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The associations between psychotic experiences and substance use and substance use disorders: findings from the World Health Organization World Mental Health surveys

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ABSTRACT

Background and aims Prior research has found bidirectional associations between psychotic experiences (PEs) and selected substance use disorders. We aimed to extend this research by examining the bidirectional association between PEs and various types of substance use (SU) and substance use disorders (SUDs), and the influence of antecedent mental disorders on these associations. **Design, setting, participants and measurements** We used data from the World Health Organization World Mental Health surveys. A total of 30 902 adult respondents across 18 countries were assessed for (a) six types of life-time PEs, (b) a range of types of SU and DSM-IV SUDs and (c) mental disorders using the Composite International Diagnostic Interview. Discrete-time survival analyses based on retrospective age-at-onset reports examined the bidirectional associations between PEs and SU/SUDs controlling for antecedent mental disorders. **Findings** After adjusting for demographics, comorbid SU/SUDs and antecedent mental disorders, those with prior alcohol use disorders [odds ratio (OR) = 1.6, 95% confidence interval (CI) = 1.2–2.0], extra-medical prescription drug use (OR = 1.5, 95% CI = 1.1–1.9), alcohol use (OR = 1.4, 95% CI = 1.1–1.7) and tobacco use (OR = 1.3, 95% CI = 1.0–1.8) had increased odds of subsequent first onset of PEs. In contrast, those with temporally prior PEs had increased odds of subsequent onset of tobacco use (OR = 1.5, 95% CI = 1.2–1.9), alcohol use (OR = 1.3, 95% CI = 1.1–1.6) or cannabis use (OR = 1.3, 95%

CI = 1.0–1.5) as well as of all substance use disorders (ORs ranged between 1.4 and 1.5). There was a dose response relationship between both count and frequency of PEs and increased subsequent odds of selected SU/SUDs. **Conclusions** Associations between psychotic experiences (PEs) and substance use/substance use disorders (SU/SUDs) are often bidirectional, but not all types of SU/SUDs are associated with PEs. These findings suggest that it is important to be aware of the presence of PEs within those with SUDs or at risk of SUDs, given the plausibility that they may each impact upon the other.

Keywords Alcohol, cannabis, mental disorder, nicotine, prescription drug, psychotic experiences, substance abuse disorder, substance dependence disorder, substance use, tobacco.

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INTRODUCTION

Although it is widely acknowledged that acute intoxication with various legal and illicit substances can be associated with transient hallucinatory and delusional experiences, community surveys have also linked substance use (SU; i.e. the use of a particular substance, but not meeting diagnostic criteria for a disorder) and substance use disorders (SUDs) with an increased risk of psychotic experiences (PEs), outside periods of acute intoxication or withdrawal [1–6]. In particular, there is a body of evidence linking cannabis use with an elevated risk of PEs [1–5,7–9]. Recent studies have also linked commonly used substances such as tobacco and alcohol with PEs [4,10–13]. For example, a 44-country study from the World Health Survey found that current tobacco smoking was associated with increased odds of life-time PEs (OR = 1.35; 95% CI = 1.27–1.43) [10]. Illicit drugs including cocaine, amphetamines and opioids have also been linked with PEs [14–17].

Curiously, there is evidence that the relationship between PEs and SU/SUDs may be bidirectional. In our earlier paper, we found that substance use disorders (particularly alcohol abuse and dependence) were associated bidirectionally with PEs [18]. Several cohort studies have found bidirectional association between PEs and cannabis use disorders [1,2,9,19,20]. These findings highlight the importance of understanding the temporal sequence of PEs and SU/SUDs. There is also strong evidence that familial factors may confound the apparent relationship between cannabis use and subsequent psychotic disorders [21]. Based on these findings, there is a need for studies that use temporally ordered variables to explore the bidirectional associations between PEs and different types of SUs (e.g. tobacco, cannabis, cocaine, alcohol, prescription drugs, other illicit drugs). More complex models are also required in order to determine how various types of SU/SUDs influence the association between SU/SUDs and PEs. For example, it is feasible that the presence of mental disorders can influence the onset of PEs (e.g. a substance use disorder may lead to a major depression, which leads in turn to the onset of PEs). There is evidence that those with SU/SUDs have an increased risk of mental disorders [22,23], and there is a bidirectional relationship between PEs and mental disorders [18]. Thus, it is reasonable to assume that the association between PEs and SU/SUDs may be explained at least in part by antecedent mental disorders. Finally, there is a need to explore if there is a 'dose–response' relationship between PEs (e.g. number of types of PEs and frequency of PE episodes) and subsequent odds of SU/SUDs.

The aims of the study were to extend previous findings by examining: (1) the association between SUs or SUDs and the subsequent onset of PEs; and conversely, (2) the association between prior PEs and subsequent onset of SUs and SUDs, (3) the influence of number or types of PEs and (4) antecedent mental disorders together with comorbid SU/SUDs on these associations.

METHODS

Samples

Data were drawn from 18 WMH surveys from the World Health Organization (WHO) World Mental Health surveys that included both the WHO Composite International Diagnostic Interview (CIDI) psychosis module and items related to substance use. A multi-stage clustered area probability sampling strategy was used to select respondents in majority of the surveys except for Belgium, Germany and Italy. These three countries used municipal resident registries to select respondents without listing households. Details of each survey are presented in the Supporting information, Table S1. The weighted average response rate across all 18 surveys was 71.7%. Further information on samples used for different substance use, details of procedure and the assessment of mental disorders can be found in the Supporting information, Table S2.

Measures

Tobacco, alcohol and illicit drug use

All WMH surveys used the WHO CIDI (3.0), a fully structured diagnostic interview administered by trained lay interviewers. Details of the assessments of tobacco, alcohol and illicit drug use have been published elsewhere [24]. The tobacco and substance-use module of the CIDI includes an assessment of life-time occurrence and age at first initiation of alcohol, tobacco and each illicit drug use. Respondents were asked if they had ever (i) used cigarettes, cigars or pipe (tobacco use), (ii) smoked tobacco daily for a period of at least 2 months (daily tobacco use), (iii) drank alcohol (alcohol use), (iv) either marijuana or hashish (cannabis use), (v) used cocaine in any form including powder, crack, free base, coca leaves or paste (cocaine use), (vi) used tranquillizers, stimulants, pain-killers or other prescription drugs for non-medical reasons or without the recommendation of a health professional (henceforth extra-medical prescription drug use) or (vii) used other drug such as heroin, opium, glue, lysergic acid diethylamide (LSD), peyote or any other drug (other illicit drug use).

Substance use disorders

The WHO CIDI version 3.0 was used to generate DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) substance abuse or dependence disorders diagnoses. The substance use disorders were nicotine dependence, alcohol abuse, alcohol dependence, illicit drug abuse and illicit drug dependence. The CIDI 3.0 does not allow for the diagnosis of cannabis use and/or dependence disorder because there was no separate question for cannabis use or dependence. Some of the assessment details of these disorders have been published elsewhere [25,26]. Standard hierarchy rules were applied, such that people meeting criteria for DSM-IV dependence could not also meet criteria for abuse for that substance.

A series of five questions was used to operationalize the symptom criteria for alcohol abuse and a further 11 questions for alcohol dependence. These were asked of respondents who (in the year they drank most) consumed alcohol at or above a certain quantity/frequency threshold of one or more drinks per week or, if drinking less often, three or more drinks per day on the days they drank. For extra-medical prescription drug use and illicit drug use disorders, respondents were asked if they had ever used medicines for non-medical reasons or had ever used illicit drugs, respectively. Those who reported life-time use were then asked a series of questions: four questions for assessing DSM-IV drug abuse and 11 questions to assess for drug dependence (mapping to the seven DSM-IV criteria). Nicotine dependence was assessed using a similar method. Respondents who reported smoking weekly were asked a series of questions about the symptoms of nicotine dependence (e.g. tolerance, withdrawal, smoking in larger amounts or longer than intended, etc.). A number of initial surveys in the WMH survey initiative (13 in this study) only assessed symptoms of dependence among respondents without a history of abuse. In order to improve the cross-national comparability of estimates of SUDs, estimates for alcohol and illicit drug dependence were used in these surveys based on the method described in Lago *et al.* [27].

Psychotic experiences (PEs)

The CIDI Psychosis Module included questions about six PE types—two related to hallucinatory experiences (visual hallucinations, auditory hallucinations) and four related to delusional experiences (thought insertion/withdrawal, mind control/passivity, ideas of reference, plot to harm/follow) (Supporting information, Table S2a, S2b). The respondents were asked if they ever experienced each PE (e.g. 'Have you ever seen something that wasn't there that other people could not see?'; 'Have you ever heard any voices that other people said did not exist?', etc.). Only PEs occurring when the person was 'not dreaming, not half-asleep, or not under the influence of alcohol or drugs' were included. With respect to the current research questions, it is important to note that hallucinations or delusions that occurred 'under the influence of alcohol or drugs' were excluded from all analyses. Age-at-onset of respondents with PEs was also assessed. In this paper, we present two key PE-related metrics: (a) number of PE types (henceforth referred to as PE-type metric); and (b) frequency of occurrence of PE episodes. We derived frequency per year by dividing the number of PE episodes by the time since onset of the PEs (age at interview minus age of onset, henceforth referred to as annualized frequency metric [28].

Statistical analysis

In order to focus on the correlates of PEs in those without psychotic disorders, we made the a priori decision to exclude individuals who had PEs but who also screened positive for possible schizophrenia/psychosis or manic-depression/mania. In keeping with previous publications [4,18,28–30] we excluded respondents who: (a) reported (1) schizophrenia/ psychosis or (2) manic-depression/mania in response to the question: 'What did the doctor say was causing (this/these) experiences?'; and (b) those who ever took any antipsychotic medications for these symptoms. This resulted in the exclusion of 139 respondents (0.4% of all respondents), leaving 30 902 respondents for this study (Supporting information, Table S1).

The association between SU/SUDs and PEs was tested using the Rao-Scott χ^2. Discrete-time survival models

Table 1 Prevalence of life-time substance use (SU) and substance use disorders (SUDs) among respondents with and without life-time psychotic experiences (PEs).

	Total sample			*Respondents with life-time PEs*			*Respondents without life-time PEs*			*χ^2 between respondents with and without PEs*		
Substance use and substance use disorders	*n*	*%*[a]	*SE*	*n*	*%*[a]	*SE*	*n*	*%*[a]	*SE*	*X_1^2*	*(P-value)*	*Sample size used*
Life-time substance use												
I. Tobacco use	8940	51.0	0.6	819	69.5	2.2	8121	49.9	0.6	60.4*	(< 0.001)	17017[b]
No tobacco use	8077	49.0	0.6	355	30.5	2.2	7722	50.1	0.6			
II. Daily tobacco use[c]	6491	36.0	0.5	559	46.0	2.2	5932	35.4	0.5	24.2*	(< 0.001)	
No daily tobacco use	10 526	64.0	0.5	615	54.0	2.2	9911	64.6	0.5			
III. Alcohol use	22 976	74.7	0.4	2098	89.4	0.9	20 878	73.8	0.4	128.1*	(< 0.001)	30 902
No Alcohol use	7926	25.3	0.4	239	10.6	0.9	7687	26.2	0.4			
IV. Cannabis use	6091	19.2	0.4	762	32.1	1.5	5329	18.4	0.4	106.0*	(< 0.001)	28849[d]
No cannabis use	22 758	80.8	0.4	1435	67.9	1.5	21 323	81.6	0.4			
V. Cocaine use	1370	4.1	0.2	204	8.4	0.8	1166	3.8	0.2	61.6*	(< 0.001)	
No cocaine use	27 479	95.9	0.2	1993	91.6	0.8	25 486	96.2	0.2			
VI. Extra-medical prescription drug use[e]	4117	11.2	0.3	468	18.4	1.2	3649	10.8	0.3	54.1*	(< 0.001)	
No extra-medical prescription drug use	24 732	88.8	0.3	1729	81.6	1.2	23 003	89.2	0.3			
VII. Other illicit drug use[f]	1616	4.4	0.2	263	9.7	0.8	1353	4.1	0.2	91.6*	(< 0.001)	
No other illicit drug use	27 233	95.6	0.2	1934	90.3	0.8	25 299	95.9	0.2			
VIII. Any illicit drug use	8888	27.1	0.4	1006	42.4	1.6	7882	26.2	0.4	117.6*	(< 0.001)	
No other illicit drug use	19 961	72.9	0.4	1191	57.6	1.6	18 770	73.8	0.4			
Life-time substance use disorder												
I. Nicotine dependence	3037	15.1	0.4	377	28.1	2.0	2660	14.4	0.4	57.4*	(< 0.001)	17017[b]
No nicotine dependence	13 980	84.9	0.4	797	71.9	2.0	13 183	85.6	0.4			
II. Alcohol use disorders	3418	7.7	0.2	485	17.1	1.1	2933	7.2	0.2	162.5*	(< 0.001)	30 902
No alcohol use disorder	27 484	92.3	0.2	1852	82.9	1.1	25 632	92.8	0.2			
III. Alcohol abuse[g]	2113	5.2	0.2	256	10.2	0.8	1857	4.9	0.2	67.2*	(< 0.001)	
No alcohol abuse	28 789	94.8	0.2	2081	89.8	0.8	26 708	95.1	0.2			
IV. Alcohol dependence[h]	1305	2.5	0.1	229	6.9	0.6	1076	2.2	0.1	141.2*	(< 0.001)	
No alcohol dependence	29 597	97.5	0.1	2108	93.1	0.6	27 489	97.8	0.1			
V. Illicit drug use disorders	1456	3.3	0.1	240	8.2	0.7	1216	3.0	0.1	97.5*	(< 0.001)	28849[d]
No illicit drug use disorder	27 393	96.7	0.1	1957	91.8	0.7	25 436	97.0	0.1			
VI. Illicit drug abuse[g]	842	2.0	0.1	107	3.7	0.5	735	1.9	0.1	87.0*	(< 0.001)	
No illicit drug abuse	28 007	98.0	0.1	2090	96.3	0.5	25 917	98.1	0.1			
VII. Illicit drug dependence[h]	614	1.3	0.1	133	4.5	0.6	481	1.1	0.1	104.1*	(< 0.001)	
No illicit drug dependence	28 235	98.7	0.1	2064	95.5	0.6	26 171	98.9	0.1			

*Significant at the 0.05 level, two-sided test. [a]Estimates are based on weighted data. SE = standard error. [b]Tobacco section was not administered to respondents in New Zealand, Portugal, Belgium, France, Germany, Italy, the Netherlands and Spain. Information on everyday tobacco use was not collected in Nigeria, hence the exclusion from the risk set. [c]Smoked tobacco every day or nearly every day for at least a period of 2 months among those with tobacco use. [d]Drug use section was not administered to respondents in Portugal. [e]Prescription drugs such as tranquillizers, stimulants, painkillers or other prescription drugs outside doctor's recommendation. [f]Other drugs included heroin, opium, glue, lysergic acid diethylamide (LSD), peyote or any other drug. [g]Diagnosis of abuse without dependence. [h]Diagnosis of dependence regardless of whether a diagnosis of abuse is present.

operationalized as logistic regression with person-year as the unit of analysis were used to investigate the bidirectional relationship between PE and each of the SU or SUDs. A person-year data set was constructed where each year in the life of each respondent (up to and including the age-at-onset of the outcome variables or age at interview, whichever came first) was treated as a separate observational record, with the year of outcome variable coded 1 and earlier years coded 0. When examining the predictive relationship between prior SU/SUDs and the subsequent onset of PEs, SU/SUDs that occurred in the same year as PEs or following PEs were excluded. Those without PEs were censored at their age at interview. For more details, see Supporting information, Table S4. Similarly, when examining the relationship between prior PEs and subsequent onset of SU/SUDs, we excluded PEs that occurred in the same year as SU/SUDs onset or following SU/SUDs. A series of survival models was developed. The base model (M1) was adjusted for age, sex, country and person-years. We also examined a model that adjusted further for the presence of other antecedent SU/SUDs (M2), and then additionally for the presence of other antecedent mental disorders (M3) (details can also be seen in Tables 2 and 3).

We also conducted two additional analyses: (1) to explore the impact of severity of PEs we repeated the survival models (M3) for prior PEs to predict subsequent onset of SU/SUDs using measures for both PE type metric (two or more types versus one type) and PE annualized frequency metric (dichotomized with a median split —more than 0.3 versus 0.3 or less episodes per year) in the models; and (2) a *post-hoc* analysis examining the associations between PEs and subsequent onset of SUDs among those with substance use only.

As the WMH data are both clustered and weighted, the design-based Taylor series linearization implemented in version 11 of SUDAAN software was used to estimate standard errors and evaluate the statistical significance of coefficients. All significance tests were evaluated using 0.05-level two-sided tests.

RESULTS

The life-time prevalence of SU/SUDs for the total sample and respondents with and without PEs are shown in Table 1. Among the total sample 74.7% [standard error (SE) = 0.4] of the respondents reported alcohol use while only 7.7% (SE = 0.2) met criteria for alcohol use disorders. Similarly, 51.0% (SE = 0.6) of the respondents reported tobacco use, whereas only 15.1% (SE = 0.4) had nicotine dependence disorders. Overall, the prevalence of all measures of SU/SUDs were higher among those with PEs compared with those without PEs (χ^2_1 ranges between 24.2 and 162.5, $P < 0.001$).

Table 2 Associations between temporally prior substance use (SU) and substance use disorders (SUDs) and subsequent onset of psychotic experiences (PEs).

	Multivariable (base) model (M1)[a]		*Multivariate model (M2)*[b]		*Multivariate model (M3)*[c]	
	OR	*(95% CI)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*
I. Odds of PE given prior onset of						
Tobacco use	1.8*	(1.4–2.3)	1.5*	(1.1–2.0)	1.3*	(1.0–1.8)
Daily tobacco use	1.6*	(1.2–2.0)	1.3	(1.0–1.7)	1.1	(0.8–1.6)
Alcohol use	1.8*	(1.5–2.1)	1.5*	(1.2–1.8)	1.4*	(1.1–1.7)
Cannabis use	1.6*	(1.4–2.0)	1.2	(0.9–1.5)	1.0	(0.8–1.3)
Cocaine use	1.8*	(1.3–2.4)	0.9	(0.7–1.3)	0.9	(0.7–1.3)
Extra-medical prescription drug use	2.1*	(1.6–2.7)	1.7*	(1.3–2.2)	1.5*	(1.1–1.9)
Other illicit drug use	2.1*	(1.6–2.7)	1.4*	(1.0–1.8)	1.2	(0.9–1.6)
II. Odds of PE given prior onset of						
Nicotine dependence	1.8*	(1.4–2.3)	1.5*	(1.1–2.0)	1.2	(0.9–1.6)
Alcohol use disorders	2.4*	(1.9–3.0)	2.1*	(1.6–2.7)	1.6*	(1.2–2.0)
Alcohol abuse	2.1*	(1.6–2.7)	2.0*	(1.5–2.7)	1.6*	(1.2–2.2)
Alcohol dependence	2.7*	(2.1–3.6)	2.3*	(1.7–3.2)	1.5*	(1.1–2.1)
Illicit drug use disorders	2.3*	(1.7–3.1)	1.3	(0.9–1.8)	1.0	(0.7–1.4)
Illicit drug abuse	1.7*	(1.1–2.5)	1.0	(0.6–1.6)	0.9	(0.6–1.4)
Illicit drug dependence	3.2*	(2.1–4.7)	1.6*	(1.1–2.6)	1.0	(0.6–1.7)

*Significant at the 0.05 level, two-sided test. [a]Model M1: each row represents a discrete-time survival model of SU or SUDs as predictors of subsequent PE onset adjusting for person-years, age cohorts, sex and country. [b]Model M2: (i) for life-time substance use, adjusted for other temporally prior substance use in addition to person-years, age cohorts, sex and country; (ii) for life-time substance use disorder, adjusted for other temporally prior substance use disorders in addition to person-years, age-cohorts, sex and country. [c]Model M3: (i) for life-time substance use, adjusted for other temporally prior substance use and antecedent mental disorders in addition to person-years, age cohorts, sex and country; (ii) for life-time substance use disorder, adjusted for other temporally prior substance use disorders and antecedent mental disorders in addition to person-years, age-cohorts, sex,and country. OR = odds ratio; CI = confidence interval.

Associations between substance use, substance use disorders and subsequent onset of psychotic experiences

First, we examined the associations between SUs and SUDs, and the subsequent onset of PEs in the total sample (Table 2). In the multivariable base model (M1) adjusting for age-cohort, sex, person-years and country, all substance use or SUDs were associated significantly with increased odds of subsequent onset of PEs. In the multivariate model (M2), after adjusting for potential confounding factors that included age-cohort, sex, person-years, country and temporally prior SU and SUDs, the odds ratios (ORs) attenuated in all disorders while the associations with daily tobacco use, cannabis use, cocaine use and illicit drug abuse became non-significant. After additional adjustments with antecedent mental disorders (M3), those with life-time tobacco use [OR = 1.3, 95% confidence interval (CI) = 1.0–1.8], alcohol use (OR =1.4, 95% CI = 1.1–1.7) and extra-medical prescription drug use (OR = 1.5, 95% CI = 1.1–1.9) each had increased odds of subsequent onset of PEs. Unexpectedly, cannabis use was not associated with subsequent onset of PEs in the adjusted models. With respect to SUDs, alcohol use disorders (both alcohol abuse and alcohol dependence disorders) were associated with increased odds of subsequent PEs (alcohol abuse: OR =1.6, 95% CI = 1.2–2.2; alcohol dependence: OR = 1.5, 95% CI = 1.1–2.1).

Associations between psychotic experiences and later onset of SU/SUDs

In Table 3 we examined the associations between prior PEs and subsequent onset of SU/SUDs. In the multivariable base model (M1), temporally prior PEs were associated with increased odds of subsequent onset of all types of SU/SUDs. In the first multivariate models (M2), after adjusting for potential confounding factors (age-cohort, sex, person-years, country and temporally ordered SU/SUDs), the ORs for the associations attenuated, however, with additional adjustments with antecedent mental disorders (M3), those with temporally prior PEs had increased odds of subsequent tobacco use (OR = 1.5, 95% CI = 1.2–1.9), alcohol use (OR =1.3, 95% CI = 1.1–1.6) and cannabis use (OR =1.3, 95% CI = 1.0–1.5). Those with PEs also had increased odds of subsequent onset of nicotine dependence (OR =1.4, 95% CI = 1.1–2.0), alcohol abuse (OR =1.5, 95% CI = 1.2–2.0) and alcohol dependence (OR =1.4, 95% CI = 1.0–1.9) and illicit drug dependence (OR =1.5, 95% CI = 1.0–2.3).

When we repeated the survival models (M3) exploring the impact of severity of PEs on SU/SUDs that used PE type and PE annualized frequency metrics, we found a dose–response relationship between PEs and SU/SUDs (Table 4). Those with two or more PE types (compared to one type) had elevated ORs for alcohol use, cannabis use,

Table 3 Associations between temporally prior psychotic experiences (PEs) and subsequent onset of substance use (SU) and substance use disorders (SUDs).

	Multivariable (base) model (M1)[a]		*Multivariate model (M2)*[b]		*Multivariate model (M3)*[c]	
	OR	*(95% CI)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*
I. Prior onset of PE and odds of subsequent onset of						
Tobacco use	1.8*	(1.5–2.3)	1.7*	(1.3–2.1)	1.5*	(1.2–1.9)
Daily tobacco use	1.5*	(1.2–1.8)	1.2	(1.0–1.5)	1.1	(0.9–1.4)
Alcohol use	1.4*	(1.2–1.7)	1.4*	(1.1–1.6)	1.3*	(1.1–1.6)
Cannabis use	1.9*	(1.6–2.3)	1.4*	(1.1–1.7)	1.3*	(1.0–1.5)
Cocaine use	1.8*	(1.4–2.4)	1.1	(0.8–1.5)	1.1	(0.8–1.4)
Extra-medical prescription drug use	1.9*	(1.5–2.3)	1.4*	(1.1–1.7)	1.2	(0.9–1.5)
Other illicit drug use	2.1*	(1.6–2.7)	1.2	(0.9–1.6)	1.1	(0.8–1.4)
II. Prior onset of PE and odds of subsequent onset of						
Nicotine dependence	2.2*	(1.7–2.8)	1.9*	(1.4–2.4)	1.4*	(1.1–2.0)
Alcohol use disorders	2.5*	(2.0–3.0)	2.0*	(1.6–2.6)	1.5*	(1.2–2.0)
Alcohol abuse	2.1*	(1.6–2.7)	1.9*	(1.5–2.5)	1.5*	(1.2–2.0)
Alcohol dependence	2.8*	(2.1–3.6)	2.1*	(1.5–2.9)	1.4*	(1.0–1.9)
Illicit drug use disorders	2.8*	(2.1–3.6)	1.8*	(1.4–2.5)	1.5*	(1.1–2.0)
Illicit drug abuse	2.2*	(1.5–3.1)	1.6*	(1.1–2.3)	1.4	(0.9–2.1)
Illicit drug dependence	3.4*	(2.4–4.8)	2.3*	(1.6–3.3)	1.5*	(1.0–2.3)

*Significant at the 0.05 level, two-sided test. [a]Model M1: each row represents a discrete-time survival model of PEs as predictors of subsequent SU or SUDs onset adjusting for person-years, age cohorts, sex and country. [b]Model M2: (i) for life-time substance use, adjusted for other temporally prior substance use in addition to person-years, age cohorts, sex and country; (ii) for life-time substance use disorder, adjusted for other temporally prior substance use disorders in addition to person-years, age-cohorts, sex and country. [c]Model M3: (i) for life-time substance use, adjusted for other temporally prior substance use and antecedent mental disorders in addition to person-years, age cohorts, sex and country; (ii) for life-time substance use disorder, adjusted for other temporally prior substance use and antecedent mental disorders in addition to person-years, age-cohorts, sex and country. OR = odds ratio; CI = confidence interval.

cocaine use and alcohol or illicit drug use disorders. The ORs ranged between 1.4 and 1.9 among those with life-time SU, and between 1.5 and 1.9 among those with SUDs. Similarly, those with more frequent PEs (compared to those with less frequent PEs) had increased odds of tobacco use, alcohol use, nicotine dependence, alcohol use disorders and illicit drug dependence, with similar gradients of risks as in PE types. When we repeated the survival models (M3) by restricting our sample within substance users only (as a *post-hoc* analysis), we found that PEs were associated with an increased odds of transition to alcohol abuse and alcohol use disorders (Supporting information, Table S3).

DISCUSSION

Using temporally ordered analyses, we confirm that the associations between SU/SUDs and PEs are bidirectional, and that these associations mainly persisted after accounting for other forms of prior SU/SUDs, demographic factors and a wide range of antecedent mental disorders. Because of the large sample size, we were also able to examine the specific nature of these associations across different types of both SUs and SUDs. In this way, we have extended our own research that showed significant bidirectional associations between PEs and certain types of SUDs (e.g. alcohol use disorders) [18], and also previous research that focused upon cannabis use disorders only [19].

Life-time tobacco use, extra-medical prescription drug use and alcohol use and alcohol use disorders were all associated with elevated odds of subsequent PEs after controlling for comorbid SU/SUDs and antecedent mental disorders. Similarly, temporally prior PEs were associated with subsequent onset of tobacco, alcohol and cannabis use and all SUDs. In addition, we found a dose–response relationship between PEs and subsequent onset of SU/SUDs with more types or greater number of PEs were associated with several SU/SUDs. The relationship persisted after controlling for a range of potential confounding factors.

When we restricted the analysis of PEs to predict SUDs among substance users, only the associations between PEs and alcohol disorders remained significant after adjusting for antecedent mental disorders. Although PEs were associated with an overall risk in SUDs, among those with substance use they did not make an additional contribution to the risk to other drug disorders or nicotine dependence, suggesting that the presence of PEs did not alter the odds of transitions from substance users to other drugs or nicotine use disorders.

We also found that the associations between SU/SUDs and PEs identified in multivariable models were attenuated after adjustment with 21 antecedent mental disorders.

Table 4 Associations between psychotic experiences (PEs) (two or more versus one PE type, more than 0.3 annualized episodes versus 0.3 or less) and subsequent onset of substance use (SU) and substance use disorders (SUDs).

	2 or more PE types[a]		*> 0.3 episodes per year*[b]	
	OR	*(95% CI)*	*OR*	*(95% CI)*
I. Life-time substance use				
Tobacco use	1.5	(0.9–2.3)	1.5*	(1.0–2.1)
Daily tobacco use	0.9	(0.6–1.2)	1.2	(0.9–1.8)
Alcohol use	1.5*	(1.1–1.9)	1.4*	(1.1–1.8)
Cannabis use	1.4*	(1.1–1.9)	1.2	(0.9–1.5)
Cocaine use	1.9*	(1.3–2.8)	1.2	(0.9–1.8)
Extra-medical prescription drug use	1.2	(0.8–1.9)	1.0	(0.7–1.4)
Other illicit drug use	0.9	(0.6–1.4)	1.0	(0.7–1.5)
II. Life-time substance use disorder				
Nicotine dependence	1.5	(0.9–2.3)	1.6*	(1.1–2.3)
Alcohol use disorders	1.5*	(1.0–2.1)	1.6*	(1.3–2.1)
Alcohol abuse	1.3	(0.8–2.1)	1.2	(0.8–1.8)
Alcohol dependence	1.9*	(1.3–2.9)	2.0*	(1.4–2.9)
Illicit drug use disorders	1.6*	(1.1–2.3)	1.4	(1.0–2.0)
Illicit drug abuse	1.7*	(1.0–2.9)	1.2	(0.7–2.2)
Illicit drug dependence	1.6	(1.0–2.7)	1.7*	(1.1–2.6)

*Significant at the 0.05 level, two-sided test. [a]Each row represents a discrete-time survival model of two or more PE types (ref: one PE type) as predictors of subsequent SU or SUDs. (i) For life-time substance use, adjusted for other temporally prior substance use and antecedent mental disorders in addition to person-years, age cohorts, sex and country; (ii) for life-time substance use disorder, adjusted for other temporally prior substance use and antecedent mental disorders in addition to person-years, age-cohorts, sex and country. [b]Each row represents a discrete-time survival model of more than 0.3 annualized episodes (ref: ≤ 0.3 episodes) as predictors of subsequent SU or SUDs. (i) For life-time substance use, adjusted for other temporally prior substance use and antecedent mental disorders in addition to person-years, age cohorts, sex and country; (ii) for life-time substance use disorder, adjusted for other temporally prior substance use, and antecedent mental disorders in addition to person-years, age-cohorts, sex and country. OR = odds ratio; CI = confidence interval.

This was not surprising, given that previous research suggested that prior PEs increased the risk of mental disorders later in life [20], and given the extensive comorbidity between different types of substance use and mental disorders [31]. However, even after these adjustments, we identified appreciable ORs between several patterns of SU/SUDs and subsequent PEs and vice versa. These findings lend weight to the hypothesis that the presence of antecedent mental disorders does not account entirely for the relationship between SU/SUDs and PEs in either direction.

Although we found significant associations between cannabis use and subsequent onset of PEs in the bivariate model, this association did not persist after adjustment for the range of covariates we considered here, which included demographics, other temporally prior substance use and antecedent mental disorders. This is in contrast to cohort studies that included similar covariates [32]. This discrepancy may be due partly to methodological differences, as our analysis controlled for a much wider range of antecedent mental disorders than previous analyses, and excluded samples those with onset of PEs and SU/SUDs in the same year. Additionally, the mechanism of effect may be that cannabis induces PEs in those already vulnerable to developing such symptoms. We did not examine the age-at-onset of PEs among those who used (or did not use) substances, but previous research has suggested that cannabis may serve largely to decrease the age-at-onset of psychosis (rather than increasing incidence) [33]. PEs and substance use disorder may share common risk factors (e.g. traumatic life events, family history). Previous research found that the association between PEs and SUDs persisted after adjusting for trauma and victimization [4].

Although a significant body of evidence has linked SU/SUDs with subsequent PEs, the biological mechanisms underpinning the association are yet to be established. Some commentators have suggested that substance use may contribute to dysregulation of dopamine neurotransmission which, in turn, may contribute to vulnerability to psychosis [34]. However, a recent meta-analysis with 24 studies found little evidence to suggest that cannabis use affects dopamine release in striatal and pre-frontal areas among healthy subjects [35].

Several of the findings from this study warrant additional research, given their potential clinical and public health significance. First, the prevalence of SU/SUDs was higher among people who had experienced PEs, and further, that people who had experienced PEs also had greater odds of a range of different types of SUDs if they had engaged in use of any of the substances we examined here. The health risks of heavy tobacco use in particular are a concern, especially among more vulnerable and marginalized populations, which includes people with mental health problems, for whom it may also be more difficult to cease use. Secondly, once PEs have developed in an individual, the continued use of substances with psychoactive effects is of clinical concern, particularly in the case of alcohol and cannabis, which are the most commonly used substances. There is consistent evidence that continued substance use among people who have developed mental health problems increases risks for poorer mental health outcomes [36]. Our findings also provide a heuristic framework for the generation of new hypothesis related to PEs in future studies. For example, in light of the dose–response relationship between PEs and subsequent SU/SUDs, it will be of interest to see what proportion of early- versus late-onset PEs are linked to SU/SUDs and multiple use of substance use, as well as to explore if particular types of PEs (e.g. hallucinations, delusions) are associated differentially with particular types of SU/SUDs as a complex function of age at onset, time since onset and existence of complex comorbidities. As noted earlier, familial factors (e.g. genetic, shared environment) could confound the apparent relationships between the variables of interest [21], in which case public health interventions designed to reduce the prevalence of exposure to SU/SUDs may not translate to reductions in the onset of subsequent PEs.

While the current study has several strengths (large sample size from many countries, consistent methods and standardized measures of data collection and temporally sequence the variables of interest), the study has several limitations. First, although we excluded people who were screen-positive for possible psychotic disorders, the WMH surveys were administered by lay interviewers, and clinical validation of CIDI diagnoses was not available. Respondents may underestimate their use of substances—this type of bias would reduce our ability to detect a true association between the variables of interest. Secondly, our studies were based on cross-sectional studies and retrospective reports about age-at-onset of PEs, SUDs and mental disorders which, although obtained rigorously [37], would be subject to some level of recall bias. While we note that several prospective studies have confirmed the association between SUDs and PEs [1,5,19], observational studies cannot determine causal pathways. Thirdly, our measure of cannabis use was onset of first-time use (not more frequent use), which may have contributed to our lack of significant findings between cannabis use and subsequent PEs. Moreover, the data did not allow us to measure cannabis use disorders in this study. Finally, it was also not possible to analyse those who had limited alcohol use versus heavy users because there were no separate questions for this in the WMH CIDI.

In summary, this study sheds new light upon the relationship between PEs and SU/SUDs. Although arguments continue whether SU/SUDs are associated causally with PEs [38], our temporally ordered analysis confirms that the relationship between various SU/SUDs and PEs is bidirectional, and independent of antecedent mental disorders.

These findings have both clinical and public health significance, given that SU/SUDs and psychosis are important predictors of adverse health outcomes [39].

Declaration of interests

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1 World Mental Health (WMH) sample characteristics by World Bank income categories, and sample for psychotic experiences (PEs).
Table S2a Six CIDI Psychotic experiences types in six European (ESEMed[a]) sites (Belgium, France, Germany, Italy, Netherlands, Spain).
Table S2b Six CIDI Psychotic experiences types in 12 non-ESEMed sites (Colombia, Lebanon, Mexico, Brazil, Iraq, Nigeria, Peru, Portugal, Romania, USA, Argentina).
Table S2c 21 DSM-IV mental disorders across 18 WMH sites.
Table S3 Associations between temporally prior psychotic experiences and subsequent onset of substance use disorders (SUDs) among those with substance use.
Table S4 Discrete-time survival model specification using person-year (an example).