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Title	The association between the legalization of recreational cannabis and fatal motor vehicle collisions in the United States: an ecological study
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Reviewer 1	Ben Joseph MD, Resident psychiatrist, PGY3, NOSM
Institution	The Northern Ontario School of Medicine
General comments (author response in bold)	<p>It would be advisable to revise given the points below: From a toxicological perspective, "per se" levels are challenging for many reasons. Please see enclosed article by Bosker et al. ... "impairment was still observable compared to controls after 3 weeks of abstinence."</p> <p>Thank you for sharing this interesting article. We have revised the manuscript to include information from the article by Bosker et al. about detectable levels of THC in saliva after weeks of abstinence (lines 213-214). We also removed a sentence concerning the relative impairment of chronic daily versus occasional users (lines 215-217). While Bosker et al. found continued psychomotor impairment after cannabis abstinence among chronic daily users, the design of this study makes it difficult to determine whether this was due to previous cannabis use, or instead due to underlying differences between the chronic daily users and the occasional users.</p> <p>The 2 ng/mL THC "per se" level is based upon a public safety consideration and not a level based on studies of impairment at this level. (Ref 14).</p> <p>We agree that the THC "per se" level is based on public safety considerations rather than studies of impairment at this level and have added this statement to the revised manuscript (lines 205-207).</p> <p>In chronic users, the "per se" limits may be challenging in court, as chronic users may have greater than 2 ng/mL even after 6 hours. Hence, physicians must advise patients of the same wrt chronic use. (References found in 14 and in papers by Marilyn Heustis).</p> <p>We agree and have mentioned possible legal challenges to the "per se" limits (lines 207-208). We have also added that physicians should advise patients that they may exceed these limits even if they wait six hours before driving after consumption (262-265).</p> <p>Physicians also have a duty to inform patients that substance use disorder (DSM 5) is a category user which one can report to the MTO, i.e. if a patient is using cannabis for a non-medical reason. (New standard to report to MTO July, 2018 - Ontario)</p> <p>Thank you for raising this point. We agree that reporting is an important issue, and now discuss that physicians should be aware of any applicable reporting requirements in their jurisdiction (lines 273-275).</p>

The DRE program was created for police officers, by police officers. There has never been a proper scientific validation of 12 - step DRE process. The only group on which 12-steps were assessed was on the population that consumed drugs (including prison populations). DRE's (police officers) are not medically trained, however they perform complex neurological and Ophthalmological tests as part of the 12 - step examination and rule out medical conditions, i.e, a risky and unsafe interpretation of impairment (please see enclosed DRE facesheet). The 12 - step assessment of impairment is biased with an unscientific method of coming to a conclusion of impairment.

Thank you for this suggestion. We have added discussion of the scientific basis for the DRE program as part of the revised manuscript (lines 192-197).

As part of the DRE process, a sample of urine is collected and sent for analysis of carboxy-THC. Urine findings do not reflect concentrations in the blood, hence impairment, yet positive urine tests (qualitative) are used to prosecute drivers. In chronic users, one can have carboxy-THC found in the urine after 67 days (pls see enclosed ref).

Thank you for sharing this reference. In the revised manuscript, we have included that urine and blood THC concentrations may not correlate (lines 211-213), and that detectable levels of THC can be present in urine for extended periods of time (lines 213-214).

Sensitivity is not the best for the current instrument that is approved for testing saliva in the field. Pls see paper. In addition, many false positives have been reported.

We agree that sensitivity is not the optimal measure, and have revised the text to include that substantial improvements in test accuracy are needed to protect not just the general public but also legal users (lines 220-222).

Physicians should also advise patients that therapeutic uses of cannabis (prescribed by a physician) can cause one to have levels above the per se limits. Similar to certain areas of medicine (mental health / addictions), where "impairing drugs" are prescribed to cause an individual to return to function, taken for their ADHD or to lessen pain, cannabis may also be used for such purposes. In these individuals, a patient may do worse when not on the drug (alcohol, methadone, amphetamines etc.).

We agree that physicians should advise all patients who use cannabis (whether recreationally or therapeutically) that they may have THC levels which exceed legal limits, even if they wait 6 hours (lines 262-265). We now discuss this issue as part of the revised manuscript (lines 255-257). We were unable to identify any studies which examined therapeutic cannabis and driving specifically, however this is an interesting avenue for future research.

Finally, there has not been studies evaluating THC and impairment compared to alcohol and impairment. There exists paucity in the scientific literature reg. formal studies.

	<p>Please refer to article by Andrea Roth "... In fact, the few single-car crash and case-control studies that have been conducted have found no relationship between THC blood levels and an increased relative crash risk ..." Author from 14, to the Senate:</p> <p>"Unlike alcohol, however, the effects of THC do not correlate directly with THC blood concentrations. Instead, THC impairment demonstrates variability between individuals but is related to the amount, the route of administration and the time elapsed since use ... It's a very difficult exercise to try and determine a per se blood level for THC. Unlike alcohol, in which you can have blood concentrations which have links to impairment, that's not the same for THC because there's not a good correlation between impairment and blood concentrations...." said Chair of the Canadian Society of Forensic Sciences' Drugs and Driving Committee Amy Peaire at committee.</p> <p>Thank you for this excellent reference. It has been included at several points (lines 205-207; 211-213). We hope that the overall message (i.e., biochemical measures do not correlate with each other or with driving impairment) is now clear in this section (lines 198-222).</p>
Reviewer 2	Michel Bedard
Institution	Lakehead University, Health Sciences
General comments (author response in bold)	<p>This is a well-written manuscript on a timely topic. I hope you will find my comments useful.</p> <p>Thank you for the positive feedback.</p> <p>1. I found the tone of the article somewhat alarmist and requiring greater nuance for non-expert readers. For example, while you stated that "Cannabis consumption significantly impairs psychomotor skills and cognitive functions..." (p. 3), the evidence about the impairing effect of cannabis, and its impact on crash risk, is not all that clear, and in most instances is noted at blood concentrations of at least 5 ng/mL and sometimes more (e.g., Brubacher et al., 2019, Addiction). Some of the epidemiological evidence suggests there is an increase in crash involvement with cannabis use (e.g., Asbridge et al., 2012, BMJ) whereas some researchers did not find such associations (e.g., Elvik et al., 2013, Accid. Anal. Prev.) Likewise, in citing the study from Wettlaufer and colleagues (2017, Drug Alcohol Dep), it would have been desirable to point out the very wide confidence intervals reported; while you are correct that the estimate for the cost is \$1.1 billion, the lower limit is 37 million, and the lower limit for fatalities caused by cannabis-impaired driving is zero. Therefore, a more balanced presentation of the literature would help the reader appreciate the complexity of the issue.</p> <p>Thank you for these suggestions. As discussed in our response to the Editor's comments, we agree that it is important to present a balanced view, and have revised the tone of the article to give a more nuanced overview of the literature (lines 65-70; 77-79; 83-94; 104-110).</p> <p>2. It is not clear to me how this manuscript adds to the work of Lane and Hall (2019, Addiction). Furthermore, and adding to my previous point, Lane and Hall found an increase of 1 fatality per 1,000,000 in the first year post-legalization, and</p>

	<p>a decrease in subsequent years. Similarly, Aydelotte and colleagues (2017, Am J Public Health) did not find an increase in fatalities and that study should have been cited.</p> <p>Thank you for the opportunity to clarify what our manuscript adds to the works of Lane and Hall and Aydelotte et al. (lines 167-169). Aydelotte et al. recently updated their 2017 study (epub Sept 2019, Accident Analysis & Prevention); we have now included discussion of their most recent findings as part of the revised manuscript (lines 156-163; 173-176). Both of these previous publications focused on Colorado and Washington (Lane also included Oregon). Our analysis includes 6 additional states which have legalized recreational cannabis, including 12 additional years of legalization data.</p> <p>3. You made an excellent point about the need for more valid approaches to detecting cannabis and impairment. Possibly one message you could strengthen is the need for a greater understanding of the association between blood concentration and impairment. While this association is seemingly straightforward for alcohol, it is quite nebulous for cannabis.</p> <p>We agree that a greater understanding of the association between THC concentrations and driving impairment is needed, and have revised this section substantially in accordance with the comments of Reviewer 1 (lines 182-222).</p> <p>Minor comments:</p> <p>4. Page 5, second line: it would be more precise to state that “legalization was associated with [statistically] significant increases...</p> <p>We have revised this sentence according to the reviewer’s comment (line 131).</p> <p>5. Box 1, bullet 5, first line: “effects” should read “affects”.</p> <p>We have corrected Box 1, Bullet 5 to read “affects”.</p> <p>6. Key points, second bullet: it might be useful to clarify that the 2 ng/mL is in combination with alcohol.</p> <p>We have verified the second bullet in the key points – penalties begin at 2 ng/mL THC, without alcohol. Higher penalties are applicable for 2.5 ng/mL THC if alcohol is present (0.5 mg/mL).</p>
Reviewer 3	Dave Carr
Institution	Division of Geriatrics and Nutritional Science, Washington University School of Medicine, St. Louis, Missouri, USA
General comments (author response in bold)	There seem to be many additional references regarding fatal crash risk and drugged driving that could be mentioned. I would suggest the authors review and cite more of this literature. Some of these studies would add support to the concern raised about cannabis and crash risk. A few to be considered, but

certainly not a comprehensive list...

Brady, et al 2012

Marillier et al. 2019 Driving under the influence of drugs Robertson et al. 2016

Prevalence and trends of drugged driving in Canada

Thank you for this suggestion. We have included 14 additional references throughout the manuscript as part of responding to reviewer and editor comments, included Marillier et al. 2019 (lines 182-183).

The statistical methods and data set are mentioned in the Appendix but a few sentences to expand this methodology in the text would be useful

We agree, and have included additional details regarding the methods used in the text (lines 118-127).

Are the authors aware of any studies that did not show an increase risk of crash after legalization of cannabis in other countries?

We have cited two studies (Lane & Hall 2019, Aydelotte et al. 2019) which also used FARS data to examine fatal motor vehicle crashes (see Reviewer 2, comment 2). Lane & Hall found a temporary increase in motor vehicle fatalities following legalization (lines 148-155), and Aydelotte et al. found a non-significant increase in fatal collisions when using legalization dates, which was significant when using dates of commercial dispensaries opening (lines 156-163). The only other jurisdiction which has legalized the sale of recreational cannabis is Uruguay. We are not aware of any studies from Uruguay examining motor vehicle collisions and recreational cannabis use.

Since the differences you found were very small in the US data, are there other explanations for your findings of increase crash risk after legalization of cannabis in the US?

We agree that, given the ecological nature of our analysis, we are unable to fully account for other explanations for our findings. However, we are unaware of any other possible explanations for the increased crash risk. Our models included a random-effect to account for clustering by jurisdiction and calendar year, modeled using a categorical variable. Sensitivity analyses which adjusted for calendar year as a continuous (rather than categorical) variable found an even greater association between recreational cannabis legalization and fatal collisions (RR: 1.15; 95% CI 1.12, 1.17) and fatalities (RR: 1.12; 95% CI 1.10, 1.14) in jurisdictions with legalized recreational cannabis (Table 2). Nonetheless, in response to the reviewer's comment, we now acknowledge the potential effects of confounding in our revised manuscript (lines 166-167).

Table 2: What is the difference between Fatal Crashes and Deaths from Crashes? This should be explained in the text of the manuscript.

Thank you for the opportunity to clarify this point (line 123). Each fatal collision could result in more than one fatality. Therefore, we examined both

the number of collisions which resulted in at least one fatality, and the absolute number of fatalities caused by these collisions.

My understanding is there is data in Canada on how many MVC fatalities tested positive for cannabis and/or cannabis and alcohol per year. I may have missed it, but if you have not cited this information and the trend has shown an increase with legalization-this would be helpful to your paper.

We have included cannabis self-report survey data, and data concerning the potential costs of cannabis-related collisions in Canada (lines 95-114). However, we have elected not to include other data concerning collisions in which cannabis was detected for several reasons. There is substantial evidence that these kinds of data are subject to confounding (particularly pre- and post-legalization). Confounders include differences in the capacity within and between jurisdictions over time to report concentrations of drugs and associated impairment, as well as increased detection/analytical capabilities and/or resources devoted to examining the presence of cannabis among fatally injured drivers and other road users following legalization.

Also...additional comments on the combination with other drugs that alcohol (e.g. narcotics) would also be in order.

We agree that the combination of cannabis with other substances is an important issue, although available data are limited for non-alcohol combinations. We have expanded discussion of the consumption of cannabis with other substances, and included that polysubstance use makes it difficult to determine the relative contribution to cannabis to collisions (lines 85-94).

Would the authors like to make the comment that there is some data suggesting impaired driving with synthetic cannabis? Tuv et al. 2014 synthetic cannabinoids driving This area would be pertinent to health professionals who are increasingly called upon to prescribe cannabis in its myriad of forms.

Thank you for this suggestion. We now mention synthetic cannabinoids, with a reference to Tuv et al. 2014 (line 263).

The authors make the statement that the SFST has not been validated with impairment with cannabis use. Can they make any similar statements on the validity of the saliva test?

Thank you for this suggestion. We have revised this section to discuss the validity of saliva and biochemical testing in general (lines 205-208; 211-214; 220-222).

The authors make a plea for health professionals to take this topic on to educate in this area. Can the authors find/cite some literature that shows that a discussion by a health professional in the office setting can make a difference in a change in driving behaviors? Perhaps there is some literature regarding education on seat belt use and/or avoiding drinking and driving that has shown some impact? This

	<p>would at least be some indirect evidence that making an effort is worthwhile for busy clinicians, that are more focused on other health maintenance issues and have limited time in the office.</p> <p>We agree that it is important to clarify the value of educational interventions for risky behaviours. We have revised the manuscript to include evidence that brief counseling interventions in primary care settings have been shown to reduce problematic alcohol use and other risk behaviours (lines 246-248).</p> <p>The authors state there is significant evidence for waiting at least six hours when driving after cannabis use, but do not cite any references. These should be added.</p> <p>We agree this was unclear. The evidence has now been summarized in the text supporting Box 1 (lines 254-268).</p> <p>Misinformation or misleading information on the internet is well known and this section could be truncated and could be mentioned in one or two sentences.</p> <p>We agree, and have removed this section to make space for requested revisions (lines 276-292).</p> <p>Similarly, Table 3 comes out of the blue, goes beyond the scope of this paper and suggest it is deleted.</p> <p>Thank you for this comment. We have revised the flow of this paragraph to provide a better introduction to the lower-risk cannabis use guidelines (Table 3) (lines 245-251). The guidelines are one of the best available summaries of clear recommendations for safer cannabis use, which could be a useful tool for healthcare professionals providing brief counseling interventions to their patients. However, we would be open to its removal at the Editor’s discretion.</p> <p>Box 1 Item 3: Are you stating that cannabis consumption in the car is illegal just in Canada or also in other countries? Would be specific since many outside of Canada may read this journal and article. Item 4: Did you want to mention the saliva test in your list?</p> <p>We agree that this issue was unclear. This information is Canada-specific, therefore we have added “in Canada” to the title of Box 1. We have additionally revised to mention saliva testing in point 4.</p>
Reviewer 4	Bart Harvey
Institution	University of Toronto, Dalla Lana School of Public Health
General comments (author response in bold)	<p>Windle and colleagues have prepared an interesting ‘analysis’ regarding “Impaired Driving and the Legalization of Recreational Cannabis.” After reviewing the submitted manuscript, I have several questions, comments, suggestions, and even concerns regarding it.</p> <p>My greatest concern is the inclusion of what appears to be never-before published primary research results regarding the “secondary data analysis” the authors state they performed (line 44). Given the apparent and understandable importance these results play informing the submitted analysis, I would argue this portion of</p>

the manuscript should be prepared and submitted separately as a “research” submission so that its design, analysis, interpretation, and reporting can be appropriately peer reviewed and separately and uniquely published in the peer-reviewed literature. I would argue that using this ‘analysis’ manuscript for the initial reporting of this potentially important empiric undertaking is inappropriate, especially as it does not allow for the necessary and deserved research review this “secondary data analysis” requires.

We appreciate the reviewer’s concern regarding the importance of the primary research. As such, we have revised the title and first key point to draw attention to the secondary data analysis component of this manuscript (lines 1-2; 47). We elected to present our results in an Analysis manuscript, as it provided the opportunity to place the findings in a broader context, and to translate the literature in this area into practical recommendations for healthcare professionals.

Another concern I have is the authors statement that other studies found that the increased mortality and morbidity following the legalization of recreational cannabis use in other jurisdictions appears to be greatest in the first year following legalization. This is important for at least two reasons. First, given that Canada is already beyond its first year of legalization, those subsequent decreased risks of mortality and morbidity would be of greatest interest to estimate the magnitude of the risks going forward (and what interventions would be warranted given those anticipated decreased risks). Second, it is not clear whether the authors’ “secondary data analysis” described above, also examined this potential decline in risk beyond the first year of legalization. If it is possible to also estimate the risks in subsequent years this should certainly be included; and if this isn’t possible, it should be explicitly and fully discussed as a study limitation in the manuscript that I suggested in the paragraph above.

This is an important point. In response to the reviewer’s comment, we performed a sensitivity analysis in which we subclassified time post-legalization as first year versus subsequent years. We found no difference between the first and subsequent years of legalization, suggesting that the association with increased fatal motor vehicle collisions persists after the first year of legalization (lines 133-135; Appendix 2). This finding contradicts those of Lane & Hall (2019), however our analysis included 12 additional years of legalization and six additional states (lines 167-169).

I would also suggest that the authors strengthen the ‘analysis’ by including and discussing the evidence currently available regarding successful interventions for other substances that impair driving ability, particularly alcohol. For example, I was surprised that while advocating direct counselling by physicians regarding cannabis use, the authors did not appear include any discussion about what highly regarded groups such as the Canadian Task Force on Preventive Health Care and the U.S. Preventive Services Task Force had reported and recommended concerning physician counselling for alcohol-impaired driving. Given the diverse and increasing demands especially on primary care providers, I would argue that strong, rigorous evidence indicating the estimated magnitude of the benefit to be realized is required before health care professionals be asked to include the proposed counselling as part of their practice.

We appreciate this thoughtful suggestion. The Canadian Task Force on Preventive Health Care does not have a published guideline concerning counseling for alcohol-impaired driving nor any related intervention. The US Preventive Services Task Force does recommend counseling for risky alcohol and other substance use, and we have now included this evidence concerning the effectiveness of brief counseling interventions in the text (lines 246-248).

I also note that the authors state that “Effective communication has the potential to reduce impaired driving...” (lines 47 & 49) but the reference linked to this assertion (ie, reference #14) does not appear to be a peer-reviewed publication so I am unable to determine the strength of the supporting evidence. I am also concerned by the word “potential” being included in that statement, which seems to imply that the evidence supporting it is, in fact, not very strong.

Thank you for the opportunity to clarify this point. There is good evidence of an association between alcohol limit laws and reductions in collisions; this sentence has been revised, and peer-reviewed supporting literature referenced (lines 225-227).

I also have several relatively minor issues with the current manuscript. First, I had thought that opioid overdose deaths have now surpassed the number of deaths due to motor vehicle collisions, which may warrant the authors revising the statement on lines 13 and 15 of the manuscript.

The reviewer is correct. This line has been removed (lines 67-68).

In addition, on lines 40 and 42 the authors propose one of the questions guiding their analysis. I would respectfully suggest they reconsider this apparent rhetorical question and perhaps revise it to something like “By how much is the incidence and associated mortality and morbidity of motor vehicle collisions increased by the legalization of recreational cannabis?”.

We agree that the question is somewhat rhetorical. We have re-phrased the question (lines 69-70) while still leaving it somewhat open, to provide the basis for balanced discussion.

Further, it appears that the role of other ‘agencies’ (eg, federal government, provincial governments, non-governmental organizations such as MADD) and the potential role of ‘proactive policing’ are not mentioned in this ‘analysis’ by the authors. I wondered why their potential roles (as each currently plays regarding alcohol) were not discussed.

Thank you for this suggestion. We agree that the role of other groups is important, and have expanded our discussion of proactive policing and the role of other agencies (lines 231-240).

From an editorial standpoint, I wonder if "drug" should be replaced with "substance" on lines 45 & 47?

We agree, and have changed “drug” to “substance” (lines 87-88).

Finally, I wasn't sure what reference #1, listed on the 3rd line of Appendix 1 refers to. It doesn't appear to be the 1st reference of the included reference list.

Thank you for bringing this issue to our attention. The reference was inadvertently cut-off in our original submission. It is now visible (Appendix 1).

I hope these questions, comments, suggestions, and concerns are of assistance. Please do not hesitate to contact me if you would like any additional information or clarification.

Thank you to all the reviewers! We greatly appreciated your thoughtful and detailed comments, and feel that the manuscript has been improved substantially thanks to your feedback.