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ORIGINAL ARTICLE

Psychotic patients who used cannabis frequently before illness onset have higher genetic predisposition to schizophrenia than those who did not

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Background. Schizophrenia (SZ) and bipolar disorder (BD) are heritable, polygenic disorders with shared clinical and genetic components, suggesting a psychosis continuum. Cannabis use is a well-documented environmental risk factor in psychotic disorders. In the current study, we investigated the relationship between SZ genetic load and cannabis use before illness onset in SZ and BD spectrums. Since frequent early cannabis use (age <18 years) is believed to increase the risk of developing psychosis more than later use, follow-up analyses were conducted comparing early use to later use and no use.

Methods. We assigned a SZ-polygenic risk score (PGRS) to each individual in our independent sample ($N = 381$ SZ spectrum cases, 220 BD spectrum cases and 415 healthy controls), calculated from the results of the Psychiatric Genomics Consortium (PGC) SZ case–control study ($N = 81\,535$). SZ-PGRS in patients who used cannabis weekly to daily in the period before first illness episode was compared with that of those who never or infrequently used cannabis.

Results. Patients with weekly to daily cannabis use before illness onset had the highest SZ-PGRS ($p = 0.02$, Cohen's $d = 0.33$). The largest difference was found between patients with daily or weekly cannabis use before illness onset <18 years of age and patients with no or infrequent use of cannabis ($p = 0.003$, Cohen's $d = 0.42$).

Conclusions. Our study supports an association between high SZ-PGRS and frequent cannabis use before illness onset in psychosis continuum disorders.

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Key words: Bipolar disorders, cannabis, polygenic risk score, schizophrenia.

Introduction

Schizophrenia (SZ) and bipolar disorder (BD) are highly heritable disorders with polygenic inheritance (Smoller & Finn, 2003; Giusti-Rodriguez & Sullivan, 2013; Tesli *et al.* 2014). Evidence of common genetic risk variants indicates that these two disorders constitute one broad psychosis continuum (Craddock & Owen, 2010; Andreassen *et al.* 2013; Tesli *et al.* 2014). The polygenic risk score (PGRS) is computed on the basis of large genome-wide association studies (GWAS) and incorporates additional genetic variance lost to strict threshold levels of significance (Iyegbe *et al.* 2014). The method estimating cumulative genetic risk (Purcell *et al.* 2009) was recently employed to provide molecular validation of the psychosis continuum model (Bigdeli *et al.* 2014; Tesli *et al.* 2014).

It is well described in the literature that cannabis use is associated with psychotic-like symptoms [such as delusions and hallucinations (Grech *et al.* 2005)]. Current evidence, including the meta-analysis by Marconi *et al.* (2016), confirms that frequent cannabis use increases the risk of psychotic outcomes and that there is a dose–response relationship between the level of use and the risk for psychosis. However, a causal link between cannabis use and psychosis is not yet

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established. The first formal evidence relating cannabis use to SZ came from the Swedish Conscript Study from the 1969/70 survey based on more than 45 000 young inductees into the military followed up for more than 10 years. The study found that those who had used cannabis before age 18 were 2.4 times more likely to have a diagnosis of SZ than those who had never used any (Andreasson *et al.* 1987). Frequency of use was associated with the risk of developing SZ (use on more than 50 occasions); the relative risk of developing SZ increased to 6.0 [95% confidence interval (CI) 4.0–8.9] compared with non-users (Andreasson *et al.* 1987). Similar findings from the same cohort were later replicated by Zammit *et al.* (2002). The Dunedin multidisciplinary health and development study (a study of a general population birth cohort of 1037 individuals) also showed that cannabis use at age 15, as well as by age 18, was associated with more psychotic-like symptoms at age 26 (Arseneault *et al.* 2002). Specific neighborhoods with high cannabis use also show greater prevalence of psychosis cases, supporting a link between cannabis use and psychosis (Kirkbride *et al.* 2006; Kirkbride *et al.* 2007; Home Office Research Development and Statistics Directorate BMRB, 2008).

The relationship between genetic load and environmental risk factors in severe mental illness is sparsely investigated and could potentially shed new light on mechanisms behind the development of severe mental disorders. Most individuals who use cannabis never develop a psychotic disorder, and it is proposed that the link between cannabis use and development of psychosis requires an interaction with genetic vulnerability (Loberg *et al.* 2014). This is supported by the low prevalence of psychotic illnesses (estimated to 1%) (McGrath *et al.* 2008), whilst cannabis use is relatively common in the general population (prevalence estimates of 14–40% depending on frequency of use and study location) (Home Office Development and Statistics Directorate BMRB, 2008; WHO, 2016). On the other hand, it could be proposed that less genetic risk is needed to develop a psychotic episode in those exposed to cannabis, compared with non-users and that some individuals would have remained healthy if they had not been exposed. For example, Ferraro *et al.* found that patients with a first-episode psychosis who had ever smoked cannabis had significantly higher current IQ and premorbid IQ compared with patients who had never used cannabis (Ferraro *et al.* 2013). This difference was not found among controls. These findings could potentially reflect a subgroup of patients developing psychosis after cannabis use that otherwise would not have developed the illness.

Frequent cannabis use before illness onset could also be seen as an attempt to self-medicate premorbid symptoms (including handling symptoms of anxiety and depression), resulting in a vicious cycle contributing to more severe psychopathology in genetically vulnerable individuals. Another possibility is that the risk of using cannabis and developing psychosis is driven by a common genetic susceptibility. Hence, part of the association between cannabis use and psychosis might reflect the fact that individuals prone to using cannabis are also prone to developing psychosis, and that there is necessarily no causal link between cannabis use and the pathophysiology of psychosis among these individuals. This theory of shared genetic risk fits with the recent findings by Power *et al.* demonstrating a higher PGRS for SZ (SZ-PGRS) in healthy cannabis users (Power *et al.* 2014), indicating a genetic overlap between SZ and vulnerability to cannabis use. Another recent large study ($N = 14\,754$) of genetic factors in cannabis dependence includes overlapping single-nucleotide polymorphisms (SNPs) in genes associated with SZ, including the CUB And Sushi Multiple Domains 1 (*CSMD1*), and genes related to immune processes, supporting potential overlap in genes for cannabis use and SZ (Sherva *et al.* 2016). A strong genetic component of cannabis use has also been found in twin studies with a high heritable (h^2) rate, including a high heritability rate for an early onset of use ($h^2 = 80\%$), lifetime use ($h^2 = 76\%$), as well as cannabis abuse or dependence ($h^2 = 21$–72%) (Lynskey *et al.* 2012; Agrawal *et al.* 2014; Kendler *et al.* 2015).

Although there are fewer and less consistent studies investigating the link between cannabis and BD, the 3-year longitudinal study comprised of 4815 individuals from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) reported that the use of cannabis increased the risk of manic symptoms during the follow-up period independently of psychotic symptoms (Henquet *et al.* 2006). Both SZ and BD cannabis users tend to have an earlier age at onset in a dose-dependent manner (i.e. the more use, the earlier age at onset) (Di Forti *et al.* 2014; Lagerberg *et al.* 2014), supporting cannabis use as a risk factor across the psychosis continuum.

In the current study, we will investigate if cannabis is frequently used before illness onset. Our study focuses on the relationship between PGRS and cannabis use in psychotic continuum disorders (SZ and BD). The strength of our study is the well-described clinical sample, where we have information on age at illness onset and age at first cannabis use before illness onset, in addition to premorbid frequency of cannabis use (daily/weekly use compared with no/sporadic use).

We explore the following two hypotheses: According to the hypothesis that cannabis can elicit psychosis in less vulnerable individuals, patients

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Table 1. *Demographic data for psychosis spectrum cases and healthy controls*

Diagnostic spectrum	N (% females)	Mean age (S.D.)
CTR	415 (49.9)	34.6 (10.0)
BD spectrum	220 (60.9)	34.5 (11.7)
SZ spectrum	381 (42.0)	30.8 (10.1)
Total sample	1016 (50.9)	33.3 (10.6)

CTR, healthy controls; BD, bipolar disorders; SZ, schizophrenia, S.D., standard deviation.

Included in BD spectrum: bipolar type 1 ($N = 141$), bipolar disorders type 2 ($N = 65$), and bipolar disorders not otherwise specified ($N = 14$). Included in SZ spectrum: schizophrenia ($N = 224$), schizoaffective disorders ($N = 45$), schizophreniform disorders ($N = 22$), and psychosis not otherwise specified ($N = 90$).

with frequent (daily or weekly cannabis use before illness onset) will have lower SZ-PGRSs, with the most significant findings for early frequent use (weekly or daily) before 18 years of age. According to the alternative model, suggesting overlapping genetic vulnerability for cannabis use and SZ, those with frequent (daily or weekly) cannabis use before illness onset will have increased SZ-PGRS levels compared with those without frequent cannabis use.

Methods

Participants

The participants were recruited consecutively from psychiatric units (outpatient and inpatient) in four major hospitals in Oslo, as part of the larger Thematically Organized Psychosis (TOP) research study. A total of 601 patients were recruited to this study: $N = 381$ had a SZ spectrum disorder (224 SZ, 22 schizophreniform disorder, 45 schizoaffective disorder and 90 with other psychosis), and $N = 220$ had a BD with or without a history of psychosis (141 bipolar I, 65 bipolar II and 14 bipolar not otherwise specified). The mean age of the patients was 32.7 ± 10.3, and 51.5% were females. In addition, 415 heathy controls were included in the study (mean age 34.6 ± 10.0 and 49.9% females, see Table 1) for validation of the method (assessment of explained variance of case–control status). All participants were Caucasians. Exclusion criteria for all groups were: An unstable or uncontrolled medical condition that interferes with brain function, age outside the range of 18–65 years. The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study. All participants gave written informed consent.

Clinical assessment

Trained medical physicians and clinical psychologists carried out the clinical assessment. Diagnosis was based on the Structured Clinical Interview for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) Axis I disorders (SCID-I). Diagnostic reliability was found satisfactory (Ringen *et al.* 2008*a*) with overall agreement for DSM-IV diagnostic categories of 82% and the overall κ 0.77 (95% CI 0.60–0.94). Age at illness onset was defined as the age of the first SCID-verified psychotic episode. For BD patients without information on first psychotic episode ($N = 101$), first mood episode was used to define onset of illness. Cannabis assessment: Patients were asked regarding time of use and frequency of use (no, sporadic, weekly, or daily use), also see Ringen *et al.* 2016. For the purpose of this study, we divided the sample into patients with daily or weekly use (frequent use) compared with no use or sporadic use (no use) before illness onset. Lifetime use was also reported. Thirty-three cases were missing data on age at illness onset and cannabis use.

Polygenic risk score

All participants were genotyped at Expression Analysis Inc (Durham, NC, USA) using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affymetrix Inc, Santa Clara, CA, USA). Quality control was performed using PLINK (version 1.07; http://pngu.mgh.harvard.edu/purcell/plink/) (Purcell *et al.* 2009). SNPs were imputed with MACH (http://www.sph.umich.edu/csg/abecasis/MACH/download/1000G-PhaseI-Interim.html) using the European samples in the Phase I release of the 1000 Genomes project. Genotyping and imputation procedures are described in further details elsewhere (Athanasiu *et al.* 2010; Djurovic *et al.* 2010; Finseth *et al.* 2014).

The PGRS for the SZ phenotype was computed based on imputed SNPs following the method developed by Purcell *et al.* (2009). Using PLINK version 1.07 (http://pngu.mgh.harvard.edu/purcell/plink/), a meta-analysis including all Psychiatric Genomics Consortium (PGC) substudies [PGS, except ours (TOP 8; $n = 377$ SZ cases and 403 controls)] was performed to obtain risk allele effect sizes [ln(OR)] for all imputed SNPs. The SNPs remaining after removal of those within the major histocompatibility complex or with minor allele frequency <0.01 were pruned using PLINK's –clump option ($r^2 < 0.1$, 500 kb windows) to select representatives with lowest p values from all linkage disequilibrium blocks (102 635 SNPs). PGRSs were then computed for each individual in our sample by summing up the effect sizes of the selected SNPs multiplied by the number of risk alleles

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expected to be carried by that individual (dosage). A total of 10 PGRSs were computed based on different p value thresholds ($p = 1$, 0.5, 0.4, 0.3, 0.2, 0.1, 0.05, 0.01, 0.001, and 0.0001) for SNP inclusion. The area under the receiver operating characteristic curve (AUC) for case–control status prediction is reported for PGC2 SZ-PGRSs based on different p value thresholds for SNP inclusion (online Supplementary Fig. S1). For use in the analyses to follow, we selected the most parsimonious threshold that gave a significant increase in the AUC with respect to the threshold preceding it ($p = 0.05$).

Statistics

Data were analyzed using the Predictive Analytic software (PASW), Version 21 (formerly SPSS Statistics). For the main analysis, a t test was used to assess potential differences in SZ-PGRSs in those with daily or weekly cannabis use before age at onset of their psychotic disorder, compared with those without daily or weekly cannabis use before age at onset. Since the age of initiation of cannabis use has been identified as a risk factor for developing a severe mental disorder, we performed a follow up analysis investigating the association between SZ-PGRS in patient groups separated based on age at initiation of cannabis use. A cutoff of <18 years was chosen based on the initial study by Andreasson *et al.* (1987) showing that cannabis use <18 years of age was specifically linked to developing a psychotic illness in the large Swedish cohort. Other studies suggested a cutoff at age <15 (Di Forti *et al.* 2014), but our sample would have been too small for that ($N = 15$ individuals with cannabis initiation <15, *v.* $N = 46$ for initiation at <18). Regression analyses correcting for sex and population principal components were also performed. All individuals were included from the same catchment area in Oslo, Norway, with similar socioeconomic background. A follow up analysis was performed dividing into SZ and BD spectrums. Effect sizes were computed for the main analysis of cannabis and genetic correlates in patients with a psychosis continuum diagnosis using Cohen's d (Cohen, 1977). According to Rosenthal and Rosnow (Rosenthal & Rosnow, 1984), effect sizes were considered small for values between 0.20 and 0.50, moderate for values between 0.50 and 0.80, and large for values >0.80. Pre-set significance level of 0.05 was used for the main analysis of SZ-PGRS and cannabis use before illness onset.

To validate the SZ-PGRS method case–control variance, an analysis of variance (ANOVA) model was applied to determine SZ-PGRS differences between SZ spectrum cases, BD spectrum cases, and healthy controls, with post hoc Tukey's test comparing groups pairwise, adjusting p values for numbers of tests (see online Supplementary Material).

Table 2. *Summary statistics of sample divided into lifetime cannabis user and no lifetime users*

	Users	Non-users	Statistics
N	376	225	
Percentage female (%)	43.6	57.8	$\chi^2 = 11.296$, df = 1, $p = 0.001$
Mean age at initiation (S.D.)	18.2 (5.323)	–	
Mean age at onset	23. 5 (8.93)	25.4 (10.01)	$t = -2.44$, $p = 0.02$
Mean PGRS2 z score (S.D.)	0.233 (1.012)	0.0633 (0.921)	$t = -2.05$, $p = 0.04$

Results

Demographics of the sample

Sixty-two percent of the patients reported ever trying cannabis. No significant difference in lifetime cannabis use was observed between SZ and BD ($\chi^2 = 0.41$, df = 1, $p = 0.53$). Lifetime cannabis use was associated with an earlier age at onset (see Table 2). The mean age of first using cannabis was 18 years (18.2 ± 5.3 mean ± S.D.). For the validation of the SZ-PGRS method as well as the diagnostic investigation of cannabis use, please see Table 2 and Supplementary Material (online Supplementary Figs S1–S5; online Supplementary Table S1).

SZ-PGRS and cannabis use before illness onset

In patients with SZ or BD, daily or weekly cannabis use before age at onset was associated with higher SZ-PGRS (t test = −2.45, $p = 0.02$, Cohen's $d = 0.33$, see Fig. 1). Correcting for sex and population principal components, a trend was observed for higher PGRS in patients with daily or weekly cannabis use before age at onset ($\beta = 0.08$, $t = 1.87$, $p = 0.067$).

Dividing the sample into early cannabis users (N = 46) (<18 years), later ($N = 20$) (age ⩾18) cannabis users, and non-frequent cannabis users ($N = 502$), the largest difference in SZ-PGRS was observed between the early users and the non-frequent users ($t = -3.02$, $p = 0.003$, Cohen's $d = 0.42$). A dose relationship was observed with the highest SZ-PGRS in the early frequent users (age <18) with intermediate SZ-PGRS in the late frequent users (age ⩾18; ANOVA: $f = 4.19$, $p = 0.02$; Fig. 2). Comparing late frequent users (N = 20) to non-frequent users ($N = 502$), no significant difference was observed in SZ-PGRS ($t = -1.42$, $p = 0.16$). Correcting for sex and population principal components, a significantly higher PGRS was observed in early users compared with all other groups ($\beta = 0.09$, $t = 2.05$, $p = 0.04$).

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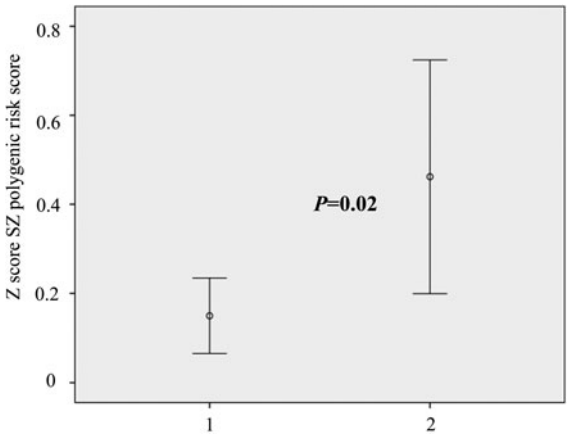

Fig. 1. Frequent cannabis use before illness onset is associated with increased PGRS. *t* test, $p = 0.02$, Cohen's $d = 0.33$. 1 = No daily or weekly cannabis use before illness onset, $N = 502$; 2 = Daily or weekly cannabis use before illness onset, $N = 66$.

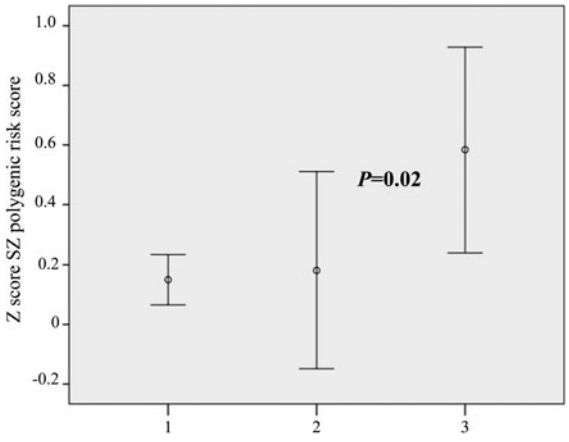

Fig. 2. Early (<18 years of age) frequent cannabis use is associated with higher SZ-PGRS. *ANOVA*, $f = 4.19$, $p = 0.02$. 1 = No daily or weekly cannabis use before illness onset, $N = 502$; 2 = Daily or weekly cannabis use before illness onset age $\geqslant 18$, $N = 20$; 3 = Daily or weekly cannabis use before illness onset <18 years, $N = 46$.

Dividing the sample into SZ and BD spectrums, both groups showed a trend toward higher SZ-PGRS in the frequent cannabis users (see online Supplementary Material S5A, S5B) with the strongest association for the young (age <18) SZ group ($t = -2.28$, $p = 0.02$, Cohen's $d = 0.37$). Correcting for sex and population principal components, an association of higher PGRS was still observed in SZ early cannabis users ($\beta = 0.11$, $t = 1.99$, $p = 0.05$).

Discussion

In the whole group, patients with weekly to daily cannabis use before illness onset had higher SZ-PGRS than those who never or infrequently used cannabis before illness onset. The largest difference was found in patients who started their daily or weekly cannabis use before the age of 18. Dividing the sample into SZ and BD spectrums, both groups showed a trend toward higher PGRS in the frequent cannabis users, with the strongest association in the young (age <18) SZ group.

Several hypotheses have emerged regarding the relationship between cannabis and psychosis [for a detailed description, see Van Winkel & Kuepper (2014)]. Our findings support the notion that genetic risk for SZ also implies a higher risk of cannabis use. New studies are needed to determine in what way genetic risk for SZ influences risk for cannabis use. One possibility is that frequent cannabis use before illness onset could be seen as an attempt to self-medicate premorbid symptoms resulting in a vicious cycle contributing to increased psychopathology in genetically vulnerable individuals. Hence, increased cannabis use as a reflection of higher symptomatic load might not explain the relationship between cannabis use and psychosis. Another possibility supported by our findings is that risk of using cannabis and risk of developing psychosis partly share genetic susceptibility. This suggests that individuals prone to developing psychosis are also prone to start using cannabis, regardless of any causality between cannabis use and the pathophysiology of psychosis. Our findings are in line with a recent large study of healthy individuals demonstrating that polygenic risk of SZ is correlated with cannabis use (Power *et al.* 2014; Verweij *et al.* 2017). Overlapping genetic components between cannabis use and SZ are also reported in the recent large ($N = 14\,754$) study by Sherva *et al.* (2016) of CUB And Sushi Multiple Domains 1 (*CSMD1*) as well as inflammatory genetic components linked to both cannabis abuse and SZ.

Several limitations to the current study should be mentioned: Most importantly, we did not have cannabis data in our control sample; therefore, we were not able to investigate the role of cannabis and SZ-PGRS in a case–control design. However, controls were selected from the population of Norway, and healthy individuals report much less frequent cannabis use. For example, the study by Ringen *et al.* (2008b) showed an increase of 44% of illicit use in SZ and in BD compared with the general population from the same catchment area in Oslo. To investigate overlap between cannabis, genetic risk, and psychosis, case–control studies are needed. Secondly, the explained variance of the SZ-PGRS was low (Nagelkerke r^2 0.12 and 0.05 for SZ and BD, respectively). As suggested by Tesli *et al.* (2014), improvement of the SZ-PGRS method could potentially increase the variance explained by the SZ-PGRS, which should be investigated in future studies. It could also be that the relatively low

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explained variance could be influenced by the nature of the two competitive hypotheses proposed in this study. However, when dividing the sample into frequent cannabis users before age at onset and non-frequent cannabis users before age at onset, we found the highest r^2 in the group with frequent cannabis use ($r^2 = 0.12$), compared with the larger group without frequent cannabis use before age at onset ($r^2 = 0.08$), indicating higher PGRS in cannabis users. Similar findings were observed in patients with lifetime cannabis use compared with controls ($r^2 = 0.11$), and patients without lifetime cannabis use compared with controls ($r^2 = 0.059$). We also used a cutoff score of before 18 years of age in the follow up analysis investigating frequent early use of cannabis and SZ-PGRS, as in the study by Andreasson *et al.* (1987). More recent studies indicate that frequent early use before age 15 could be an even better cutoff age (Di Forti *et al.* 2014). The study by Arseneault *et al.* (2002) found that both cannabis users by ages 15 and 18 were associated with more psychotic-like symptomatology in high-risk individuals, supporting 18 as a valid cutoff age. Our sample was too small to divide into younger than 18 years of age. It should also be noted that our results could also simply be a result of higher cannabis use among SZ cases than controls in the PGC study, which may have led to SNPs associated with cannabis use being misclassified as SZ risk alleles. This could specifically be an issue if GWAS controls have been selected based on more stringent substance misuse criteria than patients.

In conclusion, our data support a weak increase in SZ-PGRS in those with frequent cannabis use before illness onset, suggesting overlapping genetic susceptibility. If there is a genuinely (rather than methodologically) increased rate of cannabis use in PGC SZ cases (as we might expect given the association between cannabis use and SZ), we might find alleles that increase SZ risk via increased risk of cannabis use (or vice versa). As the effect sizes were small, the findings should be interpreted with caution. Further investigation of genetic overlap between SZ and cannabis is warranted, such as comparing SZ-PGRS to PGRS cannabis use in independent GWAS samples.

Supplementary Material

The supplementary material for this article can be found at https://doi.org/10.1017/S0033291717001209.

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Declaration of Interest

There are no potential conflicts of interest.

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