TECHNICAL COMMENTARY

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Substance use

Introduction

Various lines of evidence suggest an association between substance use and psychosis. Experimental studies and surveys of users provide evidence that cannabis and amphetamine use can produce transient, and usually mild, psychotic experiences or recurrence of psychotic symptoms in individuals with a history of psychosis. Further, neuroimaging studies have found clear similarities between functional networks impaired by cannabis use and those known to be implicated in the pathogenesis of schizophrenia.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. We also included reviews of psychotic symptoms. Due to the high volume of systematic reviews we have now limited inclusion to systematic meta-analyses. Where no systematic meta-analysis exists for a topic, systematic reviews without meta-analysis are included for that topic. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found 15 systematic reviews that met our inclusion criteria[3-17].

Tobacco

- Moderate quality evidence finds a small to medium-sized effect of increased risk of developing schizophrenia in smokers vs. non-smokers. There was also a small

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increased risk of developing schizophrenia after exposure to smoke in utero.

- Moderate quality evidence finds the prevalence of smoking in people with first-episode psychosis is around 60%. Moderate to low quality evidence suggests people with first-episode psychosis smoked tobacco for an average of 5.3 years prior to the first psychotic episode.
- Compared to general population smoking rates, there is a large effect of more smoking in males with schizophrenia, and a medium-sized effect of more smoking in females with schizophrenia. There is also an earlier age of psychosis onset in smokers compared to non-smokers.
- Compared to males with other mental illnesses, there is a medium-sized effect of more smoking in males with schizophrenia, with no significant differences between females.

Cannabis

- High quality evidence shows there is an increased risk of psychotic symptoms in people who use cannabis. Moderate to high quality evidence suggests this is a dose-dependent relationship for psychotic symptoms, or for a diagnosis of any psychotic disorder.
- A small, but non-significant association was found between cannabis use and transition to psychosis in people with subclinical psychotic symptoms, with lifetime rates in this group being around 49%. Further, 34% of people diagnosed with a cannabis-induced psychosis developed schizophrenia at follow-up (mean 4 years).
- Moderate to high quality evidence suggests prevalence of cannabis use in people with first-episode psychosis is around 34-38%. Initiation of cannabis use is around 6-7 years prior to onset of psychosis, and continuation of cannabis use declines after treatment.
- Moderate to low quality evidence indicates a relationship between cannabis use and increased relapse or re-hospitalisation, and less treatment adherence in people with schizophrenia or psychotic symptoms.

Other substances

- Moderate quality evidence suggests a medium-sized increase in prevalence and incidence of subclinical psychotic symptoms in people exposed to alcohol or other drug use. However, decreased alcohol use has also been reported in people with at-risk mental states.
- Moderate quality evidence suggests one-quarter of people with a substance-induced psychosis had a follow-up diagnosis of schizophrenia (mean follow-up 4 years). The rates were highest for cannabis (34%), hallucinogens (26%), and amphetamines (22%), and lowest for opioids (12%), alcohol (10%), and sedatives (9%).

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Curran C, Byrappa N, McBride A

Stimulant psychosis: systematic review

British Journal of Psychiatry 2004; 185: 196-204

View review abstract online

Comparison	**Single or double doses of oral or intravenous amphetamines dexamfetamine or methylphenidate given to people with schizophrenia or controls (when studies included a control group).**
Summary of evidence	**Low quality evidence (few studies with small samples, unable to assess consistency and imprecision, direct) is unable to determine whether a relationship exists between amphetamine use and psychotic symptoms.**

Schizophrenia

51.4% of patients with schizophrenia and positive symptoms (N = 149) reported a temporary increase in positive symptoms.

28.3% of patients with schizophrenia who were in remission (N = 69) reported a temporary increase in positive symptoms.

10.2% of controls (N = 9) reported a temporary increase in positive symptoms.

Risk was significantly higher for patients with schizophrenia with positive symptoms vs. patients without positive symptoms: $X^2 = 46.3$, $p < 0.0001$.

The concurrent use or non-use of antipsychotic medication did not significantly change results, regardless of disease state (remission or not).

Consistency in results‡	Unable to assess, no measure of consistency is reported.
Precision in results§	Unable to assess, no measure of precision is reported.
Directness of results‖	Direct

De Leon J, Diaz FJ

A meta-analysis of worldwide studies demonstrates an association

between schizophrenia and tobacco smoking behaviors **Schizophrenia Research 2005; 76: 135-157** View review abstract online	
Comparison 1	**Prevalence of tobacco smoking in people with schizophrenia vs. the general population.**
Summary of evidence	**Moderate quality evidence (large samples, imprecise, unable to assess consistency, direct) suggests a large effect of higher rates of lifetime tobacco smoking in males with schizophrenia compared with the general population, and a medium-sized effect for females.**
Tobacco smoking	
Males with schizophrenia showed a large effect of increased odds of lifetime smoking compared to the general population, and females showed a medium-sized effect; Overall: 9 studies, N = 2,929, OR = 3.1, 95%CI 2.4 to 3.8, $p < 0.05$ Males: 2 studies, N = 676, OR = 7.3, 95%CI 1.0 to 13.6, $p < 0.05$ Females: 3 studies, N = 231, OR = 2.8, 95%CI 1.2 to 4.4, $p < 0.05$	
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Imprecise, particularly for males.
Directness of results	Direct
Comparison 2	**Prevalence of tobacco smoking in people with schizophrenia vs. people with other mental illnesses.**
Summary of evidence	**Moderate quality evidence (large samples, imprecise, unable to assess consistency, direct) suggests males with schizophrenia showed a medium effect of higher rates of lifetime smoking compared to males with other mental illnesses, with no effect for females.**
Tobacco smoking	
Males with schizophrenia showed a medium effect of higher rates of lifetime smoking compared to males with other mental illness, with no effect for females; Overall: 5 studies, N = 2,325, OR = 2.0, 95%CI 1.6 to 2.4, $p < 0.05$ Males: 4 studies, N = 1,156, OR = 2.0, 95%CI 1.5 to 2.7, $p < 0.05$	

Females: 2 studies, N = 184, OR = 0.9, 95%CI 0.4 to 1.9, $p < 0.05$	
Consistency in results	Unable to assess, no measure of consistency is reported.
Precision in results	Imprecise
Directness of results	Direct

Farris MS, Shakeel MK, Addington J

Cannabis use in individuals at clinical high-risk for psychosis: a comprehensive review

Social Psychiatry and Psychiatric Epidemiology 2019; 55: 527-537

View review abstract online

Comparison	**Relationship between cannabis use and transition to psychosis in people at clinical high risk for psychosis.**
Summary of evidence	**Moderate to high quality evidence (large sample, consistent, some imprecision, direct) finds no significant association between cannabis use in people at clinical high risk for psychosis and transition to psychosis.**
Transition to psychosis	
A small, but non-significant relationship between cannabis use and transition to psychosis; 8 studies, N = 1,682, RR = 1.11, 95%CI 0.89 to 1.37, I^2 = 33% Lifetime cannabis use: 17 studies, prevalence = 48.7%, 95%CI 42.8% to 54.6%, I^2 = 86% Current cannabis use: 23 studies, prevalence = 25.8%, 95%CI 22.2% to 29.6%, I^2 = 76% Cannabis use disorder/abuse/dependence: 16 studies, prevalence = 14.9%, 95%CI 9.8% to 20.9%, I^2 = 93%	
Consistency in results	Consistent for transition to psychosis, inconsistent for prevalence rates.
Precision in results	Some imprecision
Directness of results	Direct

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Fusar-Poli P, Tantardini M, De Simone S, Ramella-Cravaro V, Oliver D, Kingdon J, Kotlicka-Antczak M, Valmaggia L, Lee J, Millan MJ, Galderisi S, Balottin U, Ricca V, McGuire P

Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk

European Psychiatry 2017; 40: 65-75

View review abstract online

Comparison	**Substance use in people with ultra high-risk (UHR) mental states, which are determined as; attenuated psychotic symptoms, brief and limited intermittent psychotic symptoms, and genetic risk and functional deterioration.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) suggests a medium-sized effect of increased prior tobacco use, and a small effect of decreased prior alcohol use, in people with ultra high-risk (UHR) mental states. There were no relationships between UHR and prior cannabis, cocaine, amphetamine, opiates, or hallucinogens use.**
Any substance use	
A significant association between increased tobacco use and the UHR state; 3 studies, N = 1,233, OR = 3.040, 95%CI 1.204 to 7.692, p = 0.019, I^2 = 64%, p = 0.062 *A significant association between decreased alcohol use and the UHR state;* 4 studies, N = 1,382, OR = 0.645, 95%CI 0.463 to 0.900, p = 0.01, I^2 = 30%, p = 0.232 There were no relationships between UHR and cannabis, cocaine, amphetamine, opiates, or hallucinogens use. There was no evidence of publication bias.	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Gurillo P, Jauhar S, Murray RM, MacCabe JH

Does tobacco use cause psychosis? Systematic review and meta-analysis **Lancet Psychiatry 2015; 2: 718-725** View review abstract online	
Comparison 1	**Prevalence of smoking in people with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate quality evidence (large samples, imprecise, inconsistent, direct) suggests the prevalence of tobacco smoking in people with first-episode psychosis is around 57%, and a medium-sized increased odds of tobacco smoking is apparent in patients compared with controls.**
Tobacco smoking	
61 studies, N = 13,145 *Significant, medium-sized increased risk of smoking tobacco in people with first-episode psychosis;* 11 case-control studies, OR = 3.22, 95%CI 1.63 to 6.33, $p = 0.001$, $I^2 = 82.1\%$, Q-test $p < 0.05$ 34 studies, prevalence rate = 0.57, 95%CI 0.52 to 0.62, $p < 0.0001$, $I^2 = 88.0\%$, Q-test $p < 0.05$ Authors report possible publication bias.	
Consistency in results	Inconsistent
Precision in results	Imprecise for odds ratio
Directness of results	Direct
Comparison 2	**Risk of psychotic disorders in smokers vs. non-smokers.**
Summary of evidence	**Moderate quality evidence (large samples, imprecise, inconsistent, direct) suggests a medium-sized increased risk of psychotic disorders in smokers compared with non-smokers.**
Psychotic disorders	
Significant, medium-sized increased risk of psychotic disorders in daily smokers vs. non-smokers; 5 prospective studies, RR = 2.18, 95%CI 1.23 to 3.85, $p = 0.007$, $I^2 = 97.7\%$, Q-test $p < 0.05$ Authors report possible publication bias.	
Consistency in results	Inconsistent

Precision in results	Imprecise
Directness of results	Direct
Comparison 3	**Age of psychosis onset in smokers vs. non-smokers.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests an earlier age of psychosis onset in smokers vs. non-smokers.**
Age of psychosis onset	
Significant, earlier age of psychosis onset in smokers vs. non-smokers; 23 studies, 24.25 years vs. 25.63 years, WMD = -1.04, 95%CI -1.82 to -0.26, p = 0.009, I^2 = 66.3%, Q-test $p < 0.05$ Subgroup analysis showed this difference was only observed in studies from Europe, North America, Australia, Finland, Spain, and Sweden, and not Egypt, Japan, or Turkey. No significant differences were found for age at initiation of smoking cigarettes between people with psychosis and controls. Authors report no evidence of publication bias.	
Consistency in results	Inconsistent
Precision in results	Unable to assess precision (SMD not reported).
Directness of results	Direct

Hunter A, Murray R, Asher L, Leonardi-Bee J

The Effects of Tobacco Smoking, and Prenatal Tobacco Smoke Exposure, on Risk of Schizophrenia: A Systematic Review and Meta-Analysis

Nicotine & Tobacco Research 2020; 22: 3-10

View review abstract online

Comparison	**Smoking tobacco or exposure to smoke prenatally and later risk for schizophrenia.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, some imprecision, direct) finds a small to medium-sized effect of increased risk of developing schizophrenia in smokers vs. non-**

	smokers. There was also a small increased risk of developing schizophrenia after exposure to smoke in utero.
Schizophrenia	
Smoking *A small to medium-sized effect showed smokers had a significantly increased risk of developing schizophrenia;* 5 cohort studies, N = 1,785,279, RR = 1.99, 95%CI 1.10 to 3.61, p = 0.02, I^2 = 97% The follow-up periods ranged from 4 to 40 years. There were no moderating effects of study quality or statistical measure used (ORs vs. HRs). Four of the five studies reported a dose-response effect. Prenatal exposure to smoke *A small effect showed exposure to prenatal smoke increased the risk of developing schizophrenia;* 7 cohort studies, N = 2,455,188, RR = 1.29, 95%CI 1.10 to 1.51, I^2 = 71% The follow-up periods ranged from 11 to 31 years. There were no moderating effects of study quality, diagnostic tool (ICD vs. other), or statistical measure used (ORs vs. HRs). No dose–response effects were observed.	
Consistency in results	Inconsistent
Precision in results	Imprecise for tobacco use, precise for prenatal exposure.
Directness of results	Direct

Linscott RJ, van Os J

An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders

Psychological Medicine 2013; 43: 1133-1149

View review abstract online

Comparison	**Prevalence and incidence of subclinical psychotic symptoms in people exposed to substance use.**

Summary of evidence	**Moderate quality evidence (mostly consistent, imprecise, direct, unclear sample sizes) suggests a medium-sized increase in prevalence rates of subclinical psychotic symptoms in people who misuse alcohol, cannabis or other substances.**
Subclinical psychotic symptoms	
Significant, medium increased prevalence and incidence of subclinical psychotic symptoms in people who misuse alcohol, cannabis or other substances; Alcohol Prevalence: 6 studies, N not reported, OR = 1.99, 95%CI 1.59 to 2.47, $p < 0.05$, $I^2 = 50\%$, Q-test $p > 0.05$ Incidence: 2 studies, N not reported, OR = 2.05, 95%CI 1.12 to 3.73, $p < 0.05$, $I^2 = 41\%$, Q-test $p > 0.05$ Cannabis Prevalence: 8 studies, N not reported, OR = 2.52, 95%CI 1.84 to 3.43, $p < 0.05$, $I^2 = 66\%$, Q-test $p < 0.01$ Incidence: 3 studies, N not reported, OR = 1.77, 95%CI 1.20 to 2.61, $p < 0.05$, $I^2 = 28\%$, Q-test $p > 0.05$ Other substances Prevalence: 7 studies, N not reported, OR = 2.64, 95%CI 1.91 to 3.66, $p < 0.05$, $I^2 = 41\%$, Q-test $p > 0.05$ Incidence: 3 studies, N not reported, OR = 1.95, 95%CI 1.30 to 2.94, $p < 0.05$, $I^2 = 0\%$, Q-test $p > 0.05$	
Consistency in results	Inconsistent for cannabis prevalence rates only.
Precision in results	Imprecise
Directness of results	Direct

Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E

Meta-analysis of the association between the level of cannabis use and risk of psychosis

Schizophrenia Bulletin 2016; 42(5): 1262-9

View review abstract online

Comparison	**Relationship between level of cannabis use (scaled from non-user = 0 to heavy user = 1) and risk of schizophrenia or psychosis.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) indicates a dose-dependent relationship between increased cannabis use and increased risk of psychotic symptoms, psychotic disorder or schizophrenia.**
Schizophrenia or other psychotic disorders	
A medium-sized effect of increased risk or schizophrenia or psychosis with higher levels of cannabis use; 10 studies, N = 66,816, OR = 3.90, 95%CI 2.84 to 5.34, $p < 0.05$, $I^2 = 82\%$ *The relationship was dose-dependent;* Logistic regression coefficient = 1.36, 95%CI 1.04 to 1.68, $p < 0.05$ *Similarly, the relationship was higher with heaviest use than for any use;* Top 20% - heaviest use: OR = 3.40, 95%CI 2.55 to 4.54, $p < 0.05$ Any cannabis use: OR = 1.97, 95%CI 1.68 to 2.31, $p < 0.05$ *The relationship was higher for diagnosis of schizophrenia or psychotic disorder than for psychotic symptoms;* Schizophrenia or psychotic disorder: OR = 5.07, 95%CI 3.62 to 7.09, $p < 0.05$ Psychotic symptoms: OR = 3.59, 95%CI 2.42 to 5.32, $p < 0.05$ Subgroup analyses showed no differences in effect sizes according to study design (cross-sectional vs. cohort), outcome measure, and year of publication. There was no evidence of publication bias.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

McLaren JA, Silins E, Hutchinson D, Mattick RP, Hall W

Assessing evidence for a causal link between cannabis and psychosis: A review of cohort studies

International Journal of Drug Policy 2010; 21: 10-19 View review abstract online	
Comparison	**Cohort studies assessing the relationship between cannabis use and schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, unable to assess precision, direct) indicates an increased risk of psychotic symptoms and schizophrenia in people who used cannabis prior to onset of symptoms.**
Psychotic symptoms	
Significant, increased risk of psychotic symptoms in people who have used cannabis compared to people who have never used cannabis; 5 studies, N = 11,686, effect sizes ranged from 1.6 to 16.9 1 study reported no significant effect.	
Schizophrenia	
Significant, increased risk of a schizophrenia (measured as either hospital admission for schizophrenia, initiation of treatment, or a diagnosis by age 26) in people who have used cannabis compared to people who have never used cannabis; 5 studies, N = 54,960, effect sizes ranged from 3.1 to 10.9 2 studies reported no significant effect. 1 follow up study reported significant effect only in participants with genetic vulnerability.	
Consistency in results	Authors report results are consistent.
Precision in results	Unable to assess; no confidence intervals are reported.
Directness of results	Direct

Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G

Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review

Lancet 2007; 370(9584): 319-328

View review abstract online	
Comparison 1	**Psychotic symptoms in people who have previously used cannabis compared to people who have never used cannabis.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) shows a relationship between cannabis use and an increased risk for psychotic symptoms. Moderate to high quality evidence (imprecise) suggests the relationship is dose-dependent.**
Psychotic symptoms	
Significant, increased risk of psychotic symptoms in people who have ever used cannabis compared to people who have never used cannabis; 7 studies, N = 61,485, OR = 1.41, 95%CI 1.20 to 1.65, $p < 0.05$, $I^2 = 19.2\%$, Q-test $p = 0.28$ Authors state that this effect persisted, though attenuated on average by 45%, after adjustment for approximately 60 different confounding factors, including other substance use, personality traits, socio-demographic markers, intellectual ability, and other mental health problems. *This risk was highest in people who used cannabis most frequently;* 6 studies, N = 60,726, OR = 2.09, 95%CI 1.54 to 2.85, $p < 0.05$, $I^2 = 44\%$, Q-test $p = 0.11$ *Subgroup analysis to investigate moderate heterogeneity (one study removed);* 5 studies, N = 56,681, OR = 1.92, 95%CI 1.50 to 2.47, $p < 0.05$, $I^2 = 25\%$, Q-test $p = 0.26$	
Consistency in results	Consistent
Precision in results	Precise for full sample, imprecise for dose-dependence analysis.
Directness of results	Direct
Comparison 2	**Diagnosis of schizophrenia, schizophreniform or psychotic disorder in people who have previously used cannabis compared to people who have never used cannabis.**
Summary of evidence	**Moderate to high quality evidence (imprecise) indicates a relationship between cannabis use and increased risk of a diagnosis of schizophrenia, schizophreniform or psychotic disorders.**
Schizophrenia	

Significant, increased risk of schizophrenia, schizophreniform or psychotic disorder diagnosis in people who have ever used cannabis compared with people who have never used cannabis; 3 studies, N = 53,285, OR = 2.58, 95%CI 1.08 to 6.13, $p < 0.05$, $I^2 = 66.9\%$, Q-test $p = 0.049$ *Subgroup analysis to investigate significant heterogeneity (one study removed);* N = 49,240, OR = 1.82, 95%CI 1.01 to 3.30, $p < 0.05$, $I^2 = 48.3\%$, Q-test $p = 0.16$

Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct

Murrie B, Lappin J, Large M, Sara G

Transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-analysis

Schizophrenia Bulletin 2019; 46(5): 505-516

View review abstract online

Comparison	**Transition rate to schizophrenia in people with a substance-induced psychosis.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests one-quarter of people with substance-induced psychosis had a follow-up diagnosis of schizophrenia (mean follow-up 4 years). The rates were highest for cannabis, hallucinogens, and amphetamines, and lowest for opioids, alcohol, and sedatives.**

Transition to schizophrenia

One-quarter of people with substance-induced psychosis had a follow-up diagnosis of schizophrenia;

25 cohort studies, N = 34,244, transition rate = 25%, 95%CI 18% to 35%, $I^2 = 99\%$

Mean follow-up period was 4 years

The highest rates were associated with cannabis (34%), hallucinogens (26%) and amphetamines

(22%). Lower rates were associated with opioids (12%), alcohol (10%), and sedatives (9%).	
Consistency in results	Inconsistent
Precision in results	Appears imprecise
Directness of results	Direct

Myles N, Newell HD, Curtis J, Nielssen O, Shiers D, Large M

Tobacco Use Before, At and After First-Episode Psychosis: A Systematic Meta-Analysis

Journal of Clinical Psychiatry 2012; 104: 719-733

View review abstract online

Comparison	**Tobacco smoking in people with first-episode psychosis vs. people without psychosis.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests the prevalence of smoking in people with first-episode psychosis is around 60%, with the odds of smoking being 6 times higher than in people without first-episode psychosis. Smoking initiation is around 5.3 years prior to onset of psychosis.**
Tobacco smoking	
Overall prevalence of smoking was around 60%; 31 samples, N = 4,082, prevalence = 58.9%, 95%CI 54.3% to 63.4%, I^2 = 86.7% *Significant, large effect of increased smoking rates in people with first-episode psychosis;* Odds of tobacco use: 10 samples, N = 1,299, OR = 6.04, 95%CI 3.03 to 12.02, I^2 = 80% *Significant, large effect of more early than late smoking initiation in people with first-episode psychosis (mean 5.3 years prior to onset);* 14 samples, N = 1,618, SMD = -0.85, 95%CI -0.97 to -0.72, I^2 = 47.5% Prevalence rates varied by region (p = 0.014), with the highest smoking prevalence being reported in Australia (72%) with Britain, Europe, USA and Canada reporting similar rates (51-59%). There were no differences in prevalence rates based on different study recruitment methods, measurement of tobacco use, diagnostic criteria, proportion of males, proportion of affective	

subtypes, age, or year of study.	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Myles H, Myles N, Large M

Cannabis use in first episode psychosis: Meta-analysis of prevalence, and the time course of initiation and continued use

Australian and New Zealand Journal of Psychiatry 2015; 1-2: 208-219

View review abstract online

Comparison	**Prevalence, initiation, and continuation of cannabis use in people with first-episode psychosis.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests prevalence of cannabis use in first episode psychosis patients is around 34-38%. Initiation of cannabis use is around 6-7 years prior to onset of psychosis, and continuation of cannabis use declines after treatment.**

Cannabis use

The overall prevalence of cannabis use in people with first-episode psychosis is around 34-38%;

35 studies, N = 6,321, prevalence = 33.7%, 95%CI 29% to 38%, I^2 = 92.1%, Q-test $p < 0.001$

Removing 5 samples that may have biased the results increased the prevalence estimate to 38.0%.

Subgroup analyses found the highest rate of cannabis use was in studies from Australia, followed by Europe, the United Kingdom and North America.

Lower rates of cannabis use were recorded in studies conducted prior to 1995, with peak rates between 1995 and 2000, followed by a steady decline.

There were no differences in study results according to sex or age.

Significant, large effect of more early than late cannabis use initiation in people with first-episode psychosis (mean 6.3 years prior to onset);

10 studies, N = 796, SMD = 1.56, 95%CI 1.40 to 1.72, I^2 = 49.6%, Q-test $p = 0.04$

Removing 3 samples that may have biased the results increased the SMD to 1.65, equating to an

increased initiation interval of 9 months. *Significant, medium to large effect shows continued cannabis use reduces after treatment (2 months to 10 years of follow-up);* 19 studies, N = 3,645, OR = 0.56, 95%CI 0.40 to 0.79, I^2 = 84.2%, Q-test $p < 0.001$ Removing 1 sample that may have biased the result resulted in an OR of 0.65. Studies with a higher proportion of users prior to treatment had a greater reduction of use. There were no differences in study results according to length of follow-up.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Semple DM, McIntosh AM, Lawrie SM

Cannabis as a risk factor for psychosis: systematic review

Journal of Psychopharmacology 2005; 19(2): 187-194

View review abstract online

Comparison	**Schizophrenia or schizophrenia-like psychosis in people who have previously used cannabis compared to people who have never used cannabis.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, imprecise, direct) indicates a relationship between any cannabis use and increased risk of schizophrenia or schizophrenia-like psychosis.**
Schizophrenia spectrum disorders	
Significant, medium-sized increased risk of schizophrenia, or schizophrenia-like psychosis in people who have ever used cannabis compared with people who have never used cannabis; 7 studies, N = 51,688, OR = 2.90, 95%CI 2.30 to 3.60, $p < 0.05$, I^2 = 18.3%, Q-test $p = 0.54$	
Consistency in results	Consistent
Precision in results	Imprecise

Directness of results	Direct

Zammit S, Moore TH, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G

Effects of cannabis use on outcomes of psychotic disorders: systematic review

British Journal of Psychiatry 2008; 193(5): 357-363

View review abstract online

Comparison	**Relationships between cannabis use and relapse rates, hospitalisation, symptom severity and response and adherence to treatment (by various measures) in patients with schizophrenia, schizophreniform, schizoaffective or psychotic disorders, non-affective or affective psychoses, psychosis not otherwise specified (NOS), psychotic symptoms, delusions, hallucinations or thought disorder.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, some inconsistency, unable to precision, direct) indicates a relationship between cannabis use and increased relapse or re-hospitalisation and decreased treatment adherence for patients with schizophrenia or psychotic symptoms.**
Relapse	
7 studies, N = unclear 4/4 studies reported increased relapse rates in patients using cannabis. 3/3 studies reported increased hospitalisation rates in patients using cannabis.	
Symptoms	
7 studies, N = unclear 4/6 studies reported some increase in positive symptoms in patients using cannabis. 1/4 studies reported increased negative symptoms in patients using cannabis. 2/2 studies report no association of cannabis use with anxiety, depression, or aggression scores.	
Adherence to treatment	

Substance use

3 studies, N = unclear 2 studies reported increased non-adherence being associated with cannabis dependence at baseline, although this was eliminated in 1 study after adjusting for confounding. 1 study reported continued cannabis use during follow-up, but not at baseline was weakly associated with reduced adherence.	
Consistency in results	Authors state relapse, re-hospitalisation, and treatment adherence outcomes were mostly consistent.
Precision in results	Unable to assess, no confidence intervals are reported.
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, HR = hazard ratio, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), ICD = international classification of diseases, N = number of participants, OR = odds ratio, *p* = probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic (chi-square) for the test of heterogeneity in results across studies, RR = risk ratio, vs. = versus, X^2 = Chi Square statistic

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[18].

† Different effect measures are reported by different reviews.

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, an RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. An RR or OR of 1.00 means there is no difference between groups. A medium-sized effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[19]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large treatment effect[18].

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed[20].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Curran C, Byrappa N, McBride A (2004): Stimulant psychosis: systematic review. *British Journal of Psychiatry* 185: 196-204.
4. Semple DM, McIntosh AM, Lawrie SM (2005): Cannabis as a risk factor for psychosis: systematic review. *Journal of Psychopharmacology* 19: 187-94.
5. Zammit S, Moore TH, Lingford-Hughes A, Barnes TR, Jones PB, Burke M*, et al.* (2008): Effects of cannabis use on outcomes of psychotic disorders: systematic review. *British Journal of Psychiatry* 193: 357-63.
6. McLaren JA, Silins E, Hutchinson D, Mattick RP, Hall W (2010): Assessing evidence for a causal link between cannabis and psychosis: a review of cohort studies. *International Journal of Drug Policy* 21: 10-9.
7. Linscott RJ, van Os J (2013): An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological Medicine* 43: 1133-49.
8. de Leon J, Diaz FJ (2005): A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophrenia Research* 76: 135-57.
9. Myles N, Newall HD, Curtis J, Nielssen O, Shiers D, Large M (2012): Tobacco use before, at, and after first-episode psychosis: a systematic meta-analysis. *Journal of Clinical Psychiatry* 73: 468-75.
10. Myles H, Myles N, Large M (2015): Cannabis use in first episode psychosis: Meta-analysis of prevalence, and the time course of initiation and continued use. *Australian and New Zealand journal of psychiatry* 50: 208-19.
11. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M*, et al.* (2007): Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 370: 319-28.
12. Gurillo P, Jauhar S, Murray RM, MacCabe JH (2015): Does tobacco use cause psychosis? Systematic review and meta-analysis. *The Lancet Psychiatry* 2: 718-25.
13. Fusar-Poli P, Tantardini M, De Simone S, Ramella-Cravaro V, Oliver D, Kingdon J*, et al.* (2017): Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk. *European Psychiatry* 40: 65-75.
14. Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E (2016): Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin* 42: 1262-9.
15. Farris MS, Shakeel MK, Addington J (2019): Cannabis use in individuals at clinical high-risk for psychosis: a comprehensive review. *Social Psychiatry and Psychiatric Epidemiology* Dec: oi.org/10.1007/s00127-019-1810-x.
16. Hunter A, Murray R, Asher L, Leonardi-Bee J (2020): The Effects of Tobacco Smoking, and Prenatal Tobacco Smoke Exposure, on Risk of Schizophrenia: A Systematic Review and Meta-Analysis. *Nicotine & Tobacco Research* 22: 3-10.
17. Murrie B, Lappin J, Large M, Sara G (2019): Transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-analysis. *Schizophrenia Bulletin* 16.
18. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
19. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.

20. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*