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Supplementary appendix

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Supplement to: Cheng W, Parker N, Karadag N, et al. The relationship between cannabis use, schizophrenia, and bipolar disorder: a genetically informed study. *Lancet Psychiatry* 2023; **10:** 441–51.

Supplementary Appendix 1 for *The relationship between cannabis use, schizophrenia, and bipolar disorder: a genetically association informed study*

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Supplementary Methods

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Supplementary Methods

GWAS Data

GWAS summary statistics were acquired from the latest large-scale studies on schizophrenia (SCZ),[1] bipolar disorder (BIP),[2] lifetime cannabis use (LCU),[3] and cannabis use disorder (CUD)[4] as part of our discovery analyses. For SCZ, summary statistics a total of 53,386 cases and 77,258 controls of European ancestry were included. For BIP, 41,917 cases and 371,549 controls of European ancestry were included. Here, participants from the UK Biobank were excluded to avoid sample overlap with cannabis phenotypes for all analyses except MiXeR and the genetic correlations, which can model and handle sample overlap, leaving 40,463 BIP cases and 313,436 controls. For LCU, a total sample of 184,765 participants were included approximately 28.8% of which had used cannabis in their lifetime. For CUD, 14,080 cases and 343,726 controls were included.

To validate conjFDR findings (see below) additional summary statistics were used from independent samples in a SNP sign test (see the section on "variant annotation, locus definition, and SNP sign test"). These include an East Asian SCZ sample from the Psychiatric Genomic Consortium (PGC),[5]which included 22,778 cases and 35,362 controls. Additionally, summary statistics for a BIP sample from FINNGEN was acquired with 4,501 cases and 192,220 controls.

Notably, for polygenic risk score analyses (PGS, see below), the Norwegian Thematically Organized Psychosis (TOP) cohort was used. To avoid sample overlap, summary statistics that excluded the TOP sample were generated and used from the latest PGC GWAS for SCZ and BIP. For comparison, we included a PGS of non-melanoma skin cancer (NMSC) as a somatic comparator. The NMSC-PGS was calculated based on a NMSC GWAS dataset[6] consisting of 18,944 cases and 255,886 controls.

MiXeR Analysis

The tool MiXeR v1.3[7] was used to assess the genetic architecture for each of the studied phenotypes. MiXeR uses a causal mixture model which assumes genetic variants can have either null or non-null effects on the phenotype of interest. The modeling procedure allows for the estimation of heritability, polygenicity, and discoverability. More specifically, for each SNP, i, MiXeR models its additive genetic effect of allele substitution, β_i, as a point-normal mixture, $\beta_i = (1-\pi_1)N(0,0) + \pi_1 N(0,\sigma_\beta^2)$, where π_1 represents the proportion of non-null SNPs (i.e., polygenicity) and σ_β^2 represents variance of effect sizes of non-null SNPs (i.e., discoverability). For each SNP, j, MiXeR incorporates LD information and allele frequencies for background SNPs extracted from 1000 Genomes Phase3 data to estimate the expected probability distribution of the signed test statistic, $z_j = \delta_j + \epsilon_j = N\sum_i \sqrt{H_i} r_{ij}\beta_i + \epsilon_j$, where N is sample size, H_i indicates heterozygosity of i-th SNP, r_{ij} indicates allelic correlation between i-th and j-th SNPs, and $\epsilon_j \sim N(0,\sigma_0^2)$ is the residual variance. Further, the three parameters, $\pi_1, \sigma_\beta^2, \sigma_0^2$, are fitted by direct maximization of the likelihood function. The number of independent variants is estimated as $M\pi_1$, where M is the number of selected background SNPs in the reference panel. Phenotypic variance explained on average by an independent variant is calculated as $\overline{H}\sigma_\beta^2$, where $\overline{H} = \frac{1}{M}\sum_i H_i = 0.2075$ is the average heterozygosity across SNPs in the reference panel. Under the assumptions of the MiXeR model, SNP-heritability is then calculated as $h_{SNP}^2 = M\pi_1 \times \overline{H}\sigma_\beta^2$.

To determine the suitability of summary statistics and the sufficiency of model fit, MiXeR employs the Akaike information criterion ($AIC = 2k - 2\ln L$), where k is the number of free parameters in the model, L is the value of the likelihood function, and n is the effective number of SNPs used in the optimization procedure. The AIC represents the comparison between MiXeR modelled fit and the infinitesimal model, which assumes an all variants influence a phenotype with some having an infinitesimal effect. A positive AIC value indicates the input GWAS dataset provides sufficient power to discriminate the MiXeR modelled fit from infinitesimal model and the MiXeR estimates are reliable.

Cross-Trait Enrichment

Conditional QQ plots were constructed to depict the cross-trait SNP enrichment between the primary phenotype (i.e., the trait of interest) and secondary phenotype (i.e., the conditional trait). Subsets of SNPs were selected based on the strengths of association with the secondary trait using different cut-offs ($p \leq 1$, $p \leq 0.1$, $p \leq 0.01$, $p \leq 0.001$). If the primary phenotype shares SNP associations with the secondary phenotype (i.e., shared

polygenic architecture), there will be increased enrichment of SNP association in the primary phenotype as P thresholds of SNP associations with the secondary phenotype decrease, indicated by successive leftward deflections on the conditional QQ plot.
The data points on the QQ plot are weighted according to the LD structure around the corresponding SNP. We used n=500 iterations of random pruning with an LD threshold r2=0.1 to define LD blocks throughout the genome. The variants within complex LD regions, including (i) major histocompatibility complex (MHC) chr6:25119106–33854733, (ii) Chromosome 8p23.1 deletion (8p23.1): chr8:7200000–12500000, (iii) microtubule-associated protein tau (MAPT) chr17:40000000-47000000, (iv) apolipoprotein E (APOE) chr19:44909039-45912650, were removed from the cross-trait enrichment analysis.

Conjunctional False Discovery Rate Analyses

A conjunctional false discovery rate (conjFDR) analysis is an extension of a conditional false discovery rate (condFDR) analysis.[8] CondFDR improves the power to discover SNPS for a primary phenotype by conditioning on the SNP associations with a secondary phenotype. First condFDR analysis is applied twice using a pair of phenotypes. Initially, a phenotype is chosen as the primary phenotype using the other as the secondary to boost power. Then the roles are reversed. conjFDR analysis identifies the shared genetic variants, between the two phenotypes, based on the results from the two condFDR analyses. The procedure for determining the condFDR and conjFDR are described in more detail below.

The condFDR analysis is based on the empirical Bayesian statistical framework outlined by Efron[9]. A condFDR analysis re-calculates the significance of SNP associations with the primary phenotype by utilizing the concept of cross-trait SNP enrichment between the primary and secondary phenotype. The stratified empirical cumulative distribution functions (cdfs) for the primary phenotype conditional on nominal p-values of the secondary phenotype being at or below a given threshold ($p\leq1$, $p\leq0.1$, $p\leq0.01$, $p\leq0.001$) is calculated. Then, condFDR values (i.e., the significance of SNP associations for the primary phenotype) from the stratified cdfs are computed. Thus, the condFDR value represents the posterior probability that a genetic variant has no association with the primary phenotype, given that the P values for that SNP in both phenotypes are as small as or smaller than the observed P value. Given the cross-trait SNP enrichment between the primary and secondary phenotypes, the condFDR procedure re-orders SNPs and results in a different ranking than that using p-values alone.

After running two condFDR analysis on a pair of traits, reversing the role of the primary and secondary traits for each analysis the conjFDR values is determined as the largest of the two condFDR values. The conjFDR value is a conservative estimate of the FDR for association with both phenotypes. The conjFDR value is defined as the posterior probability that a given SNP is null for both phenotypes simultaneously when the p-values for both phenotypes are as small or smaller than the observed p-values. The significance threshold for the conjFDR analysis was defined as a conjFDR value < 0.05 in line with prior studies.[10–12,12–14]

Variant Annotation and Loci Definition

All SNPs from conjFDR analysis were annotated regarding variant function, the predicted deleteriousness (Combined Annotation Dependent Depletion, CADD score), and regulatory effect (RegulomeDB scores and chromatin states). To define loci among those SNPs, we first applied clumping to extract the independent significant SNPs using LD $r^2<0.6$. A SNP was defined as a candidate SNP if it had a conjFDR<0.1 and was located within a LD r2>=0.6 with at least one related independent significant SNP. Second, we defined the lead SNPs among independent SNPs using LD $r^2<0.1$. If two or more lead SNPs showed that their candidate SNPs have physical overlap, or located within 250kb of a complex LD region, including MHC, 8p23.1, MAPT, and APOE, we considered those two genetic signals as overlapped. In this case, the one with a more significant conjFDR value was defined as the lead SNP. Next, for each lead SNP, we defined borders for its genomic locus based on its candidate SNPs. For each phenotype pair, we compare its shared genomic loci across phenotype pairs. If two or more loci associated with a phenotype pair showed overlap, we combined them into one distinct locus. Details for shared loci are shown in Supplementary Table 5. The LD information was obtained from the European population in the 1000 Genomes Project reference panel.[15]

SNP Sign Test

We performed a SNP sign test for SCZ and BIP, separately, with the following protocol using SCZ as an example. First, we obtained the lead SNPs for SCZ by combining the shared loci for SCZ and LCU with those

for SCZ and CUD. Z score from the corresponding GWAS summary statistics was used to represent effect direction. Some share loci were found in both phenotype pairs (i.e., SCZ and LCU, and SCZ and CUD) with distinct lead SNPs. For such shared loci, if those two distinct lead SNPs were both available in the independent SCZ GWAS, we included the more significant lead SNP in the following SNP sign test. The significance of lead SNPs was compared using P values from the discovery SCZ GWAS (see Supplementary Table 5). Next, we performed the exact binomial test to examine whether the direction of the effect of lead SNPs replicate *en masse* in the independent cohort by the following algorithm. The null hypothesis assumed randomly oriented effects while the alternative hypothesis was true probability of discordant direction of effect is less than 50%. The N_{SNP} represents the number of lead SNPs that are available in independent samples and the N_{CON} is the number of lead SNPs that have concordant effect directions between discovery and independent samples.

$$\text{binom.test}(N_{SNP} - N_{CON}, N_{SNP}, \text{alternative="less"})$$

A binomial $P < .05$ with concordancy proportion > 50% indicates the effect directions of lead SNPs replicated *en masse* in independent samples. For LCU and CUD, we were not able to find an independent sample. Therefore, the SNP sign test was only applied for SCZ and BIP.

Gene Mapping and Enrichment Analyses

All candidate SNPs within the loci identified by conjFDR were then mapped to genes using three strategies implemented by FUMA[16] (i) position, (ii) expression quantitative trait loci [eQTL] in GTEx (v8) and BRAINEAC brain tissues, and (iii) chromatin interactions in PsychoENCODE, HIC brain tissues. We only used genes that were mapped using at least two of these methods or were mapped by a putatively deleterious exonic variant using a Combined Annotation Dependent Depletion threshold of 12.37. We again excluded genes within MHC, 8p23.1, MAPT, and APOE.

Genes shared by a psychotic disorder and each of the cannabis phenotypes were combined and tested for enrichment for gene ontology terms, Kyoto encyclopedia of genes and genomes (KEGG) pathways, and cell types (curated gene sets [C8] with genes identified from single cell studies of human tissue). This was performed using gene set enrichment analyses (GSEA) and gene sets provided by the molecular signatures database (https://www.gsea-msigdb.org/gsea/index.jsp).[17] Additionally, GSEA was used to test for the enrichment of drug-gene interactions that were obtained from the Drug Gene Interaction Database 4.0 (DGIdb; download date: 2022 Feb; https://www.dgidb.org/). The DGIdb provides information on drug-gene interactions from 22 diverse sources that are aggregated and normalized. The DGIdb collects drug-gene interactions based on information about therapeutic targets and their corresponding drugs, knowledge from clinical trials, as well as potentially clinically actionable drug-gene associations based on metadata such as molecule structure and molecular weight.[18]

Mendelian Randomization

Mendelian randomization (MR) is an approach that estimates causal associations between two phenotypes (i.e., exposure and outcome) by leveraging the fact that individuals are randomly assigned genetic risk for the exposure of interest.[19] Genetic variants associated with the exposure phenotype are selected as “instruments” for MR analyses. The MR framework is based on three major assumptions (i) the instruments are associated with the exposure, (ii) the instruments are not associated with confounders, (iii) the instruments influence the outcome only through the risk factor. It is important to note that violations of these assumptions produce unreliable MR estimates. Therefore, it has become good general practice to use multiple robust methods of MR to test causal associations. When multiple methods converge on the same result, the claim can be seen as well supported.

There are many methods to perform MR. One of the more robust approaches is two-sample MR which uses GWAS summary statistics, from independent samples, for the exposure and outcome phenotypes of interest. Here we use the R package TwoSampleMR where we report results using 3 methods (i) inverse variance weighted [IVW],[20] (ii) weighted median,[21] and (iii) MR Egger.[21] The IVW approach is a classic MR method which is essentially a fixed-effect meta-analyse of the SNP effects on the outcome over the SNP effects on the exposure. Both the weighted median and MR egger approaches are more robust to heterogeneity in estimates (i.e., a potential sign of violation of MR assumptions) than the IVW approach. We also apply another robust method, MR-PRESSO. MR-PRESSO identifies and removes outliers in estimates and then recalculates a new unbiased causal estimate. In addition, we used the Causal Analysis Using Summary Effect estimates (CAUSE)

method[22] which unlike the other included approaches use all overlapping SNPs to estimate the causal effect. CAUSE determines if an association between two traits is likely to be causal or represent horizontal pleiotropy. Finally, Latent Causal Variable (LCV) analysis was performed.[23] LCV estimates the genetic causality proportion (GCP) between two traits. If the GCP is high, there is greater likelihood of a causal effect. If the GCP is low, the relationship between the two traits is likely not causal but may be a result of horizontal pleiotropy.

Due to low power of the GWAS of the cannabis phenotypes, we performed additional analyses relaxing the p-value threshold for the inclusion of SNPs in our MR analyses. For the main analyses IVW, MR Egger, weighted median, and MR-PRESSO include SNPs at a level of $p<5e-8$. For the additional supplemental analyses, we relaxed this threshold to $p<1e-6$. Relaxing the p-value threshold for low power GWAS is consistent with previous studies[3,24,25].

Polygenic Score Participants

The PGS analyses were conducted in a sample from the ongoing Norwegian Thematically Organized Psychosis (TOP), which started in 2002. Participants were recruited from psychiatric inpatient and outpatient units at major hospitals in the Oslo, Norway area as well as Trondheim, and Southeast regional hospitals in Norway (Diakonhjemmet Hospital, Lovisenberg Hospital, and St Olav's Hospital). Eligible participants met the inclusion criteria of a DSM-IV diagnosis of schizophrenia, schizoaffective, and schizophreniform disorder or bipolar disorder I, bipolar disorder II or bipolar disorder not otherwise specified, age between 18-65 years and ability to give written informed consent. Exclusion criteria were presence of a pronounced cognitive deficit (IQ below 70), severe somatic illness, and brain damage. Healthy controls were randomly selected from statistical records (Statistics Norway) from the same catchment area and age range as patients, and invited to participate. They were screened for psychiatric and substance use disorders, and somatic disease. Additional information was collected through interviews and hospital records to determine demographic factors, lifestyle, psychiatric and medical history, current use of psychotropic medication, tobacco, alcohol, and illicit drugs. All participants were screened for illicit substances in the urine, and blood samples were drawn, and standard clinical biochemistry assessment was performed. In addition, symptoms were rated at baseline. Details about recruitment procedures, inclusion and exclusion criteria, and clinical assessments for the TOP cohort are provided in previous publications and continue to be the standard for ongoing recruitment.[26] All participants provided written consent and the study was approved by The Regional Committee for Medical and Health Research Ethics of South-East Norway. The participants from TOP showed a high inter-rater reliability of the symptom assessments, with an Intraclass Coefficient (ICC) of 0.82 for PANSS symptoms, 0.86 for GAF-S and 0.85 for GAF-F. The inter-rater reliability is also satisfactory for diagnosis, with overall agreement for diagnostic categories of 82 % and overall $\kappa = 0.77$ (95% CI: 0.60 - 0.94). For more details, see Rødevand et al. 2019[27].
Quality control on genetic data was performed including following steps. First, PLINK was used to perform pre-imputation sample and variant quality-controlled steps. Eagle was applied for phasing and MaCH to impute missing genotypes. Details for pre-imputation quality control, phasing and imputation are demonstrated in a previous publication.[28] Next, the post-imputation filtering included variant filters for including call rates (1% missingness), minor allele frequencies (0.01), and departure from Hardy-Weinberg equilibrium (1E-06). After quality control, 2181 participants with genotype data were included in the analyses, consisting of 440 BIP cases, 697 SCZ cases, and 1044 healthy controls. All participants are of European ancestry, and 1,060 (48.88%) are female. The mean age of those samples was 33.09 years (standard deviation=11.76 years).

Information on recent cannabis use was obtained for 1388 participants, including 495 SCZ cases, 396 BIP cases, and 497 healthy controls. Recent cannabis use was defined as a binary variable based on self-reported cannabis use within the past 2 years. A total of 1031 participants had not used any cannabis in the past 2 years, including 322 SCZ cases, 267 BIP cases, and 442 healthy controls. We applied Fisher tests to examine the discrepancy in recent cannabis use between cases and controls.

We classified BIP patients as either having experienced psychosis (i.e., have experienced at least one psychotic episodes in their lifetime using a structured clinical interview) or not having experienced psychosis (i.e., have never experienced a psychotic episode) using a structured clinical interview. In total, 235 BIP patients reported psychotic experience and 170 BIP patients have never experienced a psychotic episode.

Polygenic Score Calculation

We calculated the PGS of SCZ, BIP, LCU, and CUD, separately, for TOP samples (i.e., target sample) using the above GWAS datasets as the GWAS discovery sample (i.e., base set). To avoid sample overlap, we calculated

the leave-one-out PGS for BIP- and SCZ- PGSs as the TOP cohort was included in the GWAS discovery sample. The leave-one-out PGS was calculated by leaving the TOP cohort out of the GWAS discovery sample and using a meta-analysis of the remaining cohorts as the discovery sample.

Each PGS was calculated by LDpred2, auto-model (LDpred2-auto), given its advanced performance for the prediction of psychotic disorders.[29] LDpred2-auto derived each PGS for TOP samples based on GWAS summary statistics and an external LD reference. As a Bayesian approach, LDpred2-auto assumes a point-normal mixture distribution for variant effect sizes, where a fraction of those variants is causal and contributes to the SNP heritability. LDpred2-auto is a method free of hyper-parameters, which automatically estimates the proportion of causal variants and the SNP heritability from the data without the need of a tuning cohort to choose the best parameter. As recommended, the PGS calculation was constricted to HapMap3 variants.[30] The LD reference used in this analysis was based on UK Biobank data for European ancestry, provided by Prive et al.[30]

In single-PGS models, we examined the association between each PGS and BIP diagnosis using BIP cases and healthy controls from the TOP cohort. We also examined the variance of the target phenotype (BIP diagnosis in this case) that is explained by the included PGS variables (namely PGS.R2). Sex, age, genetic batch ID, and the first 20 genetic principal components were adjusted in all PGS models in the present study. This single-PGS model BIP-PGS (i.e., the PGS of target phenotype) is here forward referred to as the 'baseline' models. The baseline model was therefore used to compare with the multi-PGS model, which consists of the BIP-PGS, and LCU- and CUD- PGSs, and with the control model, which consists of the BIP-PGS and NMSC-PGS. Next, we used more complete models to examine if LCU- and CUD- PGSs improve predict BIP diagnosis when both SCZ- and BIP- PGSs were included. We compared the complete baseline model, which consists of BIP- and SCZ- PGSs, and the complete multi-PGS model, which consists of BIP-, SCZ-, LCU-, and CUD- PGSs. We also computed the PGS.R2 for SCZ by applying the same protocol.

We also tested for interaction effects of sex with PGSs on SCZ and BIP diagnoses. First, for each of the above single-PGS models, we included the interaction between sex and the PGS. The interaction effect was examined using ANNOVA. Next, for the multi-PGS models, we incorporated the interaction effects of sex with each PGS, including psychotic-specific PGS and LCU-, and CUD- PGSs, and assessed each interaction effect by ANNOVA. The Benjamini-Hochberg correction was performed.

The discrepancy in cannabis use between cases and controls in the TOP cohort may bias the association analysis between psychotic disorder diagnosis and PGS of cannabis phenotypes. Therefore, we applied sensitivity analyses within the subset of individuals that did not have recent cannabis use (n=1031). The same PGS analyses were applied to this sample including assessment of prediction efficiency for each cannabis phenotype PGS in the single-PGS models as well as evaluation of improvement in prediction efficiency for multi-PGS models by adding LCU- and CUD- PGSs.

Finally, we examined the association between PGS of cannabis phenotypes and psychotic experience. For LCU- and CUD- PGSs, we first compared each between BIP patients with and without psychotic experience using a generalized logistic regression model, controlling the effect of sex, age, genetic batch ID, and the first 20 genetic principal components. Then, for BIP patients with and without psychotic experience, we applied single- and multi- PGSs models to distinguish them from healthy controls, respectively.

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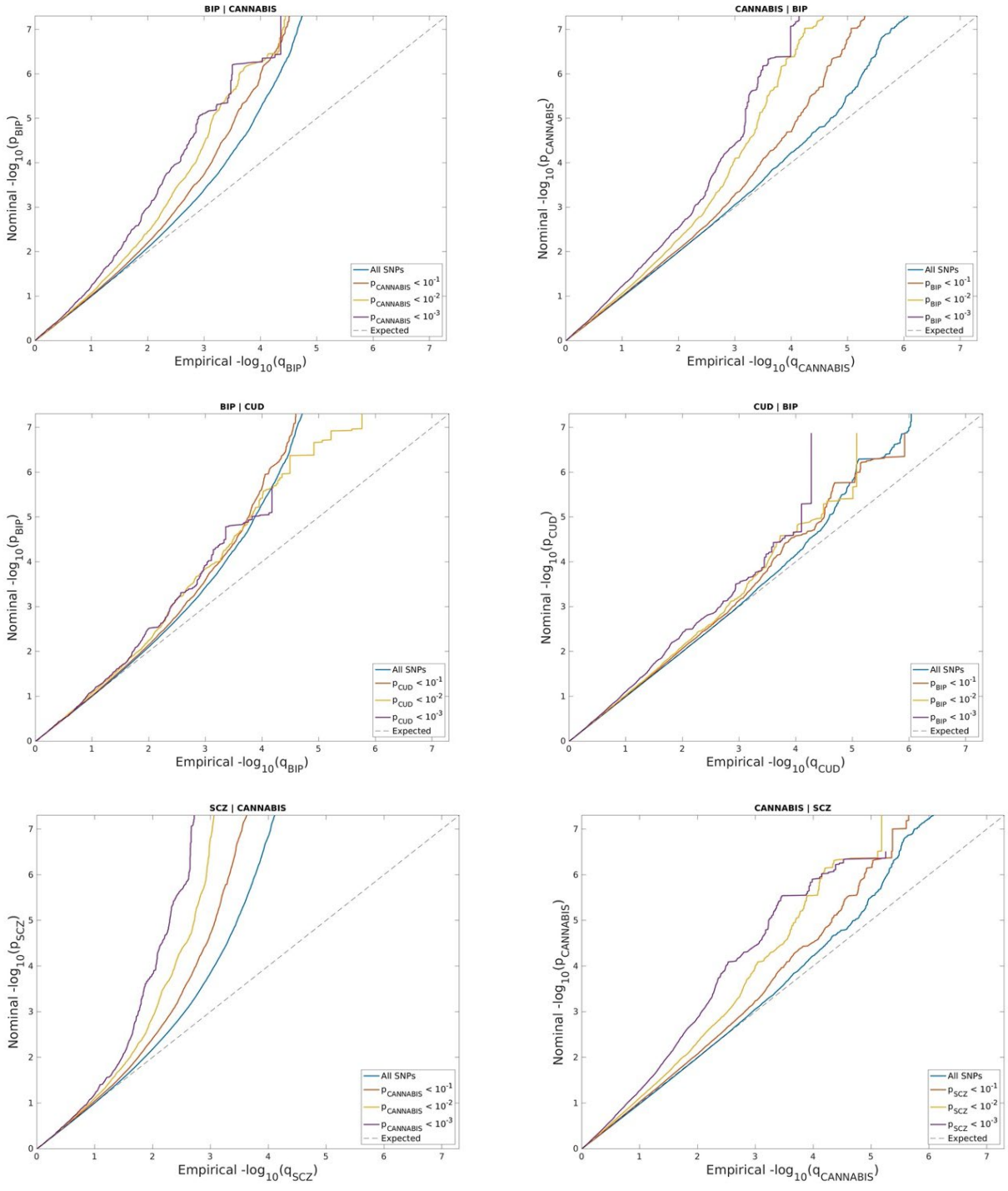
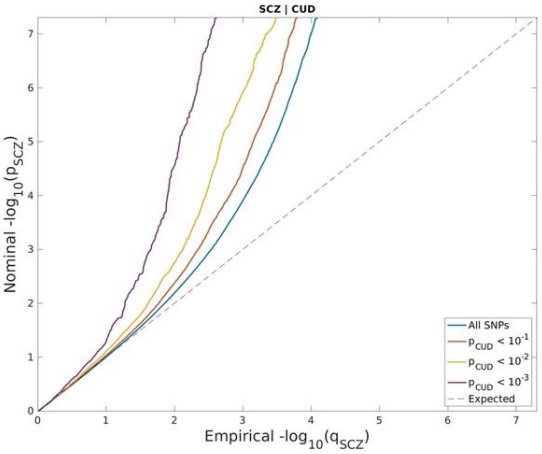
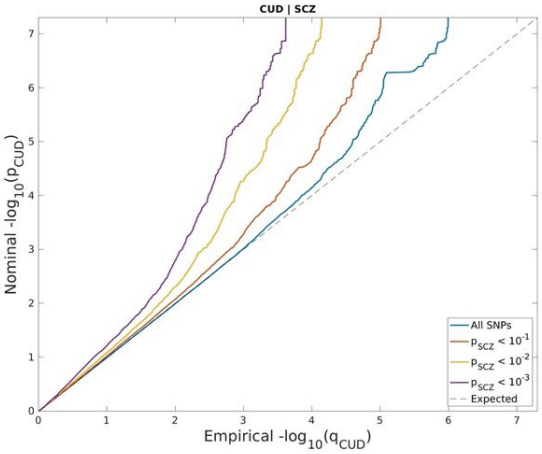
Supplementary Figures

Supplementary Figure 1. The conditional QQ plots for each phenotype pair.

SCZ: schizophrenia; BIP: bipolar disorder; CANNABIS: lifetime cannabis use; CUD: cannabis use disorder.




SCZ | CUD
Nominal -log10(pSCZ)
Empirical -log10(qSCZ)
All SNPs
pCUD < 10-1
pCUD < 10-2
pCUD < 10-3
Expected


CUD | SCZ
Nominal -log10(pCUD)
Empirical -log10(qCUD)
All SNPs
pSCZ < 10-1
pSCZ < 10-2
pSCZ < 10-3
Expected

Supplementary Figure 2. Distribution of MiXeR Estimates.

SCZ: schizophrenia; BIP: bipolar disorder; CANNABIS: lifetime cannabis use; CUD: cannabis use disorder.