

Characteristics of incident substance-induced psychosis compared to first-episode psychotic disorders: A nationwide register-linkage study from Sweden

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ABSTRACT

Background: There is no previous research comparing preceding characteristics between incident substance-induced psychosis (SIP) and first-episode psychotic disorders (FEPD).

Aims: To compare work-related factors and psychiatric morbidity preceding the incident psychotic episode between persons with SIP to persons with FEPD (ICD-10 F20–F29).

Methods: Incident SIP aged 16–65 years ($n = 7320$, 79.4 % male) were identified from the Swedish National Patient Register (NPR) during the years 2006–2016, matched 1:1 (age, sex, year) with FEPD. Information on work-related factors and preceding psychiatric morbidity was collected from national registers. Comparisons between SIP vs FEPD were made using logistic regression analysis, adjusted (aOR) with education level, family situation, living area, country of origin, and Charlson Comorbidity Index.

Results: Previous self-harm (22.9 % vs 11.3 %; aOR 2.4, 95%CI 2.2–2.6), ADHD (14.4 % vs 8.9 %; aOR 1.8, 95%CI 1.6–2.0), and SUD (68.3 % vs 22.3 %; aOR 7.2, 95%CI 6.6–7.9) were more prevalent among SIP, while all other psychiatric disorders were less common compared to FEPD. Also, persons with SIP were more often unemployed (24.6 % vs 18.6 %; aOR 1.2, 95%CI 1.1–1.3), had less any income from work (29.3 % vs 31.1 %; aOR 0.9, 95%CI 0.8–0.98), but were also less often on a sickness absence (8.6 % vs 9.9 %; aOR 0.8, 95%CI 0.7–0.95) or on a disability pension (18.6 % vs 26.3 %; aOR 0.6, 95%CI 0.5–0.7) compared to FEPD.

Conclusions: Persons with SIP have less premorbid psychiatric morbidity than those with FEPD, apart from self-harm, ADHD, and SUD. Also, there is a higher likelihood of labour market marginalisation among persons with incident SIP than persons FEPD.

1. Introduction

Substance-induced psychosis (SIP) is defined as a brief psychotic syndrome that occurs during or following psychoactive substance use but that is not explained based on acute intoxication alone and does not form part of a withdrawal state (Diagnostic and Statistical Manual of Mental Disorders DSM-V, International Classification of Diseases ICD-

10). Recently, register-based studies have implied that persons with SIPs are relatively common in the general population, with estimates of incident rates ranging up to 14 per 100,000 persons (Hjorthøj et al., 2019; Rognli et al., 2022). These studies have also indicated that the incidence rate of cannabis-induced psychosis has increased in recent years while the incidence rate of alcohol-induced psychosis has decreased.

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So far, most previous SIP-related register-linkage studies have focused on prognosis of SIP, conversion to schizophrenia in particular (Kendler et al., 2019; Murrie et al., 2020; Starzer et al., 2018). Previous studies suggest that the prognosis of SIP may not be significantly different from that of other types of psychoses: in the meta-analysis by Murrie et al., the conversion rate estimate for schizophrenia was 25 % for any SIP and 34 % for cannabis-induced psychosis, while the conversion rate for other brief, atypical and not specified psychosis varied from 30 % to 46 % (Murrie et al., 2020). This raises a question: if the prognosis of SIP may not differ from other types of psychoses, what is the background of persons with incident SIP, and are there any differences when compared to first-episode psychoses in the psychotic disorder category, often also defined as “primary psychotic disorders”.

A better understanding of the premorbid factors, such as socio-demographic factors, psychiatric morbidity and level of functioning, among persons with SIP is essential for improving prevention and treatment of SIP. In comparison, a considerable amount of research has been conducted on premorbid factors associated with the first-episode psychotic disorders, such as schizophrenia (Fusar-Poli et al., 2017; Penn et al., 2005). Thus, our knowledge concerning premorbid factors before the incident of psychotic episodes among persons with SIP is minimal. Unfortunately, previous research on incident psychotic episodes has mostly comprised persons with “primary psychotic disorders”, excluding persons with SIP (Fusar-Poli et al., 2017; Penn et al., 2005). Therefore, we know very little about the differences between persons with incident SIP compared to first-episode psychotic disorders (FEPD), that are usually described in the first-episode psychotic literature.

The previous studies that have compared incident SIP with first-episode psychotic disorders other than SIP are scarce, and with low number of SIP cases. Thompson et al. (2016) reported no differences between persons with SIP ($n = 67$) and first-episode psychosis disorder other than SIP ($n = 962$) in terms of quality of life, functioning, or psychosis relapse in a 12-month follow-up (Thompson et al., 2016). In a small Australian study, in turn, persons with SIP ($n = 34$) were reported as having higher rates of forensic and trauma history compared to first-episode psychosis other than SIP ($n = 27$) (Fraser et al., 2012). Also, more similarities than differences between the SIP ($n = 56$) and first-episode psychosis other than SIP ($n = 488$) groups were reported (O’Connell et al., 2019). However, persons with SIP were more likely to be male, unemployed, and had a comorbid SUD compared to those with first-episode psychosis other than SIP (O’Connell et al., 2019). In addition, a small Norwegian study by Weibell et al. (2013) reported poorer academic performance during adolescence among persons with SIP ($n = 30$) compared to persons with first-episode psychotic disorders (FEPD) without comorbid substance use disorders (SUD) ($n = 66$) or persons with FEPD with comorbid SUD ($n = 45$). Interestingly, no differences in age, marital status, living arrangements, or daily functioning between any of those patient groups (Weibell et al., 2013).

The preliminary evidence from previous research hints that outcome of incident substance-induced psychosis resembles prognosis of “primary psychotic disorders”. To understand the differences between SIP and FEPD, it is crucial to study the characteristics of these groups at their treatment entry. First, studying preceding characteristics of incident SIP helps us to understand the natural course of SIP. Second, spotting subtle differences how SIP and FEPD present at their first treatment entry, may help to tailor prevention, early intervention, and management strategies that directly address the unique challenges posed by SIP.

This study aims to compare sociodemographic and work-related factors and psychiatric morbidity preceding the incident psychotic episode between persons with incident substance-induced psychosis (SIP) and persons with first-episode psychotic disorders (FEPD) as defined in the ICD-10 diagnostic system (F20–F29). The analyses were done separately for alcohol-, cannabis-, amphetamine-, and multi-use/other substance-induced psychoses. We have included a wide range of sociodemographic and work-related factors and clinically relevant psychiatric diagnoses to characterize differences between persons with SIP

and FEPD, as previous research on this topic is nonexistent.

2. Methods

2.1. Study design and population

The SIP cohort included all individuals with primary or contributory International Classification of Diseases, version 10 diagnoses (ICD-10) of incident substance-induced psychosis (F10.5, F11.5, F12.5, F13.5, F14.5, F15.5, F16.5, F18.5 or F19.5) recorded in the National Patient Register (NPR), which encompasses inpatient and specialised outpatient care contacts in Sweden. NPR has shown reasonable validity of diagnoses. This cohort incorporated individuals who received their first SIP diagnosis without a preceding SIP diagnosis since 1996 (“incident SIP”) during the years 2006 to 2016 ($n = 11,239$). The cohort was limited to working-aged individuals aged 16 to 65 years ($n = 10,755$). Exclusions were made for those with a previous occurrence of any of the following ICD-10 psychosis-related diagnoses in the NPR at any time before the first SIP diagnoses (since 1996): 1) non-affective psychotic disorders (F20–F29), 2) organic catatonic disorders (F06.1), 3) mania or bipolar disorder (F30–F31), and 4) late-onset or residual substance-induced disorders (F1X.7). The final study sample was constituted with 7320 SIP persons. Detailed numbers of cases were illustrated in the flow chart in Fig. 1.

2.2. Substance-induced psychosis (SIP)

Specific SIP categories were defined as follows: alcohol (F10.5), opioids (F11.5), cannabis (F12.5), sedative (F13.5), cocaine (F14.5), other stimulants, primarily (meth)amphetamine (F15.5), hallucinogens (F16.5), solvents (F18.5), and multi-use/other (F19.5). Of these, the four most prevalent categories—alcohol, cannabis, (meth)amphetamine, and multi-use/other—were separately described due to the low sample size in the remaining SIP categories. The cohort entry date for SIP cases was established as the date of their first SIP diagnosis. Consequently, the SIP category was defined using the first occurring SIP diagnosis group in the analyses with specific categories.

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2.3. Comparison group with other first-episode psychotic disorders (FEPD)

As a comparison group, a matched cohort of persons with first-episode psychotic disorders (FEPD) with ICD-10 psychotic disorder diagnoses F20–F29 was formed. They were chosen with the same exclusion criteria as persons with SIP and were identified from the NPR as persons who had recorded their first psychotic disorder (F20–F29) diagnoses during the years 2006–2016, aged 16–65 years, and without a previous diagnosis of F20–F29 or any exclusion diagnosis listed in 2.1 since 1996. A comparison person with FEPD was matched by age, sex, and calendar year of first diagnoses (1:1) for each person with SIP. The cohort entry date for FEPD controls was the date of their first psychosis diagnosis, as seen in Fig. 1. The distribution of FEPD diagnoses is presented in the Supplement Table S1.

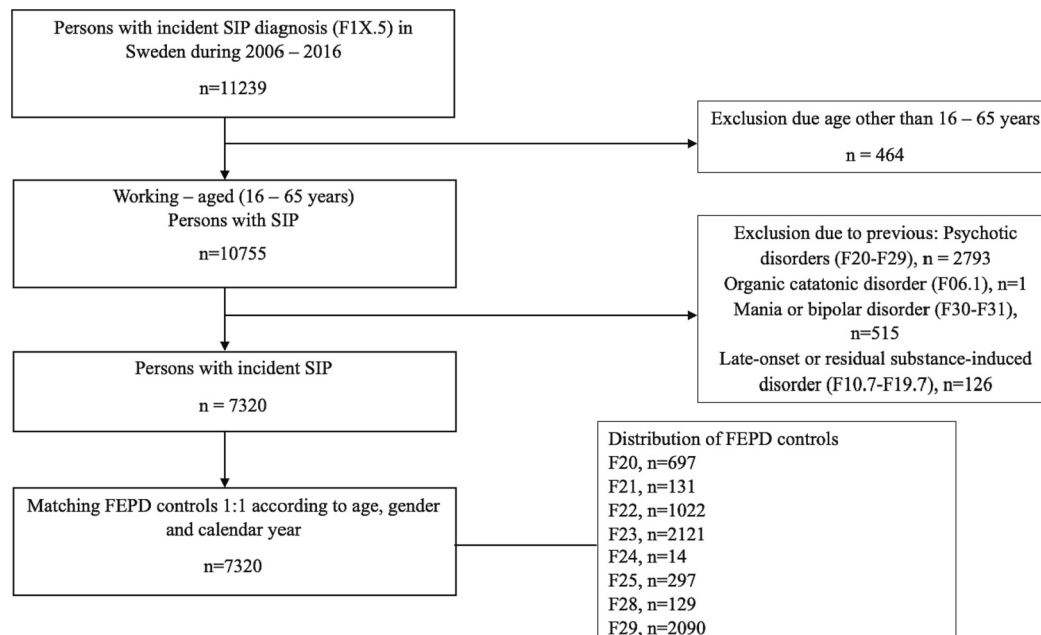


Fig. 1. Flow chart of exclusions conducted for substance-induced psychosis (SIP) cohort and their matching with other first-episode psychosis patients (FEPD).

2.4. Sociodemographic variables

In addition to age and sex, sociodemographic variables during the previous calendar year before the incident SIP/FEPD episode were collected from The Longitudinal Register for Health Insurance and Labor Market Studies (LISA). These included the family situation, which was operationalized as: 1) married and living without children; 2) married and living with children; 3) single, living without children; 4) single, living with children; and 5) persons aged <20 years and living with their parents. Educational level was categorized as 1) low educational level (<9 years), 2) medium level (10–12 years), and 3) high educational level (>=13 years). Information on dwelling, i.e., type of living area, was analyzed as 1) large cities (Stockholm, Gothenburg, Malmö), 2) medium-sized cities (>90,000 residents within 30 km distance from the center of the city), and 3) small cities/villages. Country of birth was categorized as 1) Sweden; 2) other Nordic countries; 3) other European countries, and 4) the rest of the world.

2.5. Psychiatric morbidity before the first SIP/FEPD episode

Previous clinical in- and outpatient diagnoses since 1996 before the first SIP or FEPD diagnosis were defined using ICD-10 diagnosis codes from the NPR. Psychiatric morbidity variables included any mental and behavioral disorder (F00–F99), depression (F32–F33), anxiety disorders (F40–F43), eating disorders (F50), personality disorders (F60–F69), mental retardation (F70–79), pervasive developmental disorders/autism spectrum disorders (F84), hyperkinetic disorders (ADHD) (F90), and information about suicide attempts or severe self-harm requiring medical attention, defined as ICD-10 codes X60–X84 and Y10–Y34. In addition, substance use disorder (SUD) was analyzed as any substance use disorder other than tobacco (F10–16, F18–19) and substance dependence other than tobacco (F1X.2). For more detailed information, previous (2 years before the incident psychosis) and concomitant substance-related ICD-10 diagnoses among FEPD and SIP persons were described in Supplement Table 1 (S1).

The Charlson Comorbidity Index (CCI) was constructed to quantify the burden of diseases impacting mortality risk. CCI was an independent predictor of mortality and long-term survival (Charlson et al., 1987). The analyses used CCI as a three-class variable with 0, 1, or >=2 conditions.

2.6. Work- and income-related variables

Work- and income-related information during the preceding year before the first psychotic episode was collected from nationwide registers. Days registered as unemployed in the employment services (the basis for receiving unemployment benefits) and any income from work were derived from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) (Ludvigsson et al., 2011). Unemployment benefits in Sweden were a part of the social insurance system designed to provide financial assistance to individuals temporarily out of work and actively seeking employment simultaneously (Kananen, 2012). Information concerning the total duration of sickness absence during the 365 days before diagnosis was measured as gross days, whereas unemployment and employment were measured during the previous calendar year. Unemployment during the previous calendar year was used as a three-class variable: 1) no unemployment, 2) <180 days of unemployment, and 3) >=180 days. Similarly, any income from work as a marker of any paid work (yes/no) was measured during the previous calendar year (and was referred to as “employment”). The same person could naturally have employment and unemployment during the same year if and when unemployment covered fewer than 365 days. The MiDAS register included all individuals living in Sweden aged >=16 years who had been granted a disability pension or who were sick-listed for >14 consecutive days. All working-aged people living in Sweden were covered by national sickness insurance, covering up to 80 % of income lost due to work incapacity for medical reasons. Previous sickness absence was analyzed as a three-class variable: 1) no sickness absence, 2) sickness absence <90 days, and 3) >=90 days. Disability pension could be granted for persons aged >=19 years. Information concerning disability pension at the time of the diagnoses of SIP/FEPD was analyzed as a two-class variable (no/yes). Information on disability pension benefits and sickness absence benefits was derived from Micro-data for analyses of the social insurance (MiDAS) register (Svedberg et al., 2010). Disability pension and sickness absence were a part of the social insurance scheme of Sweden, and they could be seen as a proxy of reduced health status to describe labor market marginalization (LLM).

2.7. Statistical analyses

SIP and FEPD were compared using logistic regression analysis,

yielding odds ratios and their 95 % confidence intervals (OR 95%CI) (Table 1). Multivariable logistic regression models on psychiatric morbidity (Table 2) incorporated all psychiatric diagnoses under study, educational level, family situation, dwelling, country of origin, and Charlson’s comorbidity index, with age and sex accounted for in the matching. Multivariable logistic regression models on work-related factors. Specifically aims to elucidate the distributions and associations of various psychiatric diagnoses across SIP and FEPD cohorts, providing a detailed overview of psychiatric morbidity within and between these groups.

Table 3 included variables such as any income from work, unemployment (yes vs no), ongoing disability pension, and previous sickness absence, in addition to educational level, family situation, dwelling, country of origin, and Charlson’s comorbidity index.

2.8. Ethical considerations

The study was approved by the Regional Ethics Review Board of Stockholm, Sweden (decision 2007/762-31). We utilised data from the REWHARD consortium supported by the Swedish Research Council (grant number 2017-00624).

3. Results

3.1. Distribution of SIP and FEPD diagnoses

The most common SIP type was psychosis induced by multi-use/other substance use, which constituted 35 % of subjects, followed by alcohol-induced psychosis 25.3 %, (meth)amphetamine-induced psychosis 18 %, and cannabis-induced psychosis 16.2 %. Only a small number of patients were diagnosed with hallucinogens, opioids, cocaine, sedative, and inhalant-induced psychosis (Fig. 2).

In the FEPD group, the most common first psychosis diagnosis (39.7 %) was unspecified non-organic psychosis (ICD-10 code F29), and only 9.5 % (F20) had a schizophrenia diagnosis (Supplement Table S1).

3.2. Sociodemographic background

As seen in Table 1 and Tables S2–S5 in the Supplement, most persons across all SIP types were male, ranging from 77.4 % among alcohol-SIP to 86.2 % among cannabis-SIP. Overall, the mean age at any SIP diagnosis was 35.0 years (SD 13.3). Of cannabis-induced psychosis, 95.4 % of the persons were aged 16 to 29 years, and only 0.4 % were aged 50 or older. Of alcohol-induced psychosis, 52.9 % of the persons were aged over 50 years.

Compared to persons with FEPD (70.9 %), persons with any SIP (80.8 %) were more likely to be Swedish-born. However, persons with alcohol-induced psychosis were likelier to be born in other Nordic countries and less likely to be born elsewhere in Europe or the rest of the world. Those with cannabis-induced psychosis, in turn, were more likely to be born outside of Europe. In contrast, persons with (meth)amphetamine or multi-use/other substance-induced psychosis were less likely to be born outside of Europe compared to their matched comparison persons with FEPD. Most persons with SIP (79.9 %) lived in big cities or other urban areas. Compared to persons with FEPD, living in a small or rural municipality was less likely for all SIP types except multi-use/other SIP.

The educational level among all SIP types was generally lower than among FEPD. The percentage of low-level education, i.e., completing only nine years of schooling or less, ranged from 32.3 % among persons with alcohol-SIP to 51.2 % among multi-use/other SIP. In addition, compared to FEPD, persons with SIP were less likely to be married with children but more likely to live alone or be single parents with children.

Table 1

Characteristics of the incident substance-induced psychosis (SIP) and first episode psychosis disorder (FEPD) patients. Comparisons between SIP and FEPD patients are expressed as odds ratios with 95 % confidence intervals (OR95 %CI).

	FEPD (n = 7320)		Any SIP (n = 7320)		OR (95 %CI)
Mean age (SD)	35.02 (SD13.3)		35.02 (SD13.3)		
	n	%	n	%	
Sociodemographic variables					
Age					
16–29	3356	45.9	3356	45.9	Matched
30–49	2564	35.0	5920	80.9	Matched
50–65	1400	19.1	7320	100	Matched
Sex					
Male	5814	79.4	5814	79.4	Matched
Female	1506	20.6	7320	100	Matched
Country of origin					
Sweden	5189	70.9	5913	80.8	1
Other Nordic countries	167	2.3	339	4.6	1.84 (1.51–2.24)
Rest of the Europe	175	2.4	152	2.1	0.74 (0.60–0.93)
Rest of the World	1521	20.8	818	11.2	0.46 (0.41–0.50)
Missing information	268	3.7	98	1.3	0.31 (0.24–0.39)
Dwelling					
Big cities ^{1, 2, 3}	3210	43.9	3405	46.5	1
Medium-sized cities	2354	32.2	2370	32.4	0.95 (0.88–1.02)
Small towns/villages	1756	24.0	1545	21.1	0.82 (0.76–0.90)
Educational level					
Low	2265	30.9	3210	43.9	1
Medium	3130	42.8	3243	44.3	0.71 (0.65–0.76)
High	1320	18.0	591	8.1	0.29 (0.27–0.33)
Missing information	605	9.2	276	3.8	0.30 (0.26–0.36)
Family situation					
Married without children	351	4.8	325	3.2	1
Married with children	730	9.9	368	5.0	0.76 (0.61–0.95)
Single without children	4879	66.6	5561	75.9	1.83 (1.53–2.19)
Single with children	210	2.8	229	3.1	1.66 (1.28–2.17)
Children <20 years living with their parents	874	11.9	229	11.1	1.27 (0.98–1.64)
Missing information	276	3.8	108	1.5	0.57 (0.42–0.76)
Psychiatric morbidity					
Any psychiatric disorder	4431	60.5	5667	77.4	2.20 (2.04–2.37)
Previous substance-related diagnosis	1630	22.3	4996	68.3	7.20 (6.58–7.88)
Anxiety disorder	2682	36.6	2646	36.1	0.98 (0.91–1.05)
Depression	2126	29.0	1804	24.6	0.80 (0.74–0.86)
ADHD	656	8.9	1057	14.4	1.76 (1.58–1.96)
Eating disorder	119	1.6	74	1.0	0.61 (0.45–0.82)
Personality disorder	818	11.1	852	11.6	1.05 (0.94–1.16)
Mental retardation	306	4.1	98	1.3	0.30 (0.24–0.39)
Autism spectrum diagnosis	416	5.6	185	2.5	0.42 (0.35–0.51)
Suicide attempts	827	11.3	1683	22.9	2.38 (2.16–2.61)
Charlson’s comorbidity index					

(continued on next page)

Table 1 (continued)

	FEPD (n = 7320)		Any SIP (n = 7320)		OR (95 %CI)
	35.02 (SD13.3)		35.02 (SD13.3)		
	n	%	n	%	
Mean age (SD)	35.02 (SD13.3)		35.02 (SD13.3)		
0	6723	91.4	6606	90.3	1
1	477	6.5	576	7.8	1.25 (1.10–1.42)
≥2	120	1.6	138	1.8	1.21 (0.94–1.57)
Work-related factors					
Any employment during previous year	2279	31.1	2148	29.3	0.92 (0.84–0.98)
Unemployment					
No unemployment 0–180 days	5530	75.6	5015	68.5	1
unemployment ≥180 days	1362	18.6	1800	24.6	1.18 (1.07–1.31)
unemployment ≥180 days	428	5.9	505	6.9	1.05 (0.89–1.25)
Sickness absence					
No sick leave	6041	82.53	6068	82.9	1
<90 days sick leave	548	7.4	622	8.5	1.13 (1.00–1.27)
≥90 days sick leave	731	9.9	630	8.6	0.84 (0.73–0.95)
Disability pension	1926	26.3	1366	18.6	0.59 (0.54–0.65)

¹ Stockholm, Göteborg, Malmö.

² Any ICD-10 F10–F16, F18–F19 diagnosis.

³ Any F10.2–F16.2, F18.2–F19.2 diagnosis.

3.3. Psychiatric morbidity before the first psychotic episode disorders

In general, the occurrence of psychiatric disorders, in terms of depression, anxiety disorders, eating disorders, mental retardation, and autism spectrum disorder, was less common among persons with SIP compared to persons with FEPD. Within SIP categories, the highest prevalence for preceding psychiatric disorders, including SUD, was observed among persons with alcohol-SIP (81.5 %), (meth)amphetamine-SIP (81.6 %), and multi-use/other-SIP (82.0 %), while the lowest prevalence was observed for persons with cannabis-SIP (59.4 %) (Table 1 and Table 2, Supplement Tables S2–S5).

ADHD was more common among persons with SIP than FEPD (14.4 % vs 8.9 %; aOR 1.5, 95%CI 1.4–1.8), although this was not evident among persons with alcohol- or cannabis-SIP. The highest ADHD prevalence (20.28 % vs 7.28; aOR 3.37 95%CI 2.28–4.39) was observed among persons with (meth)amphetamine-induced psychosis (Table 1

Table 2

Results of the multivariable logistic regression analyses¹ of psychiatric comorbidity, FEP patients as a comparison group.

	Any SIP (n = 7320)	Alcohol SIP (n = 1851)	Cannabis SIP (n = 1184)	(met)amphetamine SIP (n = 1292)	Multi/other SIP (n = 2561)
	OR (95%CI), p-value	OR (95%CI), p-value	OR (95%CI)	OR (95%CI)	OR (95%CI)
Substance dependence	4.71 (4.10–5.41), <0.0001	9.64 (7.29–12.74), <0.0001	3.49 (2.42–5.02), <0.0001	3.34 (2.37–4.70), <0.0001	3.12 (2.45–3.97), <0.0001
Anxiety disorders	0.86 (0.79–0.94), 0.0006	0.92 (0.76–1.12), 0.403	0.58 (0.47–0.72), <0.0001	0.74 (0.59–0.93), 0.0092	1.13 (0.98–1.32), 0.094
Depression	0.71 (0.65–0.78), <0.0001	0.78 (0.64–0.95), 0.0154	0.72 (0.58–0.89), 0.003	0.62 (0.49–0.79), 0.0001	0.73 (0.62–0.86), 0.0001
ADHD	1.54 (1.35–1.76), <0.0001	0.72 (0.47–1.09), 0.1219	1.18 (0.88–1.58), 0.2827	2.88 (2.02–4.09), <0.0001	1.80 (1.47–2.20), <0.0001
Eating disorder	0.57 (0.40–0.81), 0.0017	0.30 (0.12–0.76), 0.0110	0.38 (0.15–0.97), 0.0427	0.60 (0.24–1.50), 0.2756	0.79 (0.46–1.36), 0.3899
Mental retardation	0.31 (0.23–0.40), <0.0001	0.27 (0.14–0.52), 0.0001	0.32 (0.17–0.60), 0.0004	0.27 (0.13–0.55), 0.0003	0.30 (0.20–0.47), <0.0001
Autism spectrum	0.35 (0.28–0.43), <0.0001	0.34 (0.18–0.65), 0.001	0.36 (0.23–0.56), <0.0001	0.40 (0.23–0.70), 0.0013	0.28 (0.20–0.39), <0.0001
Suicide attempt/self-harm	2.21 (1.97–2.47), <0.0001	3.27 (2.50–4.28), <0.0001	1.06 (0.79–1.43), 0.7084	2.62 (1.97–3.48), <0.0001	2.12 (1.76–2.54), <0.0001

¹ Adjusted with education level, family situation, dwelling, country of origin and Charlson comorbidity index, in addition to all factors listed in the table.

and Table 2, Supplement Tables S2–S5).

Previous suicide attempts were twofold more common among persons with SIP than persons with FEPD (22.9 % vs 11.3 %; aOR 2.2, 95% CI 2.0–2.5). This was evident for all SIP types apart from cannabis-induced psychosis (Table 1 and Table 2, Supplement Tables S2–S5).

Expectedly, persons with SIP were likelier to have a previous substance dependence diagnosis than persons with FEPD (21.8 % vs 4.6 %; aOR 4.9, 95%CI 4.3–5.7). This was evident for all SIP types, and this difference was most pronounced among persons with alcohol-SIP (34.6 % vs 4.8 %; aOR 10.2, 95%CI 7.8–13.3). Additional information on the distribution of previous and concurrent substance-related diagnoses for both SIP and FEPD groups is presented in the Supplement (Tables S1–S6).

3.4. Work-related factors before the first psychotic episode disorders

Persons with SIP had, to a slight extent, less often income from work during the previous year before the incident psychotic episode, compared with persons with FEPD (31.1 % vs 29.3 %; aOR 0.9, 95%CI 0.8–0.96). In turn, the prevalence of any unemployment among persons with FEPD was higher than among persons with SIP (24.4 % vs 31.5 %; aOR 1.2, 95%CI 1.1–1.4).

Prior to or at the time of the incident psychotic episode, persons with SIP received less often benefits for both long-term sickness absence over 90 days (8.6 % vs 9.9 %, aOR 0.8; 95%CI 0.7–0.95) and for disability pension (18.6 % vs 26.3 %, aOR 0.45; 95%CI 0.40–0.50) compared to persons with FEPD. The highest rate of a disability pension was found among those with alcohol SIP (29.2 %) and the lowest among those with cannabis SIP (8.5 %) (Tables 1 and 3 and Supplement Tables S2–S5).

4. Discussion

This large nationwide register-linkage study from Sweden aimed to investigate the differences between persons with incident substance-induced psychosis (SIP) compared to persons with first-episode psychotic disorders (FEPD) regarding sociodemographic background, psychiatric morbidity, and work-related factors. To our knowledge, no previous research addresses these questions to this extent.

Our findings indicate that before the first psychotic episode, persons with SIP have less registered psychiatric morbidity than those with FEPD, apart from self-harm events/suicide attempts ADHD, and SUDs. The occurrence of previous self-harm events or suicide attempts among persons with SIP was alarmingly high: 23.0 % of all persons with SIP had had a self-harm/suicide attempt event requiring medical attention before the incident psychotic episode since 1996. This rate was two-fold

Table 3

Results of the multivariable logistic regression analyses¹ of work-related factors, FEP patients as a comparison group.

	Any SIP OR (95%CI), p-value	Alcohol SIP OR (95%CI)	Cannabis SIP OR (95%CI)	(Met)amphetamine SIP OR (95%CI)	Multi/other SIP OR (95%CI)
Any employment	0.87 (0.79–0.96) 0.0034	1.00 (0.84–1.21) 0.9275	1.05 (0.85–1.31) 0.6528	0.82 (0.65–1.05) 0.1101	0.76 (0.64–0.90) 0.0013
Any unemployment	1.24 (1.14–1.35) <0.0001	1.29 (1.06–1.56) 0.0111	1.12 (0.92–1.36) 0.2705	1.26 (1.02–1.57) 0.0354	1.23 (1.06–1.42) 0.0053
Disability pension	0.45 (0.41–0.50) <0.0001	0.47 (0.38–0.57) <0.0001	0.35 (0.26–0.48) <0.0001	0.48 (0.36–0.62) <0.0001	0.48 (0.39–0.58) <0.0001
Sickness absence					
<90 days	1.09 (0.94–1.25) 0.2549	1.13 (0.88–1.46) 0.3487	0.88 (0.61–1.27) 0.4845	1.08 (0.75–1.56) 0.6687	1.09 (0.84–1.42) 0.4981
≥90 days	0.84 (0.73–0.95) 0.0076	0.80 (0.63–1.01) 0.0601	0.87 (0.57–1.33) 0.5206	0.71 (0.51–0.98) 0.0345	1.01 (0.80–1.29) 0.9174

¹ Adjusted with all work-related factors listed in the table, and with education level, family situation, dwelling, country of origin and Charlson comorbidity Index.

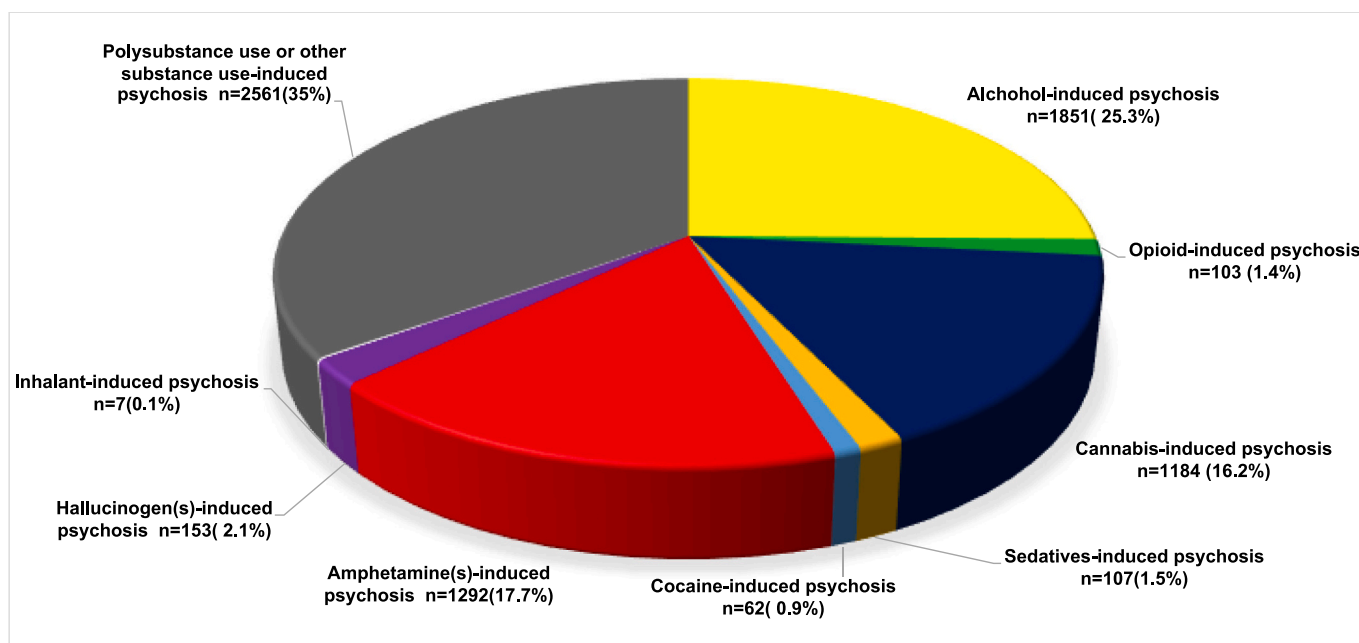


Fig. 2. Distribution of specific subcategories of substance-induced psychosis (n = 7320) in Sweden from 2006 to 2016.

compared to persons with FEPD. Previous suicide attempts were most prevalent among those with multi-use/other SIPs and least prevalent among persons with cannabis-induced psychosis. Our finding aligns with the earlier, yet limited, epidemiological research concerning suicidality or self-harm among persons with SIP. A recent Danish register-linkage study by Hjørthøj et al. (2021) reported that persons with SIP had higher risk of death due to suicide compared to those with schizophrenia. Also, in a Finnish general-population-based study, with a small number of persons with SIP, the rate of life-time suicide attempts was higher among persons with lifetime SIP compared with other types of psychosis (Suokas et al., 2010). In addition, results from a small Iranian study with one year follow-up hinted that persons with methamphetamine-induced psychosis are at greater risk of suicide than persons with other types of first-episode psychoses (Hajebi et al., 2018).

The complexity of understanding substance-induced psychosis stems from the intricate diagnostic process. Clinical diagnosis provides a detailed assessment of individual patient circumstances, considering symptoms and history, while registry definitions rely on standardized coding systems for broader research but may overlook individual nuances. (Poole and Brabbins, 1996) discuss the difficulties in identifying psychosis caused explicitly by drug use, emphasizing the importance of understanding the link between substances and psychosis. Likewise, Mathias et al. (2008) discuss the complexity in pinpointing whether the

psychosis is due to substance use or an independent condition. The debate between using detailed clinical diagnoses and broad register definitions highlights the need for a balanced approach, combining personalized assessment with standardized research methods.

According to our findings, ADHD is more prevalent among persons with incident SIP than with other first-episode psychoses. This was evident particularly among persons with (meth)amphetamine-induced psychosis, as 20 % had a register-based diagnosis of ADHD compared to 7 % among their matched comparison persons with FEPD. It may be plausible that those with (meth)amphetamine-induced psychosis start to use street stimulants as a self-treatment of ADHD symptoms (Varga, 2012). In addition, previous studies have indicated that ADHD is associated with an increased risk for both substances use disorders and subsequent psychotic disorders (Nourredine et al., 2021). However, Nourredine et al. (2021) left out substance-induced psychosis as an outcome from their recent meta-analysis focusing on the subsequent risk of other psychotic disorders among persons with childhood ADHD. To date, our knowledge of associations between ADHD and substance-induced psychosis is very limited. Therefore, the relationship between ADHD and SIP should be addressed in future studies.

Apart from self-harm/attempts, ADHD, and SUD, persons with SIPs had fewer psychiatric diagnoses before the first psychotic episode than persons with FEPD, which may indicate less severe premorbid

psychopathology among persons with substance-induced psychosis compared to other first-episode psychosis. Further, a higher prevalence of e.g. autism spectrum disorder diagnoses among persons with FEPP compared to persons with SIP may be explained by a divergent etiology of psychosis between these two groups (Varcin et al., 2022). Also, when using register-based data, our results may also indicate less treatment seeking to psychiatric services across all SIP types under study (Priester et al., 2016). Psychiatric disorders are very prevalent among persons with SUD, independently of substance use (Saha et al., 2022). In addition, psychiatric disorders among persons with SUD may be underdiagnosed as withdrawal symptoms, including anxiety, depression, irritability, and mood swings (Vorspan et al., 2015). Thus, underlying psychiatric disorders may be misinterpreted as substance-use-related psychiatric symptoms.

Compared to persons with FEPP, persons with SIP were more often unemployed, had less likely to have any income from work, and were also less often on a long-term sickness absence or on a disability pension. The differences in these variables between persons with SIP and other FEPP are likely due to the lower eligibility level for these benefits and lower psychiatric morbidity preceding the first psychotic episode. Both sickness absence and disability pension benefits require medical assessment by a physician, whereas an assessment by a physician is not necessary for unemployment benefits. The relatively low prevalence of previous sickness absence may be related to relatively young age distribution. It is possible that a large proportion of persons were not in gainful employment and, thus, not eligible to get sickness absence benefits. It may also be plausible that SIP is associated with poorer premorbid functional ability in general compared to other kinds of first-episode persons. Although there is no fully comparative previous research, our findings on premorbid work disability among persons with SIP align with earlier reports that underline that persons with SUD are at high risk for marginalisation (Levola et al., 2014). Taken together, our findings indicate a poorer social security network and a higher likelihood of labour market marginalisation and falling out of monetary and social benefits among persons with SIP compared to persons with first-episode psychotic disorders.

5. Strengths and limitations

The main strength of this study is the utilisation of nationwide registers covering all residents in Sweden, where all persons, regardless of their socioeconomic status, have equal access to healthcare services (Oliver, 2004). This enabled us to identify a large cohort of persons with SIP and match comparison persons with FEPP for them without the risk of selection bias. Also, data loss is minimal when using personal identification numbers to link data from several national registers. However, there are also limitations related to the register-based nature of data. For example, diagnoses have been recorded in real-world clinical practice. The precision and accuracy of register-based diagnoses can depend on various factors, including adherence to diagnostic coding practices. Previous work on NPR has shown that diagnostic accuracy is very good (85–95 %) (Ludvigsson et al., 2011) However, we are unaware of validation studies regarding SIP specifically.

Furthermore, as SIP persons were identified from the patient register, this leaves out persons who do not seek treatment for their substance-induced psychosis. Thus, only the most severe SIP episodes requiring medical attention are identified, which is a limitation. Also, one of the aims was to compare work-related factors, and persons were restricted to those aged 16 to 65 years, which can be considered a limitation. The population register does not have information on different ethnicities, which is also a limitation. One significant limitation of our study is the inherent challenge of accurately differentiating between SIP and FEPP. While our analysis has provided insights into both groups' sociodemographic and clinical characteristics, there remains a possibility of misclassification. The diagnostic criteria for these conditions overlap considerably, and the reliance on register-based diagnoses, which may

not capture the full clinical picture, adds to this complexity. Consequently, some individuals categorized under FEPP might have experienced a substance-induced episode.

Concerns regarding the validity of SIP diagnoses also present a limitation. Given the diagnostic challenges, there might be cases of SIP within the FEPP control group. This overlap can impact the accuracy of our findings, particularly in understanding the distinct pathways and treatment needs of SIP and FEPP patients. Still, we are not studying anything about treatments. The register-based nature of our study might not fully reflect the nuances of individual cases where substance use and psychotic symptoms are intricately intertwined.

These limitations underscore the need for further research with more refined diagnostic tools and approaches. Future studies should focus on developing clearer diagnostic criteria and methodologies that can more effectively distinguish between substance-induced psychosis and first-episode psychotic disorders. Such advances will not only enhance the accuracy of research findings but also can improve interventions tailored to the specific needs of these patient groups in the future.

6. Conclusions

Our findings indicate that before the first psychotic episode, persons with substance-induced psychosis have less registered psychiatric morbidity than those receiving a psychotic disorder category diagnosis, apart from self-harm events/suicide attempts ADHD, and SUDs. Thus, suicidality and ADHD treatment should be assessed for persons with substance-induced psychosis entering the health care system. In addition, there is a higher likelihood of labour market marginalisation among persons with SIP than persons with FEPP.

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The funders had no role in the design, analysis, interpretation, or writing of the report for this study.

CRedit authorship contribution statement

Jeyaniroshan Jeyapalan: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation. **Pihla Sassi:** Writing – review & editing, Visualization, Methodology, Investigation, Formal analysis. **Ellenor Mittendorfer Rutz:** Visualization, Validation. **Jari Tiihonen:** Visualization, Validation. **Heidi Taipale:** Supervision, Methodology, Investigation. **Solja Niemelä:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation.

Declaration of competing interest

Drs Jeyapalan and Sassi no conflicts of interest therefore the declaration of interest is none. Dr. Solja Niemelä has received personal fees from Shire-Takeda outside the submitted work.

Drs Taipale, Mittendorfer-Rutz, and Tiihonen reported participating in research projects funded by grants from Janssen-Cilag to their employing institution outside the submitted work. In addition, Dr. Taipale reported receiving personal fees from Gedeon Richter, Janssen, Lundbeck, and Otsuka. Dr. Tiihonen reported receiving grants and personal fees from Eli Lilly and Janssen-Cilag and personal fees from Lundbeck, Otsuka, the Finnish Medicines Agency (Fimea), and the European Medicines Agency outside the submitted work and is a member of the advisory board for Lundbeck. Jari Tiihonen has participated in research projects funded by grants from Eli Lilly and Janssen-Cilag to his employing institution; has been a consultant to HLS Therapeutics, Orion, and WebMed Global; has received personal fees from Eli Lilly, Evidera, Janssen-Cilag, Lundbeck, Mediuutiset, Otsuka, Sidera, and Sunovion; all outside the submitted work. Dr. Niemelä reports receiving personal fees

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During the preparation of this work, the authors didn't use any generative AI and AI-assisted technologies in the writing process.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2024.01.033>.

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