Author's response to reviews

Title: The impact of drug use patterns on mortality among polysubstance users in a Canadian setting: a prospective cohort study

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Author's response to reviews: see over
Natalie Pafitis  
Executive Editor, BMC Public Health  

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Dear Ms. Pafitis:  

Re: MS 2021963812129180 “The impact of drug use patterns on mortality among polysubstance users in a Canadian setting: a prospective cohort study”  

Thank you for your correspondence dated the 30th of June 2014. We are very pleased that the Editorial Board is favourably disposed toward considering our research manuscript for possible publication in BMC Public Health.  

As requested, we have revised the manuscript in light of the comments we received. In the appended document we have outlined the changes made to the manuscript. Each response is numbered according to the comment it is meant to address, and any new text has been noted in bold font. A copy of the revised manuscript is also enclosed.  

We found the comments of the reviewer to be very helpful, and feel that the manuscript has been greatly improved as a result of the advice.  

All authors of the manuscript have reviewed the referee’s comments, and reviewed and approved the revised manuscript.  

We hope you find these revisions acceptable. If there is any other information you require, please do not hesitate to ask.  

Thank you again for your consideration.  

Yours Sincerely,  

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Reviewer 1:

1. We were pleased to learn that Reviewer 1 felt our manuscript was “an article of outstanding merit and interest in its field.” We agree with the reviewer that the manuscript is improved by providing some information about the impact of the local supervised injecting facility. To address this suggestion the following text has been added to the fourth paragraph of the Discussion section:

Harm reduction strategies, including a supervised injecting facility, in Vancouver’s DTES have been shown to be successful at attracting cocaine injectors, reducing rates of fatal overdose [1, 2] and reducing syringe sharing and HIV risk behavior [3, 4] among the local PWID population. It is noteworthy that both cocaine and heroin injectors utilize this unique program, [4] which is widely accessible for extended hours. It also connects PWIDs to addiction services, contributing to quicker entry into detoxification programs [5] and leading to increased likelihood of stopping drug injecting [6].

2. We agree that the paper is improved by expanding the discussion of harm reduction and addiction treatment interventions for cocaine injectors. The following text has been added to the fifth paragraph of the Discussion section:

The findings of this study highlight a need to further identify addiction treatment and public health strategies tailored for cocaine injectors. Currently, there is no standard pharmacotherapy proven effective for cocaine addiction, though multiple therapeutic agents, including anticonvulsants and stimulants have been investigated as potential treatments [7, 8]. A recent comprehensive review of human clinical trials for potential novel therapies for treatment of cocaine dependence outlined burgeoning research in this field. It identified multiple promising pharmacotherapies including dopamine agonists, serotonergic agents and GABA-ergic medications and a cocaine vaccine. One promising randomized controlled trial from 2013 demonstrated that topiramate was more efficacious than placebo at reducing weekly cocaine use [9].
Reviewer 2:

We thank Reviewer 2 for their comprehensive review of our manuscript. We appreciate the suggestions regarding our data analysis, particularly in regards to how the drug exposures were considered and have addressed these issues as outlined below.

1a. As suggested, we have revised the manuscript to include non-injecting heroin, speedball and non-injecting amphetamine use. The tables as well as the methods, results and discussion sections have been updated accordingly (see revised manuscript). The following text has also been added to the methods section:

The primary endpoint in this analysis was all-cause mortality. The primary explanatory variables of interest included a number of substance use behaviors in the previous six months including at least daily alcohol use, at least daily cocaine injection, at least daily heroin injection and non-injection use, at least daily amphetamine injection and non-injection use, at least daily crack cocaine smoking and at least daily speed ball (a mixture of cocaine and heroin) injecting. Additionally, we examined risk associated with non-daily heroin and amphetamine use.

1b. The Reviewer requested that we examine heroin use not only in daily heroin users but in heroin users who do not use on a daily basis since lower tolerance from less frequent use has been associated with overdose and death in heroin users. We therefore added data to our paper looking at mortality risk associated with non-daily heroin use. Relevant text of the results section reads:

A bivariate analysis of non-daily heroin use (HR = 0.99, 95% CI: 0.72 - 1.37) and amphetamine (HR = 0.47, 95% CI: 0.23 – 1.02) use, which was not included in the tables showed no significant association with mortality.

The relevant text of the discussion section reads:

Heroin use has been shown to carry the highest mortality risk amongst illicit drugs in some studies [10-12]. Particularly, non-daily heroin use is thought to carry mortality risk due to diminished tolerance to respiratory depression effects with sporadic use leading to increased accidental overdose [30]. However, our analysis showed no significant increase in mortality risk in both daily and non-daily heroin users.

1c. Please see Reviewer 2, Comment 1 where we describe the details regarding the additional drug and alcohol use variables we considered.

1d. As suggested we have added daily speedball injection to the drug use patterns examined in this paper. As mentioned above (1a), the data has been added to the tables, results and discussion section. Please see revised manuscript.

1e. Please see Reviewer 2, Comment 1 where we describe the details regarding the additional drug and alcohol use variables we considered. Though we recognize further
examining additional patterns of cocaine use would be interesting, unfortunately we do not have additional data to further explore these patterns.

2. We agree with the Reviewer that the manuscript is improved by justifying why variables other than drug use patterns, such as HIV disease were included. To address this suggestion, we added this text to the first paragraph of the discussion section:

   **These variables are known risk factors for mortality and were included in the analysis in order to adjust for their potential confounding effects [8].**

3. We agree that the manuscript is improved by describing the losses to follow up. To address this suggestion the text in the first paragraph in the results reads:

   **A total of 2597 individuals were recruited between May 1996 and December 2011, among whom 305 were excluded as a result of no follow-up information or incomplete data. In comparing the study sample to those that were excluded, the excluded sample was younger, and was more likely to inject amphetamine and smoke crack, but was less likely to inject cocaine (all \( p < 0.05 \)).**

4. Due to the differential risk of mortality between cocaine injectors and crack smokers, Dr. Hahn requested that we provide mortality rates for these populations. Mortality rates for smokers and injectors were difficult to assess since these measures were time updated and individuals could transition from smoking, injecting or both over time. The relative hazards from the Cox model is used as the descriptor to provide an estimate of the risk associated with these behaviors.

5. We agree that the manuscript is improved by noting the limitation that drug use in the period directly before death is not reported. To address this, we added the following text to paragraph 6 of the discussion section:

   **Third, drug use patterns directly before or at the time of death are not described due to the method of self-reporting, which inhibits our ability to ascertain data as proximal to the time of death.**

6. We agree with the Reviewer that there are differences between the analysis of all cause mortality and accidental mortality but feel this is not surprising given that these are different endpoints.

7. We agree that reporting frequency of drug injecting would be of value. Please see above where we have addressed the frequency and types of drugs injected.

8. As suggested, we have added the eligibility criteria with respect to drug use. The following text has been added to the methods section:

   **To be eligible, participants were 18 years of age or older, had used illicit drugs other than cannabinoids in the previous month, and resided in the greater Vancouver region. All participants provided written informed consent.**

11. We agree with the Reviewer that unclassified deaths, as well as deaths from competing causes (e.g. cardiopulmonary and drug intoxication) are a limitation in
studies of drug users including the present study. For this reason, we elected to examine all cause mortality as our primary endpoint.