PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparing asphyxia and unexplained causes of death: a retrospective cohort analysis of sleep-related infant death cases from a state child fatality review program
AUTHORS	Macdonald, Megan; Thompson, Daniel; Perry, Robin; Brooks, Robert

VERSION 1 – REVIEW

REVIEWER	Young, Jeanine University of the Sunshine Coast, School of Nursing & Midwifery
REVIEW RETURNED	29-Dec-2021

GENERAL COMMENTS	For all articles This retrospective comparative study of a 5-year cohort of infants who died in Florida (2014-2018) examines characteristics associated with unexplained infant deaths for infants who died in sleeping environments. The study was stated as a cross-sectional analysis (Abstract) however would be more accurately described as a retrospective cohort design with comparative analysis involving infant deaths occurring 2014-2018. While this study was not original it contributes to existing knowledge, supporting previous findings internationally. Results further supported that known risk factors and infant characteristics previously demonstrated to be associated with SUDI remain prevalent within this cohort, with the subgroup analysis illustrating that deaths classified as unexplained and those attributed to asphyxia has similar characteristics, further supporting consistent and standardised infant death investigation processes internationally. The study aim that underpinned this manuscript was clearly articulated and achievable within the retrospective cohort design that used sub-group comparisons - however classification of partial, complete and unknown asphyxia requires detail of criterion used in allocating these cases to these groups. Data analysis methods were described and appropriate for the comparative analysis conducted. Ethical approval information was stated as not necessary; this is interesting as in other countries or jurisdictions a further information relating to ethical approval processes and/or exemption status would be required. The ethical statement in this manuscript ideally should clarify clearly that ethical approval or use of sensitive de-identifiable data without patient permission was not required. The study abstract provided a coherent and clear summary of this study however a clearer description of retrospective cohort design is required. Improvements Abstract: This study would be better described as a retrospective

	cohort of infant deaths than a cross sectional analysis. The study was stated as a cross-sectional analysis (Abstract) however would be more accurately described as a retrospective cohort design with comparative analysis involving infant deaths occurring 2014-2018. Please define NCDR CRS - assuming National Child Death Review CRS but this was assumed and not provided before abbreviation used. Page 6 of 23, Line 27: May wish to note Shipstone et al., 2019 in which a reclassification exercise was undertaken; this supported differences in practices in Australia as an example of other countries, not just USA. Krous classification system was demonstrated to have high level of agreement when applied consistently by an experienced child death review team that also provided inter-rater reliability comparisons. Page 8 of 23, Line 33: Considerable limitation; recent review (Shipstone et al 2019) demonstrated reduction of natural causes from 14.5% to 9.2%. Page 9 of 23, Line 10-14: Statement here is required that ethical approval of use of records without patient permission was not required. eg. Due to the retrospective nature of the study, ethical approval included a waiver of the requirement for participant consent to use their information. Permission to access coronial documents was granted under XXXXXXXXXXXXX (Eg in Qld this would be Part 3 Section 53 of the Coroners Act 2003). Page 10 and 17 of 25: Line 43-39: Further detail is required for criteria used to determine partial, complete and unknown airway obstruction as this appeared to be a defining characteristic for comparisons. Please provide outcomes of independent reliability checking of categories used to determine asphyxial deaths versus those which remained 'unexplained' by research team, or inter-rater reliability checking between local CADR committees (indicated as more than one) which performed reviews of case records to provide context for any potential differences in coding practices at that level given these appear to be committees that focus on suspicion of abuse and neglect in the first instance, although final determination of infant deaths did not necessarily include child maltreatment. Use of CADR was noted as a limitation but not the checking of inter-rater reliability between committees. If criteria not clear from CADR, or inter-rater reliability not noted between CADR committees or assessed independently by members of author team, please note as limitation due to potential bias in assessment criteria used between CADR teams that may differ with other CDR team approaches internationally.

REVIEWER	Ramakrishnan , Rema George Institute Oxford
REVIEW RETURNED	07-Feb-2022

GENERAL COMMENTS	The authors used data from the Florida Child Abuse Death Review program and death certificate data and aimed to describe the demographic characteristics, sleep environment risk factors and other incident circumstances for sleep-related infant deaths that occurred in Florida from 2014 to 2018 and assess the relationship

between these factors and the likelihood of an unexplained cause of death.

MAJOR COMMENTS
The methods' section is poorly written (specifics given below). The authors have not described the independent variables/exposures for this study in sufficient detail. The method (based on p-value threshold) for selection of final model is sub-optimal; therefore, the reliability of the results from the multivariable regression models is questionable.

SPECIFIC COMMENTS

Title: This title seems misleading because only deaths due to unintentional asphyxia or unexplained cause were included. Please change the title to reflect the research question and methods.

Abstract: Please provide relevant prevalence ratios rather than just providing text.

Introduction
Page 5, lines 18-26: Please provide rate/statistic for SUIDs due to sleep-related factors and modifiable risk factors instead of saying 'most' and 'many' SUIDs.

Methods
Please provide flowchart of participants.

The description of the data source could be shortened to some extent.

Page 8, lines 50-56: In the STROBE statement, for the section on variables, 'clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers', the authors have given that this information is given on page 7. However, very little information is given on exposures, predictors, potential confounders, and effect modifiers.
Please provide sufficient information about demographic characteristics, sleep environment risk factors and other incident circumstances for sleep-related infant deaths in separate paragraphs. That is, please provide a separate paragraph that briefly describes the variables for demographic characteristics, another paragraph for sleep environment risk factors and other incident circumstances for sleep-related infant deaths.

Data Analysis:
All the variables included in the study are independent variables/exposures. The research question was to examine the relationship between demographic characteristics, sleep environment risk factors and other incident circumstances for sleep-related infant deaths and the likelihood of an unexplained cause of death and not a subset of these factors (significant factors based on p-values). As such, they are not covariates and one should report the statistic for each one of them and not use methods such as p-values to select few variables for the regression models.
Another issue is that for the adjusted models, one cannot use a single multivariable model to compute the prevalence ratios for all the independent variables in the study. Please select the covariates for each variables judiciously and not use a common list for all variables. For example, to compute the prevalence ratios for 'sex'

	there might be a different list of variables in the final model compared to when has to compute the prevalence ration for the variable, airway obstruction. It would be more appropriate to use a robust method such as a DAG to select the variables for the adjusted model. Please refer to 'Principles of confounder selection' by VanderWeele to select variables in the adjusted model for each factor https://pubmed.ncbi.nlm.nih.gov/30840181/ . Smoking is an important variable for SUIDs. Why wasn't this included in this study? The authors have used the terms, sex and gender, interchangeably. Please use a consistent term; preferably, sex Please describe how missing data was accounted for in the analysis and what sensitivity analyses were conducted to examine the impact of missing data on the results. Results It is unnecessary to include p-values in all the tables; therefore, please delete the p-value columns. For Tables 1 & 2 the differences in characteristics are self-evident. In addition to this, the p-value is reported for the overall variable and not for specific categories. For example, there is a clear difference between both groups in the percentage for the variable, 'Position when found'; however, the overall p-value is 0.10. For Table 3, it is sufficient to report confidence intervals; p-values do not provide any additional information. For example, for sex the lower confidence limit is close to zero but p-value is 0.03. Did the authors test for multicollinearity? It seems some of the variables included in the multivariable model such as sleep location and sharing sleep surface could be highly correlated which could have biased the findings – for example, the prevalence ratio for couch/bed vs crib was 0.65 in the unadjusted model but 1.03 in the adjusted model. Discussion Could you please explain or provide evidence on how missing values impacted the results? Could the authors please describe how the findings from this study aligns with studies that used data from child fatality review program to examine SUIDs? Contributor's Statement Ms. Macdonald and Dr. Brooks carried out the initial analysis. Please clarify who conducted the final analysis.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1. The study was stated as a cross-sectional analysis (Abstract) however would be more accurately described as a retrospective cohort design with comparative analysis involving infant deaths occurring 2014-2018.

We agree that retrospective cohort is a more accurate description of the study design nd have changed it.

2. Please define NCDR CRS - assuming National Child Death Review CRS but this was assumed and not provided before abbreviation used.

The database acronym has been amended and defined accordingly. Initially, we chose an acronym taken from state agency documentation, but we now feel that it would be more appropriate and recognizable to readership to use the "National Fatality Review Case Reporting System" or NFR-CRS to describe this data source.

3. Page 6 of 23, Line 27: May wish to note Shipstone et al., 2019 in which a reclassification exercise was undertaken; this supported differences in practices in Australia as an example of other countries, not just USA. Krous classification system was demonstrated to have high level of agreement when applied consistently by an experienced child death review team that also provided inter-rater reliability comparisons.

Thank you for this suggestion. The Shipstone reference has been added in the discussion section.

4. Page 8 of 23, Line 33: Considerable limitation; recent review (Shipstone et al 2019) demonstrated reduction of natural causes from 14.5% to 9.2%.

We have included this as a limitation and also added a Shipnote citation to the discussion section.

5. Page 9 of 23, Line 10-14: Statement here is required that ethical approval of use of records without patient permission was not required.

eg. Due to the retrospective nature of the study, ethical approval included a waiver of the requirement for participant consent to use their information. Permission to access coronial documents was granted under XXXXXXXXXXXXX (Eg in Qld this would be Part 3 Section 53 of the Coroners Act 2003).

We have added a statement regarding ethical approval of record use without patient permission.

6. Page 10 and 17 of 25: Line 43-39: Further detail is required for criteria used to determine partial, complete and unknown airway obstruction as this appeared to be a defining characteristic for comparisons.

Please provide outcomes of independent reliability checking of categories used to determine asphyxial deaths versus those which remained 'unexplained' by research team, or inter-rater

reliability checking between local CADR committees (indicated as more than one) which performed reviews of case records to provide context for any potential differences in coding practices at that level given these appear to be committees that focus on suspicion of abuse and neglect in the first instance, although final determination of infant deaths did not necessarily include child maltreatment. Use of CADR was noted as a limitation but not the checking of inter-rater reliability between committees.
If criteria not clear from CADR, or inter-rater reliability not noted between CADR committees or assessed independently by members of author team, please note as limitation due to potential bias in assessment criteria used between CADR teams that may differ with other CDR team approaches internationally.

A more detailed description of criteria used to determine airway obstruction has been added to the methods section under "Study Sample." The limitation due to bias introduced in the absence of reliability checking between CADR committees in the assessment of cause of death has been added to the discussion section.

Reviewer 2

1. This title seems misleading because only deaths due to unintentional asphyxia or unexplained cause were included. Please change the title to reflect the research question and methods.

Thank you for your suggestion. The title has been changed to "Comparing asphyxia and unexplained causes of death: a retrospective cohort analysis of sleep-related infant death cases from a state child fatality review program."

2. Please provide relevant prevalence ratios rather than just providing text.

We have added the relevant adjusted prevalence ratios to the results section of the abstract.

3. Page 5, lines 18-26: Please provide rate/statistic for SUIDs due to sleep-related factors and modifiable risk factors instead of saying 'most' and 'many' SUIDs.

The sources, the American Academy of Pediatrics' Task Force on Sudden Infant Death Syndrome technical report and policy statement, unfortunately did not provide these statistics, but stated that sleep-related deaths included SIDS, accidental suffocation and strangulation in bed and ill-defined deaths, which comprise the major categories of SUID.

4. Please provide flowchart of participants.

A flowchart has been added as a supplementary document.

5. The description of the data source could be shortened to some extent.

We have shortened the description of the data source.

6. Page 8, lines 50-56: In the STROBE statement, for the section on variables, 'clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers', the authors have given that this information is given on page 7. However, very little information is given on exposures, predictors, potential confounders, and effect modifiers.

We have added more information on independent variable definitions. All independent variables are assessed for association with the dependent variable and are adjusted for potential confounding due to correlations among the independent variables, but the terms exposures, predictors, potential confounders, and effect modifiers would not be applicable in describing this analysis.

7. Please provide sufficient information about demographic characteristics, sleep environment risk factors and other incident circumstances for sleep-related infant deaths in separate paragraphs. That is, please provide a separate paragraph that briefly describes the variables for demographic characteristics, another paragraph for sleep environment risk factors and other incident circumstances for sleep-related infant deaths.

Thank you for this suggestion which we think adds clarity to the methods. Additional details about the demographic characteristics, sleep environment risk factors and other incident circumstances for sleep-related infant deaths have been added and arranged in separate paragraphs.

8. All the variables included in the study are independent variables/exposures. The research question was to examine the relationship between demographic characteristics, sleep environment risk factors and other incident circumstances for sleep-related infant deaths and the likelihood of an unexplained cause of death and not a subset of these factors (significant factors based on p-values). As such, they are not covariates and one should report the statistic for each one of them and not use methods such as p-values to select few variables for the regression models.

For clarity and consistency, we have replaced the word "covariates" with "independent variables" in the text. We ran an adjusted model with all variables and the results were very close to the results of our final adjusted model with only the significant variables.

9. Another issue is that for the adjusted models, one cannot use a single multivariable model to compute the prevalence ratios for all the independent variables in the study.

Please select the covariates for each variables judiciously and not use a common list for all variables. For example, to compute the prevalence ratios for 'sex' there might be a different list of variables in the final model compared to when has to compute the prevalence ration for the variable, airway obstruction. It would be more appropriate to use a robust method such as a DAG to select the variables for the adjusted model. Please refer to 'Principles of confounder selection' by VanderWeele to select variables in the adjusted model for each factor https://pubmed.ncbi.nlm.nih.gov/30840181/.

The intent of our study was to assess the relationships between all independent variables and the dependent variable. In this context adjusting is used to assess the association between the independent variables and the dependent variable adjusting for the influence of any associations between the independent variables. We felt that excluding some of the independent variables might remove potential influence of associations between the independent variables.
All independent variables were selected based on their relevance to sleep-related infant death according to previous literature and subset of these variables were further selected for multivariate regression analysis if they were found to be statistically significantly associated with unexplained cause of death vs asphyxia in the univariate chi-square analysis. We understand that variable selection models are often useful, particularly in analyses which are designed to assess causal relationships, however in this study we did not aim to establish causality between any of the independent variables of interest and the outcome, but rather to assess the statistical associations between each independent variable and the outcome of an unexplained death classification.

10. Smoking is an important variable for SUIDs. Why wasn't this included in this study?

While smoking is a known risk factor for SUIDs, other studies similar to this one did not include it as a predictor of specific causes of death within SUID. Also, while second-hand smoke exposure is a data element in the NFR-CRS, a very high proportion of these values were unknown (44%) in the study sample, which we believed made it unsuitable for the analysis. For these reasons, we decided not to include smoking in this study.

11. The authors have used the terms, sex and gender, interchangeably. Please use a consistent term; preferably, sex.

Thank you for this suggestion. Gender has been changed to sex for consistency.

12. Please describe how missing data was accounted for in the analysis and what sensitivity analyses were conducted to examine the impact of missing data on the results.

Missing values were a small enough proportion of the data set that we believed a sensitivity analysis was not necessary. A sentence about missing data has been added to the methods section under "Data Analysis."

13. It is unnecessary to include p-values in all the tables; therefore, please delete the p-value columns. For Tables 1 & 2 the differences in characteristics are self-evident. In addition to this, the p-value is reported for the overall variable and not for specific

categories. For example, there is a clear difference between both groups in the percentage for the variable, 'Position when found'; however, the overall p-value is 0.10. For Table 3, it is sufficient to report confidence intervals; p-values do not provide any additional information. For example, for sex the lower confidence limit is close to zero but p-value is 0.03.

P-values have been removed from Table 3, since confidence limits around the prevalence ratios are sufficient to determine the statistical significance of each estimate. For Tables 1 & 2, we preferred to keep p-values there to denote statistical significance, as confidence limits alone would be insufficient to make this determination for a simple proportion.

14. Did the authors test for multicollinearity? It seems some of the variables included in the multivariable model such as sleep location and sharing sleep surface could be highly correlated which could have biased the findings – for example, the prevalence ratio for couch/bed vs crib was 0.65 in the unadjusted model but 1.03 in the adjusted model.

A variance inflation factor analysis was performed for the adjusted model and the results showed that all but one of the independent variables in the model had VIFs between 1.0 and 2.0. Fully obstructed airway condition and unknown airway condition, respectively, had VIFs of 3.2 and 3.3. While there is no universal standard for determining a cutoff based on VIF values, we interpreted this result to indicate moderate correlation and followed the VIF analysis with a correlation test. The correlation test showed moderate correlation (r=0.20) of airway obstruction with the outcome variable (unexplained cause of death) but not with any of the other independent variables. Type of sleep surface and sleep surface sharing had an r value of 0.25, which indicated to us that multicollinearity should not be a problem.

15. Could you please explain or provide evidence on how missing values impacted the results?

Missing values were very low (at a range of 0-3.7% in five of the variables studied) and were relatively evenly distributed between the two outcome groups. Based on this observation, we believed missing data were unlikely to have affected the results.

16. Could the authors please describe how the findings from this study aligns with studies that used data from child fatality review program to examine SUIDs?

We have added a description of how our findings align with other studies using CDR data in the discussion section.

17. Ms. Macdonald and Dr. Brooks carried out the initial analysis. Please clarify who conducted the final analysis.

Ms. Macdonald conducted the final analysis. This clarification has been added to the contributor's statement.

VERSION 2 – REVIEW

REVIEWER	Young, Jeanine University of the Sunshine Coast, School of Nursing & Midwifery
REVIEW RETURNED	01-May-2022

GENERAL COMMENTS	Thankyou for making suggested revisions. I have noted several minor revisions in your resubmitted version for noting: Point 1: Page 6: Lines 31-38 As the study was a retrospective analysis performed using an existing data set, ethical approval for use of the records without patient permission was not required . Please rewrite this to: As the study was a retrospective analysis performed using an existing data set, the relevant ethical governance committee determined that this study was exempt from IRB review. Please reframe this as from an ethical perspective this is not entirely consistent with international practice across jurisdictions - many ethical committees required review of access to existing datasets and make a determination for an exemption based on the ethical principles and the consent process for the original study - many would review and provide an exemption for the need for direct consent from original participants for a study like this (based on the ethical principle of beneficence) however this is not consistent with the statement made that due to this being a retrospective study of an existing dataset, approval for use of records without patient permission is not required. As the study was a retrospective analysis performed using an existing data set, the relevant ethical governance committee determined that this study was exempt from IRB review. Point 2: missing references Refs 10 and 11 are missing from manuscript, In reference list 10 and 11 appear to relate to the sentence: The diagnostic shift is thought to be influenced by several factors: stricter adherence to SIDS definitions, a greater understanding of environmental risk factors for SUIDs, improvement in the quality of death scene investigation (DSI), more thorough autopsy practices and influence from child death review teams.5 8 9 Point 4: Page14: Lines 21-22 - reference 16 is mentioned twice: 16sex16 Point 5: Page 16, Line 23-23: edit causing to contributing - SUID is a classification, not a ‘cause’ of death…the role the sleep environment played in contributing to the death

REVIEWER	Ramakrishnan , Rema George Institute Oxford
REVIEW RETURNED	12-May-2022

GENERAL COMMENTS	Thank you for responding to the comments and revising the paper accordingly. The paper has improved a lot, but I still have major

	concerns about the methodology used and the over-emphasis on findings from the descriptive analyses the details of which are given below. ABSTRACT Results: Lines 9-10: Please add, 'compared to unintentional asphyxia' after 'unexplained cause of death' and avoid using the term, significantly. It is sufficient to say, associated with an unexplained cause of death. The confidence intervals can enable to assess if the findings are significant or not. INTRODUCTION Page 3, lines 10-14: It is unclear what risk factors the authors are referring to. Presumably, it is risk factors related to sleep environment. If yes, please specify. METHODS The abbreviation, NFR-CRS, was elaborated in the abstract. Please state the full form in the main text too (on page 32, lines 37-38). Page 4, lines 28-30: It is unclear what is meant by incident characteristic. In epidemiological studies, incident would indicate new occurrence of an outcome. Therefore, it is unclear what is meant by incident here. Even though the results from the model with all variables were very close to the results of our final adjusted model it is preferable to not resort to significant p-values to determine the list of variables to be retained in the model. And this is applicable not only to causal models but to all models. The authors' response that the aim was not to establish causality but rather to assess the statistical associations between each independent variable and the outcome of an unexplained death classification is not sufficient. It is difficult to establish causality in most observational studies (except using methods such as Mendelian randomization and more advanced causal methods) and most published studies are about associations. There are multiple epidemiologic and statistical papers that discourage the use of p-value to retain variables in the model. Please delete the information on lines 46-54 that refer to this and report the results from the models with all variables. Alternatively, please provide a more robust method for variable selection, preferably by citing a recent paper that has used this method. Page 6, lines 53-57: I apologize for an oversight when I reviewed this paper previously. The measure of effect depends on the nature of the outcome and not the independent variables. Prevalence cannot be a measure for death. Therefore, one cannot have prevalence ratios for death. It should be risk ratio or rate ratio. Please revise accordingly (abstract, methods, results, Table 3, and discussion) Page 7, lines 3-9: It is not necessary to say why negative binomial regression was used. Therefore, these lines can be deleted. As mentioned before, please delete the p-values in Tables 1 and 2 as they do not provide any important information. One can assess which variables are important by examining the descriptive statistics. STROBE guidelines discourage the reporting of p-values for descriptive tables (Please refer to the paper: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE):

	Explanation and Elaboration – Vandenbroucke JP et al, 2007, Annals of Internal Medicine). TABLE 3 It is sufficient to have the column as risk or rate ratio (95%CI). Please delete the word, Unexplained. DISCUSSION Page 13, lines 19-20: Shouldn't this be NFR-CRS instead of CADR? Lines 30-33: It is not advisable to report results as statistically meaningful relationship. It would have been acceptable to report as clinically meaningful or meaningful in terms of public health significance but not statistically meaningful relationship. Therefore, please rephrase (for example, these factors were associated with cause of death classification) or delete these words. Page 13, lines 35-45: The information conveyed here is unclear and not statistically relevant or robust (except perhaps the small sample size). The authors have perhaps tried to over-emphasize the important of significant results in the descriptive analyses and non-significant results in the regression models. This is not the important message of the study and would also be an incorrect way to interpret the findings. Please delete these lines (and comment on the small sample size in the limitations section). Page 13, lines 40- 45: It is unclear what the authors are trying to convey. If statistical assumptions are not met one cannot use a regression model and if used the results from these models are biased. Based on then comments above, lines 28- 44 can be deleted. Page 13, lines 44-45: The words, initial findings in this study, can be deleted because it's unclear what initial findings this refers to. It is sufficient to say, Findings from this study are consistent with other research showing that cause of death classification varies based… FLOWCHART Shouldn't it be NFR-CRS instead of NCDR CRS database?

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

1. Page 6: Lines 31-38; As the study was a retrospective analysis performed using an existing data set, ethical approval for use of the records without patient permission was not required. Please rewrite this to: As the study was a retrospective analysis performed using an existing data set, the relevant ethical governance committee determined that this study was exempt from IRB review.

Please reframe this as from an ethical perspective this is not entirely consistent with international practice across jurisdictions - many ethical committees required review of access to existing datasets and make a determination for an exemption based on the ethical principles and the consent process for the original study - many would review and provide an exemption for the need for direct consent from original participants for a study like this (based on the ethical principle of beneficence) however this is not consistent with the statement

made that due to this being a retrospective study of an existing dataset, approval for use of records without patient permission is not required.
As the study was a retrospective analysis performed using an existing data set, the relevant ethical governance committee determined that this study was exempt from IRB review.

Thank you. The statement has been revised accordingly.

2. Missing references: Refs 10 and 11 are missing from manuscript, In reference list 10 and 11 appear to relate to the sentence: The diagnostic shift is thought to be influenced by several factors: stricter adherence to SIDS definitions, a greater understanding of environmental risk factors for SUIDs, improvement in the quality of death scene investigation (DSI), more thorough autopsy practices and influence from child death review teams.5 8 9

Thank you, this has been corrected.

3. Lines 21-22 - reference 16 is mentioned twice: 16sex16

Unfortunately we were unable to locate this error in the manuscript we submitted as part of the first revision package.

4. Page 16, Line 23-23: edit causing to contributing - SUID is a classification, not a 'cause' of death…the role the sleep environment played in contributing to the death

The sentence has been edited accordingly.

Reviewer 2

1. Results: Lines 9-10: Please add, 'compared to unintentional asphyxia' after 'unexplained cause of death' and avoid using the term, significantly. It is sufficient to say, associated with an unexplained cause of death. The confidence intervals can enable to assess if the findings are significant or not.

Thank you, the results section of the abstract has been revised accordingly.

2. Page 3, lines 10-14: It is unclear what risk factors the authors are referring to. Presumably, it is risk factors related to sleep environment. If yes, please specify.

We have added specific examples next to the term "sleep environment risk factors" in the statement referenced.

3. The abbreviation, NFR-CRS, was elaborated in the abstract. Please state the full form in the main text too (on page 32, lines 37-38).

Thank you, the full name has been added in the main text.

4. Page 4, lines 28-30: It is unclear what is meant by incident characteristic. In epidemiological studies, incident would indicate new occurrence of an outcome. Therefore, it is unclear what is meant by incident here.

We have modified the statement on lines 28-30 to clarify.

5. Even though the results from the model with all variables were very close to the results of our final adjusted model it is preferable to not resort to significant p-values to determine the list of variables to be retained in the model. And this is applicable not only to causal models but to all models. The authors' response that the aim was not to establish causality but rather to assess the statistical associations between each independent variable and the outcome of an unexplained death classification is not sufficient. It is difficult to establish causality in most observational studies (except using methods such as Mendelian randomization and more advanced causal methods) and most published studies are about associations. There are multiple epidemiologic and statistical papers that discourage the use of p-value to retain variables in the model. Please delete the information on lines 46-54 that refer to this and report the results from the models with all variables. Alternatively, please provide a more robust method for variable selection, preferably by citing a recent paper that has used this method.

We have included all independent variables in the final regression model, updated the results and removed the text in the methods section of the paper indicating that p-values were used to select variables for regression.

6. Page 6, lines 53-57: I apologize for an oversight when I reviewed this paper previously. The measure of effect depends on the nature of the outcome and not the independent variables. Prevalence cannot be a measure for death. Therefore, one cannot have prevalence ratios for death. It should be risk ratio or rate ratio. Please revise accordingly (abstract, methods, results, Table 3, and discussion).

We removed the term "prevalence ratio" from the text and results table and replaced it with "risk ratio."

7. Page 7, lines 3-9: It is not necessary to say why negative binomial regression was used. Therefore, these lines can be deleted.

These lines have been deleted.

8. As mentioned before, please delete the p-values in Tables 1 and 2 as they do not provide any important information. One can assess which variables are important by examining the descriptive statistics. STROBE guidelines discourage the reporting of p-values for descriptive tables (Please refer to the paper: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration – Vandenbroucke JP et al, 2007, Annals of Internal Medicine).

P-values have been removed from the tables.

9. It is sufficient to have the column as risk or rate ratio (95%CI). Please delete the word, Unexplained.

The word "unexplained" has been removed from the table columns.

10. Page 13, lines 19-20: Shouldn't this be NFR-CRS instead of CADR?

Thank you, we agree that NFR-CRS is more appropriate here. The text has been updated accordingly.

11. Lines 30-33: It is not advisable to report results as statistically meaningful relationship. It would have been acceptable to report as clinically meaningful or meaningful in terms of public health significance but not statistically meaningful relationship. Therefore, please rephrase (for example, these factors were associated with cause of death classification) or delete these words.

Page 13, lines 35-45: The information conveyed here is unclear and not statistically relevant or robust (except perhaps the small sample size). The authors have perhaps tried to over-emphasize the important of significant results in the descriptive analyses and non-significant results in the regression models. This is not the important message of the study and would also be an incorrect way to interpret the findings. Please delete these lines (and comment on the small sample size in the limitations section).

Page 13, lines 40- 45: It is unclear what the authors are trying to convey. If statistical assumptions are not met one cannot use a regression model and if used the results from these models are biased.

Based on then comments above, lines 28- 44 can be deleted.

These lines have been deleted from the text.

12. Page 13, lines 44-45: The words, initial findings in this study, can be deleted because it's unclear what initial findings this refers to. It is sufficient to say, Findings from this study are consistent with other research showing that cause of death classification varies based…

The statement has been modified as suggested.

13. Shouldn't it be NFR-CRS instead of NCDR CRS database?

Yes, thank you for noting, the correction has been made.