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Title: 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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Reviewer 1: Karim Ladha
Institution: Department of Anesthesia, St Michael's Hospital
General comments (author response in bold)

The authors conducted a case-crossover study to investigate the association between hot weather and acute drug toxicity. Overall, I found the study interesting and well-written, however I do have some concerns listed below:

In the introduction, there is a strong argument made to test for the association between cocaine and hot weather. However, it is unclear why there would be a relation between opioids or amphetamines and hot weather. In other words, the justification for the hypothesis and need for the study should be made more explicit in the introduction.
More information has been added to the last paragraph of the introduction. In brief, we wanted to examine opioid toxicity due to the ongoing crisis in British Columbia and across Canada. We wanted to examine amphetamine toxicity because its biological effects are similar to those of cocaine.

I am familiar with case-crossover studies but not with the “time-stratified bidirectional referent approach”. From the description it is unclear what the control dates were. Either more description or a figure would be useful.
More information has been added, and a specific example is now included in the text as described above.

The need to standardize temperatures by percentiles across zones is not justified in the manuscript. I am unsure why relative temperature to usual climate is more important than simply the absolute temperature. Analyzing the associations in terms of actual temperature would also help with the interpretation of the results to places that might be generally hotter or colder than BC.
Further, the categorization of temperature causes a loss of information. How were these categories chosen? Using a continuous exposure and accounting for non-linearity may reveal a potential temperature threshold at which the risk is increased which could then inform future interventions.
We now use absolute temperatures in the analysis and include a comparison with the 90th percentile temperatures, as described above. However, we did examine non-linearity in the temperature-mortality relationship because regionality does matter. Instead, we show stratified results by different climatic regions in BC.

Was there any adjustment for multiple testing?
We did not adjust for multiple testing. The deaths included in each model are mutually exclusive.

Perhaps another limitation is that non-fatal overdoses were not captured in the study.
The objective of our study was to examine mortality associated with drug toxicity, a hard endpoint that is relatively easy to measure. A study on overdose would need to consider non-fatal overdoses, which are challenging to measure.

The study takes place over a long span of time. Why not test for effect modification in relation to time since the healthcare system's ability to deal with acute toxicity has likely changed as perhaps coding practices.
This question would be better addressed with a conventional time series analysis. The case-crossover design is self-matched and controls for potential confounders that do not vary over short periods, such as treatment and coding practices. It would be interesting to evaluate this question in the context of the warming climate in BC and elsewhere. That was not the objective of this assessment, but we have added a note about climate change to the conclusions.

Given that the analysis was conducted with 7 categories table 2 should reflect that as well. Also, a row with the total number of patients in each category would be helpful.
Sincere apologies again, but we missed this comment in the revised document. We will address this in the next round if we get the opportunity. Note that the total number is in the top row of the table.

Reviewer 2: Irina Kudrina
Institution: Faculty of Medicine, Family Medicine, McGill University
General comments (author response in bold)

Thank you for the opportunity to review this manuscript. There are six authors with excellent qualifications in public and environmental health.
The objective of this study was to evaluate the relationship between temperature and risk of mortality related to cocaine, amphetamines, and opioids in British Columbia, Canada using BC vital statistics data for 1998-2017.
The time-stratified case-crossover design is appropriate for this type of question.
I have several serious and minor concerns about this work, which I will list below.
The legal (medically prescribed) and illegal (pharmaceutical, non-pharmaceutical and mixed) use have different risks of mortality and should be, as much as possible, analyzed, interpreted, and described separately. For example, IV heroin use presents a very different risk of death as compared to regular codeine use for back pain. Similarly, someone whose ADHD is treated with Ritalin for life cannot be compared with a person who uses illegal stimulants and cocaine chronically. This should be reflected in the study design.
This is an excellent point, and we have gone carefully through the manuscript to ensure that it refers to drug toxicity without suggesting a drug source.
We are limited to the information we can derive from vital statistics records, which are not generated for research purposes. Vital statistics in BC code according to this resource: https://www.cdc.gov/nchs/data/dvs/2a_2016.pdf, which is referenced in the text. Page 161 states, "Interpret all these statements to mean poisoning by drug and code as poisoning whether or not the drug was given in treatment," referencing the T codes we have used here. We have added this to the methods.
Our conversations with the coroners have indicated that they will not include a T code unless poisoning by the drug was indicated by a toxicological report. We have added this information to the methods. We assume that any medications that include these drugs would not be prescribed at a poisonous dose, though a poisonous dose may occur through accident or misuse. Further interpretation of the vital statistics codes may indicate whether medications were implicated in the

poisoning, as might linkage with pharmaceutical dispensation data. However, this level of scrutiny was beyond the scope of our study question, which was to assess the association between drug toxicity deaths and temperature, regardless of the toxic source.
Similarly, there is no simple mechanism to differentiate F codes for mental and behavioural disorders from illicit drugs versus those who use medications.

Several alternative explanations were mentioned in the discussion however, they could these findings be expanded based on the recent literature and trends on the black market? Would for example, part of these deaths be attributable to the summertime tourism, gatherings at concerts, partying in airconditioned spaces and sharing of experimental substances, stronger stimulants, and an increased popularity of some party drugs? I would assume that a densely populated Vancouver core has more deaths and different drug supply than remote rural areas. Yet, I would not expect these differences affect chronic user of prescribed medications neither in terms of temperature exposure nor in terms of their residential code.
Tourists are excluded from these analyses because they do not have residential postal codes in British Columbia. As noted, we have suggested that hotter temperatures may be associated with more drug use for the reasons suggested. There are more deaths in the greater Vancouver area, which is included in the coastal climatic region and is now discussed in the results. Once again, we are not easily able to differentiate between illicit and prescribed drug use in these analyses and have adjusted the language throughout the manuscript accordingly

Exposures to all three classes of substances, from legal and illegal supply, have changed significantly in the past 20 years, so did the temperatures. This should be reflected in your work and discussed accordingly.
This question would be better addressed with a conventional time series analysis. The case-crossover design is self-matched and controls for potential confounders that do not vary over short periods, such as drug supply and pharmaceutical advances. Again, it would be interesting to evaluate this question in the context of the warming climate in BC and elsewhere. That was not the objective of this assessment, but we have added a note about climate change to the conclusions.

When analyzing mortality trends, most important substances that significantly increase mortality risks are benzodiazepines, cannabis and alcohol. How were these accounted for? If they were not, why authors chose not to? Please, explain.
We did not account for these substances, as they were beyond the scope of the research question. Our objective was to evaluate the association between drug toxicity mortality and temperature. Further study could be done to assess the association with these other substances.

Please, add a sentence explaining why this study is important and what it will contribute to the existing literature.
We have added this as the final sentence of the introduction.

Line 40. “Most pronounced when amphetamine and opioid toxicity were also present”. This is probably about the ICD categorization by the coroner? This needs to be distinguished from the colloquial use for clinical toxicity of individual substances. Please, clarify this sentence.

This sentence has been removed. It has also been clarified that the T codes only appear when poisoning by the drug has been confirmed with laboratory testing.

Line 52-55. “Opioids act on nerve cells, induce analgesia and euphoria via effects on the peripheral and central nervous systems, respectively”. This is technically correct. I would still porose a better wording: “Opioids affect multiple organ systems, including central and peripheral nervous system. Strong opioids such as morphine, oxycodone, hydromorphone, and especially fentanyl and its derivatives carry significant risk of acute toxicity and fatal outcome if used inappropriately.” Or something similar.
Thank you. This information has been added.

Line 62. “Sudomotor targets” – Was it meant to be “sudomotor function”?
Correct.

Line 64. “While the risk of opioid use is higher during cold weather” – please add an explanation of this phenomenon like you did it for cocaine few sentences prior. Please, use this further in the discussion, including for the mixed use.
Potential mechanisms underlying the association between cold weather and opioid toxicity have been added to the introduction. More information on mixed use has been added to the discussion.

Line 76-78. Hotter and cooler regions are mentioned. Please, explain how these regions are compared in terms of the outcome of interest (mortality rates), availability of these drugs, access to services (odds of death prevention, for ex.), population density, alternative activities (like gym, parks) etc. Some basic descriptors would help to understand the context. For example, student and tourist-populated areas will likely be higher risk of exposure and death if compared to middle class suburbs.
Our interest is in climatic differences across BC rather than localized differences within these climatic regions. We have added a new sub-group analysis by the same climatic zones we have used in other studies of temperature and mortality outcomes in the province. Summary information has been given for each region, along with a table of temperatures.

Line 84. ICD-10 was introduced in Canada around 2000. Data covered in this study is from the period of 1998-2017. It is possible that some deaths from this sample were classified using ICD-9, possibly for 5-6 years. Please, expand this sentence to include a clarification and discuss in Limitations how this affects your data and your conclusion.
All data in the study were coded according to the ICD-10. The ICD-10 was first adopted for vital statistics data in BC in 2004, and records from previous years were cross-walked. Given the specificity of drug toxicity coding, we do not feel that this change affected our study results. Indeed, the subset analyses for the post-2004 data (to compare the location of residence with the location of death) show that results are consistent with the 1998-2017 results.

Line 89. “overdose, poisoning, or toxicity due to a specific drug” I propose less stigmatizing wording: “Legal or illegal drug poisoning event”.
The language has been changed.

Line 92-95. Last 2 sentences are confusing. Deaths with F code for one of the drugs were examined, and when 2-3 drugs were used chronically, these deaths were excluded? Please, clarify or give an example.

We have clarified that deaths with F codes for more than one drug were excluded.

Line 102. Please, comment if there was any possibility to identify if the death occurred within this residential code area?
We have now included a subgroup analysis comparing results by location of residence and location of deaths for deaths after 2004.

Line 133. “This was to better evaluate whether effects were associated with drug use in general”. Are we talking about legal or illegal drug use? Would a person using Ritalin for ADHD or cancer patient on fentanyl and polypharmacy identified as different category from chronic IV heroine users?
Technically, the same codes would be used. It would be interesting to evaluate how often these F codes are used associated with prescribed medications, but that would require data linkage beyond the scope of this study.

Line 164. Comment: “OR were smaller”. Cocaine use is still a non-medical use, even if stable. Cocaine and illegal opioid users' behaviors are known to be very different. Please ensure to return to this finding and include this into you further discussion.
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). This is a very interesting Figure, showing decreasing risk of mortality for opioids and amphetamines only. Its discussion should be added to the text and compared with other findings.
Based on comments from the editor and this reviewer, we have added more details about the results to the Results section (including odds ratios and Ns to contextualize confidence intervals). We have also highlighted the finding in the first paragraph of the discussion to indicate that the association between temperature and cocaine-related mortality may have acute and chronic contributions. This makes sense, given that cocaine use affects acute and chronic cardiovascular outcomes.

Reviewer 3: Ann Jolly
General comments (author response in bold)

This is an interesting approach to an important question into overdose and drug related deaths in British Columbia, which experiences some of the highest drug related deaths in Canada. It is important because the topic is widely applicable to many international jurisdictions. In addition, the methods used by the researchers are innovative and likely to produce accurate and precise results. Briefly, the researchers extracted detailed death records which recorded causes of death being toxicity resulting from drug use, and/or chronic drug use. They also were able to determine types of drug use, cocaine, opioids or amphetamines, or combinations of these. They also defined places where deaths occurred by 6-character postal code, through which they obtained temperature data, for which they determined median 75th and 90th percentiles for heat. The case-cross over design allows them to measure differences in mortality in times of cooler weather for the same group of people compared with those during warmer weather. They find that people who use cocaine are at highest risk of death in hot weather, and of those women are at higher risk than men. Polydrug users who used cocaine were also at high risk of death in hot weather than in cooler weather.
I think this paper is innovative and has an interesting approach to a difficult topic. The authors have used secondary data to address a problem which is a very important cause

of premature life lost and is preventable. The careful recording of drug related deaths is noteworthy, as is their elegant method of analysis; the case crossover design. From what I understand this method allows for the group of individuals under study to act as their own controls over a period of time when the exposure – in this case high temperatures does not exist. When temperatures then are higher, the mortality rate is then compared with that of the time with cooler temperatures. The use of this method produces a sensitive measure with low biases of place of residence. which is correlated both with temperature, and with low socioeconomic housing conditions.
Secondary data is an important method of studying risk in this group of people as interviews are difficult to conduct and may yield variable results.
Last and most important the authors have contributed new knowledge to explain a proportion of the drug related deaths, which due to climate change are likely to increase, in many areas of the world.

We appreciate that the reviewer has found the analyses to be valuable, despite the many limitations of using secondary administrative data. We thank the reviewer for highlighting the climate change context, which we have now included in the introduction and discussion sections.

This paper is important and should be published after the following comments have been addressed.
The authors use the term case crossover study several times in the paper, though the method is not clearly defined. To reach the highest number of readers I would encourage the authors to insert a sentence or two on how the method works.
We have added more information about the case-crossover design and how we have used it. We have also moved the Study Design section to the first subsection of the Methods, so readers have more information about the design as they read other parts of the manuscript. Thanks again to the editor and reviewers for these suggestions.

Once this is done, the tables and figures should clearly reference or refer in the text what the reference group/time refers to along with the interpretation. For example, " The 90th percentile temperature was associated with an OR [CI] of 1.44 [1.02, 2.05] for deaths with only cocaine toxicity recorded, indicating that the people who used cocaine were 1.44 times more likely to die when temperatures exceeded the 90th percentile of the highest temperatures recorded over … period..in that area"
We have now switched the exposure metric to a 1C increase in temperature for most of the analyses. We have tried to ensure that the temperature metric is clearly stated when the results are reported.

The authors state in their limitations that the precise location of people when they die is unknown, and so may not be represented precisely by the 6-character postal code recorded at the time. While this is true other work has shown that street involved people cluster in space, and in one study the diameter of the places where use drugs, hang out and reside is only 3km; (Logan JJ, Jolly AM, Blanford JI; The Sociospatial Network: Risk and the Role of Place in the Transmission of Infectious Diseases. PLOS One 2016: (https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0146915) Although clustering is likely dependent on the physical environment of a city or town, initial investigations may provide data for areas in which to focus prevention measures.

We have now added subgroup analyses based on the postal code of death. When someone dies outside of a building, the postal code of the nearest building is used.

I would invite the authors to add additional references on drugs, and drug related death results, similar to the above, which relate to the context of the current paper. For example, to prevent these deaths would it be helpful to encourage people who use drugs to use cocaine with others, so as to limit the chances of death? Would education as to the risk help people be more cautious in hot weather, and go to cooler places? Or use safe consumption sites?
We have added more detail about how these results are being used in British Columbia, especially in light of the catastrophic 2021 western North America heat dome.