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Relation of substance use disorders to mortality, accident and emergency department attendances, and hospital admissions: A 13-year population-based cohort study in Hong Kong

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ABSTRACT

Background: The impact of substance use disorders (SUD) in an Asian population has not been fully explored. We aimed to assess the risk of mortality, accident and emergency (A&E) department attendances, and hospital admissions associated with SUD in a population-based cohort study.
Method: Patients diagnosed with SUD in public A&E departments from 2004 to 2016 (N = 8,423) were identified in the Clinical Database Analysis and Reporting System of the Hong Kong Hospital Authority and 1:1 matched to patients without SUD by propensity score (N = 6,074 in each group). Relative risks of mortality, A&E attendances and hospital admissions were assessed using Cox regression and Hurdle negative binomial regression.
Results: Patients with SUD had higher mortality (hazard ratio=1.43; 95% confidence interval [CI]=1.26–1.62) and more often died from poisoning or toxicity and injuries. The odds ratio (OR) for A&E attendances and all-cause hospital admissions associated with SUD were 2.80 (95% CI=2.58–3.04) and 3.54 (95% CI=3.26–3.83), respectively. The impact of SUD on the above outcomes was greatest among school-aged individuals (≤ 21 years) and decreased with age. The relative risk of mental disorder-related hospital admissions was much higher than that for infections, respiratory diseases, and cardiovascular diseases. In patients with SUD, ketamine and amphetamine use were associated with increased A&E attendances than opioid use.
Conclusions: SUD was associated with increased mortality, A&E attendances and hospital admissions, especially in school-aged individuals. Our findings suggest prioritising early treatment and preventive interventions for school-aged individuals and focusing on the management of comorbid mental disorders and the use of ketamine and amphetamine.

1. Introduction

Substance use refers to the compulsive seeking of substances, including drugs without medical advice or prescription, or the illegal use of dangerous drugs including psychotropic substances for non-treatment purposes (Koob and Volkow, 2010; United Nations, 2021). The United

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Nations estimates that 275 million people misused substances in 2020, and over 500,000 died from substance use disorders (SUD) worldwide (United Nations, 2021). Excessive use of illicit drugs is associated with a number of health conditions, including mental disorders, cardiovascular, respiratory, and infectious diseases, and increased global disease burden (Degenhardt et al., 2018). SUD and the associated outcomes places additional pressure on the healthcare system, particularly accident and emergency (A&E) departments (Chan et al., 2020; Schulte and Hser, 2014). In Hong Kong, a multi-modal approach has been adopted to manage SUD, including compulsory and voluntary SUD treatment centres, clinics and counselling centres, provided by the government, and voluntary residential drug treatment and rehabilitation programmes supported by non-government organisations (Narcotics Division, 2021b). Understanding the burden of disease and healthcare utilisation associated with SUD, using the outcomes of mortality, A&E attendances and hospital admissions, can inform policy, clinical practice and development of effective interventions.

Currently, North America has the highest annual prevalence of opioid use and is the principal market for fentanyl and cocaine (United Nations, 2021). In contrast, ketamine is more commonly used in Asia, especially in China (Sun et al., 2014; United Nations, 2021). Methamphetamine is also a concerning substance in South-East Asia (United Nations, 2021). In Hong Kong, ketamine, methamphetamine, and cocaine are the main drugs used by school-aged individuals, while opioids are more likely to be used by the elderly (Chan et al., 2020; United Nations, 2021). Due to the different patterns of substance misuse in Asia, it is unclear whether the findings from outside Asia can be generalised to this population.

To date, most studies that have examined SUD and the outcomes of mortality and healthcare utilisation have been conducted in the United States or in Europe (Aldridge et al., 2018; Chang et al., 2010; Gryczynski et al., 2016; Hedegaard et al., 2020; Lewer et al., 2020; Opsal et al., 2011). A study from the United States found that people with SUD had 2.2 times higher odds of all-cause hospitalisation than abstainers during four years of follow-up, but the underlying causes of hospitalisation were not investigated (Gryczynski et al., 2016). Existing studies from Asia are limited by their main focus on opioid users and the small sample size (Chen et al., 2015; Li et al., 2020; Nguyen et al., 2017; Quan et al., 2007). A population-based cohort study in Taiwan described an overall one-year mortality rate of 1.71% in heroin users, but the comparative risk of death in patients diagnosed with SUD to controls was not assessed (Lee et al., 2013).

Currently, valid comparisons of mortality and healthcare utilisation between patients with SUD and their counterparts without SUD have not been established in Asia. The health outcomes of patients misusing different types of substance has also rarely been studied. In addition, evaluating the impact of SUD on cause-specific hospital admissions and in different age groups could help to identify high-risk populations and the main reasons for increased healthcare utilisation, which have not been systematically investigated in previous studies.

To address these knowledge gaps, we performed a population-based study to assess the association of SUD with mortality, A&E attendances, and hospital admissions in Hong Kong.

2. Methods

2.1. Data source

We obtained data from the Clinical Data Analysis and Reporting System (CDARS), an electronic health record database of the Hong Kong Hospital Authority. Since 1991, the Hospital Authority has managed 43 public hospitals and institutions and 49 specialist and 73 general outpatient clinics; it serves a population of over 7 million people (Hong Kong Hospital Authority, 2020). In Hong Kong, the public healthcare sector provides 70% of hospital beds and nearly all A&E departments (Hong Kong Hospital Authority, 2018). The Hospital Authority has an integrated electronic health record for all public hospitals, A&E departments and outpatient clinics and this data is accessible in CDARS, including anonymised patient identifiers, demographics, consultation date, hospital admission and discharge dates, diagnoses, procedures, prescriptions, and laboratory tests. Data from CDARS has been used for a variety of high-quality population-based pharmacoepidemiological studies (Lau et al., 2017; Law et al., 2018; Wong et al., 2016). This study was approved through the expedited review procedure of the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW 17–107).

2.2. Study design and patient identification

This was a population-based retrospective cohort study. The exposed group, *patients with SUD*, included patients with at least one diagnosis of SUD in any public A&E department between January 1, 2004 and December 31, 2016 in CDARS. This is because A&E departments are often the first point of contact for individuals with SUD, and A&E attendance has been recognised as an opportunity to identify and link patients to healthcare for SUD in previous studies (D'Onofrio et al., 2015; Hawk and D'Onofrio, 2018). Diagnosis codes for SUD (Table S1) have been validated by ATYC and MLT from the Hong Kong Poison Information Centre, with a positive predictive value of 99.7% (95% confidence interval [CI]=87.4%−94.0%). The unexposed group, *patients without SUD*, was a cohort of patients who were randomly selected from CDARS. We then excluded patients with a diagnosis of SUD (Fig. 1). Follow-up began on the index date and ended on December 31, 2016 or the date of death (whichever came first). The index date for the exposed group was defined as the date of first record of SUD in a public A&E department during the study period. A random date between January 1, 2004 or the date of birth (whichever came later) and the end of follow-up was assigned to each patient in the unexposed group as the index date, as per method used by Oza et al. (Oza et al., 2017). Patients in either group were excluded if they had incomplete demographic information or died on the index date.

2.3. Outcomes

The primary outcomes were all-cause mortality and healthcare utilisation, defined as A&E attendances and all-cause hospital admissions. To further explore the reasons for hospital admission, secondary outcomes were cause-specific hospital admissions, including those related to mental disorders, infections, respiratory, and cardiovascular diseases. A&E attendances and hospital admissions were assessed across different follow-up durations (1-month, 3-month, 1-year, 3-year, 10-year and the entire follow-up period) to measure the short-term and long-term impact of SUD. Causes of death were identified using the diagnosis codes from demographic data (Table S2), while causes of hospital admissions were identified using the primary diagnosis code from inpatient records (Table S3).

2.4. Confounding and propensity score matching

We performed propensity score matching to balance baseline characteristics and to control for confounders (Austin, 2011). The conditional probability of being diagnosed with SUD was estimated using logistic regression, given the following observed baseline covariates: sex; age on the index date; baseline healthcare utilisation (number of A&E attendances and hospital admissions) and psychotropic medication use (including hypnotics and anxiolytics, antipsychotics, antidepressants, and stimulants and drugs used for attention deficit hyperactivity disorder, measured by the number of prescriptions) as defined in Table S4; baseline chronic medical conditions, including depressive disorder, adjustment disorder, schizophrenic disorder, anxiety/dissociative/somatoform disorder, personality disorder, bipolar disorder, attention deficit hyperactivity disorder, suicidal attempt and

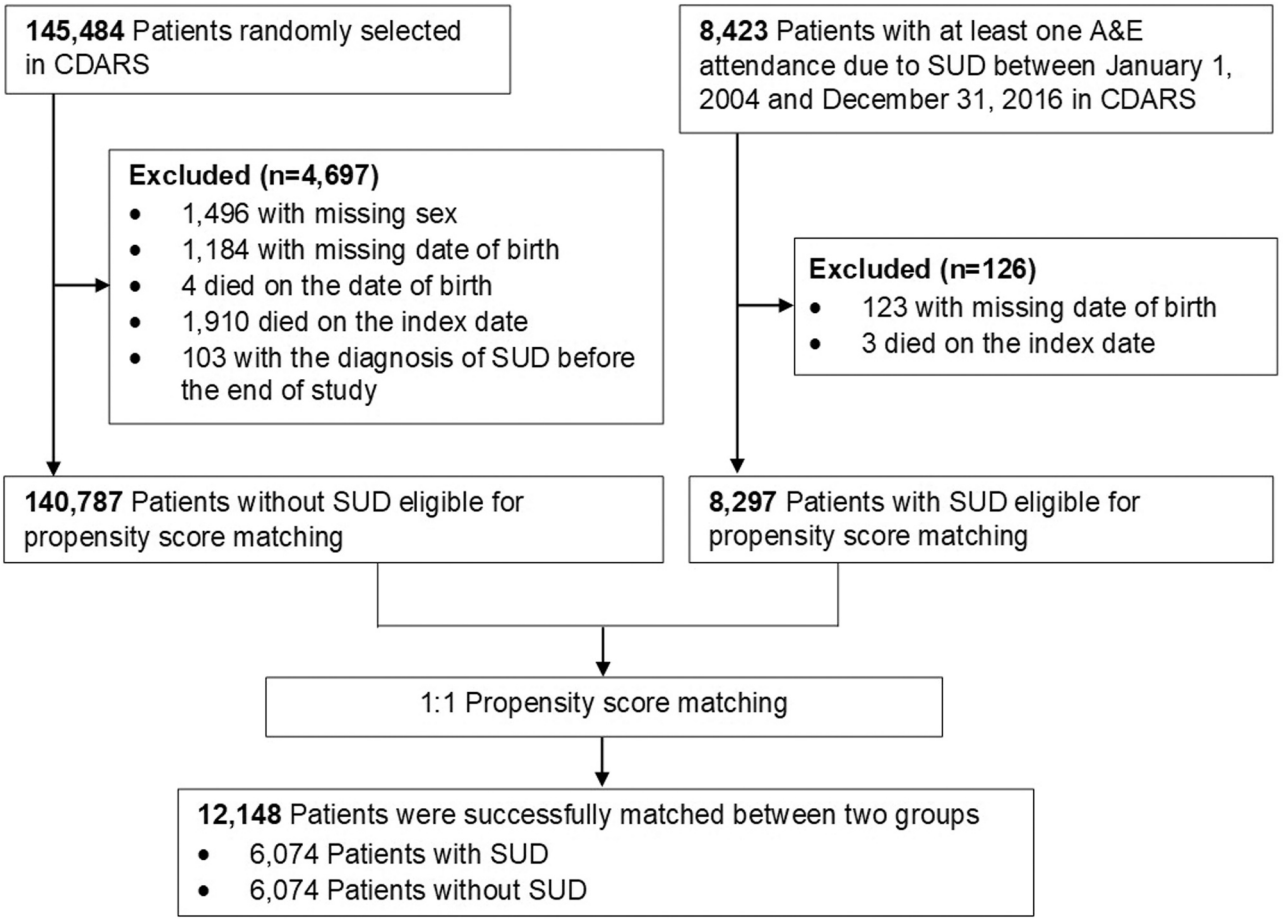

Fig. 1. Identification of patients with and without substance use disorder in CDARS. Abbreviations: CDARS, Clinical Data Analysis and Reporting System; A&E, accident and emergency; SUD, substance use disorder.

self-inflicted injury, other mental disorder, deep vein thrombosis, hypertension, ischaemic stroke, atrial fibrillation, congestive heart failure, myocardial infarction, gastric/duodenal/peptic/gastrojejunal ulcer, constipation, chronic obstructive pulmonary disease, asthma, acute renal failure, chronic kidney disease, anaemia, diabetes mellitus, epilepsy/seizure, viral hepatitis, other liver disease, human immunodeficiency virus, and malignant neoplasm (Table S4). Patients with and without SUD were matched at a 1:1 ratio on the propensity score using nearest neighbour matching with a calliper of 0.1. A standardised mean difference (SMD) < 0.1 was considered as a negligible difference between groups (Austin, 2011).

2.5. Statistical analyses

Baseline characteristics for continuous variables were expressed as means (standard deviation [SD]) and for categorical variables as frequencies (percentages). We estimated hazard ratios (HR) with 95% CI using Cox regression for all-cause mortality. Since the distribution of individual A&E attendance and hospital admission data was generally skewed to the right and contained a large proportion of zeros, the assumption of Poisson regression was violated (Cameron and Trivedi, 2013). Thus, we used a Hurdle negative binomial model to manage excess zeros and overdispersion to determine the odds ratio (OR) with 95% CI and incidence rate ratio (IRR) with 95% CI for the association of SUD with A&E attendances and hospital admissions, using time from the index date as an offset to account for varying lengths of follow-up (Cameron and Trivedi, 2013). Hurdle models are widely used to evaluate the effect of exposure on healthcare utilisation (Bowen et al., 2014; Channick et al., 2015; Comtois et al., 2019). They simultaneously evaluate two different distributions of data. The first component models the odds of any A&E attendance and hospital admission (presence or absence of outcome event) using logistic regression in the whole cohort. The second component uses negative binomial regression to estimate the number of A&E attendances and hospital admissions (frequency of outcome event) among those who have had at least one such event, in the whole cohort (Cameron and Trivedi, 2013).

We then examined the association between SUD with mortality, A&E attendances, and hospital admissions stratified by age on the index date. Age groups included school-aged individuals ($\leq$ 21years), young adults (22–45 years), middle-aged adults (45−65) and the elderly ($\geq$ 65 years). We also investigated the impact of different types of substance (Table S1). Since opioids have been widely studied and little is known about other types of substance use in Asian populations, we directly compared the outcomes between patients diagnosed with ketamine, amphetamine, cocaine or cannabis misuse versus opioid misuse (reference group) among patients with SUD. For each direct comparison, we used the same propensity score model and matching algorithm. To assess the robustness of our main analysis, we performed two sensitivity analyses. First, drug withdrawal syndromes are a physiologic response to the abrupt withdrawal or reduced use of a drug and occur frequently with misused substances (Tetrault and O'Connor, 2008). Patients identified by a diagnosis of drug withdrawal (Table S1) may have stopped misusing substances at baseline and would be misclassified, although some are highly likely to continue using the substance. Therefore, we excluded individuals with an index diagnosis of drug withdrawal. Second, to assess whether the differences in mortality between the two groups biased our results, the Fine-Gray competing risk regression was used for A&E attendances, all-cause hospital admissions and

cause-specific hospital admissions (Fine and Gray, 1999).

YW conducted the statistical analyses which were independently cross-checked by JXZ. All analyses were performed using R software (Version 3.6.0, R Core Team 2019, Austria). Hurdle negative binomial models were fitted using the R-package "pscl" (Version 1.5.2) (Zeileis et al., 2008). All hypothesis tests were two-sided, with a significance level of 0.05.

3. Results

3.1. Baseline characteristics and matching

We identified a total of 8,423 patients diagnosed with SUD in A&E departments between 2004 and 2016 (Fig. 1). A total of 145,484 patients were randomly selected from CDARS for the unexposed group. After application of the exclusion criteria, 8,297 patients with SUD and 140,787 patients without SUD were eligible for matching. Baseline characteristics before and after matching are summarised in Table 1. Patients with SUD were relatively young, and the majority were men. The most common comorbidities in patients with SUD were mental disorders and suicide attempts.

After matching, 12,148 individuals (6,074 each group) were included for comparison. All baseline characteristics were well balanced between the two groups, with SMDs of less than 0.1 (Table 1 and Fig. S1). The median (interquartile range) duration of follow-up was 6.0 (6.3) years.

3.2. Risk of mortality

In the matched cohort, deaths occurred in 9.5% (N = 577) of patients with SUD and 6.5% (N = 397) of patients without SUD during follow-up (Table 2). The overall risk of all-cause mortality was higher in patients with SUD (HR=1.43; 95% CI=1.26–1.62) and a significantly higher proportion of patients with SUD died from poisoning or toxicity (N = 89 [15.4%] versus N = 18 [4.5%]; $p < 0.001$) and injuries (N = 48 [8.3%] versus N = 16 [4.0%]; $p = 0.012$) compared with patients without SUD (Table 2).

Table 1
Baseline characteristics of patients with and without substance use disorder before and after propensity score matching.

	Before Matching			After Matching		
	Patients with SUD (N = 8,297)	Patients without SUD (N = 140,787)	SMD	Patients with SUD (N = 6,074)	Patients without SUD (N = 6,074)	SMD
Male (%)	5,932 (71.5)	67,381 (47.9)	0.496	4,275 (70.4)	4,337 (71.4)	0.022
Age, mean (SD)	35.68 (13.09)	37.67 (23.49)	0.105	35.38 (13.74)	35.69 (14.52)	0.022
Baseline healthcare utilisation (within one year before index date)						
No of A&E attendances, mean (SD)	1.87 (4.07)	0.24 (0.94)	0.554	1.13 (3.69)	0.93 (3.08)	0.057
No of hospital admissions, mean (SD)	0.74 (1.87)	0.17 (1.60)	0.328	0.37 (1.43)	0.33 (1.51)	0.029
Baseline psychotropic medication use (within one year before the index date)						
Total, mean (SD)	20.79 (60.50)	6.38 (27.84)	0.306	12.10 (47.46)	12.15 (45.69)	0.001
No of hypnotics and anxiolytics prescriptions, mean (SD)	1.79 (7.31)	0.07 (0.99)	0.329	0.70 (4.60)	0.55 (3.42)	0.036
No of antipsychotics prescriptions, mean (SD)	2.24 (9.89)	0.11 (2.08)	0.297	1.00 (7.26)	0.83 (5.31)	0.027
No of antidepressants prescriptions, mean (SD)	1.57 (6.92)	0.09 (1.17)	0.299	0.62 (3.56)	0.57 (3.72)	0.014
No of stimulants and drugs used for attention deficit hyperactivity disorder, mean (SD)	0.01 (0.35)	0.00 (0.11)	0.018	0.01 (0.33)	0.01 (0.20)	0.003
Baseline chronic medical conditions (before the index date)						
Depressive disorder (%)	677 (8.2)	1,081 (0.8)	0.364	239 (3.9)	243 (4.0)	0.003
Adjustment disorder (%)	591 (7.1)	637 (0.5)	0.355	222 (3.7)	213 (3.5)	0.008
Schizophrenic disorder (%)	418 (5.0)	764 (0.5)	0.276	167 (2.7)	169 (2.8)	0.002
Anxiety/ dissociative/ somatoform disorder (%)	377 (4.5)	1,047 (0.7)	0.239	177 (2.9)	171 (2.8)	0.006
Personality disorder (%)	325 (3.9)	100 (0.1)	0.278	75 (1.2)	55 (0.9)	0.032
Bipolar disorder (%)	76 (0.9)	155 (0.1)	0.113	41 (0.7)	48 (0.8)	0.014
Attention deficit hyperactivity disorder (%)	14 (0.2)	164 (0.1)	0.014	9 (0.1)	14 (0.2)	0.019
Suicidal attempt and self-inflicted injury (%)	1,721 (20.7)	596 (0.4)	0.700	430 (7.1)	365 (6.0)	0.043
Other mental disorder (%)	3,288 (39.6)	2,722 (1.9)	1.049	1,201 (19.8)	1,260 (20.7)	0.024
Deep vein thrombosis (%)	313 (3.8)	152 (0.1)	0.268	69 (1.1)	61 (1.0)	0.013
Hypertension (%)	179 (2.2)	5,298 (3.8)	0.095	119 (2.0)	127 (2.1)	0.009
Ischaemic stroke (%)	90 (1.1)	2,082 (1.5)	0.035	50 (0.8)	56 (0.9)	0.011
Atrial fibrillation (%)	31 (0.4)	1,035 (0.7)	0.049	23 (0.4)	27 (0.4)	0.010
Congestive heart failure (%)	32 (0.4)	1,181 (0.8)	0.058	26 (0.4)	30 (0.5)	0.010
Myocardial infarction (%)	21 (0.3)	609 (0.4)	0.031	14 (0.2)	18 (0.3)	0.013
Gastric/ duodenal/ peptic/ gastrojejunal ulcer (%)	181 (2.2)	1,486 (1.1)	0.089	100 (1.6)	120 (2.0)	0.025
Constipation (%)	138 (1.7)	878 (0.6)	0.098	69 (1.1)	68 (1.1)	0.002
Chronic obstructive pulmonary disease (%)	437 (5.3)	2,666 (1.9)	0.182	231 (3.8)	238 (3.9)	0.006
Asthma (%)	268 (3.2)	1,454 (1.0)	0.153	142 (2.3)	150 (2.5)	0.009
Acute renal failure (%)	66 (0.8)	170 (0.1)	0.100	19 (0.3)	19 (0.3)	< 0.001
Chronic kidney disease (%)	33 (0.4)	77 (0.1)	0.072	9 (0.1)	11 (0.2)	0.008
Anaemia (%)	281 (3.4)	2,412 (1.7)	0.106	131 (2.2)	131 (2.2)	< 0.001
Diabetes mellitus (%)	126 (1.5)	3,063 (2.2)	0.049	76 (1.3)	84 (1.4)	0.012
Epilepsy/ seizure (%)	165 (2.0)	567 (0.4)	0.146	61 (1.0)	73 (1.2)	0.019
Viral hepatitis (%)	395 (4.8)	1,419 (1.0)	0.226	155 (2.6)	155 (2.6)	< 0.001
Other liver disease (%)	239 (2.9)	989 (0.7)	0.165	109 (1.8)	112 (1.8)	0.004
Human immunodeficiency virus (%)	14 (0.2)	25 (0.0)	0.049	5 (0.1)	8 (0.1)	0.015
Malignant neoplasm (%)	242 (2.9)	5,180 (3.7)	0.043	168 (2.8)	182 (3.0)	0.014

Abbreviations: SUD, substance use disorder; SMD, standardised mean difference; SD, standard deviation; A&E, accident and emergency.

Table 2
Characteristics and cause of death in patients who died during follow-up before and after propensity score matching.

	Before Matching		After Matching		
	Patients with SUD (N = 994)	Patients without SUD (N = 7,721)	Patients with SUD (N = 577)	Patients without SUD (N = 397)	P value[a]
Male (%)	820 (82.5)	4,266 (55.3)	476 (82.5)	324 (81.6)	0.788
Age at death, mean (SD)	48.74 (15.28)	76.26 (14.82)	51.32 (16.51)	59.20 (17.15)	< 0.001
Cause of death					
Poisoning or toxicity (%)	193 (19.4)	49 (0.6)	89 (15.4)	18 (4.5)	< 0.001
Poisoning due to heroin (%)	93 (9.4)	5 (0.1)	42 (7.3)	4 (1.0)	
Poisoning due to other opioids (%)	50 (5.0)	4 (0.1)	24 (4.2)	2 (0.5)	
Toxicity due to carbon monoxide (%)	18 (1.8)	31 (0.4)	13 (2.3)	7 (1.8)	
Respiratory diseases (%)	120 (12.1)	2,061 (26.7)	74 (12.8)	84 (21.2)	< 0.001
Injuries involving multiple body regions (%)	87 (8.8)	64 (0.8)	48 (8.3)	16 (4.0)	0.012
Cancer (%)	84 (8.5)	1,929 (25.0)	67 (11.6)	96 (24.2)	< 0.001
Cardiovascular diseases (%)	75 (7.5)	1,299 (16.8)	49 (8.5)	50 (12.6)	0.048
Other sepsis (%)	26 (2.6)	172 (2.2)	12 (2.1)	4 (1.0)	0.300
Asphyxiation (%)	19 (1.9)	26 (0.3)	10 (1.7)	6 (1.5)	0.991
Other causes (%)	126 (12.7)	1,048 (13.6)	78 (13.5)	63 (15.9)	
Missing cause of death (%)	264 (26.6)	1,073 (13.9)	150 (26.0)	60 (15.1)	

Abbreviations: SUD, substance use disorder; SD, standard deviation.
[a] In the matched-cohort, generated from two-sample T test or Chi-Square test.

3.3. Accident and emergency department attendances

According to the zero-part model (based on all patients in the propensity score-matched cohort), the OR for A&E attendances for patients with versus without SUD at one month was 4.72 (95% CI=4.08–5.45). ORs decreased with longer durations of follow-up: 3.12 (95% CI=2.89–3.37) at three years and 2.80 (95% CI=2.58–3.04) at the end of follow-up (Table 3). Estimates for the count-part model were based on patients with at least one outcome event and assessed the effect of SUD on the number of events over a given follow-up period. In general, patients with SUD and at least one outcome event had an increased rate of A&E attendances (IRR=1.52; 95% CI=1.38–1.67, whole follow-up), although differences were not significant at three months and one year of follow-up.

3.4. Hospital admissions

SUD was consistently associated with a higher odds of all-cause hospital admissions during the entire follow-up period (OR=3.54; 95% CI=3.26–3.83). However, for patients with at least one hospital admission, SUD was associated with a significantly lower rate of hospital admissions after one month of follow-up (Table 3). For the cause-specific outcomes, SUD was associated with significantly higher odds of hospital admissions for mental disorders (OR=8.90; 95% CI=7.76–10.21, whole follow-up) and infectious diseases (OR=2.62; 95% CI=2.25–3.06, whole follow-up). Associations between SUD and an increased odds of hospital admissions for respiratory or cardiovascular diseases were significant only during long-term follow-up (10 years and beyond). Overall, the odds of mental disorder-related hospital admissions were much higher than that of other cause-specific hospital admissions (Table 3). In total, 1,664 (27.4%) patients with SUD and 266 (4.4%) patients without SUD were hospitalised for mental disorders. The most frequent reasons included nondependent abuse of drugs (843 [13.9%] out of patients with SUD versus 21 [0.3%] out of patients without SUD), drug-induced mental disorders (489 [8.1%] versus 16 [0.3%]), drug dependence (268 [4.4%] versus 12 [0.2%]), other nonorganic psychoses (179 [3.0%] versus 25 [0.4%]) and schizophrenic disorders (175 [2.9%] versus 71 [1.2%]).

3.5. Subgroup and sensitivity analyses

SUD was related to a higher risk of death in school-aged individuals (HR=2.74; 95% CI=1.00–7.49), young adults (HR=2.38; 95% CI=1.89–3.01) and middle-aged adults (HR=1.40; 94% CI=1.15–1.71). In contrast, SUD was significantly associated with a lower risk of death in patients aged ≥ 65 years (HR=0.73, 95% CI=0.55–0.96) (Fig. 2a). Patients ≤ 21 years had the highest demand for A&E attendances (OR=7.24; 95% CI=5.76–9.09) and hospital admissions (OR=8.12; 95% CI=6.40–10.30); point estimates also moved closer to 1 as age group increased (Fig. 2b). Similar effects were observed for hospital admissions related to mental disorders and infections, but not for respiratory or cardiovascular disease-related hospital admissions due to the limited number of these events in school-aged individuals.

The number of patients included for each direct comparison between different substances is shown in Table S5. There was no significant difference in mortality between any psychotropic substances and opioid use (Fig. S2a, S3a, S4a and S5a). Ketamine use was associated with a significantly higher odds of A&E attendances (OR=2.21; 95% CI=1.53–3.19) than opioid use (Fig. S2b). Increased A&E attendances (OR=2.12; 95% CI=1.44–3.11), all-cause hospital admissions (OR=1.94; 95% CI=1.39–2.74) and mental disorder-related hospital admissions (OR=2.69; 95% CI=1.94–3.75) were found in patients using amphetamine when compared with their counterparts using opioids (Fig. S3b). Ketamine (OR=0.21; 95% CI=0.08–0.55) and amphetamine use (OR=0.21; 95% CI=0.07–0.64) were associated with a lower odds of cardiovascular disease-related hospital admissions than opioids. No significant differences were found for cocaine and cannabis use when compared with opioid use (Fig. S4b and S5b) in terms of any outcomes.

After excluding 1,363 patients with an index A&E diagnosis of drug withdrawal, the risk of death remained significantly higher in patients with SUD (HR=2.49; 95% CI=2.13–2.90). Results for A&E attendances and hospital admissions were also consistent with the main analyses (Table S6 and S7). After accounting for the competing risk of death, the relative risks of A&E attendances or hospital admissions were consistent with the trend in the main Hurdle model, suggesting that the findings were not biased by differences in mortality between the two groups (Fig. S6).

4. Discussion

To our knowledge, this is the first cohort study to compare healthcare utilisation between patients with versus without SUD in an Asian population. The large sample size and up to 13 years of follow-up allow for precise estimates of the impact of any SUD, not only opioid misuse, in Hong Kong. We found that SUD was significantly associated with an increased risk of mortality, A&E attendances, and hospital admissions, especially in school-aged individuals (≤ 21 years). We analysed different causes of hospitalisation in the same cohort and identified

Table 3
Comparison of all-cause A&E attendances, all-cause hospital admissions, cause-specific hospital admissions between patients with versus without SUD after propensity score matching.

Length of follow-up	All patients in the matched cohort Zero model part (logistic regression) Odds Ratio (95% CI)	Patients with at least one event in the matched cohort Count model part (negative binomial regression) Incidence Rate Ratio (95% CI)
All-cause A&E attendances		
1-month	4.72 (4.08, 5.45)*	1.86 (1.34, 2.57)*
3-month	3.60 (3.25, 4.00)*	1.12 (0.92, 1.37)
1-year	3.09 (2.85, 3.35)*	1.10 (0.96, 1.26)
3-year	3.12 (2.89, 3.37)*	1.27 (1.14, 1.43)*
10-year	2.79 (2.57, 3.03)*	1.52 (1.38, 1.67)*
Whole	2.80 (2.58, 3.04)*	1.52 (1.38, 1.67)*
All-cause hospital admissions		
1-month	7.82 (6.47, 9.44)*	0.67 (0.44, 1.03)
3-month	5.24 (4.56, 6.02)*	0.54 (0.41, 0.71)*
1-year	3.75 (3.39, 4.15)*	0.53 (0.44, 0.64)*
3-year	3.52 (3.23, 3.83)*	0.60 (0.52, 0.70)*
10-year	3.53 (3.26, 3.83)*	0.72 (0.63, 0.82)*
Whole	3.54 (3.26, 3.83)*	0.73 (0.64, 0.83)*
Mental disorder-related hospital admissions		
1-month	41.20 (25.04, 67.79)*	2.12 (0.26, 17.60)
3-month	20.38 (14.79, 28.09)*	1.02 (0.45, 2.30)
1-year	12.52 (10.09, 15.54)*	0.73 (0.47, 1.14)
3-year	9.50 (8.07, 11.18)*	0.84 (0.61, 1.17)
10-year	8.84 (7.70, 10.15)*	0.97 (0.73, 1.28)
Whole	8.90 (7.76, 10.21)*	0.98 (0.74, 1.29)
Infection-related hospital admissions		
1-month	3.52 (1.74, 7.11)*	1.67 (0.25, 10.94)
3-month	3.13 (1.89, 5.18)*	3.82 (0.73, 20.04)
1-year	2.28 (1.69, 3.07)*	0.81 (0.41, 1.59)
3-year	2.23 (1.83, 2.71)*	0.99 (0.63, 1.54)
10-year	2.56 (2.19, 2.98)*	0.93 (0.66, 1.31)
Whole	2.62 (2.25, 3.06)*	0.92 (0.66, 1.29)
Respiratory disease-related hospital admissions		
1-month	1.20 (0.52, 2.78)	1.78 (0.53, 6.03)
3-month	1.38 (0.72, 2.63)	1.24 (0.55, 2.79)
1-year	1.11 (0.70, 1.76)	0.84 (0.32, 2.19)
3-year	1.27 (0.89, 1.82)	0.88 (0.4, 1.92)
10-year	2.04 (1.54, 2.70)*	0.56 (0.3, 1.06)
Whole	2.07 (1.56, 2.73)*	0.57 (0.3, 1.06)
Cardiovascular disease-related hospital admissions		
1-month	2.41 (0.85, 6.84)	0.87 (0.08, 8.94)
3-month	1.73 (0.82, 3.64)	0.51 (0.09, 2.73)
1-year	1.73 (0.98, 3.07)	0.98 (0.36, 2.66)
3-year	1.33 (0.96, 1.84)	0.81 (0.41, 1.62)
10-year	1.43 (1.13, 1.81)*	0.62 (0.38, 1.03)
Whole	1.44 (1.14, 1.81)*	0.61 (0.37, 1.00)

Abbreviations: A&E, accident and emergency; SUD, substance use disorder; CI, confidence interval.
* Estimate is statistically significant ($P < 0.05$).

mental disorders as a major factor related to the increased healthcare burden of patients with SUD. Our study also revealed the higher healthcare utilisation, in terms of A&E attendances and all-cause hospital admissions, among patients misusing ketamine and amphetamine when compared with opioid misusers, which has rarely been investigated before.

In this study, the most common cause of death in patients with SUD was poisoning by opioid or carbon monoxide, which is consistent with previous research (Hedegaard et al., 2020; Weaver, 2009). Locally, carbon monoxide poisoning is a common cause of intentional suicide attempts (Ching et al., 2017). Although previous descriptive studies found that ketamine was commonly misused in Hong Kong, it rarely causes death directly. Rather, vomiting due to ketamine-related paralysis, and accidents or injuries associated with its dissociative effects, are more likely to result in life-threatening consequences (American Addiction Centers, 2020). The lower proportion of mortality from cancer, respiratory or cardiovascular diseases for patients with versus without SUD was probably due to the competing risk of death related to poisoning and injuries.

This study quantifies the increased use of emergency treatment and inpatient care associated with SUD. Given the higher odds of A&E attendances and hospital admissions in patients with SUD, it is worth investigating whether access to outpatient drug treatment services in primary care can reduce reliance on A&E and inpatient care (Wakeman et al., 2019). However, among patients with at least one hospital admission, SUD was associated with a lower rate of admission. This could be a consequence of the pattern of health seeking behaviour in these individuals. First, SUD is a risk factor for treatment non-adherence, possibly leading to a lower rate of subsequent hospital admissions (Ascher-Svanum et al., 2006). Second, evidence is accumulating to show that patients with SUD experience discrimination and stigmatisation in the healthcare sector (Lloyd, 2012). These negative treatment experiences could cause delay in seeking healthcare or treatment refusal later in the course of illness, especially for long-term treatment (Lloyd, 2012). Therefore, we hypothesise that the higher risk of hospital admissions and the lower rate of subsequent admissions in our study is a result of barriers to accessing adequate healthcare owing to patient and healthcare system-related factors after a first hospital admission. Further studies are needed to investigate this finding.

Our findings also revealed the cause for increased hospital admissions in patients with SUD, which could inform decision-making in the management of this population. Overall, mental disorders were the major reason for excess hospitalisations in patients with SUD. Although baseline mental disorders were balanced, SUD can cause the relapse of mental disorders because they often share common risk factors (National Institution on Drug Abuse, 2018). Infectious diseases, including human immunodeficiency virus, hepatitis C virus and sexually transmitted infections are common in patients with SUD (Schulte and Hser, 2014), therefore, SUD is associated with a higher risk of infection-related hospital admissions. Although SUD is correlated with multiple respiratory diseases and cardiovascular diseases (Schulte and Hser, 2014), significantly increased odds of hospital admissions for these reasons was observed only during long-term follow-up. This likely reflects the mean age of the matched cohort (35.5 years) and most patients were unlikely to experience a cardiovascular event during short-term follow-up. Additionally, the impact of SUD on the cardiovascular system is usually not acute; hence long-term follow-up is needed to identify an adequate number of events.

The findings from different age groups provide insight into the age effect on the impact of SUD and could help clinicians to identify high-risk populations. Overall, the impact of SUD was greatest for patients aged ≤ 21 years, suggesting a critical need for substance use management of school-aged individuals to reduce healthcare utilisation and premature mortality in Hong Kong. Our findings are consistent with previous studies reporting that the relative risk of death and psychosocial problems for patients with SUD versus controls diminishes with age (Chang et al., 2010). However, among patients aged ≥ 65, SUD was associated with a lower risk of death, which could be explained by selection bias. As SUD usually begins in adolescence or early adulthood, those surviving into older age may have different traits from patients who died younger, or may have a higher tolerance to drugs (including prescription drugs) (Chang et al., 2010).

The high prevalence of opioid misuse has made it the most widely studied substance in both Western and Asian populations (Aldridge et al., 2018; Chang et al., 2010; Chen et al., 2015; Gryczynski et al., 2016; Hedegaard et al., 2020; Lee et al., 2013; Lewer et al., 2020; Li et al., 2020; Nguyen et al., 2017; Opsal et al., 2011; Quan et al., 2007). In Hong Kong, over half of patients misuse psychotropic substances (including ketamine, amphetamine, cocaine and cannabis), especially in patients aged ≤ 21 (Narcotics Division, 2021a). The direct comparisons between these psychotropic substances and opioids suggest that ketamine and amphetamine were potentially associated with higher healthcare utilisation. However, the sample size of the matched cohort

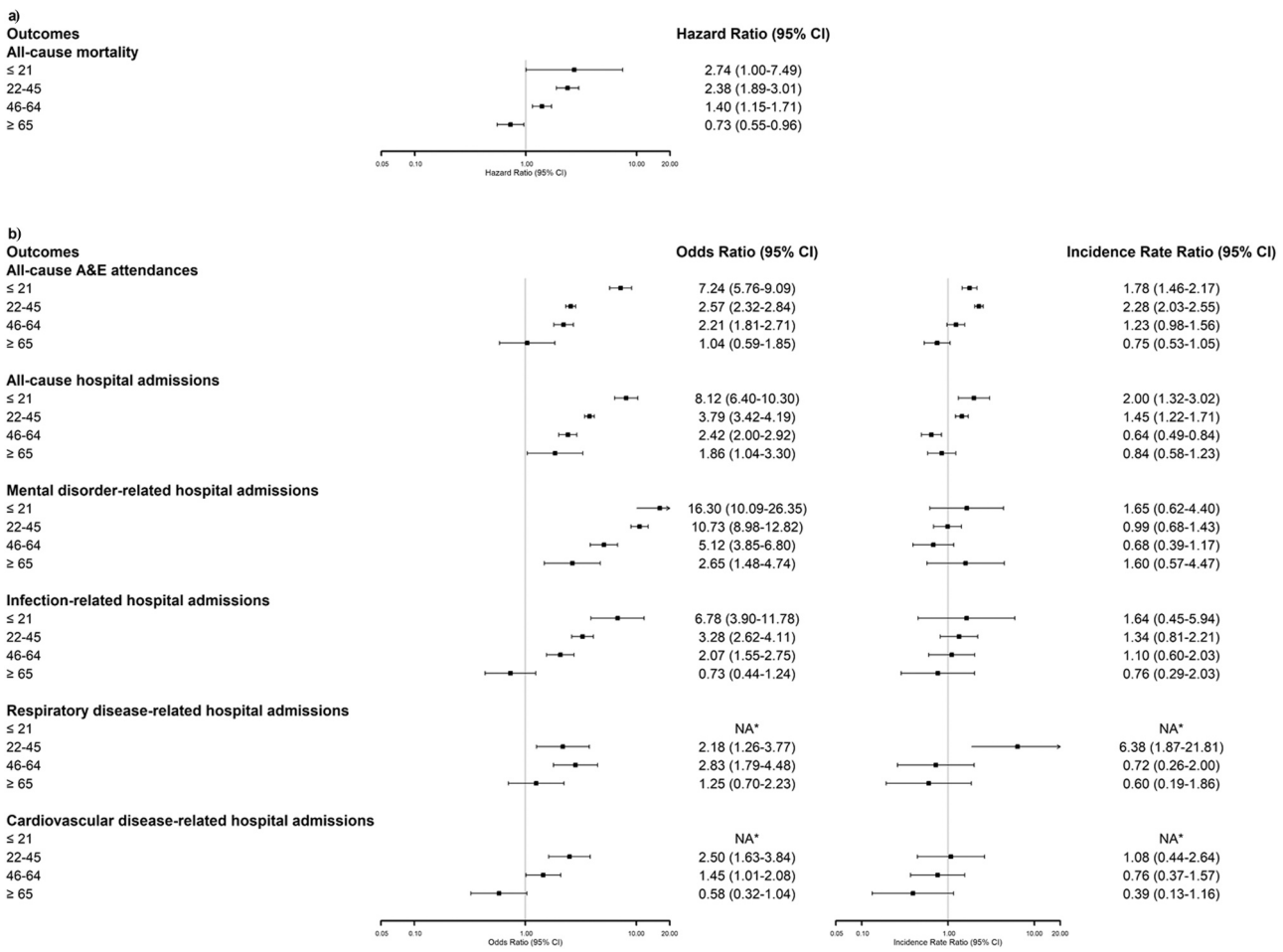

Fig. 2. Comparison of all-cause mortality (Fig. 2a), all-cause A&E attendances, all-cause hospital admissions and cause-specific hospital admissions (Fig. 2b) between patients with and without SUD after propensity score matching, stratified by age. Abbreviations: A&E, accident and emergency; SUD, substance use disorder.
* Not estimable.

was limited.

The mortality rate in our study was much higher than the study from Taiwan due to follow-up duration of 13 years and broader inclusion criteria (Lee et al., 2013). A meta-analysis from Aldridge et al. reported a higher prevalence of infections, mental disorders, cardiovascular and respiratory diseases in patients with SUD (Aldridge et al., 2018). Our findings are consistent with their study, and further adds to these previous reports that mental disorders are responsible for much of the hospitalisations, suggesting that interventions targeting mental disorders could help reduce the excessive burden on inpatient care among patients with SUD.

This study has limitations. First, our cohort does not include the entire population with SUD in Hong Kong as patients were identified from public A&E departments. However, the Hospital Authority serves all Hong Kong residents and covers over 80% of all hospital admissions (Hong Kong Hospital Authority, 2018). Only a minority of patients may choose or can afford to have the entirety of their care in the private sector. Second, similar to other studies about SUD, some patients in the community may not seek formal healthcare or report their substance use behaviours due to the fear of legal issues. Since substance use can be hidden from healthcare providers (Opsal et al., 2011), we were not able to capture patients who were not diagnosed with SUD in the A&E department.

5. Conclusion

In this population-based cohort in Hong Kong, patients with SUD have higher mortality, and greater demand for A&E attendances and hospital admissions. We found the impact of SUD was greatest among school-aged individuals ($\leq$ 21 years), suggesting that they should be given priority among the patients with SUD in Hong Kong. We found that mental disorders were the main factors related to the excess hospital admissions among patients with SUD. In order to reduce the healthcare utilisation of patients with SUD, mental disorders, especially drug-induced mental disorders, should be the focus of daily management. Our study also highlighted the importance of reducing psychotropic substance misuse, especially ketamine and amphetamine, since use of these substances were associated with negative impacts on individual health and the healthcare system.

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CRediT authorship contribution statement

EWC and YW had full access to all data in the study and accept responsibility for the integrity of the data and accuracy of data analysis. YW, JXZ, ICKW and EWC developed the study design and methods. YW

conducted data analyses and JXZ cross-checked the results. YW, JXZ and JEB wrote the manuscript. EWC and ICKW provided research government support. All authors critically reviewed the manuscript for important intellectual content.

Conflict of Interest

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf; Dr Chan has received research grants from the Hong Kong Research Grant Council, Narcotics Division of the Security Bureau of the Government of the Hong Kong SAR, Research Fund Secretariat of the Food and Health Bureau, National Natural Science Fund of China, National Health and Medical Research Council in Australia, Wellcome Trust, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, and Takeda, outside the submitted work; Prof Wong has received research funding outside the submitted work from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong Research Grant Council, and the Hong Kong Health and Medical Research Fund, National Institute for Health Research in England, European Commission, National Health and Medical Research Council in Australia, and also received speaker fees from Janssen and Medice in the previous 3 years. Other co-authors declared no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2021.109119.

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