Author's response to reviews

Title: Association analysis of cigarette smoking with onset of primary open-angle glaucoma and glaucoma-related biometric parameters

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

We greatly appreciate the positive evaluation that our manuscript received from the editor and the reviewers. We carefully read their comments and suggestions and have now completed a revision of the manuscript that addresses their concerns. As you will see in the revised manuscript, we have focused on active smokers by removing a small number of ex-smokers in our study subjects. The title of the manuscript has been updated as “Association analysis of cigarette smoking with onset of primary open-angle glaucoma and glaucoma-related biometric parameters”. The results have been updated accordingly, without changing the main structure and original idea of our previous submission. Thorough and extensive revisions as highlighted in yellow have been made throughout the manuscript following the suggestions from the reviewers. We thank the reviewers for their constructive suggestions that have improved both the quality and the clarity of the manuscript and we believe that the revised paper is now acceptable for publication in BMC Ophthalmology in the category of “Research Article”. A response letter to the reviewers is appended at the end of this cover letter.

Sincerely,

Prof. Mingzhi Zhang

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Response to Reviewer 1:

It would be of merit if the authors clarify if ex smoking status was considered.
Response:
Thanks for this important suggestion. There are only a small number of ex-smokers (18 in controls, 4 in POAG) in the original dataset, which may complicate the study and analysis. To make the results easier to understand, we have removed these ex-smokers and included more active smokers in our revised manuscript. The study subjects have been updated in Page 11, Tables 1 and 2.

Response to Reviewer 2:

Major compulsory revision

1. Manuscript seems to have lots of missing pieces of information, as to I am unclear how many were current smokers, past smokers. Also were the JOAG smokers? How many? They tend to be younger than AOAG. CCT declines with age, although only about 6-10 microns per decade it cannot be ignored so they will have to account for age.
Response:
Many thanks for the questions. There are only a small number of ex-smokers (16 in controls, 4 in POAG) in the original dataset, which may complicate the study and analysis. To make the results easier to understand, we have removed these ex-smokers and included more active smokers in our revised manuscript. The study subjects have been updated in Page 11, Tables 1 and 2. Effect of age was considered in the current study and p-values were adjusted for age in Tables 3-5.

2. Methods: Cross sectional design, I am unsure how the variables were controlled. I understand they did univariate regression analysis. However the correct statistic will be multiple regression analysis because these risk factors are not independent of each other and interactions will have to be checked.
Response:
Thanks for this suggestion. Actually the regression results in the current study were from multiple regression instead of univariate regression. We have clarified this in the statistical methods in Page 5, line 2-7. Two-factor Interaction analysis has been performed but no significant interactive effect is found. We have added this in Page 5, lines 19-29 and Page 6, lines 6-9.

3. The authors have not given physiological basis of the question and nor have they discussed why CCT will be lower in the group of smokers versus nonsmokers. This is far important and must be included.

   Response:
   Thank you for this important suggestion. The findings in current study suggested that in POAG patients, the cornea tended to be thinner in smoker than in non-smokers. Central corneal thickness is an important risk factor for glaucoma. Individuals with thinner cornea tend to have lower measurement of IOP. Therefore, our findings may suggested that POAG smokers may have their actual IOP lower estimated, and caution should be taken when evaluating IOP level in these patients. The exact reason for this is unclear. However, cigarette smoking may exert this effect through hypoxia and collagen in the cornea. Smoking has been reported to decreases oxygen and collagen production in tissues during wound healing. Ocular hypertension causes damage to the cornea. This Smoking probably deteriorate ocular hypoxia caused by ocular hypertension, and consequently affected the biosynthesis of collagen, which could be an explanation to the decreased corneal thickness. We have added this to the discussion in Page 7, lines 18-24.

4. Due to the fact that authors have performed more than 3 regression analysis they will have to account for inflation of alpha error by decreasing the p value. Bonferroni correction or a similar analysis will be acceptable. They may find that the one variable that they found to be significant may not be significant after Bonferroni correction.

   Response:
   Bonferroni correction is usually applied to multiple comparisons. However, in the current study, multiple regression analysis but not multiple comparisons were used, and thus no
Bonferroni correction was applied.

5. Due to the fact smoking is known to be a risk in numerous diseases, authors will have to also discuss how the pathogenesis of certain other diseases or processes may influence the prevalence and development of OAG.

Response:
Ocular hypertension causes damage to the cornea. Smoking probably deteriorate ocular hypoxia caused by ocular hypertension, and consequently affected the biosynthesis of collagen, which could be an explanation to the decreased corneal thickness. We have added this to the discussion in Page 7, lines 18-24.

In addition, the change of CCT in POAG may affect the disease course. A previous study on corneal thickness and functional damage in patients with ocular hypertension showed that patients with ocular hypertension plus thinner corneas have a greater risk of developing functional damage over time [27]. We have added this to the discussion in Page 7, lines 13-17.

Response to Reviewer 3:
Major compulsory revision

1. It is not clear from the Methods and Materials section what were the inclusion criteria or subjects in the study.

Response:
Thank you for pointing out the problem. We have added more details of the diagnosis and inclusion criteria in Page 4, line 11-22.

2. Were the study subjects recruited over time? In the Background section (last sentence) the authors refer to the study subjects as a ‘Southern Chinese cohort’.

Response:
The study subjects were recruited from Mar, 2008 to Nov 2011. We have added this to Page 3, line 20.
3. The authors examined the relationship between smoking history (Tables 3-5) using multiple linear regression. They refer to these regression models as the effects on smoking history, age and gender on glaucoma-related biometric parameter. Could the authors explain why linear regression was used instead of logistic regression with smoking history status as the response variable?

Response:
Thank you for the question. Multiple linear regression was used to assess the effects on smoking history, age and gender on glaucoma-related biometric parameters, because the glaucoma-related biometric parameters were continuous variables and were treated as the response variable. We have added more details in the statistical analysis section in Page 5, lines 2-7.

4. The fitted regression models presented on Tables 3-5 model each subject group separately, this is not efficient, it would be useful to fit a single model that allows for comparisons of the groups, with say the controls as the baseline group.

Response:
Thank you very much for this suggestion. The current study focused on the relationship between cigarette smoking history and glaucoma-related biometric parameters different subject groups, and did not try to fit a single simple model. This is because such relationship is probably changed in glaucoma patients compared to controls. Our analysis on CCT actually supported this, with significant effects of smoking history in POAG but not in controls. A possible explanation is given in Page 7, lines 18-24.

5. The fitted regression models presented on Tables 3-4 include the CCT and or IOP whereas the model in Table 5 does not. Could the authors explain the inclusion these terms (CCT and IOP) in the models? Is this meaningful with respect to the study objectives?

Response:
Thank you very much for pointing out this problem. To make the data more uniform and clear, we have removed these terms, and keep only smoking history, age and sex as the independent variables in Pages 12-13, Tables 3-5.
- Minor Essential Revisions

1. Page 5: Statistical analysis: Delete 2nd sentence since p-values and odds ratios are implicit outputs of a logistic regression analysis.

Response:
Thank you for the suggestion. The sentence has been deleted accordingly from the statistical analysis section in Page 5.

2. Page 5: Statistical analysis: Delete 5th sentence since p-values and regression coefficients are implicit outputs of a linear regression analysis.

Response:
Thank you for the suggestion. The sentence has been deleted accordingly from the statistical analysis section in Page 5.