Author's response to reviews

Title: The effect of changes in intraocular pressure on the risk of primary open-angle glaucoma in patients with ocular hypertension: an application of latent class analysis

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Author's response to reviews: see over
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Dear Dr. Adrian Aldcroft:

First, we would like to thank the Associate Editor and the two referees for their constructive comments. Please find the revised manuscript MS #1038179538622446 for the *BMC Medical Research Methodology*. To follow the guidelines of the Journal, we changed the title as “The effect of changes in intraocular pressure on the risk of primary open-angle glaucoma in patients with ocular hypertension: an application of latent class analysis” (Original: The effect of changes in IOP on the risk of developing POAG in patients with ocular hypertension: an application of latent class analysis). The responses to the referees’ comments item by item are also attached at the end of this letter.

All authors of this research paper have directly participated in the planning, execution and/or analysis of the study and have read and approved the final version of the manuscript. This manuscript has not been published previously and is not being considered concurrently by another publication. None of the authors have any conflicts of interest to report.

Thank you for your efforts on this manuscript and looking forward to hearing from you soon.

Sincerely,

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Response to the Referee’s Report on MS #1038179538622446

“The effect of changes in intraocular pressure on the risk of primary open-angle glaucoma in patients with ocular hypertension: an application of latent class analysis” by Gao et al.

Comments from 1st reviewer:

Page 7 Line 7 Why were values for the eye-specific variables for each patient the average of two eyes? Why not choose one of them?

We appreciate the reviewer for pointing this out. In this study, all the baseline variables were patient-specific (i.e., averaging values from two eyes if available), while the post-randomization IOPs were eye-specific.

Patient-specific baseline covariates were used for two reasons: 1) the treatment decision often patient-specific rather than eye-specific in clinical practice; and 2) to compare with the results of previous analysis on OHTS and EGPS.

Since one goal of this study is to assess the fluctuation of follow-up IOP on POAG, we anticipate that the patient-level IOP may underestimate the true intra-patient variability. We therefore used eye-specific follow-up IOP, either from the eye developed POAG or an eye selected randomly for these without POAG. This has been clarified in the revision (page 6, lines 12-16).

Comments from 2nd reviewer:

1. In the conditional LCA analysis, total of 13 variables on demographic and clinical characteristics were included. It is not clear how these 13 variables were selected, were they selected based on its statistical significant association with POAG or statistical significant association with IOP in the OHTS, EGPS, or other studies? This should be clarified.

These 13 baseline demographic and clinical characteristics were determined a priori during the planning phase of OHTS. They were also the candidate predictors used to develop the OHTS-EGPS prediction. This has been clarified in the revision (page 5, lines 20-22).

2. In the OHTS, 24.8% were Black, but only 0.1% were Black in EGPS. Latent class analysis on POAG and EGPS provided different number of latent classes. It is possible that this difference in the Black proportion may contribute this difference in the number of latent classes, because the IOP fluctuation and its effect on POAG may be different in Blacks. Probably a LCA analysis (at least as a sensitivity analysis) should be performed by excluding Black, so that OHTS and EGPS are more comparable, to see whether both data provided the same latent classes.
We appreciate the reviewer’s comments on this. A sensitivity analysis has been performed after excluding the Black participants in OHTS. Similar patterns of IOP changes were identified as in the LCA using the whole OHTS dataset. This result is consistent to the tree-based analysis performed in the OHTS-EGPS meta-analysis (reference #17). The tree-based analysis showed that race was no longer an important predictor for the risk of POAG development after adjusting other risk factors such as CCT and VCD. This has been clarified in the Results (page 15, 2nd paragraph, and Figure 5) and Discussion (page 17, lines 2-5).

3. It will be useful to add the observed proportion of patient with POAG for each latent class determined from LCA in OHTS and EGPS. This information can be added into either Table 3, or Figures 2 &3.

This information has been added to Table 3 and also in the Results (page 11, lines 10-13).

4. The treatment of ocular hypertension has substantial impact on the IOP change over time, and this can distort the relationship of natural IOP fluctuation with POAG development. It is clinically important to evaluate the effect of natural IOP fluctuation on POAG development. This can be done by performing LCA on the data only from untreated group.

We appreciate the reviewer’s comments on this. A sensitivity analysis has been performed using data from the observation group in OHTS (page 15, 2nd paragraph, and Figure 5). Similar patterns of IOP changes were identified as in the LCA using whole OHTS data, except that the mean IOP in Class 1 (the class with the lowest IOP level) was around 20 mmHg rather than 17 mmHg.

Other revisions:
1. Added a reference (reference #24) for statistical package R;
2. Added a list of abbreviations.