Hot weather and mortality related to acute cocaine, opioid, and amphetamine toxicity in British Columbia, Canada: A time-stratified case-crossover study

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Abstract:	Background: Previous research has reported that cocaine-associated deaths occur more frequently in hot weather. This effect has not been described for other illicit drugs, or for combinations of drugs. The objective of this study was to evaluate the relationship between ambient temperature and risk of mortality related to cocaine, amphetamines, and opioids alone and in combination using vital statistics data from British Columbia, Canada. Methods: All deaths with cocaine, amphetamine or opioid toxicity recorded as an underlying or contributing cause were extracted from BC vital statistics data for 1998-2017. Cases were grouped by drug category and a time-stratified case-crossover design was used to estimate the effect of daily maximum temperature on risk of death associated with acute drug toxicity during the warmer months (May through September). Conditional logistic regression was used to estimate the odds ratio (OR) and the 95% confidence interval (CI) for daily maximum temperatures over the median, 75th and 90th percentiles of the regional distribution. Results: There were 3,058 deaths included in the analyses. The 90th percentile temperature was associated with an OR [CI] of 1.44 [1.02, 2.05] for deaths with only cocaine toxicity recorded. The effect was similar when both cocaine and opioid toxicity were present. The effect

	was most pronounced for cases in which toxicity due to all three drugs was evident, with an OR of 3.11 [1.39, 6.95] for the 90th percentile temperature. Interpretation: Hot weather was associated with higher odds of mortality related to cocaine toxicity, and this was most pronounced when amphetamine and opioid toxicity were also present. Targeted interventions are necessary to prevent death associated with cocaine use during hot weather, especially for users of multiple substances.

Hot weather and mortality related to acute cocaine, opioid, and amphetamine toxicity in British Columbia, Canada: A time-stratified case-crossover study

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Abstract

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Methods: All deaths with cocaine, amphetamine or opioid toxicity recorded as an underlying or contributing cause were extracted from BC vital statistics data for 1998-2017. Cases were grouped by drug category and a time-stratified case-crossover design was used to estimate the effect of daily maximum temperature on risk of death associated with acute drug toxicity during the warmer months (May through September). Conditional logistic regression was used to estimate the odds ratio (OR) and the 95% confidence interval (CI) for daily maximum temperatures over the median, 75th and 90th percentiles of the regional distribution.

Results: There were 3,058 deaths included in the analyses. The 90th percentile temperature was associated with an OR [CI] of 1.44 [1.02, 2.05] for deaths with only cocaine toxicity recorded. The effect was similar when both cocaine and opioid toxicity were present. The effect was most pronounced for cases in which toxicity due to all three drugs was evident, with an OR of 3.11 [1.39, 6.95] for the 90th percentile temperature.

Interpretation: Hot weather was associated with higher odds of mortality related to cocaine toxicity, and this was most pronounced when amphetamine and opioid toxicity were also present. Targeted interventions are necessary to prevent death associated with cocaine use during hot weather, especially for users of multiple substances.

Introduction

Psychoactive substances act on the brain to change mood, perception, and behaviour, but differ in their mode of action and effects on the body. Some of these effects and their accompanying health risks can be exacerbated by environmental conditions. Both cocaine and amphetamines are psychostimulants that can increase levels of dopamine in the brain (1). Cocaine use increases the risk of many life-threatening health outcomes, including convulsions, kidney failure, cardiovascular emergencies, and brain hemorrhage (2) and is one of the leading causes of drug-related deaths in North America (3). Cocaine also causes a hypermetabolic state that increases body temperature, and its associated health risks are higher during hot weather (2). Opioids act on nerve cells, induce analgesia and euphoria via effects on the peripheral and central nervous systems, respectively (4). Opioids include legally prescribed analgesics such as codeine, oxycodone, hydrocodone, morphine, hydromorphone, and fentanyl, as well as illicit drugs such as heroin. There has been an ongoing crisis worldwide due to entry of the synthetic opioids fentanyl and carfentanyl into the illicit drug supply (5).

Two ecologic studies in New York, USA and one individual-level study in Quebec, Canada have reported that cocaine-associated mortalities occur more frequently in hot weather (6–8). Broadly, three underlying mechanisms may explain this observation: (I) increased heat production due to agitation and delirium and associated muscular activity; (II) reduced heat dissipation due to central inhibition of sympathetic outflow to cutaneous vasodilatory and sudomotor targets; and (III) reduced sense of discomfort in the face of heat stress which inhibits heat avoidance behaviours (2,9–12). While the risk of opioid use is higher during cold weather, increased risk has not been shown during hot weather (6,7,13). The effects of hot weather on the risk of death due to amphetamines have not been examined to date. The objective of this study was to evaluate

the relationship between hot weather and mortality associated with cocaine, amphetamine, and opioid toxicity when present in the vital statistics death record, either alone or in combination, using a time-stratified case-crossover design.

Methods

Study area and period

British Columbia (BC) is the westernmost province in Canada, with a landmass covering 944,735 km^2 and spanning 25 degrees of longitude and 11 degrees of latitude. The current population is approximately 5.0 million people, most of whom live in the temperate southwestern region where the average daytime high is 22°C during the summer months. Temperatures are higher in the arid interior region, located between the Coast Mountain and Rocky Mountain ranges, and lower in the sparsely populated northwestern region. The study examines the relationship between overdose mortality and hot weather during the warmer months (May-September) of the 20-year period from 1998-2017.

Outcome: death associated with illicit drug toxicity

Vital statistics data on all deaths in BC are made available to the BC Centre for Disease Control (BCCDC) for environmental health surveillance and assessment. The death records include date of death, underlying and contributing causes of death, age, sex, and residential 6-digit postal code. Deaths associated with cocaine, amphetamines, or opioids were identified based on the 10th revision of the International Classification of Diseases (ICD-10).

Deaths attributed to specific drugs can have an ICD-10 code starting with T (acute toxicity) or F (chronic use). While coding practices differ across agencies, BC Vital Statistics uses the US National Vital Statistic System guidelines (14) and will only use a T code when a coroner

specifies known overdose, poisoning, or toxicity due to a specific drug. All deaths from May-September 1998-2017 with any T code for cocaine, opioid, or amphetamine toxicity as a primary or secondary cause were included in the analyses. Many of these deaths also had an F code for chronic drug use as an underlying or contributing cause (Table 1). As a comparator, deaths with only an F code for chronic cocaine, opioid, or amphetamine use were also examined. Deaths without a T code and with F codes for more than one of the three drugs were excluded from the comparative analyses.

Exposure: daily maximum temperature

The complex topography of BC creates many microclimates, and there are clear differences in heat-related health risks across the province (15,16). Our previous work has identified 32 zones for use in the BC Heat Impacts Prediction System (BCHIPS), which forecasts health risks associated with high temperatures during the summer months (https://maps.bccdc.ca/bchips/). The death records were linked with temperature information for one of the 32 zones based on the residential 6-digit postal code of the decedent. In addition, we extracted all daily maximum temperature observations for the 32 zones from May-September for the study period. These data were used to characterize the typical warm weather median, 75th percentile, and 90th percentile temperatures for each zone (Figure 1).

Study design

A time-stratified case-crossover design was used to describe the effect of temperature on deaths associated with cocaine, opioid, and amphetamine toxicity. The case-crossover design was developed to study the immediate determinants of acute onset disease (e.g., myocardial infarction) and to avoid selection and information bias (17). This method had been widely applied in diseases and mortality risks related to air pollution (18–21), temperature (22–25), and

adverse drug events (26,27). The case-crossover design is suited for acute outcomes caused by transient exposures and can avoid confounding effects of factors that do not vary over the short-term, such as sex, age, social-economic status, lifestyle, underlying comorbidities, and seasonality (17). It also allows for examination of effect modification by stratification.

To evaluate the association between the outcome and the exposure, the maximum temperature on the day of death (event date) was compared with the maximum temperatures for similar dates on which the death did not occur (control dates). The control dates were selected with the time-stratified bidirectional referent approach, meaning that they were matched by day-of-week and calendar month to the death date for each individual. All temperatures were categorized to indicate whether they were greater than the median, 75th percentile, and 90th percentile temperatures for the microclimatic zone (Figure 1).

Statistical analysis

All deaths with cocaine, opioid, and amphetamine toxicity (T codes) were stratified into one of seven groups based on the ICD-10 codes present in the vital statistics record: (I) cocaine only; (II) opioid only; (III) amphetamine only; (IV) cocaine + opioid; (V) cocaine + amphetamine; (VI) opioid + amphetamine; and (VII) all three drugs. Conditional logistic regression was used to estimate the odds ratios (OR) and 95% confidence intervals (95% CI) for the association between temperature category (over the median, 75th, and 90th percentile for the zone) and mortality among these groups. Subgroup analyses were also conducted by sex and by residence within or outside of the greater Vancouver metropolitan area. Finally, analyses were repeated for deaths that had one chronic drug use (F code) but no acute toxicity (T code) present in the vital statistics record. This was to better evaluate whether effects were associated with drug use in general, or

with acute toxicity. The R statistical computing environment version 3.5.1 was used for all data management, analysis, and visualization (28).

Results

Study subjects

During the May-September months of 1998-2017 there were 3058 deaths with acute cocaine, opioid, or amphetamine toxicity (T code) present in the vital statistics record. Of these, 488 (16.0 %) had cocaine only, 1426 (46.6%) had opioids only, 111 (3.2%) had amphetamines only, and 1033 (33.8%) had more than one of the three drugs. The mean age at death was approximately 41 years, 72.7% of decedents were male, and 53.9% lived in greater Vancouver, where approximately half of the provincial population resides (Table 2). During the same period there were 553 deaths that only had chronic cocaine use (F code) present in the vital statistics record; they did not have codes for chronic opioid or amphetamine use, nor for acute toxicity from any of the three drugs. There were 235 deaths that only had chronic opioid use and 82 that only had chronic amphetamine use.

Primary analysis

In the regression models, odds of mortality generally increased with increasing temperature for all seven categories of drug combinations (Figure 2). However, the odds ratios (ORs) and 95% confidence intervals (CIs) were only significantly increased when acute cocaine toxicity was present, either alone or in combination with other drugs. When cocaine toxicity was present alone (N=488), temperatures over the regional median, 75th, and 90th percentiles were all associated with increased risk and OR [CI] values ranged from 1.33 [1.05, 1.68] for the median to 1.44 [1.02, 2.05] for the 90th percentile. When cocaine was present with opioids (N=754) the

ORs were smaller for the median and 75th percentile temperatures, but similar for the 90th percentile at 1.40 [1.07, 1.84]. The combination of cocaine and amphetamines is more difficult to interpret, due to very small numbers (N=37). When all three of cocaine, opioids, and amphetamines were present (N=103), risk was clearly elevated for all thresholds, ranging from 1.65 [1.00, 2.72] for the median to 3.11 [1.39, 6.95] for the 90th percentile (Figure 2).

Secondary analyses

When the same models were applied for death records with chronic (F code) drug use but not acute toxicity (T code), the odds ratios generally decreased for increasing temperatures (Figure 3). Deaths with chronic use of cocaine were the exception, though the ORs were smaller than those for acute cocaine toxicity and they were not statistically significant. Subset analyses by sex and residential location were restricted to models for temperatures over the zonal 90th percentile. These showed that females were at higher risk than males, even though most deaths occurred among males (Figure 4). For deaths with acute cocaine toxicity alone, the OR [CI] was 2.36 [1.17, 4.75] for females (N=107) compared with 1.24 [0.83, 1.86] for males (N=381) suggesting that the female group drove the overall OR of 1.44 [1.02, 2.05]. For deaths with acute opioid toxicity alone, the OR [CI] was 1.52 [1.08, 2.13] for females (N=436) compared with 0.98 [0.76, 1.25] for males (N=990), where the overall OR of 1.13 [0.93, 1.38] indicated no significant risk. There were no clear differences by residential location, even though greater Vancouver is generally cooler than other parts of BC (Figure 1).

Interpretation

Overall, there was clear evidence that odds of cocaine-related mortality were higher on hot days, and that the combination of cocaine, amphetamines and opioids was particularly risky.

Temperatures over the zonal 90th percentile were associated with a 44% [2%, 105%] increase in odds of mortality when acute cocaine toxicity was present. The effect of higher temperatures was most pronounced for deaths where toxicity associated with all three drugs was present.

Our findings are consistent with the small body of epidemiologic evidence on this topic (6–8). Auger et al. (2017) studied 762 cases of death involving cocaine during the summer months of 2000-2013 in Quebec, Canada using a similar case-crossover design. They reported that a maximum temperature of 30°C was associated with an OR of 1.53 [1.03, 2.27] for death involving cocaine toxicity (T codes), compared with a maximum temperature of 20°C (6). Marzuk et al. (1998) studied 2,886 cases involving unintentional drug overdose from 1990 to 1995, in New York, USA. They compared three mutually exclusive case groups (cocaine, opioids, and other drugs) with two other groups (homicides and deaths from motor vehicle crashes). Mortality involving cocaine was 33% higher than on hotter days than on cooler days, where the threshold value was 31.1°C (7). Bohnert et al. (2010) reported a similar conclusion in their study from 1990 to 2006 in New York, USA, but with a substantially lower temperature threshold of 24°C (8).

Several mechanisms are potentially related to the higher risk of mortality for cocaine users in hot weather. Previous studies have reported hyperthermia caused by cocaine, mediated by increased heat production, and reduced heat dissipation. The conventional view suggests that hyperthermia in cocaine users can be predominantly attributed to a hypermetabolic state, where heat production increases dramatically by agitation and increased muscular activity (29). This is supported by the work of Ansah et al. (1996), who observed a significant increase in locomotor activity in rats when cocaine was repeatedly injected (9). Crandall et al. (2002) conducted a double-blind trial to study the effects of cocaine on human body temperature regulation, and

found delayed onset of thermoregulatory responses (e.g., cutaneous vasodilation and sweating) and attenuated feelings of discomfort. They concluded that the hyperthermic effect of low dose cocaine was mainly related to impaired temperature dissipation rather than augmented heat production (2).

We observed that concurrent exposure to both amphetamines and cocaine had an additive effect on odds of mortality in hot weather. One possible explanation is that both drug classes lead to heat generation and reduced heat dissipation through different mechanisms, including (I) inhibition of neuronal receptors resulting in elevated synaptic dopamine levels (30–32), and (II) increased brain serotonin levels leading to increased body temperature (33,34). There is also evidence that "speedball" (taking stimulants and opioids in combination at low doses) synergistically enhances locomotor activity and hyperactivity. Studies in humans have found that stimulant-opioid combinations produce cardiovascular and subjective effects that differ from the effects produced by either drug alone (35–37).

Our finding of increased risk of cocaine death on hot days in females is consistent with sex-linked differences in the effects of cocaine in rats. Several *in vivo* studies have shown that intrinsic sex differences in drug metabolism result in variation in the levels of active drug metabolites between males and females (38–40). In response to cocaine, female rats were found to have increased striatal dopamine levels (41) and serum adrenocorticotropic hormone secretion (42) compared with male rats. Several rodent studies have also shown higher rotational sensitivity and locomotor activity in intact female rats than in male and ovariectomized female rats (43–45). Together, these studies suggest an interaction between ovarian hormones and cocaine metabolism and cocaine-induced effects.

Our study has some important limitations. Although there are many potential mechanisms that could explain our observations, we cannot discount the possibility that our findings are confounded by heat and cocaine-associated behaviours. It is possible that cocaine use is more likely to occur on warmer rather than cooler days, or that cocaine users are more likely to engage in risky behaviour on hotter days. Both alternative hypotheses could explain, at least in part, the observed association. Individuals were matched to temperatures based on their residential 6-digit postal code in the vital statistics record, but they may not have been exposed at these locations on the date of death or the control dates. Finally, the vital statistics records do not include any information on the toxic dose of drugs present at the time of death, meaning that we cannot evaluate the degree of intoxication, only the fact of intoxication. All these limitations are shared by similar studies on the topic (6–8).

This study found that hotter temperatures were associated with a higher risk of mortality when the code for acute cocaine toxicity was present in the vital statistics record. The effect was more pronounced when cocaine was combined with both opioids and amphetamines, and risk was higher in females than males. The mechanism is likely related to the hyperthermia effects caused by cocaine, which had been demonstrated in human and animal studies. Further research is necessary to investigate the interaction between cocaine, opioids, and amphetamines, and to evaluate whether this interaction can be observed consistently in other settings. Targeted interventions are necessary to prevent death from drug toxicity during hot weather, especially for people who use multiple psychoactive substances.

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Table 1. International Classification of Disease (ICD-10) codes for deaths related to toxic (starting with T) and chronic (starting with F) use of cocaine, opioid, and amphetamines. These totals are not mutually exclusive; any death with codes for multiple drugs is counted here for each of those drugs. All deaths with a T code (first row for each drug) were included in the main analyses, and any deaths with an F code for only one of the drugs were used as a comparator.

Code	Description	Number of deaths included in study (number with code as the primary cause)
Cocaine		
Any T405	Poisoning by or adverse effect of cocaine.	1382 (0)
Any F140-F149	Cocaine related mental and behavioral disorders.	1195 (42)
Both T and F code present		438
Only F140-F149		757
Opioids		
Any T400-T404 or T406	Poisoning by or adverse effect of opioids.	2422 (0)
Any F110-F119	Opioid related mental and behavioral disorders.	870 (12)
Both T and F code present		498
Only F110-F119		372
Amphetamines		
Any T436	Poisoning by or adverse effect of psychostimulants.	390 (0)
Any F150-F159	Psychostimulant related mental and behavioral disorders.	262 (3)
Both T and F code present		116
Only F150-F159		146

Table 2. Summary information for all deaths included in the main analyses, with cocaine, opioid, or amphetamine toxicity (T code) present in the vital statistics record.

	Cocaine only	Opioid only	Amphetamine only	More than one drug
Median Age	42	44	38	39
	Number of deaths (percentage)			
Sex				
Female	107 (21.9%)	436 (30.6%)	28 (25.2%)	266 (25.8%)
Male	381 (78.1%)	990 (69.4%)	83 (74.8%)	767 (74.2%)
Region				
Greater Vancouver	271 (55.5%)	669 (46.9%)	80 (72.1%)	628 (60.8%)
Rest of BC	217 (44.5%)	757 (53.1%)	31 (27.9%)	405 (39.2%)
Regional percentile of maximum temperature (°C) on date of death				
< 50%	232 (47.5%)	714 (50.1%)	54 (48.6%)	495 (47.9%)
50-75%	116 (23.8%)	332 (23.3%)	27 (24.3%)	233 (22.6%)
75-90%	80 (16.4%)	216 (15.1%)	19 (17.1%)	179 (17.3%)
>= 90%	60 (12.3%)	164 (11.5%)	11 (9.9%)	126 (12.2%)
Total	488	1426	111	1033

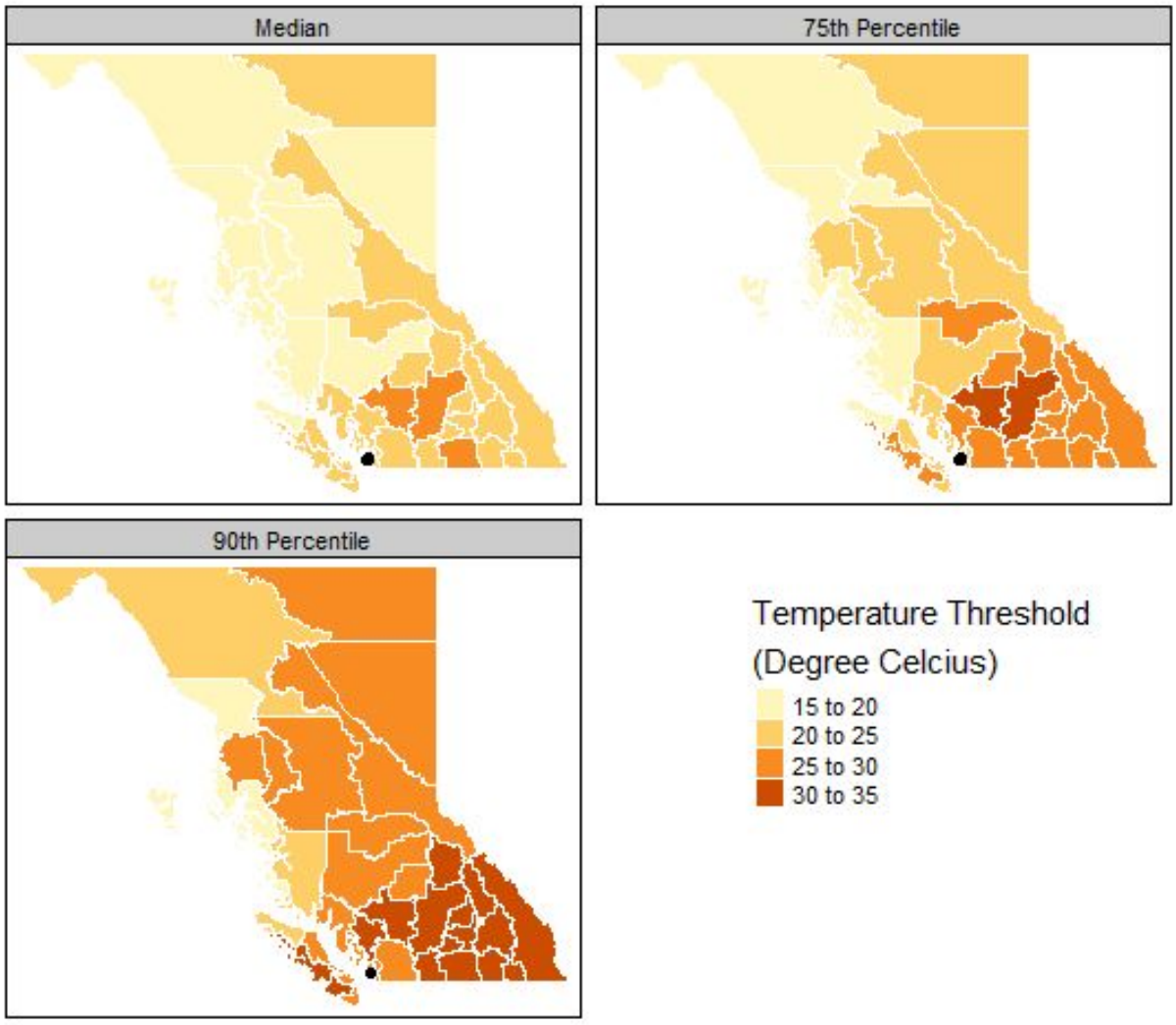

Figure 1. Thresholds corresponding to the median, 75th percentile and 90th percentile for the 32 temperature zones in British Columbia, Canada. The greater Vancouver area is indicated by the black dot.

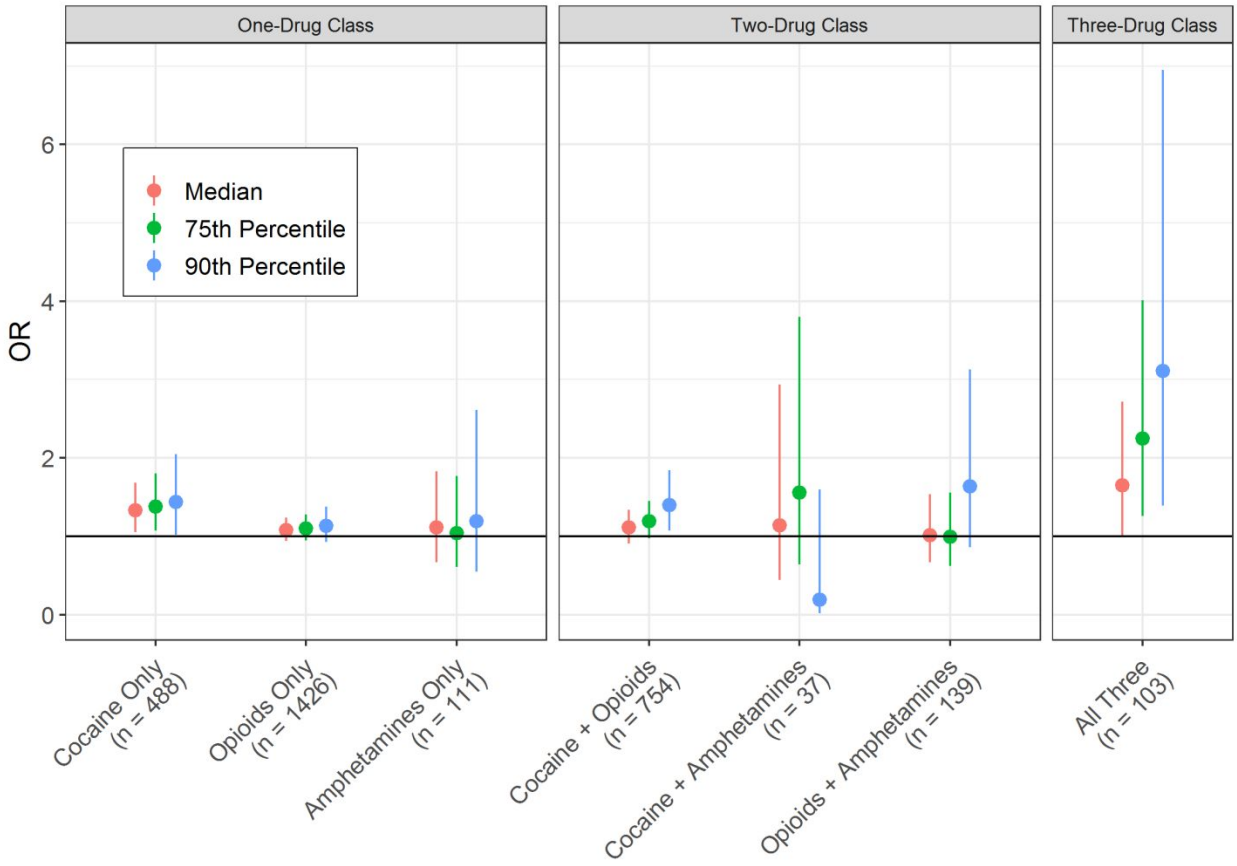

Figure 2. Odds ratios (ORs) and 95% confidence intervals for mortality associated with acute cocaine, opioid, and amphetamine toxicity (T code) on May-September days with maximum temperatures over the zonal median, 75th, and 90th percentiles.

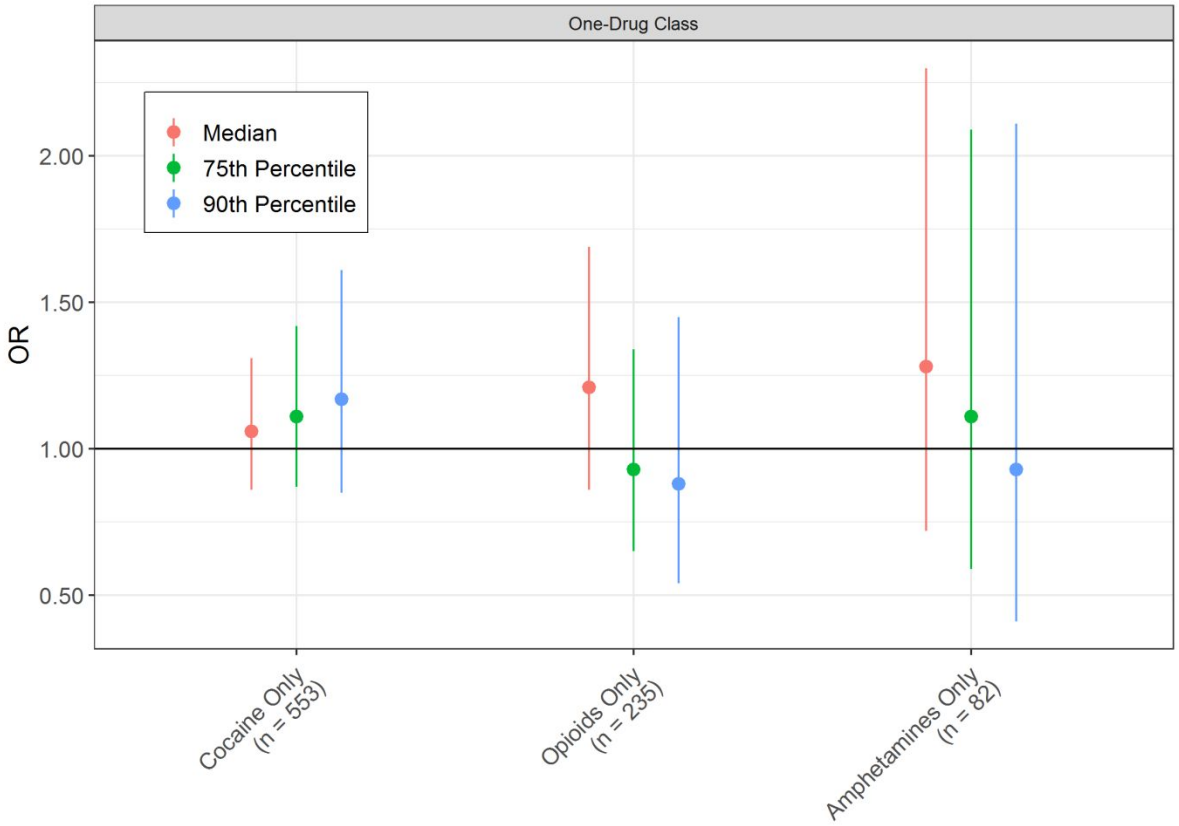

Figure 3. Odds ratios (ORs) and 95% confidence intervals for mortality associated with chronic cocaine, opioid, or amphetamine use (F code) without evidence of acute toxicity (T code) on May-September days with maximum temperatures over the zonal median, 75th, and 90th percentiles. Analyses include deaths with an F code for a single drug, and no T codes for any of the drugs.

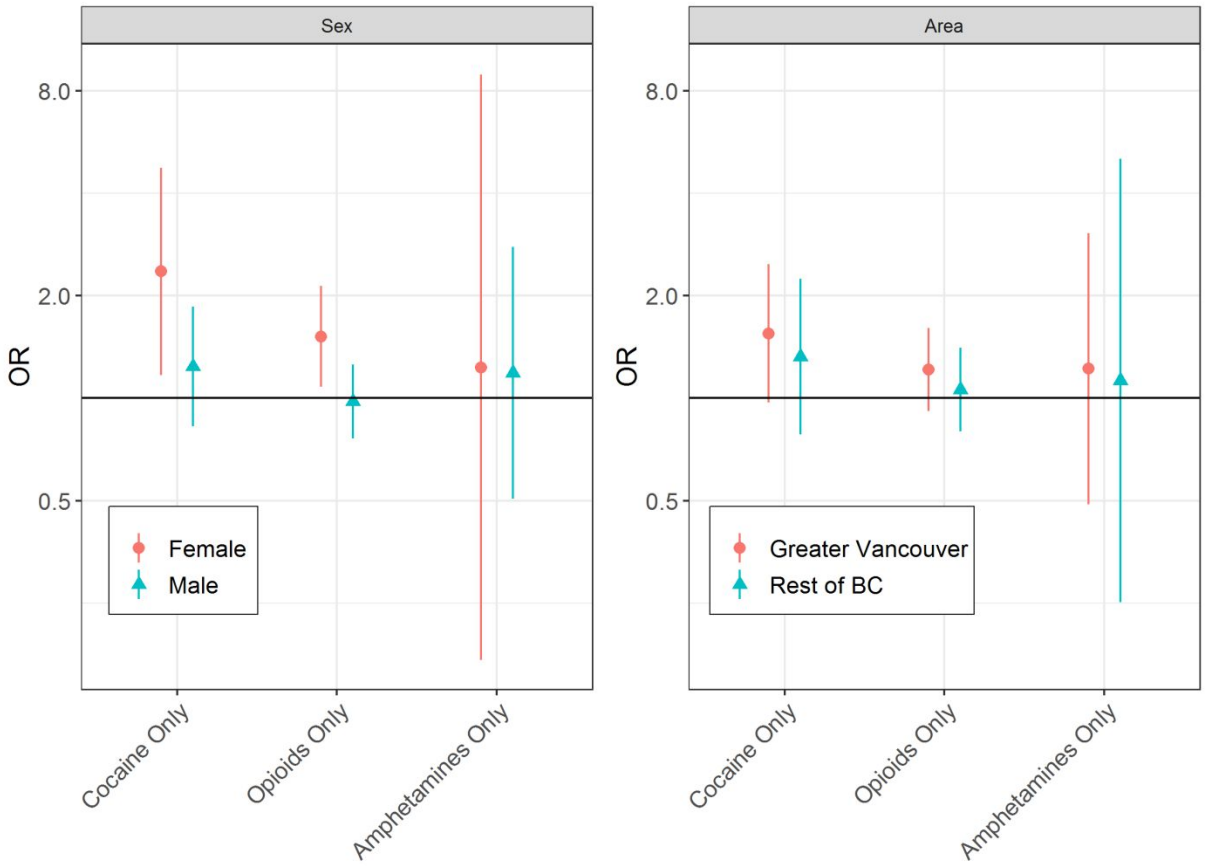

Figure 4. Odds ratios (ORs) and 95% confidence intervals for mortality associated with acute cocaine, opioid, and amphetamine toxicity (T code) on days with maximum temperatures over the zonal 90th percentile, stratified by sex (left) and residential location (right).

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies*** (or ***case-crossover***)

	Item No	Recommendation	Line Nos
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	29-40
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	46-70
Objectives	3	State specific objectives, including any prespecified hypotheses	68-70
Methods			
Study design	4	Present key elements of study design early in the paper	68-70
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	73-80
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	82-95 108-123
		(*b*) For matched studies, give matching criteria and the number of controls per case	108-123
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	81-106
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	81-106
Bias	9	Describe any efforts to address potential sources of bias	125-136
Study size	10	Explain how the study size was arrived at	82-95 138-147
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	98-106
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	125-137
		(*b*) Describe any methods used to examine subgroups and interactions	125-137
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how matching of cases and controls was addressed	108-116
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	139-148 Table 1
		(b) Give reasons for non-participation at each stage	N/A

		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure	Table 2

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	145-159 Figure 2
		(*b*) Report category boundaries when continuous variables were categorized	Figure 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	162-175 Figure 3-4
Discussion			
Key results	18	Summarise key results with reference to study objectives	177-181
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	224-235
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	194-214
Generalisability	21	Discuss the generalisability (external validity) of the study results	182-193
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.