PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Schizophrenia, antipsychotic treatment adherence, and driver responsibility for motor vehicle crash: A population-based retrospective study in British Columbia, Canada
AUTHORS	Staples, John; Daly-Grafstein, Daniel; Khan, Mayesha; Pei, Lulu; Erdelyi, Shannon; Rezansoff, Stefanie N; Chan, Herbert; Honer, William; Brubacher, Jeffrey

VERSION 1 – REVIEW

REVIEWER	Ul-Haq, Zia Khyber Medical University, Institute of Public Health & Social Sciences
REVIEW RETURNED	12-Nov-2023

GENERAL COMMENTS	A very important article in an era where we live in the higher burden of mental health diseases. You have mentioned already in the paper for the interpretation to not simply a "go ahead' but at the same time not 'over reaction'. Please, clarify a bit more in the abstract. Some of the references no in the manuscript may be checked manually and correct accordingly. Table 1; has all P-values significant with a little difference in the two groups, does a larger number influence the P-value in descriptive table? In few places, only numbers are given percentage could be added, please.

REVIEWER	Steinert, Tilman Universität Ulm Medizinische Fakultät
REVIEW RETURNED	04-Jan-2024

GENERAL COMMENTS	As a reviewer who reviews many papers each year for a wide range of journals, I really have to praise this one. It is exceptional in many ways: Clear objective, really sophisticated methods considering all relevant aspects, impressive data set from multiple sources, not lengthy presentation of objectives and reasonable discussion and conclusions, clear results with obvious knowledge gain, extensive results supplemets, all limitations addressed. Congratulations!!! I have little to add, perhaps I would appreciate some clarifications. 1. Responsibility is a somewhat difficult term in the context of schizophrenia because it is mostly used with a different meaning. There is a huge literature on legal issues, mainly related to forensic psychiatry (being responsible or not for a crime on psychopathological grounds). So at least an explanation (or a different term) might be helpful. 2. I did not understand how you could classify > 600,000 car

	accidents (or what was the number in terms of driver responsibility?) with a responsibility score. This must have been done with a software application, I assume. Please clarify. 3. Methods, study cohort. You write that you focused on incidence rather than prevalence and excluded those drivers with some treatment indicators before the study inclusion period. I am not sure if I have captured your ideas on this point. Some further clarification might be helpful. 4. Presentation of results: There are several groups to consider with different Ns: All drivers, all with crashes, those with police attended crashes, those excluded from the analysis for some reason, the N of people with schizophrenia, people with schizophrenia with crashes, those with and without responsibility, and those with and without optimal medication adherence. This makes the results sometimes difficult to read. For example, it was only in analysis 2 that I read for the first time that there were 21,280 drivers with a diagnosis of schizophrenia. An overview of the different groups and their Ns in a table or a CONSORT figure would be helpful.

REVIEWER	Riala, Kaisa University of Oulu, a Research Unit of Clinical Medicine, Psychiatry
REVIEW RETURNED	16-Feb-2024

GENERAL COMMENTS	The article assesses police-attended crashes between years 2000-2016 and driver responsibility among drivers with schizophrenia. The article is generally well written and addresses an interesting and less studied topic. An important strength of the study is that the authors have been able to study the association between driver responsibility and preceding antipsychotic medication use by using register-based information to calculate MPR (medication possession ratio) for each driver. Furthermore, they have been able to consider the road exposure among drivers. The authors provide a good description the issues around driving safety among schizophrenia patients. The method sections is clear and well-organized, the analyses appear appropriate, and the results are displayed in a clear and organized fashion. With some clarifications, I believe that the article would be of interest to readers of BMJ open. 1) Introduction: The authors should add information how common in general is driving among schizophrenia patients. 2) Page 7: “Account for road exposure (the hours or miles driven per year) ”: this item remains unclear as it is not mentioned in results or tables S9 and 10, where responsibility score components are listed. 3) Methods, page 8. The authors focused on “incident rather than prevalent cases” – and excluded those with hospitalization, physician visit due to schizophrenia or other psychosis, or an outpatient prescription fill for an antipsychotic medication during 3 year “washout period” during 1997-1999 before the study. The authors should discuss this – would the results be different if prevalent cases of schizophrenia were also included? Schizophrenia typically is life-long condition and patients tend to have repetitive inpatient hospitalizations due to relapses. Is the conclusion of not recommending driving restrictions too courageous? 4) Methods, page 10; “Prior diagnosis of schizophrenia”: the drivers were identified to have schizophrenia if they had one hospital admission or three clinical visits for schizophrenia “withing 36 months”. Item S4: “To qualify as an exposure, schizophrenia diagnosis date must occur any time prior to the crash”. There seems

	to be a discrepancy with the description of “washout period”. Please clarify. 5) Methods page 10, first paragraph vs. Results – Tables 1 and 2. The authors have described in their methods section that “drivers with intermediate responsibility count” were excluded from the analyses. However various factors of this group are presented in tables 1, 2, S9 and S10. It seems that this group has been included when counting statistical differences between three groups of responsibly categorization. Please clarify. 6) Supplementary material of the study is extensive and includes a lot of interesting information. Based on study findings, can the authors give any practical recommendation on minimum temporary driving restriction for patients after hospitalization for schizophrenia?

REVIEWER	Hakko, Helinä Oulu University Hospital, Department of Psychiatry
REVIEW RETURNED	19-Feb-2024

GENERAL COMMENTS	The study analysed the relationship between schizophrenia, antipsychotic medication adherence and driver responsibility for motor vehicle crash. Retrospective observational cohort study utilised 20-year population-based register data from British Columbia, Canada, Incident schizophrenia was defined based on the information extracted from the hospitalization and physician services registers. Antipsychotic adherence was evaluated utilising prescription fill data for calculation of the 'medication possession ratio' (MPR) in the 30 days prior to crash. The crash responsibility was defined utlizing a crash responsibility scoring tool, which address seven external factors that potentially contribute to a crash. The data included for 808,432 drivers involved in a police-attended crash. A total of 1689 o fthe 2551 drivers) with schizophrenia and 432,430 of the 805,881 drivers without schizophrenia were deemed responsible for their crash. In general, the study is well conducted, and the data, analyses, and the results are thoroughly reported. It is diffucult fo find what could have missing from the manuscript. On the other hand, there are huge number of tables, figures etc. included either to the manuscript or presented as supplementary material. This can confuse the readers because it is not easy to see the material which is the most essential for this manuscript. Perhaps, the authors could leave out some material, which is not so relevant with regard to study findings. Otherwise,some very minor comments are below. * The outcome measure in the study was crash responsibility, which was assessed utilizing a crash responsibility scoring tool covering seven external factors that potentially contribute to a crash. The readers would interest to know whether this tool is internationally applied in research of motor vehicle accidents, specifically those leading to death of the driver? * The authors described that drivers involved in multiple police-attended crashes over the study interval could contribute more than one set of crash data to the analysis. The term 'crash-involved drivers' refer to unique driver-crash combinations, each treated as an independent observation. On the other hand, since the observations for an individual with multiple involvement to crashes

	are correlated, did the researchers evaluate whether it could have impacted to the results? • The drivers diagnosed with schizophrenia included those with having one hospital admission or three physician visits for schizophrenia within 36 months and the diagnosis date had to precede the crash date. On the other hand, excluded were those crash involved drivers who had, during a 3-year washout period (1997-1999), either a hospitalization or physician visit for schizophrenia or psychosis, or an outpatient prescription fill for an antipsychotic medication. If the excluded cases for schizophrenia cases were analysed, could the researcher evaluate what the results would have been? * RESULTS - First sentence of the results, there is reported that "final study cohort included 747,840 unique drivers, 612,304 unique crashes, and 935,527 unique driver-crash combinations". Please, check the sentence, because it is not possible that number of unique drivers is higher than number of crashes they were involved.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1 COMMENTS (Prof. Zia Ul-Haq, Khyber Medical University):

R1: A very important article in an era where we live in the higher burden of mental health diseases. You have mentioned already in the paper for the interpretation to not simply a "go ahead' but at the same time not 'over reaction'. Please, clarify a bit more in the abstract.

Authors' response: We thank Dr Ul-Haq for taking the time to thoughtfully review our work.

Our revised abstract softens its conclusions and now states:

"Crash-involved drivers with schizophrenia are more likely to be responsible for their crash, but the magnitude of risk is similar to socially acceptable risk factors such as older age or possession of a learner license. Contemporary driving restrictions for individuals with schizophrenia appear to adequately mitigate road risks, suggesting more stringent driving restrictions are not warranted." (p 3)

R1: Some of the references no in the manuscript may be checked manually and correct accordingly.

Authors' response: We thank Reviewer 1 for noting this. We have now manually checked the references in the revised manuscript and believe they are correct.

R1: Table 1; has all P-values significant with a little difference in the two groups, does a larger number influence the P-value in descriptive table? In few places, only numbers are given percentage could be added, please.

Authors' response: We agree with Reviewer 1 that the very large sample size in our study causes all differences in Table 1 to appear 'statistically significant' ($p<0.001$), even when the magnitude of the difference is not clinically meaningful. We have provided p-values when presenting descriptive data in Table 1, Table 2, Item S7, Item S9, Item S10, Item S16 and Item S17 to allow readers to consider the magnitude of difference. However, we now clarify in the legend of each relevant table that the very large sample size in our study results in p-values <0.001 even when the difference between groups is not clinically meaningful.

We considered removing the p-values entirely as we are aware they are controversial in this context but have retained them as we feel they may still be of some use to readers.

REVIEWER 2 COMMENTS (Dr. Tilman Steinert, Universität Ulm Medizinische Fakultät):
R2: As a reviewer who reviews many papers each year for a wide range of journals, I really have to praise this one. It is exceptional in many ways: Clear objective, really sophisticated methods considering all relevant aspects, impressive data set from multiple sources, not lengthy presentation of objectives and reasonable discussion and conclusions, clear results with obvious knowledge gain, extensive results supplements, all limitations addressed. Congratulations!!!

Authors' response: We are humbled and grateful for this recognition. We thank Dr Steinert for the time and effort they took to review our manuscript.

R2: I have little to add, perhaps I would appreciate some clarifications.
1. Responsibility is a somewhat difficult term in the context of schizophrenia because it is mostly used with a different meaning. There is a huge literature on legal issues, mainly related to forensic psychiatry (being responsible or not for a crime on psychopathological grounds). So at least an explanation (or a different term) might be helpful.

Authors' response: In the context of our study, a driver is deemed 'responsible' for their crash if they disobeyed road laws or if there are no other mitigating factors (such as the actions of other drivers, adverse road conditions, or lack of illumination) that contributed to the crash.

We agree that 'driver responsibility for crash' is a difficult term because of the different types of responsibility that can occur in this context (e.g., criminal [legal] responsibility, including the Canadian legal term "Not Criminally Responsible on Account of Mental Disorder" (NCRMD); civil [legal] responsibility; insurance responsibility, such as when a driver is deemed "at fault" by an insurance company). However, we believe this term to be the best available option due to its interpretability and broad usage in other studies of crash responsibility.

Another term commonly used in other studies of crash reasonability is "crash culpability", but we feel this term is less intuitive and can still be confused with criminal/civil/financial culpability.

Our revised manuscript now clarifies that:

"The scoring tool assesses crash responsibility independent of any determination of financial responsibility for the crash (as established by the insurance industry), any determination of legal responsibility for the crash (as established by criminal or civil law courts), and any determination of criminal responsibility for the crash (as established by experts in forensic psychiatry)." (p 9)

R2: 2. I did not understand how you could classify > 600,000 car accidents (or what was the number in terms of driver responsibility?) with a responsibility score. This must have been done with a software application, I assume. Please clarify.

Authors' response: Reviewer 2 is correct. Our revised manuscript now states:

"We used analytic software to algorithmically calculate responsibility scores for all crash-involved drivers." (p 9)

R2: 3. Methods, study cohort. You write that you focused on incidence rather than prevalence and excluded those drivers with some treatment indicators before the study inclusion period. I am not sure if I have captured your ideas on this point. Some further clarification might be helpful.

Authors' response: We focused on incident (rather than prevalent) schizophrenia. This means we aimed to include only individuals with schizophrenia who had schizophrenia diagnosed during the study interval. To do so, we excluded individuals who had schizophrenia diagnosed before the study interval started.

Our revised manuscript now clarifies this process and our motivations for this exclusion:

"By focusing on incident schizophrenia (i.e., newly diagnosed in the study interval) and excluding prevalent schizophrenia (i.e, diagnosed prior to the study interval), we improved the homogeneity of the exposure, facilitated assessment of whether 'time since schizophrenia onset' influenced the relationship between schizophrenia and crash responsibility (important because the clinical features of schizophrenia change over time and these changes might influence driving safety), and made more explicit the group to whom our results apply." (p 7)

R2: 4. Presentation of results: There are several groups to consider with different Ns: All drivers, all with crashes, those with police attended crashes, those excluded from the analysis for some reason, the N of people with schizophrenia, people with schizophrenia with crashes, those with and without responsibility, and those with and without optimal medication adherence. This makes the results sometimes difficult to read. For example, it was only in analysis 2 that I read for the first time that there were 21,280 drivers with a diagnosis of schizophrenia. An overview of the different groups and their Ns in a table or a CONSORT figure would be helpful.

Authors' response: Although the manuscript is much stronger with both analyses, we agree that the relationship between the studies could be more explicit. Our revised manuscript now contains a CONSORT/"Flow" diagram to clarify the relationship between the cohorts examined in Analysis 1 and in Analysis 2 (Figure 1, p23).

<u>REVIEWER 3 COMMENTS (Prof. Kaisa Riala, University of Oulu):</u>
R3: The article assesses police-attended crashes between years 2000-2016 and driver responsibility among drivers with schizophrenia. The article is generally well written and addresses an interesting and less studied topic. An important strength of the study is that the authors have been able to study the association between driver responsibility and preceding antipsychotic medication use by using register-based information to calculate MPR (medication possession ratio) for each driver. Furthermore, they have been able to consider the road exposure among drivers. The authors provide a good description the issues around driving safety among schizophrenia patients. The method sections is clear and well-organized, the analyses appear appropriate, and the results are displayed in a clear and organized fashion. With some clarifications, I believe that the article would be of interest to readers of BMJ open.

Authors' response: We thank Dr Riala for her thoughtful and complementary review of our study.

R3: 1) Introduction: The authors should add information how common in general is driving among schizophrenia patients.

Authors' response: We agree that this is a critical point. Our revised manuscript now states:

"This is important because the median annual driving distance among individuals with schizophrenia is less than half that of the general population" (p 6)

The revised manuscript also now includes two supportive references. These references report that study participants with schizophrenia drove considerably less than the general population (Steinert Psychiatry Res 2015, median kilometers per year, 4160 vs 14,200) and are much less likely to currently drive relative to control participants drawn from the general population (Palmer Schizophrenia Res 2002, proportion of individuals who currently drive, 43% vs 96%).

R3: 2) Page 7: "Account for road exposure (the hours or miles driven per year) ": this item remains unclear as it is not mentioned in results or tables S9 and 10, where responsibility score components are listed.

Authors' response: We thank Dr Riala for requesting clarification, because this is a critically important point.

Responsibility analyses do not use regression techniques to 'adjust' for road exposure. In fact, responsibility analyses are most useful when road exposure cannot be reliably measured. They account for road exposure through restriction: Responsibility analyses only include drivers who are involved as a driver in a crash, thereby ensuring all participants were driving at the instant of their enrollment (i.e., at the instant they crashed).

Our revised manuscript now tries to clarify this point:
"Traffic safety evaluations should ideally account for road exposure (the hours or miles driven per year) because a crash risk of "1% per year" implies a very different level of risk for Driver A (who travels 100 km/year) and for Driver B (who travels 10,000 km/year). Responsibility analysis is a type of case-control study that inherently accounts for unmeasured differences in road exposure. This study design only includes drivers who are involved in a crash, thereby ensuring all participants were driving at the instant they were enrolled in the study. Police-reported crash data is used to categorize crash-involved drivers as cases ('responsible' for contributing to their crash) or controls ('non-responsible' for their crash). Responsibility analysis assumes factors that increase crash risk will be more prevalent among 'responsible' drivers than among 'non-responsible' drivers, as has been demonstrated for well-established crash risk factors including intoxication, distraction, and sleep deprivation." (p 6)

R3: 3) Methods, page 8. The authors focused on "incident rather than prevalent cases" – and excluded those with hospitalization, physician visit due to schizophrenia or other psychosis, or an outpatient prescription fill for an antipsychotic medication during 3 year "washout period" during 1997-1999 before the study.
The authors should discuss this – would the results be different if prevalent cases of schizophrenia were also included? Schizophrenia typically is life-long condition and patients tend to have repetitive inpatient hospitalizations due to relapses. Is the conclusion of not recommending driving restrictions too courageous?

Authors' response: Our revised manuscript now clarifies why we focused on incident schizophrenia: "By focusing on incident schizophrenia (i.e., newly diagnosed in the study interval) and excluding prevalent schizophrenia (i.e, diagnosed prior to the study interval), we improved the homogeneity of the exposure, facilitated assessment of whether 'time since schizophrenia onset' influenced the relationship between schizophrenia and crash responsibility (important because the clinical features of schizophrenia change over time and these changes might influence driving safety), and made more explicit the group to whom our results apply." (p 7)

As suggested by Reviewer 3, our revised Supplemental Appendix now reports the results of a sensitivity analysis that includes all incident and prevalent cases of schizophrenia (i.e., in the sensitivity analysis, we did not exclude individuals with hospitalizations or physician visits for psychosis or prescription fills for antipsychotics in the washout period (1997-1999)).

This sensitivity analysis yielded an adjusted odds ratio similar to that of the main analysis: For incident schizophrenia only (main analysis): aOR 1.67; 95%CI, 1.53-1.82; p<0.001

For all incident and prevalent schizophrenia: aOR 1.68; 95%CI, 1.58-1.79; p<0.001

These results are presented in the Supplemental Appendix, Item S13, p 26.

R3: 4) Methods, page 10; "Prior diagnosis of schizophrenia": the drivers were identified to have schizophrenia if they had one hospital admission or three clinical visits for schizophrenia "withing 36 months". Item S4: "To qualify as an exposure, schizophrenia diagnosis date must occur any time prior to the crash". There seems to be a discrepancy with the description of "washout period". Please clarify.

Authors' response: When creating our cohort, we first excluded drivers with evidence of schizophrenia during a 3-year washout period (1997-1999). We did so in order to have a more homogenous cohort of exposed individuals with a new diagnosis of schizophrenia in the study interval. Drivers with prevalent schizophrenia (pre-existing; diagnosed prior to the study interval) were completely removed from the cohort and from all subsequent analyses.

Next, we established whether the remaining crash-involved drivers were diagnosed with schizophrenia in the study interval. To do so, we applied a validated administrative data algorithm for the diagnosis of schizophrenia: "One hospital admission for schizophrenia (ICD-10-CA codes F20 or F25 or corresponding daughter codes in most responsible diagnosis field of DAD), or three physician visits for schizophrenia within 36 months (ICD-9-CM code 295 or daughter codes in diagnosis field of MSP)." (Supplemental Appendix, Item S4).

For each individual who met this diagnostic criteria, we used their administrative health data to establish the following:
Diagnosis date: date of first hospitalization or clinic visit for schizophrenia.
Onset date: date of first hospitalization or clinic visit for schizophrenia or psychosis in the 3 years prior to diagnosis date.

We compared these dates to the date of the crash. We only considered a crash-involved driver to be "exposed" (i.e., to have a diagnosis of schizophrenia) if the schizophrenia "diagnosis date" was <u>before</u> the crash date. No individuals with a schizophrenia diagnosis date during the washout period were present in the study cohort at this stage because we had already excluded anyone with prevalent schizophrenia.

Our revised manuscript clarifies this point:

"We only considered a crash-involved driver to be exposed if the schizophrenia diagnosis date preceded the crash date." (p9)

"We only considered a crash-involved driver to be "exposed" (i.e., to have a diagnosis of schizophrenia) if the schizophrenia "diagnosis date" was before the crash date." (Supplemental Appendix, Item S4 p 6)

R3: 5) Methods page 10, first paragraph vs. Results – Tables 1 and 2. The authors have described in their methods section that "drivers with intermediate responsibility count" were excluded from the analyses. However various factors of this group are presented in tables 1, 2, S9 and S10. It seems that this group has been included when counting statistical differences between three groups of responsibly categorization. Please clarify.

Authors' response: Our revised manuscript clarifies these points.

It now states in the text: "Drivers with 'indeterminate responsibility' (score 14-15) were excluded from analyses." (p 9)

We have now included the following clarification in table legends: "Drivers with indeterminate responsibility were not included in analyses and are presented here for descriptive purposes only." (Legends for Tables 1 & 2, and Items S9, S10, S16, S17)

The table headers and the table legends also now clarify: "The displayed p-values compare responsible drivers to non-responsible drivers." (Legends for Tables 1 & 2, and Items S9, S10, S16, S17)

R3: 6) Supplementary material of the study is extensive and includes a lot of interesting information. Based on study findings, can the authors give any practical recommendation on minimum temporary driving restriction for patients after hospitalization for schizophrenia?

Authors' response: We agree that it is best to provide readers with relevant data to assess the results of the study. We have done so in the Supplementary Appendix.

We agree that assessment of risk after hospitalization for schizophrenia is highly relevant. We have a forthcoming paper that will directly address this issue.

REVIEWER 4 COMMENTS (Dr. Helinä Hakko, Oulu University Hospital):

R4: The study analysed the relationship between schizophrenia, antipsychotic medication adherence and driver responsibility for motor vehicle crash. Retrospective observational cohort study utilised 20-year population-based register data from British Columbia, Canada, Incident schizophrenia was defined based on the information extracted from the hospitalization and physician services registers. Antipsychotic adherence was evaluated utiising prescription fill data for calculation of the 'medication possession ratio' (MPR) in the 30 days prior to crash. The crash responsibility was defined utlizing a crash responsibility scoring tool, which address seven external factors that potentially contribute to a crash. The data included for 808,432 drivers involved in a police-attended crash. A total of 1689 of the 2551 drivers) with schizophrenia and 432,430 of the 805,881 drivers without schizophrenia were deemed responsible for their crash.

In general, the study is well conducted, and the data, analyses, and the results are thoroughly reported. It is diffucult fo find what could have missing from the manuscript. On the other hand, there are huge number of tables, figures etc. included either to the manuscript or presented as supplementary material. This can confuse the readers because it is not easy to see the material which is the most essential for this manuscript. Perhaps, the authors could leave out some material, which is not so relevant with regard to study findings.

Authors' response: We thank Dr Hakko for a thoughtful and complementary review of our manuscript.

We have curated the most relevant tables and figures for inclusion in the main paper. Very few studies with robust methodology have examined crash risk in drivers with schizophrenia; most were limited in their sample size, lacked controls, or did not include objective sources of data. Therefore, we have opted to publish additional relevant findings from our study in a supplemental appendix so that other researchers can build on our work and advance the understanding of schizophrenia and driv*ing fitness.*

R4: Otherwise, some very minor comments are below.

*** The outcome measure in the study was crash responsibility, which was assessed utilizing a crash responsibility scoring tool covering seven external factors that potentially contribute to a crash. The readers would interest to know whether this tool is internationally applied in research of motor vehicle accidents, specifically those leading to death of the driver?**

Authors' response: The "responsibility analysis" (also known as "culpability analysis") study design has been used for traffic safety evaluations based in countries including the United States,[1] Canada,[2],[3] Norway,[4] France,[5] and Australia.[6] It has been used to evaluate crash risk factors including chronic disease,[1] intoxication,[2] sleep deprivation,[3] prescription medication use,[4] and distraction.[5] The effect estimates generated by responsibility analyses are similar to those generated by conventional roadside case-control studies, highlighting the validity of the method.

The crash responsibility scoring tool that we applied in this study was developed and validated in British Columbia using the province's standard police-reported crash data.[7] Direct application of the scoring tool in other jurisdictions require adaptation based on the available variables that describe features of the crash. Outside of British Columbia, the responsibility scoring tool was adapted and validated for use in the Canadian province of Alberta,[8],[9] highlighting the potential for its use in other jurisdictions. Other jurisdiction-specific responsibility scores have been developed elsewhere.

We have modified our manuscript to clarify this point: "Responsibility analysis assumes factors that increase crash risk will be more prevalent among 'responsible' drivers than among 'non-responsible' drivers, as has been demonstrated for well-established crash risk factors including intoxication, distraction, and sleep deprivation. Responsibility analyses have been used to evaluate risk factors for traffic collisions in jurisdictions including the United States, Canada, France, Norway, and Australia." (p 6)

R4: * The authors described that drivers involved in multiple police-attended crashes over the study interval could contribute more than one set of crash data to the analysis. The term 'crash-involved drivers' refer to unique driver-crash combinations, each treated as an independent observation. On the other hand, since the observations for an individual with multiple involvement to crashes are correlated, did the researchers evaluate whether it could have impacted to the results?

Authors' response: Our revised manuscript now clarifies this point:

"We assumed each set of crash data was an independent observation because a) crashes are rare and the vast majority of crash-involved drivers were only involved in a single police-attended crash during the study interval; b) police complete crash reports for involved drivers without any input from prior crash reports (making crash responsibility independent of the driver's responsibility for prior crashes); and c) each driver involved in a crash is scored independently, with no requirement that one driver to be deemed responsible and the others to be deemed non-responsible." (p9)

No two crash-involved drivers with a prior diagnosis of schizophrenia were involved in the same crash.

We performed an assessment of correlation that found use of cluster robust standard errors (clustered by individual driver) had very little impact on the precision of our results, suggesting our assumptions about the independence of observations were reasonable (Appendix Item S22, page 39).

R4: The drivers diagnosed with schizophrenia included those with having one hospital admission or three physician visits for schizophrenia within 36 months and the diagnosis date had to precede the crash date. On the other hand, excluded were those crash involved drivers who had, during a 3-year washout period (1997-1999), either a hospitalization or physician visit for schizophrenia or psychosis, or an outpatient prescription fill for an antipsychotic

medication. If the excluded cases for schizophrenia cases were analysed, could the researcher evaluate what the results would have been?

Authors' response: As noted in our response to a similar thoughtful comment by Reviewer 3, our revised Supplemental Appendix includes a sensitivity analysis that includes all incident and prevalent cases of schizophrenia (i.e., in which we did not exclude individuals with hospitalizations or physician visits for psychosis or prescription fills for antipsychotics in washout (1997-1999)).

We found that the adjusted odds ratio for the sensitivity analysis is similar to that of the main analysis:
For incident schizophrenia only (main analysis): aOR 1.67; 95%CI, 1.53-1.82; p<0.001
For all incident and prevalent schizophrenia: aOR 1.68; 95%CI, 1.58-1.79; p<0.001

These results are presented in the Supplemental Appendix, Item S13, p 26.

R4: RESULTS - First sentence of the results, there is reported that "final study cohort included 747,840 unique drivers, 612,304 unique crashes, and 935,527 unique driver-crash combinations". Please, check the sentence, because it is not possible that number of unique drivers is higher than number of crashes they were involved.

Authors' response: As requested, we have double checked the numbers we provide. They are correct. The number of drivers can exceed the number of crashes because more than one driver can be involved in the same crash.

References

[1] Tefft BC. Acute sleep deprivation and culpable motor vehicle crash involvement. Sleep. 2018 Oct 1;41(10).

[2] Brubacher JR, Chan H, Erdelyi S, Zed PJ, Staples JA, Etminan M. Medications and risk of motor vehicle collision responsibility in British Columbia, Canada: a population-based case-control study. Lancet Public Health. 2021 Jun;6(6):e374-e385.

[3] Asbridge M, Brubacher JR, Chan H. Cell phone use and traffic crash risk: a culpability analysis. Int J Epidemiol. 2013 Feb;42(1):259-67.

[4] Breen JM, Naess PA, Gjerde H, Gaarder C, Stray-Pedersen A. The significance of preexisting medical conditions, alcohol/drug use and suicidal behavior for drivers in fatal motor vehicle crashes: a retrospective autopsy study. Forensic Science, Medicine and Pathology. 2018 Mar;14:4-17.

[5] Orriols L, Avalos-Fernandez M, Moore N, Philip P, Delorme B, Laumon B, Gadegbeku B, Salmi LR, Lagarde E. Long-term chronic diseases and crash responsibility: a record linkage study. Accident Analysis & Prevention. 2014 Oct 1;71:137-43.

[6] Longo MC, Hunter CE, Lokan RJ, White JM, White MA. The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability: part II: the relationship between drug prevalence and drug concentration, and driver culpability. Accid Anal Prev. 2000 Sep;32(5):623-32. doi: 10.1016/s0001-4575(99)00110-4. PMID: 10908134.

[7] Brubacher J, Chan H, Asbridge M. Development and validation of a crash culpability scoring tool. Traffic Injury Prevention. 2012;13(3):219-29.

[8] Pitt TM, Aucoin J, Nettel-Aguirre A, McCormack GR, Howard AW, Graff P, Rowe BH, Hagel BE. Adaptation of a Canadian responsibility scoring tool to Alberta police traffic collision report data. Traffic Injury Prevention. 2019 Mar 18;20(3):270-5.

[9] Pitt TM, Howard A, HubkaRao T, Hagel B. Identifying modifiable factors related to novice adolescent driver fault in motor vehicle collisions. Traffic injury prevention. 2021 Aug 18;22(6):437-42.

VERSION 2 – REVIEW

REVIEWER	Steinert, Tilman Universität Ulm Medizinische Fakultät
REVIEW RETURNED	26-Mar-2024

GENERAL COMMENTS	you have excellently answered to all issues raised by the reviewers and have revised the ms accordingly. The publication will be an important milestone in the field.

REVIEWER	Hakko, Helinä Oulu University Hospital, Department of Psychiatry
REVIEW RETURNED	27-Mar-2024

GENERAL COMMENTS	The authors have performed several important clarifications into the manuscript. Especially I want tho thank authors for adding the flow-chart. It makes it a lot easier to figure out the groups analyzed in the study. In my opinion the manuscript can now be accepted to be published.