

Association of Substance Use Disorders With Conversion From Schizotypal Disorder to Schizophrenia

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IMPORTANCE Understanding the role of substance use disorders in conversion from schizotypal disorder to schizophrenia may provide physicians and psychiatrists with important tools for prevention or early detection of schizophrenia.

OBJECTIVE To investigate whether substance use disorders, in particular cannabis use disorder, are associated with conversion to schizophrenia in individuals with schizotypal disorder.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study included a population-based sample of all individuals born in Denmark from January 1, 1981, through August 10, 2014, with an incident diagnosis of schizotypal disorder and without a previous diagnosis of schizophrenia. Follow-up was completed on August 10, 2014, and data were analyzed from March 10, 2017, through February 15, 2018.

EXPOSURES Information on substance use disorders combined from 5 different registers.

MAIN OUTCOMES AND MEASURES Cox proportional hazards regression using time-varying information on substance use disorders and receipt of antipsychotics and adjusted for parental history of mental disorders, sex, birth year, and calendar year were used to estimate hazard ratios (HRs) and 95% CIs for conversion to schizophrenia.

RESULTS A total of 2539 participants with incident schizotypal disorder were identified (1448 men [57.0%] and 1091 women [43.0%]; mean [SD] age, 20.9 [4.4] years). After 2 years, 16.3% (95% CI, 14.8%-17.8%) experienced conversion to schizophrenia. After 20 years, the conversion rate was 33.1% (95% CI, 29.3%-37.3%) overall and 58.2% (95% CI, 44.8%-72.2%) among those with cannabis use disorders. In fully adjusted models, any substance use disorder was associated with conversion to schizophrenia (HR, 1.34; 95% CI, 1.11-1.63). When data were stratified by substance, cannabis use disorders (HR, 1.30; 95% CI, 1.01-1.68), amphetamine use disorders (HR, 1.90; 95% CI, 1.14-3.17), and opioid use disorders (HR, 2.74; 95% CI, 1.38-5.45) were associated with conversion to schizophrenia. These associations were not explained by concurrent use of antipsychotics, functional level before incident schizotypal disorder, or parental history of mental disorders.

CONCLUSIONS AND RELEVANCE Substance use disorders, in particular cannabis, amphetamines, and opioids, may be associated with conversion from schizotypal disorder to schizophrenia. However, conversion rates are high even in those without substance use disorders, indicating a need for universal and substance-targeted prevention in individuals with schizotypal disorder.

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One-quarter to one-half of patients with schizotypal disorder experience conversion to schizophrenia within 5 years.¹⁻³ This potential link is further strengthened by studies showing that parental schizotypal disorder is associated with schizophrenia in offspring.^{4,5}

Substance use disorders are common in patients with schizotypal disorder,⁶ and cannabis has been shown to be a risk factor for developing schizotypal disorder.⁷ Cannabis has also been linked to an increased risk of schizophrenia.⁸ Other substance use disorders, in particular alcohol use disorder, may also increase risk of later schizophrenia.⁹

These previous results suggest that substance use, in particular cannabis, may be associated with conversion to schizophrenia in individuals with schizotypal disorder. Two small studies from Denmark^{1,3} failed to find such a link but were based on only 79 and 83 individuals each. Conversely, one of these studies found that in fully adjusted analyses, antipsychotic treatment and level of functioning were the only statistically significant variables associated with transition to psychosis,³ whereas only sex was significantly associated in the other study.¹ This finding may have been attributable to low power because the odds ratio for the association of cannabis use with psychosis was 2.5 but with a very wide CI. Consequently, an association cannot be ruled out and needs to be investigated in larger samples. The potential role of other substances has not to our knowledge been investigated previously. Further investigation of this proposed association may provide physicians and psychiatrists with better tools for preventing or detecting onset of schizophrenia in individuals with schizotypal disorder regardless of whether such an association is causal or simply an indicator of risk.

In the present study, we aimed to investigate whether substance use disorders are associated with conversion to schizophrenia in individuals with schizotypal disorder. Our hypothesis was that individuals with substance use disorders would be at increased risk compared with those without substance use disorders. We also hypothesized that cannabis use disorders would be more strongly associated than other substance use disorders. Finally, we aimed to investigate whether this association was confounded by use of antipsychotics or parental history of mental illness.

Methods

Population

We used the nationwide Danish registries linked through the civil registration number that has been provided to all individuals with legal residence in Denmark since 1968.¹⁰ We identified all persons born in Denmark from January 1, 1981, through August 10, 2014, with an incident diagnosis of schizotypal disorder (code F21 from *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [ICD-10]) without a previous diagnosis of schizophrenia (ICD-10 code F20 or code 295 from the *International Classification of Diseases, Eighth Revision* [ICD-8]) through the Danish Psychiatric Central Research Register.¹¹ January 1, 1981, was chosen

Key Points

Question Are substance use disorders, in particular cannabis use disorders, associated with conversion from schizotypal disorder to schizophrenia?

Findings In this Danish nationwide, register-based cohort study that identified 2539 participants with incident schizotypal disorder, any substance use disorder was associated with conversion to schizophrenia at a rate of 33.1%; for cannabis use disorders, the conversion rate was 58.2%. Results were statistically significant after controlling for confounders.

Meaning Universal and substance-targeted prevention efforts are needed to reduce conversion to schizophrenia in individuals with schizotypal disorder.

so that the cohort was unlikely to have had incident schizotypal disorder before the introduction of ICD-10 in 1994. According to Danish law, register-based studies do not require informed consent or approval by ethics committees.

Data

The exposure of substance use disorders was established from linkage of 5 registers. The Psychiatric Central Research Register and the National Patient Register provide ICD-8 and ICD-10 diagnostic codes for inpatient psychiatric (since 1969) and somatic hospital contacts (since 1977), respectively.^{11,12} Since 1995, both registers have also included outpatient and emergency department contacts. In these registers, the ICD-8 and ICD-10 codes shown in Table 1 were used to define the different substance use disorder categories.

In addition, we used the following Anatomical Therapeutic Chemical (ATC) codes from the National Prescription Registry¹³ to identify medication given for alcohol use disorders: N07BB01 (disulfiram), N07BB02 (calcium carbimide), and N07BB03 (acamprosate calcium). The following ATC codes identified medication given for opioid use disorders: N07BC01 and N07BC51 (buprenorphine hydrochloride), N07BC02 (methadone hydrochloride), and N07BC03 (levacetylmethadol). Finally, we used the National Alcohol Treatment Register and the Register of Substance Abusers in Treatment to identify individuals receiving treatment for substance use disorders outside hospital settings.

The outcome of schizophrenia was established in the Psychiatric Central Research Register as ICD-10 code F20. Information regarding parental psychiatric history was obtained by linking data on biological parents from the Civil Registration System with the Psychiatric Central Research Register.¹⁰ This information was stratified into parental history of schizophrenia, schizotypal disorder, or any other mental disorder (all remaining diagnostic codes).

Information regarding antipsychotics prescribed while the individual had a diagnosis of schizotypal disorder was obtained from the National Prescription Registry and defined as all ATC codes in the N05A category. For this purpose, we included antipsychotics prescribed within 1 year before the first diagnosis of schizotypal disorder.

Table 1. ICD Codes Used to Define Study Variables

ICD Code	Description
Alcohol Use Disorder	
<i>ICD-8</i>	
291.x	Alcoholic psychosis
303.x	Alcoholism
571.0	Alcoholic cirrhosis
<i>ICD-10</i>	
F10.x	Mental and behavioral disorders due to use of alcohol
E52.x	Niacin deficiency
G31.2	Degeneration of nervous system due to alcohol
G62.1	Alcoholic polyneuropathy
G72.1	Alcoholic myopathy
I42.6	Alcoholic cardiomyopathy
K29.2	Alcoholic gastritis
K70.x	Alcoholic liver disease
K86.0	Alcohol-induced chronic pancreatitis
O35.4	Maternal care for (suspected) damage to fetus from alcohol
Y57.3	Alcohol deterrents
Z50.2	Alcohol rehabilitation
Z71.4	Alcohol abuse counselling and surveillance
Z72.1	Problems related to alcohol use
Opioid Use Disorder	
<i>ICD-8</i>	
304.0	Drug dependence: opium, opium alkaloids, and their derivatives
304.1	Drug dependence: synthetic analgesics with morphinelike effects
<i>ICD-10</i>	
F11.x	Mental and behavioral disorders due to use of opioids
Cannabis Use Disorder	
<i>ICD-8</i>	
304.5	Drug dependence: cannabis sativa
<i>ICD-10</i>	
F12.x	Mental and behavioral disorders due to use of cannabinoids
Sedative Use Disorder	
<i>ICD-8</i>	
304.2	Drug dependence: barbiturates
304.3	Drug dependence: other hypnotics and sedatives or tranquilizers
<i>ICD-10</i>	
F13.x	Mental and behavioral disorders due to use of sedatives or hypnotics
Cocaine Use Disorder	
<i>ICD-8</i>	
304.4	Drug dependence: cocaine
<i>ICD-10</i>	
F14.x	Mental and behavioral disorders due to use of cocaine
Amphetamine Use Disorder	
<i>ICD-8</i>	
304.6	Drug dependence: other psychostimulants
<i>ICD-10</i>	
F15.x	Mental and behavioral disorders due to use of other stimulants
Hallucinogen Use Disorder	
<i>ICD-8</i>	
304.7	Drug dependence: hallucinogens
<i>ICD-10</i>	

(continued)

Table 1. ICD Codes Used to Define Study Variables (continued)

ICD Code	Description
F16.x	Mental and behavioral disorders due to use of hallucinogens
Other Substance Use Disorders	
<i>ICD-8</i>	
304.8	Drug dependence: other
304.9	Drug dependence: unspecified
<i>ICD-10</i>	
F18.x	Mental and behavioral disorders due to use of volatile solvents
F19.x	Mental and behavioral disorders due to multiple drug use and use of other psychoactive substances

Abbreviations: ICD-8, *International Classification of Diseases, Eighth Revision*; ICD-10, *International Classification of Diseases and Related Health Problems, Tenth Revision*.

Information regarding functional level was obtained from the DREAM (Danish Rational Economic Agents Model) database¹⁴ and defined as work or student history in the year preceding the incident diagnosis of schizotypal disorder. This information was divided into full-time work or student history vs at least some periods of unemployment. Information regarding sex and year of birth were obtained from the Civil Registration System.

Statistical Analysis

Data were analyzed from March 10, 2017, through February 15, 2018, using using Cox proportional hazards regression. The cohort was followed up from incident schizotypal disorder diagnosis until incident schizophrenia diagnosis, death, migration, or August 10, 2014 (the last update of the current set of registers), whichever came first. Diagnoses of substance use disorders and receipt of antipsychotics were treated as time-varying covariates. If an exposure was incident before incident schizotypal disorder, the exposure was thus present for the entire time at risk for that individual. All analyses were adjusted for sex, calendar year, and year of birth. In model 1, each variable was entered independently. In model 2, all variables were entered simultaneously. We tested for multicollinearity, which was not an issue (highest variance inflation factor, 1.44; mean, 1.23). We performed sensitivity analyses by censoring patients when they started receiving antipsychotics rather than adjusting for this information. Consequently, individuals receiving antipsychotics before the date of incident schizotypal disorder were never entered into these sensitivity analyses. These analyses were conducted owing to the possibility that patients had already developed schizophrenia at the first prescription of an antipsychotic without the proper change in diagnosis in the hospital registers. We conducted further sensitivity analyses of individuals regardless of their year of birth to increase statistical power but at the cost of reduced confidence in the diagnoses of schizotypal disorder being truly incident. A final set of sensitivity analyses distinguished between onset of substance use disorder before or after incident schizotypal disorder. Analyses were conducted using Stata/MP software (version 14.1; StataCorp).

Table 2. Characteristics of the Cohort of Patients With Incident Schizotypal Disorder

Characteristic	Data (n = 2539)
Follow-up time, person-years	11 157.02
No. with conversion to schizophrenia	549
Age at first diagnosis of schizotypal disorder, mean (SD), y	20.9 (4.4)
Men, No. (%)	1448 (57.0)
Unemployed before onset, No. (%) ^a	1220 (48.1)
History of schizophrenia in either parent, No. (%)	95 (3.7)
History of schizotypal disorder in either parent, No. (%)	31 (1.2)
History of any other mental disorder in either parent, No. (%)	907 (35.7)
Any substance use disorder, No. (%)	
Incident before schizotypal disorder	408 (16.1)
Incident after schizotypal disorder ^b	334 (13.2)
Alcohol use disorder, No. (%)	
Incident before schizotypal disorder	241 (9.5)
Incident after schizotypal disorder ^b	164 (6.5)
Opioid use disorder, No. (%)	
Incident before schizotypal disorder	11 (0.4)
Incident after schizotypal disorder ^b	30 (1.2)
Cannabis use disorder, No. (%)	
Incident before schizotypal disorder	167 (6.6)
Incident after schizotypal disorder ^b	236 (9.3)
Hypnotic use disorder, No. (%)	
Incident before schizotypal disorder	8 (0.3)
Incident after schizotypal disorder ^b	20 (0.8)
Cocaine use disorder, No. (%)	
Incident before schizotypal disorder	19 (0.7)
Incident after schizotypal disorder ^b	37 (1.5)
Amphetamine use disorder, No. (%)	
Incident before schizotypal disorder	22 (0.9)
Incident after schizotypal disorder ^b	64 (2.5)
Hallucinogen use disorder, No. (%)	
Incident before schizotypal disorder	5 (0.2)
Incident after schizotypal disorder ^b	6 (0.2)
Other substance use disorder, No. (%)	
Incident before schizotypal disorder	90 (3.5)
Incident after schizotypal disorder ^b	115 (4.5)
Prescribed antipsychotics, No. (%)	
Within a year before schizotypal disorder	673 (26.5)
First prescription after schizotypal disorder ^b	875 (34.5)

^a Dichotomized into fully employed (or studying) vs any history of unemployment in the year before first diagnosis of schizotypal disorder.

^b Indicates until end of follow-up, before censoring or conversion to schizophrenia.

Results

We identified 3027 individuals born in Denmark since 1981 with incident schizotypal disorder (Table 2). Of these, 275 (9.1%) were excluded because they had had a diagnosis of schizophrenia before their diagnosis of schizotypal disorder. A further 213 (7.0%) were excluded because they had lived outside

Table 3. Association of Substance Use Disorders With Conversion to Schizophrenia in a Population With Schizotypal Disorder

Variable	HR (95% CI)	
	Model 1 ^a	Model 2 ^b
Any substance use disorder	1.39 (1.15-1.67)	1.34 (1.11-1.63)
Alcohol use disorder	1.25 (0.98-1.59)	1.09 (0.85-1.40)
Opioid use disorder	3.55 (1.90-6.67)	2.74 (1.38-5.45)
Cannabis use disorder	1.49 (1.18-1.89)	1.30 (1.01-1.68)
Sedative use disorder	1.12 (0.42-3.01)	0.66 (0.24-1.84)
Cocaine use disorder	1.54 (0.85-2.81)	0.73 (0.37-1.45)
Amphetamine use disorder	2.41 (1.52-3.82)	1.90 (1.14-3.17)
Hallucinogen use disorder	2.17 (0.81-5.83)	1.91 (0.68-5.34)
Other substance use disorders	1.59 (1.18-2.15)	1.13 (0.80-1.59)
Antipsychotic medication	1.49 (1.24-1.79)	1.42 (1.18-1.70)
Parental schizophrenia	0.97 (0.62-1.49)	1.11 (0.70-1.76)
Parental schizotypal disorder	0.41 (0.13-1.28)	0.43 (0.13-1.37)
Other parental mental illness	0.95 (0.79-1.13)	0.92 (0.77-1.11)
Unemployed before onset ^c	1.09 (0.89-1.33)	1.05 (0.86-1.29)

Abbreviation: HR, hazard ratio.

^a Adjusted for sex, birth year, and calendar year.

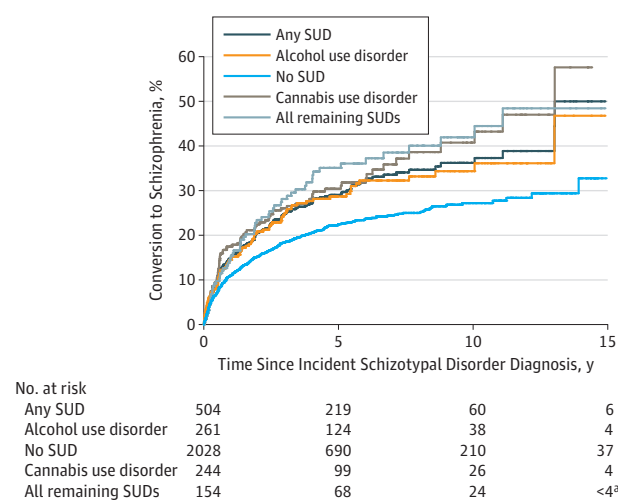
^b Adjusted for sex, birth year, calendar year, and all other individual types of substance use disorders. Any substance use disorder is further adjusted for prescription of antipsychotics and parental mental disorders.

^c Dichotomized into fully employed (or studying) vs any history of unemployment in the year before first diagnosis of schizotypal disorder.

Denmark before their incident diagnosis of schizotypal disorder to ensure full history of psychiatric disorders in the register. Consequently, 2539 individuals remained for the analyses (1448 men [57.0%] and 1091 women [43.0%]; mean [SD] age at first diagnosis of schizotypal disorder, 20.9 [4.4] years).

Table 3 gives hazard ratios (HRs) and 95% CIs for conversion to schizophrenia. Any substance use disorder (HR, 1.34; 95% CI, 1.11-1.63), opioid use disorder (HR, 2.74; 95% CI, 1.38-5.45), cannabis use disorder (HR, 1.30; 95% CI, 1.01-1.68), amphetamine use disorder (HR, 1.90; 95% CI, 1.14-3.17), and antipsychotic use (HR, 1.42; 95% CI, 1.18-1.70) were all associated with conversion to schizophrenia in the fully adjusted analyses. Other substance use disorders were associated with conversion to schizophrenia in the basically adjusted model 1 (HR, 1.59; 95% CI, 1.18-2.15) but not in the fully adjusted model.

The Figure shows a Kaplan-Meier curve of conversion rates to schizophrenia. The overall 20-year conversion rate from schizotypal disorder to schizophrenia was 33.1% (95% CI, 29.3%-37.3%). The 1- and 2-year conversion rates were 11.7% (95% CI, 10.5%-13.0%) and 16.3% (95% CI, 14.8%-17.8%), respectively. For ease of presentation and because no statistically significant risk factors for conversion were present, substance use disorders other than alcohol and cannabis use disorders were pooled into a single category. After 20 years, 58.2% (95% CI, 44.8%-72.2%) of individuals with cannabis use disorder had experienced conversion to schizophrenia. For individuals with alcohol use disorder, the 20-year conversion rate was 47.0% (95% CI, 35.3%-60.2%). For those without any substance use disorder, the 20-year conversion rate was 30.6% (95% CI, 27.7%-34.5%). In sensitivity analyses censoring individuals at first receipt of antipsychotics, the association for any

Figure. Conversion Rates From Schizotypal Disorder to Schizophrenia

Includes 2539 participants. Data are stratified by substance use disorder (SUD) categories. Numbers do not add up to 2539 because a single person can have more than 1 type of SUD.

^a Danish law does not allow us to give counts of less than 4 from registers.

substance use disorder was not present (HR, 1.11; 95% CI, 0.86-1.45). For individual substance use disorders, estimated HRs were largely unchanged, but none were statistically significant, presumably because of decreased power.

We conducted further sensitivity analyses regardless of the birth year of the cohort ($n = 6598$). In these fully adjusted analyses, alcohol use disorder was also associated with conversion to schizophrenia (HR, 1.18; 95% CI, 1.05-1.32), but amphetamine use disorder (HR, 0.92; 95% CI, 0.65-1.30) and opioid use disorder (HR, 0.99; 95% CI, 0.73-1.33) were not. Low level of functioning was also associated with conversion to schizophrenia in these analyses (HR, 1.30; 95% CI, 1.16-1.46). Conversion rates in this sensitivity analysis were almost identical to those in the main analysis.

Finally, we conducted sensitivity analyses stratifying substance use disorders into those with onset before or after incident schizotypal disorder. Cannabis use disorder with onset before incident schizotypal disorder was not associated with conversion (HR, 1.00; 95% CI, 0.70-1.41; $P = .98$), and generally no substance use disorder other than opioid use disorder (HR, 2.59; 95% CI, 0.99-6.77; $P = .05$) with onset before incident schizotypal disorder was associated with conversion to schizophrenia.

Discussion

Cannabis, amphetamine, and opioid use disorders were associated with conversion to schizophrenia in the fully adjusted model. Cannabis use has been extensively studied as a risk factor for schizophrenia in the general population, and our study revealed this association.^{8,9} A previous study⁹ investigated cannabis and other substance use disorders as risk factors for schizophrenia and found that even after full adjustment, can-

nabis use disorders led to a more than 5-fold increased risk of schizophrenia. The HRs estimated in individuals with schizotypal disorder were markedly lower, which probably reflects a higher baseline risk of conversion to schizophrenia in this population, with 16.3% of those without any substance use disorders experiencing conversion to schizophrenia within a 2-year period.

Several explanations may be proposed for this association. The association may be causal. This explanation is supported by a number of indicators from studies establishing an association between cannabis use and schizophrenia in the general population. First, the association appears to be dose dependent^{8,9}; second, the association is stronger for more potent types of cannabis^{15,16}; third, cannabis use is associated with earlier onset of psychosis¹⁷; and fourth, age at onset of cannabis use is associated with age at onset of schizophrenia.¹⁸ If such associations are true in the general population, they likely would also be true in a high-risk population, such as individuals with schizotypal disorder. A different explanation of the association is that schizophrenia increases the risk of commencing use of cannabis or other substances.¹⁹ In favor of this hypothesis is that such diverse substances as cannabis, amphetamines, and opioids are associated with conversion to schizophrenia. In our study, the first registered date of substance use disorder came before the first registered date of schizophrenia, but delays in diagnoses may have caused schizophrenia or its preclinical symptoms to predate substance use. Many other studies have applied different methods to minimize the risk of this occurrence, and the association is unlikely to be explained by this theory of reverse causation.^{8,9} Finally, the association may be explained by common underlying or confounding factors. Sensitivity analyses showed that conversion was almost exclusively driven by substance use disorder with onset after incident schizotypal disorder.

Alcohol use disorder was not associated with conversion from schizotypal disorder to schizophrenia in the main analysis, but it was in sensitivity analyses when ignoring the birth year of the cohort, possibly owing to increased power in these analyses. This finding is in line with a previous study of the Danish general population.⁹ Further research is needed in this area to establish whether the association is causal.

Low level of functioning was not associated with conversion to schizophrenia in the main analysis, but it was in the sensitivity analysis when disregarding birth year. This finding is in line with those of previous studies regarding conversion to schizophrenia.^{3,20,21} This variable may be an indicator of degree of illness, and thus, it is not surprising that those most severely affected by schizotypal disorder are also at higher risk for subsequent conversion to schizophrenia. Adjusting for level of functioning did not, however, remove the associations between substance use disorders and conversion to schizophrenia.

Use of antipsychotics was associated with conversion to schizophrenia. This association is probably a case of confounding by indication because patients who are deemed to be most severely ill among those with schizotypal disorder are treated with antipsychotics. However, adjustment for antipsychotic use did not remove the association between substance use dis-

orders and conversion to schizophrenia. A large proportion of patients with schizotypal disorder in Denmark are prescribed antipsychotics, which raises the concern that some of these patients with schizotypal disorder might already have met the threshold for a psychotic disorder such as schizophrenia before the eventual diagnosis of schizophrenia. For this reason, we conducted sensitivity analyses in which we censored individuals at the time when they first started receiving antipsychotics. Apart from loss of power, this censoring had little effect on the estimated associations. Therefore, antipsychotic use is unlikely to be a causal risk factor for conversion from schizotypal disorder to schizophrenia. Instead, it may be a marker of already increased risk.

Parental schizophrenia and other types of parental mental illness were not associated with conversion from schizotypal disorder to schizophrenia. This finding may be surprising because parental history of schizophrenia is a well-known risk factor for schizophrenia in the offspring²² and parental severe mental illness is associated with substance use in the offspring²² but is probably a ceiling effect to the high overall conversion rates from schizotypal disorders. The reasons for this lack of an association are not clear. The high overall conversion rate from schizotypal disorder to schizophrenia may not allow for other genetic risk factors to influence the risk greatly, whereas environmental risk factors such as cannabis use disorders are able to increase the risk of conversion even further.

Apart from cannabis use, amphetamine and opioid use disorders were associated with conversion to schizophrenia. In a previous study in the background population, these 2 types of substance use disorders were associated with development of schizophrenia.⁹ To our knowledge, little research has been conducted on this association. Because these substances are rather different, schizophrenia might not be associated with the substances but with the underlying addiction or even a selection mechanism. However, this process would not explain why the same results were not observed for the remaining substances. Opioids may also hold an antipsychotic effect²³ and thus may be used for self-medication.

More years of following up incident schizotypal disorder were required before previously reported conversion rates were reached in our study. Previous studies have relied on clinical settings in which patients were reassessed for schizophrenia at preset times. In our study, we had to rely on diagnoses given in treatment settings. This process may have introduced a delay between the actual time of conversion and the date that was recorded in registers, which could at least in part explain this discrepancy. Thus, it seems unlikely that participants with late conversion were originally misdiagnosed with schizotypal disorder.

Strengths and Limitations

The population of individuals with schizotypal disorder was drawn from unselected nationwide registers, thus eliminating the risk of selection bias and attrition bias. Validation studies of severe mental illness have shown that the register is highly valid for establishing populations with these disorders.¹¹

We were not able to validate the diagnoses of schizotypal disorder. The large proportion of antipsychotics prescribed to the population might indicate that not all of them had true schizotypal disorder but may in fact have had misdiagnosed schizophrenia from the start. We performed sensitivity analyses in which we censored individuals when they started receiving antipsychotics, with negligible changes to results. Thus, misdiagnosis of schizotypal disorder does not seem to be a likely explanation for the associations with cannabis use disorder.

A second limitation is that substance use disorders were only registered if and when they were treated or became prominent enough to be registered in patient medical records, although we attempted to minimize this effect by combining information on substance use disorder from several different sources. Therefore, our estimates were likely to be conservatively biased toward the null hypothesis. Similarly, only substance use disorders were registered, which also likely led to conservative estimates. An implication of this limitation could also be that the neurologic processes of addiction rather than the substances themselves drive the association.

The extent to which our results are generalizable to *DSM-V* is unclear. However, given that *ICD-10* requires the presence of fewer criteria than *DSM-V*, individuals diagnosed using *DSM-V* criteria could be considered to be further along the path to schizophrenia, in which case we would expect that the associations be at least as strong using *DSM-V* criteria as in the present study.

A final limitation lies in the limited number of variables for which we could adjust analyses. We did not have information on the use of tobacco, which often co-occurs with cannabis use and with some evidence indicating that it may be linked to development of psychosis.²⁴ However, 1 analysis²⁵ has suggested that cannabis may be the explanatory factor in the link between tobacco and psychosis.

Conclusions

Secondary analyses of the OPUS trial found that integrated, specialized treatment decreased the rate of conversion to schizophrenia.¹ Another trial found that low doses of risperidone combined with cognitive behavior therapy reduced the rate of conversion to psychosis from ultrahigh-risk states such as schizotypal disorder,²⁶ but 2 later trials failed to replicate this finding.^{27,28} Of note, with the exception of the OPUS trial, all trials to our knowledge that have found significant reductions in conversion rates for psychosis have included patients fulfilling any ultrahigh-risk criterion and not just individuals with schizotypal disorder. Thus, an increased focus on how to prevent conversion from schizotypal disorder to schizophrenia is required. Preventing or treating substance use disorders, especially cannabis and amphetamine use disorders, may have some efficacy in reducing the additional risk attributable to substance use disorders but probably not below the already high baseline conversion rate.

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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Hjorthøj.
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