Author's response to reviews

Title: Prevalence and risk factors of superior segmental optic hypoplasia in a Korean population: the Korea National Health and Nutrition Examination Survey

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Author's response to reviews: see over
Response to Editor and Reviewers for

Dear Editor:

We would like to convey our sincere thanks for the in-depth review of our manuscript.

We have made several changes that were recommended by the reviewers and that are discussed below.

Editor.
you mention that "All the data of KNHANES is opened to the public after removal of personal identifiers and being anonymized." - Could you please provide further information on how you accessed this data. Is there a link/website that you can include in your manuscript which demonstrates that the data is freely available and anonymised?

Thank you for your valuable comments. You can get more information about KNHANES at the Korean Center for Disease Control (KCDC) website. KCDC freely provides anonymized data. Detailed information on the design, content, and operation of the KNHANES and access to the public-use data files and documentation can be found at the following website: http://knhanes.cdc.go.kr. We added that fact to the Methods section (page 5, lines 9-10).

Reviewer#1

#1. The authors state that they performed slit-lamp examination. Did it include funduscopy as well? Were the RFNL defects defined by means of funduscopy or by means of photography? Did they also use red-free illumination for the RNFL defects?

We are sorry that the explanation of the methods was not clear. We screened subjects using digital fundus images obtained with a non-mydriatic fundus camera. Retinal nerve fiber layer (RNFL) defects were observed on color fundus photography. Two investigators defined the localized wedge-shaped defects in a masked fashion. Red-free fundus photography was not used in this study. We modified the descriptions in the Methods section (page 6, lines 4-5).

#2. It is mentioned that “The readers, as masked to all information other than the fundus photographs, came to their final decisions by consensus”. Could the authors please provide a bit more information for how the readers reached consensus?

Two independent readers, who were masked to all information other than the fundus photographs,
evaluated the color fundus photography for the presence of abnormalities of the optic nerve head and RNFL. Discrepancies between their findings were resolved by consensus. In cases where no consensus could be reached the final decision was made by a third reader, the principal investigator (page 6, lines 6-7).

#3. Can you please mention in the text, the worst BCVA found in the study subjects? Was it 0.3 logMAR? (as seen in the table)

The worst BCVA among the study subjects was logMAR 3.0, and the worst BCVA in the SSOH group was logMAR 0.3. It is well known that patients with SSOH usually have relatively good visual acuity. And most of the SSOH patients in the present study had excellent visual acuity. (page 7, lines 11-12).

#4. Could you please report also in the text/results (apart from the table) the comparison between SSOH subjects and controls regarding refractive error and BCVA?

Thank you for your recommendation. Per your recommendation, we added a comparison of refractive error and BCVA to the revised version of the manuscript (page 7, lines 11-15).

“The visual acuity in the SSOH group was 0.07±0.10, and in the normal group, 0.17±0.33. The worst visual acuity in the SSOH group was 0.3. The SSOH group showed lower logMAR scores (better visual acuity) than were recorded for the normal group. This finding is consistent with a previous study, which showed that patients with SSOH typically have good visual acuity. The mean refraction in the SSOH group was -1.06±1.86 D, which was similar to that in the normal group (-0.80±2.17 D).”

#5… In the beginning of discussion the authors cite the Han et al study, which found a lower prevalence of SSOH. Was the inclusion of only one institution in the above study the only reason for this discrepancy in the findings, or are there more differences between the 2 studies explaining this discrepancy?

We deeply appreciate your valuable comments. The discrepancy in the prevalence of SSOH between the present study and Han’s study is attributable to the difference in the study population. Our study participants constituted a representative Korean population, while those in Han’s study are patients who had visited a health promotion center in a tertiary referral hospital. Han et al. noted, as a limitation, the possibility that participants with a known optic disc anomaly might not have been included. Additionally, different examinations were used for SSOH diagnosis. A combination of stereo disc photography, red-free retinal nerve fiber layer, and Humphrey visual field test was used in the study by Han et al., whereas fundus photography and frequency-doubling technology (FDT) perimetry were used in our study. The difference in the diagnostic ability between these examination sets would have led to the difference in the prevalence. The difference in the diagnostic ability
between these examination sets would have led the difference in the prevalence. In this regard, we have expanded our discussion following your comments (page 8, lines 8-16).

#6. Could they also please provide briefly some data on the prevalence of SSOH in populations of non-Japanese, non-Asian origin? An incidence of SSOH up to 8% has been reported (Taylo and Hoyt, Book, pediatric Ophthalmology and Strabismus, 4th Ed)


However we can't find any data on the prevalence of SSOH in populations of non-Asian origin. To our knowledge, the study by Yamamoto et al., cited in the manuscript, has been the only published report based on population and written in English.

#7. The authors mention that there are some reports suggesting a female predisposition for SSOH. Could they please cite these publications?

Thank you for your recommendation. Per your recommendation, we made the relevant citations in the revised version of the manuscript (page 8, line 23). Twelve of 17 patients reported on by Petersen and Walton, all four patients reported on by Nelson et al., and eight of ten patients reported on by Kim et al. were women.


#8. Could the authors also briefly mention in the Introduction or Discussion which are some other risk factors associated with SSOH? i.e. short gestational time, low birth weight, poor control of maternal diabetes....

Thank you for your valuable recommendation. We added some other risk factors associated with SSOH to enhance the readers’ understanding. Please see the Discussion of the revised version of the manuscript (page 8, lines 25-28).


#9. The interesting finding of paternal IHD as a risk factor for SSOH should be discussed further. How was IHD defined? Was it present at time of conception? Are there any data regarding paternal age at conception (and maternal as well) or history of smoking? IHD would be relatively uncommon in young males at reproductive age. (However, this does not preclude subclinical endocrine disorders, growth hormone deficiency and insulin resistance leading to microvascular disease at a later age) What kind of tests had the affected individuals undergone, in order to set this diagnosis? What was the severity of IHD and how many years was it present, was there a staging system or any similar data? Did the affected males take any relevant medication?

We are sorry that the explanation in the Methods section was not sufficient. We supplemented the text to improve it in this regard (page 5, lines 19-22).

The individual component of the health interview questionnaire includes information on individual medical condition, nutrition, and family medical history that is collected via self report. The risk factors were determined on the basis of the answers to a question about parental medical history.

Specifically, the participants were asked whether any biological member of their family, living or deceased, had ever been told he/she had diabetes, hypertension, or ischemic heart disease (IHD). We defined family history as having a first-degree relative (parent) with diabetes, hypertension, or IHD diagnosed by a doctor and treated with medication, regardless of disease severity or duration. Family history was categorized as maternal and paternal.

Even though IHD is uncommon in pubescent males, there is a possibility that any genetic background that may predispose paternal IHD could affect offspring’s SSOH. However, the current study has a limitation in that it was not possible to assess the onset, duration, or severity of IHD, due to the questionnaire methodology in KNHANES as relates to family history. We discussed the possibility of genetic association and the study limitations in the Discussion (page 9, lines 14-25).

Reviewer 2.

#1. further explanation about data collection and the reason for discarding 137 eyes from the evaluation are missing
We are sorry that the explanation of the methods was inadequate. In the present study, fundus photographs of 11,087 eyes of 5,612 subjects were successfully reviewed. A total of 137 eyes was excluded due to poor image quality. That is, 137 photographs were unreadable owing to media opacities or other problems such as a small pupil or a poor focus. We added this clarification to the Results (page 7, line 3-4).

#2. A more detailed discussion of the study limitation would be appropriate, e.g. the possibility for incorrect reporting in the interviews

Thank you for your recommendation. As you pointed out, the questionnaire method using self-reported data could underestimate the prevalence and be influenced by the individual’s memory. This limitation was noted in the Discussion (page 9, lines 22-25).

#3. A general sentence or two about other ocular pathologies found during this study would be helpful – definitely the subtle abnormality found at the disc in the 14 patients with SSOH was not the only abnormal ocular finding in such a large screening sample

Thank you so much for your helpful comments regarding other ocular abnormalities. Of the 11,087 eyes of 5,612 cases reviewed, Optic disc anomalies were detected in 53 eyes of 48 subjects with a prevalence rate of 0.48% per eye and 0.86% per subject. Optic disc drusen were detected on the fundus photographs of 10 eyes of nine patients. Myelinated nerve fibers were detected in 27 eyes of 24 subjects. SSOH case were detected in 16 eyes of 14 cases (about 0.14% of the eyes, and about 0.24% of the cases) (page 7, lines 5-9). According to our recorded data, there was no other ocular pathology among the 14 SSOH subjects.

#4. paternal ischemic heart disease could only have played a role in the pathogenesis of SSOH in the offspring if present at conception. Thus a more detailed explanation about the way paternal IHD was evaluated in the questionnaire is needed

We are sorry that the explanation in the Methods was insufficient. We modified the relevant text in order to improve it in that regard (page 5, lines 19-22).

The individual component of the health interview questionnaire includes information on individual medical conditions, nutrition, and family medical history, all of which are collected via self-report. On the basis of the answers to those history-related questions, the relevant risk factors were determined.

Participants were asked whether any biological member of their family, living or deceased, had ever been told he/she had diabetes, hypertension, or ischemic heart disease (IHD). We defined family history as having a first-degree relative (parent) with diabetes, hypertension, or IHD diagnosed by a doctor and treated with medication, regardless of disease severity or duration. Family history was
categorized as maternal and paternal.

Even though IHD is uncommon in pubescent males, there is a possibility that any genetic background that may predispose paternal IHD could affect offspring’s SSOH. However, the current study has a limitation in that it was not possible to assess the onset, duration, or severity of IHD, due to the questionnaire methodology in KNHANES as relates to family history. We discussed the possibility of genetic association and the study limitations in the Discussion (page 9, lines 14-25).

#5. On page 4, line 11: This is an incorrect citation: Reference 1 involves 10 patients who were ALL offsprings of diabetic mothers. Please revise (= discretionary revision).

Thank you for your valuable observation. We found that the citation was incorrect and corrected it in the revised manuscript.

Again, thank you so much for all of your advice and help with our paper.

Best regards,
Ki Ho Park M.D., Ph.D. on behalf of the authors