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Prevalence of co-occurring mental illness and substance use disorder, and association with overdose: a linked data cohort study among residents of British Columbia, Canada

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Abstract

Aims

To estimate the treated prevalence of mental illness, substance use disorder (SUD), and dual diagnosis, and the association between dual diagnosis and fatal and non-fatal overdose, among residents of British Columbia, Canada.

Design

A retrospective cohort study using linked health, income assistance, corrections, and death records.

Setting

British Columbia (BC), Canada

Participants

921,346 BC residents (455,549 males and 465,797 females) aged 10 and older.

Measurements

Hospital and primary care administrative data were used to identify a history of mental illness only, SUD only, dual diagnosis, or no history of SUD or mental illness (2010-2014), and overdoses resulting in medical care (2015-2017). We calculated crude incidence rates of non-fatal and fatal overdose by dual diagnosis history. Andersen-Gill and competing risks regression were used to examine the association between dual diagnosis and non-fatal and fatal overdose, respectively, adjusting for age, sex, comorbidities, incarceration history, social assistance, history of prescription opioid and benzodiazepine dispensing, and region of residence.

Findings

Of the 921,346 people in the cohort, 176,780 (19.2%), 6147 (0.7%) and 15269 (1.7%) had a history of mental illness only, SUD only, and dual diagnosis, respectively. 4,696 (0.5%) people experienced 688 fatal and 6,938 non-fatal overdoses. In multivariable analyses, mental illness only, SUD only, and dual diagnosis were associated with increased rate of non-fatal (hazard ratio (95%CI): 1.8(1.6-2.1), 9.0(7.0-11.5), 8.7(6.9-10.9), respectively) and fatal overdose (1.6(1.3-2.0), 4.3(2.8-6.5), 4.1(2.8-6.0), respectively) compared with no history.

Conclusions

In a large sample of residents of British Columbia (Canada), approximately one in five people had sought care for a substance use disorder or mental illness in the past five years. The rate of overdose was elevated in people with a mental illness alone, higher again in people with a substance use disorder

alone, and highest in people with a dual diagnosis. The adjusted hazard rates were similar for people with substance use disorder only and people with a dual diagnosis.

Introduction

In 2016, over 1 billion people (16% of the global population) were affected by a mental disorder (i.e., mental illness and/or substance use disorder (SUD)), accounting for almost 6% of disability adjusted life years lost and 19% of years lived with a disability (1). Mental disorders predominantly emerge in adolescence and early adulthood, yet many people do not receive appropriate diagnosis and treatment until long after the age of onset, if ever (2-5).

The co-occurrence of mental illness and SUD among people with a mental disorder is commonly referred to as 'dual diagnosis' (6). Dual diagnosis may compound the impact of both mental illness and SUD, and has been associated with an increased risk of suicidal ideation and attempts, interpersonal violence, hospitalisation, traumatic brain injury, poorer treatment outcomes, criminal justice system involvement, and premature death compared people with a mental illness only, SUD only, or no mental disorder (7-12).

In the United States, drug overdose is the leading cause of death due to injury (13,14). Similarly, Canada has high rates of drug overdose primarily due to fentanyl and fentanyl analogues being introduced into the illegal drug supply (15,16). The high rates of overdose in British Columbia (BC), Canada, led to the declaration of a public health emergency in April 2016. The rate of non-fatal overdose, estimated to be 20-30 times more common than fatal overdose (17), has also increased in recent years.(15) Non-fatal overdose is associated with substantial health consequences including physical injury, seizure, pulmonary conditions, cognitive impairment, and an increased risk of fatal overdose (18-20). Although North America is currently experiencing particularly high rates of overdose (21), the overdose rate is also rising across Australia, the United Kingdom, and Europe (22).

Both SUD and mental illness have been found to be independently associated with an increased risk of overdose (23-27). The risk of unintentional overdose associated with SUDs has been found to be generally greater than the risk of unintentional overdose associated with mental illness, while the reverse has been found for intentional overdose (i.e., mental illness has a greater association with intentional overdose than SUD) (28,29).

Given the compounding effect of dual diagnosis on a range of health issues, people with a dual diagnosis may be at greater risk of overdose than people with either a mental illness or a SUD alone. However, few studies have examined the association between co-occurring SUD and mental illness and overdose, and, within the existing literature, the association between dual diagnosis and overdose varies. For example, among six studies that examined the association between co-occurring mental illness and SUD and overdose among people with a SUD, four found that co-occurring mental illness increased the risk of overdose compared to SUD only (30-33), while two found no association between co-occurring mental illness and SUD and overdose compared to SUD only (34,35). Further, a study that used a cohort sampled irrespective of SUD or mental illness found that the association between mental illness and overdose was greater in people with no SUD (adjusted hazard ratios ranging from 1.47 to 2.39)than in

people with a SUD (adjusted hazard ratios from 1.24-1.53) (27). Another study found that, among people leaving prison, the risk of non-fatal overdose was greater in people with a dual diagnosis than in people with SUD or mental illness only (adjusted hazard ratios of 4.9, 2.1 and 1.0, respectively) (36). Given the limited and conflicting literature, further research on the association between dual diagnosis and overdose is necessary.

Using a large, population-based sample of residents of BC, this study aimed to: 1) estimate the treated prevalence of mental illness, SUD, and dual diagnosis in BC; 2) calculate rates of fatal and non-fatal overdose according to dual diagnosis status; 3) examine the association between dual diagnosis and fatal and non-fatal overdose; and 4) examine whether the association between dual diagnosis and overdose is modified by age.

Methods

Study population

This study used a 20% random sample of people in the BC Ministry of Health's Provincial Client Roster which is contained within the BC Provincial Overdose Cohort (37). The 20% random sample was created and linked to administrative datasets as part of the BC public health emergency response to the overdose crisis (38). Registration in the Provincial Client Roster is compulsory for residents of BC (Canadian citizens, permanent residents, people on visas longer than 6 months, and dependents of people in these categories residing in BC) and provides access to provincial health insurance. Our cohort included all people with a record in the client roster between 1 January 2015 and 31 December 2017, aged 10 years and older as of 1 January 2015, and who had their sex recorded in the roster. Information from administrative data sources, including death, coronial, drug and poison control, emergency department, and ambulance opioid surveillance records (1 January 2015 - 31 December 2017), and hospital, primary care, BC provincial corrections, social assistance (e.g., government unemployment and disability payments), and community pharmacy prescription medication dispensing records (1 January 2010 - 31 December 2017) were linked for all members of the cohort using name, date of birth, sex, and personal health number using a series of deterministic and probabilistic linkage algorithms (37). The cohort was followed from 1 January 2015 ("baseline") to the first of date of death or end of follow-up (31 December 2017). Further information on all datasets is provided in the supplementary material. The analyses were not pre-registered, and all results should be considered exploratory.

Outcome measure

Drug overdose was identified through poison control, ambulance, emergency department, hospital, and physician billing records. The source-specific case definitions are provided in Table S1 and discussed in detail elsewhere (37). Some, although not all, case definitions required the overdose to be recorded as having involved opioids. To reduce the possibility of over-counting overdose events, records that were

separated by less than 24 hours (e.g., if a person had two records on the same day, or if a hospitalisation was less than 24 hours from a previous discharge) were collapsed into a single overdose episode. Overdoses were classified as fatal if the episode included a BC Coroner record for accidental or undetermined illicit drug toxicity, or if a person's date of death was during an overdose episode. All other overdoses were classified as non-fatal. Persons could experience multiple non-fatal overdoses.

Exposure measures

Consistent with the International Classification of Disease 10th edition (ICD-10), we considered mental disorder to include both SUD and mental illness (39). A history of mental disorder was defined using ICD-9 and ICD-10 codes in five years (1 January 2010 - 31 December 2014) of retrospective hospital and primary care records (SUD: ICD-10 F10-F19; ICD-9 291-292, 303-305; mental illness: ICD-10 F00-F09, F20-F99; ICD-9 290, 293-302, 306-319, 50B). We required people to have at least one hospitalisation or two primary care visits within one year of each other with a relevant ICD code. History of mental disorder was categorised into four discrete categories: no recent history of mental disorder, mental illness only, SUD only, and dual diagnosis. For descriptive statistics, reasons for mental illness- and SUD-related healthcare visits by people with a history of mental disorder were disaggregated using ICD-10 subchapters (Table S2).

Age on 1 January 2015 was calculated using date of birth and categorised into three groups: 10-24 years, 25-39 years, and ≥40 years, chosen to be consistent with an internationally accepted definition of adolescence (40). We created comorbidity groups from 2010-2014 hospital records using Quan and colleagues' ICD-10 coding algorithm (41) for Elixhauser's 31 comorbidity categories (42). ICD-10 codes are provided in Table S3. We summed the number of comorbidity groups, excluding the four groups related to mental disorder (alcohol abuse, substance abuse, psychosis, and depression – as these overlapped with the main exposure of interest), and categorised the number of comorbidity groups present into three groups (0, 1, 2+). Using community medication dispensing records from 2010-2014, we identified people who had been dispensed opioids for pain, and people who had been dispensed benzodiazepines. Medications were identified using the drug identification/product identification number (DIN/PIN; Table S4). Linked BC corrections data provided information on the admission and discharge date for people remanded and sentenced (to less than 2 years in prison) in provincial correctional institutions from 1 January 2010 - 31 December 2017. A time-varying count of the number of incarcerations was created using the number of previous admissions to prison on any given date from 1 January 2010 - 31 December 2017. For baseline descriptive statistics, the number of incarcerations as of 31 December 2014 was used. Other covariates were sex (male/female), having received a recent social assistance payment (defined as one or more social assistance payment records in linked BC Ministry of Social Development and Poverty Reduction records, between 1 January 2014 and 31 December 2014) (yes/no), and region of residence (health authority area, defined using participants' residential postcode as of 31 December 2014). We used only one year of social assistance payments to capture recent social assistance payments (i.e., only those within a year of the start of the study period).

Data analysis

We calculated descriptive statistics for all baseline exposures, including the number of individuals who experienced a fatal or non-fatal overdose during follow-up. We calculated the crude incidence rate of fatal and non-fatal overdose, respectively, overall and for all baseline exposure categories, assuming a Poisson distribution for confidence intervals.

We constructed univariable and multivariable Andersen-Gill regression models to examine non-fatal overdose, as it accounts for the dependence of recurrent events (43), and Fine and Gray competing risks regression models to examine fatal overdose (44). Death from any other cause was considered a competing risk and we report the sub-distribution hazard ratio for fatal overdose. We used cumulative incidence functions to graphically represent the time to fatal overdose by mental disorder and age category. We tested for an interaction between age category and history of mental disorder in both the non-fatal and fatal overdose models using a Wald test for significance, deciding *a priori* that a p-value ≥ 0.05 indicated no evidence of interaction. Multivariable models included all the exposure variables described above.

Sensitivity analyses

In sensitivity analyses, we used Cox regression models instead of Fine and Grey competing risks to report cause-specific hazards, as recommended by Latouche et al (45). We also restricted the ascertainment of treated mental disorder history to one year of retrospective records (1 January 2014 - 31 December 2014), to determine whether recency of care affected results. All analyses were conducted using SAS EG 7.1.

Ethics

The 2016 BC public health emergency declaration under the *Public Health Act,* and subsequent orders issued by the Provincial Health Officer, facilitated the formation of the Provincial Overdose Cohort. This work was completed as part of the BCCDC's public health functions, therefore institutional ethics approval for this project was not required.

Results

Prevalence of dual diagnosis

Of the 1 048 647 people in the 20% random sample, 127 260 (12.1%) were excluded as they were under 10 years of age on 1 January 2015 and 41 (0.004%) were excluded as their sex was unknown, leaving 921 346 people in the study cohort. As shown in Table 1, using 5 years of medical records, 198 196 (21.5%) persons in the cohort had a history of mental disorder, with 176 780 (19.2%) having a history of a mental illness only, 6147 (0.7%) having a history of SUD only, and 15 269 (1.7%) having a history of dual diagnosis. Females were more likely to have a mental illness only while males were more likely to have a

history of SUD only or dual diagnosis (Table 1). The most common reasons for mental illness healthcare visits were mood disorders (n=110 689, 12.0%) and neurotic, stress-related and somatoform disorders (n=124 530, 13.5%) (Table S6). The most common reasons for SUD healthcare visits were multiple, other, and unspecified SUD (n=13 315, 1.5%), and alcohol use disorder (n=11 371, 1.2%).

<Table 1 here>

Dual diagnosis and the rate of fatal and non-fatal overdose

As shown in Table 2, 4696 people experienced 7626 overdoses during follow-up: 688 overdoses (9.0%) were fatal and 6,938 (91.0%) were non-fatal. Of the 4149 people who experienced a non-fatal overdose, 1152 (27.8%) experienced more than one non-fatal overdose (median (interquartile range (IQR)=1 (1-2)). Of the 688 people who experienced a fatal overdose, 141 (20.5%) had experienced at least one prior non-fatal overdose during the follow-up period. People with a dual diagnosis were overrepresented among those who overdosed; 1.7% of all study cohort members had a dual diagnosis (n=15 269) and 36.4% of people who overdosed had a dual diagnosis (n=1512).

The crude overdose mortality rate in the cohort was 0.3 (95%CI 0.2-0.3) per 1000 person-years and the crude non-fatal overdose incidence rate was 2.5 (95%CI 2.5-2.6) per 1000 person years (Table 2). Compared to those without a history of mental disorder, the rate of both fatal and non-fatal overdose was higher for people with mental illness only, higher again for people with a SUD only, and highest in those with a dual diagnosis. People who had received social assistance and people with a history of incarceration also experienced overdose rates higher than the overall crude rates. Among persons with at least one SUD, the highest overdose mortality rates were among persons with a stimulant use disorder (13.6 per 1000 person-years, 95%CI 11.9-20.8), sedative or hypnotic use disorder (15.0, 95%CI 9.4-23.8), cocaine use disorder (13.6, 95%CI 11.0-16.9), and opioid use disorder (12.8, 95%CI 10.4-15.7). Among persons with a mental illness, the highest overdose mortality rates were among those with schizophrenia and other psychotic disorders (2.7, 95%CI 2.3-3.3), personality disorders (2.3, 5%CI 1.8-3.0), and neurocognitive disorders (1.2, 95%CI 0.9-1.5) (Table S7).

<Table 2 here>

The association between dual diagnosis and fatal and non-fatal overdose

All regression analyses showed that people with a mental illness only, SUD only, and dual diagnosis had an increased risk of overdose compared to people with no diagnosed mental disorder (Table 3). In unadjusted analyses, people with a dual diagnosis had a higher risk of overdose than people with SUD only. However, in adjusted models, people with SUD only and dual diagnosis had approximately the same increase in risk of overdose compared to people with no mental disorder. Hazard ratios for all variables included in the adjusted models are provided in Table S8. People who had received social

assistance and people with a history of incarceration also had an increased risk of both fatal and non-fatal overdose. Figure 1 presents the cumulative incidence functions of fatal overdose, over time, by mental disorder and age category.

<Table 3 here>

< Figure 1 here>

Modification by age

The test of interaction between age and dual diagnosis was significant in unadjusted ($p<0.0001$) and adjusted ($p<0.0001$) non-fatal overdose models. However, there was no evidence of interaction in unadjusted and adjusted fatal overdose models ($p=0.69$ and $p=0.55$, respectively). The interaction between mental disorder categories and age with respect to non-fatal overdose is shown in Figure 2. While the pattern of association remained similar in each age group (i.e., mental illness increasing risk of non-fatal overdose slightly and both SUD only and dual diagnosis associated with a similar, higher risk of non-fatal overdose), people aged 10-24 years with a SUD or dual diagnosis had a higher risk of non-fatal overdose than people in the older age groups. Results from fatal and non-fatal overdose models examining the association between mental disorder and overdose within each age group are provided in Table S9.

<Figure 2 here>

Sensitivity analyses

When limited to one year of medical records, 9.3% (n=85 359) of the cohort had a history of treated mental disorder; 8.3% (n=76 264) had a mental illness only, 0.5% (n=4205) had a SUD only, and 0.5% (n=4890) had a dual diagnosis (Table S10). The association between mental disorder and overdose was slightly attenuated when using one year compared to five years of records, but the same pattern existed as in the primary analysis (Table S11). Cause-specific hazard ratios from a Cox regression model of fatal overdose were similar to those from the primary analyses (Table S11).

Discussion

To our knowledge, this is the first longitudinal study that has examined the prevalence of dual diagnosis and its association with overdose in a representative population sample. Over one in five people in the cohort had sought care for a mental disorder in the past five years, and almost one in ten had sought care in the past year. Compared to people with no mental disorder, the rate of overdose was elevated in

people with a mental illness alone, higher again in people with a SUD alone, and highest in people with a dual diagnosis. After adjusting for covariates, people with a mental illness only had over 1.5 times the hazard rate of fatal and non-fatal overdose, and people with a SUD only or dual diagnosis had over four times the hazard rate of fatal overdose and nine times the hazard rate of non-fatal overdose, compared to people with no history of mental disorder.

Our results show that the effects of mental illness and SUD on overdose are inter-related and indicate a need for a client-centred and seamless service approach that concurrently addresses mental illness and SUD (46). Fatal and non-fatal overdoses were concentrated in people with a SUD and the incidence rate was highest among persons with a dual diagnosis. In Canada and the United States, mental illness and SUD treatment services are often siloed, resulting in clients receiving care for only one health problem or receiving parallel treatments with inadequate continuity or coordination (47,48). While there can be difficulties in implementing integrated treatment (49), and the quality of research on integrated care has limited firm conclusions on its benefits (50,51), previous research has shown that integrated mental illness and SUD treatment can improve health outcomes and reduce substance use (52,53). Within the past five years, there has been a substantial effort in BC to expand overdose prevention services and supports for persons who use substances, including the creation of supervised consumption sites (54), increasing the availability of take-home naloxone (55), medications for opioid use disorder (56), and updated guidance for opioid and benzodiazepine prescribing (57). Additional interventions that are designed with and for people with co-occurring mental illness is an important next step to reduce the burden of fatal and non-fatal overdose at the population level (27,58).

The causal pathway connecting mental illness to overdose is unclear. Research suggests that mental illness may increase exposure to other factors known to increase risk of overdose, such as use of benzodiazepines, antipsychotics, and antidepressants (59-63), and may reduce resilience to social and environment stressors (27,29). Regardless of the precise mechanism, the association between mental illness and overdose suggests that mental health service provision could be an important opportunity to assess and monitor risk of overdose, and provide prevention and mitigation strategies, such as distributing take-home naloxone, providing medications for opioid use disorder, and referral to overdose prevention and supervised consumption sites.

We found that the risk of overdose was higher in people with a dual diagnosis than in people with SUD only. However, this difference was attenuated in multivariable models, suggesting that dual diagnosis can be viewed as a proxy marker for psychosocial complexity and vulnerability. These models showed a high risk of overdose in people who had received social assistance, and in people with a history of incarceration, both proxy measures for socioeconomic disadvantage and marginalisation (64-66). Similarly, previous studies have found markers for socioeconomic disadvantage, such as homelessness and incarceration, to be associated with an increased risk of overdose (67-69). These findings suggest that an integrated response from multiple areas outside the health sector, including housing, employment, and the justice system, are key to addressing overdose risk (58). Given the strong

association between social assistance and overdose found in our study, further research on the potential time-dependent effects and/or mediating role of social assistance payments on overdose is required (70). Multi-sectoral data linkage may be an important tool for examining the impact of social service provision on overdose prevention.

Consistent with previous research, we found that the association between age and overdose differed for fatal and non-fatal overdose, with older age being a risk factor for fatal overdose (25,71) and younger age being associated with an increased risk of non-fatal overdose (72). Experiencing a non-fatal overdose increases the risk of future overdose (20,73). Therefore, a high rate of fatal overdose in older age groups may represent a failure to engage and retain young people in overdose prevention services and medications for opioid use disorder. These findings emphasise the importance of providing overdose prevention programs for young people, and targeted age-appropriate responses for young people who use substances.

Strengths and limitations

This study used a large, population sample and multiple linked data sources, increasing the ascertainment of overdose and mental health conditions beyond those captured by a single source. However, this study is subject to the same limitations as all studies using linked administrative data. As noted above, it is likely that we under-ascertained mental disorder, due to a lack of records from community mental health and addictions services that are not funded through provincial insurance, inaccurate coding of visits for mental disorders within available records, and the large number of people who may not seek treatment for mental illnesses or SUD. Nevertheless, our findings are largely consistent with previous research and demonstrate the high burden of mental disorders in the general population (74-76).

Similarly, as up to 50% of non-fatal overdoses are not attended by health services (77-79), by relying on health records, we likely substantially underestimated the number of overdoses. There were also limitations to the definition of overdose used in this study, which may have excluded overdoses that did not involve illicit substances or drugs other than opioids.

As with most data linkage studies, the variables we could include were limited to those present in the linked administrative datasets and we cannot exclude the possibility of unmeasured confounders. For example, we did not have information on the occurrence of non-fatal overdoses prior to 2015. Given the association between a history of non-fatal overdose and future fatal overdose (80), this may be an important unmeasured confounder. Other possible confounders include drug use characteristics, such as injecting drug use. Because we ascertained medication exposure and mental disorder diagnosis during the same time period, there is also the possibility of confounding by indication and/or that the use of benzodiazepines and opioids may act as a mediator rather than a confounder. Further research is necessary to ascertain the impact of medication use on overdose risk and whether this differs among people with a mental illness, SUD or dual diagnosis.

Further, the study sample was created using a client roster of BC health insurance and may not be entirely representative of the population of BC, as it excludes people in BC on short-stay visas or there without a valid visa. However, registration in public health insurance is incentivised as it allows access to free healthcare and as a result coverage of those eligible is likely high, although no formal tests for representativeness have been performed.

Conclusions

Given the high rate of overdose among people with a SUD and dual diagnosis, integrated treatment is needed to appropriately address and manage these health conditions and reduce the risk of overdose. These findings suggest that mental health care providers can have a critical role in assessing and reducing the risk of overdose among their patients. Overdose prevention and response needs to be broadened from a focus solely on opioids or those seeking treatment for opioid use disorder, to include people experiencing problems with other illicit or licit substances and who many also be experiencing a co-occurring mental illness.

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TABLES

Table 1: Baseline characteristics by mental disorder status

	No mental disorder n(%)	MI only n(%)	SUD only n(%)	Dual diagnosis n(%)	Total n(%)
Total N(%)	723 150 (78.5)	176 780 (19.2)	6147 (0.7)	15 269 (1.7)	921 346 (100)
Age in years					
10-24	160 503 (22.2)	24 000 (13.6)	495 (8.1)	1562 (10.2)	186 560 (20.3)
25-39	171 159 (23.7)	37 052 (21.0)	1645 (26.8)	4625 (30.3)	214 481 (23.3)
≥ 40	391 488 (54.1)	114 728 (65.5)	4007 (65.2)	9082 (59.5)	520 305 (56.5)
Sex					
Male	375 782 (52.0)	66 273 (37.5)	4549 (74.0)	8945 (58.6)	455 549 (49.4)
Female	347 368 (48.0)	110 507 (62.5)	1598 (26.0)	6342 (41.4)	465 797 (50.6)
Received social assistance					
No	722 300 (99.9)	175 885 (99.5)	5708 (92.9)	13 187 (86.4)	917 080 (99.5)
Yes	850 (0.1)	895 (0.5)	439 (7.1)	2082 (13.6)	4266 (0.5)
Number of Elixhauser comorbidity groups*					
0	671 644 (92.9)	147 546 (83.5)	4604 (74.9)	10 873 (71.2)	834 667 (90.6)
1	30 776 (4.3)	15285 (8.7)	755 (12.3)	2026 (13.3)	48 842 (5.3)
≥ 2	20 730 (2.9)	13 949 (7.9)	788 (12.8)	2370 (15.5)	37 837 (4.1)
History of incarceration					
No	720 276 (99.6)	175 709 (99.4)	5523 (89.9)	13 504 (88.4)	915 012 (99.3)
1-2 incarcerations	2137 (0.3)	758 (0.4)	343 (5.6)	961 (6.3)	4199 (0.5)
3 or more incarcerations	737 (0.1)	313 (0.2)	281 (4.6)	804 (5.3)	2135 (0.2)
Dispensed opioids					
No	52 1396 (72.1)	88 794 (50.2)	2314 (37.6)	4549 (29.8)	617 053 (67.0)
Yes	201 754 (27.9)	87 986 (49.8)	3833 (62.4)	10 720 (70.2)	304 293 (33.0)
Dispensed benzodiazepines					
No	673 019 (93.1)	107 591 (60.9)	4371 (71.1)	5922 (38.8)	790 903 (85.8)
Yes	50 131 (6.9)	69 189 (39.1)	1776 (28.9)	9347 (61.2)	130 443 (14.2)
Location of residence					
Interior	101 730 (14.1)	30 525 (17.3)	1136 (18.5)	2672 (17.5)	13 6063 (14.8)
Fraser	233 845 (32.3)	62 075 (35.1)	1771 (28.8)	4699 (30.8)	30 2390 (32.8)
Vancouver Coastal	176 627 (24.4)	40 650 (23.0)	1212 (19.7)	3692 (24.2)	22 2181 (24.1)
Vancouver Island	103 124 (14.3)	32 488 (18.4)	1227 (20.0)	2857 (18.7)	139 656 (15.2)
Northern	41 682 (5.8)	10 117 (5.7)	637 (10.4)	1077 (7.1)	53 513 (5.8)
Unknown	66 142 (9.2)	965 (0.6)	164 (2.7)	272 (1.8)	67 543 (7.3)

MI: Mental illness, SUD: substance use disorder

*Excluding mental illness and substance use categories

Table 2: Crude incidence rate of non-fatal and fatal overdose, according to baseline characteristics

	Person-years (1000s)	Any overdose	Non-fatal overdose			Fatal overdose	
		N	>=1 non-fatal overdose n	Overdose episodes	Incidence rate* (95%CI)	n	Mortality rate* (95%CI)
Total	2729.4	4696	4149	6938	2.5 (2.5-2.6)	688	0.3 (0.2-0.3)
Mental disorder							
No history	2151.3	1686	1467	2191	1.0 (1.0-1.1)	245	0.1 (0.1-0.1)
MI only	516.4	901	791	1032	2.0 (1.9-2.1)	131	0.3 (0.2-0.3)
SUD only	17.9	429	379	777	43.5 (40.6-46.7)	61	3.4 (2.7-4.4)
Dual diagnosis	43.9	1680	1512	2938	66.9 (64.6-69.4)	251	5.7 (5.1-6.5)
Age							
10-24 years	559.0	1048	988	1621	2.9 (2.8-3.0)	84	0.2 (0.1-0.2)
Aged 25-39	642.1	1802	1619	2962	4.6 (4.4-4.8)	237	0.4 (0.3-0.4)
Aged 40 and over	1528.3	1846	1542	1528	1.5 (1.5-1.6)	367	0.2 (0.2-0.3)
Sex							
Male	1348.7	3228	2798	4853	3.6 (3.5-3.7)	535	0.4 (0.4-0.4)
Female	1380.8	1468	1351	2085	1.5 (1.4-1.6)	153	0.1 (0.1-0.1)
Received social assistance**							
No	2717.2	2776	2456	3644	1.3 (1.3-1.4)	383	0.1 (0.1-0.2)
Yes	12.2	1920	1693	3294	268.8 (259.8-278.2)	305	24.9 (22.2-27.8)
Number of Elixhauser comorbidity groups***							
0	2488.7	3942	3499	5890	2.4 (2.3-2.4)	559	0.2 (0.2-0.2)
1	140.8	398	351	628	4.5 (4.1-4.8)	56	0.4 (0.3-0.5)
≥ 2	99.9	356	299	420	4.2 (3.8-4.6)	73	0.7 (0.6-0.9)
History of incarceration							
No history	2710.9	3720	3280	5054	1.9 (1.8-1.9)	538	0.2 (0.2-0.2)

1-2 incarcerations	12.4	459	402	765	61.9 (57.7-66.5)	76	6.2 (4.9-7.7)
3 or more	6.2	517	467	1119	180.2 (169.9-191.1)	74	11.9 (9.5-14.7)
Dispensed opioids							
No	1835.7	1769	1586	2488	1.4 (1.3-1.4)	233	0.1 (0.1-0.1)
Yes	893.7	2927	2563	4450	5.0 (4.8-5.1)	465	0.5 (0.5-0.6)
Dispensed benzodiazepines							
No	2349.5	2781	2468	4068	1.7 (1.7-1.8)	373	0.2 (0.1-0.2)
Yes	379.9	1915	1681	2870	7.6 (7.3-7.8)	315	0.8 (0.7-0.9)
Location of residence							
Interior	401.0	675	571	834	2.1 (1.9-2.2)	125	0.3 (0.3-0.4)
Fraser	896.4	1620	1424	2537	2.8 (2.7-2.9)	244	0.3 (0.3-0.4)
Vancouver Coastal	659.4	1134	1009	1699	2.6 (2.5-2.7)	167	0.3 (0.2-0.3)
Vancouver Island	158.5	721	642	1058	2.6 (2.4-2.7)	100	0.2 (0.2-0.3)
Northern	202.3	349	320	514	3.2 (3.0-3.5)	36	0.2 (0.2-0.3)
Unknown	202.3	197	183	296	1.5 (1.3-1.6)	16	0.1 (0.0-0.1)

*Per 1000 person-years, **During 2014, ***Excluding mental illness and substance use categories

SUD: substance use disorder; MI: mental illness

Table 3: Associations between history of mental disorder and overdose

	Non-fatal overdose*		Fatal overdose**	
	Unadjusted HR (95%CI)	**Adjusted HR (95%CI)**	**Unadjusted HR (95%CI)**	**Adjusted HR (95%CI)**
Mental disorder				
No mental disorder	1 (ref)	1 (ref)	1 (ref)	1 (ref)
MI only	2.0 (1.8-2.2)	1.8 (1.6-2.1)	2.2 (1.8-2.7)	1.6 (1.3-2.0)
SUD only	43.0 (36.4-50.7)	9.0 (7.0-11.5)	29.4 (22.2-38.9)	4.3 (2.8-6.5)
Dual diagnosis	66.2 (59.7-73.3)	8.7 (6.9-10.9)	48.9 (41.0-58.4)	4.1 (2.8-6.0)

*Non-fatal overdose regression model: Andersen-Gill model including all recurrent non-fatal overdose events, **Fatal overdose regression model: Fine and Gray competing risks model, competing risk of death from any other cause, reporting the sub-distribution hazard ratio for fatal overdose. Adjusted models included: history of mental disorder, age category, sex, history of social assistance, number of Elixhauser comorbidity groups, history of incarceration, dispensed opioids for pain, dispensed benzodiazepines, and location of residence. The full results for all covariates can be found in Supplementary Table S8. MI: mental illness; SUD: substance use disorder

FIGURES

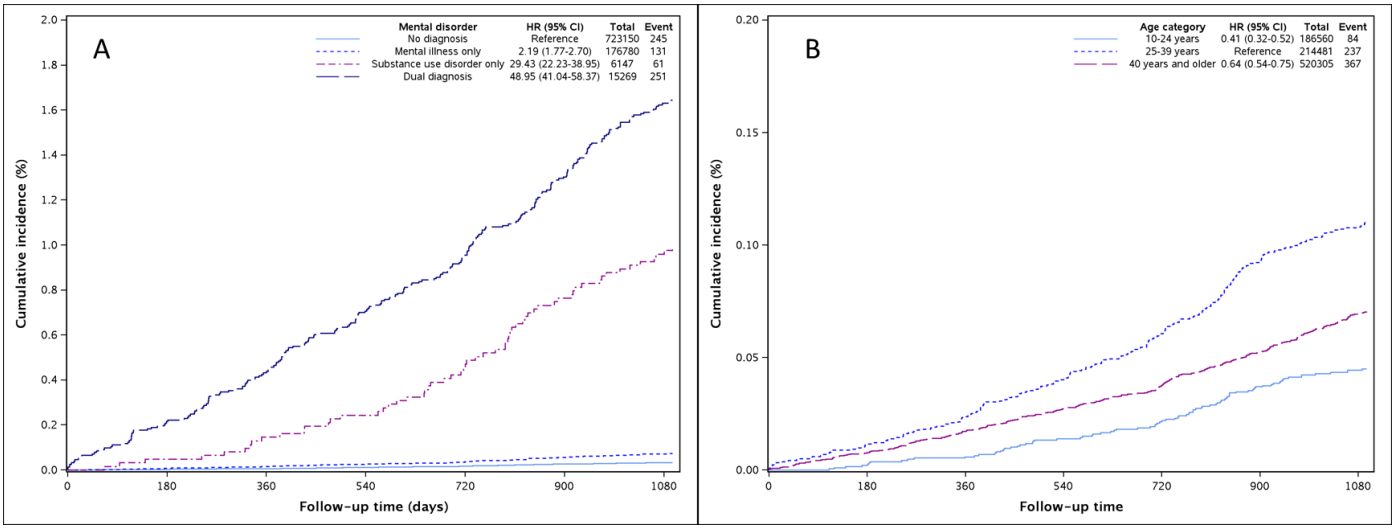

Figure 1: Unadjusted cumulative incidence functions of time to fatal overdose by (A) mental disorder category and (B) age

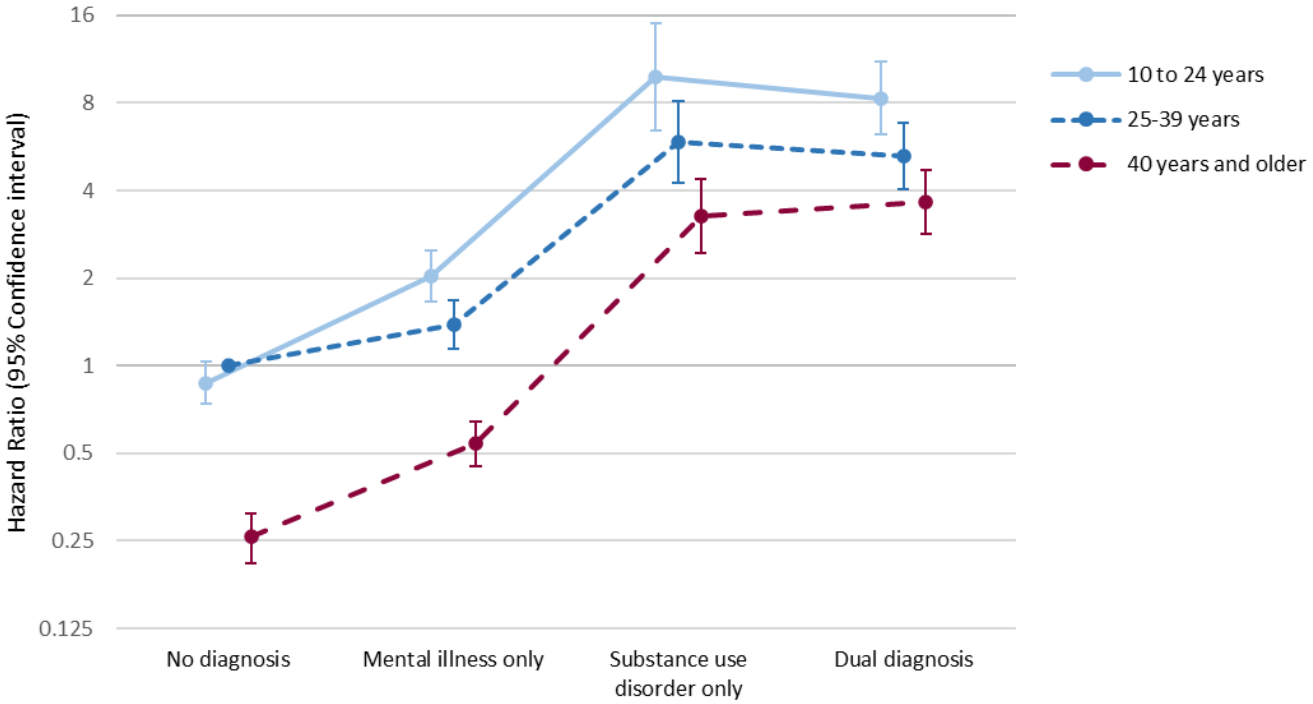

Figure 2: The association between mental disorder and age category, and non-fatal overdose

Reference group: No diagnosis, aged 25-39

Adjusted for: sex, receiving social assistance, number of comorbidities, history of incarceration, dispensed opioids for pain, dispensed benzodiazepines, and location of residence