Effect of Risk Mitigation Guidance for opioid and stimulant dispensations on mortality and acute care visits during dual public health emergencies: retrospective cohort study

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Abstract

Objective

To determine the effect of opioid and stimulant Risk Mitigation Guidance (RMG) dispensations on mortality and acute care visits during the dual public health emergencies of overdose and covid-19.

DESIGN

Population based retrospective cohort study.

SETTING

British Columbia, Canada.

PARTICIPANTS

5882 people with opioid or stimulant use disorder who received RMG prescriptions for opioids (n=5356) and/or stimulants (n=1061) (535 received both) from 27 March 2020 to 31 August 2021.

MAIN OUTCOME MEASURES

All cause and overdose specific mortality and acute care visits in the week after RMG opioid or stimulant dispensation. RMG recipients were matched 1:1 with controls through use of high dimensional propensity score matching. Marginal structural models, executed on weekly time steps, were used to measure the effect of dispensations on outcomes.

RESULTS

RMG opioid dispensations of one day or more were associated with reduced all cause mortality (adjusted hazard ratio 0.39, 95% confidence interval 0.25 to 0.60) and overdose related mortality (0.45, 0.27 to 0.75) in the subsequent week. Dispensations of RMG stimulants (≥1 days) were not significantly associated with reduced all cause mortality (adjusted hazard ratio 0.50, 0.20 to 1.23) or overdose related mortality (0.53, 0.18 to 1.56). The protective effect of RMG opioid dispensations increased with the number of days the medications were dispensed in a given week. People who received four or more days of RMG opioid dispensations had reduced all cause mortality (adjusted hazard ratio 0.09, 0.04 to 0.21) and overdose related mortality (0.11, 0.04 to 0.32) compared with the control group. Opioid RMG dispensations did not significantly modify the odds of all cause or overdose related acute care visits. Dispensations of RMG stimulants were associated with a significant decrease in the odds of acute care visits for any cause but did not affect the odds of overdose related acute care visits.

CONCLUSIONS

RMG opioid dispensations were associated with reduced overdose related and all cause mortality among a sample of people with opioid use disorder. Pharmaceutical alternatives to the illegal drug supply are promising interventions to reduce mortality in people with opioid use disorder.

WHAT IS KNOWN ABOUT THIS TOPIC

Qualitative research on the impact and implementation of Risk Mitigation Guidance (RMG) prescribing to date has been conducted in a large urban centre and a supportive housing unit

The effect of RMG prescribing on overdose related mortality, all cause mortality, and acute care visits is unknown

WHAT THIS STUDY ADDS

Compared with a matched control group, opioid RMG dispensations were associated with reduced all cause and overdose related mortality in the subsequent week after dispensation

Opioid RMG dispensations were not associated with significant reductions in the likelihood of all cause or overdose related acute care visits in the subsequent week

Stimulant RMG dispensations were not significantly associated with reduced mortality but were associated with a significant decrease in the odds of acute care visits for any cause

Introduction

Unregulated drug poisoning (overdose) is a public health emergency in North America and internationally that worsened during the covid-19 pandemic.[1 2] Since March 2020, overdose related mortality has increased in Canada and the United States, where 7560 and 80816 people respectively died of overdose in 2021.[3-5] Adulteration of the illegal drug supply with fentanyl is the leading contributor to overdose related deaths in Canada.[3] British Columbia (Canada's westernmost and third most populous province) has been under a public health emergency declaration since 2016 when adulteration of the illegal drug supply with fentanyl led to a rapid increase in overdose deaths.[6] Overdose has had a detrimental impact on population health in British Columbia, where drug poisoning is the leading cause of death for people aged 10-59.[7] Responses to the public health emergency in British Columbia have included an expansion of prevention, treatment, and harm reduction services across the healthcare continuum, including increasing the number of substance use treatment beds, assertive community treatment teams, and overdose prevention sites across the province.[8]

At the onset of the covid-19 pandemic, new policies and interventions were rapidly developed to support

public health measures.[9 10] The first iteration of Risk Mitigation Guidance (RMG) was issued by the British Columbia Ministry of Health and British Columbia Centre on Substance Use (BCCSU) on 26 March 2020.[11] The RMG provided clinical guidance to physicians and nurse practitioners about prescribing select medications to people at risk of SARS-Cov-2 infection in the interest of reducing harm from exposure to the illegal drug supply.[11] The practice of prescribing pharmaceutical alternatives to the illegal drug market is commonly known as "prescribed safer supply." The RMG referenced existing BCCSU guidelines for the treatment of opioid use disorder and suggested additional or alternative medications that could be prescribed to people who decline treatment for opioid use disorder, who use illegal opioids but do not meet criteria for opioid use disorder, or who use substances other than opioids.[9 10] The substances listed in the first iteration of the RMG included opioids (tablet hydromorphone, oral morphine), stimulants (dextroamphetamine, methylphenidate), benzodiazepines (clonazepam, diazepam), and alcohol withdrawal management medications (carbamazepine, gabapentin, clonidine).[11] Publicly funded health insurance coverage for these medications is available for eligible residents of British Columbia.[11] The RMG was initially focused on supporting people experiencing withdrawal due to public health quarantine and isolation protocols.[11] On 15 July 2021, the Province of British Columbia released a provincial Prescribed Safer Supply policy that extended prescribing outside the covid-19 pandemic.[12] The RMG was the first known clinical guidance issued by a provincial or state government in North America to support physicians and nurse practitioners in prescribing alternatives to the illegal drug supply.[15 16]

Although hydromorphone and diacetylmorphine have shown effectiveness as injectable forms of opioid agonist treatment in highly controlled trials and clinical settings,[13 14] evidence on the outcomes of prescribing pharmaceutical alternatives to the illegal drug supply in community settings is limited, and no evidence exists at the population level. The published literature to date on RMG prescribing in British Columbia includes a case report,[15] a chart review,[16] a cross sectional survey of people who use drugs,[17] and a qualitative study that used interview data.[18] Existing studies use data collected from medical records, interviews, or surveys of people who have received RMG from urban areas such as Vancouver and Victoria, British Columbia. None of these studies included an unexposed comparison group. These studies have found that RMG prescribing was effective at supporting quarantine and isolation[18]; however, awareness of RMG prescribing was low among people who use unregulated drugs,[17] and barriers to obtaining an RMG prescription were reported.[18] Access to psychiatric medications and opioid agonist treatment was found to be associated with increased retention on RMG medications.[16] A qualitative study found that RMG prescribing reduced self-reported illegal drug use and overdose related risks among 40 people who use unregulated drugs in British Columbia.[18] An urgent need exists to understand the effect of RMG prescribing on mortality to inform drug policy in North America. Observational studies of changes in social, health, or economic policy have been recognised as essential to strengthening public health evidence.[19] Randomised controlled trials are rarely appropriate or feasible to evaluate real world public health interventions; in the absence of such trials, observational studies can provide robust measurement of effectiveness and other outcomes.[20] Given the strengths of this study design and the critical need for evidence on the outcomes of RMG prescribing, the objective of this study was to determine the effect of opioid and stimulant RMG dispensations on all cause and overdose related mortality and recurrent acute care visits.[21] Mortality and acute care visits are the focus of this project because they are among the most severe outcomes associated with substance use during the unregulated drug poisoning crisis. Acute care visits include emergency department and hospital attendance, which allows for assessment of some of the most severe cases of non-fatal overdose including overdose events that require immediate healthcare treatment, resuscitation, or ventilation.

Methods

This paper reports on the primary outcomes of a mixed methods evaluation of the implementation and impacts of RMG in British Columbia that has been previously described.[21] This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[22]

Data sources

We used a linkage of population level administrative databases to define the cohort of all residents of British Columbia with an indication of an opioid use disorder or stimulant use disorder from 1 January 1996 to 31 August 2021. The administrative databases in our study data were linked using probabilistic matching by the British Columbia Ministry of Health. After the rigorous, standardised linkage procedures resulting in a high linkage rate, we were given data extracts with unique, individual level identifiers before data analysis.[18] The linked databases captured provincial health insurance plan registration (Client Roster), physician billing records (Medical Services Plan), hospital admissions (Discharge Abstract Database), community pharmacy dispensations (PharmaNet), incarceration in 10 provincial correctional institutions (Ministry of Public Safety and the Solicitor General), emergency department visits (National Ambulatory Care Reporting System), perinatal services for all provincial births (British Columbia Perinatal Data Registry), receipt of income assistance (Ministry of Social Development and Poverty Reduction), and mortality (British Columbia Coroner's Service and Vital Statistics). A detailed description of earlier iterations

Table 1 | Characteristics of Risk Mitigation Guidance (RMG) recipients and non-recipients at time of first RMG dispensation (high dimensional propensity score matched cohort). Values are numbers (percentages) unless stated otherwise

	Opioid RMG				Stimulant RMG*			
			SMD† (matching)				SMD† (matching)	
Characteristics	No RMG (n=5356)	RMG (n=5356)	Before	After	No RMG (n=1058)	RMG (n=1058)	Before	After
Female sex	1948 (36.4)	1951 (36.4)	−0.03	0.00	388 (36.7)	407 (38.5)	−0.04	0.02
Median (IQR) age, years	38 (30-48)	38 (31-47)	−5.46	0.07	39 (31-48)	39 (31-47)	−3.77	−0.08
Rural region	536 (10.0)	529 (9.9)	−0.03	0.00	155 (14.7)	162 (15.3)	0.00	0.01
Vancouver or South Central Vancouver Island	2794 (52.2)	2835 (52.9)	0.23	0.01	587 (55.5)	606 (57.3)	0.25	0.02
Receipt of income assistance in previous year	4566 (85.3)	4447 (83.0)	0.34	−0.02	864 (81.7)	838 (79.2)	0.46	−0.02
Unstable housing in previous year	2062 (38.5)	2043 (38.1)	0.25	0.00	436 (41.2)	416 (39.3)	0.29	−0.02
OAT dispensation in previous week	2689 (50.2)	2666 (49.8)	0.18	0.00	480 (45.4)	493 (46.6)	0.32	0.01
Years since first indication of opioid use disorder:								
<5	2543 (47.5)	2503 (46.7)	0.05	−0.01	-	-	-	-
5-9	1219 (22.8)	1242 (23.2)	−0.02	0.00	-	-	-	-
≥10	1594 (29.8)	1611 (30.1)	−0.03	0.00	-	-	-	-
Years since first indication of stimulant use disorder:								
<5	-	-	-	-	424 (40.1)	437 (41.3)	0.04	0.01
5-9	-	-	-	-	136 (12.9)	118 (11.2)	−0.08	−0.02
≥10	-	-	-	-	498 (47.1)	503 (47.5)	0.04	0.00
Charlson Comorbidity Index >0	301 (5.6)	323 (6.0)	0.00	0.00	68 (6.4)	63 (6.0)	0.00	0.00
Median (IQR) Chronic Disease Score	1.8 (1.2-2.4)	1.8 (1.3-2.5)	0.12	0.02	1.9 (1.3-2.5)	1.8 (1.3-2.5)	0.17	0.01
Overdose related acute care visits in previous 30 days	290 (5.4)	293 (5.5)	0.04	0.00	70 (6.6)	63 (6.0)	0.04	−0.01
Substance use disorder diagnosis (ever)	4828 (90.1)	4818 (90.0)	0.12	0.00	-	-	-	-
Opioid use disorder diagnosis (ever)	-	-	-	-	908 (85.8)	886 (83.7)	0.38	−0.02
Alcohol use disorder diagnosis (ever)	2335 (43.6)	2344 (43.8)	0.09	0.00	465 (44.0)	472 (44.6)	−0.08	0.01
Diagnosis of mental health disorder (ever)	1559 (29.1)	1572 (29.4)	0.01	0.00	413 (39.0)	401 (37.9)	−0.06	−0.01
Diagnosis of HIV (ever)	354 (6.6)	391 (7.3)	0.05	0.01	91 (8.6)	90 (8.5)	0.04	0.00
Diagnosis of hepatitis C (ever)	1168 (21.8)	1181 (22.1)	0.10	0.00	230 (21.7)	231 (21.8)	0.09	0.00
Chronic pain diagnosis in previous year	1339 (25.0)	1391 (26.0)	−0.02	0.01	244 (23.1)	224 (21.2)	0.09	−0.02
Tobacco use disorder diagnosis in previous year	756 (14.1)	766 (14.3)	0.02	0.00	160 (15.1)	140 (13.2)	0.06	−0.02
Any cancer or palliative care in previous year	403 (7.5)	412 (7.7)	−0.01	0.00	74 (7.0)	76 (7.2)	0.03	0.00
Incarcerated in previous year	495 (9.2)	463 (8.6)	0.05	−0.01	96 (9.1)	89 (8.4)	0.06	−0.01
Physician attachment: single general practitioner >50%	2736 (51.1)	2739 (51.1)	−0.05	0.00	456 (43.1)	465 (44.0)	0.00	0.01
Opioid dispensation other than OAT in previous 60 days	901 (16.8)	976 (18.2)	0.09	0.01	156 (14.7)	168 (15.9)	0.07	0.01
Benzodiazepine dispensation in previous 60 days	258 (4.8)	268 (5.0)	−0.03	0.00	80 (7.6)	69 (6.5)	−0.01	−0.01
Stimulant dispensation in previous 60 days	205 (3.8)	215 (4.0)	0.02	0.00	-	-	-	-
Opioid RMG dispensation in previous week	-	-	-	-	116 (11.0)	117 (11.1)	0.10	0.00

IQR=interquartile range; OAT=opioid agonist treatment.
*Of 1061 people with simulant RMG, 1058 were matched with control group.
†Standardised mean difference between RMG and non-RMG recipients before/after matching based on high dimensional propensity score for all cause mortality outcome.

of the British Columbia Substance Use Disorder cohort is available elsewhere.[21]

Study population

The study population was composed of people who had an indication of an opioid use disorder (in the case of opioid RMG) or stimulant use disorder (in the case of stimulant RMG). We identified diagnoses of opioid use disorder and stimulant use disorder by using case finding algorithms applied to data from the Medical Services Plan, Discharge Abstract Database, PharmaNet, National Ambulatory Care Reporting System, and British Columbia Perinatal Data Registry. Case finding algorithms used ICD (international classification of diseases) codes and drug identification numbers for opioid agonist treatment to identify opioid use disorder and ICD codes to identify stimulant use disorder (supplement section A, tables S1-S2). The study followed from the calendar week of 27 March 2020 or the first week of indication of opioid use disorder (for opioid RMG) or stimulant use disorder (for stimulant RMG), whichever occurred later. Follow-up concluded at incarceration, death, or the end of the study period (31 August 2021), whichever occurred first. We used common demographic measures (age, sex, unstable housing), healthcare use measures (dispensations of opioids for pain), and chronic disease indices to describe the study population and conduct matching, which is further described below. The diagnostic codes used to measure demographics, chronic conditions, and healthcare measures are described in supplement section B, tables S6-S7.

Outcome measures

The primary outcomes were mortality (all cause and overdose related) and recurrent acute care visits (all cause and overdose related) in the subsequent week. We used British Columbia Vital Statistics data to identify deaths and British Columbia Coroners Service data to identify whether these deaths were caused by unregulated drug poisoning (overdose). All deaths attributed to overdose in British Columbia are reported to the British Columbia Coroners Service, which investigates suspected overdose related deaths and conducts postmortem toxicology to characterise the substances and circumstances that contributed to death.[23] Coroners' records are the gold standard for identification of deaths attributed to unregulated

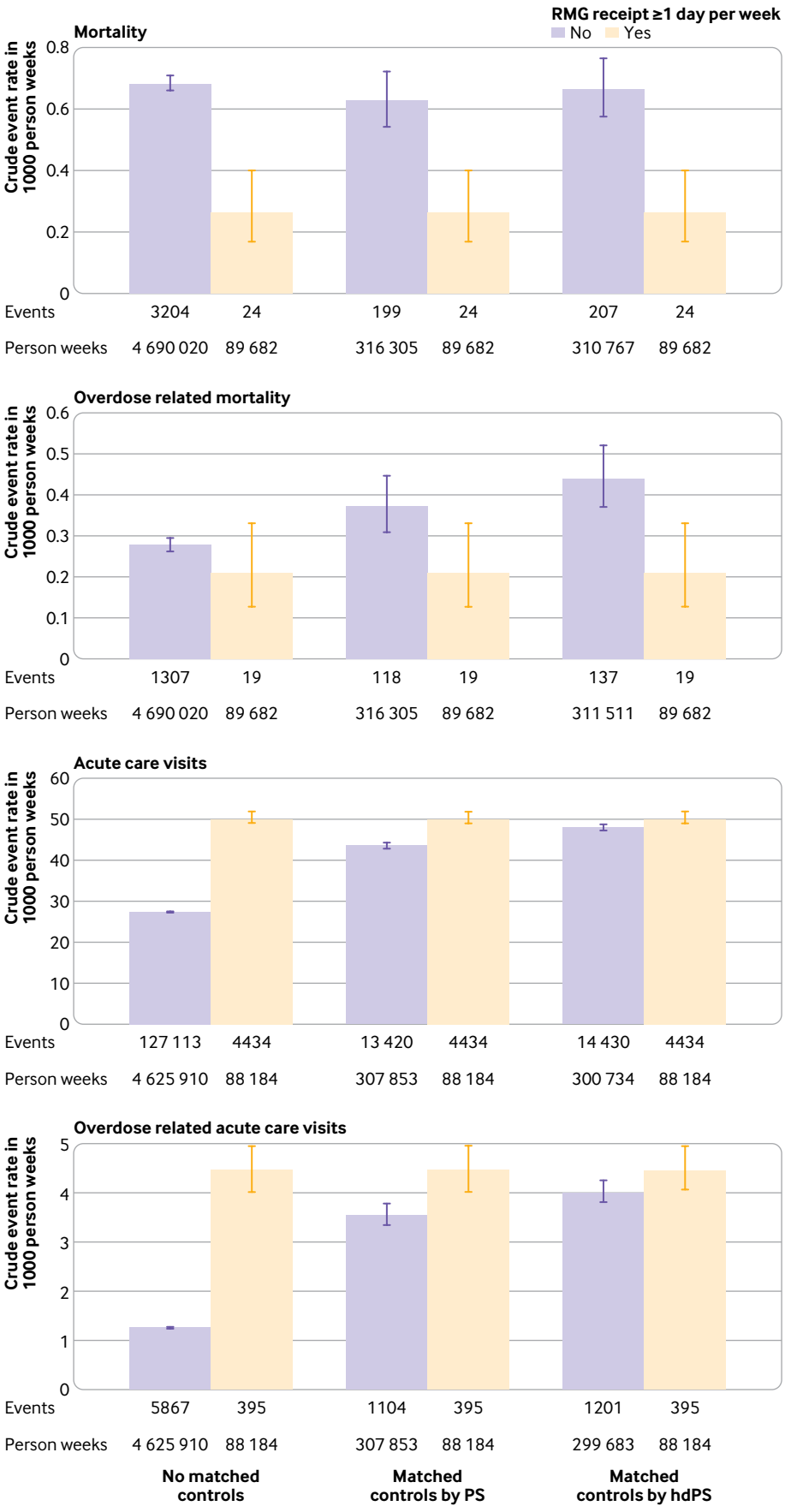

Fig 1 | Crude event rates stratified by receipt of Risk Mitigation Guidance (RMG) opioid medications. hdPS=high dimensional propensity score; PS=propensity score

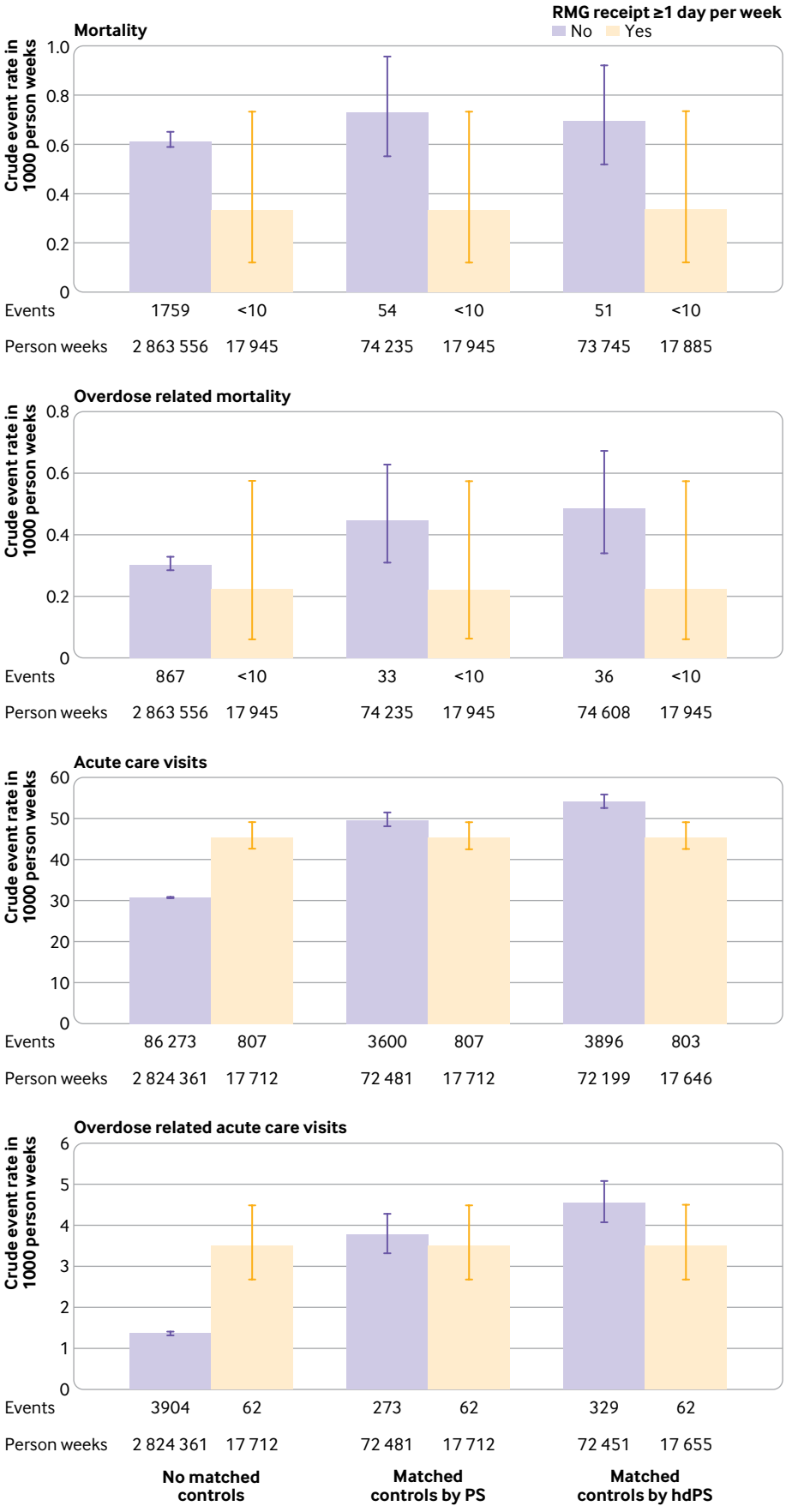

Fig 2 | Crude event rates stratified by receipt of Risk Mitigation Guidance (RMG) stimulant medications. hdPS=high dimensional propensity score; PS=propensity score

drug poisoning.[24 25] We identified overdose related acute healthcare visits from emergency department (National Ambulatory Care Reporting System extract) and hospital admission records (Discharge Abstract Database extract) (supplement section B, table S3). Because of the contamination of the illegal drug supply with substances such as fentanyl and benzodiazepines, we used a broad ascertainment of the substances associated with overdose related acute care visits.[23]

Exposure measures

When RMG prescribing was introduced, unique drug identification numbers were not assigned to RMG medications, which prevented the immediate identification in PharmaNet of medications specifically for RMG purposes. We used case finding algorithms that applied restrictions to prescription data from PharmaNet to identify RMG dispensations. To limit misclassification, we developed two case definitions—one that was hypothesised to have higher sensitivity and lower specificity and one with lower sensitivity and higher specificity (supplement section B, tables S4-S5). Once we had identified RMG medications by using these algorithms, we merged PharmaNet records into continuous episodes with no interruptions in prescribed doses lasting more than seven days. We defined exposure to RMG medication in a given week (t) as receipt of at least one day of dispensations in that week.

Matching techniques

We constructed unexposed groups, matching individuals who were eligible but unexposed to RMG prescriptions to exposed individuals sequentially, on the month of initial receipt of RMG prescription. We did the matching on an individual basis, accounting for the time at which each RMG recipient received their first RMG dispensation. We constructed matched unexposed groups by using both investigator selected covariates (variables listed in table 1) and high dimensional propensity score matching methods to balance measurable confounding at baseline (supplement section E). The major categories of covariates identified from the literature review (that is, demographic factors, socioeconomic status) are described in a directed acyclic graph in supplement section E, figure S2. High dimensional propensity scoring is an automated data driven approach to derive important proxy variables from administrative data for inclusion in propensity score models. This approach uses an algorithm to identify covariates associated with both exposure and outcome from data that are primarily collected for billing and routine administrative purposes.[26] The high dimensional propensity score algorithm identified 50 influential proxy variables in each month from the Medical Services Plan, Discharge Abstract Database, and PharmaNet extracts (supplement section E, tables S9-S10), and we identified investigator specified covariates based on the outcomes of a systematic review (supplement section C).

Using logistic regression, we estimated propensity scores per month as the predicted probability of exposure on investigator defined covariates only and additional high dimensional propensity score covariates. Covariates were measured at the first week of RMG receipt among the exposed group, and the first week of each month (before the month of RMG initiation) among all individuals from the weekly datasets ranging from 27 March 2020 to 27 August 2021. We matched the unexposed groups one to one with people who received RMG medications at the calendar month of initiation from March/April 2020 combined to August 2021, 17 times in total, on the basis of the propensity scores.[27] Once selected in the unexposed group in an early month, an individual

Table 2 | Sample and effect sizes for each outcome analysis using high dimensional propensity score matched cohort

Cohort and outcome	RMG status*	No of individuals†	No of outcomes‡	No of weeks‡	Event rate‡§	Effect size (95% CI)‡¶
Opioid use disorder (n=70 360 before matching)						
All cause mortality	RMG	5356	24	89 682	0.3	HR=0.39 (0.25 to 0.60)
	No RMG	5356	207	310 767	0.7	
Overdose related mortality	RMG	5356	19	89 682	0.2	HR=0.45 (0.27 to 0.75)
	No RMG	5356	137	311 511	0.4	
All cause acute care visits	RMG	5330	4434	88 184	50.3	OR=1.02 (0.95 to 1.09)
	No RMG	5330	14 430	300 734	48.0	
Overdose related acute care visits	RMG	5330	395	88 184	4.5	OR=1.09 (0.93 to 1.27)
	No RMG	5330	1201	299 683	3.9	
Stimulant use disorder (n=41 890 before matching)						
All cause mortality	RMG	1058	<10	17 885	SU	HR=0.50 (0.20 to 1.23)
	No RMG	1058	51	73 745	0.7	
Overdose related mortality	RMG	1061	<10	17 945	SU	HR=0.53 (0.18 to 1.56)
	No RMG	1061	36	74 608	0.5	
All cause acute care visits	RMG	1056	803	17 646	45.5	OR=0.82 (0.72 to 0.95)
	No RMG	1056	3896	72 199	54.0	
Overdose related acute care visits	RMG	1057	62	17 655	3.5	OR=0.88 (0.63 to 1.23)
	No RMG	1057	329	72 451	4.5	

CI=confidence interval; HR=hazard ratio; OR=odds ratio; SU=suppressed due to low number of outcomes.
*Risk Mitigation Guidance prescriptions of opioid (or stimulant) among opioid (or stimulant) use disorder cohort.
†Based on RMG receipt ≥1 day at time zero.
‡Based on time dependent weekly RMG receipt ≥1 day per week.
§Per 1000 person weeks.
¶RMG versus no RMG.

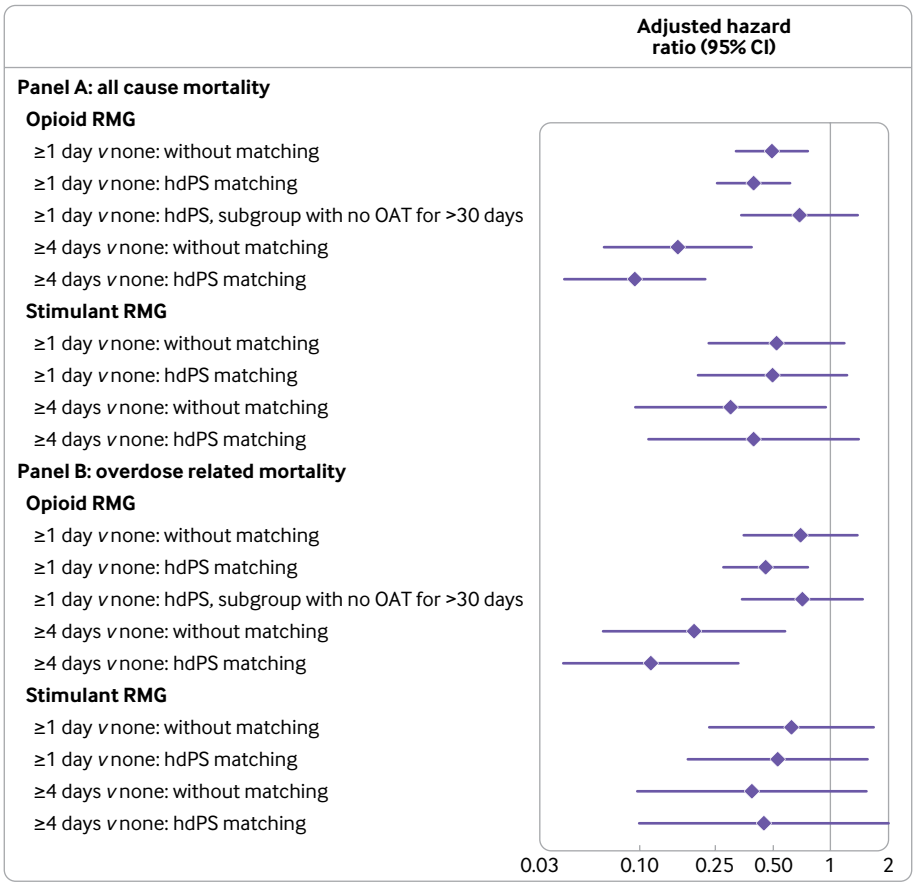

Fig 3 | Results of marginal structural models on mortality. Hazard ratios are plotted on log scale. hdPS=high dimension propensity score matching; OAT=opioid agonist treatment; RMG= Risk Mitigation Guidance

could not be selected again in the unexposed group in the later months. However, exposed individuals could be selected for the unexposed group before their first RMG dispensation, and the observations were censored at the receipt of RMG dispensing (supplement section D, figure S1). We used nearest neighbour matching by both the propensity score on the investigator defined covariates only and the additional high dimensional propensity score covariates. Nearest neighbour matching occurred if the difference in the logit of propensity between nearest neighbours was within a caliper of width equal to 0.2 of the standard deviation of the logit of the propensity score.[28] We assessed the distributions of covariates before and after matching by the high dimensional propensity score by using standardised mean differences between the exposed and unexposed groups. A positive standardised mean difference means that the exposed group has a larger mean than the unexposed group, and the absolute standardised mean difference should be ≤0.1 for good variable balance.[29] We used an SAS macro version 2 (available at www.drugepi.org) for high dimensional propensity score covariate selection and matching.

Statistical analysis

For the matched cohort, data were structured using weekly time steps from "time zero," the week of initial RMG dispensation for the exposed group and a corresponding unexposed group. We used weekly time steps to capture the instantaneous effect of time varying RMG medications, received intermittently during the study period, on primary and secondary outcomes. We used weekly time steps to measure outcomes because of the assumption that the intervention would have a short term effect. Like other harm reduction interventions, the effect of the intervention exists if the intervention is in active use. We used marginal structural models to determine the effect of RMG dispensations on each of the primary outcomes.[30] To control for time varying confounding in the time varying exposure and outcome relation after baseline, we estimated time varying inverse probability weights to create a pseudo-population in which the exposure is independent of the measured confounders. The pseudo-population is the result of assigning to each participant a weight that is inversely proportional to the participant's probability of receiving their own exposure history. Weighted estimation of the parameters of marginal structural models requires the fitting of several models: the structural (that is, weighted) model, the exposure model, and the censoring model. We estimated the time varying stabilised inverse probability treatment weights by using separate logistic models by exposure status in the previous week to control for time varying confounders. Similarly, we estimated censoring weights

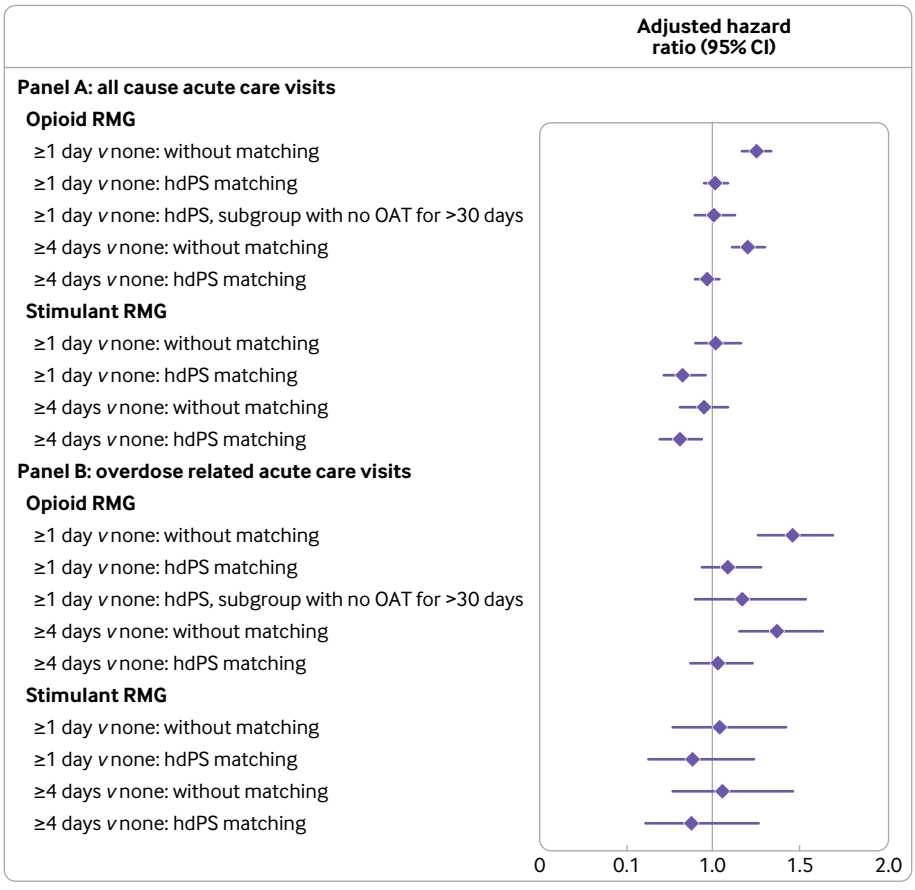

Fig 4 | Results of marginal structural models on acute healthcare visits. hdPS=high dimension propensity score matching; OAT=opioid agonist treatment; RMG= Risk Mitigation Guidance

by using pooled logistic regression models adjusted for potential post-baseline confounders.[31] Follow-up was censored at incarceration, RMG initiation (if selected for the unexposed group), or administrative loss to follow-up (or death in the analysis on the acute care visit outcome). We calculated the final weights by the product of the estimated inverse probability of treatment weights and inverse probability of censoring weights, truncated at the first and 99th centiles. We included the same sets of covariates for treatment and censoring weights listed in table 1, with weeks since time zero (a linear and a quadratic term) and month of time zero from one to 17 (a linear and a quadratic term). Finally, we fitted a pooled weighted logistic regression model adjusted for baseline confounders. For the mortality outcome, we considered the weighted estimator as the hazard ratio because the model approximates the Cox model well when the risk of events is less than 10% per person-time interval.[32] We used robust variance estimators to calculate confidence limits for marginal structural models.

Sensitivity analyses

We did a series of sensitivity analyses to determine the robustness of our findings in relation to the composition of the unexposed group, classifications of exposure and outcome, and the specification of statistical models. Firstly, we included all individuals in the cohort without matching. Time zero was set to 27 March 2020 or the first indication of opioid use disorder (or stimulant use disorder) for the opioid use disorder (or stimulant use disorder) cohort, and we used marginal structural models to determine the effect of RMG dispensation in the cohort without excluding any individuals. We used two intensities of exposure to determine whether a dose-response relation existed between exposure in a given week t and outcome in week t+1. We used two categories to model two levels of exposure: dispensations of one or more days of opioid or stimulant RMG and four or more days of opioid or stimulant RMG dispensed in a given week. We hypothesised that receiving four or more days of opioid or stimulant RMG dispensations would increase protection against mortality and acute care visits. Although opioid agonist treatment during follow-up time was controlled for in the main analyses, to ensure that results were not driven by the residual effect of opioid agonist treatment, which itself reduces the risk of mortality among recipients, we also did subgroup analyses among people who had not received opioid agonist treatment in the 30 days before RMG initiation.

To account for the variance in daily dosing, we reclassified RMG medication exposure into morphine equivalents of opioid RMG dispensations in a given week. We used two categories of dose based on the first

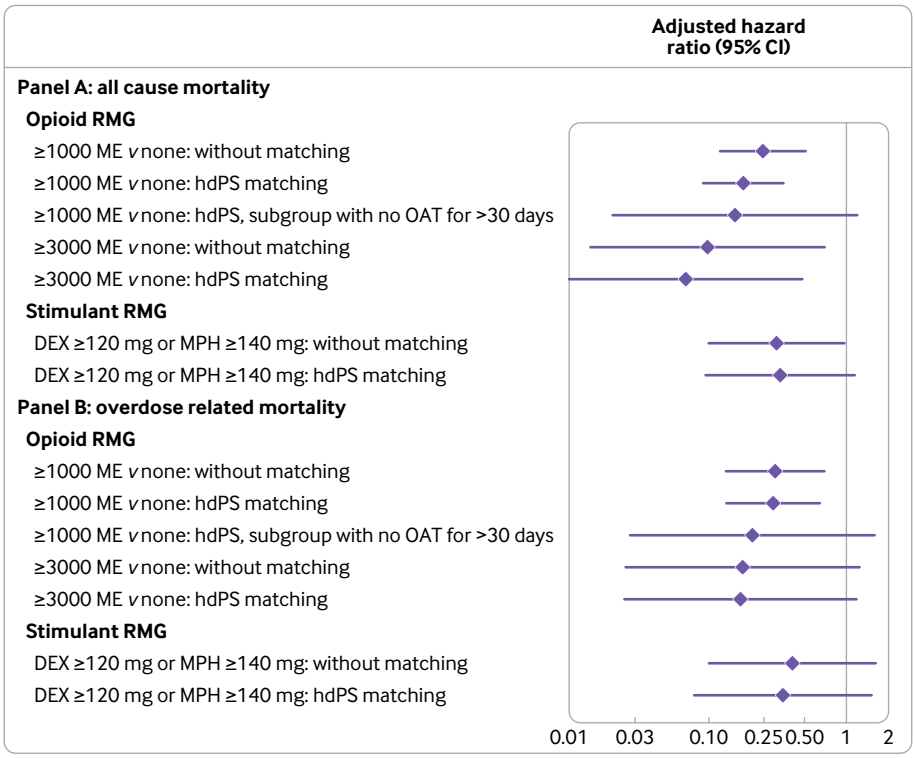

Fig 5 | Sensitivity analyses: primary and secondary outcomes by weekly dose dispensed. Hazard ratios are plotted on log scale. DEX=dextroamphetamine; hdPS=high dimension propensity score matching; ME=morphine equivalent; MPH=methylphenidate; OAT=opioid agonist treatment; PS=propensity score; RMG= Risk Mitigation Guidance

(1000 morphine equivalents) and third quarters (3000 morphine equivalents) of all opioid RMG dispensations. The RMG recommended dosing of ≤14 8 mg oral hydromorphone tablets (560 morphine equivalents), per day. Similarly, for stimulant RMG dispensations, we examined outcomes for two groups: people who were dispensed ≤120 mg dextroamphetamine or ≤140 mg methylphenidate in a given week (low dose group); and people who received dispensations for ≥280 mg of dextroamphetamine or ≥420 mg of methylphenidate in a given week (high dose group). The RMG recommended that people with active stimulant use disorder should have 10-20 mg of sustained release dextroamphetamine dispensed twice a day up to a maximum of 40 mg twice daily and/or 10-20 mg of dextroamphetamine immediate release twice or three times a day with a maximum dose of 80 mg a day. For methylphenidate, the RMG recommended 20-40 mg sustained release with a maximum daily dose of 100 mg in a 24 hour period and/or 10-20 mg immediate release twice a day to a maximum dose of 100 mg a day. Sensitivity analyses allowed us to determine whether the dose had an effect on mortality and acute care use outcomes in comparison with the number of days dispensed. Time zero for matching was defined as the first week of RMG. Further details on matching procedures and descriptive information about RMG dosing are available in supplement sections E and F.

Patient and public involvement

People with lived or living experience of substance use and/or overdose from across British Columbia were engaged as research assistants and advisors in the broader evaluation project of which this study is a part. They provided input into this specific manuscript at quarterly consortium meetings in which this analysis was reported, findings were discussed, and key messages were identified.

Results

Characteristics of RMG recipients and non-recipients

Among 70 360 people with opioid use disorder, 5356 (7.6%) received dispensations of an opioid RMG medication. Among 41 890 people with stimulant use disorder, 1061 (2.5%) received dispensations of a stimulant RMG medication. A total of 5882 people received dispensations of opioid (91.1%; n=5356) or stimulant (18.0%; n=1061) RMG medications between 27 March 2020 and 31 August 2021. Both opioid and stimulant RMG medications were dispensed to 535 people. The number of people receiving RMG medication dispensations increased from March to May 2020, with an average of 337 (range 51-501) people per month receiving opioid (n=289) or stimulant (n=49) RMG for the first time (supplement section G, figure S7). Among people who received opioid RMG,4281 (80.1%) had RMG opioid dispensations for more than one week intermittently through the follow-up period (supplement section G, table S12). Sample trajectories are shown in supplement G, figure S8. People who received opioid and/or stimulant RMG medication dispensations were predominantly male and a median of 38 (opioid RMG) and 39 (stimulant RMG) years of

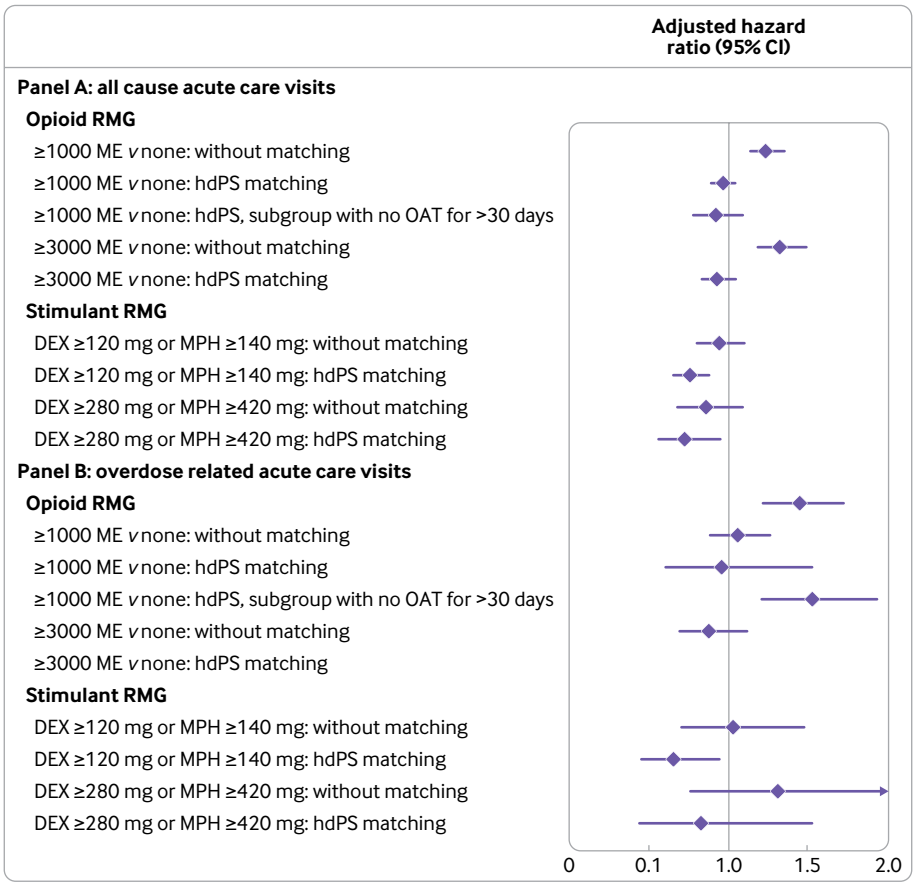

Fig 6 | Sensitivity analyses: primary and secondary outcomes by weekly dose dispensed. DEX=dextroamphetamine; hdPS=high dimension propensity score matching; ME=morphine equivalent; MPH=methylphenidate; OAT=opioid agonist treatment; PS=propensity score; RMG= Risk Mitigation Guidance

age (table 1). A large proportion of people (opioid RMG: 83.0%; stimulant RMG: 79.2%) who received RMG medications had received income assistance in the previous year. Among people who received opioid RMG, 38.1% had unstable housing in the previous year compared with 41.2% of people who received stimulant RMG. After matching by propensity scores, the covariates were balanced between exposed and unexposed groups, indicated by low (<0.1) absolute standardised mean differences (table 1). The crude event rates stratified by status of periods of receipt of RMG opioid medications and by receipt of RMG stimulant medications are described in figure 1 and figure 2, which show concordance in the alternative formulations of control groups.

Mortality

Using the high dimensional propensity score matched cohort and controlling for time varying covariates, we found that one day or more of RMG opioid dispensations was associated with significantly reduced all cause mortality (adjusted hazard ratio 0.39, 95% confidence interval 0.25 to 0.60) and overdose related mortality (0.45, 0.27 to 0.75) in the subsequent week (table 2 and fig 3). Four days or more of opioid RMG dispensations was associated with a strengthening of the protective effect on mortality in the subsequent week. Dispensation of four days or more of RMG opioids was associated with reduced all cause mortality (adjusted hazard ratio 0.09, 0.04 to 0.21) and overdose related mortality (0.11, 0.04 to 0.32) compared with the unexposed group. In sensitivity analysis, we found a similar point estimate for the effect on mortality among people who did not receive dispensations for opioid agonist treatment 30 days before opioid RMG initiation; however, the 95% confidence intervals for the hazard of all cause and overdose related mortality exceeded 1.0 (fig 3). Point estimates and 95% confidence intervals for the weighted regression models are available in supplement section H, table S13 and section I, tables S15 and S16.

In the high dimensional propensity score matched cohort, dispensations of one day or more of stimulant RMG were not significantly associated with reduced all cause mortality (adjusted hazard ratio 0.50, 0.20 to 1.23) or overdose mortality (0.53, 0.18 to 1.56) (table 2 and fig 3). We found similar results when examining overdose related mortality (adjusted hazard ratio 0.45, 0.10 to 2.05) and all cause mortality (0.39, 0.11 to 1.39) for people who received four or more days of RMG stimulant dispensations. Point estimates and 95% confidence intervals for the weighted regression models are available in supplement section H, table S14 and section I, tables S19 and S20. Figure S3

(section E) shows Kaplan-Meier survival plots of all cause mortality using the high dimensional propensity score matched cohort based on RMG receipt at baseline. Log-rank tests indicate a significant (P<0.05) statistical difference in all cause mortality among people who received opioid RMG but not stimulant RMG dispensations.

Acute healthcare visits

In contrast to the associations between the exposure and all cause and overdose related mortality, RMG opioid dispensations were not associated with significant reduction in the odds of acute healthcare visits for overdose or any cause (table 2 and fig 4). Point estimates and 95% confidence intervals for the weighted regression models are available in supplement section I, tables S17 and S18. Dispensations of at least one day or at least four days of RMG stimulants significantly decreased the adjusted odds of acute care visits for any cause among the high dimensional propensity score matched cohort and had no significant effect on overdose related acute care visits (table 2 and fig 4). Point estimates and 95% confidence intervals for the weighted regression models are available in supplement section I, tables S21 and S22.

Dose sensitivity analyses

We did sensitivity analyses of dispensation dose for opioid and stimulant RMG medications to determine whether outcomes varied according to dispensation of low or high dose RMG. We observed a greater protective effect on all cause mortality among people who received high dose compared with low dose RMG opioids (fig 5). Similarly to the main results, we found that RMG opioid dispensations at low and high dosages were not associated with acute care use for overdose or any cause (fig 6).

For RMG stimulants, we found results similar to the main findings that modelled days dispensed. We found that low dose stimulant RMG dispensations (≤120 mg of dextroamphetamine or ≤140 mg of methylphenidate in a given week) were not significantly associated with reduced overdose related and all cause mortality. We were unable to measure the effect of high dose stimulant RMG dispensations (≥280 mg of dextroamphetamine or ≥420 mg of methylphenidate in a given week) on mortality as we observed no substance use related or all cause deaths among recipients of high dose stimulant RMG. Low and high dose weekly dispensations of RMG stimulants were associated with reduced odds of all cause acute care visits. Low dose weekly dispensations of RMG stimulants were associated with decreased overdose related acute care visits (adjusted odds ratio 0.65, 95% confidence interval 0.45 to 0.94).

Discussion

This study found that RMG opioid dispensations were associated with a reduced likelihood of all cause and overdose related mortality among people with a diagnosis of opioid use disorder. The results suggest that a small proportion of people with opioid use disorder (7.6%) received opioid RMG dispensations, and a smaller proportion of people with stimulant use disorder (2.5%) received stimulant RMG dispensations. These findings indicate that RMG medications were not dispensed to most people who are at risk of overdose in British Columbia. The demographic, health service use, and chronic disease profiles of people who received RMG dispensations were similar to the profiles of participants in previous studies on the risk of overdose among people who use substances in British Columbia.[33-36] More men than women received RMG dispensations, echoing demographic trends in overdose and substance use across the population in British Columbia.[23 33 37]

Many people who received opioid RMG dispensations had previous diagnoses of chronic conditions such as alcohol use disorder, indicating that healthcare providers may have been prescribing to people at the highest risk of mortality.[33 34] These trends were similar among people who received stimulant RMG dispensations. The disproportionately high rates of unstable housing and poverty (as indicated by receipt of income assistance) suggest that many people who received RMG dispensations have experienced layered and complex social and economic inequalities that have been shown to contribute to poor health outcomes.[38-41]

Comparison with other studies

The protective effect of RMG opioid dispensations on mortality is congruent with findings from an evaluation of a prescribed opioid safer supply programme in Ontario in which mortality was rare among participants receiving medications and primary care compared with a four to one matched control group of people with opioid use disorder.[42] Previous studies have reported that prescribed safer supply reduced reliance on the illegal drug supply,[43] which may have contributed to reduced mortality risk among opioid RMG recipients. The protective effect of opioid RMG on mortality could also be attributable to the healthcare provided by RMG prescribers to identify and manage health conditions that contribute to premature mortality among people who use illegal opioids.

In our study, RMG stimulant dispensations were not associated with significant reductions in all cause or overdose related mortality. Several clinical trials of RMG stimulant medications (dextroamphetamine and methylphenidate) found reductions in illicit stimulant use and improvements in physical and mental health.[44-47] Nevertheless, these studies have been conducted in controlled clinical settings, intended for the treatment of stimulant use disorder, and have not been implemented with the primary objective of reducing mortality risk in the context of dual public health emergencies of an unregulated drug crisis and covid-19. Additional research is needed with a larger sample size over a longer period to ascertain the effect of stimulant RMG dispensations on mortality.

We observed a dose-response relation, whereby receiving an opioid RMG dispensation on four or more

days was associated with an increased protective effect against all cause and overdose related mortality in the subsequent week to a greater extent than observed with receipt of one or more days of opioid RMG. A chart review of retention on RMG opioids previously conducted in one clinic found that retention increased by 3% for each morphine equivalent of RMG dispensed. This study also reported that dispensations of mental health related medications and continued use of opioid agonist treatment was associated with increased RMG medication retention.[16] Additional research and quality improvement interventions are needed to identify best practices to retain people on opioid RMG to reduce mortality. Promising interventions to increase retention on prescribed medications include providing take-home doses and having peer support workers available to support clients, attend appointments, and deliver medications.[48 49]

We found that opioid RMG dispensations were not associated with acute care use for any cause or for overdoses specifically. These findings contrast with those of a study conducted in Ontario that found that participation in a prescribed opioid safer supply programme with comprehensive primary care reduced emergency department visits and hospital admissions.[42] Risk factors for acute care use among people who received opioid RMG dispensations included having multiple physical and/or mental health chronic conditions and unstable housing in the previous year. These risk factors are similar to those found in previous studies in which previous overdose events and chronic conditions were associated with the future use of acute care for an overdose.[33 38 39 50]

We found that stimulant RMG dispensations were associated with decreased odds of acute care visits for any cause. This may reflect the benefits to be gained by engaging a population in care who have had limited previous access to interventions. For example, in British Columbia, interventions for stimulant use disorder are very limited.[21] Stimulant RMG dispensations may have provided an opportunity for improvement in outcomes to be observed among people with stimulant use disorder who may have been less engaged with healthcare services.

Strengths and limitations of study

The results of this study should be interpreted relative to several strengths and limitations. A strength of this study is the use of linked administrative health data that allowed for population level ascertainment of RMG dispensations, all cause and overdose related mortality, and acute healthcare use in most major hospitals and emergency departments in British Columbia. Within these databases, however, we relied on two algorithms for the identification of RMG dispensations, and although we have modified the case definition with the goal of excluding dispensations for specific causes (for example, prescriptions for pain) we might have misclassified some opioid and stimulant dispensations prescribed for alternative purposes (for example, palliative care, cancer). The algorithms used to identify RMG dispensations were developed in consultation with policy makers, RMG prescribers, and a regional health authority that was conducting surveillance of RMG prescribing. Data on RMG dispensations do not include dispensations from programmes or sites where data are not entered into PharmaNet, such as hospitals. We were unable to determine from linked administrative health data whether people used the medications as prescribed or whether they were transferred to other people (commonly referred to as diversion). The transfer of medications to others is not measurable with existing administrative health data, and additional research is needed to understand the impact of transfers on community substance use. The data for this study were derived from people who had a diagnosis of opioid use disorder or stimulant use disorder, and the results may not be generalisable to other settings or populations, particularly if people are not engaged in healthcare or do not have a diagnosed opioid use disorder or stimulant use disorder.

A protocol paper published in 2021 outlined the proposed methods and structure of the larger mixed methods evaluation of the RMG in British Columbia.[21] The data for this paper extend beyond the date range in the protocol owing to the relatively small sample size of people identified as having received RMG opioid and stimulant dispensations. This paper focused on two primary outcomes—mortality and acute care use—and does not include measurement of other primary outcomes such as SARS-Cov-2 infection that were unavailable at the time of the study. We did not stratify the results for three of the four identified population subgroups (pregnant people, people with criminal legal system involvement, and First Nations people) owing to the relatively small number of RMG prescription recipients among these population subgroups. Although we have shown the robustness of these results at the population level, a longer observation period, with broader intervention uptake, will be needed to determine the extent of heterogeneity across these important population subgroups.

Conclusions

This paper reports results from a broad mixed methods evaluation on the implementation and impact of RMG dispensations during the dual public health emergencies in British Columbia.[21] We found that among people with a diagnosis of opioid use disorder, dispensations of RMG opioids were associated with reduced overdose related and all cause mortality. Pharmaceutical alternatives to the illegal drug supply are promising interventions to reduce the mortality of people with opioid use disorder.

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Ethical approval: Providence Health Care Research Institute and the Simon Fraser University Office of Research Ethics determined that this project was exempt from research ethics board review as per Article 2.5 of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

Data sharing: Owing to confidentiality requirements, the data for this project are not available outside of the immediate research team at Providence Health Care. The protocol used for the evaluation project and further information about coding, case definitions, and data management are available on request from the corresponding author. Data for this publication were provided by Vital Statistics BC, the British Columbia Ministry of Health (PharmaNet, Medical Services Plan, the National Ambulatory Care Reporting System, and the BC Discharge Abstract Database), Perinatal Services BC, the Ministry of Public Safety and the Solicitor General, Ministry of Social Development and Poverty Reduction, and BC Coroner's Service. All inferences, opinions and conclusions drawn are those of the authors and do not reflect the opinions or policies of the data stewards.

The lead authors (the manuscript's guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Study findings will be disseminated through the Provincial Advisory Committee that was assembled to oversee the entire Provincial Prescribed Safer Supply evaluation project. The committee includes people with lived/living experience of overdose and/or substance use who have been engaged in this project from its establishment. We will also disseminate results through the British Columbia Overdose Emergency Response Centre and social media posts through our organisational partners such as the Centre for Advancing Health, British Columbia Centre for Disease Control, and Canadian Institutes for Substance Use Research.

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Web appendix: Supplementary materials