

Transition From Substance-Induced Psychosis to Schizophrenia Spectrum Disorder or Bipolar Disorder

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Objective: The authors investigated transitions to schizophrenia spectrum or bipolar disorder following different types of substance-induced psychosis and the impact of gender, age, number of emergency admissions related to substance-induced psychosis, and type of substance-induced psychosis on such transitions.

Methods: All patients in the Norwegian Patient Registry with a diagnosis of substance-induced psychosis from 2010 to 2015 were included (N=3,187). The Kaplan-Meier method was used to estimate cumulative transition rates from substance-induced psychosis to either schizophrenia spectrum disorder or bipolar disorder. Cox proportional hazard regression was used to estimate hazard ratios for transitions to schizophrenia spectrum or bipolar disorders associated with gender, age, number of emergency admissions, and type of substance-induced psychosis.

Results: The 6-year cumulative transition rate from substance-induced psychosis to schizophrenia spectrum

disorder was 27.6% (95% CI=25.6–29.7). For men, the risk of transition was higher among younger individuals and those with either cannabis-induced psychosis or psychosis induced by multiple substances; for both genders, the risk of transition was higher among those with repeated emergency admissions related to substance-induced psychosis. The cumulative transition rate from substance-induced psychosis to bipolar disorder was 4.5% (95% CI=3.6–5.5), and the risk of this transition was higher for women than for men.

Conclusions: Transition rates from substance-induced psychosis to schizophrenia spectrum disorder were six times higher than transition rates to bipolar disorder. Gender, age, number of emergency admissions, and type of substance-induced psychosis affected the risk of transition.

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Substance-induced psychosis is characterized by transient psychotic symptoms following the use of a psychoactive substance, typically subsiding after a few days of abstinence (1). Among individuals initially diagnosed with substance-induced psychosis, a substantial proportion are later diagnosed with schizophrenia (2). Transition rates vary across studies, ranging from 6% (3) to 54% (4) when all substance-induced psychoses are grouped together. A recent meta-analysis found a pooled transition rate of 25% (95% CI=18–35) from substance-induced psychosis to schizophrenia (5).

To our knowledge, only four studies have directly compared transition rates to schizophrenia among individuals with different types of substance-induced psychoses. Three studies found the highest transition rates following cannabis-induced psychosis, ranging from 18% to 47%, and the lowest rates following alcohol-induced psychosis, ranging from 5% to 15% (3, 6, 7). The fourth study found similar transition rates following cannabis-, stimulant-, opioid-, and multiple-drug-induced psychoses and the lowest rate following alcohol-induced psychosis (8).

Although use of substances, particularly cannabis, has been found to increase the risk of bipolar disorder (9–11), few studies have looked at the transition from substance-induced psychosis to bipolar disorder. A 20-year transition rate of 8% from substance-induced psychosis to bipolar disorder (7) and an 8-year transition rate of 6% from cannabis-induced psychosis to a manic episode or bipolar disorder (12) have been reported.

Identifying risk factors for these transitions would improve identification of patients with substance-induced psychosis in need of closer follow-up. Male gender and younger age at the incident substance-induced psychotic episode have been identified as such factors (7, 8, 12). Also, familial predisposition to psychosis is associated with increased risk of transition to schizophrenia (6).

The present registry-based study had two aims: to investigate transition rates to schizophrenia spectrum disorder or bipolar disorder following different types of substance-induced psychoses and to investigate how these transition rates are affected by gender, age, number of emergency

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admissions related to substance-induced psychosis, and type of substance-induced psychosis.

METHODS

Data Source

Data for this study were drawn from the Norwegian Patient Registry. The registry includes data on all patients treated in specialist health care services in Norway, including inpatient and outpatient somatic and mental health facilities, substance use treatment facilities, private specialist practices, and rehabilitation institutions receiving governmental reimbursement. For each contact, the registry includes a unique person identifier, dates of admission and discharge, and primary and secondary diagnoses. A primary diagnosis is the diagnosis most relevant for the treatment provided at a particular contact, with decreasing relevance for secondary and tertiary diagnoses.

All treatment in the specialized health care services is based on referral and is either planned or acute treatment. Adults pay a maximum annual cost equivalent to US\$310 for outpatient treatment. Hospitalizations are always free of charge. Services not covered in the Norwegian Patient Registry are municipal services, including those provided by general practitioners, and private health care from providers without governmental reimbursement.

Population and Selection of Patients

We included all inpatients and outpatients ages 18 to 79 who were diagnosed at discharge with substance-induced psychosis in the period from 2010 to 2015. Patients who had a diagnosis of schizophrenia spectrum disorder or bipolar disorder prior to the diagnosis of substance-induced psychosis were excluded. The years 2008 and 2009 were used as a washout period to ensure a minimum 2-year observation time prior to the substance-induced psychosis. All diagnoses were defined by ICD-10 diagnostic codes (1).

Substance-Induced Psychosis

Substance-induced psychosis was defined as a diagnosis of psychosis induced by any of the following substances (ICD-10 code): psychosis induced by alcohol (F10.5), opioids (F11.5), cannabis (F12.5), sedatives (F13.5), cocaine (F14.5), amphetamines (F15.5), hallucinogens (F16.5), volatile solvents (F18.5), and multiple substances (F19.5). For each person with substance-induced psychosis, we included information about gender, age, the number of emergency admissions related to substance-induced psychosis, and the substance that induced the psychosis. Persons who received more than one type of specific substance-induced psychosis diagnosis during the observation period were categorized according to the first diagnosis. Persons who received more than one type of substance-induced psychosis diagnosis at the same event were categorized according to the diagnosis that was highest in the hierarchy of primary and secondary diagnoses. For the number of emergency admissions related to substance-induced psychosis, we counted an event as a new admission when there

was at least 1 week since the discharge date for the previous emergency hospitalization. Two or more admissions were considered repeated emergency admissions.

Schizophrenia Spectrum Disorder and Bipolar Disorder

Schizophrenia spectrum disorder was defined as ICD-10 code F20, F22, or F23, and bipolar disorder was defined as ICD-10 code F30 or F31. Patients who received both diagnoses within the inclusion period were categorized according to the first diagnosis.

Statistical Analysis

Patients were followed from the first diagnosis of substance-induced psychosis in the observation period until a diagnosis of schizophrenia spectrum disorder or bipolar disorder, death, migration, the month they turned 80, or the end of 2015, whichever came first. The Kaplan-Meier method was used to estimate cumulative transition rates from substance-induced psychosis to schizophrenia spectrum disorder or bipolar disorder. Cox proportional hazard regression analyses with years at risk as the underlying time scale were conducted to estimate adjusted hazard ratios with 95% confidence intervals for the transition from substance-induced psychosis to schizophrenia spectrum disorder or bipolar disorder. Because of an interaction between gender and age group for the schizophrenia spectrum outcome, these analyses were stratified by gender.

We investigated how transition rates were affected by gender, age, number of emergency admissions related to substance-induced psychosis, and type of substance-induced psychosis. The number of emergency admissions was entered as a time-varying covariate. In analyses of the effect of substance-specific types of psychosis on risk of transition, the type of substance-induced psychosis with the lowest cumulative transition was chosen as the reference category. In analyses of the effect of age on the risk of transition, the youngest age group was chosen as the reference category.

Because of the small number of individuals in each substance-induced psychosis group for opioids, sedatives, cocaine, hallucinogens, and volatile solvents, results for these diagnoses from the Cox regression analyses are not presented. Results in cells with fewer than 10 patients are not shown. The analyses were performed using SAS, version 9.4 (SAS Institute, Cary, N.C.).

Ethics

All patient data had been fully de-identified when accessed by the investigators. In Norway, studies with de-identified information from medical health registries do not require participant consent. Use of personal health data in this research was granted by the regional committee for medical and health research ethics (2014/72/REK Nord).

RESULTS

The study included 3,187 patients with substance-induced psychosis, with a mean age of 33.6 years (SD=12.3) at the time of

TABLE 1. Patient characteristics, measures of substance-induced psychosis, and cumulative hazard for subsequent diagnosis of schizophrenia spectrum disorder or bipolar disorder during follow-up in a Norwegian registry study

Variable	N	Age at Index Diagnosis (years)		Transition to Schizophrenia			Transition to Bipolar Disorder		
		Mean	SD	N	Cumulative Hazard (%)	95% CI	N	Cumulative Hazard (%)	95% CI
Any substance-induced psychosis	3,187	33.6	12.3	636	27.6	25.6–29.7	100	4.5	3.6–5.5
Male	2,341	33.3	12.1	482	28.6	26.2–31.2	59	3.5	2.6–4.5
Female	846	34.3	13.0	154	24.8	21.2–28.8	41	7.1	5.1–9.7
Age (years) at index diagnosis									
18–25	1,090			265	32.7	29.1–36.7	32	4.4	3.0–6.4
26–30	570			136	32.9	28.1–38.3	20	5.1	3.2–8.0
31–35	410			78	27.8	22.4–34.2	11	4.4	2.4–8.3
36–40	331			52	22.2	17.1–28.7	18	6.8	4.3–10.6
41–45	255			42	22.2	16.5–29.3	<10	—	—
46–50	208			31	20.7	14.6–29.0	<10	—	—
51–79	323			32	13.8	9.3–20.1	<10	—	—
Emergency admissions related to substance-induced psychosis									
0	793	32.9	12.4	113	21.5	18.2–25.4	24	4.7	3.1–7.3
1	1,679	34.3	13.0	254	23.8	21.3–26.5	57	4.7	3.5–6.1
>1	715	32.4	10.2	269	39.4	34.8–44.4	19	3.6	2.3–5.7
Substance									
Alcohol	453	47.0	14.9	45	13.2	9.8–17.8	15	4.6	2.7–7.7
Opioids	67	39.9	13.0	10	16.5	9.2–28.8	<10	—	—
Cannabis	562	26.7	8.0	157	36.0	31.4–41.0	20	4.9	3.1–7.7
Sedatives or hypnotics	67	40.0	13.0	10	18.5	10.3–31.9	<10	—	—
Cocaine	23	28.0	7.3	<10	—	—	<10	—	—
Amphetamines	707	33.0	9.7	125	25.0	21.1–29.5	18	3.8	2.3–6.3
Hallucinogens	69	28.4	11.5	<10	—	—	<10	—	—
Volatile solvents	4	30.3	13.5	<10	—	—	<10	—	—
Multiple substances	1,235	31.8	10.1	279	32.0	28.5–35.8	40	4.5	3.2–6.2

the index diagnosis. The majority were men (N=2,341; 73.5%) (Table 1). There were 453 (14.2%) individuals with alcohol-induced psychosis, 562 (17.6%) with cannabis-induced psychosis, 707 (22.2%) with psychosis induced by amphetamines, and 1,235 (38.8%) with psychosis induced by multiple substances. Psychosis induced by opioids, sedatives or hypnotics, cocaine, hallucinogens, and volatile solvents were more infrequent, with fewer than 70 individuals in each category of substance-induced psychosis. A total of 484 individuals (15.2% of the total sample) had more than one type of substance-induced psychosis during the observation period, of which 179 (37.0%) were diagnosed with psychosis induced by multiple substances (F19.5) at their first episode. A total of 36 individuals (1.1%) had more than one type of substance-specific diagnosis at the first episode. Across the different categories of substance-induced psychosis, the mean age was lowest for cannabis-induced psychosis (26.7 years) and highest for alcohol-induced psychosis (47.0 years).

Transition From Substance-Induced Psychosis to Schizophrenia Spectrum Disorder or Bipolar Disorder

Among the 3,187 individuals with substance-induced psychosis, 636 were diagnosed with schizophrenia spectrum disorder during the follow-up period (Table 1). The 6-year cumulative hazard for transition from substance-induced psychosis to schizophrenia spectrum disorder was 27.6%;

the cumulative hazard was 28.6% among men and 24.8% among women. The cumulative hazard was highest for the youngest patients (32.7% for those ages 18–25 and 32.9% for those ages 26–30), and among the different types of substance-induced psychosis, it was highest for cannabis-induced psychosis and lowest for alcohol-induced psychosis.

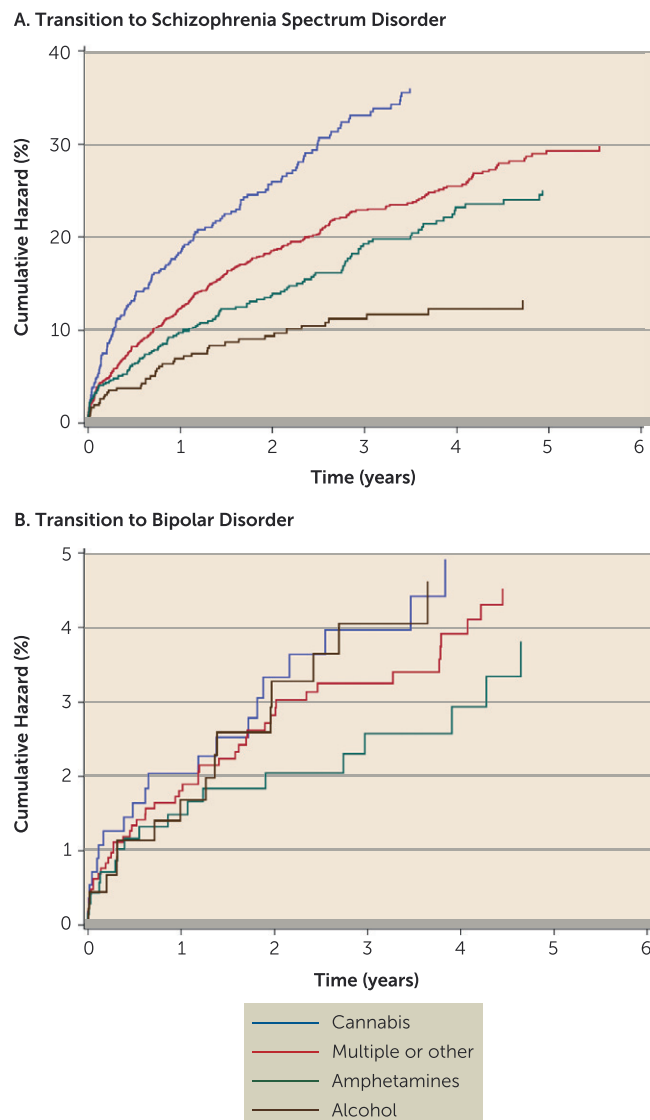
The median time from the diagnosis of substance-induced psychosis to a diagnosis of schizophrenia spectrum disorder was 0.8 years (Q1–Q3=0.2–1.9). Within the first year of the index diagnosis of substance-induced psychosis, 56.4% of the observed transitions had occurred; the figures were 76.7%, 90.4%, and 96.4% after 2, 3, and 4 years, respectively.

A total of 100 individuals were diagnosed with bipolar disorder during follow-up. The cumulative transition from substance-induced psychosis to bipolar disorder was 4.5%, with a higher transition rate among women (7.1%) than among men (3.5%).

The median time from the diagnosis of substance-induced psychosis to a diagnosis of bipolar disorder was 1.0 year (Q1–Q3=0.2–2.0). Within the first year of the index diagnosis of substance-induced psychosis, 52.0% of the observed transitions had occurred; the figures were 77.0%, 87.0%, and 95.0% after 2, 3, and 4 years, respectively.

The cumulative transition to schizophrenia spectrum disorder or bipolar disorder for psychosis induced by alcohol,

FIGURE 1. Cumulative transition rates from substance-induced psychosis to schizophrenia spectrum disorder (panel A) and bipolar disorder (panel B) in a Norwegian registry study



cannabis, amphetamines, and multiple or other substances during the 6-year observation period is depicted in Figure 1. The highest and steepest curve was obtained with cannabis-induced psychosis transitioning to schizophrenia spectrum disorder. All the diagnostic changes following cannabis-induced psychosis occurred within a little more than 3 years, after which there were no additional transitions to schizophrenia spectrum disorder.

Predictors of Transition

Age was inversely associated with hazard ratios for transition from any substance-induced psychosis to schizophrenia spectrum disorder in men but not in women (Table 2). In both men and women, there was an increased risk of transition with repeated emergency admissions related to substance-induced psychosis.

Compared with alcohol-induced psychosis and after adjustment for age, psychoses induced by cannabis (hazard ratio=2.66, 95% CI=1.72–4.10) and multiple substances (hazard ratio=1.73, 95% CI=1.15–2.61) were associated with higher risk of transition to schizophrenia spectrum disorder among men. Among women, the results also suggested that cannabis-induced psychosis was associated with the highest risk of transition to schizophrenia spectrum disorder (hazard ratio=1.95, 95% CI=0.95–3.98).

Compared with men, women had higher risk of transition from any substance-induced psychosis to bipolar disorder (hazard ratio=2.02, 95% CI=1.35–3.02) (Table 3). The number of emergency admissions related to substance-induced psychosis and the type of substance-induced psychosis did not affect the risk of transition to bipolar disorder; age also had no consistent effect on the risk of transition. There were, however, few individuals in each group in these analyses.

Additional Description of the Data and Sensitivity Analyses

To explore how our definition of the psychosis outcome influenced the results, we conducted sensitivity analyses with schizophrenia defined only as ICD-10 code F20. Because there were fewer washout diagnoses (F20, F30, and F31 in the sensitivity analysis in contrast to F20, F22, F23, F30, and F31 in the original analysis), a somewhat larger sample of 3,755 patients with substance-induced psychosis was identified. The cumulative hazard of transition from any substance-induced psychosis to schizophrenia, defined as ICD-10 code F20 only, was 18.8%. Among men, lower age, repeated emergency admissions (hazard ratio=2.53, 95% CI=1.91–3.34), and psychoses induced by cannabis (hazard ratio=3.20, 95% CI=1.80–5.70) and multiple substances (hazard ratio=2.17, 95% CI=1.25–3.79) were associated with increased risk of transition. Among women, repeated emergency admissions (hazard ratio=3.00, 95% CI=1.66–5.44) and cannabis-induced psychosis (hazard ratio=4.82, 95% CI=1.35–17.28) were associated with increased risk of transition. These results are provided in Tables S1 and S2 in the online supplement.

A total of 34 individuals were diagnosed with both schizophrenia spectrum disorder and bipolar disorder during the observation period. We conducted sensitivity analyses where these individuals were categorized according to the last diagnosis rather than the first, resulting in a category change for 20 individuals: 12 individuals changed from schizophrenia spectrum to bipolar disorder, and eight individuals changed from bipolar to schizophrenia spectrum disorder. The other 14 individuals had either the same diagnosis at the first and last event (N=11) or both diagnoses at the last event (N=3). The new categorization resulted in 632 individuals with schizophrenia spectrum disorder and 104 individuals with bipolar disorder. The cumulative transition rate from any substance-induced psychosis to schizophrenia spectrum disorder was 27.6%, and the transition rate to bipolar disorder was 4.7%. Changes in the regression analysis results were not notable for the schizophrenia spectrum disorder outcome. For the bipolar

TABLE 2. Gender-wise hazard ratios for the transition from substance-induced psychosis to schizophrenia spectrum disorder, according to age, number of emergency admissions, and type of substance-induced psychosis

Variable	Men					Women				
	N	Unadjusted		Adjusted ^a		N	Unadjusted		Adjusted ^a	
		Hazard Ratio	95% CI	Hazard Ratio	95% CI		Hazard Ratio	95% CI	Hazard Ratio	95% CI
Age (years) at first substance-induced psychotic episode										
18–25	786	1.00	Reference	1.00	Reference	304	1.00	Reference	1.00	Reference
26–30	458	0.85	0.67–1.06	0.88	0.70–1.11	112	1.09	0.68–1.75	1.10	0.69–1.77
31–35	316	0.68	0.52–0.91	0.74	0.56–0.99	94	0.86	0.49–1.52	0.86	0.49–1.53
36–40	246	0.53	0.38–0.74	0.59	0.42–0.83	85	0.63	0.33–1.20	0.63	0.33–1.21
41–45	175	0.41	0.27–0.63	0.47	0.30–0.73	80	1.23	0.74–2.06	1.30	0.77–2.19
46–50	138	0.52	0.33–0.83	0.68	0.42–1.09	70	0.69	0.36–1.32	0.76	0.40–1.46
51–79	222	0.29	0.18–0.47	0.43	0.26–0.73	101	0.70	0.39–1.26	0.95	0.49–1.83
Emergency admissions related to substance-induced psychosis										
0	588	1.00	Reference	1.00	Reference	219	1.00	Reference	1.00	Reference
1	1,285	1.23	0.97–1.55	1.33	1.05–1.68	448	1.51	0.98–2.33	1.54	0.99–2.40
>1	468	2.66	2.06–3.44	3.06	2.35–3.98	179	2.69	1.68–4.29	2.85	1.75–4.65
Substance										
Alcohol	330	1.00	Reference	1.00	Reference	123	1.00	Reference	1.00	Reference
Cannabis	448	3.91	2.64–5.79	2.66	1.72–4.10	114	2.15	1.13–4.08	1.95	0.95–3.98
Amphetamines	499	1.81	1.20–2.73	1.16	0.75–1.80	208	1.58	0.86–2.91	1.25	0.63–2.45
Other substance ^b	163	1.48	0.85–2.60	1.10	0.62–1.97	67	1.13	0.50–2.55	1.23	0.54–2.83
Multiple substances	901	2.71	1.86–3.95	1.73	1.15–2.61	334	1.61	0.90–2.87	1.28	0.67–2.45

^a Estimates for number of emergency admissions and type of substance-induced psychosis were adjusted for age group.

^b Other substances included opioids (ICD-10 code F11), sedatives or hypnotics (F13), cocaine (F14), hallucinogens (F16), and volatile solvents (F18).

disorder outcome, the increased risk among women remained but was somewhat lower (hazard ratio=1.71, 95% CI=1.15–2.56), and there was an increased risk of transition associated with psychosis induced by alcohol (hazard ratio=2.55, 95% CI=1.16–5.60), cannabis (hazard ratio=2.63, 95% CI=1.31–5.28), and multiple substances (hazard ratio=1.94, 95% CI=1.04–3.61).

To explore the consequence of length of washout period, we conducted a sensitivity analysis with a 4-year washout instead of a 2-year washout. This resulted in 2,228 patients with substance-induced psychosis, of whom 397 were subsequently diagnosed with schizophrenia spectrum disorder and 51 with bipolar disorder. The cumulative transition rate from any substance-induced psychosis to schizophrenia spectrum disorder was 25.8%, and the transition rate to bipolar disorder was 3.1%. The risk for transition to schizophrenia spectrum disorder in men was higher among the younger patients (men ages 40 and above had significantly lower risk of transition compared with men ages 18–25) and those with repeated emergency admissions (hazard ratio=2.02, 95% CI=1.45–2.83). Among the different specific substance-induced psychoses, the risk for transition was highest following cannabis-induced psychosis (hazard ratio=2.57, 95% CI=1.42–4.68). Among women, having repeated emergency admissions was associated with increased risk of transition from substance-induced psychosis to schizophrenia spectrum disorder (hazard ratio=1.82, 95% CI=1.03–3.20). No significant associations were found for the transition from substance-induced psychosis to bipolar disorder.

DISCUSSION

In this study of more than 3,000 patients with substance-induced psychosis, the 6-year cumulative rate of transition to schizophrenia spectrum disorder was 27.6%, with the highest rate associated with cannabis-induced psychosis (36.0%). The risk of transition from substance-induced psychosis to schizophrenia spectrum disorder was higher among younger men and higher among men and women with more emergency admissions related to substance-induced psychosis. The importance of these three factors in men—younger age, repeated emergency admissions, and cannabis-induced psychosis—was repeatedly identified in three sets of sensitivity analyses, suggesting that these factors are robust to nuances in definitions of variables and data-handling choices.

The transition rate from substance-induced psychosis to bipolar disorder was 4.5%, with a higher rate of transition among women, and this risk of transition was not affected by the number of emergency admissions related to substance-induced psychosis or type of substance-induced psychosis. When considering the last rather than the first diagnosis, psychoses induced by alcohol, cannabis, and multiple substances were associated with an increased risk of transition to bipolar disorder.

Transition to Schizophrenia Spectrum Disorder

The cumulative risk of transition to schizophrenia spectrum disorder of 27.6% in our study is similar to an estimate from a recent meta-analysis (5). In our sensitivity analyses, the transition rate was similar when using a 4-year washout but

TABLE 3. Hazard ratios for the transition from substance-induced psychosis to bipolar disorder, according to gender, age, number of emergency admissions, and type of substance-induced psychosis

Variable	Unadjusted		Adjusted ^a	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Gender				
Male	1.00	Reference	1.00	Reference
Female	1.89	1.27–2.82	2.02	1.35–3.02
Age (years) at index diagnosis of substance-induced psychosis				
18–25	1.00	Reference	1.00	Reference
26–30	1.14	0.65–1.99	1.29	0.73–2.26
31–35	0.89	0.45–1.77	1.02	0.51–2.05
36–40	1.79	1.00–3.19	1.91	1.05–3.47
41–45	1.00	0.46–2.18	1.05	0.48–2.31
46–50	0.64	0.22–1.80	0.60	0.21–1.74
51–79	0.79	0.35–1.79	0.66	0.27–1.64
Emergency admissions related to substance-induced psychosis				
0	1.00	Reference	1.00	Reference
1	1.29	0.80–2.09	1.36	0.83–2.21
>1	1.25	0.68–2.30	1.34	0.71–2.51
Substance				
Alcohol	1.40	0.71–2.79	1.78	0.85–3.74
Cannabis	1.55	0.82–2.93	1.75	0.90–3.39
Amphetamines	1.00	Reference	1.00	Reference
Other substance ^b	1.30	0.54–3.11	1.40	0.58–3.40
Multiple substances	1.27	0.73–2.21	1.31	0.75–2.28

^a Estimates for gender were adjusted for age group, and estimates for age group were adjusted for gender. Estimates for number of emergency admissions and type of substance-induced psychosis were adjusted for gender and age group.

^b Other substances included opioids (ICD-10 code F11), sedatives or hypnotics (F13), cocaine (F14), hallucinogens (F16), and volatile solvents (F18).

lower (18.8%) when using only schizophrenia (ICD-10 code F20) as an outcome. The first large study comparable to ours used schizophrenia spectrum disorders (codes F20, F22, and F23) as the outcome. The study did not report the pooled transition rate for any substance-induced psychosis but found high transition rates for some specific substance-induced psychoses (3). Three subsequent studies used schizophrenia (code F20) as the outcome, but there was a wide range in transition rates for any substance-induced psychosis, from 11% to 26% (6–8). Some of these studies had a long follow-up period, which may have increased estimates, although Kendler and colleagues (6) found a relatively low cumulative risk of transition of 11% with a 19-year follow-up. A large portion of their sample (40%) was recruited from primary care and outpatient facilities, however, and possibly had less severe illness.

Similar to previous studies, we found the highest transition rate following cannabis-induced psychosis and the lowest rate following alcohol-induced psychosis (3, 6, 7). Cannabis use has long been considered a risk factor for schizophrenia (13, 14). Initiation of cannabis use at a young age (15, 16), more frequent use (17), and more potent cannabis products (18, 19) further increase the risk. Moreover, parallel to an increase in cannabis potency (20), there have been increases in the prevalence of self-reported psychosis (21), the incidence of schizophrenia (22), and the population-attributable risk fraction for cannabis use in schizophrenia (23). Although these findings may suggest a dose-response

relationship and a causal relationship between cannabis use and schizophrenia, genetic or familial factors and reverse causation may explain much of the association (24). Regardless of the causal explanation, it seems that some individuals who develop schizophrenia after cannabis use make this transition via cannabis-induced psychosis. Importantly, the annual incidence of cannabis-induced psychosis has been increasing in Scandinavia since around 2008 (25).

An effect of age on transition to schizophrenia spectrum disorder was found only among men in this study. Previous studies found that having substance-induced psychosis at a younger age was a risk factor for transition to schizophrenia (7, 8, 12), but gender-specific rates were not reported in these studies.

Repeated emergency admissions predicted transition from substance-induced psychosis to schizophrenia spectrum disorder among men in the main analysis and all sensitivity analyses and among women when the outcome was schizophrenia only. Repeated emergency admissions may be a marker of more severe substance use, poorer mental health, or less social support. It could also be a marker of a schizophrenia development, that

is, rather than a separate risk factor, it could be viewed as partly embedded in the outcome, as a transitional step toward schizophrenia.

The age groups with the highest transition rates to schizophrenia spectrum disorder in our study coincided with the ages where schizophrenia typically has its onset in the population, in the late teens and early 20s (26). In our sample, individuals with repeated emergency admissions were somewhat younger on average than those with no admissions or only one admission, and cannabis-induced psychosis was associated with the lowest mean age. These associations between younger age, cannabis use, and multiple admissions following substance-induced psychosis make it challenging to disentangle the specific risk factors for transition. Adjustment for age in our study attenuated the associations between cannabis-induced psychosis and schizophrenia spectrum disorder, but the estimate remained significant.

Transition to Bipolar Disorder

The transition rate of 4.5% from substance-induced psychosis to bipolar disorder over 6 years was, as expected, somewhat lower than in a study with a 20-year observation time and a transition rate of 8.4% (7). Our transition rate of 4.9% for cannabis-induced psychosis is comparable to that in a study that followed patients with cannabis-induced psychosis for 8 years, in which 5.6% of patients were later diagnosed with manic episode or bipolar disorder (12).

Although the few studies on the transition from substance-induced psychosis to bipolar disorder differ in observation time, type of substance-induced psychosis, and the definition of bipolar disorder (bipolar disorder with or without manic episodes), they all show transition rates substantially lower than those found for schizophrenia.

Although the incidence of bipolar disorder in men and women in the general population is approximately the same (11, 27), we found a higher risk of transition from substance-induced psychosis to bipolar disorder among women. Interestingly, a higher transition rate from substance-induced psychosis to bipolar disorder among women was also found in a previous study (7).

Substance-Induced Psychosis as a Diagnostic Entity

Substance-induced psychosis is one of the few diagnoses defined by its assumed etiology. However, the causal role of substance use implied by the name has been criticized (28). Both the probability of having a substance-induced psychotic episode and the risk of substance-induced psychosis transitioning to schizophrenia are affected by familial risk for psychosis (6). Similar to previous studies, the present study shows high transition rates to schizophrenia. Particularly high transition rates have been found following cannabis-induced psychosis—36% in our study, which is comparable to transition rates to schizophrenia following brief, atypical, and not otherwise specified psychoses (5) and for individuals at ultra-high risk of psychosis (29). Because many countries have separate treatment systems for mental disorders and addiction, the fact that substance-induced psychosis is identified as a third-digit specification of a substance use disorder (1) may affect the treatment these patients receive. Differentiation of patients with “only” a substance-induced psychosis from patients in a prodromal phase with acute psychotic symptoms related to substance use or consecutive substance-induced psychotic episodes with gradual health impairment not only seems difficult but also may be neither possible nor meaningful. In our view, accumulated evidence raises the question of whether substance-induced psychosis would be more appropriate to consider within the schizophrenia spectrum. We have previously suggested that a continuity perspective and a stress-vulnerability model would provide a more nuanced perspective on these clinical phenomena (30).

Limitations and Strengths

First, having only a 2-year washout period before the diagnosis of substance-induced psychosis is a limitation of this study, because we cannot be certain that these are in fact incident cases. However, analyses based on a 4-year washout period replicated the main findings. Second, the relatively short follow-up time may have led to an underestimation of some of the transition rates. Third, this study relies on diagnostic codes and thus on the validity of the diagnostic practices. These may be of varying quality, and we cannot rule out the possibility that they vary systematically. It may be, for instance, that knowledge about cannabis use as a risk

factor for schizophrenia affects clinicians' assessments and hence their diagnostic practices in such a way that cannabis-induced psychosis is more quickly reassessed as schizophrenia compared with other types of substance-induced psychosis. Fourth, a specific diagnosis of a substance-induced psychosis cannot be interpreted as exposure to that substance only, as many patients are polydrug users. Fifth, we included only substance-induced psychoses treated in the specialized health care services. This is less of a problem because, to our knowledge, substance-induced psychoses are rarely treated in the municipal health services.

A strength of the study is that it has a relatively large sample, including all patients with substance-induced psychosis in a country with a comprehensive health care system with free access to care, over a period of 6 years.

In summary, our findings indicate that substance-induced psychosis, particularly cannabis-induced psychosis, is a major risk factor for schizophrenia, and that younger age among men and repeated emergency admissions are associated with higher risk. This should inform and guide how the health services provide care for individuals with substance-induced psychosis.

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Examination Questions for Transition From Substance-Induced Psychosis to Schizophrenia Spectrum Disorder or Bipolar Disorder

1. **What were the 6-year cumulative transition rates from substance-induced psychosis to schizophrenia spectrum disorder or bipolar disorder found in this study?**
 - A. 25.5% to both disorders
 - B. 27.6% to schizophrenia spectrum disorder and 4.5% to bipolar disorder
 - C. 12.2% to schizophrenia spectrum disorder and 2.8% to bipolar disorder
 - D. 31.2% to bipolar disorder and 12.2% to schizophrenia spectrum disorder
2. **Which type of substance-specific substance-induced psychosis had highest cumulative transition rate to schizophrenia-spectrum disorder?**
 - A. Cannabis-induced psychosis
 - B. Amphetamine-induced psychosis
 - C. Psychosis induced by multiple substances
 - D. Alcohol-induced psychosis
3. **Three sensitivity analyses were conducted in this study, which all resulted in the same risk-factors for transition from substance-induced psychosis to schizophrenia for men. Which were they?**
 - A. Familial disposition for psychosis, higher age and the presence of an alcohol use disorder
 - B. Cannabis-induced psychosis and homelessness
 - C. Younger age, cannabis induced psychosis and repeated emergency admissions
 - D. High PANSS score at admission for substance-induced psychosis and longer duration of substance use