Number of words in the manuscript (abstract, text, references): 4496
Number of words in the text: 3488
Number of tables: 3
Number of figures: 1

Transition from substance-induced psychosis to schizophrenia spectrum disorder or bipolar disorder

Running title: Substance-induced psychosis and transition

Eline B. Rognli, Ph.D.[1*], Ina H. Heiberg, Ph.D.[2], Bjarne K. Jacobsen, Ph.D.[2,3,4], Anne Høye, M.D., Ph.D.[2,5,6] and Jørgen G. Bramness, M.D., Ph.D.[5,7,8]

[1)] Section for Clinical Addiction Research, Department on Substance Use Disorder Treatment, Oslo University Hospital, Oslo, Norway; [2)] Center for Clinical Documentation and Evaluation (SKDE), Tromsø, Norway; [3)] Center for Sami Health Research, Department of Community Medicine, University of Tromsø – The Arctic University of Norway, Tromsø, Norway; [4)] Department of Community Medicine, University of Tromsø – The Arctic University of Norway, Tromsø, Norway; [5)] Department of Clinical Medicine, University of Tromsø - The Arctic University of Norway, Tromsø, Norway; [6)] Division of Mental Health and Substance Abuse, University Hospital of North Norway, Tromsø, Norway; [7)] Norwegian Institute of Public Health, Oslo, Norway; [8)] Norwegian National Advisory Unit on Concurrent Substance Abuse and Mental Health Disorders, Inland Hospital Trust, Hamar, Norway

*Corresponding author

Section for Clinical Addiction Research, Department on Substance Use Disorder Treatment, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway. P.O.Box 4956 Nydalen, 0424 Oslo.

E-mail: elboka@ous-hf.no

Telephone: +47 480 52 157

Disclaimer:

Data from the Norwegian Patient Registry has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by this registry is intended nor should be inferred.

Abstract

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

Methods: Based on the Norwegian Patient Registry, we included all subjects with a SIP diagnosis from 2010 to 2015 (N=3,187). The Kaplan-Meier method was used to estimate cumulative transition rates from SIP to schizophrenia spectrum disorder or bipolar disorder. Cox proportional hazard regression was used to estimate hazard ratios (HRs) for transition to schizophrenia spectrum or bipolar disorders associated with gender, age, number of SIP emergency admissions, and type of SIP.

Results: The six-year cumulative transition rate from SIP to schizophrenia spectrum disorder was 27.6% (95% CI=25.6-29.7) The risk of transition was in men increased in the younger and those with cannabis-induced psychosis and psychosis induced by multiple substances, and in both genders it was increased for those with repeated SIP emergency admissions. The cumulative transition rate from SIP to bipolar disorder was 4.5% (95% CI=3.6-5.5), and women had higher risk of transition than men.

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

Key words: substance-induced psychosis, schizophrenia, bipolar disorder

Introduction

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

To our knowledge only four studies directly compare transition rates to schizophrenia between different types of SIPs. Three found highest transition rate of for cannabis-induced psychosis, ranging from 18% to 47%, and lowest for alcohol-induced psychosis, ranging from 5% to 15% (3, 6, 7). The fourth study found transition rates of similar magnitude for cannabis, stimulant, opiate and multiple drug induced psychosis, but also here lowest for alcohol-induced psychosis (8).

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

Identifying risk factors for transition would improve identification of SIP patients in need of closer follow-up. Male gender and younger age of the incident SIP 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 the transition rates to schizophrenia spectrum disorder or bipolar disorder following different types of SIPs, and to

investigate how gender, age, number of SIP emergency admissions, and SIP type affected these transitions.

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, both in- and outpatient facilities for somatic and mental health, substance use treatment facilities, private specialists and rehabilitation institutions receiving governmental reimbursement. For each contact, the registry includes a unique person identifier, date 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 sinking relevance for secondary, tertiary diagnoses and so forth.

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

Population and selection of cases

We included all in- and outpatients aged 18 to 79 years, who in the period from 2010 to 2015 were diagnosed at discharge with a SIP. Patients who had a diagnosis of schizophrenia spectrum disorder or bipolar disorder prior to the SIP diagnosis were excluded. The years 2008 and 2009 were used as washout period to ensure a minimum of two years observation time prior to the SIP. All diagnostic codes were according to the International Classification of Disease version 10 (ICD-10) (1).

Substance-induces psychosis

SIPs were defined as the following: Psychosis induced by alcohol (ICD-10 code 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). SIP was operationalized as any SIP, number of SIP emergency admissions, and according to which substance that induced the psychosis. If a person had more than one type of specific SIP diagnosis during the observation period, the person was categorized according to the type of SIP that occurred first. If a person had more than one type of SIP diagnosis at the same event, the person was categorized according to the SIP diagnosis that was highest in the hierarchy of primary and secondary diagnoses. For number of SIP emergency admissions, we counted a new admission when the discharge date for the previous SIP emergency hospitalization was at least a week ago. Two or more were considered repeated emergency admissions.

Schizophrenia spectrum disorder and bipolar disorder

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

Statistical analyses

Subjects were followed from the first SIP 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 SIP 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 the gender- and age group adjusted hazard ratios (HRs) with 95% confidence intervals (CI) for transition from SIP to schizophrenia spectrum disorder or bipolar disorder. Due to an interaction between gender and age group for the schizophrenia-outcome, some analyses were stratified for gender. In the analyses where schizophrenia spectrum disorder was the end point and both genders were included in the data set, we also included an interaction term (the interaction between gender and age group) in addition to gender and age group in the statistical model.

We investigated how gender, age, number of SIP emergency admissions, and SIP type, affected the transition rates. The number of SIP emergency admissions was entered as a time-varying covariate. When investigating the effect of substance-specific type of SIP on risk of transition, the SIP type with the lowest cumulative transition was chosen as reference category. When investigating the effect of age on the risk of transition, the youngest age group was chosen as reference category.

Due to few individuals in each SIP group for opioids, sedatives, cocaine, hallucinogens and volatile solvents, results for these SIPs from the Cox regression analyses are not presented. Results in cells with less than 10 cases are not shown. The analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, N.C.).

Ethics

All patient data were fully de-identified when accessed by the investigators. In Norway, studies with de-identified information from medical health registries do not require participant consent. Legal basis and exemption from professional secrecy requirements for the use of personal health data in research was granted by the regional committee for medical and health research ethics (2014/72/REK Nord).

Results

The study included 3,187 SIP cases, with a mean age of 33.6 (SD=12.3) years at the time of the SIP. 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 amphetamines-induced psychosis and 1,235 (38.8%) with psychosis induced by multiple substances. Psychosis induced by opioids, sedatives and hypnotics, cocaine, hallucinogens, and volatile solvents occurred more seldom, with less than 70 individuals in each SIP category. A total of 484 individuals (15.2% of the total sample) had more than one type of specific SIP during the observation period, of which 179 (37.0%) were diagnosed with a 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 SIP diagnose on the first episode. The mean age for the different SIP categories was lowest for cannabis-induced psychosis (26.7 years), and highest for alcohol-induced psychosis (47.0 years).

Transition from SIP to schizophrenia spectrum disorder or bipolar disorder

Among the 3,187 individuals with SIP, 636 were diagnosed with schizophrenia spectrum disorder during follow up (Table 1). The six-year cumulative hazard for transition from SIP to schizophrenia spectrum disorder was 27.6%; 28.6% in men and 24.8% in women. It was highest among those with cannabis-induced psychosis and lowest for alcohol-induced psychosis, and highest for the youngest patients.

The median time from SIP to a diagnosis of schizophrenia spectrum disorder was 0.8 years (Q1-Q3=0.2-1.9). Within the first year of the index SIP, 56.4% of the observed transitions had occurred, the figures being 76.7%, 90.4% and 96.4% after two, three and four years, respectively.

A total of 100 individuals were diagnosed with bipolar disorder during follow up. The cumulative transition from SIP to bipolar disorder was 4.5%, with higher transition in women (7.1%) than in men (3.5%).

The median time from SIP to a diagnosis of bipolar disorder was 1.0 year (Q1-Q3=0.2-2.0). Within the first year of the index SIP, 52.0% of the observed transitions had occurred, the figures being 77.0%, 87.0% and 95.0% after two, three and four years, respectively.

Insert Table 1 about here.

The cumulative transition to schizophrenia spectrum disorder or bipolar disorder for psychosis induced by alcohol, cannabis, multiple substances, and other substances during the six-year observation period is depicted in Figure 1. Cannabis-induced psychosis transitioning to schizophrenia spectrum disorder was the type of SIP with highest and steepest curve. For this SIP, all the diagnostic changes occurred within a little more than three years, after which there were no more cases of transition to schizophrenia spectrum disorder.

Insert Figure 1 about here.

Predictors of transition

Higher age was associated with lower HR for transition from any SIP 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 SIP emergency admissions.

Compared with alcohol-induced psychosis, psychosis induced by cannabis (HR=2.66, 95% CI=1.72-4.10) and multiple substances (HR=1.73, 95% CI=1.15-2.61) were in men

associated with higher risk of transition to schizophrenia spectrum disorder, persisting after adjustment for age. Also in women, the results suggested that cannabis-induced psychosis was the type of SIP with highest risk of transition to schizophrenia spectrum disorder (HR=1.95, 95% CI=0.95-3.98).

Compared to men, women had higher risk of transition from any SIP to bipolar disorder (HR=2.02, 95% CI=1.35-3.02) (Table 3). Number of SIP emergency admissions and type of SIP did not affect the risk of transition to bipolar disorder, and apart from the age group 36-40 years, neither did age. There were, however, few individuals in each group in these analyses.

Insert Tables 2 and 3 about here

Additional description of the data, and sensitivity analyses

To explore the consequences of variable definitions and the choices made when preparing data for analyses, three sensitivity analyses were conducted.

To explore how our definition of the psychosis outcome impacted the results, we conducted sensitivity analyses with schizophrenia defined as F20 only. Because of fewer washout-diagnoses (F20, F30-F31), this gave a somewhat larger sample, 3,755 SIP cases. The cumulative hazard from any SIP to schizophrenia, defined as ICD-10 code F20 only, was 18.8%. In men, lower age, repeated emergency admissions (HR = 2.53, 95% CI 1.91-3.34) and psychosis induced by cannabis (HR = 3.20, 95% CI 1.80-5.70) and multiple substances (HR = 2.17, 95% CI 1.25-3.79) was associated with increased risk of transition. In women, repeated emergency admissions (HR = 3.00, 95% CI 1.66-5.44) and cannabis induced psychosis (HR = 4.82, 95% CI 1.35-17.28) was associated with increased risk of transition. The results are provided in supplementary tables S1 and S2.

A total of 34 individuals had both schizophrenia spectrum disorder and bipolar disorder during the observation period. We conducted sensitivity analyses where these were categorized according to the last diagnosis rather than the first, which gave 623 individuals with schizophrenia spectrum disorders and 113 individuals with bipolar disorder. The cumulative transition rate from any SIP to schizophrenia spectrum disorder was 27.1% and to bipolar disorder 5.2%. The results of regression analyses did not change noteworthy. The exception was cannabis-induced psychosis, which was associated with increased risk of transition to schizophrenia spectrum disorder also for women (HR = 2.13, 95% CI 1.01-4.52) and to bipolar disorder for both genders (HR =2.13, 95% CI 1.12-4.02).

Lastly, to explore the consequence of length of washout period, we conducted a sensitivity analysis with a four-year washout instead of two years. This gave 2,228 SIP cases, of which 397 were later diagnosed with schizophrenia spectrum disorder and 51 with bipolar disorder. The cumulative transition rate from any SIP to schizophrenia spectrum disorder was 25.8% and to bipolar disorder 3.1%. The risk for transition to schizophrenia spectrum disorder in men was increased for the younger and those with repeated emergency admissions (HR=2.02, 95% CI 1.45-2.83), and among the different substance-specific SIPs it was highest for cannabis-induced psychosis (HR = 2.57, 95% CI 1.42-4.68). In women, repeated emergency admissions were associated with increased risk of transition from SIP to schizophrenia (HR = 1.82, 95% CI 1.03-3.20). No significant associations were found for the transition from SIP to bipolar disorder.

Discussion

In this study of more than 3,000 cases of SIP, the six-year cumulative transition rate to schizophrenia spectrum disorder was 27.6%, with highest rate for cannabis-induced psychosis (36.0%). The risk of transition from SIP to schizophrenia spectrum disorder increased by younger age in men, and by more SIP emergency admissions in both genders. The importance of these three factors in men: younger age, repeated emergency admissions and cannabis-induced psychosis, was repeated in three sets of sensitivity analyses, suggesting they are robust to nuances in definitions of variables and choices of data handling.

The transition rate from SIP to bipolar disorder was 4.5%, with higher transition in women, and with risk of transition not affected by number of SIP emergency admissions or type of SIP. When counting last rather than the first diagnosis, increasing the number of individuals with bipolar disorder to 113, cannabis-induced psychosis was associated with increased risk of transition from SIP to bipolar disorder.

Transition to schizophrenia spectrum disorder

The cumulative risk of transition to schizophrenia spectrum disorder in our study of 27.6% resembles the estimate from a recent meta-analysis (5). In our sensitivity analyses, the transition was almost similar when using a four-year washout, but somewhat lower (18.8%) when using schizophrenia only (F20) as outcome. The first large study comparable to ours used schizophrenia spectrum disorders (F20, F22-F23) as the outcome. It did not report pooled transition rate for any SIP, but found high transition rates for some specific SIPs (3). Three later studies have used schizophrenia (F20) as outcome, but with wide range in transition rates for any SIP, from 11% to 26% (6-8). Some studies have long follow up, which may increase estimates, but still, Kendler and colleagues found a relatively low cumulative risk of transition of 11% even with a 19 years follow-up (6). They did, however, recruit a

large portion of their sample (40%) from primary care and outpatient facilities, with possibly less severe illness.

Comparable to previous studies, we found highest transition rate for cannabis-induced psychosis and lowest for alcohol-induced psychosis (3, 6, 7). Cannabis use has long been considered a risk factor for schizophrenia (13, 14). Young age of cannabis initiation (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 has been increased prevalence of self-reported psychosis (21), incidence of schizophrenia (22), and of population attributable risk fraction for cannabis in schizophrenia (23). Though this may suggest a dose-response relationship and a causal relationship between cannabis and schizophrenia, genetic or familial factors and reversed 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 in our study only found in men. Previous studies have described lower age of the SIP as 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 SIP to schizophrenia spectrum disorder in men in the main analyses and all sensitivity analyses, and for 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 towards schizophrenia.

The age groups with 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 twenties (26). In our sample, those with repeated emergency admissions were somewhat younger than those with none or only one, and cannabis-induced psychosis was the type of SIP with lowest mean age. These associations, between younger age, cannabis use and multiple SIP admissions, 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 from SIP to bipolar disorder of 4.5% over six years was as expected somewhat lower than the Danish study with 20 years observation time and a transition rate of 8.4% (7). Our transition rate of 4.9% for cannabis-induced psychosis is comparable with a study following patients with cannabis-induced psychosis for eight years, where 5.6% were later diagnosed with manic episode or bipolar disorder (12). Although the few studies on transition from SIP to bipolar disorder differ regarding observation time, type of SIP, and the definition of bipolar disorder (only bipolar disorder or also manic episode), 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 higher risk of transition from SIP to bipolar disorder in women. Interestingly, a higher transition rate from SIP to bipolar disorder among women was also found in a previous study (7).

The diagnostic entity SIP

SIP is one of the few diagnoses defined by its assumed aetiology. However, the causal role of substance use implied by the name has been criticized (28). Both the probability of having a SIP, and the risk of the SIP transitioning to schizophrenia, are impacted by familial risk for psychosis (6). The current study, as earlier studies, shows high transition rates to schizophrenia. Particularly high rates are found for cannabis-induced psychosis, 36% in our study, which is comparable to transition rates to schizophrenia for brief, atypical and not otherwise specified psychosis (5), and for those at ultra-high risk of psychosis (29). As many countries have separate treatment systems for mental disorders and addiction, the fact that SIP today 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 SIP from patients in a prodromal phase with acute psychotic symptoms related to substance use, or consecutive SIP episodes with gradual health impairment, seems not only difficult, but also maybe neither possible nor meaningful. In our view, accumulated evidence raises the question of whether SIP would be more appropriate to consider within the schizophrenia spectrum. A continuity perspective and a stress-vulnerability model has been suggested by the authors as a more nuanced perspective on these clinical phenomena (30).

Limitations and strengths

Having only a two-year washout-period before the SIP is a limitation of this study, as we cannot be certain that these cases are in fact incident. However, analyses based on a 4-year washout period repeated 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 rests on diagnostic codes, and thus, on the validity of the diagnostic practices. These may be of varying quality, and we cannot rule out that they vary systematically. It may for instance be that the knowledge about cannabis use as a risk factor for schizophrenia affect clinicians and

hence diagnostic practices in such a way that cannabis-induced psychosis is quicker reassessed as schizophrenia, compared to other types of SIP. Fourth, a specific SIP diagnosis cannot be interpreted as exposure for that substance only, as many patients are poly-drug users. Fifth, we only included SIPs treated in the specialized health care. This is less of a problem, as to our knowledge, SIPs are rarely treated in the municipal health services.

It is a strength of the study that it has a relatively large sample, including all patients with SIP in a country with a comprehensive health care system with free access to care, over a period of six years.

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

References

1. World Health Organization. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines: World Health Organization; 1992.
2. Caton CLM, Hasin D, Shrout PE, et al. Stability of early-phase primary psychotic disorders with concurrent substance use and substance-induced psychosis. Br J Psychiatry. 2007;190: 105-111.
3. Niemi-Pynttäri J, Sund R, Putkonen H, et al. Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases. J Clin Psychiatry. 2013;74(1): e94-99.
4. Whitty P, Clarke M, McTigue O, et al. Diagnostic stability four years after a first episode of psychosis. Psychiatr Serv. 2005;56(9): 1084-1088.
5. Murrie B, Lappin J, Large M, et al. Transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-analysis. Schizophr Bull. 2020;46(3): 505-516.
6. Kendler KS, Ohlsson H, Sundquist J, et al. Prediction of onset of substance-induced psychotic disorder and its progression to schizophrenia in a Swedish national sample. Am J Psychiatry. 2019;176(9): 711-719.
7. Starzer MSK, Nordentoft M, Hjorthøj C. Rates and predictors of conversion to schizophrenia or bipolar disorder following substance-induced psychosis. Am J Psychiatry. 2017;175(4): 343-350.
8. Alderson HL, Semple DM, Blayney C, et al. Risk of transition to schizophrenia following first admission with substance-induced psychotic disorder: a population-based longitudinal cohort study. Psychol Med. 2017;47(14): 2548-2555.
9. Rognli EB, Bramness JG, von Soest T. Cannabis use in early adulthood is prospectively associated with prescriptions of antipsychotics, mood stabilizers, and antidepressants. Acta Psychiatr Scand. 2020;141(2): 149-156.
10. Van Laar M, Van Dorsselaer S, Monshouwer K, et al. Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? Addiction. 2007;102(8): 1251-1260.

11. Rowland TA, Marwaha S. Epidemiology and risk factors for bipolar disorder. Ther Adv Psychopharmacol. 2018;8(9): 251-269.

12. Arendt M, Rosenberg R, Foldager L, et al. Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases. Br J Psychiatry. 2005;187(6): 510-515.

13. Andréasson S, Engström A, Allebeck P, et al. Cannabis and schizophrenia A longitudinal study of swedish conscripts. Lancet. 1987;330(8574): 1483-1486.

14. Marconi A, Di Forti M, Lewis CM, et al. Meta-analysis of the association between the level of cannabis use and risk of psychosis. Schizophr Bull. 2016;42(5): 1262-1269.

15. Arseneault L, Cannon M, Poulton R, et al. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ. 2002;325(7374): 1212-1213.

16. Radhakrishnan R, Wilkinson ST, D'Souza DC. Gone to Pot–A Review of the Association between Cannabis and Psychosis. Front Psychiatry. 2014;5.

17. Moore TH, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet. 2007;370(9584): 319-328.

18. Di Forti M, Quattrone D, Freeman TP, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. Lancet Psychiatry. 2019;6(5): 427-436.

19. Di Forti M, Marconi A, Carra E, et al. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. The Lancet Psychiatry. 2015;2(3): 233-238.

20. Chandra S, Radwan MM, Majumdar CG, et al. New trends in cannabis potency in USA and Europe during the last decade (2008–2017). Eur Arch Psychiatry Clin Neurosci. 2019;269(1): 5-15.

21. Livne O, Shmulewitz D, Sarvet AL, et al. Association of cannabis use–related predictor variables and self-reported psychotic disorders: US adults, 2001–2002 and 2012–2013. Am J Psychiatry. 2021: appi. ajp. 2021.21010073.

22. Kühl JOG, Laursen TM, Thorup A, et al. The incidence of schizophrenia and schizophrenia spectrum disorders in Denmark in the period 2000–2012. A register-based study. Schizophr Res. 2016;176: 533-539.

23. Hjorthøj C, Posselt CM, Nordentoft M. Development over time of the population-attributable risk fraction for cannabis use disorder in schizophrenia in denmark. JAMA psychiatry. 2021;78(9): 1013-1019.

24. Gillespie NA, Kendler KS. Use of genetically informed methods to clarify the nature of the association between cannabis use and risk for schizophrenia. JAMA psychiatry. 2021;78(5): 467-468.

25. Rognli EB, Taipale H, Hjorthøj C, et al. Annual incidence of substance-induced psychoses in Scandinavia from 2000 to 2016. Psychol Med. 2022: 1-10.

26. Messias EL, Chen C-Y, Eaton WW. Epidemiology of schizophrenia: review of findings and myths. Psychiatr Clin North Am. 2007;30(3): 323-338.

27. Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA. 1996;276(4): 293-299.

28. Mathias S, Lubman DI, Hides L. Substance-induced psychosis: a diagnostic conundrum. J Clin Psychiatry. 2008;69(3): 358-367.

29. Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry. 2012;69(3): 220-229.

30. Bramness JG, Gundersen ØH, Guterstam J, et al. Amphetamine-induced psychosis-a separate diagnostic entity or primary psychosis triggered in the vulnerable? BMC psychiatry. 2012;12(1): 221.

Table 1. Number of individuals with SIP according to gender, age at index diagnosis, number of SIP emergency admissions, and types of SIPs, and cumulative hazard for being diagnosed with schizophrenia spectrum disorder or bipolar disorder during follow-up

	Patients	Age at index diagnosis		Transition to schizophrenia			Transition to bipolar disorder		
	n	Mean (SD)		Cum hazard%	(95% CI)	(n)	Cum hazard%	(95% CI)	(n)
Any SIP	3,187	33.6	(12.3)	27.6	(25.6-29.7)	(636)	4.5	(3.6-5.5)	(100)
Any SIP, men	2,341	33.3	(12.1)	28.6	(26.2-31.2)	(482)	3.5	(2.6-4.5)	(59)
Any SIP, women	846	34.3	(13.0)	24.8	(21.2-28.8)	(154)	7.1	(5.1-9.7)	(41)
Any SIP and age at index diagnosis									
18-25	1,090			32.7	(29.1-36.7)	(265)	4.4	(3.0-6.4)	(32)
26-30	570			32.9	(28.1-38.3)	(136)	5.1	(3.2-8.0)	(20)
31-35	410			27.8	(22.4-34.2)	(78)	4.4	(2.4-8.3)	(11)
36-40	331			22.2	(17.1-28.7)	(52)	6.8	(4.3-10.6)	(18)
41-45	255			22.2	(16.5-29.3)	(42)	< 10 cases		
46-50	208			20.7	(14.6-29.0)	(31)	< 10 cases		

51-79	323			13.8	(9.3-20.1)	(32)		< 10 cases	
Number of SIP emergency admissions									
No emergency admissions	793	32.9	(12.4)	21.5	(18.2-25.4)	(113)	4.7	(3.1-7.3)	(24)
One emergency admission	1,679	34.3	(13.0)	23.8	(21.3-26.5)	(254)	4.7	(3.5-6.1)	(57)
Repeated emergency admissions	715	32.4	(10.2)	39.4	(34.8-44.4)	(269)	3.6	(2.3-5.7)	(19)
SIP type									
Alcohol induced psychosis	453	47.0	(14.9)	13.2	(9.8-17.8)	(45)	4.6	(2.7-7.7)	(15)
Opioids induced psychosis	67	39.9	(13.0)	16.5	(9.2-28.8)	(10)		< 10 cases	
Cannabis induced psychosis	562	26.7	(8.0)	36.0	(31.4-41.0)	(157)	4.9	(3.1-7.7)	(20)
Sedatives and hypnotics induced psychosis	67	40.0	(13.0)	18.5	(10.3-31.9)	(10)		< 10 cases	
Cocaine induced psychosis	23	28.0	(7.3)		< 10 cases			< 10 cases	
Amphetamines induced psychosis	707	33.0	(9.7)	25.0	(21.1-29.5)	(125)	3.8	(2.3-6.3)	(18)
Hallucinogens induced psychosis	69	28.4	(11.5)		< 10 cases			< 10 cases	
Volatile solvents induced psychosis	4	30.3	(13.5)		< 10 cases			< 10 cases	
SIP induced by multiple substances	1,235	31.8	(10.1)	32.0	(28.5-35.8)	(279)	4.5	(3.2-6.2)	(40)

Table 2. Hazard ratio for transition from SIP to schizophrenia spectrum disorder, stratified by gender, and according to age group, number of SIP emergency admissions and SIP type

	Men					Women				
		Unadjusted		Adjusted[a]			Unadjusted		Adjusted[a]	
	n	HR	(95% CI)	HR	(95% CI)	n	HR	(95% CI)	HR	(95% CI)
Age group at first SIP										
Age 18-25	786	1.00	ref	1.00	ref	304	1.00	ref	1.00	ref
Age 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)
Age 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)
Age 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)
Age 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)
Age 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)
Age 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)
SIP emergency admissions										
No emergency admissions	588	1.00	ref	1.00	ref	219	1.00	ref	1.00	ref
One emergency admission	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)

Repeated emergency admissions	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)
SIP type										
Alcohol-induced psychosis	330	1.00	ref	1.00	ref	123	1.00	ref	1.00	ref
Cannabis-induced psychosis	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-induced psychosis	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)
SIP induced by other substances[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)
SIP induced by 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 were adjusted for age group (26-30, 31-35, 36-40, 41-45, 46-50 and 51-79 years at index SIP), with age 18-25 years as reference.

[b] Other substances: opioids (F11), sedatives and hypnotics (F13), cocaine (F14), hallucinogens (F16) and volatile solvents (F18)

Table 3. Hazard ratio for transition from SIP to bipolar disorder, according to gender, age group, number of SIP emergency admissions, and SIP type

	Unadjusted		Adjusted[a]	
	HR	(95% CI)	HR	(95% CI)
Gender				
Men	1.00	ref	1.00	ref
Women	1.89	(1.27-2.82)	2.02	(1.35-3.02)
Age group at first SIP				
Age 18-25	1.00	ref	1.00	ref
Age 26-30	1.14	(0.65-1.99)	1.29	(0.73-2.26)
Age 31-35	0.89	(0.45-1.77)	1.02	(0.51-2.05)
Age 36-40	1.79	(1.00-3.19)	1.91	(1.05-3.47)
Age 41-45	1.00	(0.46-2.18)	1.05	(0.48-2.31)
Age 46-50	0.64	(0.22-1.80)	0.60	(0.21-1.74)
Age 51-79	0.79	(0.35-1.79)	0.66	(0.27-1.64)
SIP emergency admissions				
No emergency admissions	1.00	ref	1.00	ref

One emergency admission	1.29	(0.80-2.09)	1.36	(0.83-2.21)
Repeated emergency admissions	1.25	(0.68-2.30)	1.34	(0.71-2.51)
SIP type				
Alcohol-induced psychosis	1.40	(0.71-2.79)	1.78	(0.85-3.74)
Cannabis-induced psychosis	1.55	(0.82-2.93)	1.75	(0.90-3.39)
Amphetamines-induced psychosis	1.00	ref	1.00	ref
SIP induced by other substances[b]	1.30	(0.54-3.11)	1.40	(0.58-3.40)
SIP induced by multiple substances	1.27	(0.73-2.21)	1.31	(0.75-2.28)

[a] Estimates of gender were adjusted for age group (26-35, 31-35, 36-40, 41-45, 46-50 and 51-79 years at index SIP, with age 18-25 years as reference) and estimates of age group were adjusted for gender. Other estimates were adjusted for gender and age group.

[b] Other substances: opioids (F11), sedatives and hypnotics (F13), cocaine (F14), hallucinogens (F16) and volatile solvents (F18).

Figure 1. Cumulative transition rate to schizophrenia spectrum disorder and bipolar disorder following substance-induced psychosis

Schizophrenia spectrum disorder

Bipolar disorder