575	7.26E-11	logistic
Cocaine	0.19352187	0.02977622	1.21351593	8.07E-11	logistic
Medical	0.20542748	0.03222049	1.22804992	1.82E-10	logistic
Opiate	0.20344576	0.03201536	1.22561868	2.09E-10	logistic
Tobacco	0.18317787	0.0289779	1.20102801	2.59E-10	logistic
Cocaine	0.18509499	0.02961159	1.20333274	4.08E-10	logistic
Cocaine	0.18399714	0.0296881	1.20201238	5.73E-10	logistic
Alcohol	0.18078625	0.02970684	1.19815905	1.16E-09	logistic
Cocaine	0.18025271	0.02972799	1.19751995	1.33E-09	logistic
Tobacco	0.17550663	0.02896764	1.19184989	1.37E-09	logistic
Tobacco	0.17305649	0.02952732	1.18893326	4.60E-09	logistic
Tobacco	0.16803601	0.02876898	1.18297921	5.19E-09	logistic
Opiate	0.17970606	0.03121737	1.1968655	8.58E-09	logistic
Opiate	0.18597017	0.03233074	1.20438634	8.81E-09	logistic
Tobacco	0.1676643	0.02923075	1.18253957	9.70E-09	logistic
Opiate	0.18303503	0.03201512	1.20085647	1.08E-08	logistic
Alcohol	0.30401074	0.05332061	NA	1.25E-08	linear
Cocaine	0.16887376	0.02982262	1.18397067	1.49E-08	logistic
Opiate	0.19312391	0.03423986	1.2130331	1.70E-08	logistic
Alcohol	0.16660358	0.02968084	1.18128589	1.99E-08	logistic
Demographic	-0.1690934	0.03081569	NA	4.26E-08	linear
Alcohol	0.16039817	0.02952538	1.17397822	5.56E-08	logistic
Tobacco	0.15521124	0.02869718	1.16790464	6.35E-08	logistic
Cocaine	0.16226056	0.03030813	1.17616667	8.62E-08	logistic
Tobacco	0.15494979	0.03020314	1.16759934	2.89E-07	logistic
Cocaine	0.20962037	0.04085136	NA	2.97E-07	linear
Cocaine	0.17159665	0.03382578	1.18719888	3.92E-07	logistic
Cocaine	0.15328647	0.03031641	1.16565886	4.28E-07	logistic
Sedatives	0.15058073	0.02978375	1.16250915	4.29E-07	logistic

Tobacco	0.2363401	0.04695974	1.26660501	4.83E-07	logistic
Cocaine	0.15076501	0.03017199	1.1627234	5.83E-07	logistic
Tobacco	0.16856109	0.03415761	1.18360053	8.02E-07	logistic
Alcohol	0.14333593	0.02922413	1.15411744	9.36E-07	logistic
Demographic	-0.1666661	0.03403779	0.84648216	9.76E-07	logistic
Cocaine	0.14502542	0.02971382	1.15606896	1.06E-06	logistic
Alcohol	0.16639622	0.03476485	1.18104096	1.70E-06	logistic
Alcohol	0.14320936	0.0301735	1.15397137	2.07E-06	logistic
Alcohol	0.14074823	0.02979195	1.15113479	2.31E-06	logistic
Cocaine	0.14494053	0.03100281	1.15597083	2.94E-06	logistic
Marijuana	0.14170219	0.0305424	1.15223345	3.49E-06	logistic
Alcohol	0.16009419	0.03470906	1.17362141	3.98E-06	logistic
Tobacco	0.13230023	0.0291287	1.14145097	5.57E-06	logistic
Alcohol	0.14273766	0.03145614	1.15342718	5.69E-06	logistic
Other drug	0.15609407	0.03443683	1.16893616	5.82E-06	logistic
Cocaine	0.13298381	0.02980864	1.1422315	8.15E-06	logistic
Sedatives	0.13315942	0.02991385	1.14243211	8.53E-06	logistic
Cocaine	0.18796245	0.04264719	1.20678819	1.05E-05	logistic
Tobacco	0.13099046	0.03033869	1.1399569	1.58E-05	logistic
Cocaine	0.1314329	0.03049256	1.14046138	1.63E-05	logistic
Cocaine	0.13672425	0.03183881	1.14651195	1.75E-05	logistic
Medical	0.47011404	0.10941731	NA	1.76E-05	linear
Alcohol	0.13472327	0.03150905	1.1442201	1.91E-05	logistic
Cocaine	0.13199106	0.03097039	1.14109812	2.03E-05	logistic
Demographic	0.07399335	0.01755613	NA	2.54E-05	linear
Tobacco	0.12262435	0.02921896	1.13045968	2.71E-05	logistic
Tobacco	0.12600729	0.03010503	1.13429043	2.84E-05	logistic
Alcohol	0.12536764	0.03001186	1.13356511	2.95E-05	logistic
Tobacco	0.12530087	0.03023112	1.13348943	3.40E-05	logistic
Medical	0.1965211	0.04770893	1.217161	3.80E-05	logistic
Alcohol	0.12404596	0.03013071	1.1320679	3.84E-05	logistic
Sedatives	0.2180257	0.05328449	1.24361903	4.28E-05	logistic
Opiate	0.20390121	0.05063221	1.22617701	5.65E-05	logistic
Alcohol	0.12101218	0.03043471	1.12863866	7.00E-05	logistic
Marijuana	0.14163101	0.03580003	1.15215144	7.62E-05	logistic
Medical	0.32198086	0.08135767	NA	7.66E-05	linear
Alcohol	0.13782113	0.03487421	1.14777022	7.75E-05	logistic
Alcohol	0.12345611	0.03127843	1.13140035	7.91E-05	logistic
Alcohol	0.12135452	0.03080106	1.1290251	8.15E-05	logistic
Marijuana	0.1490445	0.03796919	1.16072464	8.66E-05	logistic
Other drug	0.13708103	0.03494717	1.14692108	8.76E-05	logistic
Alcohol	0.11512282	0.03020132	1.12201124	0.00013793	logistic
Tobacco	0.12574465	0.03316721	1.13399256	0.0001499	logistic

Sedatives	0.256275	0.06762468	1.29210801	0.00015085	logistic
Depression	0.10839846	0.02861203	1.11449173	0.00015152	logistic
Alcohol	0.07676267	0.02033079	NA	0.0001612	linear
Other drug	0.13813651	0.03671935	1.14813227	0.00016859	logistic
Cocaine	0.11409814	0.03047639	1.12086212	0.00018124	logistic
Sedatives	0.17763533	0.04745692	1.19438968	0.00018177	logistic
Alcohol	0.11073575	0.02975035	1.11709968	0.00019752	logistic
Stimulants	0.15266722	0.04101949	1.16493724	0.00019779	logistic
Sedatives	0.15137826	0.04097997	1.16343666	0.00022079	logistic
Marijuana	-0.2250448	0.06105233	NA	0.00023033	linear
Sedatives	0.13354508	0.03626428	1.14287279	0.00023091	logistic
Other drug	0.15982683	0.04366551	1.17330767	0.00025197	logistic
Alcohol	0.11610063	0.03174579	1.12310888	0.00025499	logistic
Alcohol	0.11159406	0.03067062	1.1180589	0.00027426	logistic
Sedatives	0.16653218	0.04649821	1.18120155	0.00034166	logistic
Stimulants	0.10974474	0.03083404	1.11599316	0.00037198	logistic
Depression	0.10033232	0.02833985	1.10553825	0.00039963	logistic
Medical	0.0871167	0.02477755	NA	0.0004416	linear
Cocaine	0.179935	0.0523438	1.19713955	0.00058698	logistic
Stimulants	0.10590838	0.03090607	1.11172002	0.00061078	logistic
Sedatives	0.11446975	0.03350094	NA	0.0006378	linear
Depression	0.10005805	0.02939588	1.10523507	0.00066452	logistic
Other drug	0.18866025	0.05554758	1.20763059	0.00068285	logistic
Medical	0.28876176	0.08512472	NA	0.00069809	linear
Sedatives	0.16012084	0.0474676	1.17365269	0.00074282	logistic
Cocaine	0.11649668	0.03465623	1.12355378	0.00077522	logistic
Depression	0.0943285	0.02810603	1.09892068	0.00079031	logistic
Opiate	0.17558437	0.05249978	1.19194255	0.00082438	logistic
Medical	0.21715144	0.06497804	NA	0.0008374	linear
Other drug	0.09933775	0.02975246	1.10443927	0.00084139	logistic
Marijuana	0.10560652	0.03179668	1.11138448	0.00089597	logistic
Depression	0.09203404	0.02807551	1.09640215	0.00104512	logistic
Anxiety	0.11676364	0.03575157	NA	0.00109739	linear
Opiate	0.14752761	0.04519714	1.15896529	0.00109816	logistic
Marijuana	0.11411634	0.03508779	1.12088252	0.00114472	logistic
Anxiety	0.22631546	0.07039915	1.25397118	0.00130559	logistic
Anxiety	0.22750808	0.07098777	1.25546758	0.00135113	logistic
Alcohol	0.12127465	0.03796344	1.12893493	0.00140068	logistic
Marijuana	0.10176784	0.03203967	1.10712641	0.00149163	logistic
Sedatives	0.16839626	0.05304903	1.18340545	0.00150172	logistic
Sedatives	0.1719537	0.05432037	1.18762285	0.00154791	logistic
Anxiety	0.26657712	0.08424944	1.30548826	0.00155541	logistic
Alcohol	0.15179291	0.04818757	1.16391917	0.00163246	logistic

Medical	0.04482802	0.0142315	NA	0.00164166	linear
Alcohol	0.09967009	0.03168745	1.10480637	0.00165853	logistic
Other drug	0.13487643	0.0430004	1.14439537	0.00170901	logistic
Depression	0.15599856	0.04984192	NA	0.00175773	linear
Anxiety	0.21129102	0.06765411	1.23527179	0.00178953	logistic
Sedatives	0.17902634	0.05740536	1.19605225	0.00181691	logistic
Anti-Social Pe	0.10794645	0.03469949	1.11398809	0.00186522	logistic
Stimulants	0.17609146	0.05663645	1.19254712	0.00187624	logistic
Alcohol	0.11285597	0.03639758	1.11947069	0.00193099	logistic
Anxiety	0.10414915	0.03371817	1.10976597	0.00200958	logistic
Sedatives	0.10124098	0.03282328	NA	0.00204925	linear
Other drug	0.13443695	0.04362597	1.14389253	0.00205905	logistic
Suicide	0.17056434	0.05535423	1.18597395	0.00206082	logistic
Anxiety	0.19700535	0.06395905	1.21775056	0.00206876	logistic
Alcohol	0.17479068	0.05712268	1.19099689	0.00221398	logistic
Depression	0.08767483	0.02866945	1.0916331	0.00222725	logistic
Anti-Social Pe	0.08823357	0.02914083	1.09224321	0.00246314	logistic
Conduct Diso	0.13066082	0.04323569	1.1395812	0.00251061	logistic
Sedatives	0.16139641	0.0535352	1.17515072	0.00257173	logistic
Environment	-0.1356516	0.04507168	0.8731468	0.00261518	logistic
Sedatives	0.18862998	0.06282292	1.20759403	0.00267714	logistic
Other drug	0.12711994	0.04270902	1.13555321	0.00291636	logistic
Other drug	0.11827077	0.03977604	NA	0.00295741	linear
Anti-Social Pe	0.08960425	0.03022377	1.09374135	0.00302983	logistic
Other drug	0.09936681	0.03372508	1.10447135	0.0032152	logistic
Environment	0.09450834	0.03208807	1.09911833	0.00322662	logistic
Anti-Social Pe	0.09598761	0.03276338	1.10074542	0.00339265	logistic
PTSD	0.13546294	0.04636537	1.14506675	0.00348193	logistic
Stimulants	0.11942901	0.04109884	1.12685325	0.00366202	logistic
Marijuana	1.66203937	0.57696016	NA	0.00398744	linear
Depression	0.08023247	0.02792451	1.08353893	0.00406348	logistic
Alcohol	0.0847251	0.02950601	1.08841782	0.0040859	logistic
Anxiety	0.23018249	0.08017889	1.25882972	0.00409355	logistic
Anxiety	0.17929379	0.06267895	1.19637217	0.0042296	logistic
Other drug	0.09614462	0.03361957	1.10091827	0.00423933	logistic
Other drug	0.14311882	0.05014297	1.1538669	0.00431433	logistic
Medical	0.08150356	0.02872937	1.08491707	0.00455479	logistic
ADHD	0.09778068	0.03464473	NA	0.00478341	linear
Marijuana	0.11730164	0.04171975	NA	0.0049456	linear
Stimulants	0.19066709	0.06788087	1.21005655	0.0049719	logistic
Medical	-0.246266	0.08807249	0.78171427	0.00517116	logistic
Stimulants	0.12954341	0.04646202	1.13830852	0.00530089	logistic
Other drug	-0.8623746	0.30816544	NA	0.00537018	linear

Sedatives	0.14084985	0.05060722	1.15125177	0.00538262	logistic
PTSD	0.10033527	0.03608307	1.10554152	0.00542461	logistic
Panic Disorde	0.11378939	0.04094337	1.12051611	0.00544947	logistic
Gambling	0.21177823	0.07644821	1.23587377	0.00560187	logistic
Anti-Social Pe	0.0907706	0.03278411	1.09501778	0.00562739	logistic
Anxiety	0.25566133	0.09234384	1.29131533	0.00563011	logistic
Anxiety	0.03065006	0.01108218	NA	0.0056984	linear
Alcohol	0.12311671	0.04456777	1.13101642	0.00573675	logistic
ADHD	0.11308685	0.0409253	NA	0.00574133	linear
Other drug	0.12171051	0.04410088	1.1294271	0.00578331	logistic
Stimulants	0.0748321	0.02711779	NA	0.00580718	linear
ADHD	0.18095193	0.06579451	1.19835758	0.00595482	logistic
Alcohol	0.08634587	0.03140274	1.09018332	0.00596629	logistic
Medical	0.33641556	0.12309124	NA	0.00629443	linear
Other drug	0.12146812	0.04470362	1.12915337	0.00658393	logistic
Suicide	0.20342168	0.07495948	1.22558916	0.00665253	logistic
Other drug	0.12977854	0.04826653	1.1385762	0.00717116	logistic
Anxiety	0.19139176	0.0712414	1.21093375	0.00721997	logistic
Schizophrenia	0.20527289	0.07652247	1.22786008	0.00730702	logistic
Stimulants	-0.3652228	0.13619636	NA	0.00739678	linear
Anxiety	0.24294127	0.09119035	1.27499375	0.00771919	logistic
Anxiety	0.20961346	0.07878845	1.23320128	0.00780342	logistic
Medical	0.10091151	0.0379526	1.10617875	0.00784002	logistic
Anti-Social Pe	0.07858155	0.02955566	1.08175157	0.00784277	logistic
Medical	0.26138132	0.09860071	NA	0.00804993	linear
ADHD	0.12005287	0.04541001	1.12755647	0.00819924	logistic
Alcohol	0.07641804	0.02893064	1.07941372	0.00825588	logistic
Medical	0.11766656	0.04479924	NA	0.00864923	linear
Sedatives	0.11921888	0.04577138	1.12661649	0.00919654	logistic
Panic Disorde	0.10712283	0.04117275	1.11307096	0.00927387	logistic
Sedatives	0.13178023	0.05073447	1.14085756	0.00939189	logistic
Depression	-0.0946334	0.03644043	0.90970634	0.00940598	logistic
Other drug	0.11561956	0.04466798	1.12256872	0.0096417	logistic
Sedatives	0.17977089	0.06968043	1.1969431	0.00988193	logistic
Anxiety	0.21091993	0.08202715	1.23481348	0.0101305	logistic
Other drug	0.14188618	0.05527006	1.15244547	0.01025401	logistic
Sedatives	0.18365375	0.07160287	1.20159969	0.01032074	logistic
Marijuana	0.09850326	0.03862302	1.103518	0.01076064	logistic
Sedatives	0.1207169	0.04750301	1.12830545	0.01104578	logistic
Stimulants	0.16628784	0.06567266	1.18091297	0.0113391	logistic
Sedatives	0.09614955	0.03798169	1.1009237	0.01135851	logistic
Depression	-0.578022	0.22830833	NA	0.01141423	linear
Depression	0.07074683	0.0279897	1.07330947	0.01148443	logistic

Anxiety	0.17921272	0.07091727	1.19627519	0.01150194	logistic
ADHD	0.17145593	0.06857011	1.18703183	0.01240367	logistic
ADHD	0.15789365	0.06316417	1.17104165	0.01242864	logistic
Stimulants	0.16289274	0.06542312	1.17691044	0.01278026	logistic
Anxiety	0.15663481	0.0631273	1.16956842	0.01309213	logistic
Stimulants	0.16173971	0.06532469	1.17555422	0.01328876	logistic
Alcohol	0.07898233	0.03194048	1.0821852	0.01340602	logistic
Other drug	0.10331775	0.04218515	1.10884369	0.01431938	logistic
Anti-Social Pe	0.07363952	0.03009835	1.07641871	0.01441987	logistic
ADHD	0.03448814	0.01417316	NA	0.01499086	linear
Other drug	0.11905979	0.04894476	1.12643727	0.01499359	logistic
Depression	0.07196125	0.02958515	1.07461371	0.01500146	logistic
Marijuana	0.08044547	0.03313072	1.08376975	0.01517718	logistic
Stimulants	0.15350486	0.06329614	1.16591345	0.01530058	logistic
Medical	0.09538939	0.03944025	1.10008714	0.01558123	logistic
Cocaine	0.07876518	0.03258008	1.08195023	0.0156238	logistic
Sedatives	0.16244833	0.06733254	1.17638753	0.015838	logistic
Sedatives	0.13302239	0.05525232	1.14227558	0.01606023	logistic
Alcohol	0.08453172	0.03531493	1.08820736	0.01668149	logistic
Alcohol	0.09378277	0.03918113	1.09832114	0.01668531	logistic
Panic Disorde	0.09258327	0.03872777	1.09700449	0.01682009	logistic
Panic Disorde	0.09411124	0.03943338	1.09868196	0.01700554	logistic
Stimulants	0.07240084	0.03048375	1.0750862	0.01754594	logistic
Stimulants	0.16152713	0.06802609	1.17530434	0.01757331	logistic
Alcohol	0.24949718	0.10519336	1.28337994	0.01770187	logistic
Panic Disorde	0.11877524	0.05008251	1.12611679	0.01771168	logistic
Anxiety	0.24057173	0.10170012	1.27197617	0.0180057	logistic
Stimulants	0.14471746	0.06124095	1.15571299	0.01812359	logistic
Marijuana	0.0896005	0.03793906	1.09373724	0.01819158	logistic
Sedatives	0.1267718	0.05376989	1.13515794	0.0183899	logistic
Other drug	0.11143498	0.04744583	1.11788105	0.01884021	logistic
Panic Disorde	0.12358821	0.05269707	1.13154982	0.01901392	logistic
Sedatives	0.11795992	0.05050664	1.12519902	0.01951559	logistic
Alcohol	0.07785853	0.03348657	1.08096972	0.02006835	logistic
Cocaine	0.12107136	0.05244632	1.12870545	0.02097237	logistic
Sedatives	0.11254852	0.04885157	1.11912655	0.02122896	logistic
Anxiety	0.17504938	0.07600566	1.19130504	0.02127266	logistic
Alcohol	-0.1117243	0.04849861	NA	0.02127838	linear
Environment	0.06607256	0.0290314	1.06830423	0.02285201	logistic
Medical	0.28635377	0.12625291	NA	0.02336112	linear
Stimulants	0.12595226	0.05568935	1.13422802	0.02371634	logistic
Environment	0.0674231	0.02989695	1.06974799	0.02412183	logistic
Sedatives	0.12908148	0.05748749	1.13778283	0.0247435	logistic

Panic Disorde	0.09541535	0.04259653	NA	0.02513097	linear
Other drug	0.09557039	0.04271446	1.10028627	0.02525859	logistic
Anti-Social Pe	0.07561085	0.03399843	1.07854277	0.02615171	logistic
Marijuana	0.07068094	0.03178762	1.07323874	0.02617966	logistic
Agoraphobia	0.0772022	0.03517703	1.08026048	0.02818683	logistic
Stimulants	0.16512081	0.07544032	1.17953561	0.02861423	logistic
Medical	0.04054658	0.01854974	NA	0.02886875	linear
Sedatives	0.17296293	0.07919133	1.18882204	0.02895384	logistic
Stimulants	0.04804838	0.02204241	NA	0.02931213	linear
PTSD	0.06233089	0.02865441	NA	0.02965166	linear
Tobacco	0.09509488	0.04437285	1.0997632	0.0321061	logistic
Other drug	0.08490589	0.03986475	1.08861461	0.03318408	logistic
Sedatives	0.10164837	0.04773395	1.10699415	0.03321476	logistic
Gambling	0.11305696	0.05335895	1.11969571	0.03410735	logistic
Stimulants	0.12334756	0.05839712	1.13127754	0.0346676	logistic
Stimulants	-0.9137805	0.43200138	NA	0.03508042	linear
Alcohol	0.11013683	0.05270131	1.11643082	0.03663299	logistic
Environment	0.19905162	0.09531971	1.22024496	0.03677505	logistic
Anti-Social Pe	0.09945628	0.04770095	1.10457018	0.03706967	logistic
ADHD	0.09980169	0.0481671	1.10495177	0.0382665	logistic
Depression	0.12043298	0.05850759	1.12798514	0.03955019	logistic
Other drug	0.10399701	0.05054856	1.10959714	0.0396508	logistic
Medical	0.08613664	0.04188946	1.08995525	0.03975513	logistic
Stimulants	0.11260028	0.054951	1.11918448	0.04045202	logistic
Other drug	0.10817116	0.05296665	1.11423844	0.04112671	logistic
Other drug	0.09645315	0.04753878	1.10125798	0.04246478	logistic
Opiate	0.29469188	0.14527254	NA	0.04262238	linear
Tobacco	0.06742366	0.03337755	1.0697486	0.04338023	logistic
Marijuana	-0.3555757	0.17760573	NA	0.04554978	linear
Panic Disorde	0.08504513	0.04261422	1.0887662	0.04596675	logistic
Panic Disorde	0.08164779	0.04092909	1.08507357	0.04605818	logistic
Anxiety	0.14311733	0.07213208	1.15386518	0.04724459	logistic
Sedatives	0.1895516	0.09555063	1.20870749	0.04728017	logistic
Stimulants	0.11063238	0.05585096	1.11698421	0.04760807	logistic
Panic Disorde	0.08251263	0.04179371	1.08601239	0.04834949	logistic
Depression	0.05536292	0.02805023	1.05692412	0.04841518	logistic
Stimulants	0.12925018	0.0654876	1.13797478	0.04842055	logistic
Gambling	0.04974174	0.02520254	NA	0.04846687	linear
Other drug	0.1091382	0.05540257	NA	0.04889695	linear
Alcohol	-0.0850914	0.04324377	0.91842835	0.04910095	logistic
Anti-Social Pe	0.06143814	0.03127179	1.06336472	0.04945467	logistic
Stimulants	0.113348	0.05782464	1.12002164	0.04997214	logistic
Sedatives	0.09948776	0.05082608	1.10460495	0.05029863	logistic

Suicide	0.08377104	0.04297148	1.0873799	0.05124088	logistic
Medical	-0.1253292	0.06459342	0.8822064	0.05234584	logistic
Marijuana	0.06646687	0.03425878	1.06872555	0.05236253	logistic
Panic Disorde	0.09199802	0.04760849	1.09636265	0.0533118	logistic
Alcohol	0.13975235	0.07244479	1.14998897	0.05371996	logistic
Gambling	0.0691692	0.03631456	1.07161751	0.05681602	logistic
Suicide	0.09739941	0.05163537	1.10230056	0.05925554	logistic
Panic Disorde	0.0702096	0.03730256	1.072733	0.05981354	logistic
Tobacco	-1.014273	0.54256927	NA	0.0616556	linear
Environment	0.11245148	0.06018136	1.11901796	0.06168638	logistic
Panic Disorde	0.01627428	0.00872818	NA	0.0622937	linear
Other drug	-0.1615507	0.08696132	NA	0.0633296	linear
Other drug	0.11497348	0.06192839	1.12184368	0.06337444	logistic
Tobacco	0.1043253	0.05659848	1.10996147	0.06529211	logistic
Panic Disorde	0.08696082	0.04721464	1.09085394	0.0655016	logistic
Other drug	0.08811358	0.04788121	1.09211216	0.06573094	logistic
Medical	-0.1442876	0.07847222	0.86563879	0.06595804	logistic
Marijuana	0.0683601	0.03721283	1.07075082	0.0662094	logistic
PTSD	0.05812448	0.03192235	1.05984692	0.06863602	logistic
Agoraphobia	-1.039555	0.57282573	NA	0.07019172	linear
PTSD	0.07043531	0.03901698	1.07297516	0.07103595	logistic
Medical	0.17327504	0.09619408	1.18919314	0.07165454	logistic
Other drug	0.08810941	0.04903729	1.09210761	0.07236992	logistic
Gambling	0.11885066	0.06658051	1.12620172	0.07425047	logistic
Gambling	-0.0295291	0.01667426	NA	0.07663608	linear
Cocaine	-58.248418	33.0656554	NA	0.0783471	linear
Medical	0.09159873	0.05205421	NA	0.07851637	linear
Stimulants	0.10281008	0.05863693	1.1082809	0.0795448	logistic
Other drug	0.10687317	0.06149198	1.11279312	0.08221047	logistic
Other drug	0.09790244	0.05633192	1.10285519	0.08221842	logistic
PTSD	0.07493565	0.04315965	1.07781479	0.08252087	logistic
Conduct Diso	0.14846723	0.08552273	1.16005478	0.08256432	logistic
Marijuana	0.0577121	0.03350113	1.05940995	0.08494439	logistic
Gambling	0.12111388	0.07053599	1.12875345	0.08596988	logistic
Demographic	-0.0614583	0.03579501	0.94039213	0.0859879	logistic
Other drug	0.07254932	0.04237685	1.07524583	0.08689599	logistic
Panic Disorde	0.07607043	0.04461444	1.07903857	0.08818268	logistic
Conduct Diso	0.10055933	0.05936004	1.10578925	0.09025433	logistic
Conduct Diso	-0.6064641	0.35782068	NA	0.09033073	linear
Sedatives	1.68872093	1.0022062	NA	0.09214517	linear
Medical	0.05161003	0.03070001	NA	0.09279712	linear
PTSD	0.04676019	0.02787795	1.04787069	0.09348035	logistic
PTSD	0.05219506	0.03114199	1.05358123	0.09373138	logistic

Medical	0.09522515	0.05721237	1.09990647	0.09602946	logistic
Conduct Diso	0.06541173	0.03931443	1.06759849	0.09615046	logistic
Other drug	0.06522331	0.03929538	1.06739736	0.0969504	logistic
Anxiety	0.16256788	0.09882451	1.17652818	0.09996656	logistic
Panic Disorde	0.05904955	0.03625776	1.0608278	0.10339679	logistic
Mania	0.14179105	0.08759603	1.15233584	0.10551342	logistic
PTSD	0.06338519	0.03924998	1.06543716	0.10633019	logistic
Stimulants	-0.893401	0.5526009	NA	0.1071467	linear
Other drug	0.34903686	0.21669434	NA	0.10750478	linear
Marijuana	0.08057468	0.05027413	1.08390979	0.10899947	logistic
Anxiety	0.1474268	0.09293444	1.15884846	0.1126593	logistic
Panic Disorde	0.06466582	0.04078839	1.06680246	0.11287597	logistic
Anti-Social Pe	0.04875537	0.03083852	1.04996346	0.11388054	logistic
Medical	0.11438605	0.072749	1.12118487	0.1158721	logistic
Suicide	0.07326909	0.04686247	1.07602004	0.11793695	logistic
Marijuana	0.25094567	0.16193712	NA	0.12131315	linear
Anti-Social Pe	0.10037121	0.06482544	1.10558125	0.1215427	logistic
ADHD	0.05017768	0.03249095	1.0514579	0.1225015	logistic
Depression	0.04707316	0.03064505	1.04819869	0.12451955	logistic
Alcohol	0.02133427	0.01401941	NA	0.1281233	linear
Panic Disorde	0.06551355	0.04344345	1.06770721	0.13154965	logistic
Other drug	0.09201279	0.06127354	1.09637884	0.13318175	logistic
Mania	0.09777222	0.06519326	1.10271158	0.13368463	logistic
Other drug	0.25824826	0.17243436	NA	0.13442409	linear
Other drug	0.07427434	0.04997394	1.07710226	0.13720992	logistic
OCD	-2.5027894	1.68434473	NA	0.1405452	linear
Stimulants	0.09580835	0.06510804	1.10054812	0.14114817	logistic
Other drug	0.12612493	0.08592194	1.13442388	0.14213104	logistic
Medical	0.02415168	0.01650661	NA	0.14348119	linear
OCD	0.1524821	0.10472355	1.16472162	0.14538044	logistic
Marijuana	-0.1888793	0.12986863	NA	0.14604328	linear
Other drug	0.10463767	0.07235461	1.11030824	0.14812719	logistic
Anti-Social Pe	0.0423867	0.0293955	1.04329784	0.14931779	logistic
Other drug	0.10043415	0.06984092	1.10565083	0.15042225	logistic
Stimulants	1.59401432	1.1086952	NA	0.15071076	linear
Stimulants	0.08222472	0.05742695	1.08569977	0.15219701	logistic
Panic Disorde	0.0723807	0.05066175	1.07506454	0.15308903	logistic
Anti-Social Pe	0.08974803	0.06282716	1.09389862	0.15315057	logistic
Agoraphobia	0.0847624	0.05950693	1.08845842	0.1543272	logistic
Other drug	0.06851047	0.04836149	1.07091184	0.15659029	logistic
Other drug	0.05110185	0.03615037	1.05243008	0.15748198	logistic
Stimulants	0.09711271	0.06876869	1.10198457	0.15790149	logistic
Conduct Diso	0.11677113	0.08328903	1.12386218	0.16091557	logistic

Anxiety	0.11817127	0.08510775	1.12543684	0.16498786	logistic
Marijuana	0.05556119	0.040339	1.0571337	0.16840198	logistic
Other drug	0.09625383	0.07067056	1.10103851	0.17319551	logistic
Anti-Social Pe	0.03977769	0.02924401	1.04057941	0.17376684	logistic
Panic Disorde	0.06187995	0.04585206	1.06383463	0.17715826	logistic
Mania	0.07540388	0.05611787	1.07831957	0.17905521	logistic
Anxiety	0.13853967	0.10330643	1.14859524	0.17990241	logistic
Other drug	0.12370585	0.0927784	1.13168294	0.1824178	logistic
Anti-Social Pe	0.05806549	0.04434973	1.0597844	0.19044499	logistic
OCD	0.1047847	0.08007069	1.1104715	0.19065212	logistic
Medical	0.1191435	0.09113486	1.12653156	0.19110005	logistic
Gambling	0.05772334	0.04442048	1.05942186	0.19378071	logistic
OCD	0.09222889	0.07205557	1.09661579	0.20055607	logistic
Schizophrenia	0.07998523	0.06252214	1.08327106	0.20078776	logistic
Gambling	0.07426397	0.05812273	1.07709109	0.20135182	logistic
Mania	0.06972407	0.0547381	1.07221228	0.20274285	logistic
Depression	0.03546484	0.02807155	1.03610122	0.20645515	logistic
ADHD	-0.1905912	0.15104013	NA	0.20722815	linear
Other drug	0.06582225	0.05223525	1.06803685	0.20762909	logistic
Anxiety	-0.9593282	0.76374998	NA	0.2101544	linear
Depression	0.0440414	0.03518867	1.04502562	0.21072329	logistic
Conduct Diso	-0.1271448	0.10254065	0.88060615	0.21499561	logistic
Gambling	0.06276944	0.05208895	1.06478131	0.22818658	logistic
Alcohol	0.12708725	0.10566718	1.13551609	0.22908756	logistic
Marijuana	0.04523077	0.03762062	1.04626928	0.2292524	logistic
OCD	0.00681183	0.00566676	NA	0.22938754	linear
Cocaine	-0.9541903	0.79532214	NA	0.23037132	linear
Schizophrenia	0.00667103	0.00556622	NA	0.2307788	linear
Social Phobia	0.03846752	0.03217698	1.03921698	0.23189248	logistic
Opiate	117.219527	98.1030024	NA	0.23229916	linear
Sedatives	0.09255955	0.07765728	1.09697847	0.23330125	logistic
Sedatives	-0.1958847	0.16464965	NA	0.23429031	linear
Other drug	0.10621439	0.09048655	1.11206026	0.24046951	logistic
Medical	0.05453633	0.04662041	1.05605084	0.24208338	logistic
Demographic	-0.0903757	0.07754437	0.91358784	0.24382822	logistic
Other drug	0.12126187	0.10447759	1.1289205	0.24578444	logistic
Panic Disorde	0.04986906	0.04315531	1.05113346	0.24785626	logistic
Schizophrenia	0.11653421	0.10145757	1.12359594	0.25072077	logistic
Medical	-0.0353788	0.03091957	NA	0.25258027	linear
Environment	0.03896832	0.03413867	NA	0.25372475	linear
Medical	0.1085766	0.09515491	1.1146903	0.25384872	logistic
Stimulants	0.06718257	0.05917484	1.06949072	0.25623991	logistic
Conduct Diso	0.03843892	0.03392172	1.03918726	0.25714472	logistic

Conduct Diso	0.03605467	0.03182248	1.03671252	0.25721684	logistic
Conduct Diso	0.0443532	0.03939207	1.0453515	0.2601899	logistic
Suicide	0.05715515	0.05084866	1.05882007	0.26100259	logistic
Medical	-0.0409364	0.03660951	0.95989019	0.26348583	logistic
OCD	0.11012631	0.09861374	1.11641908	0.26410377	logistic
Agoraphobia	0.07557689	0.06781616	1.07850615	0.26509139	logistic
OCD	0.07619148	0.06859769	1.0791692	0.26669733	logistic
Anti-Social Pe	-0.0324515	0.02952918	0.96806942	0.27178411	logistic
Tobacco	0.15326178	0.1400636	NA	0.27394214	linear
OCD	0.00805849	0.00745351	NA	0.27966865	linear
Medical	0.04238663	0.03935514	1.04329777	0.28146732	logistic
Mania	0.06469102	0.060883	1.06682935	0.28798758	logistic
Marijuana	-0.0970644	0.09167183	NA	0.28975078	linear
OCD	-1.0915616	1.02854569	NA	0.28988121	linear
Agoraphobia	0.0622156	0.05882946	1.06419176	0.29025672	logistic
Mania	0.07326034	0.06941577	1.07601063	0.29124937	logistic
Tobacco	0.10547975	0.10011267	NA	0.29212758	linear
OCD	0.09599498	0.09164639	1.10075354	0.29489222	logistic
Opiate	-1.0486012	1.01647229	NA	0.30240398	linear
Cocaine	-0.0933943	0.09056158	NA	0.30247634	linear
Gambling	0.07377223	0.07267307	1.07656157	0.31004636	logistic
Alcohol	0.07762376	0.07663977	1.08071597	0.31113701	logistic
Medical	0.03475884	0.03467061	1.03536999	0.31608048	logistic
Anti-Social Pe	0.07408794	0.07438332	1.0769015	0.31923613	logistic
Environment	0.045823	0.04612987	1.04688909	0.32054057	logistic
Gambling	0.05598652	0.05654243	1.05758343	0.32209188	logistic
Conduct Diso	0.07761846	0.07859512	1.08071024	0.32336159	logistic
Conduct Diso	0.08404747	0.08525334	1.08768052	0.32420404	logistic
Panic Disorde	0.04708735	0.0480853	1.04821356	0.32745829	logistic
OCD	0.08694357	0.08892234	1.09083513	0.32819936	logistic
Other drug	0.76825898	0.78652413	NA	0.32878513	linear
Opiate	0.12601336	0.12996864	NA	0.33233743	linear
Agoraphobia	0.04718758	0.04886846	1.04831864	0.3342424	logistic
Stimulants	-0.2111671	0.21868555	NA	0.3344794	linear
Demographic	0.03391599	0.03652218	1.0344977	0.35307509	logistic
Marijuana	0.03601848	0.03878889	1.036675	0.35310828	logistic
Mania	0.05860711	0.06361204	1.06035856	0.3568828	logistic
Tobacco	-0.0568798	0.06204649	NA	0.35932852	linear
Sedatives	-0.4530765	0.5012263	NA	0.36665469	linear
Social Phobia	-0.3914633	0.43554515	NA	0.36920012	linear
Alcohol	0.59611775	0.6648978	NA	0.37004864	linear
Tobacco	0.04157686	0.04688006	1.04245328	0.37514493	logistic
Suicide	-0.2928373	0.33020023	NA	0.37547686	linear

Stimulants	-0.3098534	0.35093705	NA	0.37749446	linear
Marijuana	0.03156281	0.03594175	1.03206619	0.37985388	logistic
Other drug	0.04529925	0.05256549	1.04634094	0.3888152	logistic
Demographic	0.06231684	0.07251714	1.0642995	0.39015325	logistic
Medical	-0.0068813	0.00801754	NA	0.39077557	linear
Anti-Social Pe	-0.0597238	0.0699829	0.9420247	0.39343451	logistic
Opiate	-0.0651203	0.07691153	0.93695478	0.39716764	logistic
Cocaine	0.10610949	0.12597837	NA	0.39970588	linear
Alcohol	0.06114354	0.0739318	1.0630515	0.40822212	logistic
Marijuana	0.03528708	0.04272298	1.03591706	0.40883196	logistic
Demographic	0.08515419	0.10383185	1.08888494	0.41214984	logistic
Demographic	0.0266638	0.03274478	1.02702246	0.4154778	logistic
Medical	0.03022347	0.03721809	1.03068484	0.41675485	logistic
Medical	0.01649718	0.0207014	NA	0.42553588	linear
Marijuana	-0.0823591	0.10353257	0.92094123	0.42632888	logistic
Alcohol	0.0362509	0.04580211	1.03691598	0.42867098	logistic
Medical	0.05684065	0.07267811	1.05848712	0.4341631	logistic
Demographic	0.05392392	0.06929769	1.05540431	0.43648121	logistic
Marijuana	0.03594075	0.04759117	1.03659443	0.4501303	logistic
Medical	-0.0062717	0.00847775	NA	0.45945853	linear
Medical	-0.0267682	0.03640265	0.97358689	0.46213447	logistic
OCD	0.05448243	0.0748389	1.05599392	0.46661596	logistic
Other drug	0.04673882	0.06703561	1.0478483	0.48566272	logistic
Alcohol	-0.0545177	0.07864173	NA	0.48818719	linear
Mania	0.0453685	0.0654726	1.04641339	0.48834805	logistic
Other drug	-0.9525977	1.3904104	NA	0.49341347	linear
Environment	0.02271225	0.03329748	1.02297214	0.49517497	logistic
Other drug	0.04272868	0.06421735	1.04365469	0.50581003	logistic
Other drug	-0.1853722	0.2789798	NA	0.50648327	linear
Sedatives	-0.1488936	0.22908597	NA	0.51583524	linear
Mania	-0.3152264	0.49228122	NA	0.52226831	linear
Alcohol	0.04155215	0.06932815	1.04242753	0.54893638	logistic
Gambling	0.04245999	0.07094149	1.04337431	0.5494922	logistic
Other drug	0.58979753	0.9957864	NA	0.5537501	linear
Conduct Diso	0.02786999	0.04707878	1.02826199	0.55385988	logistic
Medical	-0.0567155	0.09641398	0.94486281	0.55636439	logistic
Gambling	-0.1358974	0.24041372	NA	0.57200039	linear
Gambling	0.03001906	0.0552072	1.03047418	0.58661171	logistic
Medical	-0.0345658	0.06397465	0.96602476	0.58898683	logistic
Alcohol	0.00474399	0.00882839	NA	0.59104274	linear
Mania	0.02952933	0.05535893	1.02996965	0.59374576	logistic
Gambling	0.03243041	0.06111191	1.03296201	0.59564573	logistic
Alcohol	0.04108269	0.0785776	1.04193826	0.60109293	logistic

Other drug	0.03058349	0.05921313	1.03105597	0.6055063	logistic
Social Phobia	-0.0240685	0.04754145	0.97621882	0.61267145	logistic
Mania	0.03044546	0.06291645	1.03091366	0.62845474	logistic
Alcohol	0.04293027	0.08976354	1.04386511	0.63246547	logistic
Sedatives	0.03272487	0.06896343	1.03326622	0.63512559	logistic
Marijuana	-0.0191246	0.04062611	0.98105711	0.63782156	logistic
Marijuana	0.01750937	0.03744408	1.01766356	0.64006075	logistic
Conduct Diso	0.0298638	0.06456629	1.03031419	0.64370185	logistic
Panic Disorde	-0.1717219	0.37780816	NA	0.64956548	linear
Panic Disorde	0.02840283	0.06306254	1.02881004	0.6524282	logistic
Marijuana	-0.0440323	0.10021216	0.95692304	0.66037838	logistic
Other drug	0.10534858	0.26322322	NA	0.68910221	linear
PTSD	0.09007004	0.2263107	NA	0.69066016	linear
Mania	0.00363683	0.00934728	NA	0.69723246	linear
Stimulants	0.02545605	0.06733817	1.02578283	0.70540604	logistic
Schizophrenia	0.03533851	0.09527152	1.03597033	0.71069404	logistic
Marijuana	0.00860697	0.02400711	NA	0.71996955	linear
Social Phobia	-0.0146288	0.04292082	0.98547767	0.7332296	logistic
Depression	-0.0534841	0.15874663	NA	0.73620175	linear
Environment	-0.0102546	0.03114072	NA	0.74194171	linear
Gambling	-0.0120663	0.03690877	0.98800616	0.74372571	logistic
Anti-Social Pe	0.02253887	0.06940762	1.02279479	0.74538394	logistic
Environment	0.00916955	0.02875563	1.00921171	0.74981885	logistic
Demographic	0.02212444	0.06941373	1.022371	0.7499291	logistic
Mania	-0.0205257	0.06503858	0.97968356	0.75231217	logistic
Cocaine	0.03644482	0.11579472	NA	0.75298365	linear
Medical	0.00986571	0.03175904	1.00991453	0.75607246	logistic
Cocaine	-0.0510437	0.16899825	NA	0.76264357	linear
Depression	0.06860363	0.22912278	NA	0.7646394	linear
Schizophrenia	-0.3601033	1.21001357	NA	0.76641547	linear
Social Phobia	-0.0119071	0.04279116	0.98816354	0.78081277	logistic
Opiate	0.05488389	0.20088712	NA	0.78471987	linear
Social Phobia	-0.0131487	0.04825133	0.98693734	0.78523371	logistic
Sedatives	0.08665028	0.32014015	NA	0.78668961	linear
Alcohol	0.00843879	0.0314429	1.00847449	0.7884034	logistic
Medical	0.01686883	0.0674541	1.01701191	0.80252654	logistic
Medical	-0.0180126	0.07813485	0.98214868	0.81767847	logistic
Alcohol	0.01534074	0.0692997	1.01545901	0.82480589	logistic
Suicide	-0.0284071	0.12933211	NA	0.82615596	linear
Mania	0.01139401	0.05216563	1.01145917	0.82710202	logistic
Alcohol	-0.0176592	0.08097755	0.98249577	0.8273701	logistic
Medical	-0.0092	0.04240228	0.99084218	0.82823202	logistic
Medical	0.01236314	0.05728414	1.01243988	0.82912707	logistic

Cocaine	-15.292745	72.1462382	NA	0.83215762	linear
Other drug	0.23283504	1.16371277	NA	0.84146809	linear
Suicide	-0.0812014	0.41772856	NA	0.84594363	linear
Demographic	-0.0015973	0.00847566	NA	0.85052431	linear
Depression	0.25815235	1.36982691	NA	0.85053039	linear
Sedatives	-0.0678124	0.37014241	NA	0.85470423	linear
Alcohol	0.00683018	0.03761042	1.00685355	0.85589408	logistic
Demographic	-0.0187745	0.10826686	NA	0.86233568	linear
Environment	-0.0126792	0.07698655	0.98740083	0.86918491	logistic
Tobacco	0.00258886	0.01772281	NA	0.88386893	linear
Suicide	-0.0071094	0.05030873	0.99291578	0.88762028	logistic
Conduct Diso	-0.0049318	0.03492652	0.99508037	0.88770867	logistic
Other drug	0.04694604	0.35414769	NA	0.89459127	linear
Other drug	0.22203987	1.80325569	NA	0.90206491	linear
Suicide	0.05269864	0.43247427	NA	0.90305095	linear
Mania	-0.0058491	0.05251768	NA	0.91141933	linear
Demographic	-0.0058813	0.0553032	0.99413599	0.91530794	logistic
Anti-Social Pe	-0.0055835	0.05750507	0.99443203	0.92264991	logistic
Depression	0.00289634	0.03126437	1.00290054	0.92618929	logistic
Mania	0.00932807	0.10105585	1.00937171	0.92645484	logistic
Other drug	0.01336935	0.17167217	NA	0.93793496	linear
Marijuana	0.00242944	0.03393669	1.00243239	0.94293028	logistic
Medical	-0.0063396	0.09583164	0.99368047	0.94725573	logistic
Marijuana	0.00547568	0.09178165	1.0054907	0.95242656	logistic
Medical	-0.0017937	0.03335235	0.99820786	0.95710914	logistic
Alcohol	0.00532151	0.10618642	NA	0.96003268	linear
Depression	0.03095921	0.68308193	NA	0.96385324	linear
Medical	0.00353848	0.08486651	1.00354475	0.96674209	logistic
Social Phobia	0.00083145	0.02040682	NA	0.96750174	linear
Agoraphobia	0.00092243	0.02326006	NA	0.96836763	linear
Medical	-0.0013079	0.03894722	0.998693	0.97321196	logistic
Social Phobia	0.00108359	0.04877007	1.00108418	0.98227372	logistic
Mania	-0.0401012	2.50414885	NA	0.98723036	linear
Other drug	0.0011722	0.22592475	NA	0.99586142	linear
Demographic	NA	NA	NA	NA	logistic
Demographic	NA	NA	NA	NA	logistic
Demographic	NA	NA	NA	NA	logistic
Demographic	NA	NA	NA	NA	logistic
Demographic	NA	NA	NA	NA	logistic
Medical	NA	NA	NA	NA	logistic
Medical	NA	NA	NA	NA	logistic
Medical	NA	NA	NA	NA	logistic
Medical	NA	NA	NA	NA	NA

Medical	NA	NA	NA	NA	logistic
Medical	NA	NA	NA	NA	NA
Alcohol	NA	NA	NA	NA	logistic
Alcohol	NA	NA	NA	NA	logistic
Alcohol	NA	NA	NA	NA	logistic
Alcohol	NA	NA	NA	NA	logistic
Alcohol	NA	NA	NA	NA	logistic
Cocaine	NA	NA	NA	NA	NA
Cocaine	NA	NA	NA	NA	logistic
Opiate	NA	NA	NA	NA	logistic
Stimulants	NA	NA	NA	NA	logistic
Stimulants	NA	NA	NA	NA	logistic
Sedatives	NA	NA	NA	NA	logistic
Sedatives	NA	NA	NA	NA	logistic
Other drug	NA	NA	NA	NA	logistic
Stimulants	NA	NA	NA	NA	logistic
Sedatives	NA	NA	NA	NA	logistic
Marijuana	NA	NA	NA	NA	logistic
Marijuana	NA	NA	NA	NA	logistic
Marijuana	NA	NA	NA	NA	logistic
Stimulants	NA	NA	NA	NA	logistic
Marijuana	NA	NA	NA	NA	logistic
Marijuana	NA	NA	NA	NA	logistic
Marijuana	NA	NA	NA	NA	logistic
Schizophreni	NA	NA	NA	NA	logistic
Schizophreni	NA	NA	NA	NA	logistic
Schizophreni	NA	NA	NA	NA	logistic
Schizophreni	NA	NA	NA	NA	logistic
Schizophreni	NA	NA	NA	NA	NA
Depression	NA	NA	NA	NA	logistic
Depression	NA	NA	NA	NA	NA
Depression	NA	NA	NA	NA	logistic
Mania	NA	NA	NA	NA	logistic
Mania	NA	NA	NA	NA	logistic
Mania	NA	NA	NA	NA	logistic
Conduct Diso	NA	NA	NA	NA	logistic
Conduct Diso	NA	NA	NA	NA	logistic
Conduct Diso	NA	NA	NA	NA	logistic
Conduct Diso	NA	NA	NA	NA	logistic
Anti-Social Pe	NA	NA	NA	NA	logistic
Anti-Social Pe	NA	NA	NA	NA	logistic
ADHD	NA	NA	NA	NA	logistic
Anxiety	NA	NA	NA	NA	logistic

Anxiety	NA	NA	NA	NA	logistic
Anxiety	NA	NA	NA	NA	logistic
OCD	NA	NA	NA	NA	logistic

n_total	n_cases	n_controls
5690	3159	2531
5690	2120	3570
5607	2394	3213
5522	2276	3246
5690	2146	3544
5688	NA	NA
5690	2238	3452
5692	NA	NA
5690	3767	1923
5690	2451	3239
5690	1932	3758
5690	2205	3485
5690	2057	3633
5139	3156	1983
5690	2108	3582
5690	2175	3515
5690	2334	3356
5690	2286	3404
5692	NA	NA
5690	2041	3649
5690	3015	2675
5690	2097	3593
5692	NA	NA
5690	2041	3649
5690	2055	3635
5690	1938	3752
5690	2009	3681
5690	2024	3666
5571	2908	2663
5690	1867	3823
5690	1765	3925
5690	1764	3926
5402	2682	2720
5690	1809	3881
5690	1974	3716
5690	2057	3633
5690	2586	3104
5690	1979	3711
5690	2128	3562
5690	2052	3638

5690	1285		4405
5690	1805		3885
5690	1922		3768
5690	2336		3354
5688	3862		1826
5676	3909		1767
5690	2569		3121
5692	NA	NA	
5691	2996		2695
5690	2859		2831
5692	NA	NA	
5690	1919		3771
5691	2533		3158
5691	3251		2440
5690	2171		3519
5690	2809		2881
5690	4196		1494
5690	1654		4036
5691	2849		2842
5690	2651		3039
5690	2575		3115
5691	2551		3140
5690	2457		3233
5691	2304		3387
5691	2112		3579
5691	2705		2986
5690	1884		3806
5690	1577		4113
5691	2421		3270
5690	1658		4032
5692	NA	NA	
5690	2168		3522
5690	1286		4404
5691	2261		3430
5637	NA	NA	
5691	2466		3225
5691	2487		3204
5690	1943		3747
5691	1773		3918
5692	NA	NA	
5690	1294		4396
5690	1955		3735
5682	2267		3415

5691	5116	575
5690	2025	3665
5691	1240	4451
5691	2826	2865
4070	2313	1757
5690	2227	3463
4758	2945	1813
5691	3272	2419
5691	3036	2655
5690	1736	3954
5682	3310	2372
5286	3669	1617
5691	2145	3546
5691	3634	2057
5681	1283	4398
5690	2131	3559
5683	2126	3557
5690	705	4985
5691	1805	3886
5690	1878	3812
5690	1577	4113
5659	NA	NA
5691	1621	4070
5690	1755	3935
5692	NA	NA
5691	2078	3613
5691	1923	3768
5691	2040	3651
5691	1810	3881
5692	534	5158
5691	1970	3721
5682	423	5259
5690	480	5210
5691	1881	3810
5682	1143	4539
5668	NA	NA
5691	1176	4515
5691	1640	4051
5691	1778	3913
5682	4637	1045
5682	1209	4473
5691	3464	2227
5691	1351	4340

5682	253	5429
5672	2282	3390
5692	NA	NA
5473	1097	4376
5690	1870	3820
5682	550	5132
5691	2102	3589
5682	777	4905
5478	779	4699
4629	NA	NA
5682	1057	4625
5681	680	5001
5691	1586	4105
5691	3598	2093
5348	576	4772
5682	1758	3924
5672	3239	2433
5688	NA	NA
5690	443	5247
5682	1736	3946
5692	NA	NA
5285	3041	2244
5681	390	5291
5619	NA	NA
5683	549	5134
5690	1185	4505
5672	2715	2957
5690	444	5246
5678	NA	NA
5681	2422	3259
5262	2416	2846
5672	3109	2563
5667	NA	NA
5690	620	5070
4710	1628	3082
5667	233	5434
5667	229	5438
5691	918	4773
5682	1658	4024
5682	424	5258
5682	401	5281
5667	160	5507
5691	519	5172

5691	NA	NA	
5691	1576	4115	
5682	712	4970	
5692	NA	NA	
5667	254	5413	
5683	361	5322	
5676	1183	4493	
5683	365	5318	
5691	1044	4647	
5667	1223	4444	
5692	NA	NA	
5681	679	5002	
5666	386	5280	
5667	286	5381	
5691	369	5322	
5672	3468	2204	
5678	2678	3000	
5677	680	4997	
5682	416	5266	
5533	4925	608	
5682	295	5387	
5683	702	4981	
5692	NA	NA	
5674	1887	3787	
5683	1526	4157	
5368	3781	1587	
5677	1409	4268	
5668	570	5098	
5396	810	4586	
4387	NA	NA	
5672	2854	2818	
5691	2799	2892	
5667	178	5489	
5667	299	5368	
5681	1578	4103	
5681	494	5187	
5692	2169	3523	
5692	NA	NA	
5692	NA	NA	
5682	249	5433	
5692	146	5546	
5559	572	4987	
437	NA	NA	

5683	475	5208
5668	1049	4619
5666	760	4906
5662	195	5467
5675	1533	4142
5667	132	5535
5667	NA	NA
5691	619	5072
5692	NA	NA
5682	663	5019
5692	NA	NA
5668	266	5402
5691	1603	4088
5669	NA	NA
5683	653	5030
5666	201	5465
5681	536	5145
5667	226	5441
5671	197	5474
1749	NA	NA
5667	135	5532
4724	186	4538
5692	912	4780
5678	2310	3368
5677	NA	NA
5668	606	5062
5691	3142	2549
5682	NA	NA
5683	600	5083
5666	752	4914
5682	467	5215
3449	1869	1580
5681	641	5040
5682	236	5446
5667	169	5498
5423	386	5037
5682	223	5459
5682	909	4773
5683	542	5141
5682	266	5416
5683	972	4711
2349	NA	NA
5672	2848	2824

5667	229	5438
4481	252	4229
5668	298	5370
5683	268	5415
5667	294	5373
5682	269	5413
5691	1543	4148
5683	743	4940
5677	1974	3703
5692	NA	NA
5681	517	5164
5672	1938	3734
5682	1470	4212
5682	286	5396
5691	845	4846
5690	1424	4266
5682	255	5427
5682	388	5294
5691	1115	4576
5691	847	4844
5666	871	4795
5666	828	4838
5683	2263	3420
5682	245	5437
5691	5588	103
5236	483	4753
5667	109	5558
5682	310	5372
5683	962	4721
5682	411	5271
5681	555	5126
5666	426	5240
5682	472	5210
5691	1304	4387
5690	430	5260
5682	508	5174
5667	198	5469
5582	NA	NA
5377	2643	2734
5634	NA	NA
5682	381	5301
5378	2038	3340
5682	356	5326

5666	NA	NA	
5681	725	4956	
5677	1278	4399	
5683	1774	3909	
5666	1091	4575	
5682	198	5484	
5690	NA	NA	
5682	181	5501	
5692	NA	NA	
5669	NA	NA	
5691	624	5067	
5682	841	4841	
5682	543	5139	
5662	422	5240	
5682	341	5341	
383	NA	NA	
5691	427	5264	
5533	120	5413	
5676	539	5137	
5668	529	5139	
5672	337	5335	
5681	485	5196	
5690	717	4973	
5683	389	5294	
5681	434	5247	
5681	554	5127	
2261	NA	NA	
5691	1280	4411	
1011	NA	NA	
5666	690	4976	
5666	755	4911	
5667	222	5445	
5682	122	5560	
5682	376	5306	
5666	719	4947	
5672	3006	2666	
5682	266	5416	
5664	NA	NA	
5692	NA	NA	
3634	761	2873	
5677	1694	3983	
5682	349	5333	
5682	463	5219	

5666	674		4992
5690	291		5399
5683	1321		4362
5666	534		5132
5691	216		5475
5664	1070		4594
5666	448		5218
5666	951		4715
3375	NA	NA	
5533	322		5211
5666	NA	NA	
2415	NA	NA	
5683	306		5377
5691	366		5325
5666	543		5123
5681	545		5136
5691	185		5506
5682	1009		4673
5668	1460		4208
486	NA	NA	
5668	856		4812
5692	131		5561
5681	520		5161
5662	259		5403
4657	NA	NA	
1469	NA	NA	
5653	NA	NA	
5683	339		5344
5681	313		5368
5681	380		5301
3597	779		2818
5677	153		5524
5682	1473		4209
5662	228		5434
5692	1179		4513
5681	736		4945
5666	616		5050
5677	335		5342
1350	NA	NA	
1998	NA	NA	
5680	NA	NA	
5669	2774		2895
5668	1575		4093

5691	351	5340	
5676	886	4790	
5682	876	4806	
5667	114	5553	
5666	1026	4640	
5670	146	5524	
5668	843	4825	
275	NA	NA	
1196	NA	NA	
5683	477	5206	
5667	131	5536	
5666	765	4901	
5677	1649	4028	
5692	211	5481	
2151	860	1291	
3638	NA	NA	
5676	276	5400	
5692	1455	4237	
5672	1656	4016	
5692	NA	NA	
5666	657	5009	
5681	316	5365	
5670	272	5398	
1570	NA	NA	
5681	492	5189	
111	NA	NA	
5682	268	5414	
5681	157	5524	
5686	NA	NA	
5668	102	5566	
1549	NA	NA	
5681	224	5457	
5677	2286	3391	
5681	239	5442	
1558	NA	NA	
5683	358	5325	
5666	463	5203	
5670	294	5376	
4908	333	4575	
5681	533	5148	
3842	1269	2573	
5682	239	5443	
5692	162	5530	

5667	156	5511
5682	815	4867
5681	233	5448
5676	1963	3713
5666	579	5087
5670	371	5299
5667	104	5563
5683	131	5552
5692	663	5029
5620	176	5444
5692	133	5559
5662	647	5015
5668	219	5449
5671	296	5375
5664	349	5315
5670	392	5278
5672	2700	2972
1303	NA	NA
5681	447	5234
289	NA	NA
5672	1094	4578
5675	108	5567
5662	440	5222
5691	100	5591
5682	995	4687
5668	NA	NA
2102	NA	NA
5671	NA	NA
5666	1381	4285
1806	NA	NA
5682	188	5494
2215	NA	NA
5681	140	5541
5692	728	4964
5692	4786	906
5681	103	5578
5666	665	5001
5671	108	5563
5680	NA	NA
5368	NA	NA
5690	124	5566
5682	332	5350
5677	1280	4397

5677	1534		4143
5677	885		4792
5666	458		5208
5691	990		4701
5668	115		5553
5587	247		5340
5668	242		5426
5677	2246		3431
3009	NA	NA	
5668	NA	NA	
5690	827		4863
5670	313		5357
3613	NA	NA	
209	NA	NA	
5666	333		5333
5670	237		5433
3856	NA	NA	
5668	134		5534
1696	NA	NA	
3755	NA	NA	
5662	215		5447
5691	191		5500
5691	4538		1153
5675	204		5471
5376	622		4754
5660	371		5289
5676	183		5493
5675	155		5520
5666	515		5151
5523	141		5382
2248	NA	NA	
3129	NA	NA	
5087	512		4575
967	NA	NA	
5692	1093		4599
5682	904		4778
5690	284		5406
5111	NA	NA	
362	NA	NA	
511	NA	NA	
2348	NA	NA	
5691	550		5141
689	NA	NA	

973	NA	NA	
5683	1133	4550	
5682	432	5250	
5692	307	5385	
5688	NA	NA	
5676	232	5444	
5690	195	5495	
2646	NA	NA	
5691	205	5486	
5682	717	4965	
5692	110	5582	
5692	3077	2615	
5690	961	4729	
5691	NA	NA	
5682	105	5577	
5691	576	5115	
5692	212	5480	
5692	444	5248	
5682	549	5133	
5686	NA	NA	
5691	1112	4579	
5668	202	5466	
5681	258	5423	
5567	NA	NA	
5670	267	5403	
1108	NA	NA	
5378	1390	3988	
5681	288	5393	
1710	NA	NA	
1391	NA	NA	
479	NA	NA	
5691	235	5456	
5662	228	5434	
1411	NA	NA	
5677	562	5115	
5692	121	5571	
1204	NA	NA	
5662	391	5271	
5690	284	5406	
5692	NA	NA	
5670	382	5288	
5692	313	5379	
5691	182	5509	

5681	340	5341
5666	531	5135
5670	290	5380
5691	139	5552
5683	239	5444
5682	808	4874
5682	1007	4675
5677	278	5399
896	NA	NA
5666	289	5377
5682	112	5570
780	NA	NA
3452	NA	NA
5672	NA	NA
5682	251	5431
5671	123	5548
5692	NA	NA
5666	669	4997
3462	NA	NA
5352	NA	NA
5660	4652	1008
5675	240	5435
5667	3556	2111
5692	233	5459
5672	270	5402
3013	NA	NA
5691	4141	1550
3203	NA	NA
3332	NA	NA
165	NA	NA
5666	674	4992
2164	NA	NA
5666	513	5153
1417	NA	NA
5691	1518	4173
5690	261	5429
5692	183	5509
5691	237	5454
5623	NA	NA
5670	435	5235
5691	169	5522
5692	691	5001
5692	354	5338

1664	NA	NA	
833	NA	NA	
566	NA	NA	
5692	NA	NA	
3389	NA	NA	
560	NA	NA	
5691	924		4767
5692	NA	NA	
5373	189		5184
4438	NA	NA	
2146	632		1514
5677	1131		4546
543	NA	NA	
407	NA	NA	
691	NA	NA	
237	NA	NA	
5691	435		5256
5673	367		5306
5672	1546		4126
5670	108		5562
1700	NA	NA	
5683	1308		4375
5692	122		5570
5682	136		5546
5691	1304		4387
5581	NA	NA	
2793	NA	NA	
5692	153		5539
5666	NA	NA	
5666	NA	NA	
5691	863		4828
4798	513		4285
467	NA	NA	
878	NA	NA	
5692	27		5665
5692	9		5683
5692	3		5689
5692	62		5630
5692	54		5638
5690	91		5599
5691	61		5630
5692	52		5640
5692	NA	NA	

5692		6	5686
5692	NA	NA	
5691		70	5621
5691		74	5617
5691		60	5631
5691		62	5629
5691		31	5660
5690	NA	NA	
5690		55	5635
5690		35	5655
5682		87	5595
5682		82	5600
5682		47	5635
5682		44	5638
5681		30	5651
5682		30	5652
5682		57	5625
5682		94	5588
5682		47	5635
5682		93	5589
5683		55	5628
5682		33	5649
5682		73	5609
5683		74	5609
5671		88	5583
5671		10	5661
5671		5	5666
5671		48	5623
30	NA	NA	
5659		82	5577
5672	NA	NA	
5672		18	5654
5286		64	5222
5670		98	5572
5675		2	5673
5676		83	5593
5676		34	5642
5676		2	5674
5676		59	5617
5675		22	5653
5649		71	5578
5668		65	5603
5667		82	5585

5667	82	5585
4532	88	4444
5281	86	5195