Author's response to reviews

Title: Prevalence and Risk Factors of Primary Open-Angle Glaucoma in a City of Eastern China: A Population-Based Study in Pudong New District, Shanghai

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

Thank you for giving us the opportunity to address the reviewers’ concerns. The primary issue as raised by the reviewers is that the way measurements should be explained in methods and discussions. In the revised manuscript, we added details on the way measurements in methods and discussion. We also sought a native English speaker in this research area to edit the manuscript and hope that all the grammatical errors have been corrected and the current version met the standard of publication. We prepared an itemized response below to address each point raised by the reviewers.

Thank you again for your time and we look forward to hearing from you soon!

Sincerely

Ling Ge
Reviewer's report:

General

The authors provide a two-tier cross sectional survey by preselecting the candidates for detailed examination by a screening procedure for estimating POAG prevalence in Huamu community of Shanghai. They report a point prevalence of 2.8% and suggest that this is more than that reported in other Chinese communities. The undiagnosed glaucoma proportion was high and needed awareness.

Major revisions recommended:

1. Methods: Please explain if the Huamu community represents the population of Shanghai in general.

Reply: Huamu community cannot represent the population of Shanghai in general. Huamu community has a history of more than 30 years and is home to a stable population. The social and economical level in Huamu community has reached the average level of Pudong New District. So this community can represent the population of Pudong New district. We are doing epidemiological study in other two districts which can represent the population of Shanghai in general.

2. Methods: Please explain why 50 years and older were chosen when most epidemiological studies have included subjects more than 40 years of age.

Reply: In Shanghai, majority of people more than 50 years old have retired, especially for women. So it is easy to implement large-scale survey in this population in the community and the response rate is high.

3. Methods: Why was non-contact tonometer used both for screening and reexamination? It can overestimate IOPs and have issues with variation with higher or lower corneal thickness. Further applanation tonometry is the gold standard for IOP measurement. Explain.

Reply: Applanation tonometry is the gold standard for IOP measurement and important for clinical. However, this measurement must contact the cornea and may cause damage to the cornea, so the informed consent rate is not high in community screening. Non-contact tonometry (NCT) is non-invasive without touching cornea and
it is easy to operate and has high acceptance in community screening. According to ISGEO diagnosis criteria, we maintained consistency of IOP measurement in screening and reexamination and calculated the distribution of IOP, so we used NCT for reexamination. In addition, the Beijing Eye Study also used NCT to measure IOP in screening.

4. Screening and removal of subjects who had less than \( \frac{1}{4} \) CT for peripheral anterior chamber depth, may lead to underestimation of glaucomatous optic neuropathy; this may have bias in the estimation of prevalence.

**Reply**: All the subjects had received the present visual acuity/BCVA, anterior segment photographs, IOP measurement, fundus photographs. Those information were sent to professional glaucoma doctors for diagnosis. If the anterior segment, VCDR and IOP were normal, the subject was excluded for glaucoma. Subjects who had less than \( \frac{1}{4} \) CT for peripheral anterior chamber depth were not removed from further evaluation and reexamination.

5. Diagnostic definitions: Authors suggest that they diagnosed primary angle closure glaucoma from the population. This is controversial since they have excluded subjects with \(< \frac{1}{4} \) CT from further examination (including dilated fundus exam) from screening population. This may lead to gross underestimation of angle closure disease and glaucoma. Explain.

**Reply**: Subjects who had less than \( \frac{1}{4} \) CT for peripheral anterior chamber depth were not removed from further evaluation and reexamination. Those with \(< \frac{1}{4} \) CT just had not received dilated fundus examination when fundus photos cannot be taken clearly.

6. Authors should define how normal population (for the sake of obtaining normal variables) was defined? Did they use visual fields as criteria for defining normal subjects? If so, they should include it in the visual field section for normal subjects. What was the method of selection of normal subjects – random or every 5th or all normal subjects?
When we defined normal subjects for IOP distribution analysis, data of subjects with definite glaucomatous visual field defects or angle closure were excluded. And the distribution of VCDR was calculated by excluding eyes with definite glaucomatous visual field defects. This definition was described in Results part. And we analyzed all the normal subjects data.

7. Authors used Microsoft paint for defining peripheral anterior chamber depth and VCDR. Did they perform reliability analysis for this method? If so, provide data analysis or provide reference of published article.

Reply: We have done consistency test between two experienced glaucoma doctors, the Kappa value was 0.92 for VCDR evaluation and 0.87 for peripheral anterior chamber depth evaluation.

8. Results: Provide the specific reasons for exclusion of 56 subjects + 20% non-respondents and compare included vs excluded subjects for basic demographics. Please clarify the numbers here – it does not seem to tally.

Reply: 56 subjects were excluded because of incomplete records in one or more inspection items. Those subjects had participated in this study, but not received all the items because of long waiting time, an emergency or other reasons. Women were more likely to participate than men ($\chi^2=201.85$, $P < 0.001$). People at both ends of the age distribution were less likely to participate in this study ($\chi^2=8.89$, $P =0.003$).

9. Line 340: Authors conclusion that the prevalence rates were higher than Beijing and Guangzhou/ and other areas need to be examined using the 95% CI values and comparison of methodologies. It may not be appropriate to compare point estimates.

Reply: We have recompared the prevalence rate(95% CI) with other studies in the revised paper.

10. Authors suggest hypertension was associated with POAG in discussion. However
the univariate and multivariate analysis suggest no significance. Clarify and correct.
Reply: In results part, the univariate and multivariate analysis suggest POAG was associated with hypertension in table 5, the univariate and multivariate analysis suggest significance, and p value and 95% CI of univariate and multivariate analysis were (P = 0.01, OR and 95% CI: 1.86 (1.16-2.97)) and (P = 0.09, OR and 95% CI: 1.53 (0.93-2.50)). In multivariate logistic regression, $\alpha_{in}$ and $\alpha_{out}$ is $0.1$, so $p=0.09$ is significant here.

Minor revisions recommended:
1. Provide 95% confidence interval values for all point estimates provided in the abstract.
Reply: We had provided 95% confidence interval values for all point estimates provided in the abstract.

2. Line 82: This study selects to “This study selected”
Reply: We had corrected this error.

3. Line 83: “This community has a history of 30 years”. If this sentence does not have any relevance to the study, it can be removed. If not, please explain.
Reply : The decision to select Huamu community for the survey was taken because of its stable and a socioeconomic profile representative of Pudong New District as a whole. Since there are many new communities in Shanghai nowadays, Huamu community has a history of more than 30 years and is home to a stable population. So this community can represent the population of Pudong New district. We think that it’s better to keep this sentence.

4. Lines 84-87: These sentences appear redundant and can be removed.
Reply : We have deleted two sentences in our revised paper.
5. Line 96: Explain what is Z and B. Explain what is sample effect coefficient as well.

Reply: The required sample size by simple random sampling is calculated in the formula as follows: 
\[ n = \frac{Z^2(p)(1-p)}{B^2} \], in the formula P is the estimated prevalence, B is the presupposition error, and Z=1.96 (at 95% confidence interval. Assuming that \( p = 3.0\% \), \( B = 3.0\% \times 0.25 = 0.0075 \), and \( Z=1.96 \), then \( n = 1988 \). Suppose that the sample effect coefficient of this study is 1.1 and the estimated examination rate is 90%. The calculated number of samples is 2430.

Sample effect coefficient: The simple random sampling method cannot be applied to the whole sample investigation we plan. Cluster sampling method can reduce cost and improve ties with the survey point, but its sampling efficiency is not high, so we usually use sampling effect coefficient to correct the results calculated by the formula of simple random sampling.


Reply: Log MAR (Minimum Angle of Resolution).

7. Line 170 – What was the method (van Herick’s or modified van Herick’s) used to estimate peripheral anterior chamber depth by the technician on-site screening?

Reply: Doctors used Van Herick’s method to evaluate the peripheral anterior chamber depth.

8. Line 172 – What degree of field was captured by fundus photograph?

Reply: 45-degree of field was captured by fundus photograph.

9. Please provide the reference for ISGEO classification.
10. Authors should define reliability criteria used for perimetry and was the visual field repeated to take care of learning effects.

Reply: We used Humphrey perimetry and when it said “low test reliability” in the result paper, the examination was assessed as low reliability and this subject would be asked to do the examination again. All the glaucoma suspects were asked to test the visual field in the tertiary Eye hospital. SITA-FAST 30-2 mode white-on-white automated perimetry (Humphrey 720, Carl Zeiss, Meditec. Inc., Dublin) was performed with refractive correction. If the perimetry had low reliability, training on the check method for the suspects was conducted. If visual field defects were found, the perimetry was rechecked one hour later.

11. Authors’ use of step back technique for multivariate logistic regression is unusual. Please explain the reasons and elaborate on alpha selection criteria. What are the confounders adjusted for?

Reply: This study first performed univariate logistic regression analysis on the factors influencing POAG, and then performed multivariate logistic regression analysis on the factors that were statistically significant for the difference using the step back technique ($\alpha_{in} = 0.1; \alpha_{out} = 0.1$). For the large sample size, the inhibition effect of step back method is better than the forward method.

12. Provide the method of standardization used in statistical analysis.

Reply: The prevalence of POAG was adjusted by the standards ratio of population in Pudong New district, and the age- and gender-specific prevalence of POAG and their 95% CI were calculated.

13. Line 294: Provide 95% CI for adjusted prevalence rate.

Reply: We have added 95% CI for adjusted prevalence rate.
14. Line 392: Visional dysfunction…change to vision impairment.

Reply : We have changed Visional dysfunction to vision impairment.

15. Line 415-416: This sentence need to be carefully handled as for the ethical issues of inducement for participation is concerned. Please modify as appropriate.

Reply : We modified the sentence in manuscript.

Discretionary revisions recommended:

1. Did the authors use STROBE criteria to test the validity of their survey? If so, please provide the chart.

Reply : It is regrettable that we don’t use STROBE criteria entirely in this study, in our future study, we will use this criteria to test the validity.

2. It is recommended to provide a flow chart of included subjects and excluded subjects at each time point.

Reply : We have added the flow chart (Figure 1) in manuscript.
Reviewer's report
Title: Prevalence and Risk Factors of Primary Open-Angle Glaucoma in a City of Eastern China: A Population-Based Study in Pudong New District, Shanghai
Version: 2 Date: 30 April 2015
Reviewer: ronnie george
Reviewer's report:
Major compulsory revisions
There are methodology limitation regarding the way measurements were made and they should be addressed in the discussion:

1. IOP: the NCT is not considered a standard tool for screening or diagnosing glaucoma, In a report that gives glaucoma prevalence this is major limitation.

Reply: Applanation tonometry is the gold standard for IOP measurement and using NCT is a limitation of this study. However, applanation tonometry must contact the cornea and may cause damage to the cornea, and the informed consent rate was not high in the community screening in the pilot test. Non-contact tonometer is noninvasive intraocular pressure detection without touching cornea, and it is easier to operate and has high acceptance in community screening. And IOP is not the most important factor for diagnosing glaucoma; according to level 3 of ISGEO criteria, if the optic disc could not be examined because of severe media opacity, subjects who are blind (BCVA < 3/60) combined with either an IOP > 99.5th percentile or definite glaucoma medical records, such as filtering surgery were diagnosed as glaucoma. The distribution of IOP was considered, not the exact value of IOP was depended. In addition, the Beijing Eye Study also used NCT to measure IOP in screening.

2. Gonioscopy: the lack of an indentation gonioscope could potentially result in angle misclassifications.

Reply: This study is a large scale epidemiology survey, gonioscopy was performed with a Goldman one-mirror lens (Hagg Streit, Bern, Switzerland) at ×16 magnifications using a 1 mm long slit-lamp with low ambient illumination to prevent light from irradiating the pupil area. Though indentation gonioscopy is more suitable for narrow anterior angle evaluation, Goldman one-mirror lens or Zeiss gonioscope are both suggested for narrow anterior chamber angle according to Color Atlas & Synopsis of Clinical Ophthalmology by Wills Eye Hospital. The Beijing and
Guangzhou Study also used Goldman one-mirror lens.

3. Visual field criteria: the use of 4 contiguous abnormal points is not usually considered a standard definition of field defect.

Reply: According to Foster PJ[10], after following consultation with a group of researchers interested in the psychophysics of glaucoma, they have adopted the following as the “gold standard” of glaucomatous visual field loss. The glaucoma hemifield test graded “outside normal limits” and a cluster of three contiguous points at the 5% level on the pattern deviation plot, using the threshold test strategy with the 24-2 test pattern of the Zeiss-Humphrey field analyser 2. And when Foster PJ participated another study in Guangzhou, China with He M, they defined a visual field compatible with glaucoma as a glaucoma hemifield test result outside normal limits combined with a cluster of four or more contiguous points on the pattern deviation plot(P<5% occurring in age-matched normal subjects) not crossing the horizontal meridian.

4. The Temporal limbal pictures – What angulations were they taken at, what was the camera resolution. How were these images used – there is no reference as to how these were used to categorize patients.

Reply: The angulation was 40° and the camera (EOS-550D) resolution is 80,000,000 (3456 × 2304). Doctors used Van Herick method to evaluate the peripheral anterior chamber depth of these images. The depth of the peripheral anterior chamber and the corresponding corneal thickness (CT) in these photographs were measured using Microsoft Paint and calculated the ratio of the anterior chamber depth to the CT. And we have done consistency test between two experienced glaucoma doctors, the Kappa value was 0.87.

5. It would be informative to have actual numbers of participants for which each of the screening evaluations were performed specifically, IOP, disc photo, etc.

Reply: 2528 received all the measurements of screening including visual acuity, IOP, disc photo, Anterior segment photographs, etc. But some of them had atrophy of
eyeball or loss of eyes or was uncooperative, the IOPs were considered not measurable. For disc evaluation, if the photos were still not clear, “vague fundus” was recorded.

6. How did the authors derive “normal” values (from the tables – it appears that they arrived at normal values after the visual fields had been done). How were subjects with unreliable fields but disc suspects treated – were they too used to calculate “normal” values?

Reply: When we defined normal subjects for IOP distribution analysis, data of subjects with definite glaucomatous visual field defects or angle closure were excluded. And the distribution of VCDR was calculated by excluding eyes with definite glaucomatous visual field defects. Subjects with unreliable fields but disc suspects treated were not used to calculate “normal” values.