Peer Review File

Article info: http://dx.doi.org/10.21037/atm-20-1023

Reviewer A:

Comment 1: Missing details on cycloplegic agent used/number of measurements/criteria of the used data (if any).

Reply 1: Thank you for your valuable suggestion. We have added these missing details in the revised version.

Changes in the text:

- *The compound tropicamide eyedrops (Sinqi Pharmaceutical, ShenYang, China), which were composed of 5mg tropicamide and 5mg norepinephrine hydrochloride in 1ml, were used before refraction measurement. (In "Methods", Page 7, paragraph 1,* **Ocular examination***)*
- *Ocular aberrations were measured with iTrace (Tracey Technologies, Houston, TX, USA) aberrometry before administration of cycloplegic agent and refraction examination. (In "Methods", Page 7, paragraph 2,* **Measurement of ocular aberrations***)*
- *The average value of three consecutive measurements was used. (In "Methods", Page 7, paragraph 2,* **Measurement of ocular aberrations***)*

Comment 2: Confusing notation for HOAs, recommended to use Z(3,-3) instead of Z3,-3 etc

Reply 2: Thank you for your valuable suggestion. We have corrected the notation for HOAs as you suggested.

Changes in the text: *(In "Methods", Page 8, paragraph 1,* **Measurement of ocular aberrations***).*

Internal optic aberration was measured at pupil diameters of 4.0 mm. Internal total

RMS high order aberration (hereafter refers to as IHOA), coma aberration (Z(3, -1), Z(3,1)), trefoil aberration (Z(3, -3), Z(3,3)), spherical aberration (Z(4,0)), and secondary astigmatism (Z(4, -2), Z(4, 2)) were measured.

Comment 3: Line 121: Why p<0.2?

Reply 3: Thank you for pointing out this critical issue. The covariate is used in the multiple regression analysis if the p value of the univariate analysis is below some prespecified cut-offs. A value of 0.2 or 0.157 or even 0.5 is recommended[1]. More traditional levels such as 0.05 or 0.01 can fail in identifying variables known to be important,[2-3] and are only recommended for a very large sample size. Therefore, we chose p<0.2 as the cut-off in the univariate analysis to identify candidate variables for the multiple regression analysis. Hoping this addresses your concern.

1. Heinze Georg, Dunkler Daniela. Five myths about variable selection. Transpl. Int. 2017, 30: 6-10.

2. Bendel RB, Afifi AA. Comparison of stopping rules in forward regression. Journal of the American Statistical Association. 1977;72:46–53.

3. Mickey J, Greenland S. A study of the impact of confounder-selection criteria on effect estimation. American Journal of Epidemiology. 1989;129:125–137.

Changes in the text: *(In "Methods", Page 9, paragraph 1,* ***Statistical analysis****).*

We added related reference in the revised manuscript.

Reviewer B:

Comment 1: Although the manuscript mentioned binocular aberrations, it is better to avoid the use of interdependent data between two eyes from the same subject except for the investigation of bilateral distribution.

Reply 1: Thank you for pointing out this critical issue and we have revised the manuscript accordingly. Only the **online-only Table S1** in the original manuscript used data from both eyes. In the original manuscript, the Table 1 used logarithmic

aberration data from the right eyes, and the consistent results with binocular data were shown in the **online-only Table S1**. We are sorry for the misleading error in the sentence "*The mixed-effect model using binocular data shows consistent results for most factors (**Table 1**)*" (In "Results", Page 11, Paragraph 1), in which the "**Table 1**" should be "**Table S1**". We removed the online-only Table S1 and the sentence that refers to the Table S1 in the manuscript. Other analysis in the original manuscript except for the investigation of bilateral distribution used only the data from the right eyes. We have added a description of data sources in the "Results" section to avoid ambiguity. Hoping this addresses your concern.

Changes in the text:

- *We removed the additional online-only Table S1.*
- *We deleted the sentence: "Also mixed-effects linear model with unstructed covariance structure adjusting for correlation between two eyes was used to identify determinants of IHOAs using data from both eyes." (In "Results", Page 9, Paragraph 1, **Statistical analysis**)*
- *The results of the linear regression analyses of age-related changes in IHOAs using data **from the right eyes** are summarized in Table S1. (In "Results", Page 10, paragraph 2, **Association between Age and IHOAs**)*
- *The association between ocular and lenticular factors with logarithmic HOAs using data **from the right eyes** are summarized in Table 1. (In "Results", Page 11, paragraph 1, **Ocular and Lenticular Factors Associated with IHOAs**)*
- *We deleted the sentence: "The mixed-effect model using binocular data shows consistent results for most factors (Table 1)." (In "Results", Page 11, Paragraph 1, **Ocular and Lenticular Factors Associated with IHOAs**).*

Comment 2: The investigations of IHOA association with axial length, and that with spherical equivalent, indicate same or duplicate results.

Reply 2: Thank you for your valuable suggestion. We totally agree that axial length is associated with spherical equivalent. Therefore, in our analysis the axial length and spherical equivalent entered the multi-factor model respectively which was illustrated in the caption of the **Table 1** (the original **Table 2**). We analyzed and interpreted these two parameters respectively considering that the spherical equivalent reflects the overall refractive status of the eyeball, which is mainly affected by axial length, and also by other refractive components, such as the cornea and the lens. We have reorganized these associated results in the "Discussion" section. Hoping this addresses your concern.

Changes in the text: *(In "Discussion" Section, Page 14, paragraph 1)*

- *The associations of AL vs. internal total HOA were also confirmed by both single and multi-factor analyses in our study, which is consistent with previous study.*
- *We deleted the following sentences: "Kasahara K et al reported highly axial myopia had a higher IHOA compared with emmetropic eyes."*

Comment 3: It seems that the investigations of age-related changes may be meaningless in such young, large age-variation subjects because human beings grow variously from teens to twenties. In addition, as authors mentioned, cross-sectional design is inadequate to investigate the age-association with IHOA, especially in such subjects.

Reply 3: Thank you for pointing out this critical issue. The cross-section design and the characteristics of subjects indeed impact our investigation on the age-related changes. We appreciate your suggestion and have further explained these limitations in the "Discussion" section. What's more, we have moved the original **Table 1** to the **online-only Table S1**. Considering that age is a very important factor affecting ocular aberration, we kept this part of analysis. We are going to carry out a longitudinal study to further investigate the age-related changes in IHOAs.

Changes in the text:

- *The subjects included in this study were mostly young and displayed large age-variations. The characteristics of the subjects may influence the investigation on the age-related changes. (In "Discussion", Page 16, Paragraph 1).*