Genetic substrates of cannabis-associated psychosis
Sustratos genéticos de la psicosis asociada al cannabis

Diego Quattrone

Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, SE5 8AF, UK

ORCID: https://orcid.org/0000-0002-6051-8309

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Abstract

This paper will summarise the main substrates of cannabis-associated psychoses. First, an epistemological framework will be introduced to support the existence of a specific 'cannabis-associated psychosis' as a nosological entity distinct from idiopathic schizophrenia and other psychotic disorders. Then, the main clinical characteristics of cannabis-associated psychoses will be examined. Finally, the biological and genetic correlates of cannabis-associated psychosis will be presented.

Keywords

Cannabis; psychotic disorders; psychosis; schizophrenia.

Resumen

Este artículo resumirá los principales sustratos de las psicosis asociadas al cannabis. En primer lugar, se introducirá un marco epistemológico para apoyar la existencia de una "psicosis asociada al cannabis" específica como entidad nosológica distinta de la esquizofrenia idiopática y otros trastornos psicóticos. A continuación, se examinarán las principales características clínicas de las psicosis asociadas al cannabis. Por último, se presentarán los correlatos biológicos y genéticos de las psicosis asociadas al cannabis.

Palabras clave

Cannabis; trastornos psicóticos; psicosis; esquizofrenia.

Correspondence:
Diego Quattrone
Email: diego.quattrone@kcl.ac.uk

IS THERE A SPECIFIC CANNABIS-ASSOCIATED PSYCHOSIS? AN EPISTEMOLOGICAL PERSPECTIVE

The current nosological classification of psychotic disorders (American Psychiatric Association, 2013) does not consider the risk factors for psychosis. It relies instead upon the descriptive psychopathology derived from Kraepelin's paradigm (Kraepelin, 1921). Indeed, the Kraepelinian distinction between dementia praecox and manic-depressive insanity is still alive in the current diagnostic categories of non-affective (i.e., schizophrenia, schizoaffective disorders) and affective (i.e., bipolar and major depressive disorders with psychotic features) psychotic disorders. However, the homogeneous and static Kraepelin's conceptualisation of these two disorders as discrete natural disease entities has repeatedly been challenged (Craddock and Owen, 2005, Demjaha *et al.*, 2012). Epidemiological, experimental, and genetic studies have clarified that different pathways may lead to psychosis (Murray and Quattrone, 2022). Such multifactorial nature of psychotic disorders explains the heterogeneity of clinical presentations and outcomes and profoundly impacts how we think about, and research, the condition (Murray and Quattrone, 2022).

Notably, Kraepelin amended several times his nosology. In the last editions of his textbook (which had nine editions, from 1899 to 1927), he developed a higher consideration for Bonhoeffer's concept of 'acute exogenous reaction type', accepting the possibility that psychopathology may be nosological unspecific, as there were patients not strictly categorizable as suffering dementia praecox or manic insanity. Bonhoeffer's concept of exogenous psychoses implies that different physical conditions would lead to similar psychosis syndromes. Therefore some cases of psychosis would not occur without exposure to a specific aetiological factor (Bonhoeffer, 1917). Such an epistemological framework is a good platform for research into psychosis associated with putative risk factors, such as cannabis-associated psychosis. Indeed, the exocannabinoid hypothesis of psychosis is based on the evidence that exposure to the main psychoactive constituent of herbal cannabis, D9-tetrahydrocannabinol (THC), and synthetic endocannabinoids, leads to psychosis symptoms, that may last for a few hours in cases of intoxication; days or weeks in the acute states; and being enduring if the disorder occurs. The exocannabinoid hypothesis can be now embedded in the endocannabinoid hypothesis of psychosis, based on convergent evidence that the endocannabinoid system (ECS) is altered in individuals suffering a psychotic disorder. It is essential, therefore, to examine the clinical, biological, and genetic substrates of cannabis-associated psychosis in the context of the endocannabinoid and exocannabinoid hypotheses.

EPIDEMIOLOGICAL PLAUSIBILITY OF CANNABIS-ASSOCIATED PSYCHOSIS

In epidemiology, 'causality' can be proven when the exposure to a factor is a necessary, sufficient, or contributory cause to develop a particular condition (Rothman and Greenland, 2005). Epidemiological studies have established the causal relationship between exposure to cannabis and psychotic

disorders based on Hill's criteria for causality (D'Souza *et al.*, 2022). Assuming, therefore, causality, one would expect higher rates of psychosis in sites with higher exposure to cannabis, as it was ascertained in Europe (Di Forti *et al.*, 2019a), and an increase of the population-attributable risk fraction for cannabis use disorder in schizophrenia, as it was recently reported in Denmark (Hjorthoj *et al.*, 2021a). This evidence has a profound implication for prevention; for example, it was calculated that about 30% of the new cases of psychosis in London would not occur if high-potency cannabis were no longer available (Di Forti *et al.*, 2019a). Using the current classification system, we can undoubtedly conclude that cannabis use is a contributory cause of psychotic disorders, which is consistent with what is currently known about complex multifactorial diseases, e.g. genes and socio-environmental factors are neither sufficient nor necessary causes of the condition. Still, they interact with each other to confer risk.

PSYCHOPATHOLOGY OF CANNABIS-ASSOCIATED PSYCHOSIS AND ITS GENETIC CORRELATES

Case series. The existence of psychotic symptomatology associated with cannabis use was neglected for decades in psychiatry, even though this association was historically reported in several case series. For simplicity, only three reports are presented (Bromberg, 1934, Talbott and Teague, 1969, Chopra and Smith, 1974), although the study design limitations weaken the evident value of any case series.

In the cases reported by Bromberg (1934) in the United States, five different psychopathology presentations could be identified, i.e. (i) an acute psychotic intoxication, (ii) an acute intoxication with manic-like features, (iii) toxic psychoses with delusional and hallucinatory experiences, (iv) toxic admixture of cannabis to other psychoses and (v) dementia, described as 'an end-state of years of cannabis usage with ethical intellectual and volitional deterioration'. The most common psychotic presentation in the case series was paranoia and persecutory delusions, with one out of three patients presenting with auditory and/or visual hallucinations. These cases were described as the ones belonging to the 'toxic psychoses' group, having symptoms that 'are long-lasting and may go on to an atypical manic or depressive or schizophrenic psychosis' (Walter Bromberg, 1934). Talbott and Teague (1969) observed, in Vietnam, acute psychosis following cannabis use in soldiers, with delusions and hallucinations being a part of the presentation in 10 out of the 12 cases. Interestingly, Vietnamese cannabis was twice as potent as American cannabis at that time, which may have contributed to developing a more severe symptom profile (Talbott and Teague, 1969). Chopra and Smith (1974) described a series of confusional states in India that developed into full-blown toxic psychosis. Consistently with Talbott and Teague, they reported the worst symptomatology, which included visual hallucinations, in the subgroup of people using ganja or charas, the most potent varieties of cannabis available at the time in India (Chopra and Smith, 1974).

The relationship between the potency of cannabis and the severity of symptom presentation is suggested by case reports of psychosis associated with synthetic cannabinoids, sometimes termed spice or K2 (Papanti *et al.*, 2013). Their consumption has more substan-

tial effects than the Δ9-THC derived from the plant cannabis. There are reports of very severe perceptual disturbances in people using spice (Besli *et al.*, 2015, Hurst *et al.*, 2011, Lerner A *et al.*, 2014).

Controlled studies. The association between the use of cannabis and a more severe positive symptomatology has been reported in controlled studies of patients with psychosis using and not using cannabis. However, case-cohort studies have reported mixed findings as to whether (Addington and Addington, 2007, Bersani *et al.*, 2002, Foti *et al.*, 2010, Grech *et al.*, 2005, Negrete *et al.*, 1986b, Peralta and Cuesta, 1992, Ringen *et al.*, 2016, Seddon *et al.*, 2016) or not (Barrowclough *et al.*, 2015, Boydell *et al.*, 2007, Dubertret *et al.*, 2006, Stirling *et al.*, 2005, Thornicroft *et al.*, 1992b, Tosato *et al.*, 2013, van Dijk *et al.*, 2012) people with psychosis using cannabis express more positive symptoms than people with psychosis not using cannabis (summarised in table 1). Notably, the relationship between cannabis use and more severe positive symptomatology is evident when considering first-episode psychosis studies, which sets a standard time point of assessment and reduces the confounding effect of long-term treatments on symptoms. Moreover, there is evidence of a dose-response effect, i.e. the higher the frequency of use and/or the potency of cannabis, the more severe positive symptomatology, which supports the existence of a specific cannabis-associated psychosis.

Experimental studies on THC administration demonstrated the direct relationship between THC administration and positive symptoms. Recently, Suhas Ganesh (2020) ran a meta-analysis including 400 intravenous THC administrations from 10 double-blind, randomised, placebo-controlled, studies of healthy individuals. They showed a substantial increase in positive symptoms measured by the positive and negative syndrome scale and a dose-response relationship.

Patients with cannabis-associated psychosis also have higher premorbid cognition and social functioning, as well as better neurocognition, than their non-user counterparts (Ferraro *et al.*, 2019). They also present with neurological soft signs (Ruiz-Veguilla *et al.*, 2012) and fewer negative symptoms (Ferraro *et al.*, 2021, Quattrone *et al.*, 2021a). A plausible explanation is that idiopathic schizophrenia would have a more neurodevelopmental impairment and, therefore, more negative symptoms and poor premorbid functioning. On the other hand, those who develop psychosis following cannabis have better premorbid cognitive and social functioning, which makes them more likely to be part of peers exposed to recreational cannabis use.

The existence of specific cannabis psychopathology may be of great importance for understanding the biology of cannabis-associated psychosis. Based on the notion that cannabis use is associated with more severe positive symptoms of first-episode psychosis, three studies examined the association between genetic liability to schizophrenia, cannabis use, and the severity of positive symptoms. Quattrone *et al.* (2021) examined a sample of first-episode psychosis patients and healthy volunteers from the EU-GEI study. They found that the frequency of cannabis use and genetic liability for schizophrenia were independently associated with more positive psychotic experiences in healthy volunteers, as well as more positive psychotic symptoms in patients (Quattrone *et al.*, 2021b). Con-

sistently with these findings, Elkrieff *et al.* (2021) reported in the European IMAGEN cohort that cannabis use and genetic liability for schizophrenia were associated with more frequent psychotic experiences, and there was no evidence of mediation or moderation between these two predictors (Elkrief *et al.*, 2021). Similarly, Wainberg *et al.* (2021) examined a large sample from the UK Biobank and found that cannabis users with high schizophrenia genetic liability were more likely to report psychotic experiences, as well as hallucinations, and delusions of reference (Wainberg *et al.*, 2021). Altogether, these studies support the hypothesis that presenting psychosis following the use of cannabis is independent from individuals' genetic predisposition for schizophrenia, as well as from being a healthy individual or a patient suffering from a psychotic disorder. They also are against the often-proposed theory that those who develop cannabis-associated psychosis are genetically vulnerable to schizophrenia.

GENETIC SUBSTRATES OF CANNABIS-ASSOCIATED PSYCHOSIS

Δ9-THC elicits its acute psychoactive effects as a partial agonist of the endocannabinoid type 1 receptor (CB1R) (Pertwee, 2008). CB1R is located presynaptically on GABAergic and glutamatergic neurons and is part of the retrograde endocannabinoid system, a lipid signalling neuromodulatory pathway (Fakhoury, 2017). Indeed, the endocannabinoid system serves as a retrograde feedback signalling, through which the postsynaptic cell can control the activity of the presynaptic neuron by inhibiting its neurotransmitter release. THC has been associated with the rewarding aspects of cannabis and the induction of psychotic symptoms and cognitive impairment in experimental studies (Englund *et al.*, 2013). Its effects can be ameliorated by CBD, which may act as an antagonist for CB1R even though it lacks affinity for this receptor (Thomas *et al.*, 2007, Thomas *et al.*, 2004). Synthetic cannabinoid receptor agonists mimic the action of THC, but they are full agonists of CB1R, for which they have high affinity.

Some suggest that THC effects are mediated by the dopaminergic system (Bloomfield *et al.*, 2016, Murray *et al.*, 2014). Disruption in the dopaminergic system is thought to be the final mechanism underpinning psychotic disorders, especially positive symptoms (Di Forti *et al.*, 2007, Howes and Murray, 2014). Indeed, the endocannabinoid system modulates dopaminergic neurons through retrograde signalling. Animal research suggests that endogenous cannabinoids, anandamide and 2-AG stimulate dopamine release in the nucleus accumbens after binding CB1R (Oleson and Cheer, 2012), and exogenous cannabinoids, such as THC, enhance dopaminergic cell firing as well as dopamine synthesis and release in different brain regions (Bloomfield *et al.*, 2016). However, the interaction between endocannabinoids and the dopamine system is complex and requires more research. Studies of the effects of THC on striatal dopamine in humans have been inconsistent.

Overall, twin studies that have examined the risk of cannabis-associated psychosis concluded that family and genetic factors have some contributory role in the association between cannabis use and psychosis but cannot fully explain it (Agrawal and Lynskey 2014).

Studies on candidate genes involved in

the dopamine system have raised the question of gene x cannabis exposure interaction in psychotic outcomes in both people with psychosis and population controls (Murray *et al.*, 2016). Specifically, the best studied single nucleotide polymorphisms in interaction with cannabis are rs4680 in COMT, rs2494732 in AKT1, and rs1076560 in DRD2.

First, the COMT polymorphism Val-158Met was tested for interaction with the use of cannabis during adolescence. The authors reported an increased risk of hallucinatory experiences in adulthood among Val/Val individuals (OR = 5.3, 95% CI: 2.2–12.7) and, to a lesser extent, among Val/Met individuals (OR = 2.6, 95% CI: 1.4–4.9), but not among Met/Met individuals (OR = 1.2, 95% CI: .50–3.0) (Caspi *et al.*, 2005). This is the only interaction studied enough to allow a small meta-analysis, which showed that the initial findings were not consistently replicated (Vaessen *et al.*, 2018). Three studies that used continuous outcomes found no interaction between this COMT polymorphism and cannabis use on the severity of positive symptoms Field (52), consistent with an experimental study reporting no effect on THC-induced psychotic symptoms (Tunbridge *et al.*, 2015).

Second, two studies suggested that the AKT1 polymorphism increases the risk of psychotic illness among cannabis users (Di Forti *et al.*, 2012, van Winkel *et al.*, 2011). In addition, van Winkel (2011) showed that this interaction was associated with scoring higher in the positive schizotypy (van Winkel *et al.*, 2011). Consistently with these findings, another study has shown that this polymorphism is associated with a more severe psychotogenic response to cannabis (Morgan *et al.*, 2016).

Third, it has been reported that the DRD2 polymorphism increases psychosis risk in people using cannabis more than in those not using cannabis (Colizzi *et al.*, 2015b). It has been reported that cannabis users carrying the risk variants in both DRD2 and AKT1 genes are at an even higher risk of developing psychosis (Colizzi *et al.*, 2015a).

Of note, Bioque et al. (2019) reported that FAAH polymorphism, part of the endocannabinoid system, was associated with a higher risk of developing a first episode of psychosis in cannabis users (Bioque *et al.*, 2019).

The above reports concerning candidate genes should be cautiously treated pending further replication. Most candidate gene associations and interactions in psychiatry were not consistently replicated (Keller, 2014), and a meta-analysis highlighted their lack of statistical power (Farrell et al., 2015).

In a recent review, Carvalho et al. (2022) highlighted that most candidate gene work has been mainly directed toward dopaminergic pathways. It is essential to expand the range of genetic research (Carvalho and Vieira-Coelho, 2022).

Indeed, current research has focused on genome-wide association studies (GWAS). The last GWAS for schizophrenia has reported SNP-based heritability up to 0.24 in individuals of European ancestry, and post-GWAS fine-mapping analysis suggested enrichment for association in voltage-gated calcium channels and synaptic transmission (Trubetskoy *et al.*, 2022). This finding is of theoretical relevance given the known impact of exocannabinoids and endocannabinoids on the neurophysiology of calcium channels for the retrograde signalling through the activity of CB1R. Interestingly,

the last GWAS for bipolar disorder further showed an enriched gene set in the endocannabinoid pathway (Stahl *et al.*, 2019).

The last GWAS for cannabis use disorder has confirmed evidence for the association of three genes, i.e. *CHRNA2, EPHX2*, and *FOXP2*. *CHRNA2* was already known for being associated with tobacco smoking and schizophrenia thus its GWAS signals may be in part driven by tobacco initiation, or they may reflect a pleiotropic effect (see below). *EPHX2* participates in endocannabinoid metabolism, whereas *FOXP2* is involved in synaptic plasticity. Of note, conditioning summary statistics for the most strongly associated genes from schizophrenia did not change these results, supporting a specific role of these genes for cannabis use disorder (Johnson *et al.*, 2020). This analysis also showed a small genetic correlation between schizophrenia and cannabis use disorder ($R_g = 0.31$, $p = 2.3^{-16}$) (Johnson *et al.*, 2020).

A common method for expanding the application of GWAS is to estimate a Polygenic Risk Score (PRS), summing individuals' risk genes weighted by the GWAS summary statistics.

Using this approach, three studies found that schizophrenia PRS is associated with the frequency of use of cannabis or cannabis use disorder, however, the effect size was very small (Demontis *et al.*, 2019, Jones *et al.*, 2020, Power *et al.*, 2014); two further studies did not replicate this association (Di Forti *et al.*, 2019b, Hjorthoj *et al.*, 2021b).

Interestingly, Jones et al. (2022) reported that schizophrenia PRS predicts a pattern of cannabis use, such as late-onset adolescent cannabis use (Jones *et al.*, 2020). Guloksuz et al. (2019), in a sample of individuals with schizophrenia spectrum diagnoses and unrelated controls, found evidence of additive interaction between schizophrenia polygenic risk score and cannabis use in conferring the risk of developing the disorder (Guloksuz *et al.*, 2019).

As mentioned in the introduction, current research into the exocannabinoid hypothesis of psychosis should be ideally embedded in the endocannabinoid hypothesis of psychosis, also in consideration of recent GWAS findings showing a signal from genes that are directly or indirectly involved in the endocannabinoid system. To date, no research into psychosis has been published considering the genetics of the endocannabinoid system as a whole. Quattrone *et al.* (in submission) developed a schizophrenia polygenic risk score based on the endocannabinoid signalling and examined whether the risk of developing a psychotic disorder was driven by the genetic variation of the endocannabinoid system. In the large EU-GEI study, they found that the higher the endocannabinoid schizophrenia polygenic risk score, the higher the likelihood of developing a first-episode of psychosis. Moreover, they found evidence of an additive interaction between the endocannabinoid schizophrenia polygenic risk score and cannabis use in conferring higher risk the condition.

Some argue about the direction of the association, which cannot be ascertained with the above-mentioned PRS studies. Mendelian randomisation (MR) studies may shed some clarity on the direction of causality. However, the results are mixed to date. Two MR studies suggested a reverse causality, i.e. schizophrenia risk genes leading to cannabis use (Gage *et al.*, 2017, Pasman *et al.*, 2018); however, essential limitations include the use of lifetime cannabis use as the main variable, which is not a proxy of the true exposure to

cannabis. Another MR study found instead a causal role for cannabis use genes leading to schizophrenia (Vaucher *et al.*, 2018). Finally, a fourth recent study did not find a causal effect in any of the two directions (Jang *et al.*, 2022). All these studies have a common limitation, which relates to the fact that, currently, schizophrenia genetics is much more informative than cannabis use genetics. Moreover, a possible alternative explanation of the causal relationship is that the phenomenon of pleiotropy (i.e., the same genetic loci affecting more than one trait), in the case of this relationship, can be horizontal (i.e., the same genetic loci directly leading to both cannabis use and schizophrenia) rather than vertical (i.e., the same genetic loci leading to cannabis use indirectly leading to schizophrenia through a causal relationship between using cannabis and later developing schizophrenia). Johnson *et al. (*2021) used genomic structural equation modelling to explore this hypothesis, finding more evidence in support of genetic loci for cannabis use disorder being associated with schizophrenia (horizontal pleiotropy) than for a causal relationship between cannabis use disorder (vertical pleiotropy) (Johnson *et al.*, 2021).

CONCLUSION

The above-reviewed evidence supports the old Bonhoeffer's conceptualisation of exogenous psychosis and the existence of cannabis-associated psychosis as a peculiar and discrete nosological entity. This concept is relevant for the purposes of conducting effective focussed research and personalising primary and secondary prevention strategies in psychosis. Indeed, from an epistemological perspective, no studies could conclude that cannabis is a necessary or sufficient cause of psychosis simply because 'cannabis-associated psychosis' does not exist as a discrete diagnostic entity. In a hypothetical scenario where an exogenous cannabis-associated psychosis would exist as a discrete diagnostic entity, cannabis use would be the necessary cause of that disorder. Using the current nosology, cannabis use is an established contributory factor to psychotic disorders. Such causality has been clearly proven by epidemiological studies, however, the jury is still out for proving causality by genetic studies. MR studies could not establish a causal relationship (nor its direction) between cannabis use and schizophrenia, however, importantly, there is no convincing evidence as to date for reverse causality, nor that the genetic vulnerability to schizophrenia may lead to cannabis use. Currently, the evidence for horizontal pleiotropy in this relationship seems more robust than for vertical pleiotropy, suggesting that the same genetic loci may directly contribute to cannabis use and schizophrenia. GWAS have started to provide helpful information on risk genes and pathways. However, post-GWAS research is needed in the future to examine dysfunctional mechanisms. Although not confirming any causal hypotheses, PRS studies have been so far extremely important, showing that genetic vulnerability for schizophrenia and the use of cannabis are independent risk factors for developing psychosis outcomes, either in the form of psychotic experiences or a frank psychotic disorder. Such an essential finding elegantly challenges the position that only individuals susceptible to schizophrenia should avoid using cannabis. There is instead evidence that the more frequent cannabis use, the higher the likelihood of developing subclinical psychosis in the general population, as well frank psychotic disorders, independently from individuals' genetic vulnerability to schizophrenia.

Table I

Study	Country	No. Participants; study design; diagnosis	Positive symptoms measures	Cannabis use measures	Outcome; Test statistics; comments
(Negrete et al., 1986a)	Canada	N=137; cross sectional study; schizophrenia	'Degree of delusional activity'; and 'Degree of hallucinatory activity' ('0' absent; '1' transient; '2' continuous)	Groups of cannabis users ('active users'; 'past-users'; 'never-users')	Delusions; Hallucinations; Linear models - least squares mean; Delusions: Active users M=1.51; Past-users M=1.15; Never-user M=0.75; p=0.037 Hallucinations: Active users M=0.99; Past-users M=0.68; Never-user M=0.24; p=0.027
(Thornicroft et al., 1992a)	UK	N=90; retrospective cohort study, non-organic psychotic disorders	Syndrome checklist, including delusions and auditory hallucinations (yes; no)	Current use of cannabis validated by positive urine analysis	Delusions; Hallucinations; Thought disorder items; Chi-square; No differences with the exception of more incoherent speech (p=0.02) in cannabis users.
(Peralta and Cuesta, 1992)	Spain	N=95; cross-sectional study; schizophrenia	SAPS	1) Abuse of cannabis during the past year; 2) intensity of cannabis abuse	SAPS items; Student's t; Person's r; No differences between cannabis abusers and no abusers. There was a positive correlation between intensity of cannabis abuse and either the delusions (r=0.47; p=0.05) and the total SAPS score (r= 0.51p=0.01).
(Bersani et al., 2002)	Italy	N=125; cross-sectional study; chronic schizophrenia	SAPS, PANSS	Frequency of cannabis use (no use; occasional use; abuse)	SAPS items; Student's t and Pearson's r; No differences with exception of more severe thought disorder (t=2.9; p=0.023) in cannabis users. There were more severe hallucinations if people had started using cannabis use before schizophrenia onset (Hallucinations, p< 0.001)
(Grech et al., 2005)	UK	N=119; longitudinal study; first episode psychosis	WHO Life Chart Instrument (Illness course and changes in positive symptoms)	Groups of cannabis use (use/no use prior to index admission and/or at follow-up)	Positive symptoms; Logistic regression; People using cannabis prior to admission and continuing at follow up had the worst positive symptomatology [OR=3.67 (95% CI: 1.12 to 12.07); p=0.003]
(Stirling et al., 2005)	UK	N=69; longitudinal study; first episode psychosis	SAPS	Premorbid cannabis use ('yes', 'no')	Positive symptoms; No differences between groups were reported
(Dubertret et al., 2006)	France	N=205; cross-sectional study; schizophrenia	Lifetime hallucination and delusion syndromes	Cannabis misuse ('yes', 'no')	Lifetime positive symptoms; Multiple logistic regression; Running commentary voices (p=0.05) and other hallucinations were positively associated with cannabis and other substances misuse
(Boydell et al., 2007)	UK	N=757; retrospective cohort study; first episode schizophrenia	OPCRIT including abusive or accusatory hallucinations	Cannabis use ('yes', 'no')	Delusion and hallucination items. Multiple logistic regression; No differences except for a negative association for delusions [OR 0.65 (95% CI 0.48-0.99); p=0.049]

Study	Country	No. Participants; study design; diagnosis	Positive symptoms measures	Cannabis use measures	Outcome; Test statistics; comments
(Addington and Addington, 2007)	Canada	N=203; longitudinal study; first episode psychosis	PANSS including positive symptom score	Cannabis abuse or dependence (yes, no)	Positive symptoms; Student's t test. [Baseline: t=1.23; p=not significant; 2-year follow up: t=2.52; p<0.05; 3-year follow-up: t=2.64; p<0.05]
(Foti et al., 2010)	USA	N=229; longitudinal study; schizophrenia spectrum disorder	SAPS	Current use at baseline and at 10 years; use in the last six months at the other follow-up points	Positive symptoms; Mixed-effects logistic regression; Positive association with cannabis use over time (OR 1.64 (95% CI 1.12 to 2.43 p<0.0125). People using cannabis had more positive symptoms at four of the five assessment points, with an average β coefficient of 0.19
(van Dijk et al., 2012)	Netherlands	N=145; longitudinal study; schizophrenia	PANSS including positive symptoms	Amount of cannabis per week	Positive symptoms; Linear regression; No association at baseline (p=0.333) and at follow-up (p=0.884)
(Tosato et al., 2013)	Italy	N=555; cross- sectional study; first episode psychosis	PANSS including positive symptoms	Cannabis use (yes, no)	Positive symptoms; Mann–Whitney test not significant
(Barrowclough et al., 2015)	UK	N=110; longitudinal study; early psychosis	PANSS including hallucinations	Frequency of use and potency of cannabis	Positive symtpoms; Linear regression. There were no differences.
(Ringen et al., 2016)	Norway	N=681; cross-sectional study; schizophrenia spectrum disorders	PANSS including positive symptoms	No use, sporadic use, frequent use	Positive symptoms; Linear regression There was a positive relation (Beta=0.17; p=0.001)
(Seddon et al., 2016)	UK	N=1,027; longitudinal study; first episode psychosis	PANSS including positive symptoms	Frequency of use	Positive symptoms; GeneGeneraliseded model There was a positive relation (Beta=2.14; 95% CI 1.41 to 2.88; p<0.0001) No improvement of model fit including the interaction with the follow-up phase
(Quattrone et al., 2021a)	UK	N=901; Cross-sectional study; first episode psychosis	OPCRIT including positive symptom dimensions	Frquency of use and potency of cannabis	Positive symptoms; linear regression; there was a positibe relation (B=0.35; 95% CI 0.14 – 0.56; p = 0.001

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