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Title	Effects of exposure to second and third-hand marijuana smoke: a systematic review
Authors	Hannah Holitzki BHSc, Laura E. Dowsett MSc, Eldon Spackman PhD, Tom Noseworthy MD MSc MPH, Fiona Clement PhD
Reviewer 1	Dr. Theodore David Cosco
Institution	MRC Unit for Lifelong Health and Ageing at UCL, London, UK
General comments (author response in bold)	<p>The authors have conducted a meritorious systematic review of the effects of second- and third-hand marijuana smoke. This article is particularly timely given the pending legalization of marijuana in Canada in July 2018, which also makes this a particularly appropriate submission to <i>CMAJ Open</i>. The search strategy is clearly laid out and generally adheres to the PRISMA protocol; however, the search is outdated by a year or so. The inclusion and exclusion criteria are reasonable and limitations have been acknowledged, e.g. restricting the inclusion to English and French studies. The authors have chosen to use a narrative synthesis in their analysis of the included studies, which is warranted given the heterogeneity of study outcomes and methods invoked, making a meta-analysis virtually impossible. The discussion flows logically from the results and I don't believe the results are overstated.</p> <p>1. An area for improvement, however, could be in the contextualisation of these results in a Canadian context. The focus of the article, as indicated by the first line in the abstract, is on examining the implications of second and third hand smoke in anticipation of marijuana legalisation in Canada in July 2018. It would be beneficial to have a greater focus of the literature review to reflect this Canadian focus. The first paragraph in the background focuses specifically on US statistics. Canadian statistics would provide a better background for this study.</p> <p>Thank you for drawing our attention to this. We have updated the manuscript, particularly the background, to have a stronger focus on the Canadian context. The statistics in the background have all been replaced with Canadian-specific numbers.</p> <p>Additional comments:</p> <p>2. I think the study would benefit from updating their search to include the last year of papers (if any). The search has been updated to October 2017, and no additional studies were included. The manuscript has been updated throughout to reflect the updated literature search.</p> <p>3. Line 219: "compared to tobacco smoke..." The duplication in this sentence has been removed.</p> <p>4. Screening: Formatting error with arrow in PRISMA diagram The arrow has been reformatted.</p>
Reviewer 2	Ms. Jesse Elliott
Institution	University of Ottawa Heart Institute, Ottawa, Ont.
General comments (author response in bold)	<p>This is an interesting review on a topic that has not received much attention to date, especially in the media. Updating the search to include the most recent studies will ensure the greatest impact of this important work.</p> <p>Major</p> <p>1. The literature search was conducted more than 1 year ago and should be updated The search has been updated to October 2017, and no additional studies were included. The manuscript has been updated throughout to reflect the updated literature search.</p> <p>2. Authors switch between the terms "passive" and "second- and third-hand" smoke. Because third-hand smoke could not be assessed in this review, it may be more appropriate to use only the term "second-hand" in most instances, especially in the interpretation of the findings We have revised the manuscript so that although the term "passive" is used sparingly in the background, the rest of the manuscript now uses "second-hand smoke" and "third-hand smoke" for clarity.</p> <p>3. Methods: Please comment on whether there was an a priori protocol for this review. If the protocol was registered in PROSPERO, please add the PROSPERO number. This systematic review was not registered in PROSPERO.</p> <p>4. Methods, line 101: the search strategy included MESH terms related to outcomes and the studies were selected based on reported outcomes of interest. As such, the section on "other effects" was not assessed in systematic manner (e.g., this section can only report the "other effects" noted in studies that reported at least one of the authors' outcomes of interest). Thus, it is not clear whether there are other studies that assessed the outcome eye discomfort/irritation but were excluded from the systematic review because they did not report one of the authors' outcomes of interest. Thank you for pointing out this discrepancy. We have clarified in the manuscript that the search was not related to outcomes, but to second-hand/third-hand exposure. "The search was conducted using all MESH terms referring to marijuana (e.g. ganga, bhang, hashish, pot, shatter, weed) and MESH terms referring to second- or third-hand marijuana smoke (e.g. exposure, involuntary, passive, secondhand, third hand)." No studies were excluded based on outcomes (see comment #8 for additional clarification).</p> <p>5. Please add a justification for the focus on THC and THC metabolites out of all compounds in marijuana? Were</p>

other cannabinoids considered? Is there evidence of adverse events associated with, for example, CBD content in smoke?

All outcomes were considered and reported. Only THC and THC metabolites were reported in the included studies.

Minor

1. Abstract, line 33: please define "immediate", "short-term" and "long-term"

We have revised the objective to remove these terms.

2. Introduction, line 82: Please ensure the list of jurisdictions in which non-medicinal marijuana use is legalized or decriminalized is up to date

The list of places that have legalized, and voted to legalize marijuana is up to date.

3. Introduction line 76: are there any data from human cells that show impaired endothelial function (or other harms) after marijuana smoke exposure, or is the only data available from animal cells?

We did not find any human studies that report data on endothelial function.

4. Methods, line 95: were grey literature sources searched?

No, grey literature sources were not searched – this systematic review was limited to the published literature. We have added the following in the methods section to clarify this "A systematic review of published literature on the effects of second- and third-hand marijuana smoke was conducted."

5. Methods, line 103: add reference to PRISMA guidelines

A reference for the PRISMA guidelines has been added.

6. Methods, line 104: please specify which "reporting standards" were followed

No additional reporting standards were used, we were referring to PRISMA guidelines and reporting standards.

We have removed "reporting standards" to eliminate any misunderstanding.

7. Methods, line 108 and Results, line 214: The inclusion criteria are limited to human in vivo or in vitro studies, yet the results include 3 studies that assess the effects of smoke on non-human cells (p. 6, line 153). Please clarify this discrepancy

The three studies involving non-human cells have been removed.

8. Methods, line 109: please list all outcomes here instead of examples because screening was based on these

Studies were not selected based on outcome since all outcomes were included. We now see that this was confusing since outcome was reported as an inclusion criteria, so we have removed this from the inclusion criteria.

9. Methods, line 133: the three listed outcomes do not seem to match the headings in the results section, unless "subjective self-reported effects of second-hand smoke exposure" are "psychoactive effects"? Consider revising the subheadings to more closely align with the outcomes

This has been updated to better reflect the subheadings found in the results section.

10. Methods, line 132: please justify why quality assessment was not performed for the in vitro studies.

These studies have now been removed. Please see response to question #7.

11. Results, line 209: "other effects" do not appear to be included as outcomes of interest. Please specify how you decided which other effects to report on. (More clarity is needed in the methods section around outcomes)

For clarity, the heading "Other effects" has been changed to "Eye Irritation and Discomfort."

12. Results, line 153: please clarify why non-human studies were included (seems against inclusion criteria).

Please see answer to response to comment #7.

13. Results, line 160: please provide the range of exposure durations in studies that assessed "short-term" effects

The following has been added: All included studies assessed short-term effects of smoke exposure (within 24 hours of exposure); none assessed long-term health effects beyond 24 hours.

14. Results, line 161: meta-analysis was not included in the methods as the aim of the study. It is unclear without a protocol registration whether the authors intended to meta-analyze the results

A sentence has been added under "Analysis" to clarify that if data permitted, meta-analysis would have been used for to synthesize findings – "If data permits, results will be synthesized using meta-analysis."

15. Results, line 164: how is low to moderate quality defined using the Downs and Black assessment tool? What is the cut-off score used to determine each?

We have added a sentence to the methods section detailing the thresholds, and referencing where these thresholds have come from. "The maximum score using this checklist is 28; each paper was assigned a grade of excellent (24-28 points), good (19-23 points), fair (14-18 points) or poor (less than 14 points)."

16. Results, line 169: in the following section, please specify the duration of studies that assessed 'immediate

clinical outcomes'

We have clarified this in the manuscript: "Five reports from 3 studies assessed THC concentrations in oral fluid samples taken while the participants were being exposed to second-hand marijuana smoke."

17. Results, line 217: Did the chemical similarity between marijuana and tobacco smoke depend on the strain of marijuana?

None of the included studies compared different strains of marijuana with tobacco, so it is not known whether the chemical similarity between marijuana and tobacco depends on the strain of marijuana.

18. Interpretation, line 236: please specify which effects show a dose-response relationship with passive exposure
This has now been changed to: "There is evidence of a weak dose-response relationship between THC content of cannabis and effects on those exposed to second-hand smoke, including metabolites found in urine, blood, and psychoactive effects."

19. Interpretation, line 296: please add references for the "known harms" of marijuana use

We have added the following reference to this sentence: Volkow, Nora D., et al. "Adverse health effects of marijuana use." *New England Journal of Medicine* 370.23 (2014): 2219-2227.

20. Interpretation, line 307: please clarify how the study designs in the literature on this topic may limit the generalizability of the findings

In this sentence, we intended to highlight that we did not find any studies that looked at multiple points of exposure; having multiple times of exposure is more likely than a single exposure. We have added the following to clarify this point: "Exposure would likely be longer if individuals had been visiting with a friend of family where marijuana smoke was present, and therefore, the generalizability of the results may be somewhat limited."

21. Methods/Limitation: Why were the included studies limited to English and French studies? Please elaborate on the potential impact of this in the limitations

Due to the language limitations of the research team, only English and French studies could be included. The impact of this is discussed in the limitations section.

22. Interpretation, limitations section: please expand on the limitation of exposure duration and consider adding a limitation about study quality

The following has been added to the limitations section to address this comment: "Additionally, the study designs of included studies do not investigate effects in individuals who have been repeatedly exposed to second-hand marijuana smoke and all study participants were exposed for short periods of time. Exposure would likely be longer and more frequent if individuals had been visiting with a friend of family where marijuana smoke was present, and therefore, the generalizability of the results may be somewhat limited." We have also added the following to address study quality: "The included studies were of good, fair and poor quality; no excellent quality studies were identified. The addition of excellent quality studies may improve the robustness of these findings."

23. Interpretation, limitations: please address the potential limitation of the use of non-human cells in some of the experiments and the impact on the conclusions that can be drawn from such studies

Please see response to comment #7.

24. Conclusion, line 316: specify the time frame for retention of metabolites

We have added the following: "Individuals retain THC metabolites in their bodies upwards of four hours and report the experience of psychoactive effects after exposure to second-hand smoke."

25. Conclusion, line 317: I think the authors may mean "molecular" level instead of "cellular" level?

We have changed this from cellular to molecular.

26. Conclusion, line 320-323: the authors speculate of a potential association between second-hand smoke and respiratory and cardiac disease and mental illness. Were these outcomes searched for in this review? Is there evidence to support this hypothesis?

This research team conducted research on harms of marijuana use; this work is under review at another journal. So, although this part of the research project did not focus on harms of marijuana use (only on second-hand smoke exposure), the authors are well versed in the marijuana literature. Two prominent studies have been cited to support this hypothesis.

27. Table 1: the study design should be more explicitly stated. In particular, the studies that involved in vitro experimentation should be clearly stated. Studies that involve cell lines should specify the cell type and source (species)

We have removed the in vitro studies from eTable 1 (now Table 1).

28. Appendix: Include a list of included studies and add a note as to whether the list of excluded studies is available upon request

We have added references to eTable 1 (now Table 1), which contains all included studies, rather than creating a separate table. We have added a note that a list of excluded studies is available upon

	<p>request.</p> <p>29. Appendix, eTable 1: include the source of funding for each of the included studies Funding sources for the included studies have been added to eTable 1 (now Table 1).</p> <p>30. Appendix: an additional table should be added that provides the results of the quality assessment by domain of the assessment tool The full quality assessment results have been added to the online Appendix.</p> <p>31. Figure 1: please specify in the bottom box that only 11 unique studies were included (18 records, 11 unique studies) We have added an asterisk to clarify that only 8 unique studies were included (accounting for the exclusion of the animal cell studies).</p>
Reviewer 3	Dr. Mark Ware
Institution	MUHC MGH Pain Centre, Montreal General Hospital, Montréal, Que.
General comments (author response in bold)	<p>This is a well conducted and well written paper with importance to the community as Canada considers regulating legal cannabis. The review meets an important need, is well justified and uses robust methodology. Overall I have no major concerns and I recommend publication.</p> <p>1. I do think that there are some observations that deserve attention. On page 7 lines 174-177 there is an apparent paradox: the authors report "no direct relationship between the percent THC...and (urine) metabolites..." yet on line 177 they show that the proportion of those testing positive on UDT increases with increasing THC concentration. Can this be explained?</p> <p>Thank you for your comment. We intended to say that the correlation between THC content and THC metabolites in urine was not linear, however, we now see that this was confusing. We have revised it as follows, to improve clarity and simplify: "The evidence suggests that a higher percent THC content in smoked marijuana results in higher THC metabolite content in urine (Figure 2)."</p>