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Substance use in clinical high risk for psychosis: a review of the literature

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Abstract

Aim—In the literature, there is evidence suggesting an association between substance use and psychosis. However, little is known about substance use in those who may be in the pre-psychotic phase, that is, those who are putatively prodromal are considered to be at clinical high risk (CHR) of developing psychosis.

Methods—We conducted a review of publications measuring patterns and rates of substance use in CHR for psychosis individuals and the effects on the transition to psychosis.

Results—Of 5527 potentially relevant research papers, 10 met inclusion criteria of CHR subjects and specifically mentioned substance use in the sample. The results of these studies varied. Cannabis, alcohol and tobacco/nicotine were reported as the most commonly used substances. There was limited information on the changes in patterns of use over time. Two out of the ten studies found a significant association between the use of substances and subsequent transition to psychosis. In one of these studies, substance abuse was a predictor of psychosis when included as a variable in a prediction algorithm. In the other study, the abuse of cannabis and nicotine was associated with transition to psychosis.

Conclusions—We found limited evidence to suggest that increased rates of substance use may be associated with transition to psychosis. However, further prospective research examining the association between substance use and transition to psychosis is required before any firm conclusions can be made.

Keywords

cannabis; clinical high risk; psychosis; review; substance use

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INTRODUCTION

High rates of substance use are commonly reported in patients with schizophrenia, with data from the United States suggesting that patients are 4.6 times more likely to use and abuse substances than the general population.[1] In these studies, substance use typically refers to the use of alcohol, cannabis and other street drugs with some studies, including nicotine. Similar rates are reported for those individuals experiencing their first episode of psychosis,[2-4] ranging from 22% to over 50%.[5-10] These variations in rates may be accounted for by methodological differences such as sample selection, the use of different diagnostic criteria, and cultural and environmental differences between countries, such as the availability of substances.[11,12] Furthermore, it has been demonstrated that substance use and abuse in first-episode psychosis is associated with increased hospitalizations,[13,14] reduced treatment compliance,[15-17] higher relapse rates[18] and increased costs for mental health service providers.[19]

Epidemiological studies have found associations between substance use, generally cannabis, although a recent innovative study examines methamphetamine use,[20] and increased risk of developing psychotic symptoms.[21,22] However, there has been some controversy concerning the causal nature of this relationship.[23] The current interest in prospective research that examines individuals who are at clinical high risk (CHR) of developing psychosis offers a unique opportunity to clarify the relationship by examining substance use prior to the onset of psychosis in a cohort with a greater likelihood of developing psychosis compared with the general population. A recent meta-analysis of CHR studies found that the rates of transition to psychosis increase over time, with an 18% chance after six months, 22% after one year, 29% after two years and 36% after three years.[24] The effect of substance use during this vulnerable stage is still unclear; however, given the evidence to suggest its deleterious effect in early psychosis, it is important to identify any possible role it may play in the earliest stages of the illness.

The purpose of the current review is to increase our understanding of the prevalence of substance use in CHR populations and its putative relationship with transition to psychosis. Our aims were, therefore, to review all CHR studies to date that have reported directly on substance use to determine: (i) the patterns and rates of substance use in CHR individuals and (ii) the potential role of substance use in the transition to psychosis.

METHODS

Search method

Relevant papers on substance use in CHR individuals were identified using the following search engines ‘CINAHL’, ‘EMBASE’, ‘MEDLINE’, ‘PsycINFO’, ‘PubMed’ and ‘Web of Science’ in July 2013. To identify relevant papers, the keywords and subject headings used included ‘clinical high risk’, ‘attenuated positive symptoms’, ‘brief intermittent psychotic symptoms’, ‘genetic risk and deterioration’, ‘basic symptoms’, ‘familial high risk’, ‘substance use’, ‘substance abuse’, ‘substance use disorder’, ‘cannabis’, ‘marijuana’, ‘tobacco’, ‘alcohol’, ‘amphetamine’, ‘hallucinogens’, ‘risk factors’, ‘psychosis’ and

'schizophrenia'. The truncated keyword 'prodrom*' was also used as to include both 'prodrome' and 'prodromal'.

The search included papers published between 1995 and 3 July 2013. Our overall search, after removing duplicates, resulted in 5527 potentially relevant papers. The first step was to read the title and abstract to validate inclusion and, if necessary, the entire article to identify studies that mentioned substance use among CHR populations. This selection was carried out by NC with consultation with JA.

Inclusion and exclusion criteria

Papers were sifted for relevance to the review. Papers were included if they: (i) had been published in English-language peer-reviewed journals; (ii) contained information on prevalence of substance use in CHR populations; and (iii) reported effects of substance use on conversion rates to psychosis in CHR populations. Papers were excluded where CHR criteria were not clearly met and in which there was no reference to substance use. CHR criteria were met by studies that used internationally recognized diagnostic instruments, including the Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms (SIPS/SOPS),[25] Comprehensive Assessment of the At-Risk Mental State (CAARMS),[26] Schizophrenia Proneness Instrument, Adult Version (SPI-A),[27] Schizophrenia Proneness Instrument, Child and Youth Version (SPI-CY)[28] and Basel Screening Instrument for Psychosis (BSIP).[29]

Although the specific CHR criteria derived from these instruments vary, most studies consider subjects to be at CHR for psychosis if they fall into one of the following categories: (i) 'attenuated positive symptoms' (APS), defines individuals who have symptoms that deviate from 'normal' phenomena but which are not frankly psychotic, for example, hearing voices or having increased levels of suspiciousness; (ii) 'brief intermittent psychotic symptoms', defines individuals who have symptoms of 'psychotic intensity' but which is intermittent and spontaneously remitting; (iii) 'genetic risk and deterioration', defines individuals who have 'non-specific' symptoms such as lowered mood or anxiety symptoms plus some trait risk factor for psychotic disorder, such as family history of psychosis in first-degree relative or schizotypal personality disorder; or (iv) 'Basic Symptoms', defined by subtle disturbances of cognition and perception.

RESULTS

The search strategy resulted in identifying 10 articles that reported substance use in individuals at CHR for the development of psychosis (see Table 1). We also found a recent review[40] examining the impact of cannabis use on prodromal symptoms and transition to psychosis. This review identified 11 studies, 6 of which are also included in our review. The remainder were not included as four did not address conversion to psychosis and the fifth[41] focused on levels of anandamide in a small subsample.

Clinical diagnoses of CHR and substance abuse

In the studies currently under review, two different diagnostic instruments have been used to assess CHR criteria. Eight of the studies used the SIPS/SOPS,[31-38] and two used the

CAARMS.[30,39] Substance use/abuse was assessed by a range of instruments, including the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) Disorders (SCID),[42] the Composite International Diagnostic Interview (CIDI),[43] Schedules for Clinical Assessment in Neuropsychiatry (SCAN),[44] Diagnostic Interview for Genetic Studies (DIGS)[45] and the two versions of the Kiddie Schedule for Affective Disorders and Schizophrenia: the Present and Lifetime Version (K-SADS-PL)[46] and the Epidemiological Version (K-SADS-E).[47] Substance use disorders were defined according to DSM-IV criteria in all of the studies. Five studies[32,34,37,38,48] excluded participants with substance-induced APS (three of which[37,38,48] also excluded participants who use hard drugs). The remaining two studies[31,36] listed current substance dependence as an exclusion criterion for their samples. Two studies[30,39] excluded participants who have used antipsychotic medications. One of the studies[33] did not mention any exclusion criteria in relation to substance use.

Prevalence of cannabis use

Unfortunately, not all of the studies offered details on the types of substances used and the rates at which they were used. The most commonly used substance reported was cannabis, with rates varying in the studies from 33% to 54%.[30-32,35-38] These fall in the mid-range of those reported in first-episode psychosis studies (e.g. 13–64%).[4,10,49] Only two studies included a healthy control group, one of which demonstrated that CHR participants were significantly more likely to use cannabis than healthy controls,[36] whereas the other study was unable to compare the two groups due to methodological differences.[38]

Five of the studies reported frequency of cannabis use,[30,35-38] with two studies reporting no specific data.[31,32] Auther *et al*.[36] found that 49% of lifetime cannabis users had used cannabis 1–19 times and 51% of users had used cannabis 20 or more times. In one of their studies, Dragt *et al*.[48] reported that 42% of total participants had used cannabis more than five times in their lifetime, and in the other,[37] 60% of recent cannabis users used almost daily, 13% used three to four times per week, 20% used one to two times per week, and 7% used one to three times per month. These results paralleled those of Korver *et al*.[38] who claimed that 63% of recent cannabis users used almost daily, 13% used three to four times per week, 19% used one to two times per week, and 6% used one to three times per month. Finally, according to Phillips *et al*.[30] in the year prior to recruitment, 19% of total participants had used cannabis at least one time but less than one time per week, and 37% of participants had used cannabis at least once a week.

In relation to DSM-IV diagnoses, the highest prevalence (33%) of cannabis use disorders (abuse or dependence in remission) was reported by Kristensen and Cadenhead.[31] The other studies reported a lower incidence of cannabis use disorders ranging between 10% and 32%.[30,32,35-37]

In summary, although there is some variation in the rates of cannabis use, generally about half the samples are using or have used, with reported prevalence rates being similar to those reported for those experiencing a first episode of psychosis. Rates were higher than healthy controls but that was only reported in one study.[36]

Prevalence of alcohol use

Alcohol was the next most frequently used substance reported. Data on the use of alcohol were included in four of the studies,[31,32,34,36] with rates ranging between 17% and 44%. With the exception of Auther *et al*.,[36] none of these studies reported frequencies nor amounts.

Auther *et al*.[36] reported alcohol as being the most frequently used substance with 44% of their sample. They reported lifetime use of alcohol with frequencies ranging between 1–2 times ever (43.9%) and 5–7 days per week (2.4%) and quantities ranging from 1–2 drinks (48.4%) to six or more drinks (12.9%). Similar rates and patterns were found in the healthy comparison subjects in this study. In the other three studies, the use of alcohol ranged between 17% and 40%.[31,32,34]

In relation to DSM-IV alcohol disorder diagnoses, data were provided by three of the studies.[31,32,34] Kristensen and Cadenhead[31] reported that 10% of their sample had a diagnosis of abuse and 6% of dependence in remission, with Corcoran *et al*.[32] also reporting a 6% dependence in remission and Ruhrmann *et al*.[34] reporting 30% of their sample was diagnosed with alcohol abuse.

In summary, alcohol is used frequently by CHR participants. However, only one study reports comparable use to same-aged healthy peers.[36]

Prevalence of other substance use

The information presented on substances other than cannabis and alcohol which were used/abused by the CHR samples was limited. Furthermore, where the rates of these substances were reported, they were minimal. The most commonly used substance other than cannabis and alcohol was tobacco/nicotine.[31,32,36] The highest rate of lifetime use was reported by Author *et al*.,[36] who reported that 34% of their sample had a lifetime history of smoking tobacco. The other two studies had a range of lifetime use from 16% to 17%.[31,36]

The use of other illicit substances was also considerably lower compared with cannabis. These substances included opioids, sedatives (i.e. barbiturates), stimulants (i.e. cocaine, amphetamines, ecstasy), hallucinogens (i.e. PCP) and solvents. From these substances, the use of hallucinogens was reported as the highest, ranging from 7% to 19%.[30,32,36] The remaining substances had a range of use of 0–9%. The only study that reported data on DSM-IV diagnoses for any of these other substances was Kristensen and Cadenhead.[31] They reported that 4% of their participants met criteria for either lifetime amphetamine abuse or dependence in remission.

These results suggest that use of substances other than cannabis, alcohol and tobacco/nicotine is minimal in CHR populations, reflecting those findings in first-episode psychosis studies.

Changes over time in substance use

Although all of the studies were longitudinal with follow-up periods ranging between 12 and 36 months, none reported on changes over time in substance use. The only exception was

Corcoran *et al*.,[32] who reported no incident drug use in their 'non-user' group at follow-up and little or no change in amounts used in the 'user' group. Kristensen and Cadenhead[31] and Dragt *et al*.[48] took changes over time in substance use into account by assessing drug use at each follow-up assessment in addition to baseline.

Substance use and conversion to psychosis

All of the studies included in the review addressed the issue of conversion to psychosis, with only two reporting a significant association between substance use and transition to psychosis.[31,33] Kristensen and Cadenhead[31] found that CHR individuals were more likely to develop psychosis within one year if they had used cannabis and nicotine. In this study, 6 (12.5%) of the 48 CHR individuals made the transition to psychosis, with 5 of these individuals meeting criteria for current cannabis abuse or cannabis dependence in remission, thus showing a significant association between cannabis use and conversion to psychosis. However, because this study was also examining psychophysiological and neuropsychological variables, individuals with current cannabis dependence had been excluded from the study to avoid the risk of affecting the psychophysiological and neuropsychological test measures. Nicotine was also reported to be significantly associated with later conversion to psychosis with four out of the five cannabis using participants also using nicotine.

The only other study to find an association between substance use and transition to psychosis was the Cannon *et al*.[33] study, which had the largest sample (n = 291) and a transition rate of 35% during a 2.5-year follow-up. They found that a history of any substance use disorder was one of five predictors of conversion to psychosis when it was included in their prediction model.

Auther *et al*.[36] did not find any association between age of cannabis onset and age of psychosis onset. However, two studies[37,48] found that a younger age of onset of cannabis use resulted in a younger age of psychosis symptom onset. Thus, the majority of studies to date are not reporting a role for substance use in later conversion to psychosis.

DISCUSSION

The study of young people at risk of developing psychosis is a relatively new area and the literature is limited in addressing the issue of substance use in these populations. To the best of our knowledge, there are only 10 studies addressing this issue. Cannabis, alcohol and nicotine were found to be the most commonly used substances in CHR populations, with the use of cannabis and nicotine being higher than in healthy controls,[36] and with rates being similar to those at the first episode of psychosis.[2-4,50] The use of other substances was either minimal or absent. With the exception of two studies,[31,33] there was little evidence to suggest an association between substance use/abuse and transition to psychosis in a CHR population.

A possible explanation as to why the rates of cannabis use in CHR populations are similar to those found in first-episode psychosis cohorts is that CHR individuals may use cannabis to help alleviate some of their symptoms, for instance, anxiety, depression or negative

symptoms. This explanation is in line with the 'self-medication' hypothesis of cannabis use in psychosis which predicts that individuals may be using cannabis due in large part to their predisposition to psychosis. Some support for this theory is found in the Dragt *et al*.[35] study. Another possibility is that individuals who are prone to psychosis have a neurobiological predisposition to both cannabis use and psychotic illness. Patients with schizophrenia and CHR individuals have been shown to have abnormalities of the endocannabinoid system. For example, anandamide, an endogenous CB_1 receptor agonist, is elevated in the cerebrospinal fluid of antipsychotic- and cannabis-naïve patients with schizophrenia[51] and in CHR subjects.[41] In addition, translational studies have demonstrated the role of the endocannabinoid system in dopamine regulation.[52,53]

Only in two of the reviewed studies was cannabis use significantly associated with transition to psychosis.[31,33] A possible explanation for this lack of association could be that the use of cannabis may be considered a predictor for the development of CHR symptoms, but cannabis use during the CHR phase may not differentiate between those who develop psychosis and those who do not. For transition to occur, other environmental[54] and genetic factors[55] may be necessary to contribute to the pathway that leads to psychosis.

In one of the two studies that found a significant association between substance use and transition to psychosis,[40] no specific substance class of the seven substances tested (i.e. alcohol, cannabis, hypnotics, amphetamines, opiates, cocaine and hallucinogens) were significantly associated with conversion but only having a history of a DSM-IV diagnosis of a substance use disorder. In this study, the low base rate of substance abuse severely limited sensitivity. In the Kristensen and Cadenhead[31] study, the substance using group was categorized as those who met criteria for cannabis use disorders, thus, ensuring that the using group was well-defined diagnostically, although conversion rates were low. Ruhrmann *et al*.[34] was the only other study under review to define cannabis using in this way, with all of the other studies dividing their groups according to cannabis use versus no use. If the dose-dependent hypothesis was to be considered, then it may not be surprising that an association between cannabis use and transition to psychosis was not found, although several of the other studies[32,37,38,48] also looked at cannabis abuse but did not find a significant relationship with psychosis.

There are several limitations with the current studies. Firstly, the longitudinal use/abuse of substances has not been adequately addressed in the current studies. The only study that attempted to do this was the Corcoran *et al*.[32] study that looked at the temporal patterns of cannabis use and prodromal symptoms and found an association with one positive symptom. Other studies focused on lifetime or baseline levels of use rather than continued use over the follow-up period, which could have affected the outcome.[22,56] Furthermore, it has been demonstrated that a substantial proportion of subjects show improvements in symptoms over time,[57] and this improvement might extend to other areas as well such as reduced symptoms of depression, anxiety and substance use, especially if treatment is being provided. It is, therefore, necessary to look more closely at patterns of substance use over the follow-up period.

Secondly, the majority of studies lacked details on severity, frequency and quantity of substance use. Specifically in relation to cannabis, no details were provided on the types of cannabis used as research has shown that varying potencies of cannabis can have significant effects on symptom severity with high concentrations of 9-tetrahydrocannabinol, leading to more severe positive symptoms.[58] In addition, some of the current data come from research projects where there was an exclusion criterion with respect to substance dependence. This limited these samples to those with less severe substance use, which could affect outcomes if the relationship between substance use and conversion is dose dependent.[59-62] For example, a recent study[20] examining individuals with methamphetamine-related conditions found that this group had a higher risk of developing schizophrenia than other medical conditions and other substances, with the exception of cannabis use disorders where the risk was the same. It is possible that studies may exclude methamphetamine users or that such users may not be those who present themselves for inclusion in a research project.

Thirdly, the prevalence of substance use in these CHR populations relative to the general population is unclear. Only one study had a healthy comparison group. Fourthly, although the CHR group represents a population that is at increased risk for the development of psychosis compared with the general population, many CHR individuals will not go on to develop psychosis[33] and the rates of conversion seem to be declining.[63] Therefore, studies examining the relationship between substance use and transition to psychosis may not be finding any significant associations partly due to insufficient power in relation to small sample sizes and a low base rate of substance use. Furthermore, the recency and amounts of substances used considerably differs between the current studies, making it difficult to make accurate comparisons.

Finally, an important methodological issue that needs to be addressed when attempting to explore a causal relationship between factors, in this case substance use and psychosis, is controlling for potentially confounding factors. In studies examining conversion, this was not specifically addressed. Some of the potential control factors would include method of ascertainment of subjects, inclusion and exclusion criteria particularly, age of participants which typically vary from 12 to 31, age at first use of substances particularly cannabis, assessment of substance use which should include type and quantities and possibly biological measures, co-morbid diagnoses (e.g. mood disorders), medications including antipsychotics and other potential risk factors such as family history.

In conclusion, the literature examining substance use in those at CHR is limited. The majority of studies have not found a relationship between substances, mainly cannabis use and psychosis. Certainly, studies with a more comprehensive and longitudinal approach to assessing substance use are required. Although the low base rates currently being reported of substance use clearly limits sensitivity, its association with risk of transition is theoretically important as it is possible that a substance-related mechanism may be capable of promoting brain changes in certain high-risk individuals and it may only be in the context of other factors, such as family history, environmental risk factors or genetic background that a relationship is found.

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TABLE 1

Research studies demonstrating the prevalence of substance use in clinical high risk populations

Study	Sample	Follow-up in months	Number of participants who have used substances at baseline	Number of participants who met criteria for at least one substance use disorder	Substance use measure	Number of conversions to psychosis	Conclusions
Phillips *et al.*[30]	49 male, 51 female, aged 14–30 in Melbourne, Australia	12	Cannabis = 35 (35.0%) Opioids = 2 (2.0%) Sedatives = 2 (2.0%) Cocaine = 0 (0.0%) Stimulants = 7 (7.0%) Hallucinogens = 7 (7.0%) Solvents = 1 (1.0%)	Cannabis = 18 (18.0%)	SCAN	12 months: Cannabis users = 13 (40.6%) Non-cannabis users = 19 (59.4%)	A role for cannabis in the development of psychosis is not supported
Kristensen and Cadenhead[†31]	26 male, 22 female, aged 12–30, in San Diego, USA	24	Cannabis = 16 (33.3%) Alcohol = 8 (16.7%) Amphetamine = 2 (4.2%) Nicotine = 8 (16.7%)	Cannabis = 16 (33.3%) Alcohol = 8 (16.7%) Amphetamine = 2 (4.2%) Nicotine = Not reported	SCID K-SADS-PL	12 months: Cannabis users = 1 Non-cannabis users = 1 Cannabis and nicotine users = 4	Significant association between cannabis abuse and nicotine use and conversion to psychosis
Corcoran *et al.*[32]	26 male, 6 female, aged 12–25, in New York, USA	24	Cannabis = 13 (40.6%) Alcohol = 13 (40.6%) Cocaine = 3 (9.4%) Hallucinogens = 6 (18.8%) Stimulants = 1 (3.1%) Tobacco = 5 (16%)	Cannabis = 8 (25.0%) Alcohol = 2 (6.3%) Cocaine = 1 (3.1%)	K-SADS-PL DIGS	No differences in conversion rates between substance users and non-users – specific numbers unavailable	Cannabis use may be a risk factor for the exacerbation of subthreshold psychotic symptoms, specifically perceptual disturbances, but not for conversion to psychosis
Cannon *et al.*[33]	170 male, 121 female, aged 12–35, in North America	30	Any substance = 270 (92.8%) This included use of any of the following drugs: Alcohol Hypnotics Cannabis Amphetamines Opiates Cocaine Hallucinogens	Not reported	SCID K-SADS-PL	82 (35.3%) conversions, no specific details on differences between substance users and non-users. Cumulative conversion rates over follow-up are as follows: 6 months = 12.7% 12 months = 21.7% 18 months = 26.8% 28 months = 32.6% 30 months = 35.3%	History of substance abuse predicted conversion to psychosis although no specific substance was significantly associated with risk
Ruhrmann *et al.*[34]	137 male, 108 female, aged 16–35, in Europe	18	Any drug = 53 (23.0%) Alcohol = 69 (30.0%)	Any drug = 53 (23.0%) Alcohol = 69 (30.0%)	CIDI	18 months: 37 conversions, no specific details on differences between substance users and non-users	No association between substance abuse and conversion to psychosis
Dragt *et al.*[35]	137 male and 108 female, aged 16–35 in Europe	18	Cannabis = 102 (42.0%)	Cannabis = 45 (18.4%)	CIDI DSM-IV	18 months: Cannabis users = 15 Non-cannabis users = 22	Early age at onset of cannabis use is associated with earlier appearance of

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Study	Sample	Follow-up in months	Number of participants who have used substances at baseline	Number of participants who met criteria for at least one substance use disorder	Substance use measure	Number of conversions to psychosis	Conclusions
							symptoms, however, not related to conversion to psychosis
Auther *et al.*[36]	66 male, 35 female, aged 12–22 in New York, USA	36	Tobacco = 31 (34.4%) Cannabis = 35 (36.5%) Alcohol = 43 (44.3%) Amphetamine = 4 (4.2%) Barbiturates = 3 (3.1%) Cocaine = 6 (6.2%) Opioids = 8 (8.3%) PCP = 1 (1.0%) Hallucinogen = 11 (11.5%) Solvents = 3 (3.1%) Ecstasy = 3 (3.1%)	Cannabis = 10 (10.4%)	K-SADS-E	No differences in conversion rates between substance users and non-users – specific numbers not available	Lifetime cannabis use/abuse do not predict conversion to psychosis
Dragt *et al.*‡[37]	47 male, 21 female, aged 12–35 in Amsterdam, Holland	Not reported	Cannabis = 35 (51.5%)	Cannabis = 22 (32.4%)	CIDI	Up to 37 months: Cannabis users = 5 (29.4%) Non-cannabis users = 12 (70.6%)	Early age at onset of cannabis use is associated with earlier appearance of symptoms, not related to conversion to psychosis
Korver *et al.*[38]	42 male, 21 female, aged 12–35 in Amsterdam, Holland	36	Cannabis = 34 (54.0%)	Not reported	CIDI	Cannabis users = 7 (41.2%) Non-cannabis users = 10 (58.8%)	Cannabis use is related to increased symptoms and increased symptom severity, not related to conversion to psychosis
Thompson *et al.*[39]	51 male, 53 female, aged 14–30 in Melbourne, Australia	28	Any substance = 24 (23.5%)	Not reported	SCID	28 months: Substance users = 10 (25.6%) Non-substance users = 31 (75.6%)	Substance use does not predict conversion to psychosis in young people at UHR for psychosis

APS, attenuated positive symptoms; CHR, clinical high risk; CIDI, Composite International Diagnostic Interview; DIGS, Diagnostic Interview for Genetic Studies; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; ICD-9, International Classification of Diseases, Ninth Revision; KSADS-E, Kiddie Schedule for Affective Disorders and Schizophrenia = Epidemiologic Version; K-SADS-PL, Kiddie Schedule for Affective Disorders and Schizophrenia = Present and Lifetime; SCAN, Schedule for Clinical Assessment in Neuropsychiatry; SCID, Schedule for Clinical Interview and Diagnosis; UHR, ultra-high risk.

†All of these participants were part of the Cannon *et al.*[33] study. However, more details were available for each participant in this study.

‡All of these participants were part of the Ruhrmann *et al.*[34] study. However, this study focused only on cannabis use.