PEER REVIEW HISTORY

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### ARTICLE DETAILS

<table>
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<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Risk Factors Associated with Contrast-Associated Acute Kidney Injury in ST-Segment Elevation Myocardial Infarction Patients: A Systematic Review and Meta-Analysis</th>
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<tbody>
<tr>
<td>AUTHORS</td>
<td>Ye, Jiahao; Liu, Chaoyun; Deng, Zhanyu; Zhu, Youfeng; Zhang, Shaoheng</td>
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### VERSION 1 – REVIEW

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<th>REVIEWER</th>
<th>Kurtul, Alparslan</th>
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<td></td>
<td>Ankara Numune Education and Research Hospital Nephrology Clinic, Cardiology</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>21-Dec-2022</td>
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**GENERAL COMMENTS**

In this Review and Meta-Analysis, the authors examined Risk Factors Associated with CA-AKI in STEMI. They concluded that left anterior descending artery infarction, left main disease, and multivessel disease are risk factors for CA-AKI as well as traditional risk factors. This findings are interesting to report, but it is however, not entirely new. For example, there are 66 papers in Pubmed with the search term " CIN and STEMI risk factors", many of which are closely related to your submission. An additional minor comment: the grammar and the style of the manuscript can be improved.

<table>
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<th>REVIEWER</th>
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<td></td>
<td>Zhongshan Hospital, Fudan University, Cardiology</td>
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<td>REVIEW RETURNED</td>
<td>10-Feb-2023</td>
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**GENERAL COMMENTS**

Dr. Ye, et al performed a meta-analysis to evaluate the risk factors for contrast-associated acute kidney injury (CA-AKI) in ST-elevation myocardial infarction patients. The study showed that left anterior descending artery-related infarction, left main disease, and multivessel disease are risk factors for CA-AKI and the paradoxical short-term protective effect of smoking and family history of coronary. There are two major concerns about the methodology of data collection:

i) Mehran R, et al published a simple risk score to identify high-risk patients for AKI after STEMI in 2004. An analysis of data from 985,737 patients undergoing PCI confirmed that severe chronic kidney disease was the strongest independent risk factor for CA-AKI in 2014. The meta-analysis only included the observational studies from 2015 to 2020. More studies with large sample size and high data quality should be included.

ii) There was significant heterogeneity among the studies in the baseline characteristics of the patients and the diagnostic criteria.
of CA-AKI. The Newcastle-Ottawa Scale (NOS) or another tool should be used to perform the quality evaluation of the including studies.

**GENERAL COMMENTS**

In general, this is a well-described meta-analysis for assessing predictors associated with contra-associated acute kidney injury. While the primary analyses are well-described, detail is lacking regarding the choices surrounding subgroup and secondary analyses.

Please specify the rationale for the presented additional analyses. Were these pre-planned, included due to the paradoxical nature of the findings, or based on some other criteria? Were additional analyses presented for all variables that met these criteria? Was the decision to perform subgroup analyses for contrast volume by type of contrast agent a pre-planned analyses or did it arise due to patterns observed in the analyses? The presentation of the tables and figures is also unexpected, with the tables for the primary analysis include as a supplement (although they are quite large) and many subgroup/secondary results presented in the manuscript.

The selection method for the variables for each of the meta-regressions should be addressed. These varied and it was not clear why these variables were selected or why they differed (due to availability, different presumptions of clinical relevance for each analysis, etc.?). Clearly specifying these variables up front and the rationale for their selection would also improve the presentation of these results. For example, on page 11 (lines 12-20) the results of the meta-regression provide a list (but only a subset of the tested variables) that are not associated with heterogeneity. This immediately leads one to wonder if there are other variables that do have a significant association. A statement along the lines of “none of the variables tested were associated with heterogeneity including …” would allow for the authors point to made without having to list of the variables in the results. If there were variables that ideally should have been included but weren’t available (perhaps baseline renal function?) this should be listed as a limitation and could be addressed when presenting the variables for inclusion.

Given that none of the variables used in the meta-regression had a significant association with heterogeneity, the tables in Supplement C are not particularly informative in their current form. These tests also tend to lack power and the lack of significance may not necessarily indicate that these variables are not important. The addition of confidence intervals (instead of the standard error) would provide more context. If deemed relevant, other measures such as residual heterogeneity may also be considered.

In the methods, the quality of each included study was scored. I did not see that either the results of this assessment were presented in the manuscript or that the data were used. If not already presented, please report on this information in the manuscript. Similarly, other methods such as the funnel plots and Egger test for publication bias are not generally presented. Results are only mentioned for 1 or 2 specific subgroup/secondary analyses. An overall general statement, especially as pertains to the primary analyses would be warranted.
Limitation Section: Should restate in the limitation section that the results can only identify factors associated with CA-AKI and cannot assess causality. As noted above, consider mentioning key variables that could not be included in the meta-regression analyses. For the overall prevalence I² = 93% and none of the factors considered were significant.

Minor edits and comments.
Page 11 line 48, should read “significantly” not significant.
Page 12 line 48, the phrase “Stable result was obtained” is awkward.
Page 14 lines 12-13. What was the significance of the funnel plot becoming nearly symmetrical with the removal of the two studies? This may be the only mention in the results of the use of the funnel plots, so no other context is provided to the reader.

Page 16 line 28, "recommend that more homogeneous researches be carried out …” should be revised.
Page 16 lines 46 to 51. “Differences between the studies in the CA-AKI diagnostic criteria and the eGFR estimation method may be responsible for our negative result.” This sentence should be clarified. Is the “negative result” the lack of statistical significance between countries?

Page 17 line 20. The word Paradoxical should be used in the heading “Paradox Findings.” However, it is not clear that all these results are paradoxical or unexpected, so another heading title may be appropriate.
Page 18 line 48, “mechanisms by which smoking affects the incidence of CA-AKI”, consider revising so that it does not imply that this study found a causal relationship between smoking and the incidence of CA-AKI.

Figure 4B, consider add a reference line at 1.0 to help clearly identify the instances that are non-significant.

Responses to Reviewer 1:
Reviewer’s comment 1:
They concluded that left anterior descending artery infarction, left main disease, and multivessel disease are risk factors for CA-AKI as well as traditional risk factors. This findings are interesting to report, but it is however, not entirely new. For example, there are 66 papers in Pubmed with the search term “CIN and STEMI risk factors”, many of which are closely related to your submission.
Our response:
Thanks for pointing out this problem. We agree that some studies have suggested a potential relationship between culprit artery and CA-AKI. However, the results of these studies are inconsistent, and several of them were limited by single-center design with small sample sizes. In our study, we conducted a systematic review and meta-analysis to summarize up-to-date evidences, and might highlight new perspectives in preventing CA-AKI in the patients with different coronary artery diseases.

Reviewer’s comment 2:
The grammar and the style of the manuscript can be improved.
Our response:
We appreciate the comments of the reviewer. We have asked English-speaking professionals to revise the full text to make the article more readable for general readers of BMJ Open.

Responses to Reviewer 2:
Reviewer’s comment 1:
Mehran R, et al published a simple risk score to identify high-risk patients for AKI after STEMI in 2004. An analysis of data from 985,737 patients undergoing PCI confirmed that severe chronic kidney disease was the strongest independent risk factor for CA-AKI in 2014. The meta-analysis only included the observational studies from 2015 to 2020. More studies with large sample size and high data quality should be included.
Our response:
It is really true as reviewer mentioned that more well-designed studies with large sample are needed. Although we have not imposed stringent restrictions on the publication date, as stated in the submission [from the establishment of the database to February 2022 (Line 8-Line 9 Page 2)], analyses of some risk factors in our study were not sufficient due to a lack of sufficient sample size and research quantity support. We noted that many records closely related to our study didn’t get past screening process because they were principally founded on selective PCI cases or not specific to STEMI patients. The research you mentioned above as well. More well-designed studies with large sample on this specific population are warranted, and we have added this point to our manuscript based on your comment in Discussion section:
However, likely due to differences in the patient populations and choice of treatment strategies and diagnostic thresholds in the included studies, the significant heterogeneity reduced the strength of the evidence. Furthermore, data available for evaluating some risk factors (e.g. angiographic access site and NAGL) are not inclusive enough to draw a reliable and convincing conclusion. We, therefore, recommend that more well-designed studies with large sample on this specific population are warranted. (Line 5-Line 11 Page 22)

Reviewer’s comment 2:
There was significant heterogeneity among the studies in the baseline characteristics of the patients and the diagnostic criteria of CA-AKI. The Newcastle-Ottawa Scale (NOS) or another tool should be used to perform the quality evaluation of the including studies.
Our response:
Thank you for your reminding and we have added the results of study quality assessment, as Supplemental tab.3, using Newcastle-Ottawa Scale.

Responses to Reviewer 3:
Reviewer’s comment 1:
While the primary analyses are well-described, detail is lacking regarding the choices surrounding subgroup and secondary analyses. Please specify the rationale for the presented additional analyses.
Our response:
We feel great thanks for your professional review work on our article, and the reasons for our additional analyses are as follows:
Previous studies have demonstrated the use of low-osmolar and iso-osmolar contrast agents significantly reduces the incidence of CA-AKI compared with high-osmolar contrast agents. But the influence of selection between low-osmolar and iso-osmolar contrast agents on the incidence of CA-AKI is still controversial. So, we anticipate that differences in contrast agent types (i.e. low-osmolar nonionic, low-osmolar ionic, iso-osmolar nonionic and unspecified) may affect the pooled outcomes of risk factors related to contrast agent use. As such, we anticipate that differences in study designs (i.e. prospective and retrospective) may affect the baseline characteristics of included patients.

Accordingly, we have added the reasons and methods of subgroup analyses in the “statistical analysis” section:

Because the impact of different study designs on baseline characteristic of included patients is expected, pre-planned subgroup analyses would be conducted for all individual risk factors according to study design to assess the impact on the heterogeneity. Because the impact of different contrast agent types on risk factors related to the use of contrast agent is expected, subgroup analyses were performed to examine the influence of contrast agent on the pooled outcomes. (Line 5 - Line 11 Page 10).

Meta-regression analysis was conducted to explore the sources of heterogeneity if significant heterogeneity was observed. We have re-written this part according to your comment:

If substantial heterogeneity was present, meta-regression analysis were performed based on age, proportion of women, sample size, study design, and country of study. (Line 13 - Line 15 Page 10).

Reviewer’s comment 2:
Were these pre-planned, included due to the paradoxical nature of the findings, or based on some other criteria?
Our response:
These subgroup and secondary analyses were set up in advance, and the relevant data were intentionally collected during the data extraction phase. We have revised the text and made it clearer: pre-planned subgroup analyses were performed to assess the impact on the heterogeneity for all individual risk factors... (Line 7 - Line 8 Page 10)

Because the impact of different contrast agent types on risk factors related to the use of contrast agent is expected, subgroup analyses were performed to examine the influence of contrast agent on the pooled outcomes. (Line 8 - Line 11 Page 10)

If substantial heterogeneity was present, meta-regression analysis were performed based on age, proportion of women, sample size, study design, and country of study. (Lines 13 - Line 15 Page 10)

Reviewer’s comment 3:
Was the decision to perform subgroup analyses for contrast volume by type of contrast agent a pre-planned analyses or did it arise due to patterns observed in the analyses?
Our response:
The decision to perform subgroup analysis of contrast agent volume based on the type of contrast agent is a pre-planned analysis. We have made the change: Because the impact of different contrast agent types on risk factors related to the use of contrast agent is expected, subgroup analyses were performed to examine the influence of contrast agent on the pooled outcomes. (Line 8 - Line 11 Page 10)

Reviewer’s comment 4:
Were additional analyses presented for all variables that met these criteria?
Our response:
Additional analyses for all variables that met these criteria were conducted, and we have added a description of this in our revised manuscript: pre-planned subgroup analyses were performed to assess the impact on the heterogeneity for all individual risk factors according to study design. (Line 7 - Line 8 Page 10)
Subgroup analyses of all individual risk factors were performed according to the study designs, and no statistically significant differences were observed between prospective and retrospective studies. (Line 13- Line 15 Page 15)

Reviewer’s comment 5:
The presentation of the tables and figures is also unexpected, with the tables for the primary analysis include as a supplement (although they are quite large) and many subgroup/secondary results presented in the manuscript.
Our response:
Thanks for your valuable counsel. We have adjusted our graphs presentation in our revised manuscript. Now, the revised tables presented the primary analysis and many subgroup/secondary results in the revised manuscript. (Tab. 2-4)

Reviewer’s comment 6:
The selection method for the variables for each of the meta-regressions should be addressed. These varied and it was not clear why these variables were selected or why they differed (due to availability, different presumptions of clinical relevance for each analysis, etc.?). Clearly specifying these variables up front and the rationale for their selection would also improve the presentation of these results.
Our response:
Thanks for your valuable suggestions and the precedent version of this part has been replaced:
If substantial heterogeneity was present, meta-regression analysis were performed based on age, proportion of women, sample size, study design, and country of study. All available influencing factors (e.g. baseline sCr and contrast volume) reported in studies were included as covariates in subsequent meta regression analysis. (Line 13- Line 17 Page 10)
The differences of eGFR estimation and diagnostic criteria may affect the incidence of CA-AKI. Thus, these two factors were included as covariates in meta-regression. (Line 17- Line 19 Page 11)
As type of contrast agent was previously considered as a significant influencing factor, this factor was included as a covariate in meta-regression. (Line 15- Line 17 Page 18)

Reviewer’s comment 7:
For example, on page 11 (lines 12-20) the results of the meta-regression provide a list (but only a subset of the tested variables) that are not associated with heterogeneity. This immediately leads one to wonder if there are other variables that do have a significant association. A statement along the lines of “none of the variables tested were associated with heterogeneity including …” would allow for the authors point to made without having to list of the variables in the results. If there were variables that ideally should have been included but weren’t available (perhaps baseline renal function?) this should be listed as a limitation and could be addressed when presenting the variables for inclusion.
Our response:
We have revised the text carefully and have made the following modifications based on the your comment:
And the result showed that none of the variables tested were responsible for the heterogeneity including age, proportion of female patients... (Line19- Line 21 Page 11)
None of subgroup effects for the variables mentioned above were found in the subsequent meta-regression analysis. (Line2 - Line3 Page 16)
Subsequent meta-regression analysis revealed no subgroup effects on the variables including age, proportion of female patients...(Line 17- Line 19 Page 18 )
Meta-regression did not identify variables including age, proportion of female patients, sample size, country of study, or study design as sources of the heterogeneity. (Line 8- Line10 Page 19)
meta-regression analysis showed that variables including age, proportion of female patients...(Line 13- Line 14 Page 21)
Reviewer's comment 8:
Given that none of the variables used in the meta-regression had a significant association with heterogeneity, the tables in Supplement C are not particularly informative in their current form. These tests also tend to lack power and the lack of significance may not necessarily indicate that these variables are not important. The addition of confidence intervals (instead of the standard error) would provide more context. If deemed relevant, other measures such as residual heterogeneity may also be considered.
Our response:
Thank you for the insightful suggestion. After a considerable discussion, seeing that the information provided by these tables is relatively limited and the results have already been described in the main text, we have removed this unnecessary content (previous supplement file C).

Reviewer's comment 9:
In the methods, the quality of each included study was scored. I did not see that either the results of this assessment were presented in the manuscript or that the data were used. If not already presented, please report on this information in the manuscript.
Our response:
Thanks to Reviewer for reminder and we have added the results of study quality assessment, as Supplemental tab.3, using Newcastle-Ottawa Scale.

Reviewer's comment 10:
Similarly, other methods such as the funnel plots and Egger test for publication bias are not generally presented. Results are only mentioned for 1 or 2 specific subgroup/secondary analyses. An overall general statement, especially as pertains to the primary analyses would be warranted.
Our response:
We have added this part of the results in Supplemental Fig. 1-3, and have added statements in the revised manuscript:
Funnel plots were presented in Supplemental Fig. 1. We did not draw funnel plots of some factors due to the limited number of the included studies. (Line 10 - Line 12 Page 15)
Funnel plots of other factors were presented in Supplemental Fig. 2. (Line 21 - Line 22 Page 18)
Funnel plots were presented in Supplemental Fig. 3. (Line 11 Page 21)

Reviewer's comment 11:
Limitation Section: Should restate in the limitation section that the results can only identify factors associated with CA-AKI and cannot assess causality. As noted above, consider mentioning key variables that could not be included in the meta-regression analyses. For the overall prevalence I² = 93% and none of the factors considered were significant.
Our response:
We have redrafted this section as following:
First, given the observational nature of the included studies, a causal relationship between risk factors and CA-AKI could not be established. (Line 1- Line 3 Page 29)
Considering that no significant sources of heterogeneity were found in the meta-regression analysis, interpretation for some pooled outcomes with high heterogeneity should be cautious. (Line 6- Line 8 Page 29)

Reviewer's comment 12:
Page 11 line 48, should read “significantly” not significant.
Our response:
We have corrected this error.

Reviewer's comment 13:
page 12 line 48, the phrase “Stable result was obtained” is awkward.
Our response:
We have revised this phrase as follow:
Sensitivity analysis indicated consistency in the result. (Line 1 Page16)

Reviewer’s comment 14:
Page 14 lines 12-13. What was the significance of the funnel plot becoming nearly symmetrical with the removal of the two studies? This may be the only mention in the results of the use of the funnel plots, so no other context is provided to the reader.
Our response:
Considering the Reviewer’s comment, we have rewritten this section to make it easier to understand:
The shape of the funnel plot was asymmetric (Fig. 5B), indicating that publication bias exists, which may be related to potential studies with negative results unpublished. As type of contrast agent was previously considered as a significant influencing factor, this factor was included as a covariate in meta-regression. Subsequent meta-regression analysis revealed no subgroup effects on the variables including age, proportion of female patients, sample size, study design, country of study, and type of contrast agent. (Line 13 -Line 19 Page 18)

Reviewer’s comment 15:
page 16 line 28, "recommend that more homogeneous researches be carried out ..." should be revised.
Our response:
We have amended the relevant part in manuscript as follow:
Furthermore, data available for evaluating some risk factors (e.g. angiographic access site and NAGL) are not inclusive enough to draw a reliable and convincing conclusion. We, therefore, recommend that more well-designed studies with large sample on this specific population are warranted. (Line 8 -Line 11 Page 20)

Reviewer’s comment 16:
Page 16 lines 46 to 51. “Differences between the studies in the CA-AKI diagnostic criteria and the eGFR estimation method may be responsible for our negative result.” This sentence should be clarified. Is the "negative result" the lack of statistical significance between countries?
Our response:
We are very sorry for our confusing writing. We have rewritten this section as following:
However, we found the significant inconsistency of overall prevalence (I2 = 93%) and none of the factors considered were significant, which might be attributed to lack of key variables (e.g. baseline renal function and hemodynamic condition) in some included studies. As the criteria for diagnosing CA-AKI is still a matter of debate, another concern is that the diagnostic threshold was not the same in all studies. (Line 15- Line 19 Page 22)

Reviewer’s comment 17:
page 17 line 20. The word Paradoxical should be used in the heading “Paradox Findings.” However, it is not clear that all these results are paradoxical or unexpected, so another heading title may be appropriate.
Our response:
We have replaced “Paradox Findings" with another heading title “Unexpected Findings" (Line 7 Page 23)

Reviewer’s comment 18:
page 18 line 48, "mechanisms by which smoking affects the incidence of CA-AKI", consider revising so that it does not imply that this study found a causal relationship between smoking and the incidence of CA-AKI.
Our response:
We have revised this phrase as follow:
...the correlation between smoking and CA-AKI. (Line 4-Line 5 Page 24)

Reviewer’s comment 19:
Page 22 line 56, "focused" instead of "focus"
Our response:
We have done so.

Reviewer’s comment 20:
Figures 4-6. The column heading “NAKI” is not defined. Instead of adding another acronym, it may make more sense to change the heading to “No AKI” or “Without AKI” so that the table is easier to read. Also, of these figures use the phrasing “odds ratio in XXX”. More typically these are phrased as the “odds ratio of XXX” or “odds ratio for XXX”
Our response:
We have changed the heading to “No AKI”, and replaced the phrasing “odds ratio in XXX” with “odds ratio of XXX” in the revised Fig. 3-6.

Reviewer’s comment 21:
Tables B.2. and B.3 Increase the column width so that the word “value” will fit on one line.
Our response:
We have done so in the revised Tab. 2-4.

Reviewer’s comment 22:
Table C1 – The presentation of the categories under eGFR formula is confusing. It is not immediately clear that the two headings of “MDRD” are nested under “eGFR formula” or why the same heading of “MDRD” is used twice.
Our response:
We are very sorry for our negligence of this mistake have made the correction in the revised Tab. 1.

Reviewer’s comment 23:
Figure 4B, consider add a reference line at 1.0 to help clearly identify the instances that are non-significant.
Our response:
We have done so in the revised Fig. 4B according to your suggestion.

**VERSION 2 – REVIEW**

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<tr>
<th>REVIEWER</th>
<th>Huang, Dong</th>
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| GENERAL COMMENTS | The authors have made clear responses and added the appropriate changes in the revised manuscript. |

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<tr>
<th>REVIEWER</th>
<th>Mor. Maria</th>
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| GENERAL COMMENTS | The authors made substantial revisions and reorganized the presentation of the results to address the prior reviews. |
One unintended consequence of those edits relates to moving the sentence on the inability to assess causality to the limitations. This leaves the Discussion and the current presentation of results in the discussion open to the interpretation that they are causal. Please consider using the terminology of “association” rather than “effect” to counter this impression.

The manuscript still needs a final read to correct the grammar, including punctuation. While many changes were made to correct existing wording, the new edits and changes would benefit from additional attention.

VERSION 2 – AUTHOR RESPONSE

Responses to Reviewer 2:
Reviewer’s comment 1:
The authors have made clear responses and added the appropriate changes in the revised manuscript.
Our response:
We would like to thank you again for your decision and constructive comments on my manuscript, which have helped improve our manuscript.

Responses to Reviewer 3:
Reviewer’s comment 1:
The authors made substantial revisions and reorganized the presentation of the results to address the prior reviews.
Our response:
We sincerely thank the reviewer for taking the time to thoroughly review our work and for your very constructive and helpful comments.

Reviewer comment 2:
One unintended consequence of those edits relates to moving the sentence on the inability to assess causality to the limitations. This leaves the Discussion and the current presentation of results in the discussion open to the interpretation that they are causal. Please consider using the terminology of “association” rather than “effect” to counter this impression.
Our response:
Thanks for your suggestion. We have revised the Results and Discussion sections to address your concern and hope it is now clearer:
The unexpected favorable association between smoking, as well as family history of coronary artery disease, and CA-AKI requires further investigation. (Lines 5-7, Page 3)

Meta-analysis of six studies showed a favorable association between family history of CAD and CA-AKI. (Lines 5-6, Page 16)

This meta-analysis not only validated the established risk factors for CA-AKI (e.g., age, female sex, comorbidities, hemodynamic instability, and contrast volume), but also found that smoking and family history of CAD were negative associated with the incidence of CA-AKI. (Lines 14-18, Page 21)

Smoking and family history of CAD were negative associated with incidence of CA-AKI, which needs to be investigated in further research. (Lines 18-20, Page 29)

Reviewer comment 3:

The manuscript still needs a final read to correct the grammar, including punctuation. While many changes were made to correct existing wording, the new edits and changes would benefit from additional attention.

Our response:

We have carefully and thoroughly proofread the manuscript to correct all the grammar, punctuation, and typos.