Relapse in Substance-Induced Psychosis and Associated Risk Factors. A Nationwide Register-Linkage Study from Sweden

Running head: SIP relapse and associated risk factors

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Declaration of interest

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Abstract

Background and Aims: Substance-induced psychoses (SIP) have the potential to relapse and convert into schizophrenia-spectrum disorders. However, risk factors associated with SIP relapse remain unknown. The aim of this study was to measure the incidence and risk of SIP relapse and associating risk factors.

Design, setting and participants: Population based register study that identified people with first-time SIP between 2006 and 2016 (n=7320) from Swedish nation-wide registers to examine incidence of relapse and associated risk factors during 2-year follow-up. Participants were censored to death, emigration and the diagnosis of other psychotic illness. Risk factors associated with relapse were studied using multivariable Cox models.

Measurements: SIP was measured via related diagnostic codes (ICD-10: F1x.5) collected from the National Patient Register (NPR). SIP relapse was measured as hospitalization due to SIP during 2-year follow-up also collected from the NPR. Potential risk factors included demographic characteristics, psychiatric comorbidities, sickness absence and disability pension collected from nationwide registers.

Findings: Of the study population (n=7320), 20.0% (N=1463) had a SIP relapse during the follow-up (median time 126 days, interquartile range 56-321) and 83.3% had the same type of SIP as their first SIP. Relapse was most common for those whose first SIP was induced by cannabis (25.7%), followed by multi-substance use (23.8%) and (meth)amphetamine (19.7%). Factors associated with SIP relapse were previous substance use disorder (hazard ratio (HR) 1.37, 95% confidence interval 1.20-1.56), younger age (16-29 years, HR 1.29, 1.05-1.58, versus 50-65), being born abroad (HR 1.23, 1.07-1.41), attention deficit hyperactivity disorder (HR 1.21, 1.05-1.39), having had 1-90 days sick leave during the previous year (HR 1.19, 1.01-1.44), and cannabis- (HR 2.42, 1.98-2.96), (meth)amphetamine- (HR 1.49, 1.23-1.81) or multi-substance- (HR 1.81, 1.52-2.15) induced psychosis compared with alcohol-induced psychosis.

Conclusions: In Sweden, 20% of people with substance-induced psychosis between 2006 and 2016 had a relapse within two years follow-up. Cannabis-induced psychosis had the shortest time lapse between episodes. Risk factors for relapse included attention deficit hyperactivity disorder, substance-use disorder, younger age, previous sickness absence and being born outside Sweden.

keywords: substance-induced psychosis, relapse, substance use disorder, psychotic disorders, cannabis-induced psychosis, ADHD, register study

INTRODUCTION

Substance-induced psychoses (SIP) are defined by International Classification of Diseases, Tenth Edition (ICD-10), as psychotic episodes provoked by substance use. By definition of the ICD-10, SIP episodes persist even after cessation of substance use but resolve within a short period (1). In recent years, research on SIP has focused on understanding whether, and to what extent, SIP is clinically distinct from other psychotic disorders. Existing research has compared SIP with other psychotic disorders, both with and without concurrent substance use (2–5) as well as clinical course, diagnostic stability and outcome of SIP (6–11). In accordance with the ICD-10 definition, SIP has traditionally been viewed as a self-resolving episode, that is easier to manage than other psychotic disorders (10,12). However, recent literature also suggests a possible chronic course for SIP. For example, several studies have reported a high conversion rate of SIP to schizophrenia spectrum disorders, ranging from 20-40%, depending on the study and substance (13–16). Furthermore, concurrent substance use has been associated with higher relapse and worse outcomes in psychotic disorders (17).

Previous studies indicate that SIP has the potential to relapse (7,11,18,19). However, research on this topic is limited, mostly descriptive and focuses on comparing SIP with other psychotic disorders. Studies comparing the outcomes of SIP with other psychotic disorders have reported similar relapse rates for both (5,20,21). To date, there is a paucity of knowledge regarding relapse of substance-induced psychosis. Therefore, our aims are 1) to report the incidence of SIP relapses utilizing nationwide register-data, and 2) to identify risk factors associated with SIP relapse, focusing on clinical and socioeconomic characteristics such as psychiatric comorbidity, unemployment and disability pension.

METHODS

Data sources and study design

In this retrospective study of prospectively collected data from national Swedish register and databases we identified all patients with a registered first-time substance-induced psychosis (SIP) during 2006-2016, aged 16-65 years. The data on SIP diagnoses was derived from the National Patient Register (NPR) (22) holding data of psychiatric inpatient care in Sweden from 1968, as well as information on specialized outpatient care since 2001 and onwards.

Information on sociodemographic background was derived from the Total Population Register (23). The Total Population Register holds records of sex, birth, death, and migration for all Swedish residents. The LISA register includes data on age, sex, family situation, place of residence, educational level, unemployment, and income from work. The MiDAS register provided information on sickness absence spells since 2005 (diagnosis, grade, start and end dates) as well as disability pensions since 1994. Individual data from these registers was linked through a de-identified identification number assigned to each Swedish resident at time of birth or immigration (24).

Substance-induced psychosis

SIP was defined with the following ICD-10 codes: F10.5 (caused by alcohol), F11.5 (opioids), F12.5 (cannabis), F13.5 (hypnotics), F14.5 (cocaine), F15.5 (other stimulants), F16.5 (hallucinogens), F18.5 (volatile solvents), and F19.5 (multiple/unspecified). These SIP diagnoses were pooled into five categories according to substance: alcohol, cannabis, (meth)amphetamine, multiple/unspecified and other (hallucinogens, cocaine, opioids, solvents, and sedatives). The category of multiple/unspecified substance (F19.5) is used when there is indication of concomitant use of multiple substances or when the substance cannot be identified. The category of other substances was pooled together due small sample size in each five groups. We included individuals

with a first-time SIP diagnosis during 2006-2016, and without any prior SIP diagnosis during 1997-2005 or a history of non-affective psychosis (F20-F29), organic catatonic disorder (F06.1), bipolar disorder/mania (F30-F31), or residual psychotic disorder following substance use (F1X.7).

We then screened any SIP relapses over a two-year follow-up period extending from the date of baseline SIP until SIP relapse, diagnosis of a psychotic illness (ICD-10 F20-F29), emigration, death, two years with no event, or until 31.12.2018. SIP relapse was defined as a psychiatric hospitalization due to a registered SIP (any substance) occurring at least 30 days after the baseline SIP. The 30-day interval was chosen in order to distinguish separate SIP episodes. Inpatient care associated with initial SIP diagnosis and length of hospital stay was recorded. We also screened the cohort for any inpatient or outpatient visits due to substance use during the first 30 days after the initial SIP. A pooled two-class variable (any SIP relapse vs. no SIP relapse) was used for the analysis. Censoring events were (inpatient or specialized outpatient) diagnosis of a non-affective psychotic disorder F20-F29 or bipolar disorder F30-F31, emigration, death or end of follow-up time or 31.12.2018. We also evaluated SIP relapse rates by substance (in days) and constructed cumulative incidence graphs. In order to evaluate coverage of the two-year follow-up period, we analyzed relapse rates also over a five-year follow-up.

Sociodemographic background

Sociodemographic characteristics were recorded at the time of first SIP diagnosis, and two groups were compared: a.) No SIP relapse during follow-up and b.) Any SIP relapse during follow-up. The sociodemographic characteristics included in the analyses were age, place of birth, level of education, region of residence and family status. Age was categorized into three groups: 18-29 years, 30-49 years, and 50-65 years. Place of birth was classified into two categories: Sweden or

abroad. Family status was categorized into five groups: married without children at home, married with children, single without children, single with children, and individuals under 20 years old living at home. Region of residence was classified into three groups: large city, medium-sized city, and small city or village. Educational level was categorized into four groups: low (less than 9 years), medium (10-12 years), high (more than 13 years), and unknown.

Work and income-related characteristics included any income from work (during the previous calendar year, yes/no), ongoing disability pension at the time of diagnosis (yes/no), sickness absence during the previous year (no sickness absence, less than 90 days, more than 90 days), and long-term unemployment during the previous calendar year (no, less than 180 days, more than 180 days). The choice of sociodemographic variables was based on previous studies in other psychotic disorders.

Psychiatric comorbidities

Psychiatric comorbidities (measured at baseline and since 1997) were collected from the NPR, covering both inpatient and outpatient care. The psychiatric diagnoses included in the analysis were depression (F32-33), anxiety disorders (F40-F43), substance-use disorders (F10-16, F18-19), eating disorders (F50), attention-deficit/hyperactivity disorder (ADHD, F90), mental retardation (F70-79), autism spectrum disorders (F84), and a pooled variable of any mental or behavioral disorder (F00-F99). Also, the history of suicide attempts or other self-harm was examined (ICD-codes X60-X84 and Y10-Y34). A two-class variable for each diagnosis (yes/no) was used for the analyses.

Statistical methods

Associations between sociodemographic categorical variables and SIP relapse was analyzed with crosstabulations and Pearson's chi-square test. Age was summarized using mean and standard deviation (SD). Pearson's chi-square test was used to identify associations between psychiatric comorbidities and SIP relapse. Crude hazard ratio (HR) with 95% confidence-interval (CI) were calculated for each variable.

Time to SIP relapse (overall and for each SIP group respectively) was calculated in days and summarized using median and interquartile range (IQR). Cumulative incidence graph was made to illustrate differences.

In order to evaluate risk factors associated with SIP relapse, a multivariable Cox regression analysis was performed. Outcome was any SIP relapse defined as rehospitalization due any F1x.5 diagnosis. Evaluated risk factors included in the multivariable model were sociodemographic characteristics, sickness absence, disability pension, psychiatric comorbidities, and baseline SIP by substance. The models were tested for proportional hazard assumption.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. The study is a register-based study, thus individuals aren't identified in the results. The analysis was not pre-registered and results should be considered exploratory. The project was approved by the Regional Ethical Review Board, Karolinska Institutet, Stockholm, Sweden (Dnr: 2007/762-31 and Dnr 2021-06441-02).

RESULTS

We identified 7320 substance-induced psychoses from the NPR. Among these, 35.0% (N=2561) were unspecified/multi-substance-induced, 25.3% (N=1851) alcohol-induced, 17.7% (N=1292) (meth)amphetamine-induced, 16.2% (N=1184) cannabis-induced, and 5.9% (N=432) was induced by a substance in the pooled category (hallucinogens, cocaine, solvents, opioids or sedatives).

During the two-year follow-up period, 20.0% (N=1463) of the individuals with baseline SIP (N=7320) relapsed. Relapse was most common for those with cannabis-induced SIP at baseline, with 25.7% experiencing a relapse, followed by unspecified/multi-substance use (23.8%) and (meth)amphetamine (19.7%). The lowest relapse rate was observed among alcohol-induced SIP (12.8%). During the two-year follow-up, 522 individuals had more than one SIP relapse (i.e., 35.7% of 1463 persons with SIP relapse had multiple relapses).

Of the study cohort, 78.1% (N=5715) had inpatient care period at their first SIP diagnosis (no difference between those who experienced SIP relapse vs. did not, 77.4% vs. 78.2%, respectively). Median duration of inpatient care at initial SIP was 3 days, IQR 2-7 days. During the first 30 days after initial SIP, 24.4% (N=1785) had an inpatient or outpatient visit due to substance use: 8.3% (N=605) had a planned visit, 12.7% (N=928) had an unplanned visit and 3.4% (N=252) had both planned and unplanned visit (data not shown in tables).

Censoring events or end-of follow up without events (N=5857) were distributed as follows: the majority, 76.9% (N=4503) had neither SIP relapse nor a censoring event during the two-year follow-up, 5.0% (N=293) died, and 1.0% (N=59) emigrated. During the follow-up period, 17.1% (N=1002) of all SIP cases were diagnosed with any non-affective psychotic disorder. The highest rate for receiving a diagnosis of any psychotic or bipolar disorder during the two-year follow-up

was observed for cannabis-SIP at baseline (26.7%, n=316/1184) and lowest rate for alcohol-SIP at baseline (6.5%, n=120/1851) (See Supplement Tables 1-2).

In the univariate analyses, factors associated with SIP relapse were low level of education, place of birth outside Sweden, familial status of single with no children and having no children under 20 years old living at home, younger age, living in a large city, short-term unemployment (less than 180 days) and no disability pension at the time of diagnosis. Mean age for people with SIP relapse was 32.5 vs. 36.3 for people with only baseline SIP. Furthermore, compared to alcohol-induced SIP as the reference-group, cannabis, (meth)amphetamine and unspecified/multi-substance-induced SIP were each associated with an increased risk of SIP relapse. (Table 1)

The psychiatric comorbidities associated with SIP relapse in the univariate analyses were ADHD, anxiety disorders, personality disorders, intellectual disability, previous substance-use disorder (SUD), and having any psychiatric or behavioral disorder (Table 1).

[Please insert Table 1 here]

The median time in days to SIP relapse during the two-year follow-up period was 126 days (IQR 56-321). The shortest time to relapse was observed for cannabis-induced SIP at baseline, with a median of 89 days (IQR 49-286), compared to 122 days (IQR 53-322) for multiple/unspecified substance, 138 days (IQR 50-331) for the pooled group of substances, 148 (IQR 65-355) days for alcohol and 152 (IQR 68-373) days for (meth)amphetamine (Table 2, Figure 1).

[Please insert Table 2 here]

In extended follow-up of five-years we found that mean times to relapse across all SIP types were within the first two years: 270 days for cannabis, 361 days for the multiple group, 387 days for alcohol, 414 days for stimulants, and 438 days for the pooled group of other substances. Extending the follow-up period to five years resulted in a modest increase in the number of relapse cases (Supplementary Table 3). However, extending the follow-up period resulted in higher observed mortality rates and increased conversion to F20-F29 diagnoses (data not shown in tables).

SIP relapse was predominantly induced by the same substance as the baseline SIP: 83.3% (N=1220) had the same SIP type at relapse. Alcohol-induced psychosis was the most stable: 91.5% (N=216) had the same SIP type, whereas the highest variability was observed in the pooled class of five substances (hallucinogens, sedatives, opioids, solvents, and cocaine): a second SIP by the same substance was recorded in 67.8% (N=40). The most common substance change was towards multiple/unspecified group (Table 2, Figure 2).

In the multivariate Cox regression model, independent risk factors for SIP relapse were previous SUD (HR 1. 37, 95% CI 1.20–1.56), ADHD (HR 1.20 95%CI 1.05–1.39), younger age (16-29 years HR 1.94, 95% CI 1.66-2.27-, and 30-49-years HR 1.41, 95% CI 1.19-1.66), being born abroad (HR 1.23, 95% 1.07-1.41) and sickness absence of 1-90 days during the previous year (HR 1.19, 95% CI 1.01-1.44). Also, cannabis- (HR 2.42, 95% CI 1.98-2.96), (meth)amphetamine- (HR 1.49, 95% CI 1.23-1.81) and multi-substance- (1.81, 95% CI 1.52-2.15) induced psychosis was associated with SIP relapse in the multivariate model.

DISCUSSION

To our knowledge, this is the first longitudinal, population-based study to examine risk factors for relapse in substance-induced psychosis (SIP). We found that 20% of people with SIP experienced a SIP relapse within the two-year follow-up period, with a median time to relapse of 126 days (IQR 56-321). We identified ADHD, previous SUD, previous sickness absence 1-90 days, younger age, being born abroad, and cannabis, (meth)amphetamine or multi-substance induced psychosis as independent risk factors for SIP relapse as statistically significant risk factors for SIP relapse.

This study found that cannabis-induced SIP had the highest relapse rate, while alcohol-induced SIP had the lowest. Comparing our findings with previous studies is challenging, as existing research is very limited with a high variance in methods and study samples. Prior studies have mainly focused on the conversion rates of different SIP types to schizophrenia spectrum disorders. We identified no previous studies comparing relapse rates across different SIP types.

Our results report a 26% relapse rate for cannabis-induced psychosis. Previously, a 15% relapse rate for cannabis-induced psychosis was reported by Arendt et al. (2005) in a register-based, three-year follow-up study focusing on conversion from cannabis-induced SIP to schizophrenia-spectrum disorders. The study had a smaller but similarly identified study sample. They assessed outcome in multiple categories, namely schizophrenia-spectrum disorders, other F20-F29 diagnoses, bipolar disorder (F30-31), acute and transient psychotic conditions (F23), substance-induced psychotic disorders, and other disorders (depression, anxiety and personality disorders). The difference may be explained by different diagnostic conventions between Denmark and Sweden. While research on relapses of cannabis-induced SIP is limited, co-occurring cannabis use in other first-episode psychoses has been associated with higher relapse rate, longer hospital admissions, and more severe positive symptoms (17,25).

We observed a 20% relapse rate for (meth)amphetamine-induced psychosis during the follow-up period. Previous studies have similarly suggested high relapse and re-hospitalization rates for methamphetamine-induced psychosis (5,7,26). However, those studies do not distinguish re-hospitalization due to SIP from other psychotic disorders and are thus not directly comparable to this study.

In this study, alcohol-induced psychosis had the lowest relapse at 13% rate. A study by Soyka et al. (2012) based on German health insurance records also indicate a high risk for rehospitalization, even though alcohol-induced psychotic disorders in itself were rare (18). However, their study recorded rehospitalization for any psychiatric diagnosis, not exclusively SIP.

The most frequent SIP type was SIP induced by multiple or unspecified substance (F19.5). This category often involves individuals presenting with concurrent use of multiple substances, making it difficult to identify the primary psychosis-inducing agent. A recent population-based register study indicated F19.5 as the most or second most prevalent SIP type in Scandinavia (27). Our study also noted minimal variance in SIP type between initial diagnosis and relapse, including within the multi/unspecified substance category. We found no previous studies examining changes in SIP type during follow-up. Most longitudinal studies on diagnostic stability of SIP focus on the conversion of SIP to schizophrenia or other types of psychotic disorders without reporting possible SIP relapses or changes in SIP type (13–16).

We found no previous studies that have reported preceding risk-factors associating with subsequent SIP relapses. In our study, younger age was associated with a higher risk of SIP relapse. Younger age at onset has also been associated with a more chronic course of SIP and relapse in other psychotic disorders (13–16). We also found that previous sickness absence of 1-90 days during the

previous year was also associated with SIP relapse. Sickness absence is known to associate with poorer physical and mental health functioning (28,29).

Being born outside Sweden was also associated with a higher risk of SIP relapse. Existing literature proposes a higher risk of psychosis among migrants (30,31). In addition, people with migrant background have been associated with a higher risk of discontinuing antipsychotic medication in other psychotic disorders (32). Also, people born outside Sweden include refugees who have higher prevalence of trauma (33). However, previous research on substance use among migrants shows inconclusive results mediated through i.e. country of origin, substance of use and socioeconomic background (34): some studies found lower (35,36) while some found higher rates of substance-use disorder in migrants (37,38). For example, the risk for substance use disorder was higher in migrants with low socioeconomic status and migrants from countries with high rates alcohol-use dependence (37,38).

To our knowledge, this study is the first to identify attention-deficit hyperactivity disorder (ADHD) as a risk factor for SIP relapse. Yet, an association between ADHD and substance-use disorders has repeatedly been shown in previous studies (39–41). Previous studies also indicate that ADHD diagnosed in childhood is associated with a higher risk of psychosis in adulthood (42,43). There is also evidence of ADHD medication preventing hospitalizations due to SUD in people with ADHD and comorbid amphetamine use disorder (44). Thus, it is plausible that ADHD medication could mitigate the risk of SIP relapse, but further studies are needed.

Strengths and Limitations

As a key strength of this study, our data covered all SIPs treated in specialized care nationwide with great coverage: 11 years of SIP diagnoses in total. Due to the large sample size, the analyses were powered to differentiate between most common substances inducing SIP. Also, to our knowledge, this is the first study to report ADHD as risk factor associated with SIP relapse, and the first study to compare relapse rates between different substance groups.

When interpreting our findings, the several limitations should be considered. Variance in regional diagnostic practices may influence the results, particularly for the F19.5 category, where no specific substance information is available. Also, we cannot verify whether a laboratory-confirmed finding of each substance was present in the SIP diagnoses, and we do not have data whether substance use continued during the follow-up period. Subsequently, we did not have access to information on use frequency, thus this study cannot evaluate dose-dependent effects, which previous studies have indicated as a factor in the onset of substance-induced psychosis (45,46). We also do not have data on use of substance-use treatment services, and we lacked information on primary care visits, which could impact risk of relapse. Furthermore, we pooled every SIP type together for the multivariate models, potentially overlooking differences between substances.

Lastly, our study was limited to a relatively short two-year follow-up period, which limits the coverage of relapse cases. However, when we analyzed relapse rates in five-year follow-up we observed that within this study population, the majority of SIP relapses occurred within the first year.

As the primary focus of this study was on SIP relapses, a topic not previously explored, two-year follow-up period was also supported by high conversion rates to schizophrenia-spectrum disorders, which could be seen as competing events. Although SIP conversion to other psychotic disorders is

an important topic it has been recently studied extensively (13-16). In addition, the observed 5% mortality rate during the two-year follow-up was relatively high, further supporting the decision for a shorter follow-up period. Further analysis on mortality and causes of death have been submitted to another journal as a part of our ongoing project focusing on the long-term prognosis of SIP and thus, cannot be included in this study. Also mortality and long-term prognosis of SIP is beyond the scope of this study which investigated primarily SIP relapses.

Conclusions

In this study investigating the relapse of substance-induced psychosis, we found that 20% of the study population had a SIP relapse within two years follow-up. Cannabis-induced psychosis had the shortest time lapse between episodes and (meth)amphetamine-induced psychosis had longest. Identified risk factors for SIP relapse were ADHD, substance-use disorder, younger age, previous sickness absence and being born outside Sweden. These findings could help with identifying individuals with a higher risk of SIP relapse.

Declaration of interest

VE has received funding from Alcohol Research Foundation. JT and HT have participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution. HT reports personal fees from Gedeon Richter, Janssen-Cilag, Lundbeck and Otsuka. JT has been a consultant and/or advisor to and/or has received honoraria from Eli Lilly, Evidera, HLS Therapeutics, Janssen-Cilag, Lundbeck, Mediuutiset, Orion, Otsuka, Sidera, Sunovion, and WebMed Global. EMR has participated in research projects funded by Janssen-Cilag. SN reports personal fees from dne Pharma, Lundbeck, Otsuka, Recordati and Takeda.

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Data availability

The data used in this study cannot be made publicly available due to privacy regulations. According to the General Data Protection Regulation, the Swedish law SFS 2018:218, the Swedish Data Protection Act, the Swedish Ethical Review Act, and the Public Access to Information and Secrecy Act, these types of sensitive data can only be made available for specific purposes, including research, that meets the criteria for access to this sort of sensitive and confidential data as determined by a legal review. Readers may contact Professor Kristina Alexanderson (kristina.alexanderson@ki.se) regarding the data.

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Table 1. Risk factors associated with relapse in substance-induced psychosis (SIP) compared to individuals with a single SIP during 2-year follow-up in a Swedish national sample

	No recurrent SIP during follow-up	*Recurrent SIP during follow-up*	*Crude HR for recurrent SIP (95% CI)*	*Adjusted Hazard Ratio for recurrent SIP* (95% CI)*	*p-value*
	N=4503	*N=1463*			
	N (%)	N (%)			
Age (in years)					
18-29	1865 (41.4)	787 (53.8)	**1.94 (1.66-2.27)**	**1.29 (1.05-1.58)**	**0.016**
30-49	1646 (36.6)	480 (32.8)	**1.41 (1.19-1.66)**	1.06 (0.88-1.28)	0.54
50-65	992 (22.0)	196 (13.4)	1**	1**	
Gender					
Male	3540 (78.6)	1169 (79.9)	1**	1**	
Female	963 (21.4)	294 (20.1)	1.05 (0.93–1.20)	0.95 (0.83-1.09)	0.48
Place of Birth					
Sweden	3709 (82.4)	1173 (80.2)	1**	1**	
Abroad	794 (17.6)	290 (19.8)	1.10 (0.97–1.25)	**1.23 (1.07-1.41)**	**0.0026**
Family Status					
Married without children	171 (3.8)	28 (1.9)	1**	1**	
Married with children	268 (6.0)	49 (3.4)	1.12 (0.71–1.79)	0.91 (0.57-1.46)	0.70
Single without children	3429 (76.2)	1176 (80.4)	**1.86 (1.28–2.70)**	1.31 (0.90-1.92)	0.16
Single with children	164 (3.6)	32 (2.2)	1.15 (0.69–1.91)	0.87 (0.52-1.46)	0.61
Individuals younger than 20 years old living at home	471 (10.5)	178 (12.2)	**2.10 (1.41–3.13)**	1.30 (0.86-1.97)	0.22
Level of Education					
Low (less than 9 years)	366 (8.1)	96 (6.6)	1**	1**	
Medium (10-12 years)	2018 (44.8)	639 (43.7)	0.93 (0.84–1.04)	1.07 (0.95-1.20)	0.25
High (more than 13 years)	1964 (43.6)	683 (46.7)	**0.78 (0.63–0.97)**	1.02 (0.81-1.27)	0.88
Unknown	155 (3.4)	45 (3.1)	0.82 (0.60-1.10)	0.78 (0.57-1.07)	0.12
Sickness absence					
No sick leave	3700 (82.2)	1207 (82.5)	1**	1**	
<90 days sick leave	403 (9.0)	132 (9.0)	1.05 (0.88–1.26)	**1.19 (1.01-1.44)**	0.060
>90 days sick leave	400 (8.9)	124 (8.5)	0.96 (0.80–1.16)	1.06 (0.87-1.28)	0.58
Disability pension	887 (19.7)	239 (16.3)	**0.80 (0.70–0.92)**	0.93 (0.79-1.09)	0.36
Long-term unemployment					
No	3131 (69.5)	939 (64.2)	1**	1**	
≤180 days	1057 (23.5)	413 (28.2)	**1.27 (1.13–1.42)**	1.07 (0.95-1.21)	0.27
>180 days	315 (7.0)	111 (7.6)	1.17 (0.96–1.42)	1.11 (0.91-1.36)	0.32
Depression	1092 (24.3)	381 (26.0)	1.08 (0.96–1.21)	0.99 (0.87-1.13)	0.89
Anxiety disorder	1564 (34.7)	585 (40.0)	**1.19 (1.07–1.32)**	1.06 (0.94-1.19)	0.36
Previous SUD	3031 (67.3)	1070 (73.1)	**1.23 (1.10–1.38)**	**1.37 (1.20-1.56)**	**<0.0001**
Personality disorder	488 (10.8)	207 (14.2)	**1.28 (1.10–1.48)**	1.17 (0.99-1.37)	0.062
Eating disorder	45 (1.0)	15 (1.0)	1.01 (0.61–1.67)	0.84 (0.50-1.42)	0.52
ADHD	564 (12.5)	273 (18.7)	**1.44 (1.26–1.64)**	**1.21 (1.05-1.39)**	**0.0088**
Autism spectrum disorder	101 (2.2)	33 (2.3)	0.92 (0.65–1.30)	0.74 (0.52-1.05)	0.095
Intellectual disability	54 (1.2)	29 (2.0)	**1.50 (1.04–2.17)**	1.35 (0.93-1.97)	0.12
Self-harm	1009 (22.4)	363 (24.8)	1.09 (0.97–1.23)	0.97 (0.86-1.11)	0.67
SIP type					
Alcohol	1372 (30.5)	236 (16.1)	1**	1**	
Cannabis	542 (12.0)	304 (20.8)	**2.67 (2.29-3.22)**	**2.42 (1.98-2.96)**	**<0.0001**
Stimulant	802 (17.8)	254 (17.4)	**1.67(1.40-1.99)**	**1.49 (1.23-1.81)**	**<0.0001**
Multiple/unspecified	1493 (33.2)	610 (41.7)	**2.12 (1.82-2.46)**	**1.81 (1.52-2.15)**	**0.001**
Other***	294 (6.5)	59 (4.0)	1.15(0.86-1.52)	1.07 (0.79-1.43)	0.67

*Adjusted for all covariates mentioned in this table.

**Hazard ratio of 1 indicates the reference group

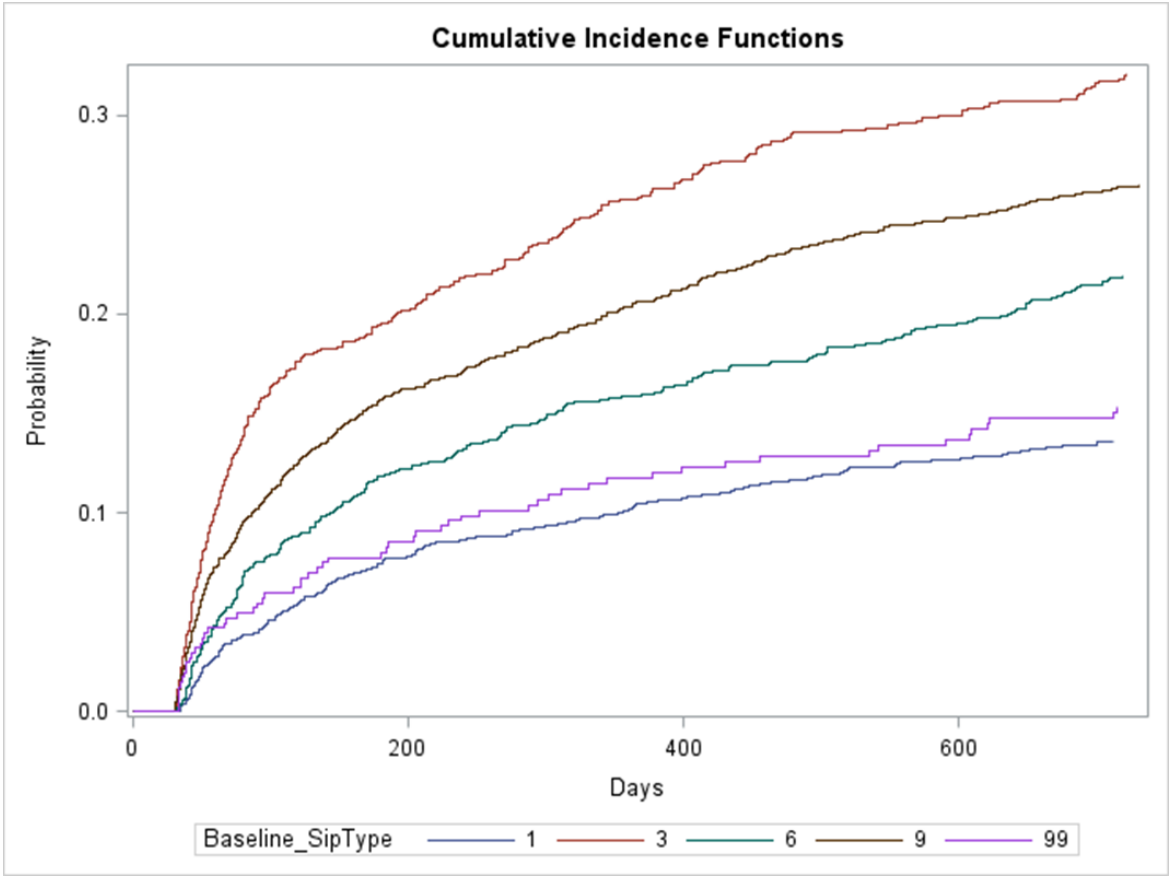
***Hallucinogens, cocaine, sedatives, solvents, opioids

Table 2. Stability of SIP type at SIP relapse, and time to relapse in a Swedish national sample, two-year follow-up

	Alcohol	*Cannabis*	*Stimulants*	*Multiple/unspecified*	*Other**
N=1463	*N=236*	*N=304*	*N=254*	*N=610*	*N=59*
	n (%)	n (%)	n (%)	n (%)	n (%)
Time (in days) to SIP relapse	*148*	*89*	*152*	*122*	*138*
Recurrent SIP by the same substance	216 (91.5)	262 (86.2)	184 (72.4)	518 (84.9)	40 (67.8)
Recurrent SIP by Alcohol	-	0 (0.0)	2 (0.8)	7 (1.1)	3 (5.1)
Recurrent SIP by Cannabis	1 (0.42)	-	6 (2.0)	24 (3.9)	2 (3.4)
Recurrent SIP by Stimulants	10 (4.2)	6 (2.0)	-	52 (8.5)	4 (6.8)
Recurrent SIP by multiple/unspecified	7 (3.0)	32 (10.5)	59 (23.2)	-	10 (16.9)
Other*	2 (0.9)	4 (1.3)	3(1.2)	9 (1.5)	-

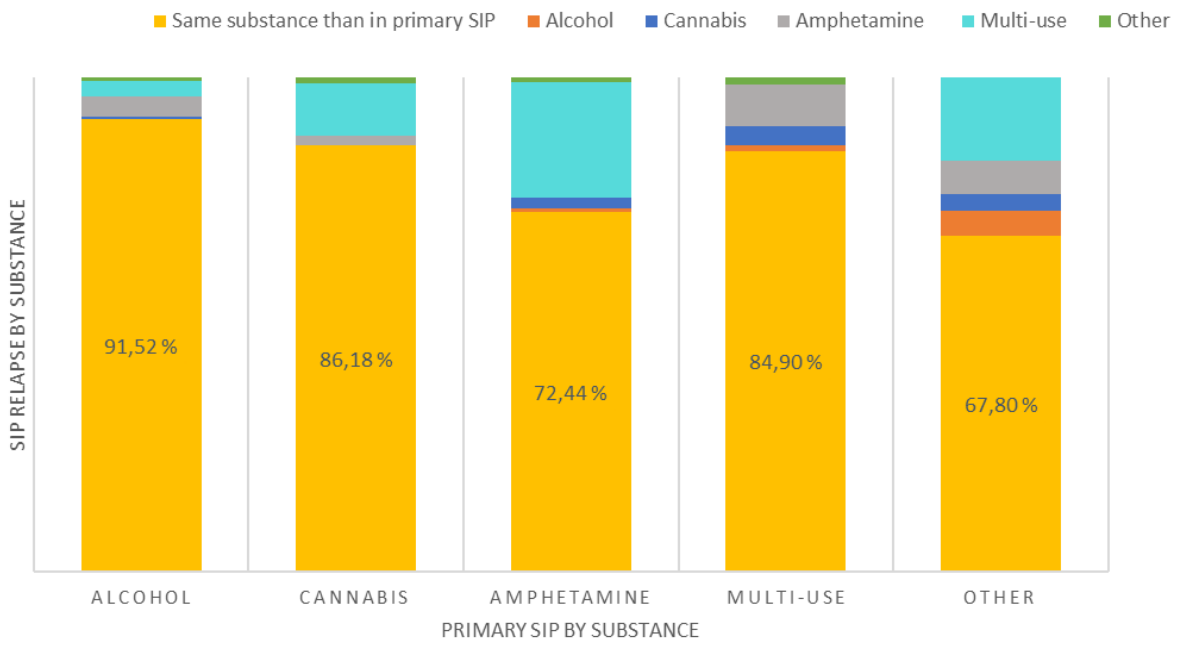
*Hallucinogens, cocaine, sedatives, solvents, opioids

Figure 1. Cumulative incidence graph of time-lapse between SIP episodes by SIP type



1=alcohol, 3=cannabis, 6=stimulants, 9=multi/unspecified, 99=other

FIGURE 2: STABLILITY OF SIP RELAPSE BY SUBSTANCE



Supplement Table 1. Distribution of F20-F29 and F30-31 diagnoses among people with any SIP during the two-year follow-up (n=1002/7320)1		
	n	**%**
F20 Schizophrenia	110	11.0
F21 Schizotypal disorder	9	0.9
F22 Delusional disorders	95	9.5
F23 Acute and transient psychotic disorders	347	34.6
F25 Schizoaffective disorders	19	1.9
F28 Other psychotic disorder	13	1.3
F29 Unspecified psychosis	542	54.1
F30-31 Manic episode or bipolar affective disorder	163	16.3
[1]An individual can receive several diagnoses during the follow-up, allowing overlap between categories		

Supplement Table 2. Distribution of F20-F29 and F30-31 diagnoses among people with any SIP during the two-year follow-up across §					
	Alcohol F10.5	*Cannabis F12.5*	*(Meth)Amphetamine F15.5*	*Multiple/unspecified F19.5*	*Other-SIP*[2]
cases at baseline (n)	1851	1184	1292	2561	432[2]
cases censorder due psychotic or bipolar disorders during the follow-up (n, %)	120 (6.5)	316 (26.7)	174 (13.5)	334 (13.0)	58 (13.4)
Distribution of F20-F29 and F30-31 diagnoses in each SIP category (n, %)					
F20 Schizophrenia	9 (7.5)	35 (11.1)	18 (10.3)	43 (12.9)	5(8.6)
F22 Delusional disorders	8 (6.7)	29 (9.2)	17 (9.8)	36 (10.8)	5 (8.6)
F23 Acute and transient psychotic disorders	25 (20.8)	113 (35.8)	63 (36.2)	123 (36.8)	23 (39.7)
F25 Schizoaffective disorders	N/A	9 (2.9)	N/A	N/A	N/A
F29 Unspecified psychosis	46 (38.3)	198 (62.7)	92 (52.9)	172 (51.2)	34 (58.6)
F30-F31 Manic episode or bipolar affective disorder	35 (29.2)	44 (13.9)	24 (13.8)	50 (15.0)	10 (17.2)
[1]An individual can receive several diagnoses during follow-up, allowing overlap between categories [2] ICD-10 diagnoses of F11.5 (n=103), F13.5 (n=107), F14.5 (n=62), F16.5 (n=153), and F18.5(n=7) which were pooled together as “other-SIP”					

Supplement table 3. Stability of SIP type at recurrent SIP, and time to recurrence in a Swedish national sample, five-year follow-up

	Alcohol	*Cannabis*	*Stimulants*	*Multiple/unspecified*	*Other**
N=1745	*N=290* n (%)	*N=335* n (%)	*N=313* n (%)	*N=733* n (%)	*N=74* n (%)
Time (in days) to recurrent SIP	*387*	*270*	*414*	*361*	*438*
Recurrent SIP by the same substance	265 (91.38)	285 (85.07)	217 (69.33)	616 (84.04)	44 (59.46)
Recurrent SIP by Alcohol	-	0 (0.00)	5 (1.60)	12 (1.64)	5 (6.76)
Recurrent SIP by Cannabis	1 (0.34)	-	11 (3.51)	30 (4.09)	3 (4.05)
Recurrent SIP by Stimulants	10 (3.45)	8 (2.39)	-	60 (8.19)	6 (8.11)
Recurrent SIP by multiple/unspecified	12 (4.14)	37 (11.04)	76 (24.28)	-	16 (21.62)
Other*	2 (0.69)	5 (1.49)	4 (1.28)	15 (2.05)	-

*Hallucinogens, cocaine, sedatives, solvents, opioids