The relationship between cannabis use, schizophrenia, and bipolar disorder: a genetically informed study

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Summary

Background The relationship between psychotic disorders and cannabis use is heavily debated. Shared underlying genetic risk is one potential explanation. We investigated the genetic association between psychotic disorders (schizophrenia and bipolar disorder) and cannabis phenotypes (lifetime cannabis use and cannabis use disorder).

Methods We used genome-wide association summary statistics from individuals with European ancestry from the Psychiatric Genomics Consortium, UK Biobank, and International Cannabis Consortium. We estimated heritability, polygenicity, and discoverability of each phenotype. We performed genome-wide and local genetic correlations. Shared loci were identified and mapped to genes, which were tested for functional enrichment. Shared genetic liabilities to psychotic disorders and cannabis phenotypes were explored using causal analyses and polygenic scores, using the Norwegian Thematically Organized Psychosis cohort.

Findings Psychotic disorders were more heritable than cannabis phenotypes and more polygenic than cannabis use disorder. We observed positive genome-wide genetic correlations between psychotic disorders and cannabis phenotypes (range 0·22–0·35) with a mixture of positive and negative local genetic correlations. Three to 27 shared loci were identified for the psychotic disorder and cannabis phenotype pairs. Enrichment of mapped genes implicated neuronal and olfactory cells as well as drug–gene targets for nicotine, alcohol, and duloxetine. Psychotic disorders showed a causal effect on cannabis phenotypes, and lifetime cannabis use had a causal effect on bipolar disorder. Of 2181 European participants from the Norwegian Thematically Organized Psychosis cohort applied in polygenic risk score analyses, 1060 (48·6%) were females and 1121 (51·4%) were males (mean age 33·1 years [SD 11·8]). 400 participants had bipolar disorder, 697 had schizophrenia, and 1044 were healthy controls. Within this sample, polygenic scores for cannabis phenotypes predicted psychotic disorders independently and improved prediction beyond the polygenic score for the psychotic disorders.

Interpretation A subgroup of individuals might have a high genetic risk of developing a psychotic disorder and using cannabis. This finding supports public health efforts to reduce cannabis use, particularly in individuals at high risk or patients with psychotic disorders. Identified shared loci and their functional implications could facilitate development of novel treatments.

Funding US National Institutes of Health, the Research Council Norway, the South-East Regional Health Authority, Stiftelsen Kristian Gerhard Jebsen, EEA-RO-NO-2018–0535, European Union's Horizon 2020 Research and Innovation Programme, the Marie Skłodowska-Curie Actions, and University of Oslo Life Science.

Introduction

Cannabis is one of the most widely used substances globally. The estimated prevalence of lifetime cannabis use in the EU is 27·2%.[1] Approximately 10% of regular cannabis users develop cannabis use disorder,[2] which is defined as a problematic pattern of use causing clinically significant impairment.[3] Cannabis use has been linked to disorders with psychotic symptoms, including schizophrenia, with psychosis as a defining feature, and bipolar disorder, with an estimated psychosis prevalence of 73·8%.[4] Individuals reporting cannabis use are at higher risk of psychotic disorders (ie, schizophrenia, bipolar disorder) than the general population, as well as having earlier onset, worse symptoms, and longer hospitalisations.[5–8] Lifetime cannabis use is less strictly defined than cannabis use disorder but is associated with adverse outcomes and is genetically associated with other substance use phenotypes and disorders.[9] However, the nature of this link between psychotic disorders and cannabis use has been widely debated within the field of psychiatry and beyond.

Although many factors might explain the association between psychotic disorders and cannabis phenotypes (ie, lifetime cannabis use and cannabis use disorder), including shared environmental risk, mutual genetic risk is plausible. Schizophrenia, bipolar disorder, lifetime cannabis use, and cannabis use disorder are partly heritable (heritability range 0·50–0·80),[10–12] and

Lancet Psychiatry 2023; 10: 441–51

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Research in context

Evidence before this study

Cannabis use often co-occurs with disorders involving psychosis, psychotic symptoms, and mood dysregulation. Twin-based studies indicate that psychotic disorders and phenotypes associated with cannabis use are heritable. Yet, it remains unclear how genetics can inform our understanding of the association between psychotic disorders and cannabis use. From database inception to April 4, 2022, we searched PubMed and Google Scholar for genetic studies, published in English, investigating the association between two psychotic disorders (ie, schizophrenia and bipolar disorder) and cannabis use. The search terms were ("genetic" or "genome wide association study" or "GWAS" or "mendelian randomization" or "mendelian randomisation" or "MR" or "genetic correlation" or "genetic overlap" or "polygenic score" or "polygenic risk score") and ("schizophrenia" or "bipolar disorder" or "bipolar") and ("cannabis" or "marijuana").

Previous studies have discovered modest genetic correlations between schizophrenia and bipolar disorder and cannabis use. Studies have shown some genetic liability to cannabis use being causally linked to increased risk of schizophrenia and bipolar disorder with additional evidence of a reverse causal association (from psychotic disorders to cannabis use). Studies using polygenic scores have reported positive associations between genetic risk for psychotic disorders and cannabis use; however, research is scarce on how genetic liability to cannabis use can be applied to improve prediction of psychotic disorders.

Added value of this study

We used a series of genetic analyses to develop a more comprehensive understanding of the relationship between schizophrenia and bipolar disorder with two cannabis phenotypes: lifetime cannabis use and cannabis use disorder. Our first novel observation showed that psychotic disorders are more polygenic than is cannabis use disorder, and each phenotype varies in its degree of genetic discoverability. We expand on previous findings of modest positive genetic correlation at a genome-wide level to show that they are a result of a mixture of effect directions at the local level. In support of a shared genetic hypothesis, we identified a total of 57 distinct shared genetic loci for the psychotic disorder and cannabis phenotype pairs. These shared loci implicate potential mechanisms, such as neuronal and olfactory cell involvement, as well as genes encoding targets of drugs, such as nicotine, alcohol, and duloxetine. We provide a novel, putatively causal association between genetic liability to lifetime cannabis use and increased risk of bipolar disorder. Finally, we provide new evidence that polygenic scores for lifetime cannabis use and cannabis use disorder improve prediction of schizophrenia and bipolar disorder above and beyond their respective polygenic scores. To address the relationship between cannabis use and psychotic experiences, we show that both cannabis polygenic scores predicted bipolar disorder in patients who experienced psychosis but not in those without a psychotic experience.

Implications of all the available evidence

Evidence suggests a genetic component contributes to the co-occurrence of schizophrenia, bipolar disorder, and cannabis use. A subgroup of individuals will have a high risk for both disorders and cannabis use; therefore, provision of support for public health efforts to reduce cannabis use, particularly in this group at high risk, is essential. Moreover, identified genetic loci could inform targeted drug development.

emerging evidence suggests a shared genetic component increases risk of psychotic disorders and cannabis use. For instance, a modest positive genome-wide genetic correlation (range 0·17–0·31) has been reported between psychotic disorders and cannabis phenotypes,[9,13] indicating genetic overlap. However, more detailed genetic and mechanistic insights remain elusive.

The bidirectional causal relationship between psychotic disorders and cannabis phenotypes is often debated. A common hypothesis is that cannabis is a risk factor in the development of psychotic disorders,[14] whereas a reverse causality hypothesis posits that psychotic disorders lead to cannabis use to alleviate symptoms.[14,15] Causation and reverse causation are not mutually exclusive and have been assessed using mendelian randomisation, a statistical framework to test causal associations using genetic liability to the phenotypes of interest.[16] For example, a bidirectional causal relationship has been suggested between cannabis use and schizophrenia.[7,9,17] The accumulation of large genome-wide association study (GWAS) datasets provides opportunities to improve the assessment of causal relationships using mendelian randomisation.

Additional support for shared genetic liability comes from polygenic score studies. Polygenic scores are calculated as a weighted sum of phenotype-associated alleles and represent individual-level genetic liability to a phenotype. Previous studies found that the polygenic score for schizophrenia was positively associated with cannabis use[18] and modulated the link between cannabis use and psychosis,[19] but one study found no association with cannabis use disorder.[20] Studies have shown that, for a given phenotype, including polygenic scores of genetically correlated phenotypes could better predict the target phenotype using their combined predictive power.[21] Yet, to our knowledge, little is known about the potential to improve the prediction efficiency of psychotic disorders using joint genetic liability to psychotic disorders and cannabis phenotypes.

In this study, we investigated the genetic foundations underlying the epidemiological associations between psychotic disorders and cannabis phenotypes, using

statistical genetic approaches and the largest relevant GWAS. We aimed to examine the genetic architecture of each phenotype; to estimate genetic overlap by investigating genome-wide and local genetic correlations, specific shared genetic loci, and putative biological mechanisms; to re-evaluate the causal and reverse causal hypotheses using mendelian randomisation; and to improve the prediction of schizophrenia and bipolar disorder by integrating the genetic liability to psychotic disorders and cannabis phenotypes.

Methods

GWAS data

In our discovery analyses we used GWAS summary statistics for schizophrenia, bipolar disorder, lifetime cannabis use, and cannabis use disorder based on individuals with European ancestry from the Psychiatric Genomics Consortium (PGC), UK Biobank, and International Cannabis Consortium (appendix 1 p 1).[9,13,22,23] Validation of single nucleotide polymorphism (SNP) effect directions was conducted using summary statistics from independent samples for schizophrenia in individuals with east Asian ancestry from the PGC,[24] and bipolar disorder in individuals with European ancestry from FINNGEN.[25]

Establishing genetic architecture using MiXeR

MiXeR version 1.3[26] was used to estimate the heritability, polygenicity, and discoverability of each phenotype (appendix 1 p 1). MiXeR uses GWAS summary statistics to model additive genetic effects on a phenotype. Polygenicity is estimated as the number of trait-influencing variants expected to explain 90% of the heritability. Discoverability is the average magnitude of additive genetic effects among trait-influencing variants. MiXeR estimates heritability as a function of the product of polygenicity and discoverability.

Genetic correlations

To estimate the genetic correlation for each pair of phenotypes, we used linkage disequilibrium score regression[27] and local analysis of (co)variant annotation (LAVA).[28] Linkage disequilibrium score regression is a method for estimating genetic correlations at a genome-wide level. LAVA estimates genetic correlations at a local level within 2495 genomic regions using the default heritability thresholds of a p value of 0·05. The Benjamini-Hochberg correction (q<0·05) was applied.

Conjunctional false discovery rate

To determine polygenic enrichment between phenotype pairs, we used conditional quantile–quantile plots (appendix 1 pp 7–8), which show the distribution of p values for one phenotype conditioning on p value cutoffs of another phenotype (p<0·1, p<0·01, p<0·001). Four complex regions of linkage disequilibrium (appendix 1 p 2) were excluded from analysis to avoid potential inflation. Shared loci between phenotype pairs were identified using a conjunctional false discovery rate (FDR) analysis.[29] This method relies on two runs of a conditional FDR analysis. First, the associations between variants and a secondary phenotype are used to re-rank the test statistic in the primary phenotype. The process is repeated switching the roles of the primary and secondary phenotypes. The largest conditional FDR value between the two runs is then used as the conjunctional FDR value. A variant with a conjunctional FDR less than 0·05 was considered to be a shared variant.[30–32] Details for conjunctional FDR, locus definition, lead SNP identification, and SNP sign tests are provided in the appendix 1 (pp 1–3).

Gene mapping and enrichment analyses

All shared loci were mapped to genes via FUMA (version 1.3.7; appendix 1 p 3).[33] For each psychotic disorder, genes shared with lifetime cannabis use or cannabis use disorder, located outside of the

See Online for appendix 1

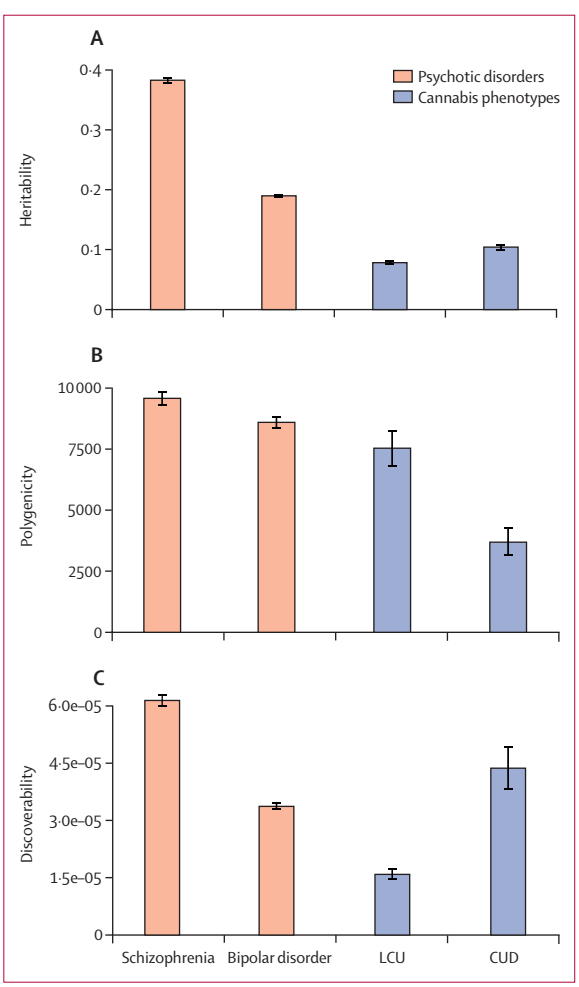

Figure 1: **Genetic architecture of psychotic disorders and cannabis phenotypes**
The MiXeR-estimated heritability, polygenicity, and discoverability for each phenotype. Error bars represent 1 SD. CUD=cannabis use disorder. LCU=lifetime cannabis use.

See Online for appendix 2

four complex regions of linkage disequilibrium, were combined for enrichment analyses. Enrichment analysis was done for gene ontology, pathways, cell types, and drug–gene interactions (appendix 1 p 3).

Mendelian randomisation

To estimate the potential causal relationship between psychotic disorders and cannabis phenotypes, we used mendelian randomisation (R version 4.1.1, TwoSampleMR version 0.5.6)[34] and reported results for inverse variance weighted,[35] weighted median,[36] and MR Egger[37] (appendix 1 pp 3–4). We also used MR Pleiotropy Residual Sum and Outlier (R version 4.1.1, MR-PRESSO version 1.0),[38] Causal Analysis Using Summary Effect estimates (R version 4.1.1, CAUSE version 1.2.0335),[39] and applied latent causal variable[40] analysis. We used the Benjamini-Hochberg correction (q<0·05) across all mendelian randomisation analyses.

Polygenic score calculation

Participants

The Norwegian Thematically Organized Psychosis (TOP) cohort[41] comprised 2181 European participants (1060 [48·6%] female, 1121 [51·4%] male; mean age 33·1 years [SD 11·8]), of whom 400 had bipolar disorder, 697 had schizophrenia, and 1044 were healthy control participants. We obtained information on cannabis use within the past 2 years before recruitment, and psychotic experience in their lifetime. Details are presented in appendix 1 (p 4) and appendix 2 (p 1). All participants provided written informed consent and the study was approved by The Regional Committee for Medical and Health Research Ethics of South-East Norway.

Statistical analysis

LD-pred2 [42] was used to calculate the polygenic scores for schizophrenia, bipolar disorder, lifetime cannabis use, and cannabis use disorder in the TOP cohort using the GWAS datasets (appendix 1 pp 4–5). For each polygenic score, we examined the significance and extent of association with bipolar disorder and schizophrenia diagnosis using a generalised logistic regression model (single-polygenic score models) adjusted for sex, age, genetic batch identification, and the first 20 genetic principal components. The Benjamini-Hochberg correction (q<0·05) was performed.

We established a multi-polygenic score model[43] for bipolar disorder and schizophrenia, separately, by combining the psychotic disorder-specific polygenic score with polygenic scores for lifetime cannabis use and cannabis use disorder in a joint model, accounting for the same covariates. This multi-polygenic score model was compared with the single polygenic score model for the psychotic disorder-specific polygenic score to evaluate the difference in explained variance due to the addition of polygenic scores for cannabis phenotypes.

We used non-melanoma skin cancer as a comparator as it does not appear to be associated

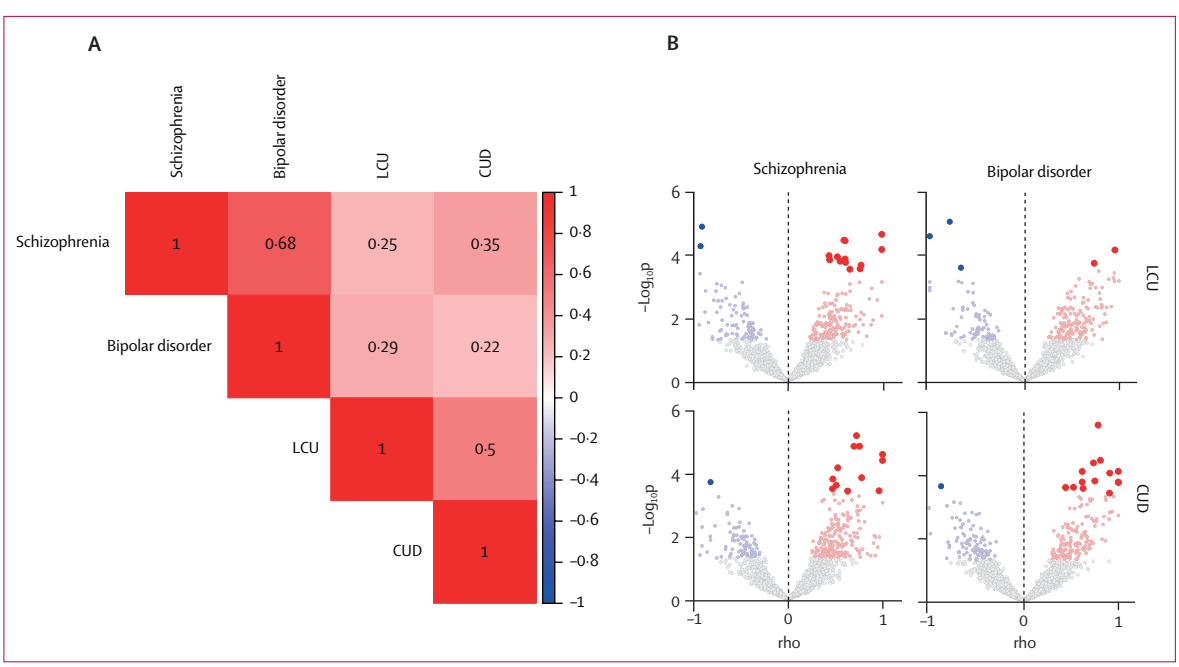

Figure 2: **Genome-wide and local genetic correlations**

(A) Results of genome-wide genetic correlations with numbers representing the correlation coefficient. All correlations were significant after correction for multiple comparisons. (B) Results of local genetic correlations with positive (red) and negative (blue) correlations across regions of the genome (each represented by one point). Grey points are genetic correlations with a p value of more than 0·05. Correlations with p value less than 0·05 are represented in red or blue depending on the direction of effect. Correlations surviving correction for multiple comparison are represented by larger points that are darker in colour. LCU=lifetime cannabis use. CUD=cannabis use disorder. Rho=local genetic correlations.

with psychotic disorders.[44] We did sensitivity analyses using 1031 participants without cannabis use in the past 2 years (appendix 1 p 5). Additional prediction of bipolar disorder was stratified on the basis of psychotic experience using 1449 participants (appendix 1 p 5).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

When analysing the genetic architecture of psychotic disorders and cannabis phenotypes, we found that estimated heritability (range 0·07–0·38) was greater among psychotic disorders than cannabis phenotypes, and polygenicity was lowest for cannabis use disorder (3700 trait-influencing variants; figure 1; appendix 2 p 2, appendix 1 p 9). Lifetime cannabis use (discoverability 1·59e–05) was 74% less genetically discoverable than schizophrenia (discoverability 6·14e–05).

When assessing the shared genetic architecture between psychotic disorders and cannabis phenotypes, we found that genome-wide genetic correlations ranged from 0·22 for bipolar disorder and cannabis use disorder, to 0·35 for schizophrenia and cannabis use disorder (figure 2A). Local genetic correlations, which give a more granular picture of genetic overlap in the presence of mixed effect directions, showed that only 65% (62% [153 of 247] to 68% [189 of 276]) of nominally significant local genetic correlations were positive between each psychotic disorder and cannabis phenotype pair (figure 2B; appendix 2 p 3).

We identified shared loci for each psychotic disorder and cannabis phenotype pair using the conjunctional FDR approach; schizophrenia and lifetime cannabis

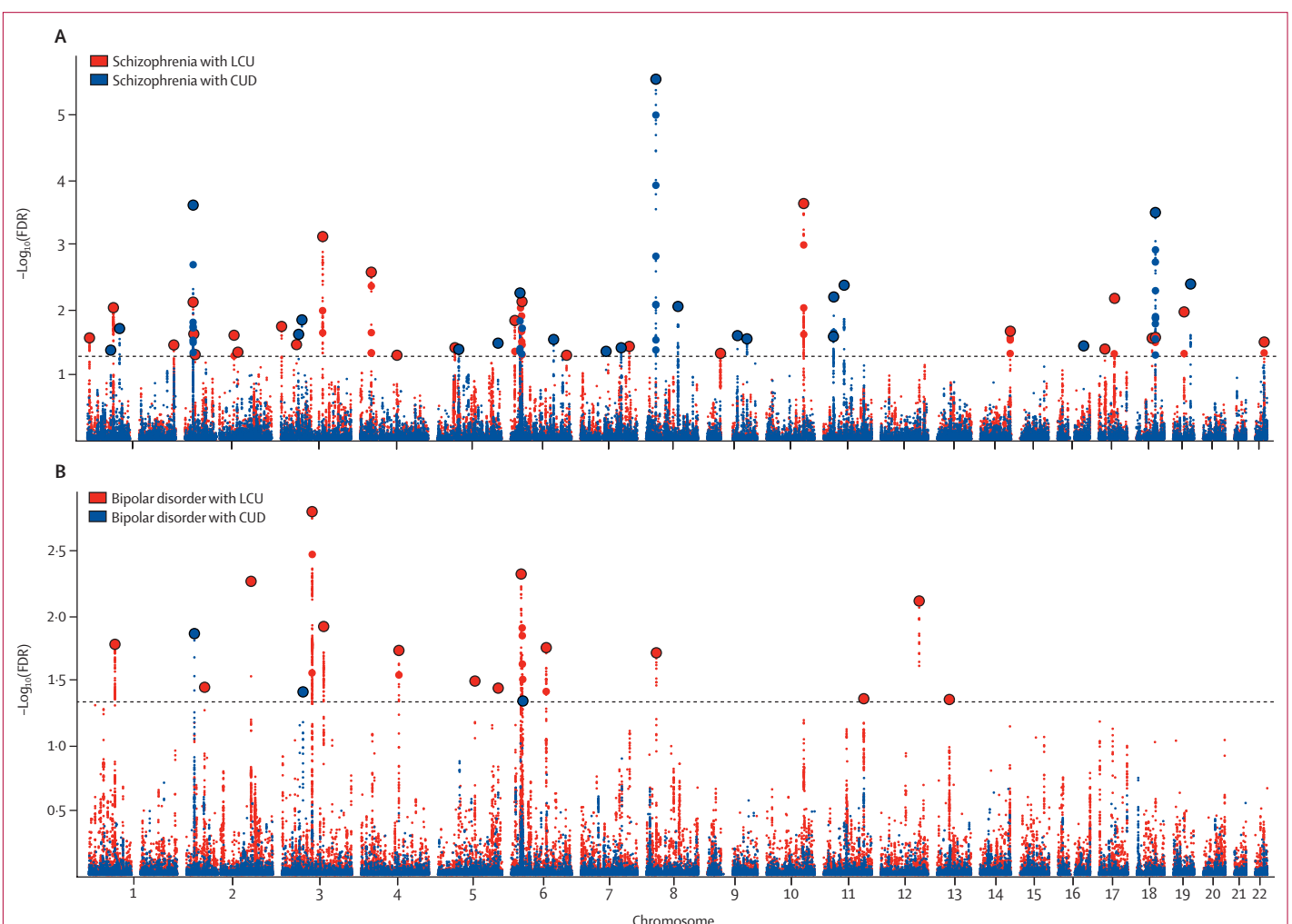

Figure 3: **Manhattan plot of shared genetic architecture**
The conjunctional false discovery rate Manhattan plot for the shared genetic architecture between schizophrenia (A) and bipolar disorder (B) with lifetime cannabis use (red) and cannabis use disorder (blue). For each plot, lead variants are represented as larger dots with a black outline. FDR=false discovery rate. LCU=lifetime cannabis use. CUD=cannabis use disorder.

use had 27 shared loci, schizophrenia and cannabis use disorder had 21 shared loci, bipolar disorder and lifetime cannabis use had 14 shared loci, and bipolar disorder and cannabis use disorder had three shared loci (figure 3; appendix 2 p 4). Five loci were shared by more than one phenotype pair (appendix 2 p 5). For example, three loci shared between lifetime cannabis use and schizophrenia overlapped with loci shared between lifetime cannabis use and bipolar disorder. Most shared lead variants for each pair showed concordant effects, ranging from 67% (two of three loci) to 93% (13 of 14 loci; appendix 2 p 4). For shared lead SNPs for schizophrenia and cannabis phenotype, 68% showed sign concordance between discovery and independent schizophrenia GWASs. For bipolar disorder, 73% showed sign concordance (appendix 2 pp 6–7).

The number of shared genes ranged from 110 genes (schizophrenia and lifetime cannabis use) to no genes (bipolar disorder and cannabis use disorder; appendix 2 p 8). The genes shared between schizophrenia and cannabis phenotypes were enriched for gene ontology terms mitochondrion and neuronal projection, and targets of alcohol, nicotine, and pharmaceutical drugs for treating dementia, AIDS, and rheumatoid arthritis (appendix 2 pp 9–11). The genes shared between bipolar disorder and lifetime cannabis use were enriched for olfactory ensheathing glia cells (appendix 2 p 9), and duloxetine, an SNRI (appendix 2 p 12).

For mendelian randomisation analyses, we focused on robust causal relationships supported by more than one mendelian randomisation method (table). A putative causal link from lifetime cannabis use to bipolar disorder was observed. Although the GWAS of cannabis use disorder lacked power to estimate causal effects on psychotic disorders using genome-wide significant loci, a relaxed threshold showed a putative causal link to schizophrenia (appendix 2 p 13). Strong evidence for reverse causal associations was observed, revealing that the genetic liability to schizophrenia increased the odds of lifetime cannabis use and cannabis use disorder, and the genetic liability to bipolar disorder increased the odds of lifetime cannabis use. Latent causal variable analyses did not support any causal association (appendix 2 p 14).

In 2181 TOP participants, single polygenic score models showed that polygenic scores for lifetime cannabis use and cannabis use disorder significantly predicted schizophrenia diagnosis (figure 4A; appendix 2 p 15), and a similar result was found for bipolar disorder in which polygenic scores for lifetime cannabis use and cannabis use disorder predicted diagnosis (figure 4B). As a comparator, the polygenic score for non-melanoma skin cancer predicted neither schizophrenia nor bipolar disorder diagnoses.

For schizophrenia and bipolar disorder, multi-polygenic score models, including polygenic scores for lifetime cannabis use and cannabis use disorder, showed a small yet significant improvement in explained variance beyond the psychosis-specific single polygenic score models (figure 4; appendix 2 pp 16–17). The improvements seen with polygenic scores for lifetime cannabis use and cannabis use disorder remained significant after including polygenic scores for both psychotic disorders in multi-polygenic score models (appendix 2 pp 16–17). Adding the polygenic score for non-melanoma skin cancer did not show significant improvement.

	SNPs (n)	Estimate	OR	SE	p value	p_{FDR}
LCU → schizophrenia						
Inverse variance weighted	4	β=0·16	1·17	0·14	0·23	3·13e–1
MR Egger	4	β=–0·96	0·38	0·88	0·39	4·74e–1
Weighted median	4	β=0·23	1·26	0·11	0·03	5·37e–2
MR-PRESSO (raw)	4	β=0·16	1·17	0·14	0·32	4·18e–1
CAUSE	6 236 335	γ=0·05	1·05	0·05	0·61	6·48e–1
LCU → bipolar disorder						
Inverse variance weighted*	4	β= 0·37	1·45	0·13	5·37e–3	1·22e–2
MR Egger	4	β=–0·63	0·53	0·90	0·55	6·23e–1
Weighted median*	4	β=0·40	1·49	0·11	1·78e–4	6·72e–4
MR-PRESSO (raw)	4	β=0·37	1·45	0·13	0·07	1·19e–1
CAUSE	6 994 919	γ=0·06	1·03	0·05	0·52	6·10e–1
CUD → schizophrenia						
Inverse variance weighted*	2	β=0·45	1·57	0·13	6·40e–4	1·98e–3
MR Egger	2	..	..	..	..	..
Weighted median	2	..	..	..	..	..
MR-PRESSO (raw)	2	..	..	..	..	..
CAUSE	6 006 946	γ=0·05	1·05	0·05	0·60	6·48e–1
CUD → bipolar disorder						
Inverse variance weighted	2	β=0·03	1·03	0·10	0·79	8·14e–1
MR Egger	2	..	..	..	..	..
Weighted median	2	..	..	..	..	..
MR-PRESSO (raw)	2	..	..	..	..	..
CAUSE	6 358 021	γ=0·05	1·05	0·04	0·38	4·74e–1
Schizophrenia → LCU						
Inverse variance weighted*	128	β=0·09	1·09	0·02	7·45e–6	5·07e–5
MR Egger	128	β=–0·02	0·98	0·09	8·45e–1	8·45e–1
Weighted median*	128	β=0·11	1·12	0·02	9·69e–6	5·49e–5
MR-PRESSO (corrected)*	124	β=0·10	1·11	0·02	4·06e–7	3·45e–6
CAUSE*	6 236 335	γ=0·05	1·05	0·01	9·90e–3	2·10e–2
Schizophrenia → CUD						
Inverse variance weighted*	129	β=0·21	1·23	0·03	3·50e–12	1·19e–10
MR Egger*	129	β=0·36	1·43	0·12	4·02e–3	1·05e–2
Weighted median*	129	β=0·21	1·23	0·04	4·97e–8	5·63e–7
MR-PRESSO (corrected)*	126	β=0·20	1·23	0·03	9·66e–12	1·64e–10
CAUSE*	6 006 946	γ=0·09	1·09	0·02	0·02	3·78e–2
Bipolar disorder → LCU						
Inverse variance weighted*	36	β=0·11	1·12	0·03	1·21e–4	5·14e–4
MR Egger*	36	β=0·69	1·99	0·15	7·90e–5	3·84e–4
Weighted median*	36	β=0·12	1·13	0·04	1·91e–3	5·41e–3
MR-PRESSO (raw)*	36	β=0·11	1·12	0·03	4·89e–4	1·66e–3
CAUSE*	6 994 919	γ=0·07	1·07	0·02	4·60e–3	1·12e–2

(Table continues on next page)

Additionally, we found no evidence of the PGSs interacting with sex to predict schizophrenia or bipolar disorder diagnosis (appendix 2 p 18).

Cannabis use was more common among people with bipolar disorder and schizophrenia than controls in the TOP cohort (appendix 2 p 1). Therefore, we performed sensitivity analyses using 1031 participants without recent cannabis use, which showed that the prediction efficiency of polygenic scores for lifetime cannabis use and cannabis use disorder remained significant in single polygenic score models (appendix 2 p 15). Multi-polygenic score models showed continued improvement in prediction for bipolar disorder (fold change R^2=1·13, p_{FDR}=0·030) but not for schizophrenia (fold change R^2=1·03, p_{FDR}=0·20; appendix 2 pp 16–17).

For 1449 participants with information on presence or absence of psychotic experience, single-polygenic score analyses showed polygenic scores for lifetime cannabis use and cannabis use disorder predicted bipolar disorder with psychotic experience but not bipolar disorder without psychotic experience (figure 4C and D). Multi-polygenic score analyses significantly improved prediction of individuals with bipolar disorder with psychotic experience (fold change R^2=1·17, p_{FDR}=7·72e–4) but not those without (appendix 2 pp 19–22.).

	SNPs (n)	Estimate	OR	SE	p value	p_{FDR}
(Continued from previous page)						
Bipolar disorder → CUD						
Inverse variance weighted	38	β=0·06	1·06	0·05	0·18	2·66e–1
MR Egger*	38	β=0·61	1·84	0·26	0·02	3·78e–2
Weighted median	38	β=0·10	1·11	0·07	0·13	2·01e–1
MR-PRESSO (raw)	38	β=0·06	1·06	0·05	0·19	2·69e–1
CAUSE	6 358 021	γ=0·06	1·06	0·03	0·12	1·94e–1

MR-PRESSO produces the same estimates as the inverse variance weighted method when no outlier SNP estimates are detected (ie, MR-PRESSO [raw]). When outliers are detected, those SNPs are removed, and the inverse variance weighted estimate is re-calculated (MR-PRESSO [corrected]). When no data were reported, the mendelian randomisation method was unable to estimate the causal effect using so few SNPs. CAUSE uses the full set of overlapping SNPs between two genome-wide association studies to estimate the causal effect. The causal effect presented is the gamma estimate from the causal model and the p value is from a test of whether the causal model is a better fit. CUD=cannabis use disorder. LCU=lifetime cannabis use. MR-PRESSO=Mendelian Randomisation Pleiotropy Residual Sum and Outlier. OR=odds ratio. pFDR=p value after the Benjamini-Hochberg correction for false discovery rate. SNPs=single nucleotide polymorphisms (genetic variants). *Significant associations after correction for multiple comparisons.

Table: **Bidirectional mendelian randomisation analysis**

Discussion

In this genetic association study, we conducted a set of genetically informed analyses to investigate the nature of the association between psychotic disorders and cannabis phenotypes. We observed differences in the genetic architectures of schizophrenia, bipolar disorder, lifetime cannabis use, and cannabis use disorder. We found evidence of genetic overlap between each psychotic disorder and cannabis phenotype pairs at the genome-wide, regional, and locus levels. A group of shared loci, ranging from three to 27, with mixed effect directions was identified for each phenotype pair. Putative causal relationships were tested using mendelian randomisation, showing some bidirectional causal associations. Combining polygenic scores for cannabis phenotypes and psychotic disorders helped to distinguish participants with schizophrenia or bipolar disorder from healthy participants. These findings suggest that a shared genetic component underlies the phenotypic link between psychotic disorders and cannabis phenotypes with implications for guiding clinical practice and public policy.

Both psychotic disorders had greater heritability than cannabis phenotypes and were more polygenic than cannabis use disorder. The polygenicity findings for schizophrenia and bipolar disorder are in line with previous reports.[45] To our knowledge, the polygenicity of lifetime cannabis use or cannabis use disorder has not been previously estimated. Cannabis phenotypes had distinctive genetic architectures from each other. Cannabis use disorder was more heritable and was associated with fewer genetic variants than lifetime cannabis use, which could be reflective of a more specific, clinically defined disorder, influenced by biological factors, such as the individual physical response to tetrahydrocannabinol consumption.[46] Lifetime cannabis use might be less specific, probably reflecting a heterogeneous, behavioural phenotype that is more responsive to environmental factors. The low discoverability of lifetime cannabis use suggests a large sample size is required to uncover its complete genetic architecture.

This study supports the shared genetic hypothesis for psychotic disorders and cannabis phenotypes by providing evidence supporting genome-wide genetic correlations,[9,13] identifying local genetic correlations in smaller genomic regions, and discovering 57 distinct shared loci. Positive genome-wide genetic correlations, positive shifts in local genetic correlations, and concordant effects in most lead shared variants for each psychotic disorder and cannabis phenotype pair indicate that, in general, genetic liability to cannabis use and psychotic disorders increases concurrently. This association suggests that genetic factors underlie the robust positive phenotypic relationship linking schizophrenia and bipolar disorder with cannabis phenotypes. Polygenic score analyses showed a link between genetic liability of cannabis phenotypes and psychotic experience in bipolar disorder. Although the association of cannabis use and bipolar disorder with but not without psychotic experience supports the established psychosis–cannabis connection,[8,47] it requires validation. Shared genes showed significant enrichment in various biological processes. Some enriched gene ontology terms have been linked to cannabis use and psychotic disorders, such as neuron projection,[48,49] whereas for others, such as glycosphingolipid biosynthesis,[50] the connection to cannabis phenotypes requires further research.

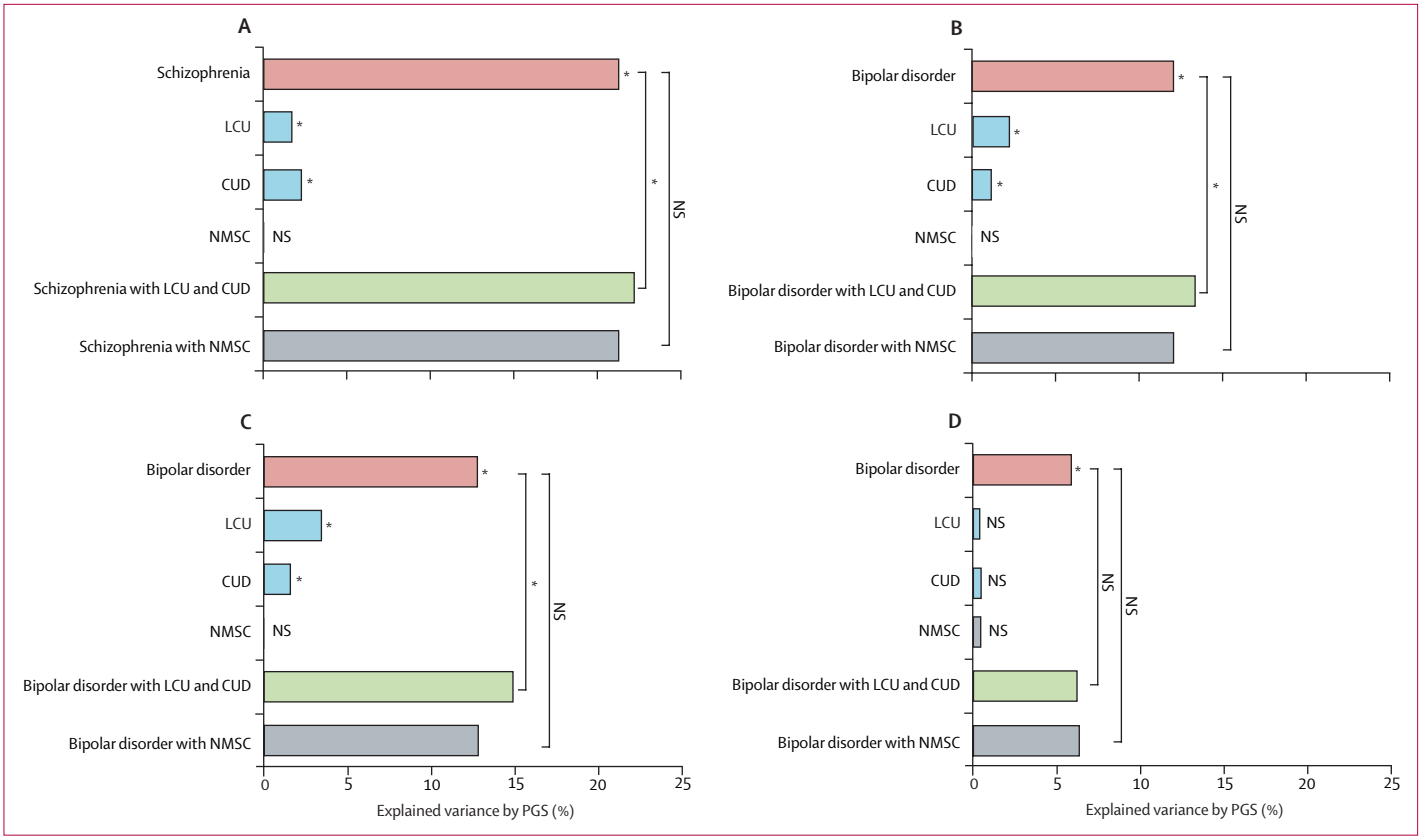

Figure 4: **Polygenic risk prediction**

A comparison of variance explained by polygenic scores in single and multi-polygenic score models to distinguish patients from healthy controls: those with schizophrenia (A), bipolar disorder (B), and bipolar disorder with psychotic experience (C) and without psychotic experience (D); note that C and D are subsets of B (bipolar disorder). Red represents the single polygenic score model with the psychotic-disorder-specific polygenic score and covariates only. Blue represents single-polygenic score models with covariates and polygenic score of lifetime cannabis use or of cannabis use disorder. Green represents the multi-polygenic score model with the psychotic-disorder-specific polygenic score, polygenic scores for lifetime cannabis use and cannabis use disorder, and covariates. Grey represents comparison models that include the polygenic scores for non-melanoma skin cancer. CUD=cannabis use disorder. LCU=lifetime cannabis use. NMSC=non-melanoma skin cancer. NS=not significant. PGS=polygenic score. *Significance after Benjamini-Hochberg correction.

Part of the shared genetic component has opposite effects on psychotic and cannabis phenotypes, such as genomic regions with negative correlation coefficients and shared loci with discordant effect directions. These results might partly be explained by the fact that schizophrenia and bipolar disorder are clinically and biologically heterogeneous disorders with a wide range of symptoms, that might have mixed associations with cannabis phenotypes. For instance, in a sample of patients with schizophrenia, cannabis use was associated with severe positive symptoms but fewer negative symptoms.[47] This mixed relationship might also be supported by the results of our enrichment analyses of drug–gene targets. Shared genes for schizophrenia and cannabis phenotypes showed significant enrichment for genes encoding targets of nicotine and alcohol. Use of nicotine or alcohol is prevalent in cannabis users, and co-users show a higher rate of psychotic disorder and symptom severity.[51] Genes shared between bipolar disorder and cannabis phenotypes were enriched for drug targets of duloxetine, an antidepressant[52] and reliever of chronic pain.[53] Medicinal cannabis use has been linked to reduced self-reported depression[54] and pain management;[55] however, cannabis use or misuse is also associated with adverse effects, including increased risk of depression, suicidal behaviours,[56] and worse analgesic outcomes.[57] Further investigation is required to explore the potential biological mechanisms linked to cannabis, antidepressants, and analgesics. The mixed effect directions and the gene–drug interactions help to explain the mixed relationship between cannabis use and symptom dimensions in psychotic disorders.

The mendelian randomisation analyses provide putative evidence for bidirectional causal effects between psychotic disorders and cannabis phenotypes. We observed robust evidence that genetic liability to schizophrenia causally increases risk of both cannabis phenotypes, which supports previous findings.[9,17,58] We present novel putative evidence that the genetic liability to lifetime cannabis use increases risk of bipolar disorder. A previous bidirectional mendelian randomisation study only found that genetic liability to

bipolar disorder increased the risk of lifetime cannabis use,[59] which we also observed. Using the latest and largest bipolar disorder GWAS probably aided this discovery. However, the CAUSE method could not distinguish causality from effects due to a shared factor related to lifetime cannabis use and bipolar disorder. Additionally, insufficient power in the lifetime cannabis use GWAS could have affected the validity of this finding. We caution readers on concluding that psychotic disorders cause cannabis use, and that cannabis use does not cause psychotic disorders. It is important to consider that for many methods there is a large difference in the number of genetic variants included in the analyses testing forward (cannabis-to-psychosis) and reverse (psychosis-to-cannabis) causal associations. Given the GWAS of psychotic disorders is more powerful than the GWAS of cannabis phenotypes, the power to detect reverse causation is greater than to detect forward causation. As more genome-wide significant loci are discovered for cannabis phenotypes, the reliability of causal estimates will improve, and more robust causal associations could be found.

Polygenic scores have become an important tool in understanding complex genetic phenotypes and for precision medicine. Consistent with previous reports,[13] we found each cannabis phenotype polygenic score to be significantly associated with bipolar disorder and schizophrenia diagnosis. A multi-polygenic score approach significantly improved the prediction of bipolar disorder and schizophrenia by adding polygenic scores for cannabis phenotypes. These findings support the idea that incorporating additional polygenic scores to the psychotic-disorder-specific polygenic scores improves prediction accuracy.[21,43] However, the improvement of our multi-polygenic score models was small, which restricts their clinical use. Still, the potential of these models for risk stratification of patients is promising and might become useful with larger GWASs in the future.

There are several clinically relevant implications for the current findings. A bidirectional causal link between psychotic disorders and cannabis use suggests public efforts to reduce cannabis use might prevent psychotic disorders and potentially reduce psychotic symptoms in individuals and patients at high risk. Moreover, the underlying genetic component that contributes to the co-occurrence of psychotic disorders and cannabis use suggests a subgroup of individuals are at high genetic risk for psychosis and cannabis use. Early identification of this subgroup is important for targeted interventions and our results suggest polygenic risk scores might help with this risk stratification and treatment in the future.

The present findings should be interpreted considering some limitations. The GWASs for bipolar disorder and schizophrenia might include cannabis users, which could bias the findings. The power of the cannabis use disorder GWAS is low for the shared locus discovery, mendelian randomisation analyses, and prediction efficiency of polygenic score for cannabis use disorder. The exclusion of linkage disequilibrium regions and removal of the overlapping UK Biobank cohort in the bipolar disorder GWAS might affect the power of the conjunction FDR analyses. Furthermore, shared loci require validation in independent cohorts for cannabis phenotypes. Additionally, psychotic disorders and cannabis use share environmental factors, which could contribute to their covariation.[60] Further work is required to disentangle shared genetics from environmental influences.

We only focused on the possibility for boosting prediction efficiency of psychotic disorders by integrating the polygenic scores of cannabis phenotypes. This decision was made on the basis of available data in the TOP cohort, but the analyses also have potential for greater clinical use than the prediction of cannabis phenotypes. We use psychotic disorders as a general term, but psychosis is not a defining feature of bipolar disorder. Most analyses relate cannabis use to schizophrenia and bipolar disorder, not psychosis. Other psychiatric disorders, such as depression, have been genetically associated with cannabis use and have relevant links to psychosis. Thus, the findings might extend beyond schizophrenia and bipolar disorder.

Our study used the largest genetic datasets and various genetic approaches to evaluate the relationship between cannabis phenotypes and psychotic disorders. The findings support a shared genetic basis, with bidirectional causality, which helps to explain the well established co-occurrence of psychotic disorders and cannabis use. A subgroup of individuals will have a high genetic risk of developing a psychotic disorder and using cannabis, supporting targeted public health efforts to reduce cannabis use particularly among these individuals at high risk. Identified shared genetic loci could also aid in treatment efforts. Ultimately, these results could help inform public health policies and aid in pursuits of customised care for patients.

Contributors

WC, NP, NK, OF, OS, and OA conceived the study and were involved in study design. LR, NES, OS, GH, and TVL collected data for the study. WC and NP had access to all the data, conducted analyses, and drafted the initial manuscript. All authors had full access to the data if they wished, contributed to data interpretation and editing of the manuscript, and accepted responsibility to submit the mauscript for publication. WC, NP, and OA verified the data and made the final decision to submit for publication.

Declaration of interests

OAA reports personal fees for the speaker's honorarium from Lundbeck, Janssen, and Sunovion, personal fees for consultancy work from Biogen and Milken, receives stock options for consultancy work for Cortechs.ai, serves as a national principal investigator for trials by Janssen (depression), MAPS (post-traumatic stress disorder), and BI (schizophrenia), receives grants from the EU, Research Council of Norway, South-East Norway Health Authority, US National Institutes of Health, and KG Jebsen Stiftelsen, and holds a patent of intranasal administration (US20160310683 A1). AMD is a founder of and holds equity interest in CorTechs Labs and serves on the scientific advisory board of CorTechs Labs, Human Longevity, and the Mohn Medical Imaging and Visualization Center in Bergen, Norway, receives research funding from the US National Institutes of Health, and is the principal

investigator of a research agreement between General Electric Healthcare and the University of California, San Diego (UCSD). RI receives honoraria for lectures from Pierre Fabre. All other authors declare no competing interests.

Data sharing

All GWAS summary statistics included in this study are publicly available. Data from the Norwegian Thematically Organized Psychosis cohort is available on request to scientists associated with an institution capable of providing appropriate data transfer agreements.

Acknowledgments

Funding was provided by the US National Institutes of Health (grants NS057198, EB00790, and 1R01MH124839), the Research Council of Norway (grants 223273, 296030, 300309, 324252), the South-East Regional Health Authority (grant 2017–112, 2022–073), Stiftelsen Kristian Gerhard Jebsen (grants SKGJ-MED-008 and SKGJ-MED-021), EEA-RO-NO-2018–0535, EU's Horizon 2020 Research and Innovation Programme (grant 847776; CoMorMent and 964874 REALMENT), the Marie Skłodowska-Curie Actions Grant 80113 (Scientia fellowship), Network of European funding for Neuroscience research (ES609126), and part of the convergence environment (MultiModal Mental Models [4MENT]) at the University of Oslo Life Science. We also received internationalisation support from University of Oslo Life Science, Norges Forskningsråd (300309), and Rådet for psykisk helse. Sigma2 (the National Infrastructure for High Performance Computing and Data Storage in Norway) and the Tjeneste for Sensitive Data facilities provided resources for this study.

References

1 European Monitoring Centre for Drugs and Drug Addiction. European drug report 2021: trends and developments. Luxembourg: Publications office of the European Union, 2021.

2 United Nations Office on Drugs and Crime. World drug report 2019. 2019. https://wdr.unodc.org/wdr2019/ (accessed April 7, 2022).

3 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fifth edition: DSM-5. Arlington, VA: American Psychiatric Publishing, 2013.

4 van Bergen AH, Verkooijen S, Vreeker A, et al. The characteristics of psychotic features in bipolar disorder. *Psychol Med* 2019; **49:** 2036–48.

5 Hjorthøj C, Posselt CM, Nordentoft M. Development over time of the population-attributable risk fraction for cannabis use disorder in schizophrenia in Denmark. *JAMA Psychiatry* 2021; **78:** 1013–19.

6 Pinto JV, Medeiros LS, Santana da Rosa G, et al. The prevalence and clinical correlates of cannabis use and cannabis use disorder among patients with bipolar disorder: a systematic review with meta-analysis and meta-regression. *Neurosci Biobehav Rev* 2019; **101:** 78–84.

7 Vaucher J, Keating BJ, Lasserre AM, et al. Cannabis use and risk of schizophrenia: a mendelian randomization study. *Mol Psychiatry* 2018; **23:** 1287–92.

8 Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Arch Gen Psychiatry* 2011; **68:** 555–61.

9 Pasman JA, Verweij KJH, Gerring Z, et al. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. *Nat Neurosci* 2018; **21:** 1161–70.

10 Hilker R, Helenius D, Fagerlund B, et al. Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish twin register. *Biol Psychiatry* 2018; **83:** 492–98.

11 Verweij KJ, Zietsch BP, Lynskey MT, et al. Genetic and environmental influences on cannabis use initiation and problematic use: a meta-analysis of twin studies. *Addiction* 2010; **105:** 417–30.

12 Pettersson E, Lichtenstein P, Larsson H, et al. Genetic influences on eight psychiatric disorders based on family data of 4 408 646 full and half-siblings, and genetic data of 333 748 cases and controls. *Psychol Med* 2019; **49:** 1166–73.

13 Johnson EC, Demontis D, Thorgeirsson TE, et al. A large-scale genome-wide association study meta-analysis of cannabis use disorder. *Lancet Psychiatry* 2020; **7:** 1032–45.

14 Gillespie NA, Kendler KS. Use of genetically informed methods to clarify the nature of the association between cannabis use and risk for schizophrenia. *JAMA Psychiatry* 2021; **78:** 467–68.

15 Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ* 2002; **325:** 1199.

16 Sanderson E, Richardson TG, Morris TT, Tilling K, Davey Smith G. Estimation of causal effects of a time-varying exposure at multiple time points through multivariable mendelian randomization. *PLoS Genet* 2022; **18:** e1010290.

17 Johnson EC, Hatoum AS, Deak JD, et al. The relationship between cannabis and schizophrenia: a genetically informed perspective. *Addiction* 2021; **116:** 3227–34.

18 Power RA, Verweij KJ, Zuhair M, et al. Genetic predisposition to schizophrenia associated with increased use of cannabis. *Mol Psychiatry* 2014; **19:** 1201–04.

19 Wainberg M, Jacobs GR, di Forti M, Tripathy SJ. Cannabis, schizophrenia genetic risk, and psychotic experiences: a cross-sectional study of 109 308 participants from the UK Biobank. *Transl Psychiatry* 2021; **11:** 211.

20 Hjorthøj C, Uddin MJ, Wimberley T, et al. No evidence of associations between genetic liability for schizophrenia and development of cannabis use disorder. *Psychol Med* 2021; **51:** 479–84.

21 Krapohl E, Patel H, Newhouse S, et al. Multi-polygenic score approach to trait prediction. *Mol Psychiatry* 2018; **23:** 1368–74.

22 Mullins N, Forstner AJ, O'Connell KS, et al. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat Genet* 2021; **53:** 817–29.

23 Trubetskoy V, Pardiñas AF, Qi T, et al. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* 2022; **604:** 502–08.

24 Lam M, Chen C-Y, Li Z, et al. Comparative genetic architectures of schizophrenia in East Asian and European populations. *Nat Genet* 2019; **51:** 1670–78.

25 Kurki MI, Karjalainen J, Palta P, et al. FinnGen: unique genetic insights from combining isolated population and national health register data. *medRxiv* 2022; published online March 6. https://doi.org/10.1101/2022.03.03.22271360 (preprint).

26 Frei O, Holland D, Smeland OB, et al. Bivariate causal mixture model quantifies polygenic overlap between complex traits beyond genetic correlation. *Nat Commun* 2019; **10:** 2417.

27 Bulik-Sullivan BK, Loh P-R, Finucane HK, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* 2015; **47:** 291–95.

28 Werme J, Sluis S van der, Posthuma D, Leeuw CA de. LAVA: an integrated framework for local genetic correlation analysis. *medRxiv* 2021; published online Jan 28. https://doi.org/10.1101/2020.12.31.424652 (preprint).

29 Andreassen OA, Thompson WK, Schork AJ, et al. Improved detection of common variants associated with schizophrenia and bipolar disorder using pleiotropy-informed conditional false discovery rate. *PLoS Genet* 2013; **9:** e1003455.

30 Cheng W, van der Meer D, Parker N, et al. Shared genetic architecture between schizophrenia and subcortical brain volumes implicates early neurodevelopmental processes and brain development in childhood. *Mol Psychiatry* 2022; **27:** 5167–76.

31 Smeland OB, Bahrami S, Frei O, et al. Genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder, and intelligence. *Mol Psychiatry* 2020; **25:** 844–53.

32 Cheng W, Frei O, van der Meer D, et al. Genetic association between schizophrenia and cortical brain surface area and thickness. *JAMA Psychiatry* 2021; **78:** 1020–30.

33 Watanabe K, Taskesen E, van Bochoven A, Posthuma D. Functional mapping and annotation of genetic associations with FUMA. *Nat Commun* 2017; **8:** 1826.

34 Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. *eLife* 2018; **7:** e34408.

35 Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol* 2013; **37:** 658–65.

36 Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol* 2016; **40:** 304–14.

37 Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015; **44:** 512–25.

38 Verbanck M, Chen C-Y, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet* 2018; **50:** 693–98.

39 Morrison J, Knoblauch N, Marcus JH, Stephens M, He X. Mendelian randomization accounting for correlated and uncorrelated pleiotropic effects using genome-wide summary statistics. *Nat Genet* 2020; **52:** 740–47.

40 O'Connor LJ, Price AL. Distinguishing genetic correlation from causation across 52 diseases and complex traits. *Nat Genet* 2018; **50:** 1728–34.

41 Steen NE, Aas M, Simonsen C, et al. Serum levels of second-generation antipsychotics are associated with cognitive function in psychotic disorders. *World J Biol Psychiatry* 2017; **18:** 471–82.

42 Privé F, Arbel J, Vilhjálmsson BJ. LDpred2: better, faster, stronger. *Bioinformatics* 2021; **36:** 5424–31.

43 Schoeler T, Choi SW, Dudbridge F, et al. Multi-polygenic score approach to identifying individual vulnerabilities associated with the risk of exposure to bullying. *JAMA Psychiatry* 2019; **76:** 730–38.

44 Lu D, Andersson TML, Fall K, et al. Clinical diagnosis of mental disorders immediately before and after cancer diagnosis: a nationwide matched cohort study in Sweden. *JAMA Oncol* 2016; **2:** 1188–96.

45 Hindley G, Frei O, Shadrin AA, et al. Charting the landscape of genetic overlap between mental disorders and related traits beyond genetic correlation. *Am J Psychiatry* 2022; **179:** 833–43.

46 Ferland JN, Hurd YL. Deconstructing the neurobiology of cannabis use disorder. *Nat Neurosci* 2020; **23:** 600–10.

47 Quattrone D, Ferraro L, Tripoli G, et al. Daily use of high-potency cannabis is associated with more positive symptoms in first-episode psychosis patients: the EU-GEI case-control study. *Psychol Med* 2021; **51:** 1329–37.

48 Danos P, Baumann B, Bernstein HG, et al. Schizophrenia and anteroventral thalamic nucleus: selective decrease of parvalbumin-immunoreactive thalamocortical projection neurons. *Psychiatry Res* 1998; **82:** 1–10.

49 Wu C-S, Zhu J, Wager-Miller J, et al. Requirement of cannabinoid CB(1) receptors in cortical pyramidal neurons for appropriate development of corticothalamic and thalamocortical projections. *Eur J Neurosci* 2010; **32:** 693–706.

50 Wood PL, Filiou MD, Otte DM, Zimmer A, Turck CW. Lipidomics reveals dysfunctional glycosynapses in schizophrenia and the G72/G30 transgenic mouse. *Schizophr Res* 2014; **159:** 365–69.

51 Yurasek AM, Aston ER, Metrik J. Co-use of alcohol and cannabis: a review. *Curr Addict Rep* 2017; **4:** 184–93.

52 de Dios Consuelo, Ezquiaga E. Ezquiaga E. Manic switching in patients receiving duloxetine. *Am J Psychiatry* 2007; **164:** 1121.

53 Lunn MPT, Hughes RAC, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev* 2014; **1:** CD007115.

54 Vázquez M, Guevara N, Maldonado C, Guido PC, Schaiquevich P. Potential pharmacokinetic drug–drug interactions between cannabinoids and drugs used for chronic pain. *BioMed Res Int* 2020; **2020:** 3902740.

55 Bicket MC, Stone EM, McGinty EE. Use of cannabis and other pain treatments among adults with chronic pain in US states with medical cannabis programs. *JAMA Netw Open* 2023; **6:** e2249797.

56 Gobbi G, Atkin T, Zytynski T, et al. Association of cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: a systematic review and meta-analysis. *JAMA Psychiatry* 2019; **76:** 426–34.

57 Boehnke KF, Scott JR, Litinas E, Sisley S, Williams DA, Clauw DJ. High frequency medical cannabis use is associated with worse pain among individuals with chronic pain. *J Pain* 2020; **21:** 570–81.

58 Gage SH, Jones HJ, Burgess S, et al. Assessing causality in associations between cannabis use and schizophrenia risk: a two-sample Mendelian randomization study. *Psychol Med* 2017; **47:** 971–80.

59 Jefsen OH, Speed M, Speed D, Østergaard SD. Bipolar disorder and cannabis use: a bidirectional two-sample Mendelian randomization study. *Addict Biol* 2021; **26:** e13030.

60 Nesvåg R, Reichborn-Kjennerud T, Gillespie NA, et al. Genetic and environmental contributions to the association between cannabis use and psychotic-like experiences in young adult twins. *Schizophr Bull* 2017; **43:** 644–53.