Author's response to reviews

Title: Alcohol and cannabis use as risk factors for injury - a case-crossover analysis in a Swiss hospital emergency department

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Author's response to reviews: see over
Answers to reviewers:

Reviewer 1: GB

1) Citation of other case-crossover studies on relationship between alcohol and injury. 
Done. We did not include these references in the first version, as they were not part of the focus of our contribution on alcohol and cannabis use.

2) Relationship between marihuana and injury:
We obviously agree with the reviewer on the necessity of studies on marihuana and injury.

3) Restriction of study to men/sample size.
Certainly, we are restricted in sample size. However, the study has enough power to yield significant relationships in the main hypothesis.

We do not agree in restricting the analyses to men, as this would further decrease the sample size, and there is no indication of an interaction effect.

4) General tone of discussion being misleading because the imprecision was not taken sufficiently into consideration.
We changed the discussion and abstract accordingly.

5) Differences in ORs
The differences in OR from regression are expected to vary slightly when different terms are entered into the equation (in the example given an additional interaction term).

6) Robust estimates
The OR from the case-crossover analyses is simply a McNemar test on the diagonal. A robust estimate of this will not yield any different estimates. All tests are within the assumptions of standard chi-squared theory, however (e.g., expected cell counts of 10)

7) Types of injury
We added the statistics on type of injury.

8) Argument of compensation for different types of injury
We indeed believe that compensation may be valid for types of injury other than MVA. If cannabis is used mainly during leisure without other activities, it may indeed be causally related to less injury. Somebody who has just used cannabis, may avoid stepping on a ladder to change a light bulb, and thus avoid risky situations as described in the text.

9) Multiple drug use
We have taken the suggestion of the reviewer and added statistics of other drug use to the manuscript.

10) Comments on recall limitations
We added a sentence (and a reference) in the discussion to recall errors that may particularly influence effect estimates in case-crossover designs. We believe, however, that these effects cannot explain the “beneficial” effect of cannabis use on injury.

**Minor points:**

1) English
*The revised manuscript has been carefully copy-edited by a native speaker.*

2) Causality
*We changed the language and interpretation throughout the text, but especially in the abstract and the discussion as suggested.*

3) Response rate
*We have now included both a response rate (based on the eligible patients as denominator) and participation rate (excluding patients unavailable due to ongoing care and interviewer workload, thus patients that weren’t contacted for participation).*

4) Description of biological specimen
*We believe, this description is necessary, as we do comparisons between self-report and biological measurements for validation of the former.*

**Reviewer 2: CP**

**Minor essential revisions**

1. The abstract is acceptable except for the Conclusions. This study did not compare epidemiological and laboratory findings so it is not appropriate to say that it confirms conflicting evidence between epidemiological and laboratory studies.

*We changed the conclusions of the abstract based on remarks by reviewers 1 and 2.*

2. The research question is implicit but needs to be stated more clearly as a general aim and specific objectives in a last paragraph in the Background section.

*Done.*

3. There are several places where the English language could be improved. This was the main area where the manuscript needed to be improved. This is easy to do and specific changes recommended have been pointed out below.

*We included almost all of the suggestions of the reviewer, and the manuscript was copy-edited by a native English speaker.*
4. With regard to the discussion of limitations in the Discussion, while only 8% of the eligible patients refused to participate it is possible, though unlikely, that they represent a particular group whose input might have had an impact on the overall findings had they been included. This should be acknowledged under limitations in the Discussion. In this section comment should also be made on the ability to recall what they had been drink and smoking a week before the incident.

*The limitations of the discussion were reformulated based on the suggestions of the reviewer. Potential recall errors have also been included, see point 10 referee 1.*

5. Abstract, page 2. change “ABSTRacT to ABSTRACT (all capital letters)

*Done*

6. Abstract, page 2, under Background, line 2, add “a” before “detrimental”. Line 3, change “fond” to “found”. Change line 4 to “…, but a protective effect of cannabis has also been found in epidemiological studies.”

*We are sorry for the many typos in the abstract of the first version. We corrected all these and made sure, that the revised version was checked carefully by a native speaker before sending it out.*

7. Background, Page 3, line 1, change “to injury” to “for injury”.

*Done*

8. Background, page 3, line 11, add “%” after “1.4”.

*Done*

9. Background, page 4, paragraph 1 (starting “In summary”), line 3, change “those” to “persons”.

*Done*

10. Background, page 4, paragraph 1, line 5, change “of” to “on”.

*Done*

11. Background, page 4, paragraph 1, line 7, change “question” to “issue”. Add a sentence to indicate why you think that the combination of cannabis and alcohol is an important public health issue. Is it because the effect of the interaction between these to substances is not properly understood? Perhaps we do not know if cannabis adds to the detrimental effect of alcohol or perhaps it mediates it in some other way?
We changed the wording as suggested. We further explained the reasons for studying the impact of concurrent alcohol and cannabis use.

12. Background, page 4, paragraph 1, line 8, change to “...research, findings have been inconsistent”.

Done

13. Background, page 4, paragraph 2, starting “The present study..”. These bullets should go into the Methods. Instead there should be a clear statement of the study aim and specific objectives. These are implicit but need to be stated clearly at the end of the Background.

We changed accordingly and added a statement with study objective and specific hypotheses.

14. Methods, page 4, line 3. Add a sentence giving more information about this hospital. Who does it serve? This might affect the generalisability of the findings?

Done

15. Methods, page 4, line 5, remove the information about the funding grant. This is already in the Acknowledgements.

Done

16. Methods, page 5, paragraph 1, 1st sentence. This is not entirely clear. I think the authors mean that out of approximately 2000 possible four-hour time slots (00:00-04:00, 04:00-08:00, etc.) between 1 September 2005 and 31 July 2006, 270 were randomly selected.

The reviewer is right in principle. However, not all the time between 9-1-2005 and 7-31-2006 was selected, but a subsample of 5 one month slots. We changed the wording to clarify the meaning.

17. Results, page 7, paragraph 2 (starting “As it can be seen”), line 1, change “table” to “Table”. It will be important to indicate that the finding was only statistically significant for some sub-groups e.g. high alcohol users (for women) and medium and high users (for men).

We clarified this part as suggested by the reviewer.

18. Results, page 8, 2nd paragraph, line 1, change “in regards to” to “With regard to” and “people” to “patients”. Line 3, not sure what is meant by “this is reversed when compared to the contrary”. Suggest the authors spell this out more clearly.
Wordings changed as requested. The meaning of line 3 has been clarified.

19. Results, page 8, paragraph 2, Line 11, change the part of the sentence referring to “were not necessarily deniers” as his is an awkward use of the English language. Perhaps say “were not necessarily persons who denied use when they had in fact used”.

Changed the English

20. Discussion, page 8, line 1, change to “The results of our study corroborate research showing the detrimental…”. 

Done

21. Discussion, page 9, lines 1 to 4, change to “This finding does not necessarily contradict findings from laboratory studies. One possibility is that persons driving under ………, becoming more cautious in real-life driving situations than they would in the laboratory”.

We changed this paragraph.

22. Discussion, page 9, paragraph 2, line 1, change 1st sentence to “The compensation hypothesis cannot be the only explanation.” Line 10, change “hat” to “that”.

Made the suggested corrections, but we wanted to keep a more probabilistic interpretation, so we used slightly different wordings.

23. Page 10, paragraph 2, line 2, change last part of the sentence to read “, than is currently available in the literature”.

Changed

24. Table 1, given that all the data refer to the 6 hour period it might be clearer to refer to this in the title and change the row headings to “Just prior to injury and “A week prior to injury”. The font sizes of the numbers are not all the same.

Changed accordingly

25. Table 3, Remark, change “There was” to “There were”.

Done

26. Table 4, re the title add in “combined” before “alcohol”.

Done
As we give RR for alcohol and cannabis use separately and jointly we believe that our title is more appropriate.

Discretionary revisions

1. Abstract, page 2, under Methods, line 3, change “different mechanisms” to “varying etiology”.

Changed

2. In the Background it might be useful to include a sentence outlining the differing physiological effects of cannabis and alcohol.

We believe this would be too distracting from the main focus of the text.

3. Background, page 3, line 5, perhaps change “more controversial” to “less clear”.

Changed

4. Background, page 3, line 8, change “done” to “conducted”.

Done

5. Methods, page 5, paragraph 1, add a last line saying something like “The final sample therefore comprised 488 (?) patients.”

After exclusion of the people incomplete data on alcohol and cannabis use, we had N=486 people.

6. Measures, page 6, line 1, also include the volume % for beer and wine.

Done

7. Measures, page 6, paragraph 2, at the end of this paragraph it is acknowledged that a positive measure of cannabis is not an indicator of possible impairment at the time of the accident. Given that biological markers for alcohol can measure alcohol up to 12 or even 18 hours, couldn’t the same be said for alcohol?

Of course the author is right, but we did not use markers such as GGT or CDT in the present study to determine level of blood alcohol concentration at the time of injury. Therefore only ethanol in the blood or the breath was used. Other markers will be used for another study on potential chronic use. As a result, we think the point raised by the reviewer is irrelevant for the present study, and detailed for alcohol in another article (Gmel, Kuendig, Augsburger, Schreyer
Daeppen, 2008) for which the reference is given. We clarified, however, that results on marker readings were not used in the present study.

8. Measures (and elsewhere), in several places the word “accident” is used. People involved in the injury prevention field generally do not refer to alcohol related incidents as “accidents” anymore, but instead refer to “motor vehicle collisions” or something like that. Make sure that using “accident” is still appropriate.

We changed the text to avoid accident.

9. Discussion, page 8, line 3, cite the reference (“cited above”).

We believe, it is easy to refer back to the intro.

10. Discussion, page 10, paragraph 1, it might be useful to recommend further research in rural communities where possibly higher cannabis levels might exist or in countries for example in Africa where levels of cannabis use is also higher.

Done

Line 4/5, say more about Borkenstein’s methodology.

We details about the methodology of Borkenstein.

Reviewer 3: ME

Thanks a lot for this review. However, since the study is finalized and we already overdrew the budget of the study as the field work was much more complicated as planned, we see no way how to collect more cases or other empirical data. Moreover, unfortunately, none of the standard measures of injury severity has been implemented at the CHUV hospital.