

**Risk of Self-harm or Suicide Associated with Specific Drug Use Disorders, 2004-2016: A  
Population-Based Cohort Study**

Yi Chai<sup>1</sup>, MSc; Hao Luo<sup>1,2</sup>, PhD; Yue Wei<sup>3</sup>, MPH; Sherry K.W. Chan<sup>4,5</sup>, MRCPsych; Kenneth K. C. Man<sup>3,6,7</sup>, PhD; Paul S. F. Yip<sup>1,8</sup>, PhD; Ian C. K. Wong<sup>3,6,7</sup>, PhD; Esther W. Chan<sup>3</sup>, PhD

<sup>1</sup> Department of Social Work and Social Administration, Faculty of Social Sciences, The University of Hong Kong, Hong Kong SAR, China

<sup>2</sup> Sau Po Centre on Ageing, The University of Hong Kong, Hong Kong SAR, China

<sup>3</sup> Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

<sup>4</sup> Department of Psychiatry, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

<sup>5</sup> State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong SAR, China

<sup>6</sup> Research Department of Practice and Policy, School of Pharmacy, University College London, London, England

<sup>7</sup> Laboratory of Data Discovery for Health, Hong Kong Science Park, Hong Kong SAR, China

<sup>8</sup> The Hong Kong Jockey Club Centre for Suicide Research and Prevention, Department of Social Work and Social Administration, Faculty of Social Sciences, The University of Hong Kong, Hong Kong SAR, China

**Correspondence:** Hao Luo, Room 521, The Jockey Club Tower, The Centennial Campus, The University of Hong Kong, Pokfulam Road, Hong Kong SAR, China.

E-mail address: [haoluo@hku.hk](mailto:haoluo@hku.hk)

**Running head:** Specific Drug Use Disorders and Self-harm

**Word count:** 3643

**Conflict of interest declaration:**

KKCM is the recipient of the CW Maplethorpe Fellowship and grants from the United Kingdom National Institute of Health Research, European Commission Horizon 2020, the Hong Kong Research Grant Council. He has received a personal fee from IQVIA Ltd. outside the submitted work.

EWC is the recipient of an honorarium from the Hong Kong Hospital Authority, and research grants from the National Health and Medical Research Council, Australia, the National Natural Science Foundation of China, the Research Fund Secretariat of the Food and Health Bureau, Hong Kong, the Research Grants Council, Hong Kong, the Wellcome Trust, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Janssen, Pfizer, RGA and Takeda outside the submitted work.

ICKW has received research grants from the Research Grants Council Hong Kong, the Innovation and Technology Commission, Hong Kong, the National Institute of Health Research, UK and the Innovative Medicines Initiative European Union FP7 program. ICKW also received education and research grant from Amgen, Bayer Shire, GSK, IQVIA, Janssen-Cilag, Novartis, and Pfizer. He also received a personal fee from IQVIA and Jacobson Pharmaceutical outside the submitted work.

## **Abstract**

**Background and Aims:** Drug use disorders are associated with increased risk of self-harm. Risk differences associated with specific types of drug use disorders are yet to be comprehensively reported. This study aimed to examine the risk of self-harm or suicide associated with different drug use disorders in Hong Kong.

**Design:** Population-based cohort study.

**Setting:** The Clinical Data Analysis & Reporting System (CDARS) managed by the Hong Kong Hospital Authority.

**Participants:** Cases were people aged 10 years or older who visited a hospital Accident & Emergency department between January 1, 2004 and December 31, 2016 with any of ten specific drug use disorders (comprising opioid; ketamine; methamphetamine; sedative, hypnotic, or anxiolytic; amphetamine or related stimulant; cocaine; cannabis; hallucinogen; unspecified or other drug; and polydrug). Each case was matched with two controls, selected from a subset of people in CDARS sharing the same gender, age, and psychiatric profile. A total of 8,270 cases and 16,540 matched controls were included.

**Measurements:** Incidence and adjusted hazard ratio (aHR) of subsequent self-harm or suicide for each specific drug use disorder were estimated.

**Findings:** The most prevalent drug use disorder was opioid use disorder (2,523; 30.51%) and the least prevalent was hallucinogen use disorder (77; 0.93%). The crude incidence of self-harm or suicide ranged from 26.57 (95% confidence interval [CI], 14.23-44.55) per 1000 person-years for cannabis use disorder to 91.97 (77.32-108.37) for polydrug use disorder. The highest risk of self-harm or suicide was observed in ketamine (aHR, 16.36; 95% CI, 11.03-24.29) and opioid (15.97; 10.73-23.23) use disorders.

**Conclusions:** In Hong Kong, all types of drug use disorders appear to be significantly associated with increased risk of self-harm or suicide, but risk levels vary by type of drug use disorder.

**Keywords:** Drug use disorders; Substance use disorders; Psychiatric disorders; Self-harm; Suicide;  
CDARS; Hong Kong

## **INTRODUCTION**

Self-harm and suicide are associated with multiple risk factors, including previous self-harm behaviors and mental and substance use disorders (1, 2). Among mental and substance use disorders, a history of drug use disorders is one of the strongest risk factors (3). A previous study found that people diagnosed with drug use disorders had a risk of self-harm nearly ten times greater than those without such a diagnosis (4). This highlights the importance of understanding mechanisms underlying the link between drug use disorders and suicidal behavior.

Drug use disorders is a broad category that includes specific disorders related to the drug type involved (e.g., opioids, cannabis, cocaine, amphetamine or related drugs, or polydrugs) (1). Drugs with different pharmacological properties can affect an individual's brain and behavior differently, and interact uniquely with the individual's existing psychiatric or physical conditions (5-7). This may result in variable levels of risk of self-harm or suicide through different pharmacological mechanisms (e.g., interruption of neurotransmitter pathways, impairment in cognitive impairment control, or physiological and metabolic stresses) (5-7). To underpin the development of effective suicide prevention strategies, it is important to determine whether an increased risk of suicidal behavior is associated with any drug use disorders, irrespective of drug type, or only with drugs with specific pharmacological properties.

To date, most research into the association between specific drug use disorders and suicidal behavior has investigated single drug type (predominately opioids) (6, 7), or reported pooled estimations generated from meta-analysis (8-10). Few studies have examined the risks of self-harm or suicide associated with specific types of drug use disorders with the same dataset. In a cohort study of people receiving US Veterans Health Administration care, the highest risk of suicide was found in sedative use disorder for both males and females (11). A US survey found that the number of substances used was more important than the type of substance in predicting suicide risk (12). A Danish study of people treated for drug use disorders found that only opioid use was a strong predictor of completed suicide (13). In contrast, a Spanish study of outpatients with substance use disorders reported that all

substances studied (including opioids, cocaine, cannabis, sedatives, and polydrugs) were associated with suicide ideation (14). These mixed findings from limited studies are attributable to substantial heterogeneity in study populations, research designs, investigation timeframes, and measures of drug use disorders. The current study adds to the existing body of evidence by estimating the longitudinal incidence and risk of self-harm or suicide associated with different drug use disorders in people living in Hong Kong.

## **METHODS**

### **Study design**

Retrospective 13-year longitudinal study (January 01, 2004-December 31, 2016).

### **Data source**

The Clinical Data Analysis and Reporting System (CDARS) is a territory-wide database that contains electronic medical records collected by the Hong Kong Hospital Authority (HA), a statutory body managing all public hospitals that currently serve over seven million Hong Kong residents (15). CDARS contains basic demographic, diagnosis, prescription, admission and discharge information from inpatient, outpatient, and Accident & Emergency (A&E) departments since 1993. Data from CDARS are reliable and have been used in epidemiological studies examining relationships between a wide range of exposures and health outcomes (4, 16, 17).

### **Ethics**

All records were de-identified by CDARS, and no individuals were contacted. This study was approved by the Institutional Review Board of the University of Hong Kong (UW 17-107).

### **Exposure cohort identification**

People with a recorded diagnosis of any type of drug use disorders who presented to a hospital A&E department between January 01, 2004 and December 31, 2016 were identified from CDARS. The date of the first record of drug use disorders in the study period was designated as the index date.

Individuals younger than 10 years of age at index diagnosis were excluded.

Drug use disorders were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: 292.0, 304.0-304.9, and 305.2-305.9, which is in line with the codes adopted by the Central Registry of Drug Abuse in Hong Kong (18). The drug use disorders records from CDARS have been validated by experts from the Hong Kong Poison Information Centre. Of 300 individuals randomly selected from 11,602 people with a record of any drug use disorders, 272 were classified as “true” drug use disorder cases. This translates to a positive predictive value (PPV) of 90.7% (95% CI, 87.4%-94.0%) and a false discovery rate of 9.3% (95% CI, 6.29%-13.23%) (19).

Drug use disorders were then classified into ten mutually exclusive groups based on diagnostic records at the index date: 1) opioid; 2) ketamine; 3) methamphetamine; 4) sedative, hypnotic, or anxiolytic; 5) amphetamine or related stimulant other than methamphetamine; 6) cocaine; 7) cannabis; 8) hallucinogen other than ketamine; 9) unspecified or other drug; and 10) polydrug (i.e., more than one drug involved) use disorders. Diagnostic records after the index date were not considered. Classification into these groups was determined by ICD-9-CM codes and supplemented by diagnosis information. Ketamine and methamphetamine were specifically examined since they have been the two most commonly-abused drugs in Hong Kong in recent years (18). Coding details for each specific drug use disorder are provided in Supplementary Table S1.

### **Control cohort selection**

Controls were selected from a randomly-selected sample from the CDARS. Eligible controls included individuals who 1) were not cases; 2) had at least one medical record in CDARS between 2004 and 2016; and 3) were aged 10 years or older. Two controls were randomly selected for each case (without replacement), matched by gender, exact age in years, and diagnosis of any psychiatric disorder of interest before or on the index date. The index date of each control is the admission date of the matched record. When suitable controls could not be identified, restriction of exact age was relaxed to the same age group (i.e., 10-24, 25-44, 45-64, and 65+ years). Figure 1 shows the detailed

selection procedure for cases and controls.

[insert Figure 1 about here]

For both cases and controls, we retrieved all medical records before and on the index date to identify the history of comorbidities, starting from January 01, 1993 (the earliest record of CDARS).

## **Outcomes**

The outcome was self-harm or suicide events subsequent to the index date during the study period. We included all self-injurious behaviors (such as poisoning, drowning, cutting, and jumping) with determined and undetermined suicidal intentions to mitigate the under-reporting problems of self-harm and suicide in the hospital administrative dataset (13, 20, 21). Self-harm was identified using ICD-9-CM codes E950-59 and E980-89 (undetermined intention), which is consistent with previous studies (4, 22). Death by suicide was ascertained from the cause of death information based on ICD-10-CM codes X60-84 and Y10-34 (undetermined intentions). All cases and controls were followed from their index date to the first record of self-harm, death by suicide or other causes, or December 31, 2016, whichever came first.

## **Statistical analysis**

The incidence of self-harm or suicide per 1000 person-years was calculated for case and control groups by each specific type of drug use disorders. The association between each specific drug use disorder and self-harm or suicide events was quantified by comparing the relative risk of suicide or self-harm in people with and without the drug use disorder. Preliminary analysis showed that 10.39 % of cases died during the study period due to causes other than suicide. The Fine-Gray competing risk regression model was thus fitted to estimate the hazard ratios (HRs) and 95% CIs, taking the competing risk of death into account (23).

For each specific drug use disorder, three competing risk regression models were fitted, with increasing levels of controls. Model 1 was adjusted only for gender and age group. Model 2 was additionally adjusted for concurrent self-harm diagnosis on the index date and record of drug use



disorders and self-harm before the index date. This step was taken because history of self-harm and drug use disorders are both established risk factors of self-harm or suicide (4, 24, 25). Model 3 included two additional variables preceding or occurring on the index date that are also established risk factors for suicide and self-harm: (2, 4, 24) 1) any psychiatric disorder (comprising depression, bipolar disorder, alcohol and tobacco use disorder, personality disorder, anxiety disorder, and schizophrenia); and 2) any physical illness (comprising asthma, diabetes, epilepsy, HIV, cancer, and dermatitis or eczema). The ICD-9-CM codes for comorbidity identifications are reported in Supplementary Table S2.

Four sets of sensitivity analyses were conducted to test the robustness of the results. In the first set (eModel 1), we adjusted for 12 covariates measuring the presence of 12 comorbidities. The second set of analysis (eModel 2) adjusted only for comorbidities with a prevalence higher than 3% in at least five drug classes. In the third set, we calculated E-values (26) to estimate the effects of unmeasured confounders on the association between specific drug use disorder and self-harm or suicide. In the last set of analysis, we applied a narrower definition of self-harm (ICD-9-CM codes, E950-59) and suicide (ICD-10-CM codes, X60-84) to examine the impact of diagnostic coding. The Bonferroni correction was used for all models to counteract the problem of multiple comparisons (27). Statistical significance of  $p < 0.05$  (2-sided) was applied in all analyses. The packages *dplyr*, *survival*, *cmprsk*, *EValue* in statistical software R (version 4.0.1) (28) were used for data cleaning and analysis.

The analysis was not pre-registered and the results should be considered exploratory.

## RESULTS

This study included 8,270 people with an index drug use disorders in the study period (Figure 1). This provided a total follow-up of 37095.20 person-years (mean: 4.49 person-years). The most prevalent drug use disorder was opioid (2,523 [30.51%]) and the least prevalent drug use disorder was hallucinogens (77 [0.93%]). The characteristics of each drug use disorder are summarized in Table 1. Males accounted for more than 60% of the sample in each drug use disorder type, except for sedative, hypnotic, or anxiolytic drugs (42.38%). The median subgroup age at index date ranged from 25 years

for ketamine (interquartile range [IQR], 22-30) and cannabis (IQR, 21-32) to 41 (IQR, 33-51) years for opioids. People aged 25-44 years predominated for all types of drug use disorders, with the smallest number of people being 65 years or older.

[insert Table 1 about here]

The highest suicide rate (3.35%) was found in polydrug use disorder. People with a history of self-harm diagnosis accounted for more than 20% of those in all drug use disorder groups, except for ketamine (17.54%), cocaine (11.38%), and cannabis (6.19%). Concurrent diagnoses of self-harm were common; except for methamphetamine (34.01%), more than 60% of cases also had a self-harm diagnosis on the index date. The prevalence of previous drug use disorders varied from 6.19 % (N=6) for cannabis to 46.65 % (N=167) for polydrugs. The control group characteristics are summarized in Table S3. The prevalence of comorbidities for case and control groups was generally low (see Table 2 and Table S4 respectively).

[insert Table 2 about here]

Table 3 reports the frequency and incidence of self-harm or suicide for cases and controls. Considerably higher frequencies and crude incidence of subsequent self-harm or suicide were observed in cases compared with controls for all drug use disorders. The highest and lowest incidence of self-harm or suicide was observed in polydrug use disorder (91.97 per 1000 person-years; 95% CI, 77.32-108.37) and cannabis use disorder (26.57;14.23-44.55), respectively.

[insert Table 3 about here]

Figure 2 reports the findings from Fine-Gray competing risk regression models. For Model 1 (adjusting only for gender and age), all types of drug use disorders were significantly associated with an elevated risk of self-harm or suicide. The highest risk was for opioids (HR, 27.32; 95% CI, 19.47-38.32), ketamine (26.15; 18.90-36.18), and polydrugs (20.24; 9.99-41.02). After adjusting for a concurrent diagnosis of self-harm and records of previous self-harm and drug use disorders (Model 2), hallucinogen use disorders were no longer associated with self-harm or suicide. However, whilst the

associations between self-harm and all other drug use disorders were attenuated compared with the previous model, all remained strong and statistically significant. People with ketamine use disorder carried the highest risk of self-harm or suicide (15.45;10.32-23.11), followed by opioids (15.05; 10.21-22.20). After further adjusting for comorbidities (Model 3), these two drugs remained those with the highest risk of self-harm or suicide (ketamine 16.36; 11.03-24.29; and opioid 15.97; 10.73-23.23). The coefficients of covariates of these models are provided in Tables S5-7. The findings from Model 3 showed that in addition to previous and index records of self-harm, previous drug use disorders (of any kind) and psychiatric disorders were significantly associated with self-harm or suicide in people with some specific drug use disorders. Sensitivity analyses yielded consistent results (see Tables S8-12). E-values for Model 3 (see Table S10) ranged from 5.69 to 11.41, meaning that strong associations between an unmeasured confounder, and both drug exposure and suicidal behaviors were needed to explain away the observed HRs.

[insert Figure 2 about here]

## **DISCUSSION**

To our knowledge, this is one of the few longitudinal studies to systematically examine the risk of self-harm or suicide associated with drug use disorders by specific drug type. All drug use disorders were significantly associated with elevated risks of self-harm or suicide. People with ketamine or opioid use disorders had more than 15 times the risk of self-harm or suicide than those without a diagnosed drug use disorders, even after adjusting for covariates. This suggests the importance of drug use disorders management and prevention in suicide prevention strategies and prioritizing the highest-risk drug use disorders (e.g., opioids and ketamine) when resources are limited.

Few longitudinal studies have comprehensively evaluated self-harm or suicide associated with more than one drug use disorders. Our study findings concur with the US veterans study (11) that cannabis and cocaine use disorder had the lowest HRs compared with other drug use disorders. Our findings of an aHR of 9.28 in people with polydrug use disorder also concur with the US survey highlighting the importance of the number of drugs used (12).

Partially attributable to the increase in opioid prescribing for chronic pain management over the past two decades, opioid use disorder has become increasingly prevalent, and is the most frequently-studied drug use disorder (3, 29). In our study, opioid use was the most prevalent drug use disorder and was associated with the highest unadjusted HR (27.32; 95% CI, 19.47-38.32) and the second-highest aHR (15.97; 10.73-23.23) for self-harm or suicide, even after controlling for important covariates. Our study of an Asian society adds important information to the current evidence on the strong relationship between opioid use disorder and self-harm or suicide that is largely from the west (10). It further supports the notion that targeted suicide prevention programs are essential for people with opioid use disorder (29). Implementation of effective suicide prevention for people with opioid use disorder in Hong Kong is urgently needed.

Ketamine was the most commonly abused psychotropic drug in Hong Kong between 2009 and 2014 according to Hong Kong Central Registry of Drug Abuse (CRDA) reports (18). In our sample, ketamine use disorder was the second most prevalent and was associated with the highest adjusted risk of self-harm or suicide. Notably, ketamine is considered an effective adjuvant treatment for treatment-resistant depression (30). Acute use of ketamine has been suggested to be effective in reducing suicide ideation and improving mood (31). However, similar to opioids, the therapeutic value of ketamine faces challenges because of its potential for misuse (32). The increased risk of suicidal behavior observed in our study possibly relates to chronic ketamine use. This is supported by animal studies that suggest chronic ketamine use may exhibit different neurobiological changes from those found in acute use (33). Intervention strategies are needed to ensure the safety of therapeutic ketamine use in the treatment of psychiatric disorders.

According to the latest CRDA report, since 2015, methamphetamines have surpassed ketamine as the most commonly abused drug in Hong Kong (18). However, this was not reflected in our sample, as the proportion of people with methamphetamine use disorder was low (1.78%). It is possible that the CRDA data came from multiple sources other than hospitals. Furthermore, people with methamphetamine use disorder may also be less likely to seek help from hospitals due to possible criminalization. The relatively low risk of self-harm or suicide in people with methamphetamine use

disorders in our study might be explained by the small sample size. Further investigations are needed to understand better the link between methamphetamine use disorder and self-harm or suicide of a representative population.

Cannabis is the most widely-used illicit drug globally (1). However, its associated health risks, including self-harm or suicide, are reportedly less than other drugs (1, 10). In the context of the legalization of cannabis in different parts of the world, the aHR of 5.45 (95% CI, 1.17-25.43) of self-harm or suicide in those using cannabis in the current study calls for some caution. Further study on the impact of cannabis legalization on the self-harm or suicide rate would be important.

The links between drug use disorders, psychiatric disorders, and self-harm behaviors are complicated (34-36). In our sample, comorbid psychiatric disorders were common, ranging from 14.43% for cannabis to 48.68% for sedatives, hypnotics, or anxiolytics. To control for the putative effect of comorbid psychiatric disorders on the risk of self-harm or suicide, we first matched the controls by the presence of any psychiatric disorders that we then adjusted in the subsequent survival analysis. Risks of self-harm or suicide in all drug use disorders groups remained much higher than in the controls, even after adjustment for confounders, suggesting an important independent role of drug use disorders in self-harm or suicide events. Given the strong links between impulsivity and suicidal behavior, and impulsivity and drug use (37, 38), the significant association between drug use disorders and self-harm or suicide, independent from past psychiatric history or suicide attempts, found in the current study suggests the potential contribution of state impulsivity to self-harm or suicide due to drug use disorders.

Given the high post-treatment relapse rate for drug use disorders (39, 40), we purposely included all people who had any diagnosis of drug use disorders in a given period, irrespective of whether the diagnosis was the first-ever for an individual. In addition to previous self-harm diagnosis, we found that previous drug use disorders was also an important contributor to self-harm or suicide events. This highlights the importance of recording drug abuse history during the assessment of suicide risk.

## **Limitations**

This study has several limitations. First, the classification of drug use disorders was based entirely on ICD-9-CM code definitions and diagnosis descriptions in CDARS. However, some drugs did not have independent categories (e.g., methamphetamine and ketamine) in the ICD-9-CM codes and could only be identified by text comments in electronic records. Misclassification may be possible for certain drugs. Second, drug use disorders can be further classified as withdrawal, dependence, and non-dependent abuse according to its severity. Due to the limited sample size, this study only considered subcategories stratified by drug types. Third, suicide cases were not validated by a Coroner's report, which may bias the estimation of suicide prevalence. Moreover, we combined suicide cases with non-fatal self-harm cases as a single category, as our focus was to examine the subsequent risk of self-harm, irrespective of whether it was fatal. We also adopted a broad definition of self-harm and suicide that included all deliberately or accidentally self-injurious behaviors. However, the sensitivity analysis, which only focused on self-harm and suicide cases with determined suicidal intentions, yielded consistent findings. Fifth, the study drew on public hospital records only. Therefore, it did not capture self-harm and suicide cases that did not present to public hospitals, leading to a probable underestimation of incidence and risk of self-harm or suicide. In addition, due to the stigma surrounding drug use disorders, people with drug use disorders may not seek help from a public hospital. However, few private hospitals in Hong Kong provide A&E services; therefore, our sample is likely to include most people seeking emergency healthcare for drug use disorders. Sixth, though the PPV of any drug use disorders is high, no detailed validation was conducted by drug type, and the false negative rate for each drug use disorder was not known. Therefore, it is important to note that diagnostic accuracies may vary by type of drug use disorders and across time points (e.g., changes in urine testing methods for ketamine) (18), which may bias our findings. Finally, the use of a specific drug can be influenced by many social determinants, including demographic characteristics, socioeconomic status, psychological factors, and policy initiatives for substance/drug use prevention. For example, cannabis is more available in jurisdictions where recreational use of cannabis has been legalized (41). Inhalants are more popular among adolescents due to their accessibility and low price (42). Psychoactive drugs such as opioids, cocaine, and amphetamines are more likely to be used by

individuals with higher levels of impulsivity (43). These determinants of a specific drug use, although may in turn affect the risk of subsequent self-harm or suicide, were not examined due to data limitation. However, the focus of this current study is to understand to what extent diagnosis of a specific drug use disorder can predict self-harm or suicide, without holding assumptions about determinants of such diagnosis. We also further calculated E-values to evaluate the effects of unmeasured confounders and found that the results were robust.

## **Conclusion**

This study found that self-harm or suicide was significantly associated with a wide range of drug use disorders, even after controlling for covariates, suggesting that persons with drug use disorders should be given special attention for suicide prevention. This information supports the importance of law enforcement and regulation effort to reduce access to potentially lethal drugs and drugs that are associated with increased risk of overdose and suicide. It also highlights opportunities for appropriate risk identification and interventions (such as psychotherapy, overdose education, and medication-assisted therapy) when an at-risk individual presents to the health care system and the need for comprehensive addiction treatment strategies.

**Author Contributions:**

YC and HL had full access to all the study data and take responsibility for the integrity of the data and the accuracy of the data analysis. HL, ICKW, and EWC initiated the study design. YC prepared the study protocol and conducted the data analysis. HL and KKCM provided expertise in statistics and cross-checked the analytical syntax. SKWC contributed clinical expertise and reviewed the study protocol. All authors contributed to the interpretation of data. YC and HL prepared the first draft of the manuscript. All authors substantially revised the drafts of the manuscript. All authors critically reviewed all drafts and approved the final version of the manuscript.

**Acknowledgement:**

We thank the Beat Drugs Fund, Narcotics Division of the Security Bureau of HK SAR for their support.



## REFERENCES

1. Degenhardt L., Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease, *Lancet* 2012; **379**: 55-70.
2. Singhal A., Ross J., Seminog O., Hawton K., Goldacre M. J. Risk of self-harm and suicide in people with specific psychiatric and physical disorders: comparisons between disorders using English national record linkage, *J R Soc Med* 2014; **107**: 194-204.
3. Ferrari A. J., Norman R. E., Freedman G., Baxter A. J., Pirkis J. E., Harris M. G. et al. The Burden Attributable to Mental and Substance Use Disorders as Risk Factors for Suicide: Findings from the Global Burden of Disease Study 2010, *PLoS One* 2014; **9**: e91936.
4. Chai Y., Luo H., Wong G. H. Y., Tang J. Y. M., Lam T.-C., Wong I. C. K. et al. Risk of self-harm after the diagnosis of psychiatric disorders in Hong Kong, 2000–10: a nested case-control study, *Lancet Psychiatry* 2020; **7**: 135-147.
5. Ahmed, S., Stanciu, C.N. Addiction and Suicide: An Unmet Public Health Crisis, *Am. J. Psychiatry* 2017; **12**: 3-6.
6. Ilgen M. A., Bohnert A. S. B., Ganoczy D., Bair M. J., McCarthy J. F., Blow F. C. Opioid dose and risk of suicide, *Pain* 2016; **157**: 1079-1084.
7. Larney S., Tran L. T., Leung J., Jr T.S., Santomauro D., Hickman M. et al. All-Cause and Cause-Specific Mortality Among People Using Extramedical Opioids: A Systematic Review and Meta-analysis, *JAMA Psychiatry* 2019; **77**: 1-10.
8. Wilcox H. C., Conner K. R., Caine E. D. Association of alcohol and drug use disorders and completed suicide: an empirical review of cohort studies, *Drug Alcohol Depend* 2004; **76 Suppl**: S11-19.
9. Armoon B., SoleimanvandiAzar N., Fleury M. J., Noroozi A., Bayat A. H., Mohammadi R. et al. Prevalence, sociodemographic variables, mental health condition, and type of drug use associated with suicide behaviors among people with substance use disorders: a systematic review and meta-analysis, *J Addict Dis* 2021; 1-29.
10. Poorolajal J., Haghtalab T., Farhadi M., Darvishi N. Substance use disorder and risk of suicidal ideation, suicide attempt and suicide death: a meta-analysis, *J Public Health* 2016; **38**: e282-e291.
11. Bohnert K. M., Ilgen M. A., Louzon S., McCarthy J. F., Katz I. R. Substance use disorders and the risk of suicide mortality among men and women in the US Veterans Health Administration, *Addiction* 2017; **112**: 1193-1201.
12. Borges G., Walters E. E., Kessler R. C. Associations of substance use, abuse, and dependence with subsequent suicidal behavior, *Am J Epidemiol* 2000; **151**: 781-789.
13. Hesse M., Thylstrup B., Seid A. K., Skogen J. C. Suicide among people treated for drug use disorders: a Danish national record-linkage study, *BMC public health* 2020; **20**: 146.
14. Rodríguez-Cintas L., Daigre C., Braquehais M. D., Palma-Alvarez R. F., Grau-López L., Ros-Cucurull E. et al. Factors associated with lifetime suicidal ideation and suicide attempts in outpatients with substance use disorders, *Psychiatry Res* 2018; **262**: 440-445.
15. Food and Health Bureau. Report of the strategic review on healthcare manpower planning and professional development; 2017.
16. Man K. K. C., Coghill D., Chan E. W., Lau W. C. Y., Hollis C., Liddle E. et al. Association of Risk of Suicide Attempts With Methylphenidate Treatment, *JAMA Psychiatry* 2017; **74**: 1048-1055.
17. Man K. K. C., Chan E. W., Ip P., Coghill D., Simonoff E., Chan P. K. L. et al. Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population based cohort study, *BMJ* 2017; **357**: j2350.
18. Narcotics Division Security Bureau. Central Registry of Drug Abuse Sixty-eight Report; 2018.
19. Chan E. W. Y., Wong I. C. K., Tse M. L., Chow A. T. Y., Zhao J. J., Wei Y. et al. Understanding drug abusers and their healthcare pathway: towards better management in Hong Kong, Hong Kong; 2020; p. 23.
20. Leung KWOK C., Yip P. S. F. Estimating Incidence Rate of Hospital-Treated Self-Harm in Hong

- Kong Using Capture-Recapture Approach, *Crisis* 2018; **39**: 205-217.
21. Bethell J., Rhodes A. E. Identifying deliberate self-harm in emergency department data, *Health Rep* 2009; **20**: 35.
  22. Geulayov G., Casey D., Bale L., Brand F., Clements C., Farooq B. et al. Suicide following presentation to hospital for non-fatal self-harm in the Multicentre Study of Self-harm: a long-term follow-up study, *Lancet Psychiatry* 2019; **6**: 1021-1030.
  23. Fine J. P., Gray R. J. A Proportional Hazards Model for the Subdistribution of a Competing Risk, *J Am Stat Assoc* 1999; **94**: 496-509.
  24. Skegg K. Self-harm, *Lancet* 2005; **366**: 1471-1483.
  25. Chai Y., Luo H., Yip P. S. F. Prevalence and risk factors for repetition of non-fatal self-harm in Hong Kong, 2002-2016: A population-based cohort study, *Lancet Reg Health West Pac* 2020; **2**.
  26. Haneuse S., VanderWeele T. J., Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies, *JAMA* 2019; **321**: 602-603.
  27. Bonferroni C. Teoria statistica delle classi e calcolo delle probabilita, *Pubblcazioni del R Istituto Superiore di Scienze Economiche e Commerciali di Firenze* 1936; **8**: 3-62.
  28. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.
  29. Bohnert A. S. B., Ilgen M. A. Understanding Links among Opioid Use, Overdose, and Suicide, *N Engl J Med* 2019; **380**: 71-79.
  30. Singh I., Morgan C., Curran V., Nutt D., Schlag A., McShane R. Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight, *Lancet Psychiatry* 2017; **4**: 419-426.
  31. Witt K., Potts J., Hubers A., Grunebaum M. F., MURROUGH J. W., LOO C. et al. Ketamine for suicidal ideation in adults with psychiatric disorders: A systematic review and meta-analysis of treatment trials, *Aust N Z J Psychiatry* 2020; **54**: 29-45.
  32. Liu Y., Lin D., Wu B., Zhou W. Ketamine abuse potential and use disorder, *Brain Res Bull* 2016; **126**: 68-73.
  33. Ahnaou A., Huysmans H., Biermans R., Manyakov N. V., Drinkenburg W. H. I. M. Ketamine: differential neurophysiological dynamics in functional networks in the rat brain, *Transl Psychiatry* 2017; **7**: e1237-e1237.
  34. Carrà G., Bartoli F., Crocarno C., Brady K. T., Clerici M. Attempted suicide in people with co-occurring bipolar and substance use disorders: systematic review and meta-analysis, *J Affect Disord* 2014; **167**: 125-135.
  35. Toftdahl N. G., Nordentoft M., Hjorthøj C. Prevalence of substance use disorders in psychiatric patients: a nationwide Danish population-based study, *Soc Psychiatry Psychiatr Epidemiol* 2016; **51**: 129-140.
  36. Hawton K., Sutton L., Haw C., Sinclair J., Deeks J. J. Schizophrenia and suicide: Systematic review of risk factors, *Br J Psychiatry* 2005; **187**: 9-20.
  37. Liu R. T., Trout Z. M., Hernandez E. M., Cheek S. M., Gerlus N. A behavioral and cognitive neuroscience perspective on impulsivity, suicide, and non-suicidal self-injury: Meta-analysis and recommendations for future research, *Neurosci Biobehav Rev* 2017; **83**: 440-450.
  38. Kozak K., Lucatch A. M., Lowe D. J. E., Balodis I. M., MacKillop J., George T. P. The neurobiology of impulsivity and substance use disorders: implications for treatment, *Ann N Y Acad Sci* 2019; **1451**: 71-91.
  39. Cornelius J. R., Maisto S. A., Pollock N. K., Martin C. S., Salloum I. M., Lynch K. G. et al. Rapid relapse generally follows treatment for substance use disorders among adolescents, *Addict Behav* 2003; **28**: 381-386.
  40. Andersson H. W., Wenaas M., Nordfjærn T. Relapse after inpatient substance use treatment: A prospective cohort study among users of illicit substances, *Addict Behav* 2019; **90**: 222-228.
  41. Connor J. P., Stjepanović D., Le Foll B., Hoch E., Budney A. J., Hall W. D. Cannabis use and cannabis use disorder, *Nat Rev Dis Primers* 2021; **7**: 16.
  42. Çiftçi Demirci A., Erdoğan A., Yalçın Ö., Yıldızhan E., Koyuncu Z., Eseroğlu T. et al. Sociodemographic characteristics and drug abuse patterns of adolescents admitted for

- substance use disorder treatment in Istanbul, *Am J Drug Alcohol Abuse* 2015; **41**: 212-219.
43. Conway K. P., Swendsen J. D., Rounsaville B. J., Merikangas K. R. Personality, drug of choice, and comorbid psychopathology among substance abusers, *Drug Alcohol Depend* 2002; **65**: 225-234.

Table 1. Characteristics of case groups

Characteristics, N (%)	Opioid	Ketamine	Methamphetamine	Sedative, hypnotic, or anxiolytic	Amphetamine or related stimulant	Cocaine	Cannabis	Hallucinogen	Unspecified or other drug	Polydrug
<b>Individuals (n=8270)</b>	2523 (30.51)	1619 (19.58)	147 (1.78)	682 (8.25)	527 (6.37)	167 (2.02)	97 (1.17)	77 (0.93)	2073 (25.07)	358 (4.33)
<b>Gender</b>										
Male	2217 (87.87)	1136 (70.17)	107 (72.79)	289 (42.38)	375 (71.16)	132 (79.04)	77 (79.38)	51 (66.23)	1258 (60.68)	274 (76.54)
Female	306 (12.13)	483 (29.83)	40 (27.21)	393 (57.62)	152 (28.84)	35 (20.96)	20 (20.62)	26 (33.77)	815 (39.32)	84 (23.46)
<b>Age</b>										
10-24 years	83 (3.29)	741 (45.77)	29 (19.73)	60 (8.80)	149 (28.27)	33 (19.76)	47 (18.45)	28 (36.36)	413 (19.92)	87 (24.30)
25-44 years	1426 (56.52)	842 (52.01)	107 (72.79)	379 (55.57)	339 (64.33)	111 (66.47)	43 (44.33)	41 (53.25)	1159 (55.91)	230 (64.25)
45-64 years	911 (36.11)	36 (2.22)	11 (7.48)	203 (29.77)	39 (7.40)	22 (13.17)	7 (7.22)	7 (9.09)	431 (20.79)	36 (10.06)
65+ years	103 (4.08)	0 (0.00)	0 (0.00)	40 (5.87)	0 (0.00)	1 (0.60)	0 (0.00)	1 (1.30)	70 (3.38)	5 (1.40)
Median (IQR)	41 (33-51)	25 (22-30)	31 (26-39)	40 (31-49)	30 (24-37)	31 (25-37)	25 (21-32)	30 (22-39)	35 (26-44)	31 (25-38)
<b>Death (all causes)</b>	578 (22.91)	72 (4.45)	1 (0.68)	74 (10.85)	18 (3.42)	15 (8.98)	1 (1.03)	4 (5.20)	206 (9.93)	29 (8.10)
<b>Suicide</b>	33 (1.31)	35 (2.16)	0 (0.00)	13 (1.91)	5 (0.95)	2 (1.20)	1 (1.03)	1 (1.30)	37 (1.78)	12 (3.35)
<b>Self-harm diagnosis before the index date</b>	580 (22.99)	284 (17.54)	30 (20.41)	234 (34.31)	115 (21.82)	19 (11.38)	6 (6.19)	17 (22.08)	500 (24.12)	114 (31.84)
<b>Self-harm diagnosis on the index date</b>	1728 (68.49)	1267 (78.26)	50 (34.01)	550 (80.65)	416 (78.94)	104 (62.28)	67 (69.07)	59 (76.62)	1368 (65.99)	233 (65.08)
<b>Drug use disorders diagnosis before the index date</b>	981 (38.88)	376 (23.22)	43 (29.25)	168 (24.63)	177 (33.59)	29 (17.37)	6 (6.19)	26 (33.77)	492 (23.73)	167 (46.65)

Abbreviation: IQR, interquartile range

Table 2. The prevalence of comorbidities before or on the index date of case groups

Comorbidities, N (%)	Opioid	Ketamine	Methamphetamine	Sedative, hypnotic, or anxiolytic	Amphetamine or related stimulant	Cocaine	Cannabis	Hallucinogen	Unspecified or other drug	Polydrug
<b>Any psychiatric disorder</b>	424 (16.81)	242 (14.95)	40 (27.21)	332 (48.68)	130 (24.67)	31 (18.56)	14 (14.43)	20 (25.97)	602 (29.04)	107 (29.89)
Depression	125 (4.95)	65 (4.01)	12 (8.16)	229 (33.58)	35 (6.64)	11 (6.59)	6 (6.19)	8 (10.39)	278 (13.41)	42 (11.73)
Bipolar disorder	9 (0.36)	7 (0.43)	1 (0.68)	14 (2.05)	6 (1.14)	2 (1.20)	1 (1.03)	1 (1.30)	35 (1.69)	1 (0.28)
Alcohol and tobacco use disorders	134 (5.31)	87 (5.37)	9 (6.12)	71 (10.41)	38 (7.21)	14 (8.38)	5 (5.15)	5 (6.49)	135 (6.51)	33 (9.22)
Personality disorder	84 (3.33)	33 (2.04)	8 (5.44)	46 (6.74)	35 (6.64)	4 (2.40)	1 (1.03)	6 (7.79)	94 (4.53)	21 (5.87)
Anxiety disorder	36 (1.43)	29 (1.79)	8 (5.44)	77 (11.29)	13 (2.47)	3 (1.80)	0 (0.00)	4 (5.19)	99 (4.78)	24 (6.70)
Schizophrenia	110 (4.36)	30 (1.85)	15 (10.20)	54 (7.92)	45 (8.54)	2 (1.20)	3 (3.09)	6 (7.79)	135 (6.51)	20 (5.59)
<b>Any physical illness</b>	270 (10.70)	123 (7.60)	16 (10.88)	114 (16.72)	52 (9.87)	11 (6.59)	5 (5.15)	4 (5.19)	262 (12.64)	36 (10.06)
Asthma	72 (2.85)	54 (3.34)	5 (3.40)	26 (3.81)	19 (3.61)	5 (2.99)	2 (2.06)	2 (2.60)	73 (3.52)	10 (2.79)
Diabetes	42 (1.66)	5 (0.31)	1 (0.68)	23 (3.37)	6 (1.14)	0 (0.00)	0 (0.00)	0 (0.00)	48 (2.32)	4 (1.12)
Epilepsy	57 (2.26)	14 (0.86)	2 (1.36)	20 (2.93)	3 (0.57)	1 (0.60)	0 (0.00)	1 (1.30)	59 (2.85)	8 (2.23)
HIV	2 (0.08)	1 (0.06)	2 (1.36)	0 (0.00)	6 (1.14)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.05)	2 (0.56)
Cancer	85 (3.37)	26 (1.61)	4 (2.72)	46 (6.74)	9 (1.71)	3 (1.80)	2 (2.06)	0 (0.00)	62 (2.99)	8 (2.23)
Dermatitis or eczema	34 (1.35)	30 (1.85)	3 (2.04)	19 (2.79)	20 (3.80)	2 (1.20)	1 (1.03)	1 (1.30)	45 (2.17)	8 (2.23)

Table 3. Frequency and incidence of self-harm or suicide in case and control groups

	No. of self-harm or suicide events (total follow-up time, person-years)			Incidence per 1000 person-years (95% CI)	
	Exposure	Control	p <sup>a</sup> value	Exposure	Control
<b>Opioid</b>	884 (11627.73)	74 (29748.15)	<0.0001	76.03 (71.12-81.15)	2.49 (1.96-3.10)
<b>Ketamine</b>	539 (6943.58)	51 (20097.78)	<0.0001	77.63 (71.26-84.36)	2.54 (1.90-3.30)
<b>Methamphetamine</b>	24 (283.24)	9 (1803.08)	<0.0001	84.73 (55.19-123.29)	4.99 (2.40-9.00)
<b>Sedative, hypnotic, or anxiolytic</b>	222 (3015.46)	48 (7915.40)	<0.0001	73.62 (64.36-83.73)	6.06 (4.51-7.95)
<b>Amphetamine or related stimulant</b>	155 (1913.76)	28 (6585.46)	<0.0001	80.99 (68.90-94.42)	4.25 (2.87-6.03)
<b>Cocaine</b>	28 (776.87)	8 (2055.83)	<0.0001	36.04 (24.29-51.09)	3.89 (1.78-7.24)
<b>Cannabis</b>	12 (451.68)	6 (1278.64)	0.0045	26.57 (14.23-44.55)	4.69 (1.86-9.51)
<b>Hallucinogen</b>	29 (438.85)	6 (918.91)	<0.0001	66.08 (44.85-93.13)	6.53 (2.59-13.23)
<b>Unspecified or other drug</b>	611 (10176.16)	72 (25105.67)	<0.0001	60.04 (55.41-64.93)	2.87 (2.26-3.58)
<b>Polydrug</b>	135 (1467.87)	18 (4302.34)	<0.0001	91.97 (77.32-108.37)	4.18 (2.54-6.42)

<sup>a</sup> Pearson's test

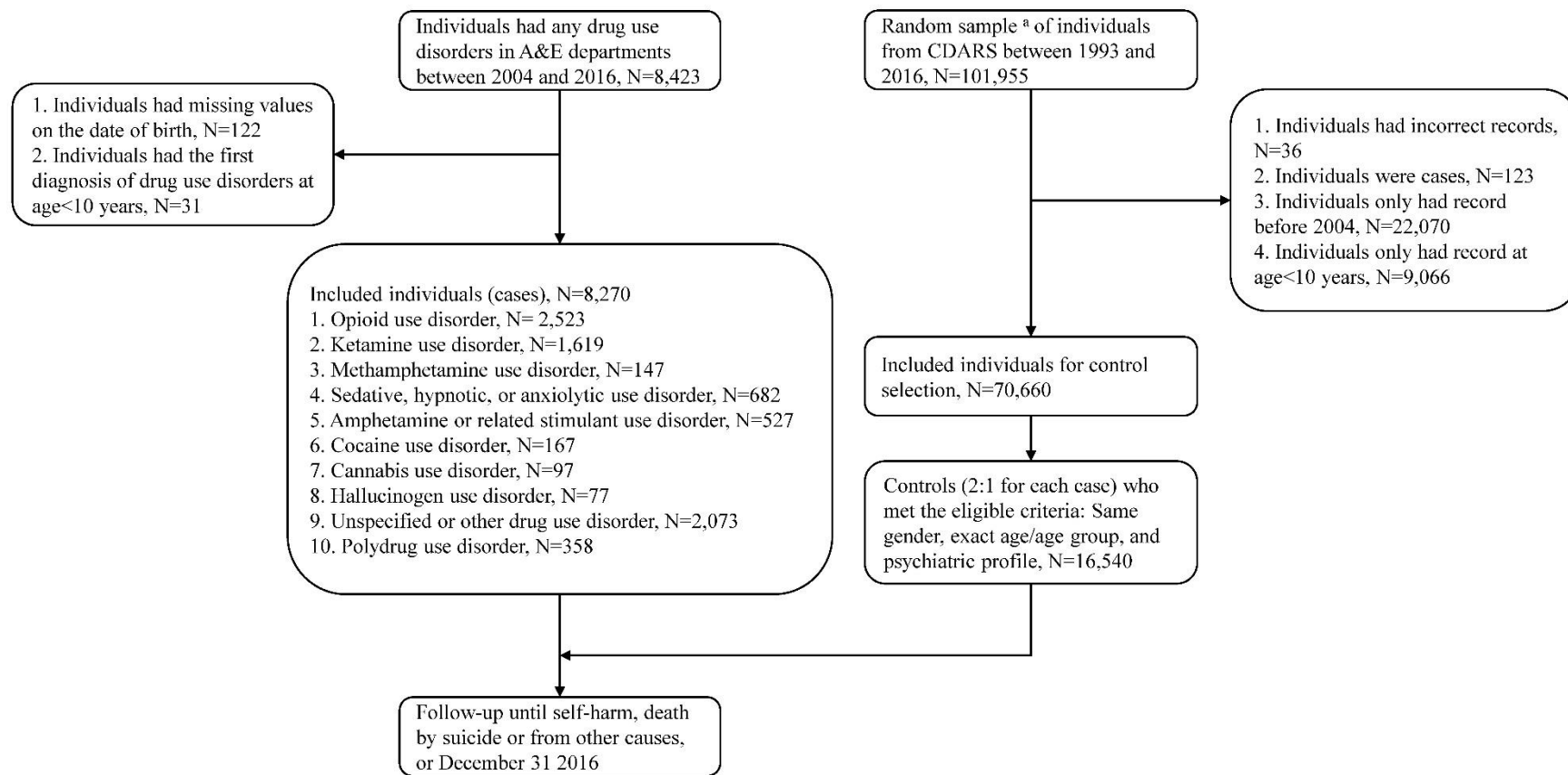


Figure 1. Flow chart for cases and controls selection

Abbreviations: A&E, Accident & Emergency; CDARS, Clinical Data Analysis & Reporting System

<sup>a</sup> A randomly-selected sample (N=101,955) from the CDARS was used as the reference population from which controls were selected (comparison cohort). To obtain this reference population, we first generated 150,000 random numbers within the range of de-identified reference key numbers used by CDARS. People with matched reference key numbers and valid healthcare records were then selected

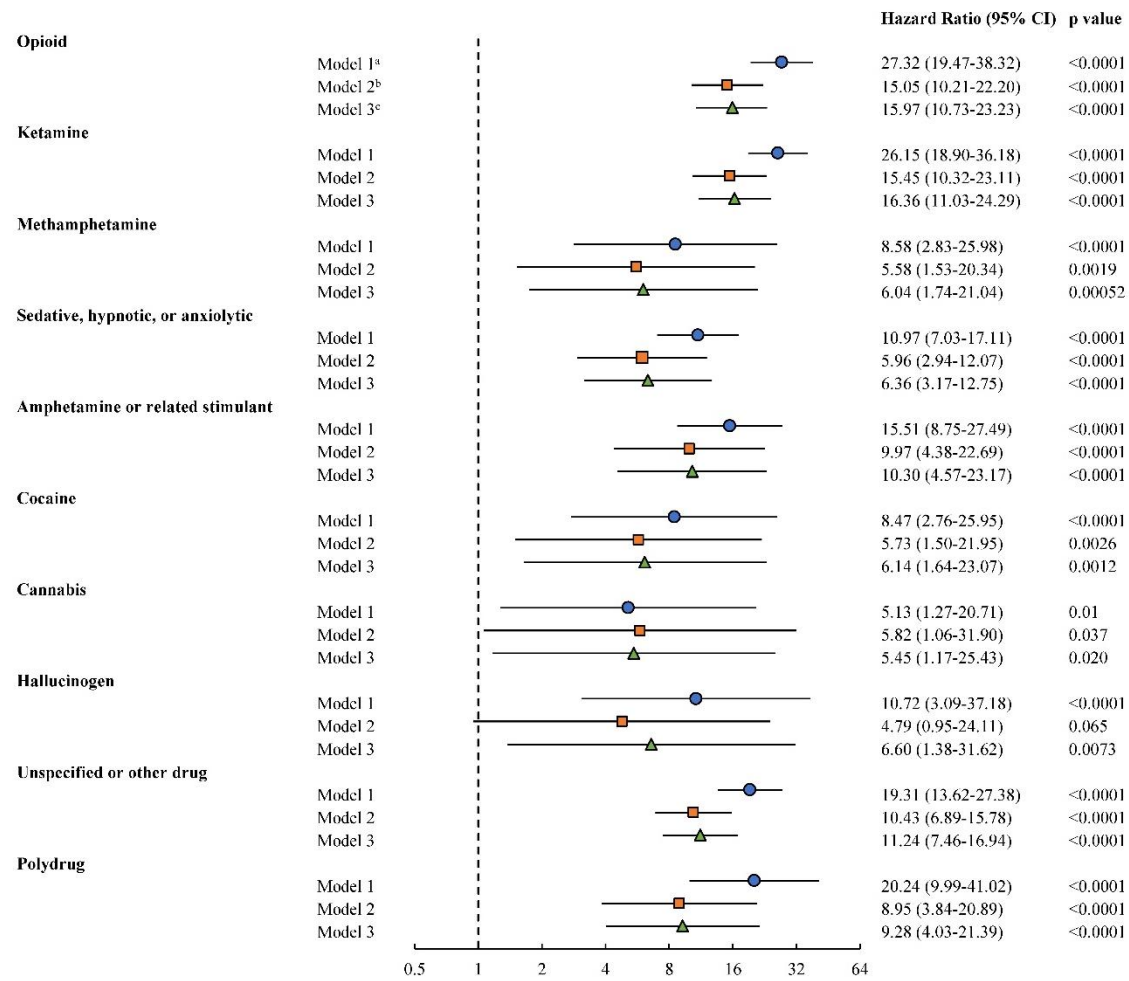


Figure 2. Results from Fine-Gray competing risk regression models

<sup>a</sup> Model 1 was adjusted for gender and age group



<sup>b</sup> Model 2 was adjusted for gender, age group, self-harm diagnosis before the index date, concurrent self-harm diagnosis on the index date, and drug use disorders diagnosis before the index date

<sup>c</sup> Model 3 was adjusted for gender, age group, self-harm diagnosis prior to the index date, concurrent self-harm diagnosis on the index date, drug use disorders diagnosis before the index date, and any psychiatric disorder (comprising depression, bipolar disorder, alcohol and tobacco abuse disorder, personality disorder, anxiety disorder, and schizophrenia) and any physical illness (comprising asthma, diabetes, epilepsy, HIV, cancer, and dermatitis or eczema) diagnosis before or on the index date