Author's response to reviews

Title: Meta-analysis of the risk of cataract in type 2 diabetes

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Author's response to reviews: see over
Dear editor,

Thank you very much for your letter concerning the manuscript 2133556114129778 titled “Meta-analysis of the risk of cataract in type 2 diabetes”. The authors appreciate the valuable suggestions from you and the reviewers. We have been carefully corrected the manuscript according to the comments and suggestions. The point-by-point responses to the concerns are listed below. All authors have approved the corrections made in the manuscript. Now we would like to resubmit the revised manuscript to the BMC Ophthalmology. Please do not hesitate to contact us if there are any questions.

Yours sincerely,

Li Li

Responses to reviewer: Francesco Oddone

General comments: The authors performed a systematic review and meta-analysis aimed at investigating the association between type 2 diabetes (T2D) and the risk of cataract. The work suffers of major problems mainly methodological. Please find below a list of the major issues.

Response: Thank you very much for your careful review. We have carefully revised the manuscript according to your kind suggestions.

Comment 1: Background, line 43: “Therefore, we performed this meta-analysis to assemble the published evidences”. A systematic review should not be aimed at assemble the published evidence but rather to answer to a clinical question such as in this case to evaluate the association between T2D and cataract.

Response: Thank you very much. We have changed this sentence to “Therefore, we performed this meta-analysis to explore the association between T2D and the risk of cataract.”

Comment 2: The explanation of study selection is poorly reported: authors state that 2 independent investigators retrieved eligible studies but do not explain how titles, abstracts and full texts have been managed. Moreover the databases explored (PubMed, Embase and SpringerLink) is incomplete.

Response: Thanks for your kind suggestion. The references (including titles and abstracts) were managed by Endnote software for study selection. As mentioned in the results of study selection, two investigators independently selected the studies successively by the title, abstracts, and finally the full text. After screening the title and abstracts there were remaining 13 studies and the full text were downloaded and read for further selection. What’s more, these databases (PubMed, Embase and SpringerLink) included most of the medical research journals, however, there might also be some studies missed, so in future more complete search on Ovid database and other databases should also be performed.

Comment 3: The description of the inclusion criteria for the studies is incomplete. The authors should state in details the type of studies considered, which patients’ population, which type of intervention or association is considered, which definition of diabetes, which definition of cataract, with which methodologies, which outcomes, existence of control group, etc. For example from the results it emerges that studies without the control group or with outcomes not fitting with the review have been eliminated but in the methods section none of these criteria
have been specified.

**Response:** Thank you very much for your careful review and kind suggestions. There was no restriction to the patients’ population, intervention, and methodologies. In addition, the criteria about groups, outcomes, and types of cataracts have been added in the inclusion criteria. Moreover, the language limitation (English) has also been detailed in the manuscript.

**Comment 4:** In the methods section it has been not specified that analysis would have been stratified for different types of cataract definition.

**Response:** Thank you very much. We have specified the stratified analysis in the section of statistical analysis in the revised manuscript, as “The meta-analysis was stratified for different types of cataract definition: AC, CC, NS and PSC.”

**Comment 5:** The sistematicity of a review does not relate only on the literature search but it relate also to the method used in all the steps. Every single step should be clearly specified in the methods section such as for example the detailed criteria for the studies selection and this is because the results strongly depend upon the choices mad during the revision process.

**Response:** Thank you very much for your kind suggestion. We have clearly specified the steps of study selection, data extraction, and heterogeneity test, as well as the pooled analysis, sensitivity analysis, and publication bias estimate in the revised the manuscript. In addition, the detailed criteria for the studies selection have been stated more clearly.

**Comment 6:** Using a random effect model allow to encompass the heterogeneity but not to eliminate or “take care of it” thus heterogeneity should be then explained with subgroups analysis and analysis of sensitivity which are fundamental when facing a large heterogeneity such as in the present work.

**Response:** Thank you very much. Because the geographical distribution of the eight included studies is dispersed, and excepting Olafsdottir(Caucasian), Foster(Chinese), and Rotimi and Leske (Black), other studies did not provided the race of the subjects, in addition, information about other factors (cataract definition) were not completely provided in all selected studies, so we did not performed the subgroup analysis. However, we have conducted the sensitivity analysis to test the robustness of our results by: “1) only the cross-sectional studies were included; 2) only the studies with Eye examination to confirm the cataract were included”. The result of sensitivity analysis was displayed in table 2. There was no significant change before and after sensitivity analysis, indicating that the results of the present meta-analysis were robust.

**Comment 7:** The number of studies considered varies along the paper (5 then 3 and at the end 8)

**Response:** Thank you very much for your careful review and we have to apologize for the mistake and inaccurate description. In fact, we totally included 8 studies [5-7, 15-19] for meta-analysis and there were 5 studies [7, 15-18] reported the overall incidence of AC, while 7 studies [5-7, 15-17, 19] reported the three types of cataract. We have corrected them in the revised manuscript.
Responses to Reviewer: gianni virgili

General comment: This review has synthesized studies on the association of cataract with diabetes. The manuscript is good to read and I recommend some changes.

Response: Thank you very much for your careful review and kind suggestions. We have substantially corrected the manuscript according to your kind suggestions.

Major compulsory revisions

Comment 1: A search specialist should review the present search strategy. To me, as a non-specialist, the restriction to the use of “risk” OR “incidence” may be problematic, and I would add at least “odds” OR “prevalence” or remove these keywords and report on the effect of removal. Also report an e-table listing excluded studies and reasons for exclusion. Related publications of included studies may be listed among references (e.g. early and late publications of the Blue Mountains), explaining that you have selected, for example, the longest term follow-up.

Response: Thank you very much for your careful review and kind suggestions. We have replaced the words “risk” and “incidence” with “prevalence”, and have removed “confidence interval” and “odd ratio” from the keywords. The reasons for excluding and numbers of the excluded studies had been listed in figure 1. Also the sixth line of the inclusion criteria have stated that “if there were multiple articles with same population or data, only the article with the longest follow-up and complete data was selected “.

Comment 2: Please expand on how the target condition (cataract) was defined and measured in each included study, e.g. using LOCS III classification and what LOCS III level was used to define the presence of cataract for each subtype. This may be an important source of heterogeneity.

Response: Thank you very much for your kind suggestion. We have to apologize for the ignorance of this issue. We have added the definition of cataract in table 1 and results show that different classification methods such as LOCS III, LOCS II, and Wisconsin Cataract Grading System. Therefore, as you have mentioned that this may be an important source of heterogeneity, it has been discussed as a limitation of this study in the discussion.

Comment 3: You should comment on the importance of study design. There is one cohort study (the Blue Mountains): was incident cataract or cataract progression assessed? Did they report risk ratios or odds ratios and, in case RRs were extracted, how did you convert RRs to ORs for analyses? There is one case-control study (Leske 1999). It seems the selection was done on diabetes (the exposure) rather than on cataract (the outcome), as classically done in case-control studies. Please clarify what was the population base of the two samples in this study (e.g. how cases were enumerated before sampling 1.1 diabetics and controls).

Response: Thank you very much for your kind suggestions. The 10 year incidence of nuclear, cortical, or PSC cataract and cataract surgery were assessed in the cohort study [18], they reported the relative risks (RR), and 95 percent confidence intervals (CI) were reported. We converted the RRs to ORs according to the formula [1] “ RR=OR/[(1-P0)+(P0*OR)]”. In addition, we found a mistake on the OR of Tan 2008 in table 1. We are very sorry for this mistake and we have corrected it in table 1 as well as the meta-analysis results in the main text and abstract, as well as providing revised figure 3-5.
Finally, from the table 2 of the original study (Leske 1999), it can be seen that the samples was grouped based on the cataract (outcome).

**Comment 4:** You have not considered study quality, and I acknowledge this is difficult for association studies, but at least the STROBE reporting initiative can be mentioned. A comment on importance of adjusted estimates can be offered.

**Response:** Thank you very much. We have provided the results of the STROBE study quality assessment which indicates that all the selected studies are high quality studies (17-21 scores, supplement table 1).

**Minor essential revisions**

**Comment 5:** There are several English grammar errors or typos. Sometimes they include technical terms such as: Page 2, line20: odd ratio… should be odds ratio

**Response:** Thank you very much. We have corrected it. In addition, we have carefully checked the whole text and tried to avoid such mistakes.

**Comment 6:** Page 6, line 110: randomized-effect model… should be random-effects model

**Response:** Thanks for your kind suggestion. We have corrected them.

**Comment 7:** Page 6, line 105: report what variables this OR was adjusted for.

**Response:** Thank you. The variables this OR adjusted for had been shown in the table 1, that mainly the age, gender, smoking and so on.

**Comment 8:** Page 6, line 117: an OR = 1.27 does not mean an increase by 27% of the risk as the authors state: the relationship between OR and RR depends of prevalence, so this is at least a wording error.

**Response:** Thank you very much for your kind suggestion. We have changed the words “1.27 time” to “higher”.

**Comment 9:** Page 8, line 156-7. Non surprising that this meta-analysis uses only observational studies, of course you cannot randomise to being diabetic. Please reword.

**Response:** Thanks for your kind suggestion. We have reworded the section of limitation as follows: “There were limitations in this meta-analysis. Although ORs were corrected by taking account of influences of age, sex and smoking in some included studies, the pooled results might also be influenced by other factors, for instance different treatments of T2D, regions of studies, and body mass index (BMI). Significant heterogeneity still exists among studies, which might be caused by the above factors. In addition, the difference of definition of cataract in deferent studies might also be a source of heterogeneity.”

**Comment 10:** Page 8, lines 162-3. No power to detect publication bias with less than 10 studies. Please correct. Be aware that there is little power to investigate heterogeneity with less than 10 studies in analyses. You may report on 95%CI of I-square, easily calculated using the heterogi macro in Stata. E.g. examine when most of the 95% CI lies below or above 50%.

**Response:** Thank you very much. The 95%CI of I-square are as follows: AC: $I^2=70.4\%$,
95%CI=24.5%-88.4%; NS: $I^2=65.8\%$, 95%CI=23.5%-84.7%; CC: $I^2=3.3\%$, 95%CI=0.0%-30.2%; PSC: $I^2=34.9\%$, 95%CI=0.0%-72.5%. However, although Higgins referred the calculation of the 95%CI of $I^2$ in the article [2] "Measuring inconsistency in meta-analyses", he assessed the heterogeneity by the value of $I^2$.

References for the response


Responses to Reviewer: Irene Floriani

Major Compulsory Revisions

Comment 1: Since at least one included study is cross-sectional, authors should explain whether they assessed incidence or prevalence of cataract. Furthermore, the duration of follow-up should be specified, since it has a great influence on results. The bibliographic search is not sufficiently detail to allow to be reproducible. It should be rewritten with more details (i.e. languages, keywords).

Response: Thank you very much for your kind suggestion. We assessed the prevalence of the cataract and we have corrected the relative descriptions in the manuscript. In addition, we completely agree with your point that the duration of follow-up greatly affects the result, and we chose the studies with the longest follow-up if there were several studies with same population of data. Not all studies specified the follow-up durations, so we could not obtain this issue. Moreover, the key words used for study search were as follows: “1) cataract OR lens opacity OR crystalline opacity; 2) diabetes OR T2DM OR type 2 diabetes; 3) risk OR incidence” which had been listed in the section of search strategy. According to your kind suggestion, we have detailed the search strategy by adding the language limitation “Only the studies written in English were screened”.

Minor Essential Revisions

Abstract

Comment 2: Line 19: please replace odd with odds

Response: Thank you. We have corrected it.

Comment 3: Line 20: the number of eligible studies as well as that of patients included should be moved to result section

Response: Thank you very much. We have moved this sentence to the results section.

Comment 4: Line 24: please provide OR and 95%CI also for CC and SPC.

Response: Thank you very much for your kind suggestion. We have added the OR and 95%CI for CC and SPC.

Keywords
Comment 5: Line 29: please remove confidence interval and odd ratio
Response: Thank you. We have removed them.

Background

Comment 6: Line 40: please remove "that"
Response: Thank you. We have removed it.

Comment 7: Line 42: please remove "."
Response: Thank you. We have removed it.

Comment 8: Line 42: please replace synthesized with assessed, evaluated
Response: Thank you very much. We have replaced synthesized with assessed.

Methods

Comment 9: Line 48: The statement "All human studies have been approved by China Ethics Committee and performed in accordance with the ethical standards." is not clear and not applicable to a systematic review.
Response: Thank you. There was no such statement in the manuscript.

Comment 10: Line 61: risk ratio and odds ratio are two different statistics, and therefore not exchangeable. the authors should state which one they used
Response: Thank you very much. Here we used the OR, which has been corrected in the revised manuscript. If they provide the RR, we converted it to OR according to the formula [1]: \( RR = \frac{OR}{(1-P0) + (P0*OR)} \). Moreover, it has to be mentioned that the RR of Tan 2008 has been converted to OR, so there were some changes in the results (table 1, figure 3-5), also we have corrected the corresponding results in the main text and abstract.

Comment 11: Line 70: see line 19 comment
Response: Thank you. We have replaced the odd with odds.

Comment 12: Line 77: please replace egger's with Egger's.
Response: Thank you very much. We have replaced egger's with Egger's.

Results

Comment 13: Line 109: The random-effect model is preferred to fixed-effect when a high heterogeneity is detected. It is not clear whether the heterogeneity reported, translating in a I2 of 70.2% refers to random- or fixed-effect model. In both cases it should be better investigated.
Response: Thanks for your kind suggestion. We had reported the methods for test the heterogeneity, which are widely used in meta-analysis, in the section of statistical analysis “The heterogeneity between studies was evaluated by Q test [11] and \( I^2 \) statistics [12], where, \( P \) of Q test > 0.05 and/or \( I^2 < 50\% \) was considered homogeneity, and a fixed-effect model was used for calculate pooled effect; otherwise, there was significant heterogeneity and random-effect model was used.”. In addition, the results indicated that the p-value of Q test was less than 0.05 (\( P < 0.05 \)) and \( I^2 = 70.4\% > 50\% \), suggesting that there was a significant heterogeneity, so a
random-effect model was used.

**Comment 14:** Line 110 and line 116: please replace randomized with random
**Response:** Thank you. We have corrected them in the revised manuscript.

**Comment 15:** Line 117: please report the exact p-value instead of p>0.05.
**Response:** Thank you. We have provided the p-value 0.070 in the revised manuscript.

**Comment 16:** Line 119: see line 109 comment
**Response:** Thank you very much. Basing on the method of heterogeneity test mentioned in response to comment 13, the results of heterogeneity test about CC and PSC indicated that the p-value of Q test were more than 0.05 (CC: $I^2 = 3.3\% < 50\%$, $P = 0.400 > 0.05$; PSC: $I^2 = 34.9\% < 50\%$, $P = 0.162 > 0.05$), suggesting no significant heterogeneities, so fixed-effect models were used.

**Comment 17:** Line 125: please report the exact p-value instead of p>0.05.
**Response:** Thank you very much for your careful review and kind suggestions. We have reported the p-value of Begg’s test and Egger’s test in a table 3, and we have also referred the table 3 in the text.

Discussion

**Comment 18:** Line 163: please remove "."
**Response:** Thank you. We have removed it.

**Comment 19:** Line 163: The statement "Despite these limitations, the present study clearly identified the positive correlation of cataract risk and T2D, which draw attention into the eye extermination of T2D patients" should be attenuated
**Response:** Thank you very much. We have removed the statement.

Conclusions

**Comment 20:** Line 169: replace confirms with suggests
**Response:** Thank you. We have changed confirms to suggests.

Reference for the response