Author’s response to reviews

Title: Associations of serum low-density lipoprotein and systolic blood pressure levels with type 2 diabetic patients with and without peripheral neuropathy: Systemic review, meta-analysis and meta-regression analysis of observational studies

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Author’s response to reviews:

Rebuttal Letter

August, 2019

Dear Prof. Shabana Saleem, Associate Editors of BMC Endocrine Disorders,

We were pleased to have an opportunity to revise our paper entitled, "Associations of serum low-density lipoprotein and systolic blood pressure levels with type 2 diabetic patients with and without peripheral neuropathy: Systemic review, meta-analysis and meta-regression analysis of observational studies (BEND-D-19-00286).” I am sure your suggestion is very good to make this paper as fruitful as possible.

In revising the paper, we have carefully considered your comments and suggestions, as well as those of the reviewers. As instructed, we have attempted to succinctly explain changes made in reaction to all comments. After providing a brief overview of ways in which the paper was
revised, we reply to each comment in point-by-point fashion. I hope this will clear up your question sufficiently.

In the revision, we sought to unpack all elements, first emphasizing each in its own right, and then integrating them. For brevity’s sake, in responding your respective comments; we used blue color for our responds to editor and reviewer comments in the rebuttal letter.

I enjoyed reading this manuscript and do hope that my comments help you to further clarify your ideas/arguments and ultimately lead to a stronger contribution. We thank you for your constructive feedback. It caused us to reconsider our approach to developing and conveying the core of our theoretical framework. We feel the revision represents an improvement and hope you do also.

Yong Xu

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Responses to Reviewer's #1 Comments – Prof. Pavlina Andreeva-Gateva

This is a well conducted meta-analysis and meta-regression aiming to explore the associations of serum LDL and SBP with diabetic polyneuropathy (DPN). Authors concluded that high SBP values carry risk for peripheral nephropathy mainly in European subjects. For patients from Asia origin it seems that high LDL levels carry higher risk for DPN. For patients older than 75 y.o. the risk for DPN is higher.

• Response: Thank you very much for your positive input and warm support of our work. It is our pleasure to be the recipient of your review!

1. The English has to be checked, i.e. p.11 the title of the table 3, p. 14 - the last sentence, p. 17 - the conclusion.

• Response: Thank you so much for your valuable comments. We have attempted to provide the revised version, edited intensively for English punctuation, grammars and syntax errors. The English language of our manuscript has been improved by someone with expertise in technical English editing before submission. I also have been working hard to improve English issues. We hope that this revised manuscript satisfies the reviewer,
and would be suitable for publication. To partly address your suggestion, we re-edited these sentences, carefully: in Results section, line 19-20, page 11, Discussion section, line 24-26, page 14, and Conclusion section, line 8-12, page 17.

2. What does Authors understand as "collision risk"?

• Response: Thank you very much for your valuable comments. As you know, the collision risk is defined based on time to avoid collision (TAC) to evaluate potential collision severity while the following train approaching [1]. Knowing whether diabetes is associated with a significantly increased risk for unfavourable traffic events (collisions, injuries, death) is important from a regulatory point of view, as proving such an association, and taking into account the effect size of this association could change the medical criteria for obtaining/revoking a driver’s license [1, 2]. Undoubtedly, understanding the role of LDL and SBP in pathogenesis and collision risk of diabetic neuropathy could help to develop effective treatments and road safety regulations for type 2 diabetic neuropathy [3-7]. With this definition, in this meta-regression analysis we tried to clear the effects of the age of patients and the year of dieses (as a potential collision severity) on collision risk in both groups of study: T2DM patients with and without peripheral neuropathy [1, 2, 8]. We found that monitored change in collision risk of DPN drivers over time shows LDL and SBP are associated with an increased collision risk of DPN. Also, we found that there is a significantly decreased collision risk of DPN by drivers over time (Result section, line 4-7, page 13) as well as the elderly (47-75 years old) T2DM patients have a higher collision risk of DPN (Result section, line 15-17, page 13).

3. References - in tables 1 and 2 there are references which are missing in the Reference list.

• Response: Thanks a lot to the reviewer for this valuable suggestion. First of all, please accept our deep apologizes for this mistake and insouciance. In the revised format of paper, the whole text was carefully revised and edited intensively for the right referencing as well as we set all references according the journal format.

4. Figures 3 and 4 are with poor resolution and one cannot read them.

• Response: Once again, thanks for pointing this out. We tried best in the revised version of paper to improve all figures quality and resolution and set all of them according the journal format with acceptable adequate resolution.

Responses to Reviewer's #2 Comments – Prof. Marcin Czech
The subject is undoubtedly relevant for the diagnosis and treatment of diabetes. Efforts of authors to review and meta-analyze so many studies should be appreciated.

- Response: Thank you for the positive comments and your kind compliments about our research. It is our pleasure to be the recipient of your review!

1. My main concern however relates to causality effect of LDL and SBP on DNP development. Is it really justified to state that LDL and SBP are promising prognostic factors for early detection of DNP? I am not mentioning practical lack of preventive treatment strategies (apart from glycemic control as such).

- Response: The authors thank the Reviewer for this insightful and critical comment. Yes, you are right! Our findings can explore the association between serum low-density lipoprotein and systolic blood pressure levels and the development of diabetic peripheral neuropathy (DPN) in patients with type 2 diabetes mellitus (T2DM). However, because of the shortcoming in study design and sample size, there is still no clear conclusion. We performed this meta-analysis to examine the exact impact of LDL and SBP on DPN in type 2 diabetic patients. So, we have corrected and removed in whole text any “prognostic” or “diagnostics” or “biomarkers” keywords and corrected the abstract (Result section, line 15-17, page 13), discussion (Result section, line 15-17, page 13) and conclusion of paper (Result section, line 15-17, page 13).

2. In the methods section and abstract I would add the information that you systematically reviewed observational studies. I would also include a time horizon of your search.

- Response: We are grateful for the helpful comments and suggestions from the Reviewer. We have attempted to provide a quantitative systematic review and a comprehensive meta-analysis and meta-regression investigation to estimate the predicting value of LDL and SBP level in T2DM patients with and without peripheral neuropathy. As you suggested we updated and highlighted our time horizon of our systematic search with adding more information in revised MS file (Method section line 16-18, page 5 and line 9-11 and line 23-25, page 6).

3. In my opinion discussion section is too wide, it covers many various pathophysiological, clinical and social aspects of T2DM not reflected in the results. One of these concerns an increased risk of unfavorable traffic events linked to driving license. Neither reference nor link to the results is provided. Limitations (clearly and rightly stated by the authors) are strong, do they allow drawing conclusions?

- Response: The authors thank the Reviewer for this insightful comment. Yes, you are right!! We polished discussion section in revised MS file and just highlighted our study innovations and creativity (We removed Discussion section, line 22-24, page 15: “We assumed that a potential description for this finding was a difference in the occurrence of the collision risk for these
races”; Discussion section, line 6-9, page 16: “In the light of these sherds evidences and results from our meta-analysis, it could be deducted that SBP is associated with DPN. It is recommended that the results of this study ought to be construed with caution.” Discussion section, line 1-3, page 16: “Knowing whether diabetes is associated with a significantly increased risk for unfavorable traffic events of collisions is essential regulatory points for obtaining a driver’s license of DPN.”; and Discussion section, line 20-25, page 16: “Quality of the original studies and poor homogeneous distribution of the population based on subgroups parameters might be other limitations in our study as well. The risk of inherent limitations in our observational studies cannot be ignored. Then, many confounding factors and missing information were not controlled in biased statistical finding”. Also, in the revised MS file, we have modified discussion of articles with more attention to our main finding (Page 4, line 20-22; Page 5, Line 1-2; Page 5, Line 6-7; and Page 13, Line 20-22). Hopefully, the revised discussion part are looks more complete and clearly and rightly reflected our results.

4. In conclusion section, you state that "LDL and SBP status could be a promising prognostic biomarker for early detection and effective intervention of DPN" - is it really proven?

   • Response: Once again, thanks for pointing this out. With note to Comments No.1 of Reviser #2, we have modified whole text of articles with more attention to the main results. So, we have replaced conclusion part with: "Despite some limitations, the data of the present meta-analysis shows that high levels of SBP and LDL are two adaptable risk factors for DPN in European adults with T2DM. However, it has been determined that discovering age &gt;75 years in T2DM patients have a higher collision risk of DPN. Therefore, the LDL and SBP status could be associated with increased risk of peripheral neuropathy in T2DM patients.”

5. Fig. 1 is not clear, fig 3 and 4 difficult, even impossible to read and assess.

   • Response: The authors would like to thank the Reviewer for pointing out this error. We reviewed our archive and tried our best to replace figure 1, 3 and 4 with the best one that is clearer and have high resolution! As well we set all of figures according the journal format with acceptable adequate resolution.

6. I would consider minor linguistic improvements: e.g. "(...) reduce" line 34, page 3; "(...) are 1.03 times suffering ", line 44, page 14; "collision risk", line 41, page 3 and line 17 page 5; “collision risk of DNP", line 27, page 15.

   • Response: We attempted to provide the revised and edited intensively for English punctuation, grammatical, and syntax errors on during the revision in whole text. As well, to partly address your suggestion, we re-edited specificity text in Abstract section line 20-22, page 3, Introduction section,
References


7. Fei Mao XZ, Siying Liu, Xiaona Qiao, Hangping Zheng, Bin Lu, Yiming Li: Age as an Independent Risk Factor for Diabetic Peripheral Neuropathy in Chinese Patients with Type 2 Diabetes. Aging and disease:0-.