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References

1. Hwang ES, Perez-Straziota CE, Kim SW, et al. Distinguishing highly asymmetric keratoconus eyes using combined Scheimpflug and spectral-domain OCT analysis. *Ophthalmology*. 2018;125:1862−1871.
2. Lopes BT, Ramos IC, Salomao MQ, et al. Enhanced tomographic assessment to detect corneal ectasia based on artificial intelligence. *Am J Ophthalmol*. 2018;195:223−232.
3. Ambrosio Jr R, Lopes BT, Faria-Correia F, et al. Integration of Scheimpflug-based corneal tomography and biomechanical assessments for enhancing ectasia detection. *J Refract Surg*. 2017;33:434−443.
4. Steinberg J, Siebert M, Katz T, et al. Tomographic and biomechanical Scheimpflug imaging for keratoconus characterization: a validation of current indices. *J Refract Surg*. 2018;34:840−847.
5. Li Y, Tan O, Brass R, et al. Corneal epithelial thickness mapping by Fourier domain optical coherence tomography in normal and keratoconic eyes. *Ophthalmology*. 2012;119:2425−2433.

Re: Hwang et al.: Distinguishing highly asymmetric keratoconus eyes using combined Scheimpflug and spectral-domain OCT analysis (*Ophthalmology*. 2018;125:1862-1871)

TO THE EDITOR: We read the case-control study by Hwang et al.[1] The authors emphasized the limitations of individual parameters from Scheimpflug imaging or spectral domain (SD) OCT alone in the discrimination of clinically unaffected fellow eyes in patients with highly asymmetric keratoconus (AKC) from healthy controls. They also presented a multivariate regression model with a great discriminating ability (sensitivity and specificity of 100%), which combines total pachymetry and epithelial thickness in various locations, epithelial thickness variability, anterior curvature, and anterior surface asymmetry indices.[1] Moreover, the authors suggest that corneal posterior elevation measurements are not mandatory to diagnose unaffected AKC eyes, against the global consensus. However, the present article failed to present the posterior metrics used for statistical analysis in the study.

We wish to provide some recommendations and opinions on this study. The study included 30 clinically unaffected fellow eyes from 30 patients with highly AKC in 1 eye and 60 normal eyes of 60 participants. However, there is an important concern that the AKC group (between 14 and 61 years of age) included pediatric patients, whereas control group (between 20 and 56 years of age) did not. Moreover, there were no data regarding the number of pediatric cases in the AKC group. It is known that pediatric and adult corneas have different structural properties.[2] The adult cornea is more rigid than the pediatric cornea owing to natural cross-linking with aging. In pediatric keratoconus, weak ectatic collagen lamellae exceeds the capacity of the natural cross-linking process and disease tends to progress more rapidly.[2] Chatzis and Hafezi[3] demonstrated that 88% of 59 eyes from pediatric patients (aged between 9 and 19 years) with keratoconus showed progression from the initial visit. Therefore, including "initially unaffected" eyes from pediatric AKC cases, which have a high potential to turn into manifest keratoconus, is confusing and might change the outcomes of the present study, because no pediatric cases were present in the control group.

Second, the authors clearly stated that subjective data were not used for statistical analysis in the study. However, the unaffected AKC group—the most critical population in the study—was selected based on the following subjective criteria as stated in the Methods section by the authors: no clinical evidence of disease, no physical findings on slit-lamp examination, no definitive abnormalities on corneal imaging, and corrected distance acuity of $\geq$20/20. We certainly agree that subjective image analysis should not be used for statistical purposes, which may affect outcomes of the study owing to interobserver variability. Therefore, the authors should provide objective and rigorous criteria for selecting "unaffected" AKC eyes after excluding the pediatric cases. The keratoconus percentage index (with a score of $<$60), the skewed radial axes, and the inferior-superior power asymmetry ($<$1.4) in addition to standard parameters such as maximum keratometry and thinnest pachymetry have been used as quantitative criteria to determine unaffected AKC eyes in recent studies.[4]

In contrast, there are no data in the text regarding the laterality of the control eyes and randomization method, although the frequency of unaffected right and left eyes in the AKC group was presented in the Results section. Furthermore, it is not clear whether there was a significant difference between the unaffected AKC and control groups regarding eye laterality. Because intereye asymmetry in corneal metrics differs between patients with keratoconus and healthy subjects, the AKC and control groups should be matched in terms of eye laterality for more reliable statistical analysis.[5]

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References

1. Hwang ES, Perez-Straziota CE, Kim SW, et al. Distinguishing highly asymmetric keratoconus eyes using combined Scheimpflug and spectral-domain OCT analysis. *Ophthalmology*. 2018;125:1862–1871.
2. Mukhtar S, Ambati BK. Pediatric keratoconus: a review of the literature. *Int Ophthalmol*. 2018;38:2257–2266.
3. Chatzis N, Hafezi F. Progression of keratoconus and efficiency of pediatric [corrected] corneal collagen cross-linking in children and adolescents. *J Refract Surg*. 2012;28:753–758.
4. Ferreira-Mendes J, Lopes BT, Faria-Correia F, et al. Enhanced ectasia detection using corneal tomography and biomechanics. *Am J Ophthalmol*. 2019;197:7–16.
5. Eppig T, Spira-Eppig C, Goebels S, et al. Asymmetry between left and right eyes in keratoconus patients increases with the severity of the worse eye. *Curr Eye Res*. 2018;43:848–855.

REPLY: We thank Drs Toprak and Yaylali for their comments and recommendations regarding our work on distinguishing between the clinically unaffected eye from highly asymmetric keratoconus (AKC) patients and a normal eye cohort.[1] We included all posterior surface metrics that are able to be directly output: a list of variables accessed is included in the Appendix of a separate letter response.[2]

The authors expressed concern regarding the inclusion of pediatric patients in the asymmetric cohort. There were 3 pediatric patients (aged 14 and 15) and all 3 had been followed for >2 years without progression in their asymmetric eye at the time of data collection. We are uncertain why the authors would suggest we exclude these eyes, because these are exactly the patients we would want to identify clinically.

Toprak and Yaylali also stated that we should provide "objective and rigorous criteria for selecting 'unaffected' AKC eyes." This theme is common in the letters we have received regarding this article. We did not use any predetermined indices to identify the study population; this was by design, because the ideal quantifiable parameters to identify subclinical disease in patients with highly AKC have not yet been determined. Determining the optimal metrics to distinguish between the clinically unaffected eye from patients with AKC and normal control eyes was clearly stated in the objective of this study. If we had objectively defined any specific metric-based exclusion criteria, that would by definition alter the sample without considering the inherent limitations of these metrics.

The authors also stated that "the AKC and control groups should be matched in terms of eye laterality for more reliable statistical analysis," but in this comment the authors seem to be confusing eye laterality with intereye asymmetry. Intereye asymmetry was by definition great in the keratoconus cohort, but there is no relationship between intereye asymmetry and eye laterality, so there is no relevance to matching the study populations based on right and left eyes.

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References

1. Hwang ES, Perez-Straziota CE, Kim SW, et al. Distinguishing highly asymmetric keratoconus eyes using combined Scheimpflug and spectral-domain OCT analysis. *Ophthalmology*. 2018;125:1862–1871.
2. Re: Hwang et al.: Distinguishing highly asymmetric keratoconus eyes using combined Scheimpflug and spectral domain OCT analysis (Letter). *Ophthalmology*. 2019;126:e57–e58.