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The relationship between cannabis and schizophrenia: a genetically informed perspective

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ABSTRACT

Background and Aims While epidemiological studies support a role for heavy, high-potency cannabis use on first-episode psychosis, genetic models of causation suggest reverse causal effects of schizophrenia on cannabis use liability. We estimated the genetic relationship between cannabis use disorder (CUD) and schizophrenia (SCZ) and tested whether liability for CUD is causally associated with increased liability to SCZ while adjusting for tobacco smoking. **Design** This study used summary statistics from published genome-wide association studies (GWAS). We used genomic structural equation modeling, latent causal variable analysis, and multivariable Mendelian randomization to examine genetic relationships between CUD, cannabis ever-use, ever-smoked tobacco regularly, nicotine dependence and SCZ, and to test for a causal relationship between liability to CUD and liability to SCZ. **Setting** Genome-wide association studies were published previously as part of international consortia. **Participants** Sample sizes of the GWAS summary statistics used in this study ranged from 161 405 to 357 806 individuals of European ancestry. **Measurements** Genome-wide summary statistics for CUD and SCZ were the primary measurements, while summary statistics for cannabis ever-use, ever-smoked tobacco regularly and nicotine dependence were included as additional variables in the genomic structural equation models and the multivariable Mendelian randomization analyses. **Findings** Genetic liability to CUD was significantly associated with SCZ [$\beta = 0.29$, 95% confidence interval (CI) = 0.11, 0.46, $P = 0.001$], even when accounting for cannabis ever-use, ever-smoked tobacco regularly and nicotine dependence as simultaneous predictors. We found mixed evidence of a causal relationship, with the latent causal variable analysis finding no evidence of causality (genetic causality proportion = −0.08, 95% CI = −0.40, 0.23, $P = 0.87$) but the multivariable Mendelian randomization analyses suggesting a significant, risk-increasing effect of CUD on liability to SCZ ($\beta = 0.10$, 95% CI = 0.02, 0.18, $P = 0.02$), accounting for the additional risk factors (cannabis ever-use, ever-smoked tobacco regularly and nicotine dependence). **Conclusions** Genetic liability for cannabis use disorder appears to be robustly associated with schizophrenia, above and beyond tobacco smoking and cannabis ever-use, with mixed evidence to support a causal relationship between cannabis use disorder and schizophrenia.

Keywords Cannabis, genome-wide association study, genomic structural equation modeling, latent causal variable model, multivariable Mendelian randomization, schizophrenia, tobacco.

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INTRODUCTION

The relationship between heavy cannabis use and schizophrenia (SCZ) is one of psychiatry's enduring controversies. An early study of Swedish conscripts found that heavy cannabis users had a sixfold higher relative risk of developing SCZ than non-users [1], while recent epidemiological studies suggest that high potency forms

of cannabis may increase risk for first-episode psychosis and subsequent SCZ [2,3]. Others have argued that these causal assertions fail to account for antecedent risk, both genetic and environmental, for cannabis use and psychosis, and prodromal schizophrenia symptoms that might exacerbate cannabis use [4]. Both SCZ and cannabis use disorder (CUD), as well as other substance use behaviors, are heritable [5,6]. Genome-wide association studies (GWAS) have found modest but significant genetic correlations between SCZ and cannabis ever-use (r_g = 0.25 [7], P = 5.8e-15) and between SCZ and CUD [5] (r_g = 0.31, P = 2.3e-16). While one Mendelian randomization (MR) study found evidence of a causal effect of cannabis use on SCZ [8] (whereby cannabis use increases risk of SCZ), the literature is mixed: two other MR studies have identified a reverse causal effect of SCZ liability on cannabis ever-use [7,9], and another study found no evidence of a causal relationship between cannabis ever-use and SCZ [10]. However, no study has yet examined whether genetic risk for CUD (dependence, as distinct from cannabis use) causally influences SCZ liability. Finally, because tobacco smoking is common in those with SCZ [11], frequently co-occurs with cannabis use [12] and is significantly genetically correlated with SCZ (r_g = 0.14, P = 1.4e-13) [13] and CUD (r_g = 0.66, P = 3.2e-83) [5], it is important to account for tobacco when modeling genetic relationships between SCZ and CUD.

Using the largest genome-wide data sets available (Table 1), we set out to disentangle the relationships between genetic liability for cannabis involvement (ever-use and CUD), tobacco smoking (ever initiated regular smoking, hereafter referred to as ever-smoked tobacco regularly), nicotine dependence (the Fagerström Test for Nicotine Dependence; FTND) and SCZ. Using genomic structural equation modelling (SEM) [14], we first investigate the relationships between genetic liability for cannabis ever-use, CUD, ever-smoked tobacco regularly, FTND and SCZ. We then use two approaches to test for evidence of causality between liability to CUD and SCZ: our primary analysis uses a latent causal variable (LCV) approach [15], which is robust to sample overlap and accounts for genetic correlation between the two traits (i.e. horizontal pleiotropy). As a secondary analysis, we perform multivariable Mendelian randomization (MVMR [16]), which has the advantage of simultaneously modeling the genetic associations between multiple risk factors and the outcome, but the disadvantage that it may be biased by sample overlap.

METHODS

Samples

- Schizophrenia: we used the Psychiatric Genomics Consortium (PGC) Phase 3 SCZ GWAS meta-analysis [6] (n = 161 405; n_{cases} = 67 390).
- Cannabis ever-use: summary statistics were derived from a meta-analysis of life-time cannabis ever-use from the International Cannabis Consortium and the UK Biobank [7] (n = 162 082; n_{ever} = 43 380).
- Cannabis use disorder (CUD): we used summary statistics from a GWAS meta-analysis of cannabis use disorder [5], combining data from the PGC, the Lundbeck Foundation Initiative for Integrative Psychiatric Research and deCODE Genetics (n = 357 806; n_{cases} = 14 080).
- Ever-smoked tobacco regularly: summary statistics came from the GWAS and Sequencing Consortium of Alcohol and Nicotine use GWAS [13] of self-reported ever/never regular cigarette smoking (n = 632 802; n_{ever} = 301 524). This phenotype was measured in a variety of ways in different cohorts (e.g. 'Have you smoked over 100 cigarettes over the course of your life?', 'Have you ever smoked every day for at least a month?', 'Have you ever smoked regularly?'). We used the publicly

Table 1 Relative sample sizes and SNP-heritabilities of different GWAS data sets included in this study.

Phenotype	*PMID*	*Sample size*	*SNP-heritability (SE)*
Schizophrenia	No PMID available; https://doi.org/10.1101/2020.09.12.20192922	n = 161 405; n_{cases} = 67 390	0.24 (0.007)
Cannabis ever-use	30 150 663	n = 162 082; n_{ever} = 43 380	0.11 (0.01)
CUD	33 096 046	n = 357 806; n_{cases} = 14 080	0.12 (0.01)
Ever-smoked tobacco regularly	30 643 251	n = 632 802; n_{ever} = 301 524	0.08 (0.002)
FTND	33 144 568	n = 46 213	0.09 (0.01)

SNP = single nucleotide polymorphism; GWAS = genome-wide association study; CUD = cannabis use disorder; FTND = Fagerström Test for Nicotine Dependence; SE = standard error.

available set of summary statistics, which does not include data from 23andMe; the sample size reported here reflects that exclusion.

- Fagerström Test for Nicotine Dependence (FTND): summary statistics for nicotine dependence came from the largest GWAS of the Fagerström Test for Nicotine Dependence scores [17] to date (FTND, n = 46 213).

Statistical analyses

These analyses were not preregistered and results should be considered exploratory.

Genomic SEM

We used genomic SEM [14] to estimate the extent to which the genetic components of four different substance use and use disorder measures—ever-smoked tobacco regularly, FTND, cannabis ever-use and CUD—are related to SCZ in a multiple regression framework (see Fig. 1 for path specification). The regression model allows substance use phenotypes to correlate with each other and estimates a single regression relationship between each substance use behavior and SCZ. Each path can then be interpreted as representing the association with SCZ above and beyond the other substance use phenotypes.

Because all substance use phenotypes were intercorrelated, it is possible that multicollinearity among these traits led to an increase in the standard errors. In an attempt to account for this, we then tested a model in which ever-smoked tobacco regularly, FTND and cannabis ever-use loaded onto a latent 'cannabis and tobacco use' factor; SCZ was then regressed on CUD and the latent factor. We allowed CUD and the latent factor to correlate. Model fit was acceptable (comparative fit index = 0.949, standardized root mean square residual = 0.073).

Latent causal variable analysis

We used the LCV R package [15] to estimate the genetic causality proportion (i.e. the extent to which the genetic component for trait 1 is causal for trait 2) between cannabis use/use disorder and SCZ. Unlike MR approaches, this method accounts for the genetic correlation between the two traits using cross-trait genetic correlations estimated from LD score regression [18]; the intercept from this regression is also used to correct for sample overlap, as in

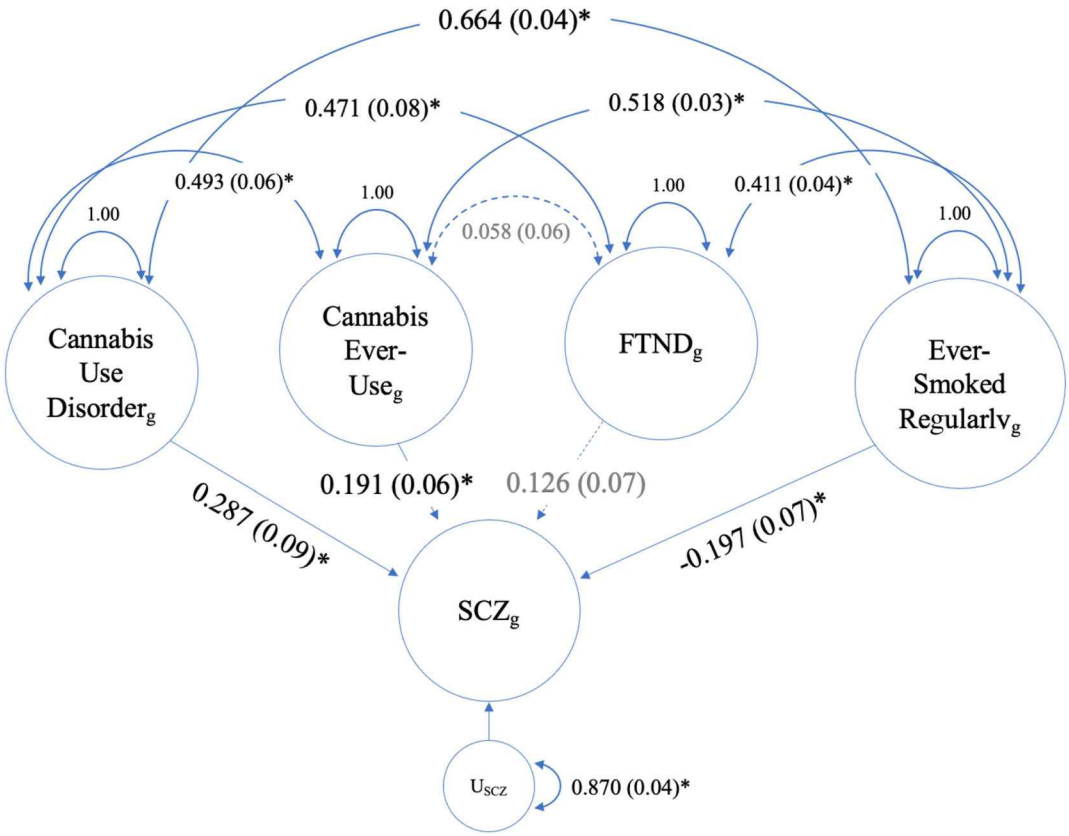

Figure 1 Genomic multiple regression model showing the associations of cannabis ever-use, cannabis use disorder, Fagerström Test for Nicotine Dependence (FTND) and ever-smoked tobacco regularly with schizophrenia (SCZ), above and beyond the other substances. All presented estimates are standardized, standard errors are presented in parentheses, and starred (*) estimates were significant ($P < 0.05$). g = genetic component [Colour figure can be viewed at wileyonlinelibrary.com]

genomic SEM. LCV includes genetic variants across the entire genome as 'instruments', unlike traditional MR approaches that select only the most strongly associated variants (typically those that are genome-wide significant).

We refer the reader to O'Connor & Price [15] for more detailed information, but briefly, the LCV model is based upon the estimation of a latent variable which has a causal effect on both traits and which mediates the genetic correlation between the two traits. If trait 1 is more strongly correlated with the latent causal variable than trait 2, we can infer that trait 1 is partially genetically causal for trait 2 (and vice versa). The extent of this causal relationship is quantified using the genetic causality proportion, an estimate of the degree to which the genetic component of trait 1 (e.g. CUD) is causal for trait 2 (e.g. SCZ); this estimate ranges from 0, representing no genetic causality, to 1, indicating full genetic causality. Notably, while LCV can detect reverse causality (i.e. trait 2 causing trait 1), this approach cannot estimate bidirectional causal relationships (i.e. trait 1 causing trait 2 and trait 2 causing trait 1); a bidirectional relationship would present as a null (i.e. close to 0) genetic causality proportion estimate.

MVMR analysis

As a secondary analysis to test for a causal relationship between CUD and SCZ, we performed two types of MVMR analysis: an inverse variance weighted approach (MVMR-IVW) and a multivariable extension of the MR-Egger method (MVMR-Egger). The advantage of these approaches is that the multivariable MR model can account for the exposure or risk factor of interest—in our case, CUD—as well as correlated risk factors, such as cannabis ever-use and tobacco smoking. The MVMR model is particularly useful for situations wherein the genetic instruments are known to be pleiotropic and associated with multiple risk factors. Briefly, the MVMR-Egger model is similar to the MVMR-IVW approach, except that the intercept term is estimated (rather than being constrained at 0); testing whether this intercept term is statistically different from 0 tests for directional pleiotropy [16]. For both models, we calculated standard errors using the multiplicative random-effects model. We included genome-wide significant independent SNPs from the ever-smoked tobacco regularly GWAS (after clumping, n SNPs = 93). For the other GWAS, we included SNPs with $P < 1e\text{-}5$ to have enough instruments for analysis: 44 SNPs for CUD [5], 70 SNPs for cannabis ever-use [7] and 44 SNPs for FTND [17]. After merging with SCZ and removing palindromic SNPs with intermediate allele frequencies, there were fewer SNPs available for final analysis (see Supporting information). As recommended [16], we orientated the genetic instruments with respect to their associations with CUD, our primary risk factor of interest.

RESULTS

When all four substance phenotypes (cannabis ever-use, CUD, ever-smoked tobacco regularly and FTND) were modeled as simultaneous predictors, cannabis ever-use and CUD were significantly positively associated with SCZ, while ever-smoked tobacco regularly showed an inverse relationship (i.e. greater genetic liability for ever-smoking tobacco regularly was associated with lower genetic predisposition for SCZ; Fig. 1, Table 2). The strongest association was between CUD and SCZ [$\beta = 0.29$, 95% confidence interval (CI) = 0.11, 0.46, $P = 0.001$] and the largest intersubstance correlation was between CUD and ever-smoked tobacco regularly ($\beta = 0.66$, 95% CI = 0.59, 0.7, $P = 3.0e\text{-}73$).

Ever-smoked tobacco regularly, FTND and cannabis ever-use all loaded significantly on a 'cannabis-tobacco use' latent factor (estimates = 0.46–0.80, $P < 1.8e\text{-}20$). The common genetic contributions of regular tobacco smoking, FTND and cannabis use in the latent factor were not significantly associated with SCZ ($P = 0.57$), but CUD continued to show a significant association with SCZ ($\beta = 0.37$, 95% CI = 0.09, 0.65, $P = 0.009$; Fig. 2, Table 2).

While the latent causal variable model confirmed the genetic correlations between cannabis ever-use, CUD and SCZ, it found no evidence of a genetically causal relationship between cannabis ever-use and SCZ [genetic causality proportion (GCP) = −0.32, 95% CI = −0.85, 0.21, $P = 0.21$] nor CUD and SCZ (GCP = −0.08, 95% CI = −0.40, 0.23, $P = 0.87$). In contrast, both the MVMR-IVW ($\beta = 0.08$, 95% CI = 0.02, 0.14, $P = 0.02$) and MVMR-Egger ($\beta = 0.10$, 95% CI = 0.02, 0.18, $P = 0.02$) approaches suggested a significant causal effect of CUD on SCZ, accounting for the additional risk factors (cannabis ever-use, ever-smoked tobacco regularly and FTND). Univariate MR tests showed evidence of bidirectional causality ($\beta = 0.12$, 95% CI = 0.06, 0.18, $P = 3e\text{-}5$ for liability to CUD causing SCZ; $\beta = 0.2$, 95% CI = 0.14, 0.26, $P = 5.5e\text{-}12$ for liability to SCZ causing CUD; see Supporting information, Tables S2 and S6), which is consistent with the null LCV results.

DISCUSSION

Our multivariable analysis of large-scale GWAS data shows that genetic liability for CUD is associated with genetic liability for SCZ, including when accounting for the genetic contributions of cannabis ever-use and tobacco smoking. Paradoxically, we found that ever-smoked tobacco regularly was negatively associated with SCZ risk when accounting for the effects of both cannabis phenotypes and FTND, despite being positively associated with SCZ in previous univariate analyses [13]. In other words, the genetic variance specific to ever-smoking (i.e. not shared

Table 2 Parameter estimates from both genomic structural equation modelling (SEM) models. Model 1 refers to the multiple regression-like model (pictured in Fig. 1), while model 2 refers to the SEM where the effects of cannabis ever-use, ever-smoked tobacco regularly and FTND are modeled as a latent factor (pictured in Fig. 2).

Model 1			
Parameter	*Standardized estimate*	*Standard error*	*P-value*
SCZ ~ ~ SCZ	0.870	0.044	1.22E-87
SCZ ~ CUD	0.287	0.090	0.001
SCZ ~ cannabis ever-use	0.191	0.056	6.73E-4
SCZ ~ ever-smoked tobacco regularly	−0.197	0.065	0.003
SCZ ~ FTND	0.126	0.070	0.069
CUD ~ ~ CUD	1.000	0.092	2.79E-27
CUD ~ cannabis ever-use	0.493	0.055	2.05E-19
CUD ~ ~ ever-smoked tobacco regularly	0.664	0.037	2.99E-73
CUD ~ ~ FTND	0.471	0.075	2.92E-10
Cannabis ever-use ~ ~ cannabis ever-use	1.000	0.066	2.14E-51
Cannabis ever-use ~ ~ ever-smoked tobacco regularly	0.518	0.034	1.38E-53
Cannabis ever-use ~ ~ FTND	0.058	0.059	0.322
Ever-smoked tobacco regularly ~ ~ ever-smoked tobacco regularly	1.000	0.034	1.02E-192
Ever-smoked tobacco regularly ~ ~ FTND	0.411	0.044	9.53E-21
FTND ~ ~ FTND	1.000	0.137	3.10E-13
Model 2			
Factor 1 = ~ cannabis ever-use	0.622	0.036	1.33E-65
Factor 1 = ~ ever-smoked tobacco regularly	0.796	0.039	1.49E-92
Factor 1 = ~ FTND	0.460	0.050	1.78E-20
Factor 1 ~ ~ CUD	0.837	0.044	7.43E-80
SCZ ~ ~ SCZ	0.903	0.041	2.90E-107
SCZ ~ factor 1	−0.073	0.129	0.573
SCZ ~ CUD	0.370	0.142	0.009
CUD ~ ~ CUD	1.000	0.092	2.79E-27
Cannabis ever-use ~ ~ cannabis ever-use	0.614	0.063	1.22E-22
Ever-Smoked tobacco regularly ~ ~ ever-smoked tobacco regularly	0.366	0.063	5.94E-09
FTND ~ ~ FTND	0.789	0.141	2.15E-08

SCZ = schizophrenia; CUD = cannabis use disorder; FTND = Fagerström Test for Nicotine Dependence.

with CUD, cannabis ever-use or FTND) is negatively correlated with genetic liability to schizophrenia. While the genetic component of ever-smoking that is shared with the other substance use measures probably reflects a combination of externalizing behaviors and predisposition to become a problematic substance user, these analyses cannot determine what the genetic component specific to ever-smoked regularly may reflect; it is, however, of great interest for future research.

In line with other recent LCV analyses (e.g. [10]), our LCV analysis indicates that the genetic overlap of CUD and schizophrenia is more consistent with a pattern of horizontal pleiotropy (genetic variants directly contributing to both CUD risk and SCZ risk) than vertical pleiotropy (genetic variants that contribute to CUD liability indirectly contributing to SCZ via a causal relationship between CUD itself and SCZ risk). However, we cannot discount causal mechanisms, as we found some evidence of a significant causal effect of liability to CUD on SCZ in our multivariable MR analyses, accounting for the genetic associations of cannabis ever-use, ever-smoked tobacco regularly and FTND as additional risk factors. Univariate MR analyses also revealed evidence of bidirectional causality between CUD and SCZ (see Supporting information). Bidirectional causality presents as a null finding from LCV; however, while these bidirectional MR findings are consistent with the null LCV results, using the current data we cannot confirm whether the null LCV finding is due to a true lack of causality or whether that estimate reflects a bidirectional relationship between CUD and SCZ. Sample overlap (i.e. individuals present in multiple GWAS samples) may have biased our MR analyses [19]; thus, we cannot exclude the possibility that significant causal effects detected by MVMR are driven by sample overlap, as there was evidence of potential overlap between the CUD and SCZ GWAS [LDSC genetic covariance intercept = 0.016, standard error (SE) = 0.007]. Overall, our study suggests that, while shared genetic vulnerabilities probably play a role in the relationship between CUD and SCZ, the role of causality remains unclear.

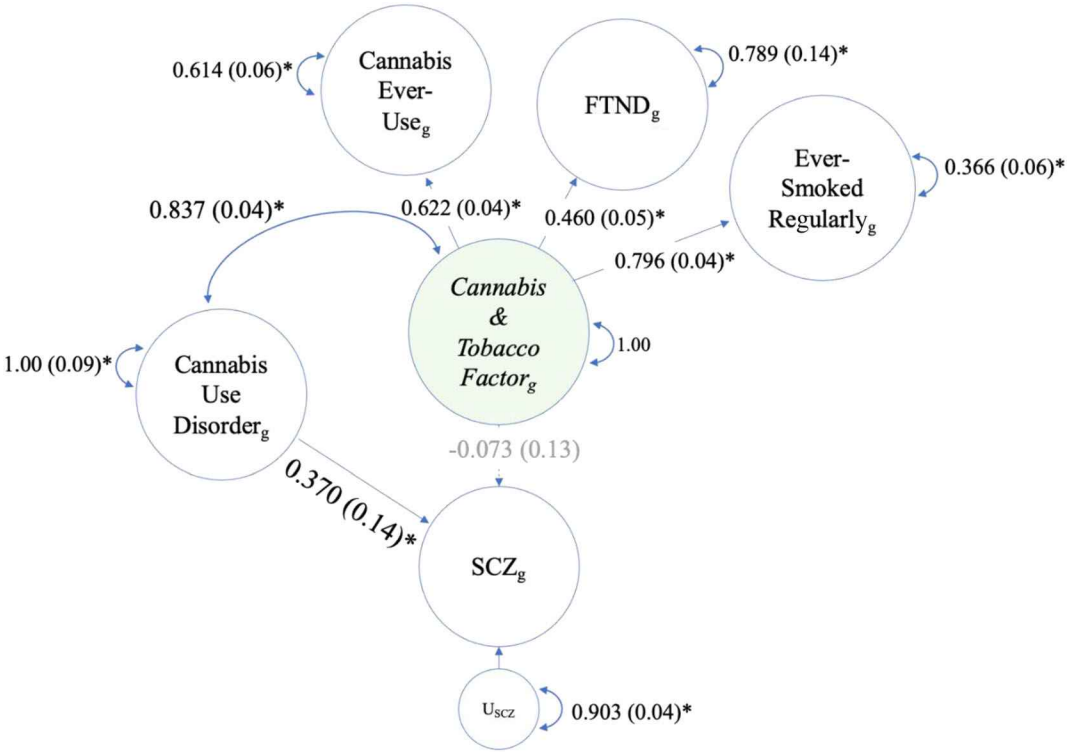

Figure 2 Genomic structural equation model showing the positive association between genetic liability to cannabis use disorder and schizophrenia, accounting for the combined influences of the other substance use phenotypes exerted via the latent 'cannabis and tobacco use factor'. This model was estimated to account for potential multicollinearity issues between the cannabis ever-use, Fagerström Test for Nicotine Dependence (FTND) and ever-smoked tobacco regularly phenotypes; model fit was relatively good (comparative fix index = 0.949, standardized root mean square residual = 0.073). Variance of the latent cannabis and tobacco use factor was scaled to 1. All presented estimates are standardized, standard errors are presented in parentheses, and starred (*) estimates were significant ($P < 0.05$). g = genetic component [Colour figure can be viewed at wileyonlinelibrary.com]

Our study has some limitations: first, these findings may be population-specific due to differences in manner of use (in Europe, cannabis is frequently mixed with tobacco [12]) and effectiveness of public health campaigns surrounding tobacco smoking. A second caveat is that the CUD GWAS has lower statistical power than the SCZ GWAS due to differences in sample size (*n* cases = 14 080 versus 67 390; Table 1) and polygenicity of the traits under study [20]. As sample sizes grow for CUD and statistical power is improved, these results may change. Finally, there may be SCZ GWAS cases who also had CUD; this comorbidity could potentially bias estimates of genetic correlation and causality.

In conclusion, we provide evidence that genetic liability for CUD is robustly associated with SCZ, above and beyond tobacco smoking and cannabis ever-use, and we find mixed evidence to support a causal relationship between CUD and SCZ.

Declaration of interests

J.G. is named as an inventor on PCT patent application number 15/878640, entitled 'Genotype-guided dosing of opioid agonists', filed 24 January 2018. No other competing interests are reported.

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Author contributions

Emma Johnson: Conceptualization; formal analysis; methodology. **Alexander Hatoum:** Formal analysis;

methodology. **Joseph Deak:** Methodology. **Renato Polimanti:** Methodology. **Robin Murray:** Conceptualization; methodology. **Howard Edenberg:** Conceptualization; methodology. **Joel Gelernter:** Conceptualization; methodology. **Marta Di Forti:** Conceptualization; methodology; supervision. **Arpana Agrawal:** Conceptualization; methodology; supervision.

Data availability statement

Data from the PGC CUD GWAS are available for download (https://www.med.unc.edu/pgc/download-results/), as are data from the GSCAN study (https://conservancy.umn.edu/handle/11299/201564). Data from the FTND GWAS are available upon request to Dr Dana Hancock. The PGC Phase 3 SCZ GWAS results are also available for download (https://www.med.unc.edu/pgc/download-results/scz/).

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 Multivariate MR results using independent instruments with $P < 1e\text{-}5$ for CUD, cannabis ever-use, and FTND, and $P < 5e\text{-}8$ for ever-smoked tobacco regularly.
Table S2 Univariate MR results using independent instruments with $P < 1e\text{-}5$ for CUD, cannabis ever-use, and FTND, and $P < 5e\text{-}8$ for ever-smoked tobacco regularly.
Table S3 Univariate MR results using independent instruments with $P < 1e\text{-}6$ for CUD, cannabis ever-use, and FTND.

Table S4 Univariate MR results using independent instruments with $P < 5e\text{-}8$ for CUD.
Table S5 Multivariate MR results using independent instruments with P < 1e-6 for CUD, cannabis ever-use, and FTND, and $P < 5e\text{-}8$ for ever-smoked tobacco regularly.
Table S6 Univariate MR results testing whether SCZ (instrument P < 5e-8) is causal for CUD.