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The associations between psychotic experiences, and substance use and substance use disorders: Findings from the World Health Organisation World Mental Health Surveys

Short title: Psychotic experiences and substance use

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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 Organisation World Mental Health surveys. A total of 30,902 adult respondents across 18 countries were assessed for (a) six types of lifetime 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 (OR=1.6, 95% 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.

Key words: Psychotic experiences, substance use, substance abuse disorder, substance dependence disorder, cannabis, alcohol, tobacco, nicotine, prescription drug, mental disorder

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 World Health Survey found that current tobacco smoking was associated with increased odds of lifetime 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 bidirectionally associated 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 in turn leads 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 at least in part explained 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 WHO World Mental Health surveys that included both the WHO Composite International Diagnostic Interview Psychosis (CIDI) 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 Supplementary table S1. The weighted average response rate across all 18 surveys was 71.7%. Further information on sample used for different substance use, details of procedure, and the assessment of mental disorders can be found in the Supplementary Methods 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 lifetime 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 two 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 tranquilizers, 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, 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, fourth 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 operationalise the symptom criteria for alcohol abuse and a further eleven 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 lifetime 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 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 6 PE types – 2 related to hallucinatory experiences (visual hallucinations, auditory hallucinations) and 4 related to delusional experiences (thought insertion/withdrawal, mind control/passivity, ideas of reference, plot to harm/follow) (Supplementary 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 (Supplementary table S1).

The association between SU/SUDs and PEs was tested using Rao-Scott chi-square. Discrete-time survival models 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 dataset 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 Supplementary 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) adjusted for age, sex, country and person-years. We also examined a model that further adjusted 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 Table 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* (2 or more types versus 1 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 .05-level two-sided tests.

RESULTS

The lifetime 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% (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*<.001).

INSERT TABLE 1 ABOUT HERE

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 significantly associated 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 attenuated in all disorders while the associations with cocaine use and illicit drug abuse became non-significant. After additional adjustments with antecedent mental disorders (M3), those with lifetime tobacco use (OR= 1.3, 95% 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).

INSERT TABLE 2 ABOUT HERE

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 odds ratios for the associations attenuated, however with additional adjustments with 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 2 or more PE types (compared to 1 type) had elevated odds ratios for alcohol use, cannabis use, and cocaine use, and alcohol or illicit drug use disorders. The odds ratios ranged between 1.4 and 1.9 among those with lifetime 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 (Supplementary table S3).

INSERT TABLE 3 and 4 ABOUT HERE

DISCUSSION

Using temporally ordered analyses, we confirm that the associations between SU/SUDs and PEs are bidirectional, and that these associations mostly 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 focussed on cannabis use disorders only [19].

Lifetime tobacco use, extra-medical prescription drug use, and alcohol use and alcohol use disorders all were 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 drugs 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. 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 odds ratios 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 entirely account 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 partly be due 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 marginalised populations, which includes people with mental health problems, for whom it may also be more difficult to cease use. Second, 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, multiple use of substance use, as well as to explore if particular types of PEs (e.g. hallucinations, delusions) are differentially associated 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 standardised 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. Second, our studies were based on cross-sectional studies and retrospective reports about age-at-onset of PEs, SUDs and mental disorders, which although rigorously obtained [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. Third, 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 was no separate questions for this in the WMH CIDI.

In summary, this study shed new lights on the relationship between PEs and SU/SUDs. Although arguments continue whether SU/SUDs are causally associated 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].

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References

1. Henquet, C., Krabbendam, L., Spauwen, J., Kaplan, C., Lieb, R., Wittchen, H. U. et al. Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people, *BMJ*, 2005; 330, 11.
2. Kuepper, R., Van Os, J., Lieb, R., Wittchen, H. U., Hofler, M. Henquet, C. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study, *Bmj*, 2011; 342, d738.
3. Ruiz-Veguilla, M., Barrigon, M. L., Hernandez, L., Rubio, J. L., Gurpegui, M., Sarramea, F. et al. Dose-response effect between cannabis use and psychosis liability in a non-clinical population: evidence from a snowball sample, *J Psychiatr Res*, 2013; 47, 1036-43.
4. Saha, S., Scott, J. G., Varghese, D., Degenhardt, L., Slade, T. Mcgrath, J. J. The association between delusional-like experiences, and tobacco, alcohol or cannabis use: a nationwide population-based survey, *BMC Psychiatry*, 2011; 11, 202-210.
5. Van Os, J., Bak, M., Hanssen, M., Bijl, R. V., De Graaf, R. Verdoux, H. Cannabis use and psychosis: a longitudinal population-based study, *Am J Epidemiol*, 2002; 156, 319-27.
6. Mcgrath, J., Welham, J., Scott, J., Varghese, D., Degenhardt, L., Hayatbakhsh, M. R. et al. Association between cannabis use and psychosis-related outcomes using sibling pair analysis in a cohort of young adults, *Arch Gen Psychiatry*, 2010; 67, 440-7.
7. Bechtold, J., Hipwell, A., Lewis, D. A., Loeber, R. Pardini, D. Concurrent and Sustained Cumulative Effects of Adolescent Marijuana Use on Subclinical Psychotic Symptoms, *Am J Psychiatry*, 2016; 173, 781-9.
8. Fergusson, D. M., Horwood, L. J. Ridder, E. M. Tests of causal linkages between cannabis use and psychotic symptoms, *Addiction*, 2005; 100, 354-66.
9. Mackie, C. J., O'leary-Barrett, M., Al-Khudhairy, N., Castellanos-Ryan, N., Struve, M., Topper, L. et al. Adolescent bullying, cannabis use and emerging psychotic experiences: a longitudinal general population study, *Psychol Med*, 2013; 43, 1033-44.
10. Koyanagi, A., Stickley, A. Haro, J. M. Psychotic symptoms and smoking in 44 countries, *Acta Psychiatr Scand*, 2016; 133, 497-505.
11. Oh, H. Y., Koyanagi, A., Singh, F. Devylder, J. Is smoking tobacco associated with psychotic experiences across racial categories in the United States? Findings from the Collaborative Psychiatric Epidemiological Surveys, *Psychiatry Res*, 2016; 246, 58-61.
12. Tien, A. Y. Anthony, J. C. Epidemiological analysis of alcohol and drug use as risk factors for psychotic experiences, *J Nerv Ment Dis*, 1990; 178, 473-80.
13. Mcgrath, J. J., Alati, R., Clavarino, A., Williams, G. M., Bor, W., Najman, J. M. et al. Age at first tobacco use and risk of subsequent psychosis-related outcomes: A birth cohort study, *Aust N Z J Psychiatry*, 2016; 50, 577-83.

14. Fiorentini, A., Volonteri, L. S., Dragogna, F., Rovera, C., Maffini, M., Mauri, M. C. et al. Substance-induced psychoses: a critical review of the literature, *Curr Drug Abuse Rev*, 2011; 4, 228-40.

15. Vergara-Moragues, E., Araos Gomez, P., Gonzalez-Saiz, F. Rodriguez-Fonseca, F. Cocaine-induced psychotic symptoms in clinical setting, *Psychiatry Res*, 2014; 217, 115-20.

16. Vorspan, F., Brousse, G., Bloch, V., Bellais, L., Romo, L., Guillem, E. et al. Cocaine-induced psychotic symptoms in French cocaine addicts, *Psychiatry Res*, 2012; 200, 1074-6.

17. Smith, M. J., Thirthalli, J., Abdallah, A. B., Murray, R. M. Cottler, L. B. Prevalence of psychotic symptoms in substance users: a comparison across substances, *Compr Psychiatry*, 2009; 50, 245-50.

18. Mcgrath, J. J., Saha, S., Al-Hamzawi, A., Andrade, L., Benjet, C., Bromet, E. J. et al. The Bidirectional Associations Between Psychotic Experiences and DSM-IV Mental Disorders, *Am J Psychiatry*, 2016; 173, 997-1006.

19. Ferdinand, R. F., Sondeijker, F., Van Der Ende, J., Selten, J. P., Huizink, A. Verhulst, F. C. Cannabis use predicts future psychotic symptoms, and vice versa, *Addiction*, 2005; 100, 612-8.

20. Connell, M., Betts, K., Mcgrath, J. J., Alati, R., Najman, J., Clavarino, A. et al. Hallucinations in adolescents and risk for mental disorders and suicidal behaviour in adulthood: Prospective evidence from the MUSP birth cohort study, *Schizophr Res*, 2016; 176, 546-51.

21. Giordano, G. N., Ohlsson, H., Sundquist, K., Sundquist, J. Kendler, K. S. The association between cannabis abuse and subsequent schizophrenia: a Swedish national co-relative control study, *Psychol Med*, 2015; 45, 407-14.

22. Swendsen, J., Conway, K. P., Degenhardt, L., Glantz, M., Jin, R., Merikangas, K. R. et al. Mental disorders as risk factors for substance use, abuse and dependence: results from the 10-year follow-up of the National Comorbidity Survey, *Addiction*, 2010; 105, 1117-28.

23. Kessler, R. C. The epidemiology of dual diagnosis, *Biol Psychiatry*, 2004; 56, 730-7.

24. Degenhardt, L., Chiu, W. T., Sampson, N., Kessler, R. C., Anthony, J. C., Angermeyer, M. et al. Toward a global view of alcohol, tobacco, cannabis, and cocaine use: findings from the WHO World Mental Health Surveys, *PLoS Med*, 2008; 5, e141.

25. Glantz, M. D., Medina-Mora, M. E., Petukhova, M., Andrade, L. H., Anthony, J. C., De Girolamo, G. et al. Alcohol abuse in developed and developing countries in the World Mental Health Surveys: Socially defined consequences or psychiatric disorder?, *The American Journal on Addictions*, 2014; 23, 145-155.

26. Slade, T., Chiu, W. T., Glantz, M., Kessler, R. C., Lago, L., Sampson, N. et al. A Cross-National Examination of Differences in Classification of Lifetime Alcohol Use Disorder Between DSM-IV and DSM-5: Findings from the World Mental Health Survey, *Alcohol Clin Exp Res*, 2016; 40, 1728-36.

27. Lago, L., Glantz, M. D., Kessler, R. C., Sampson, N. A., Al-Hamzawi, A., Florescu, S. et al. Substance dependence among those without symtoms of substance abuse in the World Mental Health Survey, *Int J Methods Psychiatr Res*, 2016, e1557.

28. Mcgrath, J. J., Saha, S., Al-Hamzawi, A. O., Alonso, J., Andrade, L., Borges, G. et al. Age of Onset and Lifetime Projected Risk of Psychotic Experiences: Cross-National Data From the World Mental Health Survey, *Schizophr Bull*, 2016; 42, 933-41.

29. Mcgrath, J. J., Saha, S., Al-Hamzawi, A., Alonso, J., Bromet, E. J., Bruffaerts, R. et al. Psychotic Experiences in the General Population: A Cross-National Analysis Based on 31261 Respondents From 18 Countries, *JAMA Psychiatry*, 2015; 72, 697-705.

30. Saha, S., Scott, J. G., Johnston, A. K., Slade, T. N., Varghese, D., Carter, G. L. et al. The association between delusional-like experiences and suicidal thoughts and behaviour, *Schizophr Res*, 2011; 132, 197-202.

31. Hall, W., Degenhardt, L. Teesson, M. Understanding comorbidity between substance use, anxiety and affective disorders: broadening the research base, *Addict Behav*, 2009; 34, 526-30.

32. Zammit, S., Moore, T. H., Lingford-Hughes, A., Barnes, T. R., Jones, P. B., Burke, M. et al. Effects of cannabis use on outcomes of psychotic disorders: systematic review, *Br J Psychiatry*, 2008; 193, 357-63.

33. Large, M., Sharma, S., Compton, M. T., Slade, T. Nielssen, O. Cannabis use and earlier onset of psychosis: a systematic meta-analysis, *Arch Gen Psychiatry*, 2011; 68, 555-61.

34. Howes, O. D., Mcdonald, C., Cannon, M., Arseneault, L., Boydell, J. Murray, R. M. Pathways to schizophrenia: the impact of environmental factors, *Int J Neuropsychopharmacol*, 2004; 7 Suppl 1, S7-S13.

35. Sami, M. B., Rabiner, E. A. Bhattacharyya, S. Does cannabis affect dopaminergic signaling in the human brain? A systematic review of evidence to date, *Eur Neuropsychopharmacol*, 2015; 25, 1201-24.

36. Foti, D. J., Kotov, R., Guey, L. T. Bromet, E. J. Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization, *Am J Psychiatry*, 2010; 167, 987-93.

37. Knäuper, B., Cannell, C. F., Schwarz, N., Bruce, M. L. Kessler, R. C. Improving accuracy of major depression age-of-onset reports in the US National Comorbidity Survey, *International Journal of Methods in Psychiatric Research* 1999; 8, 39-48.

38. Murray, R. M., Quigley, H., Quattrone, D., Englund, A. Di Forti, M. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis, *World Psychiatry*, 2016; 15, 195-204.

39. Kavanagh, D. J., Waghorn, G., Jenner, L., Chant, D. C., Carr, V., Evans, M. et al. Demographic and clinical correlates of comorbid substance use disorders in psychosis: multivariate analyses from an epidemiological sample, *Schizophr Res*, 2004; 66, 115-24.

40. Aguilar-Gaxiola, S. Policy Implications, in: M. Von Korff, K. S., and O. Gureje (Ed.) *Global Perspectives on Mental Disorders and Physical Illness in the WHO World Mental Health Surveys*, pp. 2009 302-312 (New York, NY, Cambridge University Press).

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

Substance use and substance use disorders	Total sample			Respondents with lifetime PEs			Respondents without lifetime PEs			X^2 between respondents with and without PEs		Sample size used
	n	%[a]	SE	n	%[a]	SE	n	%[a]	SE	X^2_1	[p-value]	
Lifetime substance use												
I. Tobacco use	8940	51.0	0.6	819	69.5	2.2	8121	49.9	0.6	60.4*	[<.001]	17017[g]
No tobacco use	8077	49.0	0.6	355	30.5	2.2	7722	50.1	0.6			
II. Daily tobacco use[b]	6491	36.0	0.5	559	46.0	2.2	5932	35.4	0.5	24.2*	[<.001]	
No daily tobacco use	10526	64.0	0.5	615	54.0	2.2	9911	64.6	0.5			
III. Alcohol use	22976	74.7	0.4	2098	89.4	0.9	20878	73.8	0.4	128.1*	[<.001]	30902
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*	[<.001]	
No cannabis use	22758	80.8	0.4	1435	67.9	1.5	21323	81.6	0.4			
V. Cocaine use	1370	4.1	0.2	204	8.4	0.8	1166	3.8	0.2	61.6*	[<.001]	
No cocaine use	27479	95.9	0.2	1993	91.6	0.8	25486	96.2	0.2			
VI. Extra-medical prescription drug use[c]	4117	11.2	0.3	468	18.4	1.2	3649	10.8	0.3	54.1*	[<.001]	28849[h]
No extra-medical prescription drug use	24732	88.8	0.3	1729	81.6	1.2	23003	89.2	0.3			
VII. Other illicit drug use[d]	1616	4.4	0.2	263	9.7	0.8	1353	4.1	0.2	91.6*	[<.001]	
No other illicit drug use	27233	95.6	0.2	1934	90.3	0.8	25299	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*	[<.001]	
No other illicit drug use	19961	72.9	0.4	1191	57.6	1.6	18770	73.8	0.4			
Lifetime substance use disorder												
I. Nicotine dependence	3037	15.1	0.4	377	28.1	2.0	2660	14.4	0.4	57.4*	[<.001]	17017[g]
No nicotine dependence	13980	84.9	0.4	797	71.9	2.0	13183	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*	[<.001]	
No alcohol use disorder	27484	92.3	0.2	1852	82.9	1.1	25632	92.8	0.2			
III. Alcohol abuse[e]	2113	5.2	0.2	256	10.2	0.8	1857	4.9	0.2	67.2*	[<.001]	30902
No alcohol abuse	28789	94.8	0.2	2081	89.8	0.8	26708	95.1	0.2			
IV. Alcohol dependence[f]	1305	2.5	0.1	229	6.9	0.6	1076	2.2	0.1	141.2*	[<.001]	
No alcohol dependence	29597	97.5	0.1	2108	93.1	0.6	27489	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*	[<.001]	
No illicit drug use disorder	27393	96.7	0.1	1957	91.8	0.7	25436	97.0	0.1			
VI. Illicit drug abuse[e]	842	2.0	0.1	107	3.7	0.5	735	1.9	0.1	87.0*	[<.001]	28849[h]
No illicit drug abuse	28007	98.0	0.1	2090	96.3	0.5	25917	98.1	0.1			
VII. Illicit drug dependence[f]	614	1.3	0.1	133	4.5	0.6	481	1.1	0.1	104.1*	[<.001]	
No illicit drug dependence	28235	98.7	0.1	2064	95.5	0.6	26171	98.9	0.1			

[a] Estimates are based on weighted data. SE, standard error

[b] Smoked tobacco every day or nearly every day for at least a period of two months among those with tobacco use.

[c] Prescription drug like tranquilizers, stimulants, pain killers, or other prescription drugs outside doctor's recommendation.

[d] Other drugs included heroin, opium, glue, LSD, peyote or any other drug.

[e] Diagnosis of abuse without dependence.

[f] Diagnosis of dependence regardless of whether a diagnosis of abuse is present.

[g] 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.

[h] Drug use section was not administered to respondents in Portugal.

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

	Multivariable (base) model (M1)[a]		Multivariate model (M2)[b]		Multivariate model (M3)[c]	
	OR	**(95% C.I)**	**OR**	**(95% C.I)**	**OR**	**(95% C.I)**
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)

[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 lifetime substance use, adjusted for other temporally prior substance use in addition to person-years, age cohorts, sex, and country. (ii) For lifetime 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 lifetime 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 lifetime 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.

Table 3. Associations between temporally prior psychotic experiences 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% C.I)**	**OR**	**(95% C.I)**	**OR**	**(95% C.I)**
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)

[a]Model M1: Each row represents a discrete-time survival model of PEs as predictors of subsequent SU orSUDs onset adjusting for person-years, age cohorts, sex, and country.

[b]Model M2: (i) For lifetime substance use, adjusted for other temporally prior substance use in addition to person-years, age cohorts, sex, and country. (ii) For lifetime 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 lifetime 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 lifetime substance use disorder, adjusted for other temporally prior substance use, and antecedent mental disorders in addition to person-years, age-cohorts, sex, and country.

Table 4. Associations between psychotic experiences (2 or more versus 1 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% C.I)	OR	(95% C.I)
I. Lifetime 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. Lifetime 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)

[a]Each row represents a discrete-time survival model of 2 or more PE types (ref: 1 PE type) as predictors of subsequent SU or SUDs. (i) For lifetime 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 lifetime 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 lifetime 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 lifetime substance use disorder, adjusted for other temporally prior substance use, and antecedent mental disorders in addition to person-years, age-cohorts, sex, and country.