PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between benzodiazepine co-prescription and mortality in people on opioid replacement therapy: a population-based cohort study
AUTHORS	Best, Catherine; Matheson, Catriona; Robertson, James; Ritchie, Trina; Cowden, Fiona; Dumbrell, Josh; Duncan, Clare; Kessavalou, Karthigayan; Woolston, Caroline; Schofield, Joe

VERSION 1 – REVIEW

REVIEWER	Lewer, Dan University College London, Institute of Epidemiology and Healthcare I know Joe Schofield professionally, via his role in the Drugs Research Network for Scotland (DRNS). Joe invited me to do a presentation at the DRNS in 2019. I have not collaborated in Joe in any research or other work.
REVIEW RETURNED	08-Jun-2023

GENERAL COMMENTS	Many thanks for sending me this study. It is a very important topic - as the authors say in the introduction, benzodiazepines play a central role in the current crisis in drug-related deaths, and there are important questions about clinical management/treatment and public health responses. Overall I thought this study was well-written and interesting. I have two major comments: 1. People who are prescribed benzodiazepines are different to people who are not (and likewise there are time-varying risks within individuals that are likely associated with benzodiazepine prescribing). These differences are difficult to control (ie. there is confounding). This issue is relevant to both the introduction and the results. In the introduction, prior observational studies are reported as causal effects, such as "benzodiazepine improved treatment retention", rather than "patients prescribed benzodiazepines had longer treatment durations". Therefore the existing knowledge about the benefits/risks of prescribed benzodiazepines is overstated in my opinion (even though considerable uncertainty is acknowledged in the text). In the results, the associations are also presented in a causal way (eg. "benzodiazepines increased the hazard for all-cause mortality relative to ORT alone"). Of course it is plausible that benzodiazepines increase the risk of death; however the observed associations are not large and it is quite possible that these effects are due to residual confounding. 2. I am not sure about the "retention in treatment" analysis. Can the benzodiazepine prescription happen after the ORT prescription? If so, the ORT+benzo duration will be biased upwards, since you have to "wait" for the benzo prescription.

	Other comments: - I didn't understand this bit (p6) "Individuals were defined as being 'on ORT treatment' if the time was less than 101 days from the dispensed date of their previous ORT prescription. This period was defined empirically from the distribution of observed dispense date intervals for ORT prescription." - I wasn't sure when participants join the cohort. Does everyone join the study on the day of their first ORT prescription? - You say you "compare the instantaneous hazard for mortality during time periods where there was co-prescription of ORT and a benzodiazepine compared to the hazard where ORT was prescribed alone". What about times when participants were not prescribed ORT - how is this treated? - Why is age not time-varying? (Perhaps it doesn't matter). - When you derive "ever prescription of z-drugs and ever prescription of opioid analgesics", do you use prescriptions after cohort entry, or only historical prescriptions? If you use prescriptions after cohort entry, this will create a type of immortal time bias. - I was slightly unsure about the rationale for the sensitivity/secondary analyses described on the first half of p7. I would find it useful to have a few sentences giving the purpose of each sensitivity analysis, and how you would interpret the results - ie. do you expect them to be the same as the main results? What if they are different? - I didn't understand the phrase: "There was also higher ORT prescribing in urban areas which may be confounded by socioeconomic deprivation." (p8) - In table 3, the difference in effect between methadone and buprenorphine is not actually tested, plus the results do not suggest bentos are not associated with all-cause mortality among people on buprenorphine, rather that p>0.05 and the confidence interval crosses the null value. An important association is still compatible with the results. Hence, the results don't support the conclusion "these findings suggest that buprenorphine poses less risk in combination with a benzodiazepine" (p12) - though they don't suggest this is not true either. - Personally, I prefer ratios to be written as ratios (eg. HR 1.5) rather than percentages (eg. 50% increased risk).

REVIEWER	Just, Johannes Universitatsklinikum Bonn, Institute of General Practice and Family Medicine
REVIEW RETURNED	12-Jun-2023

GENERAL COMMENTS	In this observational, retrospective cohort study using routinely collected administrative data in Scotland, Best et al. were able to display a connection between an increased mortality in people who received Opioid Replacement Therapy (ORT) AND co-therapy with benzodiazepines as compared to ORT only. The study is worthwhile, and adds to the existing literature. The method is sound and statistical analysis was well conducted. The text is written in standard scientific English. I have only some suggestions for change, the major one relating to the conclusion: Discussion: 1.)Page 11/12: "This may be because buprenorphine causes less

	respiratory depression than methadone" (https://pubmed.ncbi.nlm.nih.gov/20492579/) To my knowledge there is not only a quantitative but also a qualitatitve difference between buprenorphine and other opioids: there ist not only less respiratory depression, buprenorphine exhibits a ceiling effect at roughly 12 breaths/min which is a unique property of the substance adding strongly to its safety, especially if other substances are included that increase respiratory depression like benzos (https://pubmed.ncbi.nlm.nih.gov/20492579/). The authors may want to strengthen their statement in that direction. 2.) the main aim of ORT is to reduce heroin/opioid associated mortality. If benzodiazepines are associated with prolonged retention to therapy but also with increased mortality, why should doctors "balance against the risk" and not discontinue the benzos altogether if mortality is the relevant outcome criterion? Maybe other beneficiary effects of ORT should be mentioned in the discussion section (e.g. decrease in criminal activity, less infections, better Quality of Life, positive effects on family etc.). Conclusion: The current text of the conclusion ("In treatment planning, risk from benzodiazepine co-prescription needs to be balanced against the risk from illicit benzodiazepines and unplanned treatment discontinuation.") suggests that a co-medication should be considered for every patient on ORT depending on a balancing of usefulness vs. risk. While this is generally true for every medication it suggests that a co-medication with benzodiazepines is standard treatment and is connected with a medical indication (like e.g. statins in patients with high cardiovascular risk). In my clinical opinion, benzos should only very carefully be co-administered in patients on ORT as a mix of benzos, opioids and often alcohol increases the risk for hypoxemic events dramatically. Additionally they are often administered "off-label" which further increases the need for emphasizing drug-safety. I would suggest a conclusion that focuses on the dangers of benzodiazepines and only suggests using them in select cases after a thorough clinical balancing of usefulness and risk.

REVIEWER	MacKenzie, Meghan Nova Scotia Health Authority, Pharmacy
REVIEW RETURNED	21-Jun-2023

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. This is an important contribution to the literature that will aid in informing prescribers on the risks vs benefits of co-prescribing benzodiazepines while on ORT. The manuscript requires revision prior to publication that will help readers determine what was done and the limitations of it. Please see below for details: Introduction. Overall the introduction requires rewriting to clearly articulate the context (including patient population referred to), the problem, and clear rationalization of why it requires examination. Page 4 Line 13 and 14, morphine equivalents/opioid dose is also associated with outcomes and should be adjusted for in the analysis. The opening statement refers to Illicit drug use, and the study is evaluating patients with prescribed and dispensed ORT. Paragraph 1 does not appear to be adequately referenced. These statements should be supported. Paragraph 2, this paragraph and the statistics are not referenced. Line 37 DRD has not been defined prior.

	Line 48 it is not clear what this is the average of. Page 5 Line 5 to 6 it is unclear what increases the risk of mortality. Line 7 retention in treatment of what? Line 17 ORT has not been defined, additional context is required to understand the population of interest. Is the research question or study objective clearly defined? - Please state a clearly delineated research question or objective at the end of the introduction, the intention of the study is not clear from line 21 and 22. Is the abstract accurate, balanced and complete? - The abstract would benefit from a small intro/rationale if permitted. - It is unclear what the exposure is from the abstract. - If your population is those on ORT, then it would be clearer to state the objective as to determine the association of the co-prescription of benzodiazepine with mortality. Likewise, in figure 1. No need to carry the ORT part through as that is implied in the population. - Line 36—is this a 95% CI for all cause morality? - Line 40- a population cohort study, can not conclude causation i.e., that co prescription increased risk. It was an association that was found. Is the study design appropriate to answer the research question? - I believe it will be appropriate once the research question is clearly outlined. Are the methods described sufficiently to allow the study to be repeated? - Determination of the on-treatment definition could not be repeated and would benefit from rationalization of chosen time frame by comparing to other studies or describing in more detail how this number was arrived at. - Additional details around continuous treatment episode definition in line 42 is required. - Figure 1 o age over 17 yrs? The abstract states over 18. o It is unclear from this figure that this study is retrospective in nature or if it follows patients forward. - Please define opioid replacement therapy. Clarity is required to replicate if you are specifically looking at a population of patients that received methadone or suboxone as part of a treatment program for opioid use disorder and how you determined this and that the prescriptions aren't for the treatment of pain. If the dispensed prescription could be coded incorrectly, then this is a limitation that should be discussed. - Please elaborate on; who can prescribe and dispense these medications in Scotland? Are there any restrictions around access and utilization? Context should be provided either in the methods or defined in greater detail in the introduction so that readers can generalize the results to their populations/countries. - Clarity around the definitions is required. I am unable to tell if those in the unexposed could be those that had a prescription dispensed for ORT during the time period and a benzodiazepine, but the timing didn't overlap. It would be helpful to add details around how co-prescription was determined and how patients were selected e.g., were patients on opioids selected and then followed forward? - Time varying exposure. It appears this is describing how 'on treatment' benzodiazepine was determined. How was co-

	prescription or overlap defined? - In the analysis section it could be interpreted that patients could flip between groups If statistics are used are they appropriate and described fully? I am unable to fully/reliably assess and comment. Do the results address the research question or objective? - Research question not clearly stated. Are they presented clearly? Please see details below: Page 7 - What is the Scottish index of multiple deprivation? - There was no adjustment for potential confounders? - Line 30 substance use disorder, not substance use? - Line 55 to 56 unclear what the relevance of these numbers are. To describe the population, it should be clearly stated how many received ORT and then of those who were determined to be in the exposed group. It appears from table 1 that the exposed group is those who received a prescription for a benzodiazepine at any time during the cohort, please clarify if it was confirmed that the benzodiazepine was received during the same time period as the opioid for the analysis. Page 8, Table 1 - It appears visually that the exposed and unexposed groups were fairly evenly distributed. The analysis would benefit from statistical tests to determine if there were differences between groups based on the SIMD decile and urban rural classification. - Line 49. Please describe in more detail what is meant by time under observation. - Line 29. These are associations, not causal events. Are the discussion and conclusions justified by the results - Line 49 This statement differs vs what is outlined in the box on page 4. - Please add clarity to the statement on line 51 and 52. - Line 53 to 55 should be referenced. - Line 58 and 59 please complete this statement, e.g., buprenorphine when combined with benzodiazepine compared to buprenorphine alone? - Page 12 - Line 12 to 14 The analysis would benefit from a sample size calculation to determine if these numbers provide adequate power to detect a difference in mortality between groups. - Line 16 this discussion point would benefit from a different approach to outlining the results with a hypothesis that it indicates that those prescribed a benzodiazepine may have a longer period of retention in treatment in ORT. Eg. Please clarify by describing that patients that were co-prescribed a benzodiazepine were on ORT for a longer period than those that were no co-prescribed a benzodiazepine. - Line 21 to 24. Please clarify, it appears you are saying that contact with treatment services is beneficial and then go on to state the providing longer prescriptions (i.e., less need to seek care for refills) reduced mortality? - Line 30. Please provide references for what studies you are comparing the effect size to. - Line 33. I would suggest to remove patches prescribed for pain from this analysis vs guessing that the number is too small to have an effect without proving it statistically.

	- Line 38. Please describe what a raised ACM overall is referring to. Is this your overall population vs the general population of Scotland? If so, please reference/corroborate your statement. - Line 39. Please reference. - Line 41. This would not explain why mortality is lower. - Line 47. It is unclear what this is an explanation of, please clarify. - Line 50 to 53. Require references. - Page 13 Line 3. This is contradictory to a prior statement and requires references. - Higher doses of opioid and benzodiazepines have both been associated with increased odds of death in the literature. The amount of opioid should be determined in each arm as a sensitivity analysis to adjust for other potential confounders. If this is not possible, an explanation as to why this analysis wasn't completed should be undertaken. - Paragraph starting on Line 7 – please clarify - Limitations; a more complete examination of contributors to the outcome should be discussed. E.g., confounders not adjusted for, alternative explanations for the results that you see. - The discussion would benefit from comparison to other studies that looked at mortality associated with co-prescription. Some examples: - 5.Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ. 2015; 350:h2698 - 10.Overdyk FJ, Dowling O, Marino J, Qiu J, Chien HL, Erslon M, et al. Association of opioids and sedatives with increased risk of in-hospital cardiopulmonary arrest from an administrative database. PLoS One. 2016;11(2):e0150214. - 11. Cho J, Spence MM, Niu F, Hui RL, Gray P, Steinberg S. Risk of overdose with exposure to prescription opioids, benzodiazepines, and nonbenzodiazepine sedative-hypnotics in adults: a retrospective cohort study. J Gen Intern Med. 2020;35(3):696-703. - 12. Liang Y, Goros MW, Turner BJ. Drug overdose: differing risk models for women and men among opioid users with non-cancer pain. Pain Med. 2016;17(12):2268-79. - 13. Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisl KM, Marshall S. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. Pain Med. 2016;17(1):85-98. - 14. Day C. Benzodiazepines in combination with opioid pain relievers or alcohol: greater risk of more serious ED visit outcomes. In: The CBHSQ report. Substance Abuse and Mental Health Services Administration (US); 2014. p. 1-9. 15. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S - Please state the conclusion.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

People who are prescribed benzodiazepines are different to people who are not (and likewise there are time-varying risks within individuals that are likely associated with benzodiazepine prescribing). These differences are difficult to control (ie. there is confounding). This issue is relevant to both the

introduction and the results. In the introduction, prior observational studies are reported as causal effects, such as "benzodiazepine improved treatment retention", rather than "patients prescribed benzodiazepines had longer treatment durations". Therefore the existing knowledge about the benefits/risks of prescribed benzodiazepines is overstated in my opinion (even though considerable uncertainty is acknowledged in the text). In the results, the associations are also presented in a causal way (eg. "benzodiazepines increased the hazard for all-cause mortality relative to ORT alone"). Of course it is plausible that benzodiazepines increase the risk of death; however the observed associations are not large and it is quite possible that these effects are due to residual confounding.

Thank you for noting the subtleties in the language conferring risk and causality. We have made edits to the manuscript in line with suggestions. Regarding the retention in treatment – the text has been changed as suggested.

We have added an additional point to the strengths and weaknesses section noting the possibility that the association detected is due to unmeasured confounding.

The discussion section now states 'It is possible that the association we have found is due to residual confounding however, a number of other studies have found larger effect sizes for the association between BZD co-prescribing and ACM after adjusting for a greater range of potential confounders. For example, Abrahamsson and colleagues (13) controlled for sex, age, previous non-fatal overdose, previous psychiatric in-patient treatment, previous suicide attempt and ORT status and found a HR of 1.75 (1.28-2.39).'

2. I am not sure about the "retention in treatment" analysis. Can the benzodiazepine prescription happen after the ORT prescription? If so, the ORT+benzo duration will be biased upwards, since you have to "wait" for the benzo prescription.

This is a good reflective point. It is not unusual to start an ORT prescription, stabilise the dose then address the benzodiazepine dependence. However, if people who receive this stay longer in treatment either to receive a benzodiazepine (as a motivation to stay in treatment) or to have their benzodiazepine dependence address, doesn't matter. The longer they are in treatment, the longer they are exposed to the protective effects of ORT.

The way the data was manged and analysed did not preclude participants being on an benzodiazepine when they began opioid replacement therapy (ie entered the study).

3 I didn't understand this bit (p6) "Individuals were defined as being 'on ORT treatment' if the time was less than 101 days from the dispensed date of their previous ORT prescription. This period was defined empirically from the distribution of observed dispense date intervals for ORT prescription."

To determine the definition of 'on treatment ' for ORT we look at the distribution of dispensing intervals. We have re-worded to clarify. In the methods section, the 'on treatment' definition section now states 'To determine the 'on treatment' definition we examined the time interval between repeat prescription of ORT in the dataset. Prescription intervals of 90 days were found to be the most common. Individuals were defined as being 'on ORT treatment' if the time was less than 101 days from the dispensed date of their previous ORT prescription as this allows some leeway for holidays and illness around the most common prescription interval of 90 days. Thus, the time period used in the 'on treatment' definition was defined empirically from the distribution of observed dispense date intervals for ORT prescription. Individuals were included in the analyses while they were 'on treatment'.' We have also changed figure 1 so that it provides visual representation of participant data for the time to event analysis to hopefully make clearer how the analysis was performed.

4. I wasn't sure when participants join the cohort. Does everyone join the study on the day of their first ORT prescription?

Participants joined the cohort when they receive their first ORT prescription after January 2010.

5. You say you "compare the instantaneous hazard for mortality during time periods where there was co-prescription of ORT and a benzodiazepine compared to the hazard where ORT was prescribed alone". What about times when participants were not prescribed ORT - how is this treated?

Time periods where participants were not receiving an ORT prescription are excluded from the analysis. We have included an extra line in the methods section at the bottom of page 6 to clarify this saying 'Individuals were included in the analysis while they were 'on treatment'.

6. Why is age not time-varying? (Perhaps it doesn't matter).

Age is not time varying because it would be perfectly correlated with calendar time and therefore colinear in the models (ie the longer someone had been in the study the higher their age would be).

7. When you derive "ever prescription of z-drugs and ever prescription of opioid analgesics", do you use prescriptions after cohort entry, or only historical prescriptions? If you use prescriptions after cohort entry, this will create a type of immortal time bias.

Ever prescription of z-drugs and opioid analgesics can begin before ORT prescription.

8. I was slightly unsure about the rationale for the sensitivity/secondary analyses described on the first half of p7. I would find it useful to have a few sentences giving the purpose of each sensitivity analysis, and how you would interpret the results - ie. do you expect them to be the same as the main results? What if they are different?

We have added in the rationale for the sensitivity analyses in the methods section which states 'As the definition of 'on treatment' for ORT was determined from prescription intervals observed in this dataset we performed sensitivity analyses varying the time window for defining being on ORT treatment and for the exposure i.e. benzodiazepine co-prescription. If the effect of co-prescription on mortality outcomes was only observed under one particular definition of 'on treatment ' or exposure then this would indicate that the association may be a chance observation. However, if the effect is robust under several definitions, then this is support for the association.'

9.I didn't understand the phrase: "There was also higher ORT prescribing in urban areas which may be confounded by socioeconomic deprivation." (p8)

This has been amended to remove "may be confounded by socioeconomic deprivation"

10. In table 3, the difference in effect between methadone and buprenorphine is not actually tested, plus the results do not suggest bentos are not associated with all-cause mortality among people on buprenorphine, rather that p>0.05 and the confidence interval crosses the null value. An important association is still compatible with the results. Hence, the results don't support the conclusion "these findings suggest that buprenorphine poses less risk in combination with a benzodiazepine" (p12) - though they don't suggest this is not true either.

We have revised this section of the Discussion to read "Analysis did not find evidence of increased risk of ACM among patients prescribed buprenorphine."

Reviewer 2

Discussion:
1.)Page 11/12: "This may be because buprenorphine causes less respiratory depression than methadone" (https://pubmed.ncbi.nlm.nih.gov/20492579/) To my knowledge there is not only a quantitative but also a qualitatitve difference between buprenorphine and other opioids: there ist not only less respiratory depression, buprenorphine exhibits a ceiling effect at roughly 12 breaths/min which is a unique property of the substance adding strongly to its safety, especially if other substances are included that increase respiratory depression like benzos (https://pubmed.ncbi.nlm.nih.gov/20492579/). The authors may want to strengthen their statement in that direction.

This point is well made and we have furthered strengthened this statement and added reference to the very useful paper highlighted, as suggested.

2.) the main aim of ORT is to reduce heroin/opioid associated mortality. If benzodiazepines are associated with prolonged retention to therapy but also with increased mortality, why should doctors "balance against the risk" and not discontinue the benzos altogether if mortality is the relevant outcome criterion? Maybe other beneficiary effects of ORT should be mentioned in the discussion

section (e.g. decrease in criminal activity, less infections, better Quality of Life, positive effects on family etc.).

Yes agree this is a very good point and further benefits of ORT are now highlighted under clinical implications.

3. Conclusion: The current text of the conclusion ("In treatment planning, risk from benzodiazepine co-prescription needs to be balanced against the risk from illicit benzodiazepines and unplanned treatment discontinuation.") suggests that a co-medication should be considered for every patient on ORT depending on a balancing of usefulness vs. risk. While this is generally true for every medication it suggests that a co-medication with benzodiazepines is standard treatment and is connected with a medical indication (like e.g. statins in patients with high cardiovascular risk). In my clinical opinion, benzos should only very carefully be co-administered in patients on ORT as a mix of benzos, opioids and often alcohol increases the risk for hypoxemic events dramatically. Additionally they are often administered "off-label" which further increases the need for emphasizing drug-safety. I would suggest a conclusion that focuses on the dangers of benzodiazepines and only suggests using them in select cases after a thorough clinical balancing of usefulness and risk.

The conclusion has been reviewed and changes made to acknowledge the off label nature and the polydrug risk that exists. We cannot conclude that co-prescribing is only suitable in select cases as we do not have data to justify that statement. Instead, we have noted the need for individualised care.

Reviewer 3

Comments on introduction and background rationale

We have revised the introduction section and added more references and hopefully strengthened the rationale for the study.

Definition of the cohort

We have revised the section on the 'on-treatment' definition and the ascertainment of the cohort.

Please elaborate on; who can prescribe and dispense these medications in Scotland? Are there any restrictions around access and utilization? Context should be provided either in the methods or defined in greater detail in the introduction so that readers can generalize the results to their populations/countries.

The methods section states that the prescription information used in this study comes from the Prescribing Information System in Scotland and states 'The PIS contains information on all medicines and their costs that are prescribed and dispensed in the community in Scotland. The information is supplied by Practitioner & Counter Fraud Services Division who are responsible for the processing and pricing of all prescriptions dispensed in Scotland. GPs write the majority of these prescriptions, with the remainder written by other authorised prescribers such as nurses, psychiatrists, pharmacists and dentists. Also included in the dataset are prescriptions written in hospitals that are dispensed in the community. Prescriptions dispensed within hospitals are not included'

Clarity around the definitions is required. I am unable to tell if those in the unexposed could be those that had a prescription dispensed for ORT during the time period and a benzodiazepine, but the timing didn't overlap. It would be helpful to add details around how co-prescription was determined and how patients were selected e.g., were patients on opioids selected and then followed forward?

People entered the cohort when they received an ORT prescription after Jan 2010 and were followed forward for as long as they received ORT prescriptions within 101 days of each other. If they stopped receiving prescription for ORT and then re-started again they would re-enter the cohort. Figure 1 has been redrafted to illustrate this to readers.

Time varying exposure. It appears this is describing how 'on treatment' benzodiazepine was determined. How was co-prescription or overlap defined?

Participants were only included in the analysis while they were being prescribed Opioid replacement therapy. Therefore, any time they were exposed to benzodiazepines was co-prescription.

Page 7
- What is the Scottish index of multiple deprivation?

This is now explained as: "Socioeconomic deprivation was assessed by the Scottish Index of Multiple Deprivation (SIMD) based on post code of residence. Scotland is divided into around 7000 small areas which are ranked in terms of deprivation across the domains of: income, employment, education, health access to services, crime, and housing to create the SIMD (23)."

There was no adjustment for potential confounders?

The primary analysis was adjusted for functions of age, sex, local area deprivation, ever having received a z-drug prescription, and use of opioid analgesics.

Page 8, Table 1

- It appears visually that the exposed and unexposed groups were fairly evenly distributed. The analysis would benefit from statistical tests to determine if there were differences between groups based on the SIMD decile and urban rural classification.

Differences between groups in terms of SIMD decile and urban rural classification have been added. The following amendments have been made to the manuscript:

(1) a column added to table 1 with p values from chi square and Mann Whitney U tests.

(2) a sentence added just above table 1 reading "There was no association between exposure and either social deprivation or urbanicity."

- Page 12
- Line 12 to 14 The analysis would benefit from a sample size calculation to determine if these numbers provide adequate power to detect a difference in mortality between groups.

Post hoc power calculations are strongly discouraged in the statistical literature. For example see John M Hoenig & Dennis M Heisey (2001) The Abuse of Power, The American Statistician, 55:1, 19-24, DOI: 10.1198/000313001300339897 who state 'There is also a large literature advocating that power calculations be made whenever one performs a statistical test of a hypothesis and one obtains a statistically nonsignificant result. Advocates of such post-experiment power calculations claim the calculations should be used to aid in the interpretation of the experimental results. This approach, which appears in various forms, is fundamentally flawed. We document that the problem is extensive and present arguments to demonstrate the flaw in the logic.'

Higher doses of opioid and benzodiazepines have both been associated with increased odds of death in the literature. The amount of opioid should be determined in each arm as a sensitivity analysis to adjust for other potential confounders. If this is not possible, an explanation as to why this analysis wasn't completed should be undertaken.

The reviewer is correct that this is a limitation of the study. We have listed this as a methodological weakness of the study in the 'strengths and limitations' section.

The discussion would benefit from comparison to other studies that looked at mortality associated with co-prescription. Some examples:

- 5.Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ. 2015; 350:h2698

- 10.Overdyk FJ, Dowling O, Marino J, Qiu J, Chien HL, Erslon M, et al. Association of opioids and sedatives with increased risk of in-hospital cardiopulmonary arrest from an administrative database. PLoS One. 2016;11(2):e0150214.

- 11. Cho J, Spence MM, Niu F, Hui RL, Gray P, Steinberg S. Risk of overdose with exposure to prescription opioids, benzodiazepines, and nonbenzodiazepine sedative-hypnotics in adults: a retrospective cohort study. J Gen Intern Med. 2020;35(3):696-703.

- 12. Liang Y, Goros MW, Turner BJ. Drug overdose: differing risk models for women and men among opioid users with non-cancer pain. Pain Med. 2016;17(12):2268-79.

- 13. Dasgupta N, Funk MJ, Proescholdbell S, Hirsch A, Ribisl KM, Marshall S. Cohort study of the impact of high-dose opioid analgesics on overdose mortality. Pain Med. 2016;17(1):85-98.

- 14. Day C. Benzodiazepines in combination with opioid pain relievers or alcohol: greater risk of more serious ED visit outcomes. In: The CBHSQ report. Substance Abuse and Mental Health Services Administration (US); 2014. p. 1-9. 15. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S

Thank you for these suggestions. Our focus was to compare to other suggested studies cover, as opposed to a pain population (acknowledging there is some overlap). However we have added a paragraph which notes these risks in other clinical populations and more generally. We did not feel it was appropriate to go into detail for these studies as some are off the focus of our analysis and therefore less comparable than those already referenced. Too much detail could be distracting. We hope we have got the balance right.

VERSION 2 – REVIEW

REVIEWER	Lewer, Dan University College London, Institute of Epidemiology and Healthcare
REVIEW RETURNED	31-Jan-2024

GENERAL COMMENTS	Many thanks for sending this manuscript to me again. As explained in my first review, I think the major limitation of this study is that patients prescribed benzodiazepines will be different to patients not prescribed benzodiazepines (ie. confounding). This limitation is clearly highlighted in the "strengths and limitations of this study" box and in the discussion. I think the authors are confident the observed association reflects a causal relationship because other studies have found larger associations. I might have been more circumspect, as these other studies might have suffered from other problems. However, I think this is a useful study about a very important topic and I hope the authors will continue to pursue this research agenda. Thanks again for the opportunity to provide feedback on this study.

REVIEWER	Just, Johannes Universitatsklinikum Bonn, Institute of General Practice and Family Medicine
REVIEW RETURNED	31-Jan-2024

GENERAL COMMENTS	None.