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Day-to-day impact of COVID-19 and other factors associated with risk of nonfatal overdose among people who use unregulated drugs in five cities in the United States and Canada ☆

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ABSTRACT

Background: The COVID-19 pandemic has compounded the longstanding drug poisoning crisis in Canada and the United States (US). Research is needed to understand the contributions of COVID-19 and subsequent infection control measures. We sought to estimate the prevalence of and factors associated with nonfatal overdose among participants in nine prospective cohorts of people who use unregulated drugs (PWUD) in Canada and the US.

Methods: Data were derived from nine cohorts of PWUD in urban centres in Canada (Vancouver, BC) and the US (Baltimore, MD; Miami, FL; Chicago, IL; Los Angeles, CA) between May, 2020 and April, 2021. Multivariable logistic regression was used to identify factors associated with nonfatal overdose among participants who used unregulated drugs in the past month.

Results: Among 885 participants (including 253 females), 41 (4.6 %) experienced a non-fatal overdose in the past month, and 453 (51.2 %) reported being highly impacted day-to-day by the pandemic. In multivariable analyses, people who experienced a non-fatal overdose were more likely to be female (Adjusted Odds Ratio [AOR]= 2.18; 95 % Confidence Interval [CI]=1.10–4.30); unstably housed/homeless (AOR=2.16; 95 % CI=1.11–4.26); engaged in medications for opioid use disorder (AOR=2.45; 95 % CI=1.19–4.97); and highly impacted day-to-day (AOR=2.42; 95 % CI=1.22–5.10).

Conclusion: Our findings may reflect characteristics of participants who experienced a compounding of vulnerabilities during the pandemic and thus are vulnerable to overdose, including women, those unstably housed/ homeless, and those who perceived their daily lives were highly impacted by the pandemic. Multi-level interventions are needed to remediate the vulnerabilities and address the main driver of poisoning crisis.

1. Introduction

People who use unregulated drugs (PWUD) in Canada and the United States (US) are contending with the intersection of two simultaneous health crises: the COVID-19 pandemic and the longstanding drug poisoning crisis (Becker and Fiellin, 2020; Friedman et al., 2021; Friedman and Akre, 2021; Holland et al., 2021; Slavova et al., 2020). Since the onset of the pandemic, settings across Canada and the US have documented surges in overdose-related fatalities (BC Coroners Service, 2021; Friedman et al., 2021; Friedman and Akre, 2021; Glober et al., 2020; Holland et al., 2021; Slavova et al., 2020; Toronto Public Health, 2020), and mounting evidence suggests that the effects of COVID-19 and consequent infection control measures may have aggravated the already high risk of overdose among PWUD (Ali et al., 2021; Appa et al., 2021; Friedman and Akre, 2021; King et al., 2021; Linas et al., 2021). However, the possible contributions of COVID-related factors to these increases in overdoses are not well understood. The impacts of social/structural-level infection control measures (e.g., border/business closures, physical/social distancing, and stay-at-home measures)(Government of Canada, 2021; Lasry et al., 2020) on the risk of overdose among PWUD are numerous (Canadian Centre on Substance Use and Addiction, 2020; Chang et al., 2020; Nguyen and Buxton, 2021; Niles et al., 2020; The Ontario Drug Policy Research Network & The Office of the Chief Coroner for Ontario/Ontario Forensic Pathology Service, Public Health Ontario, 2020; World Drug Report, 2020). For instance, border closures and other restrictions on movement may have led to disruptions and shortages in the unregulated drug supply and consequently elevated levels of highly-potent synthetic opioids (Ali et al., 2021; Canadian Centre on Substance Use and Addiction, 2020; The Ontario Drug Policy Research Network & The Office of the Chief Coroner for Ontario/Ontario Forensic Pathology Service, Public Health Ontario, 2020; World Drug Report, 2020), which exposes PWUD to elevated risks of overdose. In addition, physical/social distancing, and stay-at-home measures (including reductions in service hours and closing of non-essential services) may have encouraged people to use drugs alone and undermined well-established overdose prevention measures (e.g., access to harm reduction services, engagement in medication treatment for opioid use disorder) (Ali et al., 2021; Linas et al., 2021; Nguyen and Buxton, 2021; Russell et al., 2021).

Investigating the impact of COVID-19 and the potential unintended consequences of infection control measures among populations contending with the dual public health crisis is needed to generate strategies to mitigate preventable overdoses. Research is specifically needed to examine associations between COVID-19-related factors and overdose and identify potential characteristics associated with those who are most likely to experience an overdose to inform prevention efforts.

Research prior to the COVID-19 pandemic identified a range of risk factors for having a fatal or nonfatal overdose, including demographic characteristics (e.g., male sex, young age), behavioural factors (e.g., previous overdose, polydrug use, injecting alone, and binge drug use), and social and structural conditions (e.g., housing instability, time spent incarcerated, recent release from prison) (Binswanger et al., 2011; Brady et al., 2017; Brugal et al., 2002; Caudarella et al., 2016; Darke and Hall, 2003; Kline et al., 2021; Rowe et al., 2015).

Our study objectives were to assess the prevalence of non-fatal overdose and identify factors associated with overdose among participants in nine prospective cohorts of PWUD in Canada (Vancouver, BC) and the US (Baltimore, MD; Miami, FL; Chicago, IL; Los Angeles, CA) during the COVID-19 pandemic. We further sought to examine the prevalence and identify factors associated with those who reported being highly impacted day-to-day by COVID-19. To guide these exploratory analyses, we drew on Rhodes' Risk Environment framework which conceptualizes drug-related harm as a product of individuals interacting with micro- and macro-environmental levels (Rhodes, 2009). For example, the reductions in service hours for MOUD treatment to mitigate COVID-19 transmission (macro-policy environment)

increases difficulty among PWUD in managing substance use behaviors (individual-level behavior), such as withdrawal and tolerance, which may increase exposure to contaminated and unregulated drug supplies leading to an increased risk of overdose.

2. Methods

2.1. Study sample

Established by the United States' National Institute on Drug Abuse in 2017, the Collaborating Consortium of Cohorts Producing NIDA Opportunities (C3PNO) aims to enhance data sharing opportunities and mechanisms to facilitate collaborative research efforts among NIDA-supported cohorts that examine HIV/AIDS in the context of substance use. Details of the participating cohorts and associated methodologies have been previously described (Gorbach et al., 2021). In brief, the consortium is comprised of nine NIDA-funded cohorts located in major cities in Canada (Vancouver, BC) and the US (Baltimore, MD; Miami, FL; Chicago, IL; and Los Angeles, CA) with a combined sample size of up to 12,000 active participants.

The cohorts are: the Vancouver Injection Drug Users Study (VIDUS; Vancouver, BC; HIV-negative people who inject drugs [PWID]); the AIDS Care Cohort to Evaluate exposure to Survival Services (ACCESS; Vancouver, BC; HIV-positive PWUD); the At-Risk Youth Study (ARYS; Vancouver, BC; at-risk young PWUD); the AIDS Linked to the IntraVenous Experience (ALIVE; Baltimore, MD; people who inject drugs [PWID]); the Healthy Young Men's Study (HYM; Los Angeles, CA; young men who have sex with men [MSM]); the Johns Hopkins HIV Clinical Cohort (JHHCC; Baltimore, MD; people living with HIV); the Miami Adult Studies on HIV (MASH; Miami, FL; cocaine use, HIV, and hepatitis C virus); mSTUDY (Los Angeles, CA; African American or Hispanic MSM); and the Multilevel Influences on HIV and Substance Use in young MSM Cohort (RADAR; Chicago, IL; young MSM), and the Hopkins Heart Study (HEART; Baltimore, MD; African American individuals to study the effects of HIV, cocaine, and prolonged antiretroviral therapy use on subclinical cardiovascular disease).

Between May, 2020 and April, 2021, a subset of participants in each cohort was recruited to respond to a survey about their experiences during the COVID-19 pandemic and two waves of surveys were administered at varying times by each cohort. For this study, we conducted a cross-sectional examination and included only those survey respondents who had reported unregulated drug use in the past month, including use of unregulated heroin, fentanyl, prescription opioids (non-medical use), methamphetamine, powder cocaine, or crack cocaine. If participants responded to more than one wave of the survey, we used their first survey.

2.2. Study measures

The primary outcome of interest was a binary measure (yes vs. no) of self-reported nonfatal overdose in the past month.

The explanatory variables of interest included: age (per year older); sex (female vs. male); ethnicity/ancestry (white vs. non-white); and study setting (Vancouver, Baltimore, Chicago, Los Angeles, Miami). Social/structural variables include engagement in medication for opioid use disorder (MOUD) (yes vs. no); type of residence (unstably housed or homeless vs. house/apartment); and number of sexual partners (continuous), which was included as a potential proxy measurement for people engaged in sex work. Drug use-related variables included: alcohol ($\geq$daily vs. $<$daily); injection or non-injection unregulated opioid use ($\geq$daily vs. $<$daily), defined as any use of unregulated heroin, unregulated fentanyl or unregulated/diverted prescription opioids (including misuse of prescribed opioids); injection or non-injection stimulant use ($\geq$daily vs. $<$daily), defined as methamphetamine, powder cocaine, or crack cocaine use; and injection drug use (yes vs. no). Individuals who reported not using a certain drug were included in

<daily drug categories. We also included a range of COVID-19-related factors, including: received COVID-19 testing (yes vs. no); tested positive for COVID-19 (yes vs. no); 'COVID-19 worry' (continuous), derived from asking participants to rate on a scale ranging from 1 (not at all worried) to 10 (very much worried) how worried they are about the COVID-19 pandemic; 'COVID-19 day-to-day impact' ('highly impacted' vs. 'moderate to no impact'), derived from asking participants to rate on a scale (not at all, a little, much, very much, extremely) how much/did the COVID-19 pandemic impact their day-to-day life, which we dichotomized as 'highly impacted' (very much/extremely) and 'moderate to no impact' (much/a little/not at all); avoided needle distribution sites (yes vs. no) due to the pandemic; avoided picking up medications (yes vs. no) for opioid use disorder due of the pandemic; and stocked up on drugs (yes vs. no) due to the pandemic.

All variables except for age, sex, and ethnicity/ancestry referred to the past month period prior to each study interview, unless otherwise specified.

2.3. Statistical analysis

As a first step, we examined the prevalence of each explanatory variable at baseline stratified by non-fatal overdose, testing for difference using Pearson's χ^2 test and Fisher's test for counts < 5 (for categorical variables) or the Mann-Whitney test (for continuous variables) as appropriate. We examined variance inflation factors (VIF) to detect multi-collinearity across explanatory variables and found no large VIF values. We then used bivariable logistic regression analyses to estimate the crude relationship between explanatory variables of interest and nonfatal overdose. A multivariable model was then constructed using an a priori-defined backward model selection procedure based on examination of Akaike Information Criterion (AIC) and p-values (Burnham and Anderson, 2002) All explanatory variables were included in the full multivariable model and after examining the AIC of the full model, we removed the variable with the largest p-value and built a reduced model. We continued this iterative process until no variables remained for exclusion. We selected the multivariable model with the lowest AIC score for each outcome.

After finding a strong link between being highly impacted day-to-day by the COVID-19 pandemic and non-fatal overdose, we sought to examine factors associated with being highly impacted by the pandemic. In the secondary analysis, the primary outcome of interest was COVID-19 day-to-day impact (highly impacted vs. moderate/no impact.) We first examined the sample stratified by those who were highly impacted day-to-day and tested for differences using Pearson's $\chi 2$ test and Fisher's test for counts < 5 (for categorical variables) or the Mann-Whitney test (for continuous variables) as appropriate. We then constructed a second multivariable model using the same backward model selection procedure and the explanatory variables described above, except nonfatal overdose was also included as an explanatory variable.

As a sensitivity analysis, we expanded the drug use categories from daily ($\geq$daily vs. <daily) to weekly use ($\geq$weekly vs. <weekly) and re-ran the multivariable analyses.

All p-values were two-sided, and all statistical analyses were conducted using R, version 3.6.0.33 (R Foundation for Statistical Computing, Vienna, Austria). In the multivariable analyses, p-values were adjusted for multiple comparisons using the procedure proposed by Benjamini-Hochberg (Benjamini & Hochberg, 1995).

3. Results

Between May, 2020 and April, 2021, 885 participants had used unregulated opioids or stimulants in the past month and were included in the analytic sample. The median age of the sample was 40 (Interquartile Range [IQR]: 29 – 54) years, 253 (28.6 %) reported being female, 304 (34.2 %) reported being white and 428 (48.2 %) participants resided in Vancouver, BC; 211 (24.4 %) in Los Angeles, CA; 132 (14.9 %) in

Baltimore, MD; 70 (7.9 %) in Miami, FL; and 44 (5.2 %) in Chicago, IL. Overall, 41 (4.6 %) participants reported experiencing a non-fatal overdose in the past month.

Among COVID-related factors, 551 (62.1 %) participants had been tested for COVID-19, with 18 (2.0 %) tested positive for COVID-19. Most participants reported being worried (median: 6.0 out of 10.0; IQR: 3–9) and about half reported being highly impacted day-to-day by the pandemic (453, 51.2 %). In addition, due to the pandemic, 77 (8.7 %) individuals reported avoiding needle distribution sites, 33 (3.7 %) reported avoiding picking up MOUD, and 164 (18.5 %) had reported stocking up on drugs.

The results of the main multivariable model are shown in Tables 1–3. Individuals who had experienced nonfatal overdose were more likely to report: female sex (Adjusted Odds Ratio [AOR] = 2.18; 95 % Confidence Interval [CI]:1.10–4.30), being unstably housed or homeless (AOR = 2.16; 95 % CI: 1.11–4.30), engaged in MOUD (AOR = 2.45; 95 % CI: 1.19–4.97) and highly impacted day-to-day by COVID-19 (AOR = 2.42; 95 % CI: 1.22–5.10) (all p < 0.05). Number of sexual partners was almost significantly associated with nonfatal overdose (AOR = 1.06; 95 % CI: 0.99–1.12; $p = 0.084$).

The results of the second multivariable analysis are shown in Table 4. Individuals who reported being highly impacted day-to-day by the pandemic were more likely to report: younger age (AOR = 0.98; 95 % CI: 0.97–0.99), white (AOR = 1.55; 95 % CI: 1.10–2.18), nonfatal overdose (AOR = 2.60; 95 % CI: 1.25–5.71), being tested for COVID-19 (AOR = 1.52; 95 % CI: 1.08–2.14), higher levels of COVID-19 worry (AOR = 1.30; 95 % CI: 1.23–1.37), and stocking up on drugs (AOR = 1.59; 95 % CI: 1.09–2.32). Individuals who reported being engaged in MOUD were less likely to report being highly impacted by the pandemic (AOR = 0.64; 95 % CI: 0.44–0.92).

In the sensitivity analysis, the multivariable results were essentially the same when the drug use cut-off points were changed from use ($\geq$daily vs. <daily) to weekly use ($\geq$weekly vs. <weekly).

4. Discussion

Among nine cohorts of PWUD, most of the sample reported being worried and about half reported being highly impacted day-to-day by the COVID-19 pandemic, including some participants who reported avoiding harm reduction measures (i.e., needle distribution sites and picking up MOUD). Overall, we found that about five percent of the sample had experienced a nonfatal overdose in the past month. The factors found to be significantly associated with nonfatal overdose in our study could reflect characteristics of PWUD who may be experiencing a compounding of vulnerabilities as a result of COVID-19 and thus vulnerable to overdose, including women, unstably housed or homeless people, those engaged in MOUD and highly impacted day-to-day by the pandemic. Given that prior overdose experience is a significant predictor of future overdoses (Caudarella et al., 2016), our findings among people who experienced a non-fatal overdose within the context of the dual crises are important to consider for prevention programs that aim to adapt and shift response options to the dual crises.

The association between female sex and non-fatal overdose is consistent with increases in overdoses among women within the past decade (VanHouten et al., 2019), and could be a result of the increases in gender-based violence among women during the pandemic (Rieger et al., 2021; Roesch et al., 2020; UN Women, 2020). Ethnographic research has documented the ways gender-based violence increases risk of overdose (Boyd et al., 2018). Stay-at-home measures and the shuttering of non-essential services threaten many important social and community services and support for marginalized women, which increases vulnerability to domestic violence at home by restricting movement and reducing abilities to call for help (UN Women, 2020). Public health responses to COVID-19 must account for the impact of infection control measures on service disruption for marginalized women and ensure that services remain essential and accessible (UN

Table 1

Sample characteristics of 885 participants in nine cohorts of people who use unregulated drugs in Canada (Vancouver, BC) and the United States (Baltimore, MD; Chicago, IL; Miami, FL; Los Angeles, CA), May, 2020 to April, 2021.

Characteristics	Total n = 885 (%)	Nonfatal Overdose		P Value*
		Yes n = 41 (5 %)	No n = 847 (95 %)	
Age (Median [IQR])	40 (29–54)	40 (31–54)	40 (29–53)	0.565
White (vs non-white)	304 (34.2)	15 (36.6)	289 (34.1)	0.876
Male (vs female)	635 (71.5)	23 (56.1)	612 (72.3)	0.039
House/apartment (vs unstably housed/homeless)[a]	575 (64.8)	19 (46.3)	556 (65.6)	0.018
Number of sexual partners (mean/sd)[a]	1.36 (3.3)	2.24 (5.6)	1.32 (3.1)	0.001
Study setting:				
Vancouver, BC	428 (48.4)	26 (63.4)	402 (47.6)	0.242
Baltimore, MD	132 (14.9)	6 (14.6)	126 (14.9)	
Chicago, IL	44 (5.0)	0 (0.0)	44 (5.2)	
Los Angeles, CA	211 (23.8)	7 (17.1)	204 (24.2)	
Miami, FL	70 (7.9)	2 (4.9)	68 (8.1)	
In MOUD[a]	218 (24.6)	17 (41.5)	201 (23.7)	0.017
Daily drug use[a]:				
Alcohol	78 (8.8)	4 (9.8)	74 (8.7)	0.777
Opioids[b,c]	168 (18.9)	10 (24.4)	158 (18.7)	0.484
Stimulants[b, d]	192 (21.7)	12 (29.3)	180 (21.3)	0.312
Injection drug use	297 (33.5)	20 (48.8)	277 (32.7)	0.050
COVID-19 related factor[a]:				
Tested for COVID-19	551 (62.1)	28 (68.3)	523 (61.8)	0.497
Tested positive for COVID-19	18 (2.0)	1 (2.4)	17 (2.0)	0.577
COVID-19 worry (median; IQR)[e]	6 (3–8)	7 (3–9)	6 (3–8)	0.487
Highly impacted day-to-day[f]	453 (51.2)	29 (70.7)	424 (50.2)	0.010
Avoided needle distribution sites	77 (8.7)	7 (17.1)	70 (8.4)	0.094
Avoided picking up MOUD	33 (3.7)	1 (2.4)	32 (3.8)	1.000
Stocked up on drugs	164 (18.5)	8 (19.5)	156 (18.5)	0.838

CI: Confidence interval. MOUD: medication for opioid use disorder

*Two-sided, Pearson's χ^2 test and Fisher's test for counts < 5 (for categorical variables) or the Mann-Whitney test (for continuous variables) as appropriate

[a] Denotes behaviours and events in the past six month.

[b] Injection or non-injection drug use.

[c] Refers to any heroin, fentanyl, or prescription opioid use

[d] Refers to any methamphetamine, powder cocaine or crack cocaine use

[e] Derived from asking participants to rate on a scale ranging from 1 (not at all worried) to 10 (very much worried) how worried they are about the COVID-19 pandemic

[f] Derived from asking participants to rate on a scale (not at all, a little, much, very much, extremely) how much/did the COVID-19 pandemic impact their day-to-day life (highly impacted vs. moderate to no impact)

Table 2

Sample characteristics among 885 participants in nine cohorts of people who use unregulated drugs in Canada (Vancouver, BC) and the United States (Baltimore, MD; Chicago, IL; Miami, FL; Los Angeles, CA), May, 2020 to April, 2021.

Characteristics	Total n = 885 (%)	Level of day-to-day impact of COVID-19		P Value*
		Highly impacted n = 453 (51 %)	Moderate to no impact n = 432 (49 %)	
Age (Median [IQR])	40 (29–54)	38 (29–52)	43 (30–54)	0.004
White (vs non-white)	304 (34.2)	153 (33.8)	151 (35.0)	0.765
Female (vs male)	635 (71.5)	114 (25.2)	139 (32.2)	0.026
Unstably housed/ homeless (vs. house/ apartment)[a]	575 (64.8)	163 (36.0)	150 (34.7)	0.748
Number of sexual partners (mean/sd)[a]	1.36 (3.3)	1.52 (3.9)	1.19 (2.4)	0.043
Study setting:				
Vancouver, BC	428 (48.4)	203 (44.8)	225 (52.1)	< 0.001
Baltimore, MD	132 (14.9)	48 (10.6)	84 (19.4)	
Chicago, IL	44 (5.0)	28 (6.2)	16 (3.7)	
Los Angeles, CA	211 (23.8)	142 (31.4)	69 (16.0)	
Miami, FL	70 (7.9)	32 (7.1)	38 (8.8)	
In MOUD[a]	218 (24.6)	91 (20.1)	127 (29.4)	0.304
Nonfatal overdose[a]	41 (4.6)	29 (6.4)	12 (2.8)	0.016
Daily drug use[a]:				
Alcohol	78 (8.8)	40 (8.8)	38 (8.8)	1.000
Opioids[b,c]	168 (18.9)	86 (19.0)	82 (19.0)	1.000
Stimulants[b, d b]		93 (20.5)	99 (22.9)	0.436
Injection drug use	297 (33.5)	143 (31.6)	154 (35.7)	0.225
COVID-19 related factors:				
Tested for COVID-19[a]	551 (62.1)	314 (69.3)	234 (54.2)	< 0.001
Tested positive for COVID-19[a]	18 (2.0)	12 (2.7)	6 (1.40)	0.276
COVID-19 worry (median; IQR)[a]	6 (3–8)	7 (5–9)	5 (2–7)	< 0.001
Avoided needle distribution sites[a]	77 (8.7)	41 (9.1)	36 (8.3)	0.795
Avoided picking up MOUD[a]	33 (3.7)	15 (3.3)	18 (4.2)	0.621
Stocked up on drugs[a]	164 (18.5)	101 (22.3)	63 (14.6)	0.004

CI: Confidence interval. MOUD: medication for opioid use disorder

*Two-sided, Pearson's χ^2 test and Fisher's test for counts < 5 (for categorical variables) or the Mann-Whitney test (for continuous variables) as appropriate

[a] Denotes behaviours and events in the past month.

[b] Injection or non-injection drug use.

[c] Refers to any heroin, fentanyl, or prescription opioid use

[d] Refers to any methamphetamine, powder cocaine or crack cocaine use

[e] 'COVID-19 worry' derived from asking participants to rate on a scale ranging from 1 (not at all worried) to 10 (very much worried) how worried they are about the COVID-19 pandemic

Women, 2020). These supports are especially vital for marginalized women engaged in sex work, who are overrepresented among PWUD. Our findings support the previous calls for gender-based approaches to mitigating overdose risks (Boyd et al., 2018), including low-threshold models of supervised consumption sites that include gender-specific attributes (i.e., women-only spaces, women peer workers), as these have been shown to accommodate women's drug use practices and reduce risks of overdose (Boyd et al., 2018; Collins et al., 2020).

In addition, we found that individuals who were unstably housed or homeless were significantly more likely to report a nonfatal overdose. Our findings are consistent with a study from San Francisco, CA that found that the proportion of individuals dying of overdose experiencing homelessness increased following "stay-at-home" measures (Appa et al., 2021). Being unstably housed and homelessness are well-documented risk factors for morbidity and premature mortality (Aldridge et al., 2018; Baggett et al., 2013; Bauer et al., 2016; Yamamoto et al., 2019; Zivanovic et al., 2015), including overdose (Baggett et al., 2013; Bauer et al., 2016; Yamamoto et al., 2019). Thus, these populations are at severely high risk for mortality and medical complications due to

Table 3
Bivariable and multivariable logistic regression of factors associated with nonfatal overdose among 885 participants in nine cohorts of people who use unregulated drugs in Canada (Vancouver, BC) and the United States (Baltimore, MD; Chicago, IL; Miami, FL; Los Angeles, CA), May 2020 to April, 2021.

Characteristics	Unadjusted Odds Ratio (95 % CI)	P value	Adjusted Odds Ratio (95 % CI)	P Value*
Age (per year)	1.01 (0.98–1.03)	0.578	1.00 (0.98–1.03)	0.792
White (vs non-white)	1.11 (0.56–2.10)	0.758	—	—
Female (vs male)	0.49 (0.26–0.94)	0.029	2.18 (1.10–4.30)	0.049
Unstably housed/homeless (vs. house/apartment)[a]	0.45 (0.24–0.85)	0.014	2.16 (1.11–4.26)	0.049
Sexual partners[a] (per partner)	1.04 (0.98–1.10)	0.113	1.06 (0.99–1.12)	0.084
In MOUD[a]	2.27 (1.18–4.28)	0.012	2.45 (1.19–4.97)	0.013
Daily drug use[a]:				
Alcohol	1.12 (0.33–2.90)	0.828	—	—
Opioid[b, c]	1.40 (0.64–2.82)	0.368	—	—
Stimulants[b, d]	1.53 (0.74–2.98)	0.231	—	—
Injection drug use	1.95 (1.03–3.67)	0.038	—	—
COVID-19 related factors[a]:				
Tested for COVID-19	1.46 (0.79–2.69)	0.391	2.00 (0.98–4.28)	0.084
COVID-19 worry[e]	1.01 (0.93–1.11)	0.543	—	—
Highly impacted day-to-day[f]	2.39 (1.23–4.93)	0.013	2.42 (1.22–5.10)	0.049
Avoided needle distribution sites	2.28 (0.90–5.04)	0.058	2.00 (0.75–4.72)	0.154
Avoided picking up MOUD[a]	0.63 (0.04–3.07)	0.658	—	—
Stocked up on drugs	1.07 (0.45–2.25)	0.869	—	—

CI: Confidence interval. MOUD: medication for opioid use disorder
* : P-value adjusted using Benjamini-Hochberg procedure
[a] Denotes behaviours and events in the past month.
[b] Injection or non-injection drug use.
[c] Refers to any heroin, fentanyl, or prescription opioid use
[d] Refers to any methamphetamine, powder cocaine or crack cocaine use
[e] Derived from asking participants to rate on a scale ranging from 1 (not at all worried) to 10 (very much worried) how worried they are about the COVID-19 pandemic
[f] Derived from asking participants to rate on a scale (not at all, a little, much, very much, extremely) how much/did the COVID-19 pandemic impact their day-to-day life (highly impacted vs. moderate to no impact)

Table 4
Bivariable and multivariable logistic regression of factors associated with reporting being highly impacted day-to-day by COVID-19 among 885 participants nine cohorts of people who use unregulated drugs in Canada (Vancouver, BC) and the United States (Baltimore, MD; Chicago, IL; Miami, FL; Los Angeles, CA), May, 2020 to April, 2021.

Characteristics	Unadjusted Odds Ratio (95 % CI)	P value	Adjusted Odds Ratio (95 % CI)	P Value*
Age (per year)	0.99 (0.98–1.00)	0.004	0.98 (0.97–0.99)	0.007
White (vs non-white)	0.95 (0.72–1.25)	0.712	1.55 (1.10–2.18)	0.023
Female (vs male)	0.71 (0.53–0.95)	0.021	0.78 (0.55–1.09)	0.139
Unstably housed/homeless (vs. house/apartment)[a]	1.06 (0.80–1.39)	0.695	1.37 (1.00–1.89)	0.068
Sexual partners[a] (per partner)	1.04 (0.99–1.09)	0.155	—	—
In MOUD[a]	0.60 (0.44–0.82)	0.001	0.64 (0.44–0.92)	0.023
Nonfatal overdose[a]	2.39 (1.23–4.93)	0.013	2.60 (1.25–5.71)	0.023
Daily drug use[a]:				
Alcohol	1.00 (0.63–1.60)	0.986	—	—
Opioid[b,c]	1.00 (0.71–1.40)	0.999	—	—
Stimulants[b, d]	0.87 (0.63–1.20)	0.389	—	—
Injection drug use	0.83 (0.63–1.10)	0.199	—	—
COVID-19 related factors[a]:				
Tested for COVID-19	1.91 (1.45–2.52)	< 0.001	1.52 (1.08–2.14)	0.023
COVID-19 worry[e]	1.25 (1.19–1.31)	< 0.001	1.30 (1.23–1.37)	< 0.001
Avoided needle distribution sites	1.09 (0.69–1.76)	0.705		
Avoided picking up MOUD	0.79 (0.39–1.58)	0.503	0.51 (0.24–1.11)	0.097
Stocked up on drugs	1.68 (1.19–2.39)	0.003	1.59 (1.09–2.32)	0.023

CI: Confidence interval. MOUD: medication for opioid use disorder
* : P-value adjusted using Benjamini-Hochberg procedure
[a] Denotes behaviours and events in the past month.
[b] Injection or non-injection drug use.
[c] Refers to any heroin, fentanyl, or prescription opioid use
[d] Refers to any methamphetamine, powder cocaine or crack cocaine use
[e] Derived from asking participants to rate on a scale ranging from 1 (not at all worried) to 10 (very much worried) how worried they are about the COVID-19 pandemic

COVID-19 infection. Of concern, there have been several outbreaks of COVID-19 in homeless shelters in the US and Canada (Chapman et al., 2021; Redditt et al., 2020). Simulation modelling has shown that even intensive infection control strategies are likely unable to prevent continued outbreaks in these congregate settings across the US (Chapman et al., 2021). Unfortunately, these congregate settings are typical among low-income housing options that exist for those who are homeless or unstably housed (e.g., single room occupancy hotels [SROs], supportive housing), and are often marked by dilapidated and unsanitary conditions (Shannon et al., 2006). Qualitative research in Vancouver, Canada has shown that these types of housing do not meet the survival needs of PWUD, and can lead to unlawful evictions and force people into homelessness (Fleming et al., 2019) A housing first strategy with community treatment is urgently needed for marginalized and unhoused PWUD to prevent mortality and morbidity. Evidence of the effectiveness of this approach have been demonstrated in a large multi-city randomized controlled trial in Canada (Aubry et al., 2015). In

addition, overdose prevention measures are urgently needed across types of housing, including supervised consumption sites embedded into housing models to prevent overdose and drug-related harms among unstably housed and homeless individuals (Bardwell et al., 2017).

We also found that those who were engaged in MOUD were more likely to report a nonfatal overdose compared to those not engaged in MOUD who may not use opioids or have opioid use disorder. Although systematic reviews and meta-analyses have shown that retention in MOUD is significantly associated with reductions in all-cause and overdose-related mortality (Sordo et al., 2017), our finding could be a proxy for unmeasured opioid use disorder, a reflection of gaps in treatment caused by COVID-19 related service disruptions (Russell et al., 2021), or inadequate medication dosages (B Leavitt et al., 2000). The latter two scenarios can lead to the purchasing of unregulated opioids from the contaminated drug supply to supplement/replace MOUD, a practice which could expose consumers to contaminated drugs, increasing their overdose risk. Our findings corroborate a 2018 study among HIV-positive PWUD in Vancouver, Canada, that found significant longitudinal associations between those engaged in MOUD and testing

positive for fentanyl in urine drug screen tests (Moallef et al., 2021). However, it is important to note that many jurisdictions across Canada and the US have implemented changes to expand MOUD services to account for potential impacts to delivery of services (Ivsins et al., 2021; Peavy et al., 2020), but these changes require evaluation. Regulatory reforms in 2014 in British Columbia were associated with unintended consequences, including increases in injection heroin use (Socías et al., 2017). It is also unclear the level of treatment gaps experienced by PWUD during the dual crises. A national qualitative study in Canada conducted from May to July 2020, shows that most PWUD reported high levels of treatment disruptions that led to negative health effects, including reducing their abilities to prevent overdose (Russell et al., 2021). Thus, there is an urgent need to mitigate treatment gaps and subsequent overdose risk as a result of disruptions to services, as well as evaluations of changes to MOUD to reduce potential unintended consequences related to regulatory reforms.

We also found that those who reported being highly impacted day-to-day by the pandemic were more likely to report experiences of nonfatal overdose. This is consistent with a qualitative study among PWUD across Canada, where many reported considerable impacts to their day-to-day lives caused by the pandemic (Ali et al., 2021), including difficulties in obtaining unregulated drugs due to fluctuations in potency, cost, and availability, and elevated perceived risk of overdose during the pandemic. This corroborates our secondary analysis finding where we found that those who reported stocking up on drugs were more likely to report being highly impacted by the pandemic. Stocking up on drugs could also be related to medication disruptions/discontinuations as a result of reduced services amid social disruptions caused by the pandemic (Russell et al., 2021). Although most participants reported being worried about the COVID-19 pandemic, we did not find these levels to differ by experiences of nonfatal overdose. However, we observed statistically significant associations between those who reported higher levels of worry and being highly impacted day-to-day by the pandemic. Higher levels of anxiety could be related to levels of psychological and physical distress, which have been previously linked to more intensive drug use.(Chou et al., 2011) Worry could also be related to fear and contribute to or exacerbate PWUD's well-documented avoidance of healthcare services (Biancarelli et al., 2019; Drumm et al., 2005; van Boekel et al., 2013). We note several experiences of avoidance of harm reduction measures (i.e., needle distribution sites and MOUD) in our study, which is a concern as this reduces an individual's ability to mitigate an overdose. Research is needed to investigate the potential psychological impacts of COVID-19 among PWUD.

Our findings indicate a need for a multi-level approach involving the spectrum of care services to meet the elevated risks of overdose in the context of the dual crises, including scaling up overdose prevention interventions for those at risk for overdose, particularly among women, those who are unstably housed or homeless, and highly impacted day-to-day by the pandemic. Efforts to prevent overdose, however, should prioritize addressing the root causes of the drug poisoning crisis, such as the continuous exposure to toxic and contaminated unregulated drug supplies among PWUD, including considering provisions of safe supply, or pharmaceutical-grade uncontaminated substances for PWUD at risk of overdose (Ivsins et al., 2020, 2021).

Our study findings should be considered with limitations. Due to a very low number of participants identifying as a sexual or gender minority (SGM) in some of the cohorts, our analyses were not able to clarify SGM-related dynamics that may impact risk of overdose. Future investigations should consider the gendered and racialized dynamics that produce risk of overdose given the pre-existing health inequities among these populations. Further, the non-random nature of our sample reduces our ability to generalize our results to all PWUD, while the cross-sectional nature of the study does not allow us to determine the temporal sequence between exposures and outcome. The C3PNO cohorts were not recruited via random sampling, the data were derived from a convenience sample of PWUD and are not representative of the broader population of PWUD. Most non-fatal overdose experiences were reported by respondents among the three Vancouver based cohorts, while few or no non-fatal overdose experiences were reported in the other studied settings (e.g., Baltimore, Chicago, Los Angeles, Miami). The inclusion of three Vancouver based cohorts introduces some selection bias. In addition, survey responses could vary by study setting and by time in which data collection occurred. In particular, the burden of the pandemic differed across cohort sites and surveys completed earlier on in the pandemic may differ from those completed later in the pandemic. Future longitudinal analyses are needed to remediate the temporal limitations present in our study. Also, we are unable to determine the frequency of engagement for some variables, including among those who reported being on MOUD, and we are unable to determine the type of MOUD participants accessed. Lastly, our study measures are based on self-report which may have introduced response bias.

5. Conclusion

Our findings shed light on several groups of PWUD who may be at higher risk for overdose in light of the COVID-19 pandemic. Overall, most participants reported being worried and approximately half reported being highly impacted day-to-day by the pandemic. In multivariable analysis, we found that females, people who are unstably housed or homeless, those engaged in MOUD and those highly impacted day-to-day by the pandemic were more likely to report a non-fatal overdose. In the secondary, we found that those who reported being highly impacted day-to-day were more likely to have higher levels of worry and stocked up on drugs due to the pandemic. Given the accelerating number of fatal overdoses across the span of the drug poisoning crisis, efforts should prioritize providing safe supplies of drugs to PWUD at risk of overdose to mitigate the increasingly contaminated unregulated drug supply. In addition, scaling up overdose prevention measures for people who may be vulnerable to overdose, including women, people who are unstably housed or homeless, and those highly impacted day-to-day by the pandemic is warranted.

CRediT authorship contribution statement

Soroush Moallef drafted the initial manuscript and worked with JC to conduct the statistical analyses, and incorporated feedback from all co-authors. BL, KH, Shruti Mehta, GK, KD, MK, RD, MK, SS, PG, BM, MJ, SS, and MJM designed and managed the cohorts. All authors made significant contributions to the conception of the analyses, interpretation of the data and drafting of the manuscript. All authors approved the final manuscript.

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