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Exploration of cannabis use and polygenic risk scores on the psychotic symptom progression of a FEP cohort

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ABSTRACT

Cannabis use is highly prevalent in first-episode psychosis (FEP) and plays a critical role in its onset and prognosis, but the genetic underpinnings promoting both conditions are poorly understood. Current treatment strategies for cannabis cessation in FEP are clearly inefficacious. Here, we aimed to characterize the association between cannabis-related polygenic risk scores (PRS) on cannabis use and clinical course after a FEP. A cohort of 249 FEP individuals were evaluated during 12 months. Symptom severity was measured with the Positive and Negative Severity Scale and cannabis use with the EuropASI scale. Individual PRS for lifetime cannabis initiation (PRS_{CI}) and cannabis use disorder (PRS_{CUD}) were constructed. Current cannabis use was associated with increased positive symptoms. Cannabis initiation at younger ages conditioned the 12-month symptom progression. FEP patients with higher cannabis PRS_{CUD} reported increased baseline cannabis use. PRS_{CI} was associated with the course of negative and general symptomatology over follow-up. Cannabis use and symptom progression

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after a FEP were modulated by cannabis PRS, suggesting that lifetime initiation and use disorders may have partially independent genetic factors. These exploratory results may be the first step to identify those FEP patients more vulnerable to cannabis use and worse outcomes to ultimately develop tailored treatments.

1. Introduction

Schizophrenia is a complex mental disorder, with highly heterogeneous course patterns and closely related to increased use of cannabis (Moore et al., 2007), particularly at early stages (Barbeito et al., 2013). It is estimated that approximately 50% of first-episode psychosis (FEP) individuals are cannabis users at onset (Arranz et al., 2020; González-Pinto et al., 2008). Cannabis has a remarkable effect on FEP development and outcome (Di Forti et al., 2019; Schoeler et al., 2016). Specifically, cannabis use is associated to earlier age at psychosis onset (di Forti et al., 2014; González-Pinto et al., 2008; Sugranyes et al., 2009), treatment resistance (Patel et al., 2016), more relapses (Bioque et al., 2022) and poor every-day functioning (Harrison et al., 2008). Notwithstanding the severe consequences, a high percentage of FEP patients continue using cannabis and have severe difficulties in achieving abstinence (Hiemstra et al., 2018).

The role of genetics in the co-occurrence of cannabis use and mental disorders is poorly understood, but some studies have characterized a partially overlapped genetic liability (Johnson et al., 2021, 2020; Pasman et al., 2018). Numerous genetic variants and chromosomic regions have been reported as shared risk variants (Caspi et al., 2005; Johnson et al., 2020; Müller-Vahl and Emrich, 2008; Pasman et al., 2018). A polymorphism in the *FAAH* gene was found to confer a ten-fold risk of FEP onset in cannabis consumers in the FEP sample used for the present study (Bioque et al., 2019). However, the relationship between cannabis use and psychosis is far more complex. Some authors have suggested that cannabis could also be used as a form of self-medication to deal with psychotic, depressive and anxiety (Ferdinand et al., 2005; Mané et al., 2015; Radhakrishnan et al., 2022). Both cannabis use and schizophrenia have a complex genetic architecture, associated with numerous genetic variants conferring small effects. The genome-wide genetic susceptibility measured with polygenic risk scores (PRS) has confirmed the overlap between cannabis use and schizophrenia (Johnson et al., 2021; Pasman et al., 2018). The PRS for cannabis use disorder was found associated with schizophrenia, even when accounting for smoking and cannabis ever-use (Johnson et al., 2021) and the PRS for schizophrenia with cannabis use (Hiemstra et al., 2018). Genetic predisposition to cannabis use could have an effect on cannabis use and also to some specific symptoms that would in turn be associated to cannabis use and the later onset of psychosis. If confirmed, this common genetic susceptibility could elucidate some of the biological mechanisms underlying cannabis use, its self-medication effect and psychosis.

As previously remarked, cannabis use is widely reported as a risk factor for psychosis and worse clinical outcomes. This study aims to further characterize its effect after the onset of the FEP on the psychotic symptomatology and its trajectory during 12 months. To explore the genetic underpinnings of both cannabis use and symptom severity, cannabis initiation and use disorder PRS were constructed for each participant. We expected that FEP patients with increased PRS would report increased cannabis use as well as more severe symptoms and a slower 12-month progression to recovery.

2. Methods

This study is part of the multicentric project 'Phenotype–genotype interaction: application of a predictive model in first psychotic episodes' (PEPs Project). A complete description of the PEPs protocol has been published previously (Bernardo et al., 2019, 2013).

2.1. Sample

During the recruitment period (2009–2012), 335 subjects who presented a FEP were included in the PEPs Project. Patients included met the following inclusion criteria: aged 7–35 years old at recruitment; presence of psychotic symptoms of less than 12 months' duration; ability to speak Spanish correctly and providing written informed consent. The exclusion criteria were: presenting intellectual disability according to DSM-IV criteria (American Psychiatric Association, 1994); history of head trauma with loss of consciousness and presence of an organic disease with mental repercussions.

For the present study, we included those subjects who provided blood samples for genetic analysis, passed the genetic quality control (see below), were $\geq$ 16 years old (21 individuals excluded) and had European ancestry (51 individuals excluded). The final sample comprised 249 FEP subjects. This study was conducted under the ethical principles of the Declaration of Helsinki and Good Clinical Practice and the Hospital Clinic Ethics and Research Board. Informed consent was obtained from all participants or from parents or legal guardians of under-age subjects.

2.2. Assessments

Sociodemographic and premorbid data were collected at enrollment, including age, gender, years of education and age at FEP. For the present study, we focused on cannabis use, age of FEP onset and clinical data for a period of 12 months.

Diagnoses were assessed with the Structured Clinical Interview for DSM-IV Disorders (SCID-IV). After that, diagnoses were dichotomized into affective (Bipolar Disorder, Major Depressive Disorder, Schizoaffective Disorder) and non-affective psychosis (Unspecified Psychosis, Schizophreniform Disorder, Schizophrenia, Brief Psychotic Episode).

Symptomatology related to schizophrenia was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The items of the scale can be subdivided in positive, negative and general psychotic symptoms. Higher scores on this scale indicate greater severity.

Substance use was assessed with the European Adaptation of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence (EuropASI) (Kokkevi and Hartgers, 1995). For the present study included in the analyses information about the proportion of cannabis users, monthly cannabis use (number of times cannabis was used) and age of cannabis initiation.

2.3. Blood samples and genotyping

Blood samples were collected in K2EDTA BD Vacutainer EDTA tubes (Becton Dickinson, Franklin Lakes, New Jersey), stored at −20 °C and sent to the central laboratory. DNA was extracted with the MagNA Pure LC DNA isolation Kit – Large volume and MagNA Pure LC 2.0 Instrument (Roche Diagnostics GmbH, Mannheim, Germany). DNA concentration was determined by absorbance (ND1000, NanoDrop, Wilmington, Delaware). A total of 2.5 μg of genomic DNA was sent for genotyping at the Spanish National Genotyping Centre (CeGen) using Axiom™ Spain Biobank Array.

2.4. PRS calculation

Genotyping data was submitted to the Michigan Imputation Server (Das et al., 2016), following the standard pipeline and pre-imputation

quality control required for Minimac4 software and setting a European population reference from build GRCh37/hg19, reference panel HRC 1.1 2016 and Eagle v2.4 phasing.

The PRS were constructed using PRS-CS, a method that implements a high-dimensional Bayesian regression to perform a continuous shrinkage of SNP effect sizes using GWAS summary statistics and an external linkage disequilibrium (LD) reference panel (Ge et al., 2019). Here, two GWAS summary statistics were used to calculate individual PRS conferring risk for lifetime cannabis initiation (PRS_{CI}) (Pasman et al., 2018) and cannabis use disorder (PRS_{CUD}) (Johnson et al., 2020). The LD reference panel was constructed using a European subsample of the UK Biobank (Bycroft et al., 2018). For the remaining parameters, the default options as implemented in PRS-CS were adopted.

A genetic quality control was performed with PLINK v1.07 (Purcell et al., 2007). Inclusion criteria for SNPs were minor allele frequency (MAF) > 0.01, Hardy-Weinberg equilibrium $p > 10^{-6}$, SNP missingness < 0.01 and imputation INFO > 0.8. Pruning was performed using a window/step size of 200/50 kb and $r^2 > 0.25$ prior to the heterozygosity and relatedness check. Sample quality control included individuals with heterozygosity values $\pm$ 3SD from the mean, individual missingness $<$ 0.01, matching chromosomal and database-labeled sex, relatedness π-hat < 0.125 and self-reported European ancestry.

2.5. Statistical analysis

All the analyses were performed with R v4.1.2 ("R Core Team," 2017). A genetic principal component analysis (PCA) was performed to control population stratification (Patterson et al., 2006) by means of the *SNPRelate* package, and the first 10 components were used as covariates in the statistical analyses including PRS. Multiple testing correction was applied in all the analyses by means of the FDR method, and the threshold of significance of the adjusted p value (p.adj) was set at $\alpha <$ 0.05.

The association between cannabis use, age of cannabis initiation, age at FEP onset, symptom severity and PRS at baseline was evaluated with generalized linear models and corrected by sex, age and diagnostic. Linear mixed-effects modeling was used for longitudinal analyses, considering month of assessment as a random effect and the PRS and time as fixed effect and corrected by sex, age and diagnostic.

3. Results

3.1. Description of the sample

The sample consisted of 249 FEP individuals, 74 (29.7%) females, with a mean age of 24.5 years (SD = 5.7 years). Forty-two patients (16.9%) were diagnosed with affective psychosis. The mean age of cannabis use initiation was 16.1 years (SD = 2.9 years). Table 1 shows cannabis use pattern and psychotic symptoms of the sample at each assessment point during the 12-month follow-up.

Table 1
Cannabis use and psychotic symptoms measures during the 12-month follow-up.

Assessment	Baseline n(%) or mean(SD)	2-month n(%) or mean(SD)	6-month n(%) or mean(SD)	12-month n(%) or mean(SD)
Cannabis users	114(46.2%)	50(21.3%)	49(22.5%)	41(20.7%)
Monthly cannabis use (joints)	34.0(68.6)	5.6(25.3)	3.7(15.4)	1.9(8.6)
Total symptoms (PANSS score)	73.7(24.4)	57.1(20.4)	52.3(17.1)	50.2(18.2)
Positive symptoms (PANSS score)	18.4(8.3)	11.7(5.3)	10.4(4.4)	9.9(4.5)
Negative symptoms (PANSS score)	18.0(7.9)	16.5(6.9)	15.1(6.3)	14.5(6.5)
General symptoms (PANSS score)	37.3(12.7)	29.8(10.5)	26.8(8.8)	25.7(9.5)

3.2. Cannabis use and FEP severity

Individuals reporting an earlier cannabis initiation age had their FEP at younger ages ($t = 7.044$; $R^2 = 0.281$; p.adj $= 2.85 \times 10^{-10}$). Cannabis use at baseline was also associated with FEP age, but the result did not survive multiple testing correction ($t = -2.091$; $R^2 = 0.025$; p.adj = 0.056).

The effect of cannabis use on the psychotic symptomatology was tested at baseline and for the 12-month progression. Table 2 shows the association of positive symptoms with cannabis use (p.adj = 0.002) and a trend with monthly cannabis use (p.adj = 0.056) at baseline. Only cannabis initiation age was associated with the 12-month symptom course. Individuals initiating cannabis use at younger ages reported a worse overall progression of symptoms (p.adj = 0.014), including positive (p.adj = 0.018), negative (p.adj= 0.023) and general (p.adj=0.030) subscales.

3.3. Cannabis PRS and cannabis use

To assess the role of genetics in the cannabis use pattern, the PRS capturing the genetic liability for cannabis initiation (PRS_{CI}) and cannabis use disorder (PRS_{CUD}) were included in the analyses. No PRS was associated with the age of cannabis initiation (p.adj > 0.05 for all analyses). Table 3 shows that greater PRS_{CUD} was associated with cannabis use and a monthly use at baseline (p.adj $= 2.61 \times 10^{-4}$; p.adj = 0.014). No associations were found for PRS_{CI} and cannabis use pattern.

3.4. Cannabis PRS and FEP severity

The PRS were not associated with the age at FEP (p.adj > 0.05 for all analyses). The baseline symptomatology was not associated with the PRS, but a trend was found for PRS_{CI} and the negative subscale (p.adj = 0.052). The 12-month progression of total, negative and general symptoms was associated with PRS_{CI} (p. adj = 0.017, p.adj = 0.035, p.adj = 0.024; respectively). No associations were found for PRS_{CUD} (Table 4).

4. Discussion

This prospective study explored the relationship between cannabis use, psychotic symptoms and cannabis PRS in a FEP sample longitudinally. Cannabis initiation was linked to earlier FEP onset and the progression of psychotic symptoms. Cannabis use pattern at study entry was associated with the cannabis use disorder PRS, while PRS reflecting the genetic proneness for lifetime cannabis initiation was found to have an effect on symptom progression. The present study characterizes the impact of cannabis use and the role of the genetic susceptibility underlying cannabis use in the clinical evolution after a first psychotic episode. The findings of this exploratory study establish a foundational understanding of the genetic architecture of cannabis use and its relationship with the clinical outcome in the first stages of psychotic disorders.

Earlier FEP onset was associated with cannabis initiation age and use, although the latter did not survive multiple testing correction. We replicated results found in other subsets of the present sample (Amoretti et al., 2022; Mané et al., 2017) and reported in the literature (di Forti et al., 2014; González-Blanco et al., 2021; Sugranyes et al., 2009). Additionally, we detected an effect of current cannabis use in the positive symptoms similar to the associations previously described in this FEP sample (Amoretti et al., 2022; González-Blanco et al., 2021). A statistical trend suggests a dose-dependent relationship, but increased sample sizes are needed to confirm this result. The most recent metanalysis reveals a small increase of positive symptomatology in schizophrenia patients reporting current cannabis use (Sabe et al., 2020). The effect was more conspicuous in the previous metanalysis, which included FEP samples (Large et al., 2014). The only cannabis use

Table 2
Cannabis use and psychotic symptom severity at study entry and 12-month follow-up. Significant results are marked in bold.

Cannabis use	Psychotic symptoms	Baseline			12-month		
		t	R^2	p.adj	t	R^2	p.adj
Cannabis user	Total	1.615	0.015	0.143	0.898	0.014	0.397
	Positive	3.561	0.051	**0.002**	1.398	0.010	0.998
	Negative	−1.588	0.033	0.113	−1.123	0.035	0.421
	General	1.820	0.016	0.140	1.132	0.008	0.591
Monthly cannabis use	Total	1.084	0.009	0.559	1.577	0.009	0.576
	Positive	2.481	0.031	0.056	0.799	0.003	0.662
	Negative	−0.322	0.024	0.748	0.531	0.028	0.602
	General	0.698	0.009	0.648	1.217	0.006	0.448
Cannabis use initiation age	Total	−0.676	0.009	0.667	−3.855	0.054	**0.014**
	Positive	−0.707	0.005	0.962	−3.634	0.032	**0.018**
	Negative	0.032	0.023	0.974	−2.949	0.050	**0.023**
	General	−0.844	0.011	1.000	−3.998	0.052	**0.030**

Table 3
PRS association with cannabis use pattern at study entry and during the 12-month follow-up. Significant results are marked in bold.

PRS	Cannabis use	Baseline			12-month		
		t	R^2	p.adj	t	R^2	p.adj
PRS_{CI}	Cannabis user	0.429	0.101	0.669	−0.062	0.032	0.952
	Monthly cannabis use	0.354	0.075	0.724	0.390	0.018	0.705
PRS_{CUD}	Cannabis user	3.888	0.151	**2.61E−04**	2.837	0.051	0.079
	Monthly cannabis use	2.734	0.104	**0.014**	1.497	0.029	0.422

Table 4
PRS association with psychotic symptoms at baseline and during the 12-month follow-up. Significant results are marked in bold.

PRS	Psychotic symptoms	Baseline			12-month		
		t	R^2	p.adj	t	R^2	p.adj
PRS_{CI}	Total	2.153	0.047	0.065	2.914	0.049	**0.017**
	Positive	0.887	0.025	0.376	1.582	0.017	0.121
	Negative	2.075	0.095	0.052	2.738	0.087	**0.035**
	General	2.282	0.046	0.093	3.033	0.041	**0.024**
PRS_{CUD}	Total	−0.884	0.032	0.504	−0.881	0.042	0.397
	Positive	−1.131	0.027	0.518	−1.223	0.016	0.501
	Negative	0.421	0.080	0.674	0.872	0.080	0.520
	General	−1.217	0.032	0.900	−1.530	0.034	0.609

feature linked to psychotic symptoms was initiation age. Considering that almost 50% of cannabis users achieved cessation and monthly intake was severely reduced during the 12-month follow-up, these results suggest that the – possibly dose-dependent – effect of current cannabis use on positive symptoms may be reversible. Previous longitudinal studies have described better outcomes in FEP patients who stop using cannabis (González-Pinto et al., 2011; Schoeler et al., 2016). Thus, the development of preventive tools is decisive to hinder the effect of cannabis in younger individuals at critical stages of brain development (Bara et al., 2021; Penzel et al., 2021; Schneider, 2008), that may have major impact on the clinical outcomes.

Individuals with increased PRS_{CUD} were more prone to use cannabis, as previously demonstrated in non-psychotic samples (Johnson et al., 2019; Meyers et al., 2019). This effect was not statistically significant for the 12-month progression analyses, thus implying that despite an increased genetic liability for cannabis abuse and dependency, cessation can be achieved after FEP onset. These results are particularly meaningful since cannabis use after FEP onset is associated with poor outcomes (Baeza et al., 2009; Bioque et al., 2022; González-Pinto et al., 2016, 2011; Marconi et al., 2016; Marino et al., 2020; Wisdom et al., 2011). However, the current treatment strategies for cannabis cessation are insufficient for a considerable number of FEP patients (McDonell and Oluwoye, 2019). The present results suggest that other factors might contribute to consumption persistence, which may be considered for the development of novel treatment strategies for cannabis use in FEP.

The influence of PRS_{CI} on cannabis use was not detected, but individuals with increased scores reported a worse progression of negative and general symptoms. These findings could be explained by the nature of the reference GWAS, which captures the genetic variability of lifetime cannabis use in the general population. Cannabis initiation is a complex process, and therefore the multiple genetic and environmental factors that trigger the consumption may operate differently in individuals at high clinical risk. Intriguingly, the association of PRS_{CI} with non-positive symptoms implies that the captured genetic susceptibility may also reflect the proneness for affective, depressive and other unspecific symptoms. Considering the effect of cannabis on the dopaminergic neurotransmission associated to negative symptoms (Awad and Voruganti, 2015; Howes and Kapur, 2009; Peters et al., 2021), it could be hypothesized that individuals with this genetic proneness could initiate cannabis consumption as self-medication to mitigate the symptoms. However, cannabis use would trigger the psychotic episode and a more severe manifestation of these symptoms (di Forti et al., 2014; Harrison et al., 2008) and thus its putative self-medication effect could rebound after sustained substance use (Diana, 2011; Sabe et al., 2020). Consistent with this hypothesis, some authors have shown that cannabis use, anxiety and depressive symptoms have shown to have a bidirectional association with psychotic experiences (Radhakrishnan et al., 2022).

Some limitations of the present work should be taken into consideration. Firstly, the sample size is moderately limited in the longitudinal follow-up due to patient drop-out and therefore the statistical analysis might be underpowered to detect small effects. Secondly, cannabis use pattern was not assessed through biochemical quantification of cannabinoids concentration. Instead, cannabis use pattern was obtained by the

self-reported data of EuropASI scale which may not be completely accurate. Furthermore, EuropASI does not provide quantitative objective method to assess specific cannabinoids (mainly tetrahydrocannabinol and cannabidiol), which have different clinical effects (Hahn, 2018). Subjects included in the analyses are exclusively of European ancestry, and therefore the implications of the present findings may not be generalizable to other ancestries. However, this study comprises one of the largest and best characterized FEP samples in the literature, with a naturalistic design and thus representative of the psychiatric population. Exhaustive assessment during a considerably long follow-up period enables a complete exploration of the association between cannabis use and symptom evolution after the FEP and cannabis PRS. Furthermore, these PRS have been calculated with large GWAS from international consortiums and thus the comprised genetic variants have a great capacity to capture the genetic susceptibility of the phenotypes.

In the present study, cannabis initiation was linked to earlier FEP onset and the progression of positive psychotic symptoms. Interestingly, the genetic liability for cannabis use disorder was linked to the pattern of consumption at baseline, but not at follow-up, opening the door to new strategies for cannabis use cessation in FEP. Intriguingly, the genetic susceptibility for lifetime cannabis initiation were not associated with its use but with the progression of general (anxious and depressive) and negative symptoms. If confirmed, these findings on general and negative symptoms would contribute to personalized intervention since FEP onset.

Author statement

The results presented here are part of a broader project, the PEPs study. MB is the coordinator of the PEPs study and JSR is the coordinator of the biological module. AGS and AM performed the statistical analysis and wrote the first draft of the manuscript, and both authors contributed equally to this work. LP and NR performed the sample isolation and preparation and participated in the statistical analysis.GM, SA, ARB, EJ, TL participated in the coordination of the sample shipment, the maintenance of the database and in the recruitment and assessment of the sample. MJC, EV, AL, AGP, CMDC, IB participated in the recruitment and assessment of the sample.SM designed, supervised and performed the statistical analysis, performed the interpretation of the results and wrote the first draft of the manuscript. All the authors, including the PEPs group authors listed in the acronym, contributed to the final draft of the manuscript.

Declaration of Competing Interest

C. De-la-Camara received financial support to attend scientific meetings from Janssen-Cilag, Almirall, Eli Lilly, Lundbeck, Rovi, Esteve, Novartis, and Astrazeneca.

E. Vieta has received grants and/or acted as consultant and/or speaker for the following companies: AB-Biotics, Abbott, Allergan, Angelini, Astra-Zeneca, Dainippon Sumitomo, Ferrer, Janssen, Lundbeck, Novartis, Otsuka, Pfizer, Richter, Sage, Sanofi, Servier, Sunovion, and Takeda.

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References

American Psychiatric Association, 1994. Diagnostic and statistical manual of mental disorders : DSM-IV. Washington, DC.

Amoretti, S., Verdolini, N., Varo, C., Mezquida, G., Sánchez-Torres, A.M., Vieta, E., Garcia-Rizo, C., Lobo, A., González-Pinto, A., Abregú-Crespo, R., Corripio, I., Serra, M., de la Serna, E., Mané, A., Ramos-Quiroga, J.A., Ribases, M., Cuesta, M.J., Bernardo, M., 2022. Is the effect of cognitive reserve in longitudinal outcomes in first-episode psychoses dependent on the use of cannabis? J. Affect. Disord. 302, 83–93. https://doi.org/10.1016/j.jad.2022.01.077.

Arranz, S., Mané, A., Bergé, D., Monserrat, C., Cabezas, A., Vilella, E., Sanchez-Gistau, V., 2020. The impact of sex and cannabis on clinical features in first–admitted patients with psychosis. Eur. Neuropsychopharmacol. 36, 235–243. https://doi.org/10.1016/j.euroneuro.2020.03.003.

Awad, A.G., Voruganti, L.L., 2015. Revisiting the 'self-medication' hypothesis in light of the new data linking low striatal dopamine to comorbid addictive behavior. Ther. Adv. Psychopharmacol. https://doi.org/10.1177/2045125315583820.

Baeza, I., Graell, M., Moreno, D., Castro-Fornieles, J., Parellada, M., González-Pinto, A., Payá, B., Soutullo, C., de la Serna, E., Arango, C., 2009. Cannabis use in children and adolescents with first episode psychosis: influence on psychopathology and short-term outcome (CAFEPS study). Schizophr. Res. 113, 129–137. https://doi.org/10.1016/j.schres.2009.04.005.

Bara, A., Ferland, J.M.N., Rompala, G., Szutorisz, H., Hurd, Y.L., 2021. Cannabis and synaptic reprogramming of the developing brain. Nat. Rev. Neurosci. https://doi.org/10.1038/s41583-021-00465-5.

Barbeito, S., Vega, P., Ruiz de Azúa, S., Saenz, M., Martinez-Cengotitabengoa, M., González-Ortega, I., Bermudez, C., Hernanz, M., Corres, B.F.de, González-Pinto, A., 2013. Cannabis use and involuntary admission may mediate long-term adherence in

first-episode psychosis patients: a prospective longitudinal study. BMC Psychiatry 13, 326. https://doi.org/10.1186/1471-244X-13-326.
Bernardo, M., Bioque, M., Parellada, M., Saiz Ruiz, J., Cuesta, M.J., Llerena, A., Sanjuán, J., Castro-Fornieles, J., Arango, C., Cabrera, B., 2013. Assessing clinical and functional outcomes in a gene–environment interaction study in first episode of psychosis (PEPs). Rev. Psiquiatr. Salud Ment. (English Ed.) 6, 4–16. https://doi.org/10.1016/j.rpsmen.2012.11.001.
Bernardo, M., Cabrera, B., Arango, C., Bioque, M., Castro-Fornieles, J., Cuesta, M.J., Lafuente, A., Parellada, M., Saiz-Ruiz, J., Vieta, E., 2019. One decade of the first episodes project (PEPs): advancing towards a precision psychiatry. Rev. Psiquiatr. Salud Ment. 12, 135–140. https://doi.org/10.1016/j.rpsm.2019.03.001.
Bioque, M., Mas, S., Costanzo, M.C., Cabrera, B., Lobo, A., González-Pinto, A., Rodriguez-Toscano, E., Corripio, I., Vieta, E., Baeza, I., Ibáñez, Á., Fraile, M.G., Cuesta, M.J., Mezquida, G., Lafuente, A., Bernardo, M., Amoretti, S., Meseguer, A., López, G., Vidal, J., Alonso, A., Rabella, M., Ortega, I.G., López, P., Barcones, M.F., De-La-cámara, C., Sanjuan, J., Rovira, E.L., Mané, A., Bergé, D., Solé, B., Da Costa, S.G., de la Serna, E., Castro-Fornieles, J., Contreras, F., Albacete, A., García-álvarez, L., de la Fuente Tomás, L., Zabala, A., Segarra, R., Morales-Muñoz, I., Rodriguez-Jimenez, R., Usall, J., Butjosa, A., Sarró, S., Landín-Romero, R., Saiz-Ruiz, J., López-Ilundain, J. M., Balanzá-Martínez, V., 2019. Gene-environment interaction between an endocannabinoid system genetic polymorphism and cannabis use in first episode of psychosis. Eur. Neuropsychopharmacol. 29, 786–794. https://doi.org/10.1016/j.euroneuro.2019.04.005.
Bioque, M., Mezquida, G., Amoretti, S., García-Rizo, C., López-Ilundain, J.M., Diaz-Caneja, C.M., Zorrilla, I., Mané, A., Rodriguez-Jimenez, R., Corripio, I., Pomarol-Clotet, E., Ibáñez, Á., Usall, J., Contreras, F., Mas, S., Vázquez-Bourgon, J., Cuesta, M.J., Parellada, M., González-Pinto, A., Hidalgo-Figueroa, M., Bernardo, M., 2022. Clinical and treatment predictors of relapse during a three-year follow-up of a cohort of first episodes of schizophrenia. Schizophr. Res. 243, 32–42. https://doi.org/10.1016/j.schres.2022.02.026.
Bycroft, C., Freeman, C., Petkova, D., Band, G., Elliott, L.T., Sharp, K., Motyer, A., Vukcevic, D., Delaneau, O., O'Connell, J., Cortes, A., Welsh, S., Young, A., Effingham, M., McVean, G., Leslie, S., Allen, N., Donnelly, P., Marchini, J., 2018. The UK Biobank resource with deep phenotyping and genomic data. Nature 562, 203–209. https://doi.org/10.1038/s41586-018-0579-z.
Caspi, A., Moffitt, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H.L., Taylor, A., Arseneault, L., Williams, B., Braithwaite, A., Poulton, R., Craig, I.W., 2005. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. Biol. Psychiatry 57, 1117–1127. https://doi.org/10.1016/j.biopsych.2005.01.026.
Das, S., Forer, L., Schönherr, S., Sidore, C., Locke, A.E., Kwong, A., Vrieze, S.I., Chew, E. Y., Levy, S., McGue, M., Schlessinger, D., Stambolian, D., Loh, P.R., Iacono, W.G., Swaroop, A., Scott, L.J., Cucca, F., Kronenberg, F., Boehnke, M., Abecasis, G.R., Fuchsberger, C., 2016. Next-generation genotype imputation service and methods. Nat. Genet. 48, 1284–1287. https://doi.org/10.1038/ng.3656.
Diana, M., 2011. The dopamine hypothesis of drug addiction and its potential therapeutic value. Front. Psychiatry 2. https://doi.org/10.3389/fpsyt.2011.00064.
Di Forti, M., Quattrone, D., Freeman, T.P, Tripoli, G., Gayer-Anderson, C., Quigley, H., Rodriguez, V., Jongsma, H.E., Ferraro, L., La Cascia, C., La Barbera, D., Tarricone, I., Berardi, D., Szöke, A., Arango, C., Tortelli, A., Velthorst, E., Bernardo, Miguel, Del-Ben, C.M., Menezes, P.R., Selten, J.P., Jones, P.B., Kirkbride, J.B., Rutten, B.P., de Haan, L., Sham, P.C., van Os, J., Lewis, C.M., Lynskey, M., Morgan, C., Murray, R.M., Amoretti, S., Arrojo, M., Baudin, G., Beards, S., Bernardo, Miquel, Bobes, J., Bonetto, C., Cabrera, B., Carracedo, A., Charpeaud, T., Costas, J., Cristofalo, D., Cuadrado, P., Díaz-Caneja, C.M., Ferchiou, A., Franke, N., Frijda, F., Garcínu Eernardo, E., Garcia-Portilla, P., González, E., Hubbard, K., Jamain, S., Jiménez-López, E., Leboyer, M., López Montoya, G., Lorente-Rovira, E., Marcelino Loureiro, C., Marrazzo, G., Martínez, C., Matteis, M., Messchaart, E., Moltó, M.D., Nacher, J., Olmeda, M.S., Parellada, M., González Peñas, J., Pignon, B., Rapado, M., Richard, J.R., Rodríguez Solano, J.J., Roldán Díaz, L., Ruggeri, M., Sáiz, P.A., Sánchez, E., Sanjuán, J., Sartorio, C., Schürhoff, F., Seminerio, F., Shuhama, R., Sideli, L., Stilo, S.A., Termorshuizen, F., Tosato, S., Tronche, A.M., van Dam, D., van der Ven, E., 2019. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry 6, 427–436. https://doi.org/10.1016/S2215-0366(19)30048-3.
di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S.A., Marconi, A., la Cascia, C., Marques, T.R., Pariante, C., Dazzan, P., Mondelli, V., Paparelli, A., Kolliakou, A., Prata, D., Gaughran, F., David, A.S., Morgan, C., Stahl, D., Khondoker, M., MacCabe, J.H., Murray, R.M., 2014. Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. Schizophr. Bull. 40, 1509–1517. https://doi.org/10.1093/schbul/sbt181.
Ferdinand, R.F., Sondeijker, F., Van Der Ende, J., Selten, J.P., Huizink, A., Verhulst, F.C., 2005. Cannabis use predicts future psychotic symptoms, and vice versa. Addiction 100, 612–618. https://doi.org/10.1111/j.1360-0443.2005.01070.x.
Ge, T., Chen, C.Y., Ni, Y., Feng, Y.C.A., Smoller, J.W., 2019. Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat. Commun. 10 (1), 1776. https://doi.org/10.1038/s41467-019-09718-5.
González-Blanco, L., García-Portilla, M.P., Gutiérrez, M., Mezquida, G., Cuesta, M.J., Urbiola, E., Amoretti, S., Barcones, F., González-Pinto, A., Pina-Camacho, L., Corripio, I., Vieta, E., Baeza, I., Toll, A., Sáiz, P.A., Bobes, J., Bernardo, M., Bioque, M., Sagué, M., Alonso-Solís, A., Grasa, E., González-Ortega, I., Zorrilla, I., Santabárbara, J., De-la-Cámara, C., Aguilar, E.J., Nacher, J., Bergé, D., Mané, A., Montejo, L., Anmella, G., Castro-Fornieles, J., de la Serna, E., Contreras, F., Sáiz-Masvidal, C., García-Álvarez, L., Bobes-Bascarán, T., Zabala-Rabadán, A., Segarra-Echevarría, R., Sanchez-Pastor, L., Rodriguez-Jimenez, R., Usall, J., Butjosa, A., Sarró, S., Guerrero-Pedraza, A., Ibañez, Á., Ribeiro, M., Balanzá-Martínez, V., 2021. Impact of previous tobacco use with or without cannabis on first psychotic experiences in patients with first-episode psychosis. Schizophr. Res. 236, 19–28. https://doi.org/10.1016/j.schres.2021.07.017.
González-Pinto, A., Alberich, S., Barbeito, S., Gutierrez, M., Vega, P., Ibáñez, B., Haidar, M.K., Vieta, E., Arango, C., 2011. Cannabis and first-episode psychosis: different long-term outcomes depending on continued or discontinued use. Schizophr. Bull. 37, 631–639. https://doi.org/10.1093/schbul/sbp126.
González-Pinto, A., González-Ortega, I., Alberich, S., De Azúa, S.R., Bernardo, M., Bioque, M., Cabrera, B., Corripio, I., Arango, C., Lobo, A., Sánchez-Torres, A.M., Cuesta, M.J., Ugarte, A., Fernández, M., Mezquida, G., Meseguer, A., Vieta, E., Torrent, C., Contreras, F., Albacete, A., Alonso-Solís, A., Rabella, M., Moreno-Izco, L., Usall, J., Butjosa, A., Ibáñez, Á., Bobes, J., Al-Halabí, S., Zapata-Usábel, M.T., Laporta-Herrero, I., Balanzá-Martínez, V., Bergé, D., Mané, A., Rodriguez-Jimenez, R., Morales-Muñoz, I., Gutierrez, M., Zabala, A., Sarró, S., Landin-Romero, R., De La Serna, E., Baeza, I., Parellada, M., Espliego, A., Juan, J.S., Aguilar, E., 2016. Opposite cannabis-cognition associations in psychotic patients depending on family history. PLoS One 11, 1–16. https://doi.org/10.1371/journal.pone.0160949.
González-Pinto, A., Vega, P., Ibáñez, B., Mosquera, F., Barbeito, S., Gutiérrez, M., Ruiz De Azúa, S., Ruiz, I., Vieta, E., 2008. Impact of cannabis and other drugs on age at onset of psychosis. J. Clin. Psychiatry 69, 1210–1216. https://doi.org/10.4088/JCP.v69n0802.
Hahn, B., 2018. The potential of cannabidiol treatment for cannabis users with recent-onset psychosis. Schizophr. Bull. 44, 46–53. https://doi.org/10.1093/schbul/sbx105.
Harrison, I., Joyce, E.M., Mutsatsa, S.H., Hutton, S.B., Huddy, V., Kapasi, M., Barnes, T.R. E., 2008. Naturalistic follow-up of co-morbid substance use in schizophrenia: the West London first-episode study. Psychol. Med. 38, 79–88. https://doi.org/10.1017/S0033291707000797.
Hiemstra, M., Nelemans, S.A., Branje, S., van Eijk, K.R., Hottenga, J.J., Vinkers, C.H., van Lier, P., Meeus, W., Boks, M.P., 2018. Genetic vulnerability to schizophrenia is associated with cannabis use patterns during adolescence. Drug Alcohol Depend. 190, 143–150. https://doi.org/10.1016/j.drugalcdep.2018.05.024.
Howes, O.D., Kapur, S., 2009. The dopamine hypothesis of schizophrenia: version III - the final common pathway. Schizophr. Bull. https://doi.org/10.1093/schbul/sbp006.
Johnson, E.C., Demontis, D., Thorgeirsson, T.E., Walters, R.K., Polimanti, R., Hatoum, A. S., Sanchez-Roige, S., Paul, S.E., Wendt, F.R., Clarke, T.K., Lai, D., Reginsson, G.W., Zhou, H., He, J., Baranger, D.A.A., Gudbjartsson, D.F., Wedow, R., Adkins, D.E., Adkins, A.E., Alexander, J., Bacanu, S.A., Bigdeli, T.B., Boden, J., Brown, S.A., Bucholz, K.K., Bybjerg-Grauholm, J., Corley, R.P., Degenhardt, L., Dick, D.M., Domingue, B.W., Fox, L., Goate, A.M., Gordon, S.D., Hack, L.M., Hancock, D.B., Hartz, S.M., Hickie, I.B., Hougaard, D.M., Krauter, K., Lind, P.A., McClintick, J.N., McQueen, M.B., Meyers, J.L., Montgomery, G.W., Mors, O., Mortensen, P.B., Nordentoft, M., Pearson, J.F., Peterson, R.E., Reynolds, M.D., Rice, J.P., Runarsdottir, V., Saccone, N.L., Sherva, R., Silberg, J.L., Tarter, R.E., Tyrfingsson, T., Wall, T.L., Webb, B.T., Werge, T., Wetherill, L., Wright, M.J., Zellers, S., Adams, M. J., Bierut, L.J., Boardman, J.D., Copeland, W.E., Farrer, L.A., Foroud, T.M., Gillespie, N.A., Grucza, R.A., Harris, K.M., Heath, A.C., Hesselbrock, V., Hewitt, J.K., Hopfer, C.J., Horwood, J., Iacono, W.G., Johnson, E.O., Kendler, K.S., Kennedy, M. A., Kranzler, H.R., Madden, P.A.F., Maes, H.H., Maher, B.S., Martin, N.G., McGue, Matthew, McIntosh, A.M., Medland, S., Nelson, E.C., Porjesz, B., Riley, B.P., Stallings, M.C., Vanyukov, M.M., Vrieze, S., Walters, R., Johnson, Emma, McClintick, J., Hatoum, A., Wendt, F., Adams, M., Adkins, A., Aliev, F., Batzler, A., Bertelsen, S., Biernacka, J., Bigdeli, T., Chen, L.S., Chou, Y.L., Degenhardt, F., Docherty, A., Edwards, A., Fontanillas, P., Foo, J., Frank, J., Giegling, I., Gordon, S., Hack, L., Hartmann, A., Hartz, S., Heilmann-Heimbach, S., Herms, S., Hodgkinson, C., Hoffman, P., Hottenga, J., Kennedy, M., Alanne-Kinnunen, M., Konte, B., Lahti, J., Lahti-Pulkkinen, M., Ligthart, L., Loukola, A., Maher, B., Mbarek, H., McIntosh, A., McQueen, M., Meyers, J., Milaneschi, Y., Palviainen, T., Pearson, J., Peterson, R., Ripatti, S., Ryu, E., Saccone, N., Salvatore, J., Schwandt, M., Streit, F., Strohmaier, J., Thomas, N., Wang, J.C., Webb, B., Wills, A., Boardman, J., Chen, D., Choi, D.S., Copeland, W., Culverhouse, R., Dahmen, N., Domingue, B., Elson, S., Frye, M., Gäbel, W., Hayward, C., Ising, M., Keyes, M., Kiefer, F., Kramer, J., Kuperman, S., Lucae, S., Lynskey, M., Maier, W., Mann, K., Männistö, S., Müller-Myhsok, B., Murray, A., Nurnberger, J., Palotie, A., Preuss, U., Räikkönen, K., Reynolds, M., Ridinger, M., Scherbaum, N., Schuckit, M., Soyka, M., Treutlein, J., Witt, S., Wodarz, N., Zill, P., Adkins, D., Boomsma, D., Bierut, L., Brown, S., Cichon, S., Costello, E.J., de Wit, H., Diazgranados, N., Dick, D., Eriksson, J., Farrer, L., Foroud, T., Gillespie, N., Goate, A., Goldman, D., Grucza, R., Hancock, D., Heath, A., Hewitt, J., Hopfer, C., Iacono, W., Johnson, Eric, Kaprio, J., Karpyak, V., Kendler, K., Kranzler, H., Lichtenstein, P., Lind, P., McGue, Matt, MacKillop, J., Madden, P., Maes, H., Magnusson, P., Martin, N., Montgomery, G., Nelson, E., Nöthen, M., Palmer, A., Pederson, N., Penninx, B., Rice, J., Rietschel, M., Riley, B., Rose, R., Rujescu, D., Shen, P.H., Silberg, J., Stallings, M., Tarter, R., Vanyukov, M., Wall, T., Whitfield, J., Zhao, H., Neale, B., Gelernter, J., Edenberg, H., Agrawal, A., Davis, L.K., Bogdan, R., Edenberg, H.J., Stefansson, K., Børglum, A.D., 2020. A large-scale genome-wide association study meta-analysis of cannabis use disorder. Lancet Psychiatry 7, 1032–1045. https://doi.org/10.1016/S2215-0366(20)30339-4.
Johnson, E.C., Hatoum, A.S., Deak, J.D., Polimanti, R., Murray, R.M., Edenberg, H.J., Gelernter, J., di Forti, M., Agrawal, A., 2021. The relationship between cannabis and schizophrenia: a genetically informed perspective. Addiction. https://doi.org/10.1111/add.15534.

Johnson, E.C., Tillman, R., Aliev, F., Meyers, J.L., Salvatore, J.E., Anokhin, A.P., Dick, D. M., Edenberg, H.J., Kramer, J.R., Kuperman, S., McCutcheon, V.v., Nurnberger, J.I., Porjesz, B., Schuckit, M.A., Tischfield, J., Bucholz, K.K., Agrawal, A., 2019. Exploring the relationship between polygenic risk for cannabis use, peer cannabis use and the longitudinal course of cannabis involvement. Addiction 114, 687–697. https://doi.org/10.1111/add.14512.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Kokkevi, A., Hartgers, C., 1995. EuropASI: European adaptation of a multidimensional assessment instrument for drug and alcohol dependence. Eur. Addict. Res. 1, 208–210. https://doi.org/10.1159/000259089.

Large, M., Mullin, K., Gupta, P., Harris, A., Nielssen, O., 2014. Systematic meta-analysis of outcomes associated with psychosis and co-morbid substance use. Austr. N. Z. J. Psychiatry. https://doi.org/10.1177/0004867414525838.

Mané, A., Bergé, D., Penzol, M.J., Parellada, M., Bioque, M., Lobo, A., González-Pinto, A., Corripio, I., Cabrera, B., Sánchez-Torres, A.M., Saiz-Ruiz, J., Bernardo, M., Mezquida, G., Bargalló, N., Llorente, C., Rodríguez-Toscano, E., Alonso-Solís, A., Rabella, M., de Azua, S.R., Gonzalez, I., Pires, G., Andres-Bergareche, H., Escartí, M. J., Rovira, E.L., Bulbena, A., Salgado, P., Vieta, E., del Mar Bonin, C., Baeza, I., Castro, J., Contreras, F., Albacete, À., Bobes, J., García-Portilla, M.P., Gutierrez, M., Zabala, A., Morales-Muñoz, I., Rodriguez-Jimenez, R., Usall, J., Butjosa, A., Sarro, S., Landin-Romero, R., Ibáñez, Á., Moreno-Izco, L., Balanzá-Martínez, V., 2017. Cannabis use, COMT, BDNF and age at first-episode psychosis. Psychiatry Res. 250, 38–43. https://doi.org/10.1016/j.psychres.2017.01.045.

Mané, A., Fernández-Expósito, M., Bergé, D., Gómez-Pérez, L., Sabaté, A., Toll, A., Diaz, L., Diez-Aja, C., Perez, V., 2015. Relationship between cannabis and psychosis: Reasons for use and associated clinical variables. Psychiatry Res. 229, 70–74. https://doi.org/10.1016/j.psychres.2015.07.070.

Marconi, A., di Forti, M., Lewis, C.M., Murray, R.M., Vassos, E., 2016. Meta-Analysis of the association between the level of cannabis use and risk of psychosis. Schizophr. Bull. 42, 1262–1269. https://doi.org/10.1093/schbul/sbw003.

Marino, L., Scodes, J., Richkin, T., Alves-Bradford, J.-M., Nossel, I., Wall, M., Dixon, L., 2020. Persistent cannabis use among young adults with early psychosis receiving coordinated specialty care in the United States. Schizophr. Res. 222, 274–282. https://doi.org/10.1016/j.schres.2020.05.035.

McDonell, M.G., Oluwoye, O., 2019. Cannabis use in first episode psychosis: what we have tried and why it hasn't worked. BMC Med. 17, 1–2. https://doi.org/10.1186/s12916-019-1421-7.

Meyers, J.L., Salvatore, J.E., Aliev, F., Johnson, E.C., McCutcheon, V.v., Su, J., Kuo, S.I. C., Lai, D., Wetherill, L., Wang, J.C., Chan, G., Hesselbrock, V., Foroud, T., Bucholz, K.K., Edenberg, H.J., Dick, D.M., Porjesz, B., Agrawal, A., 2019. Psychosocial moderation of polygenic risk for cannabis involvement: the role of trauma exposure and frequency of religious service attendance. Transl. Psychiatry 9. https://doi.org/10.1038/s41398-019-0598-z.

Moore, T.H., Zammit, S., Lingford-Hughes, A., Barnes, T.R., Jones, P.B., Burke, M., Lewis, G., 2007. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 370, 319–328. https://doi.org/10.1016/S0140-6736(07)61162-3.

Müller-Vahl, K.R., Emrich, H.M., 2008. Cannabis and schizophrenia: towards a cannabinoid hypothesis of schizophrenia. Expert Rev. Neurother. 8, 1037–1048. https://doi.org/10.1586/14737175.8.7.1037.

Pasman, J.A., Verweij, K.J.H., Gerring, Z., Stringer, S., Sanchez-Roige, S., Treur, J.L., Abdellaoui, A., Nivard, M.G., Baselmans, B.M.L., Ong, J.-S., Ip, H.F., van der Zee, M. D., Bartels, M., Day, F.R., Fontanillas, P., Elson, S.L., de Wit, H., Davis, L.K., MacKillop, J., Derringer, J.L., Branje, S.J.T., Hartman, C.A., Heath, A.C., van Lier, P. A.C., Madden, P.A.F., Mägi, R., Meeus, W., Montgomery, G.W., Oldehinkel, A.J., Pausova, Z., Ramos-Quiroga, J.A., Paus, T., Ribases, M., Kaprio, J., Boks, M.P.M., Bell, J.T., Spector, T.D., Gelernter, J., Boomsma, D.I., Martin, N.G., MacGregor, S., Perry, J.R.B., Palmer, A.A., Posthuma, D., Munafò, M.R., Gillespie, N.A., Derks, E.M., Vink, J.M., 2018. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal effect of schizophrenia liability. Nat. Neurosci. 21, 1161–1170. https://doi.org/10.1038/s41593-018-0206-1.

Patel, R., Wilson, R., Jackson, R., Ball, M., Shetty, H., Broadbent, M., Stewart, R., McGuire, P., Bhattacharyya, S., 2016. Association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis: an observational study. BMJ Open 6, 1–9. https://doi.org/10.1136/bmjopen-2015-009888.

Patterson, N., Price, A.L., Reich, D., 2006. Population structure and eigenanalysis. PLoS Genet. 2, 2074–2093. https://doi.org/10.1371/journal.pgen.0020190.

Penzel, N., Antonucci, L.A., Betz, L.T., Sanfelici, R., Weiske, J., Pogarell, O., Cumming, P., Quednow, B.B., Howes, O., Falkai, P., Upthegrove, R., Bertolino, A., Borgwardt, S., Brambilla, P., Lencer, R., Meisenzahl, E., Rosen, M., Haidl, T., Kambeitz-Ilankovic, L., Ruhrmann, S., Salokangas, R.R.K., Pantelis, C., Wood, S.J., Koutsouleris, N., Kambeitz, J., Koutsouleris, N., Kambeitz-Ilankovic, L., sen Dong, M., Erkens, A., Gussmann, E., Haas, S., Hasan, A., Hoff, C., Khanyaree, I., Melo, A., Muckenhuber-Sternbauer, S., Kohler, J., Ozturk, O.F., Popovic, D., Rangnick, A., von Saldern, S., Sanfelici, R., Spangemacher, M., Tupac, A., Urquijo, M.F., Weiske, J., Wosgien, A., Kambeitz, J., Ruhrmann, S., Rosen, M., Betz, L., Haidl, T., Blume, K., Seves, M., Kaiser, N., Penzel, N., Pilgram, T., Lichtenstein, T., Wenzel, J., Woopen, C., Borgwardt, S., Andreou, C., Egloff, L., Harrisberger, F., Lenz, C., Leanza, L., Mackintosh, A., Smieskova, R., Studerus, E., Walter, A., Widmayer, S., Chisholm, K., Day, C., Griffiths, S.L., Iqbal, M., Pelton, M., Mallikarjun, P., Stainton, A., Lin, A., Salokangas, R.K.R., Denissoff, A., Ellila, A., From, T., Heinimaa, M., Ilonen, T., Jalo, P., Laurikainen, H., Lehtinen, M., Luutonen, A., Makela, A., Paju, J., Pesonen, H., Armio (Saila), R.L., Sormunen, E., Toivonen, A., Turtonen, O., Solana, A.B., Abraham, M., Hehn, N., Schirmer, T., Altamura, C., Belleri, M., Bottinelli, F., Ferro, A., Re, M., Monzani, E., Percudani, M., Sberna, M., D'Agostino, A., del Fabro, L., Perna, G., Nobile, M., Alciati, A., Balestrieri, M., Bonivento, C., Cabras, G., Fabbro, F., Garzitto, M., Piccin, S., Bertolino, A., Blasi, G., Antonucci, L.A., Pergola, G., Caforio, G., Faio, L., Quarto, T., Gelao, B., Romano, R., Andriola, I., Falsetti, A., Barone, M., Passatiore, R., Sangiuliano, M., Lencer, R., Surman, M., Bienek, O., Romer, G., Dannlowski, U., Meisenzahl, E., Schultze-Lutter, F., Schmidt-Kraepelin, C., Neufang, S., Korda, A., Rohner, H., 2021. Association between age of cannabis initiation and gray matter covariance networks in recent onset psychosis. Neuropsychopharmacology 46, 1484–1493. https://doi.org/10.1038/s41386-021-00977-9.

Peters, K.Z., Oleson, E.B., Cheer, J.F., 2021. A brain on cannabinoids: the role of dopamine release in reward seeking and addiction. Cold Spring Harb. Perspect. Med. 11, 1–18. https://doi.org/10.1101/cshperspect.a039305.

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A.R., Bender, D., Maller, J., Sklar, P., de Bakker, P.I.W., Daly, M.J., Sham, P.C., 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am. J. Hum. Genet. 81, 559–575. https://doi.org/10.1086/519795.

Radhakrishnan, R., Pries, L.-K., Erzin, G., ten Have, M., de Graaf, R., van Dorsselaer, S., Gunther, N., Bak, M., Rutten, B.P.F., van Os, J., Guloksuz, S., 2022. Bidirectional relationships between cannabis use, anxiety and depressive symptoms in the mediation of the association with psychotic experience: further support for an affective pathway to psychosis. Psychol. Med. 1–7. https://doi.org/10.1017/s0033291722002756.

R Core Team, 2017. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. URL. https://www.r-project.org/.

Sabe, M., Zhao, N., Kaiser, S., 2020. Cannabis, nicotine and the negative symptoms of schizophrenia: systematic review and meta-analysis of observational studies. Neurosci. Biobehav. Rev. 116, 415–425. https://doi.org/10.1016/j.neubiorev.2020.07.007.

Schneider, M., 2008. Puberty as a highly vulnerable developmental period for the consequences of cannabis exposure. Addict. Biol. https://doi.org/10.1111/j.1369-1600.2008.00110.x.

Schoeler, T., Monk, A., Sami, M.B., Klamerus, E., Foglia, E., Brown, R., Camuri, G., Altamura, A.C., Murray, R., Bhattacharyya, S., 2016. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. Lancet Psychiatry 3, 215–225. https://doi.org/10.1016/S2215-0366(15)00363-6.

Sugranyes, G., Flamarique, I., Parellada, E., Baeza, I., Goti, J., Fernandez-Egea, E., Bernardo, M., 2009. Cannabis use and age of diagnosis of schizophrenia. Eur. Psychiatry 24, 282–286. https://doi.org/10.1016/j.eurpsy.2009.01.002.

Wisdom, J.P., Manuel, J.I., Drake, R.E., 2011. Substance use disorder among people with first-episode psychosis: a systematic review of course and treatment. Psychiatr. Serv. 62, 1007–1012. https://doi.org/10.1176/ps.62.9.pss6209_1007.