



Article

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The genetic relationship between cannabis use disorder, cannabis use and psychiatric disorders

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Increasing prevalence of cannabis use and cannabis use disorder (CanUD) may increase risk for psychiatric disorders. We evaluated the relationships between these cannabis traits and a range of psychiatric traits, running global and local genetic correlations, genomic structural equation modeling, colocalization analyses and Mendelian randomization analyses for causality. Global genetic analyses identified significantly different correlations between CanUD and cannabis use. A variant in strong linkage disequilibrium to one regulating *CHRNA2* was significantly shared by CanUD and schizophrenia in colocalization analysis and included in a significant region in local genetic correlations between these traits. A three-factor model from genomic structural equation modeling showed that CanUD and cannabis use partially map together onto a factor with major depressive disorder and ADHD. In terms of causality, CanUD showed bidirectional causal relationships with most tested psychiatric disorders, differently from cannabis use. Increasing use of cannabis can increase rates of psychiatric disorders over time, especially in individuals who progress from cannabis use to CanUD.

Studies demonstrating potential harms from the heavy and prolonged use of cannabis have been increasing¹. A 2021 report from the National Survey on Drug Use and Health in the United States showed that 52.5 and 16.3 million people aged at least 12 years old reported cannabis use and met criteria for cannabis use disorder (CanUD) in the previous year, respectively². Thus, considering these large numbers and potentially increased cannabis use related to legalization³, understanding the intricate interplay between cannabis use, CanUD and psychiatric disorders is crucial for comprehending the broader implications for mental health and well-being. Previously, we used genetic methods to evaluate the relationships and causality of CanUD and cannabis use

on traits related to alcohol, opioids and smoking; the work strongly supported previous phenotype-based evidence of CanUD increasing the risk of developing other substance use disorders, an effect that was often bidirectional⁴.

Cannabis use and CanUD show comorbidity with many psychiatric illnesses, including anxiety disorders⁵, major depressive disorder (MDD)⁵, post-traumatic stress disorder (PTSD)⁶, anorexia nervosa (AN)^{7,8}, schizophrenia (SCZ)⁹, bipolar disorder (BPD)¹⁰ and attention deficit hyperactivity disorder (ADHD)^{11,12}. In a previous systematic review with meta-analysis of eight studies, CanUD was found to be associated with MDD (odds ratio (OR) = 3.22) and anxiety (OR = 2.99)⁵.

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Table 1 | Information on datasets

| | Phenotype | Type of phenotype | Effective sample size | Year of publication | PubMed ID (ref) |
|-----------------------------|--------------------|-------------------|-----------------------|---------------------|------------------------|
| Cannabis traits | CanUD-EUR | Case-control | 161,053 | 2023 | 37985822 ¹⁹ |
| | CanUD-AFR | Case-control | 64,460 | 2023 | 37985822 ¹⁹ |
| | Cannabis use | Case-control | 122,438 | 2018 | 30150663 ²³ |
| Psychiatric traits | Anxiety symptoms | Continuous | 175,163 | 2020 | 31906708 ⁴³ |
| | MDD | Case-control | 709,980 | 2021 | 34045744 ³² |
| | SCZ | Case-control | 58,749 | 2022 | 35396580 ³⁰ |
| | BPD | Case-control | 101,963 | 2021 | 34002096 ³¹ |
| | AN | Case-control | 46,322 | 2019 | 31308545 ⁴⁴ |
| | ADHD | Case-control | 128,214 | 2023 | 36702997 ⁴⁵ |
| PTSD and subtypes | PCL-total | Continuous | 186,689 | 2021 | 33510476 ⁴⁷ |
| | PCL-avoidance | Continuous | 186,689 | 2021 | 33510476 ⁴⁷ |
| | PCL-hyperarousal | Continuous | 186,689 | 2021 | 33510476 ⁴⁷ |
| | PCL-reexperiencing | Continuous | 186,689 | 2021 | 33510476 ⁴⁷ |
| Big Five personality traits | Neuroticism | Continuous | 682,688 | 2024 | 38293137 ⁴⁸ |
| | Extraversion | Continuous | 298,772 | 2024 | 38293137 ⁴⁸ |
| | Agreeableness | Continuous | 252,749 | 2024 | 38293137 ⁴⁸ |
| | Conscientiousness | Continuous | 252,253 | 2024 | 38293137 ⁴⁸ |
| | Openness | Continuous | 237,390 | 2024 | 38293137 ⁴⁸ |

For the case-control studies, the given sample size represents the effective sample size. For CanUD and cannabis use, effective sample size was calculated as $4/(1/\text{cases}+1/\text{controls})$.

For SCZ, BPD and AN, effective sample size was provided directly in the available summary statistics. For cannabis use and MDD, the available summary statistics excluded 23andMe data. SNP-heritability values are shown in Supplementary Table 1.

CanUD and its relationship with PTSD is less well studied, and cannabis is actually approved in some US states as a treatment for PTSD^{13–15}. However, a systematic review of 45 studies on co-occurring cannabis use and PTSD reported mixed findings of cannabis use significantly predicting PTSD and vice versa⁶. This is consistent with and may suggest a bidirectional association between PTSD and cannabis use where each increases risk for the other, raising questions about whether a drug that increases the risk of a trait can reasonably also be a treatment for that same trait. A 6% prevalence of CanUD in AN and a 14% prevalence of cannabis use in AN were reported from a meta-analysis of 52 studies⁷, which are close to the prevalences of the two cannabis traits in the general population². Cannabis has been shown to increase appetite¹⁶ but is also associated with lower body mass index¹⁷. These contrasting findings require rigorous examination on the relationship between cannabis and AN.

Rates of cannabis use and CanUD are markedly elevated in individuals with BPD¹⁰ and SCZ^{9,18,19}. In patients with BPD, prevalence of cannabis use was 30% (from a meta-analysis of 10 studies), and prevalence of CanUD was 20% (from a meta-analysis of 28 studies)¹⁰. Of individuals with SCZ, 26.2% also suffer from CanUD⁹, and 42.1% reported use of cannabis. The relationship between SCZ and cannabis traits has already been a topic of many investigations considering data from genetic epidemiology, then genomewide association studies (GWAS), with significant genetic correlations found between SCZ and CanUD ($r_g = 0.307 \pm 0.037$; $P = 2.25 \times 10^{-16}$)¹⁸ and between SCZ and cannabis use ($r_g = 0.267 \pm 0.032$; $P = 6.03 \times 10^{-17}$)¹⁸. Mendelian randomization (MR) analyses identified a bidirectional causal relationship between SCZ and CanUD (SCZ → CanUD: effect = 0.165 ± 0.039 , $P = 2.07 \times 10^{-5}$; CanUD → SCZ: effect = 0.180 ± 0.070 , $P = 0.01$)¹⁹.

Despite the moderate (but highly significant) genetic correlation (r_g) between cannabis use and CanUD ($r_g = 0.50 \pm 0.05$, $P = 1.5 \times 10^{-21}$)¹⁸, these two cannabis traits show notable differences in their genetic relationships with other traits, including AN, MDD, SCZ, anxiety and PTSD subtypes (avoidance, hyperarousal and reexperiencing)^{18,19}. The genetic difference between cannabis use and CanUD was also suggested

by the post-GWAS analyses of CanUD after conditioning on cannabis use results, which did not substantially reduce CanUD heritability or modify greatly the effect sizes of CanUD GWAS top loci¹⁸.

Here we investigate the relationship between cannabis use and CanUD with psychiatric and personality traits (Table 1) to improve understanding of their relationships and how these relationships with other traits differ. We initially performed genetic correlation analyses, including personality traits (neuroticism, extraversion, agreeableness, conscientiousness and openness), with the goal of discovering shared genetic effects across the whole genome. Then we focused on psychiatric disorders, starting with local genetic correlations, analyses that have the advantage of detecting signals in independent genetic regions, different to the whole genome signal that can be identified from the genetic correlation analyses. Afterward, we ran MR analyses to infer possible causality between the traits and genetic colocalization to find possible causal variants shared between or among the studied traits. Finally, genomic structural equation modeling (genomic-SEM) was used to understand how cannabis traits map in the genomic context of psychiatric disorders. These analyses were conducted to give a broad and detailed picture of the genetic relationship intercurrent between cannabis traits and psychiatric disorders, with particular care to tease apart the differences between cannabis use and CanUD.

Results

Global genetic correlation analysis

Genetic correlation, which defines the proportion of genetic variance shared between two traits, was used to understand the genetic relationships between cannabis traits and psychiatric traits (showing their single nucleotide polymorphism (SNP-) heritability values in Supplementary Table 1) and is a global (genomewide) measure. Genetic correlation analyses showed statistically significant positive genetic correlations between CanUD and all the studied psychiatric disorders except for AN, which was not significant. There were both positive and negative genetic correlations for CanUD and the personality traits (Fig. 1 and Supplementary Table 2). The highest

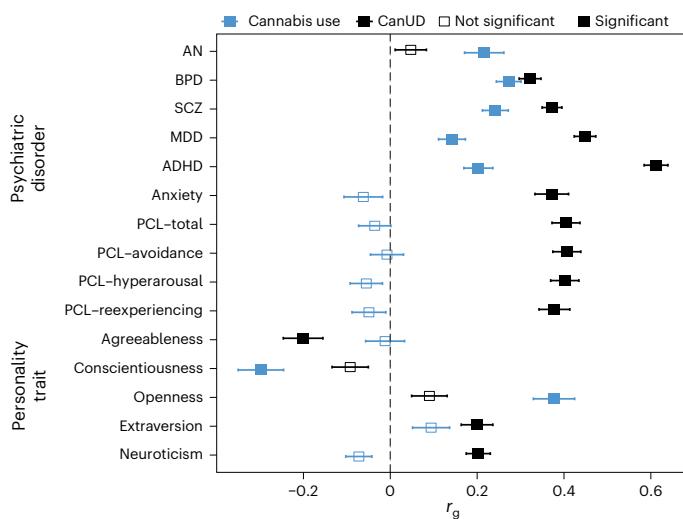


Fig. 1 | Genetic correlations. Genetic correlation (r_g) analyses (using LDSC) of CanUD and cannabis use with psychiatric disorders (EUR ancestry). All of the traits except BPD and extraversion showed significantly different correlations with CanUD and cannabis use. Tests were two-sided. Error bars represent the standard error.

genetic correlation was between CanUD and ADHD ($r_g = 0.612 \pm 0.027$; $P = 3.8 \times 10^{-10}$), followed by CanUD and MDD ($r_g = 0.448 \pm 0.025$; $P = 5.0 \times 10^{-73}$). Posttraumatic stress disorder checklist (PCL) traits had r_g between 0.378 ± 0.035 (PCL-reexperiencing; $P = 1.5 \times 10^{-26}$) and 0.407 ± 0.032 (PCL-avoidance; $P = 1.6 \times 10^{-36}$), with $r_g = 0.405 \pm 0.032$ for PCL-total ($P = 5.0 \times 10^{-73}$). Moderate positive r_g was also found with SCZ ($r_g = 0.373 \pm 0.023$; $P = 3.0 \times 10^{-70}$) and BPD ($r_g = 0.322 \pm 0.025$; $P = 1.5 \times 10^{-37}$), and with extraversion ($r_g = 0.200 \pm 0.036$; $P = 4.1 \times 10^{-8}$) and neuroticism ($r_g = 0.203 \pm 0.028$; $P = 2.8 \times 10^{-13}$). Agreeableness was the only trait showing a significant negative genetic correlation with CanUD ($r_g = -0.201 \pm 0.046$; $P = 1.1 \times 10^{-5}$).

Despite the non-significant r_g between CanUD and AN, cannabis use showed a significant moderate-low r_g with this trait ($r_g = 0.216 \pm 0.045$; $P = 1.7 \times 10^{-6}$). The other four significant r_g estimates for cannabis use with psychiatric traits (BPD, SCZ, ADHD and MDD) were lower in magnitude compared with their corresponding r_g for CanUD (Fig. 1 and Supplementary Table 2). For the personality traits, cannabis use showed a stronger significant r_g compared with CanUD for openness and conscientiousness, whereas it had non-significant r_g for the other three personality traits, different from CanUD. Thus, a significantly different r_g ($P \leq 0.0036$) between CanUD and cannabis use was seen for all the traits except BPD and extraversion (Supplementary Table 3).

We also investigated whether adjusting for genetic influences associated with socioeconomic status would influence the r_g analyses. When we considered household income as a measure of socioeconomic status, there were no statistically significant changes (Supplementary Fig. 1 and Supplementary Tables 4–6). Considering educational attainment as a measure of socioeconomic status, we found four significant changes in the r_g of cannabis use (with ADHD, PCL-total, PCL-avoidance and PCL-hyperarousal) (Supplementary Fig. 2 and Supplementary Tables 7–9). Indeed, when correcting for educational attainment, we obtained a positive significant genetic correlation instead of a null value for cannabis use with PCL-total, PCL-avoidance and PCL-hyperarousal and an increase of the positive r_g value between cannabis use and ADHD.

Cross-ancestry genetic correlations were also considered using the same European (EUR) summary statistics for the psychiatric traits and African (AFR) summary statistics for CanUD (Supplementary Table 10). There was a similar pattern for the significant results (Supplementary Fig. 3).

Local genetic correlation analysis

Local genetic correlation defines the proportion of genetic variance shared between two traits only in a genomic region, different from the whole genome, which is reflected in genetic correlation. Local genetic correlations showed 20 significant results for CanUD and 2 significant results for cannabis use. For CanUD, there were seven significant local genetic correlations with ADHD, five with SCZ, four with MDD and SCZ, two with PTSD and one with BPD and anxiety (Supplementary Table 11). These 20 local genetic correlations were all positive. A local genetic correlation on chr7:113339387-115321301 was found between CanUD and MDD and with PTSD; one on chr11:112755447-113889019 was found between CanUD with MDD, PTSD, BPD, SCZ and anxiety. For cannabis use, there were two significant local genetic correlations with SCZ (one positive and one negative) (Supplementary Table 12).

Multi-trait colocalization

Colocalization analysis determines whether a locus is responsible for the GWAS signals in the analyzed traits. Multi-trait colocalization analysis allows this testing on more than two GWAS simultaneously. Of the 101 significant genetic associations inferred by multi-trait colocalization analysis (Supplementary Table 13), 14 and 5 regions were associated with CanUD and cannabis use, respectively. The variant *GULOP**rs11783093 showed a significant colocalization between CanUD and SCZ (posterior probability = 0.99). This variant maps to a region with significant local genetic correlation between the same two traits from the local genetic correlation analyses. Two other variants, *PDE4B**rs7519259 (posterior probability between CanUD and PTSD = 0.72) and *SLC39A8**rs13107325 (posterior probability among CanUD, cannabis use and SCZ = 0.80), were previously associated with CanUD¹⁹, whereas *FURIN**rs4702 (posterior probability among CanUD, MDD, PTSD, SCZ, ADHD = 0.78) was associated with CanUD, nicotine dependence and alcohol use disorder in a multi-trait analysis of GWAS¹⁹.

Mendelian randomization

MR analyses study the inferred causality of a trait (exposure) on another trait (outcome) using genetic variants as instrumental variables (IVs). MR analyses were conducted using MRlap since it accounts for biases, including sample overlap, the use of weak instruments and ‘winner’s curse’ (Methods). Using the P value threshold = 10^{-5} for IVs, MRlap results showed significant differences between observed and corrected effects except for AN when considering CanUD as exposure or outcome (Supplementary Tables 14 and 15), so the corrected results are preferred for most traits. When considering cannabis use as exposure, significant differences between observed and corrected effects were found for SCZ, AN and ADHD (Supplementary Table 16), whereas considering cannabis use as outcome, MDD, SCZ, AN, BPD and ADHD had effects with significant differences (Supplementary Table 17).

MR analyses showed that CanUD had significant bidirectional relationships with all the psychiatric disorders except AN, which did not show a significant relationship with either cannabis trait (Fig. 2). The strongest effect of CanUD as exposure was on SCZ (effect = 0.688 ± 0.076 ; $P = 2.0 \times 10^{-19}$), followed by ADHD (effect = 0.468 ± 0.042 ; $P = 2.9 \times 10^{-29}$), BPD (effect = 0.353 ± 0.054 ; $P = 4.7 \times 10^{-11}$) and total PCL score (effect = 0.264 ± 0.033 ; $P = 2.1 \times 10^{-15}$). Considering CanUD as the outcome, the strongest effect was observed for MDD (effect = 0.429 ± 0.030 ; $P = 5.0 \times 10^{-45}$), followed by PCL-total score (effect = 0.250 ± 0.036 ; $P = 3.8 \times 10^{-12}$).

We found only one MR-supported causal relationship of per se cannabis use on psychiatric disorders, with ADHD (effect = 0.306 ± 0.066 ; $P = 3.9 \times 10^{-6}$). However, we did observe the converse relationship for some traits, and risk for using cannabis was increased by MDD (effect = 0.142 ± 0.026 ; $P = 7.2 \times 10^{-8}$), BPD (effect = 0.125 ± 0.012 ; $P = 7.3 \times 10^{-24}$), SCZ (effect = 0.0534 ± 0.0055 ; $P = 5.2 \times 10^{-22}$) and ADHD (effect = 0.094 ± 0.020 ; $P = 4.1 \times 10^{-6}$).

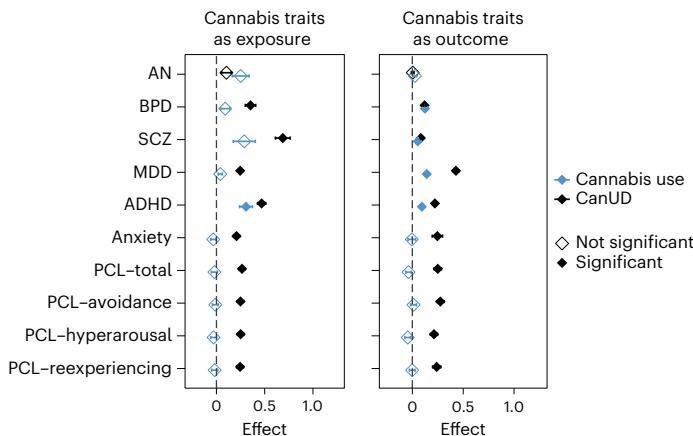


Fig. 2 | MR analyses. MR analyses of CanUD and cannabis use versus psychiatric disorders (P value threshold 10^{-5} for IVs). The two cannabis traits are represented as exposures on the left panel and as outcomes on the right panel. Tests were two-sided. Error bars represent the standard error.

Decreasing the P value threshold for IVs to 5×10^{-8} , for CanUD we found similar significant relationships except for anxiety as exposure (Supplementary Tables 18 and 19), whereas for cannabis use its effect on ADHD was no longer significant with this more conservative threshold and fewer instruments (Supplementary Tables 20 and 21).

MR analyses of cannabis use corrected for educational attainment with traits having significant differences in the genetic correlations showed consistent results with the uncorrected MR analysis (a bidirectional relationship between cannabis use and ADHD using the P value threshold 10^{-5} for the IV; a causal relationship of ADHD on cannabis use with P value threshold 5×10^{-8} for the IV; non-significant relationships between cannabis use and the PCL subtypes; Supplementary Tables 22–25).

MR analyses performed with TwoSampleMR on non-overlapping samples (CanUD with AN, and cannabis use with anxiety and the three PTSD subdomains), supported the non-significant results previously found (Supplementary Tables 26–29).

Genomic structural equation modeling

Genomic-SEM analyzes the joint genomic architecture of complex traits using their GWAS summary statistics as input to identify their relationship patterns. To understand this dimension, parallel analysis (pa) linkage disequilibrium score regression (LDSC; paLDSC) functions were considered. Examination of the paLDSC results and eigenvalues (using the greater-than-one convention) suggested that a three-factor model fits the data best (Supplementary Figs. 4 and 5 and Supplementary Table 30). Therefore, we performed a three-factor exploratory factor analysis. Results demonstrated that PTSD, anxiety and MDD loaded onto factor 1, while AN, SCZ and BPD loaded onto factor 2. CanUD and ADHD loaded onto factor 3 (Supplementary Table 31). Cross-loadings were present for two traits (cannabis use (cross-loading onto factors 2 and 3) and MDD (cross-loading on factors 1 and 3)). The three-factor model accounted for 64.8% of the variance. Next, we ran a confirmatory factor analysis (CFA) setting the psychiatric traits to load onto the three factors as described in the exploratory factor analysis, including the cross-loadings. The CFA model fit was good when considering the comparative fit index (CFI); however, the standard root mean square residual (SRMR) was above the threshold of <0.08 (CFI = 0.947, SRMR = 0.0836) but generally acceptable²⁰. Factors 1 and 2 were correlated at 0.339, factors 2 and 3 at 0.505, and factors 1 and 3 were the most strongly correlated at 0.602.

Discussion

We live in a time of increasing cannabis availability both for medical applications and for recreational use,²¹ an additional secular trend is

that cannabis has been increasing in potency²². Medical use of a drug usually requires demonstration beforehand of safety and efficacy, but extra-medical considerations have advanced some medical use of cannabis prior to strong evidence for efficacy. And to the contrary, some existing evidence suggests that use of and/or dependence on cannabis may worsen risk for some of the traits it is purported to treat.

We previously showed, using genomic data, that CanUD increases risk for other substance use disorders⁴. In the present study, we inferred the relationships between cannabis use and CanUD and a set of major psychiatric disorders, including anxiety, MDD, PTSD and PTSD subphenotypes, AN, BPD, ADHD and SCZ. Previous studies analyzed the genetic correlations between the two cannabis traits and the discussed mental disorders^{11,12,18,19,23}, with the relationship with SCZ having received by far the most attention. We report similar values; however, the possibility of accessing new, more powerful summary statistics allowed us to demonstrate a positive significant genetic correlation between CanUD and AN and significantly different correlations of CanUD and cannabis use with PTSD. The stronger overlap between CanUD and psychiatric disorders, compared with the overlap between cannabis use and psychiatric disorders, may indicate a component of dose-response relationship. We also investigated genetic correlations between CanUD and cannabis use and each of the 'Big 5' personality traits. There were noteworthy differences in the observed r_g values for these two cannabis traits, and for one personality trait, neuroticism, the correlations were in opposite directions: CanUD had a positive r_g with neuroticism, and cannabis use had a negative r_g . Cross-ancestry genetic correlations on CanUD showed similar values compared with EUR ancestry analyses for the psychiatric and personality traits, showing genetic similarity between EUR and AFR and reinforcing the possible role that CanUD has with these traits. Then we evaluated local genetic correlation to investigate which genomic regions had significant correlations between CanUD and cannabis use, and the psychiatric disorders, and to investigate possible causal genes with multi-trait colocalization analysis. For CanUD, we found significant positive local genetic correlations with psychiatric disorders consistent with the observed global genetic correlations; we did not observe any significant local genetic correlation with AN, also the only trait with a non-significant global genetic correlation with CanUD. For cannabis use, SCZ was the only trait with significant local genetic correlations. Different from the positive local genetic correlations between SCZ and cannabis use, these significant local genetic correlations showed opposite directions. Local genetic correlation and colocalization results showed a notable locus shared between CanUD and SCZ, *GULOP**rs11783093. In previous GWAS, this variant was found associated with SCZ²⁴ and smoking initiation²⁵. This variant is in strong linkage disequilibrium with rs56372821 ($r^2 = 0.992$ and $D' = 1.0$ from LDpair tool in EUR²⁶), also mapped to the *GULOP* locus but a strong expression quantitative trait locus for *CHRNA2*, which was previously reported to be associated with CanUD^{18,19,27} and smoking initiation²⁵. Considering the role of *CHRNA2*, which encodes cholinergic receptor nicotinic alpha 2 subunit, and that *GULOP* is known as a pseudogene, this supports that the observed association with *GULOP* is likely functionally more related to *CHRNA2*. In addition, gene *SLC39A8*, mentioned in our multi-trait colocalization analysis between CanUD, cannabis use and SCZ, and associated with nicotine consumption²⁸, has a role as transporter of the neurotoxic metal cadmium²⁹, present in cigarette smoke. Other relevant genes from our colocalization analyses were *PDE4B*, which codes for a protein regulating the cellular concentrations of cyclic nucleotides playing a role in signal transduction, and *FURIN*. This latter gene encodes a member of the subtilisin-like proprotein convertase family, involved in the regulation of the secretory pathway, and it has been previously associated with SCZ³⁰, BPD³¹, MDD³² and opioid use disorder³³. The findings of several genes shared by CanUD with both psychiatric disorders and substance use and use disorders reflect the high comorbidity among these traits.

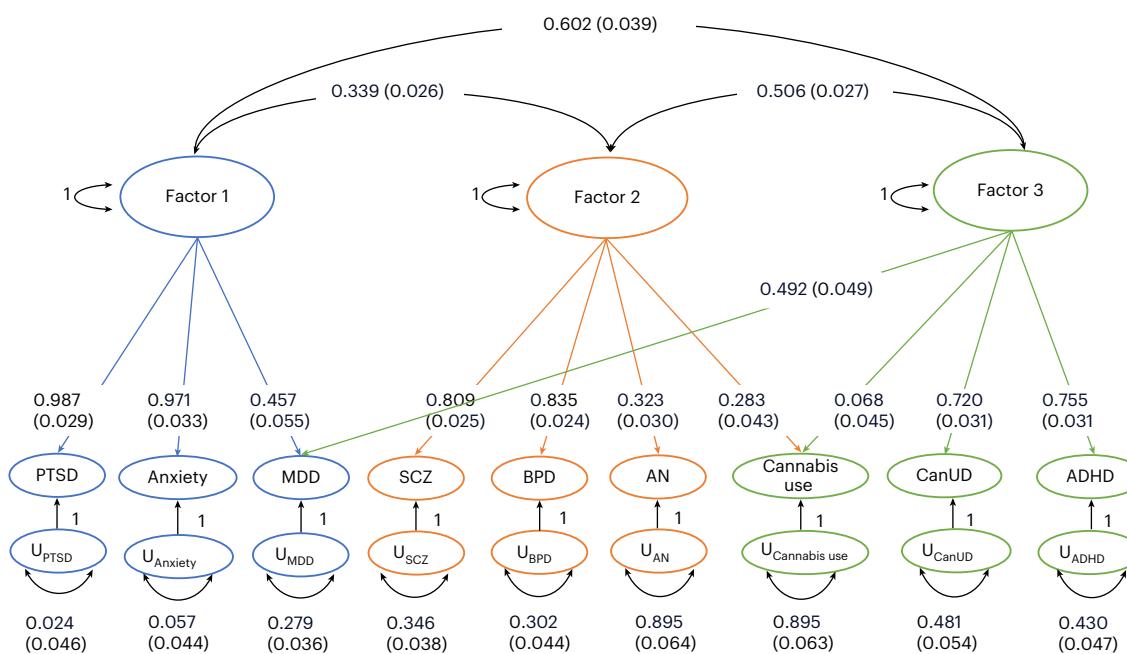


Fig. 3 | Genomic-SEM. Genomic-SEM analyses of cannabis traits (CanUD and cannabis use) and psychiatric disorders for a three-factor model.

To investigate how the traits were related to each other, we performed genomic-SEM. To infer the causality between the two cannabis traits and the mental disorders, we then ran MR analyses. Analyzing the causal relationships revealed a bidirectional relationship between CanUD and anxiety and MDD (both internalizing disorders). Evidence that MDD increases the risk of the use of cannabis was also previously reported³⁴. In addition, bidirectional causality was found for CanUD and each of the three PTSD subphenotypes (avoidance, hyperarousal and reexperiencing) and for PTSD as PCL-total. Previous work had already shown bidirectional causality between CanUD and ADHD;^{11,12} here we discovered a bidirectional causality also between cannabis use and ADHD.

Results from the three-factor genomic-SEM model demonstrated that PTSD, anxiety and MDD loaded onto factor 1, while AN, SCZ and BPD loaded onto factor 2 (Fig. 3 and Supplementary Table 27). CanUD and ADHD loaded onto factor 3. In contrast to CanUD, cannabis use loaded onto both factors 2 and 3. The difference between the two cannabis traits, reflected in the genetic correlation and MR results, and known from previous work^{19,23} (that is, that CanUD is more closely related genetically to pathological traits than per se cannabis use) was also supported by our local genetic correlation results, which showed a higher number of local genetic correlations with CanUD (20 significant local r_g with ADHD, MDD, SCZ, PTSD, anxiety and BPD) compared with cannabis use (2 significant local r_g with SCZ), and by the three-factor model in the genomic-SEM. In the three-factor model, the two cannabis traits loaded together onto factor 3, and cannabis use co-loaded onto factor 2.

Use of cannabis can induce psychotic symptoms, particularly in young individuals and those with pre-existing mental health vulnerabilities³⁵. Evidence of a bidirectional causal relationship between CanUD and SCZ has been reported in several previous studies, first using the inverse variance weighted (IVW) method (SCZ→CanUD: effect = 0.123 ± 0.029 , $P = 3.03 \times 10^{-5}$; CanUD→SCZ: effect = 0.200 ± 0.029 , $P = 5.45 \times 10^{-12}$)³⁶, and reproduced (SCZ→CanUD: effect = 0.165 ± 0.039 , $P = 2.07 \times 10^{-5}$; CanUD→SCZ: effect = 0.180 ± 0.070 , $P = 0.01$)¹⁹. Another analysis confirmed the evidence of this bidirectional relationship, although in the presence of horizontal pleiotropy³⁷. Our analyses confirm this bidirectional causal

relationship. For cannabis use and SCZ, previous MR studies showed that use of cannabis was causally associated with risk of SCZ^{38,39}. However, these MR analyses were run using a cross-ancestry meta-analysis of SCZ, so conceivably there may have been population stratification bias in the MR analyses. Another MR study showed that SCZ increases the risk of lifetime cannabis use (effect = 0.151 ± 0.046 , $P = 0.001$)²³. In our analyses, we did not find that lifetime cannabis use increases the risk of SCZ, but we observed that SCZ does increase the risk of lifetime cannabis use.

BPD has been shown to have causal effects on cannabis use and CanUD using MR, correlation analysis or polygenic risk score analysis^{40,41}, also confirmed by our analysis with the newer availability of much more powerful CanUD genomic data. However, we do not confirm a causal effect of cannabis use on BPD as previously inferred⁴⁰.

We did not find any relationship of causality between the cannabis traits and AN, despite the moderate genetic correlation between cannabis use and AN. This non-significant MR result may be potentially attributable to the comparatively low power due to the small sample size available for AN (16,992 cases and 55,525 controls).

This study has several limitations, including the lack of sex-specific data. It has been reported, for example, that the relationship between CanUD and SCZ can differ by sex⁴². Another limitation is represented by the sample size of the summary statistics for AN, limiting potential especially for MR discovery. A third limitation could be a lack of power of the cannabis use summary statistics, which could have also resulted in detection of only a few significant local genetic correlations. In addition, probably because of reduced power, MR results with a stricter cut-off showed fewer significant causal relationships than using the more lenient cut-off. Although we used a recent method to account for bias from sample overlap in our MR analyses, this method is focused specifically on an IVW approach. Finally, due to unavailability of sufficiently powerful summary statistics in non-European ancestries for most traits, we are able to address only European-ancestry relationships, with African ancestry used only for the calculation of cross-ancestry genetic correlations. However, the cross-ancestry genetic correlations, which have similar values to EUR ancestry findings, support that these results can be similar in non-EUR populations.

In conclusion, we made use of the most recent CanUD GWAS results¹⁹ with previously unprecedented power to provide a broader view of the genetic relationship between cannabis traits and major psychiatric disorders than was possible previously. We found genomic regions sharing associations among the cannabis traits and the psychiatric disorders, and a possible causal variant shared by CanUD and SCZ. Moreover, we discovered causal relationships involving CanUD. We identified bidirectional relationships between CanUD with BPD, anxiety, MDD and PTSD, which have not been observed in previous studies. Regarding cannabis use, we also discovered that MDD can increase the risk of the use of cannabis (confirming previous observations³⁴), and there was bidirectional causality with ADHD. We highlight genetic differences between cannabis use and CanUD, consistent with previous findings^{4,18,19}. Moreover, we reproduced some previous observations for CanUD—its bidirectional causal relationship with SCZ, its causal effects on BPD and its comorbidity and bidirectional causal relationship with ADHD. Further, we reproduced the causal relationship of BPD and SCZ with respect to cannabis use.

With these data, we corroborate the hypothesis that individuals affected by CanUD have increased risk of developing other psychiatric disorders and that psychiatric disorders increase the risk for individuals to develop CanUD. We reject the hypothesis that genetically predicted cannabis use or dependence has beneficial effects on predicted risk for psychiatric disorders, whereas the genetic liability of cannabis use is well known to increase the genetic liability of CanUD⁴. These findings, which should be viewed in the context of previous work showing that CanUD increases risk for multiple other substance dependencies⁴, have strong public health implications. This is a time of increasing acceptance of cannabis use. It has been represented to the public that cannabis has a therapeutic purpose for some disorders, including psychiatric disorders. With some exceptions, these claims have not been subjected to the scrutiny to which other claims of therapeutic utility are commonly exposed, for example by the US Food and Drug Administration. To the contrary, some US state legislatures have explicitly endorsed using cannabis for medical treatment of psychiatric disorders such as PTSD¹³. Our findings suggest, for example, that the opposite could be correct, that is, that cannabis may make PTSD worse rather than treat it. These results add to the growing literature of potential harms to mental health as a consequence of cannabis use and use disorder and suggest that the race toward cannabis legalization in many countries should be evaluated in the context of the consequent likely impact on the mental health of the public.

Methods

Traits and datasets

For our analyses, we used GWAS summary statistics based on EUR ancestry participants for the following investigated traits (see Table 1 for phenotypes, sample size and dataset information): CanUD¹⁹ and cannabis use (defined as any lifetime cannabis use);²³ anxiety severity (based on a widely used two-item scale (GAD-2)⁴³, MDD³², SCZ³⁰, BPD³¹, AN⁴⁴, ADHD⁴⁵ and PTSD as a total index of recent symptom severity (PCL-total) and its three symptom subdomains from the *Diagnostic and Statistical Manual of Mental Disorders* 4th edition⁴⁶ (avoidance, hyperarousal and reexperiencing)⁴⁷, and the Big Five personality traits: neuroticism, extraversion, agreeableness, conscientiousness and openness⁴⁸. For cannabis use and MDD, the available summary statistics excluded 23andMe data. For CanUD, we also used AFR GWAS summary statistics¹⁹ (Table 1).

Global genetic correlations

Genetic correlations based on EUR data were performed between the two cannabis traits with each of the psychiatric disorders, using LDSC⁴⁹, which requires GWAS summary statistics as input.

Statistically significant different correlations between CanUD and cannabis use were calculated considering $P = 2 \times \text{pnorm}(-|Z|)$; pnorm

is the value of the cumulative density function of the normal distribution of the $Z = \frac{r_{g\text{CanUD}} - r_{g\text{CanUse}}}{\sqrt{\text{se}_{\text{CanUD}}^2 + \text{se}_{\text{CanUse}}^2}}$, with mean = 0 and standard deviation = 1, as previously described⁴. The Bonferroni P value threshold = 0.0036 (0.05/14) assuming 14 independent tests was calculated considering that PCL-total was a combination of three other analyzed traits.

Cross-ancestry genetic correlations were run using POPCORN^{1,50}, which allows estimation of transethnic genetic correlation, in our case using the AFR ancestry GWAS of CanUD and the summary statistics of the psychiatric disorders and personality traits, all of which are based on EUR ancestry analyses. For POPCORN results, we calculated $Z = r_g/\text{se}$ and $P = 2 \times \text{pnorm}(-|Z|)$, where pnorm is the cumulative density of the normal distribution at a specific quantile.

To evaluate the effects of socioeconomic status on the cannabis-psychiatric trait relationships, we analytically removed income or educational attainment (as an indicator of socioeconomic status) effects on the two cannabis traits to evaluate its possible role as confounder, with a multi-trait-based conditional analysis (mtCOJO)⁵¹. The two cannabis trait summary statistics were used as target traits, whereas income (downloaded from <http://www.nealelab.is/uk-biobank/>) or educational attainment⁵² was used as a covariate trait. Income references Data-Field 738 (from UKB) with a sample size of 311,028 individuals; educational attainment had a sample size of 765,283 individuals.

Local genetic correlation

We used LAVA⁵³ software to estimate local genetic heritability and local genetic correlations of each of the two cannabis traits with the psychiatric disorders for EUR ancestry. The advantage of local genetic correlation is the possibility to detect significant regions whose signal could be lost when considering a mean across the whole genome. The whole genome was divided into 2,495 blocks, which implies a Bonferroni-corrected significant P value threshold of $0.05/2,495 = 2.0 \times 10^{-5}$ for local genetic heritability⁵³. The size of each block was about 1 MB to minimize the linkage disequilibrium between the regions. When performing local genetic correlation tests, CanUD and cannabis use resulted in 2,050 (Bonferroni-corrected P value threshold $0.05/2,050 = 2.4 \times 10^{-5}$) and 2,401 (Bonferroni-corrected P value threshold $0.05/2,401 = 2.1 \times 10^{-5}$) tests, respectively. Income references Data-Field 738 (from UKB) with a sample size of 311,028 individuals; educational attainment had a sample size of 765,283 individuals.

Multi-trait colocalization

Multi-trait colocalization analysis was run using HyPrColoc⁵⁴ on EUR ancestry data to identify genetic signals shared among the two cannabis traits and the psychiatric disorders. HyPrColoc uses GWAS input data to detect colocalized variants in defined regions and can be performed across several traits simultaneously. We ran HyPrColoc to investigate colocalization of CanUD, cannabis use, anxiety, MDD, SCZ, BPD, AN, ADHD and PCL-total for the whole genome, which was divided into 1,703 approximately independent linkage disequilibrium (LD) blocks⁵⁵. We considered significance at a posterior probability of colocalization > 0.7 .

Mendelian randomization

MR analyses were conducted to investigate the causal relationship between exposures and outcomes using genomic variants from EUR GWAS summary statistics as IVs. This allowed us to infer the impact of CanUD and cannabis use on the psychiatric disorders studied, and vice versa. MR analyses are based on three assumptions: (1) relevance: IVs are associated with the exposure phenotype; (2) independence: IVs are independent of any confounders; (3) exclusion restriction: IVs affect the exposure only through the outcome. Given that these assumptions are met, MR studies can be useful tools in determining and

providing evidence of causal relationships. To avoid bias from overlapping samples, we used MRlap software⁵⁶ version 0.03, which is based on the IVW method. We used summary statistics from GWAS adjusted for sex, age and principal components. For parameter settings, we fixed P value thresholds = 10^{-5} to select the genetic instruments, and LD threshold = 0.05 for pruning the selected genetic instruments. We also repeated the analyses using a more stringent P value threshold = 5×10^{-8} . Variants more strongly associated with the outcome than with the exposure are automatically removed by the software. MRlap generates observed results and bias-corrected results, and a test statistic to test their differences that identifies the presence-absence of statistical bias and indicates if corrected results are required. We included here psychiatric disorders (which are morbidities) but not personality traits. We used a Bonferroni P value threshold = 0.0056 (0.05/9) for each estimate of causality, where 9 rather than 10 is the denominator, determined by the non-independence of PCL-total and the other traits of which it is composed, PCL-avoidance, hyperarousal and reexperiencing.

To evaluate the instrumental strength of the instrumental variables, we calculated the f statistics as the mean of the squared effects of the instrumental variables divided by the square of their standard errors.

We also performed MR analyses with TwoSampleMR on non-overlapping samples (CanUD with AN and cannabis use with anxiety and the three PTSD subdomains).

Genomic structural equation modeling

Genomic-SEM⁵⁷ was used to examine the potential latent factor structure underlying the two cannabis traits and the selected psychiatric traits, incorporating PCL-total from the available PTSD phenotypes (Table 1), using EUR summary statistics. First, we conducted multivariable LD-score regression and applied the eigenvalues greater-than-one convention, visually examined the heat map-dendrogram (Supplementary Fig. 1) and performed parallel analysis (paLDSC function in genomic-SEM package; Supplementary Fig. 2)⁵⁸ using the standardized genetic correlation data to determine that three factors are appropriate. Population prevalence estimates were provided as input for case-control traits: 18.7% for cannabis use², 5.8% for CanUD², 1.25% for SCZ^{59,60}, 1.0% for BPD⁶¹, 20.6% for MDD^{62,63}, 2.15% for AN⁶⁴ and 7.15% for ADHD⁶⁵. Anxiety and PTSD were continuous traits. If a trait loaded >0.20, it was considered to load sufficiently onto a factor. Finally, we performed a CFA. The following fit statistics were considered when evaluating the model fit: CFI and SRMR. To determine model fit, CFI ≥ 0.90 indicates adequate fit and CFI ≥ 0.95 an excellent fit; SRMR ≤ 0.08 suggests good fit⁶⁶.

Reporting summary

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

Data availability

We used available summary statistics of already published works. Their references are reported in Table 1 of the Article.

Code availability

Codes for software used in this analysis are all publicly available through the citations for each method as introduced.

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Author contributions

M.G., D.F.L. and J.G. conceived the initial study design. D.F.L. and J.G. provided ongoing feedback and refinement of the analytic plan. M.G. performed global and local genetic correlations and Mendelian randomization analyses. D.F.L. performed POPCORN analysis. C.O. performed the genomic structural equation modeling analysis. P.G. performed mtCOJO analysis. S.B. performed HyPrColoc analysis. M.G., D.F.L., J.G., C.O. and J.D.D. contributed to data interpretation. M.G. and C.O. contributed to data visualization. M.G. and J.G. drafted the paper. J.G. supervised the work. M.G., C.O., P.G., S.B., C.D., J.D.D., H.Z., E.C.J., A.A., M.B.S., D.F.L. and J.G. critically evaluated and revised the paper.

Competing interests

J.G. is paid for editorial work for the journal *Complex Psychiatry*. M.B.S. has in the past 3 years received consulting income from Acadia Pharmaceuticals, Aptinyx, atai Life Sciences, BigHealth, Bionomics, BioXcel Therapeutics, Boehringer Ingelheim, Clexio, Eisai, EmpowerPharm, Engrail Therapeutics, Janssen, Jazz Pharmaceuticals, NeuroTrauma Sciences, PureTech Health, Sumitomo Pharma and Roche/Genentech. M.B.S. has stock options in Oxeia Biopharmaceuticals and EpiVario. He has been paid for his editorial work on *Depression and Anxiety* (editor-in-chief), *Biological Psychiatry* (deputy editor) and *UpToDate* (co-editor-in-chief for psychiatry). He has also received research support from NIH, Department of Veterans

Affairs and the Department of Defense. He is on the scientific advisory board for the Brain and Behavior Research Foundation and the Anxiety and Depression Association of America. The other authors declare no competing interests.

Additional information

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Software and code

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| | |
|-----------------|--|
| Data collection | No software used for data collection. |
| Data analysis | We used the following software: LDSC v1.0.1 for SNP-heritability and genetic correlations, LAVA 0.1.0 for local genetic correlations, MRlap v0.0.3 and TwoSampleMR v0.6.8 for Mendelian Randomization, the R PheWAS package (March 31, 2023) for phenomewide association analysis, mtCOJO (from GCTA v 1.94.1) for multi-trait conditional and joint analyses, HyPrColoc v 1.0 for multi-trait colocalization, genomic-SEM v0.05 for genomic structural equation modeling. All software packages used in this analysis are publicly available. |

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We used summary statistics from GWAS of European and African ancestry.

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We have no available information on population characteristics.

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Sample sizes were provided in the publications of the corresponding summary statistics. For the summary statistics from case-control studies, the effective sample size was calculated as $4 / (1 / \text{cases} + 1 / \text{controls})$, as described in the Methods.

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We did not exclude data from the analyses.

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We methods used were inherently robust and did not necessitate replication.

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