The Correlations of Macular Structure Characteristics With Idiopathic Epiretinal Membrane and Its Sexual Preference—A Matched Comparison Study

I-Hsin Ma,[1,2] Chung-May Yang,[1,3] and Yi-Ting Hsieh[1]

[1]Department of Ophthalmology, National Taiwan University Hospital, Taipei, Taiwan
[2]Department of Ophthalmology, National Taiwan University Hospital, Hsinchu Branch, Hsinchu, Taiwan
[3]Department of Ophthalmology, College of Medicine, National Taiwan University, Taipei, Taiwan

Correspondence: Yi-Ting Hsieh, Department of Ophthalmology, National Taiwan University Hospital, 7 Zhongshan S. Rd., Zhongzheng Dist., Taipei, 10002, Taiwan; ythyth@gmail.com.

Received: September 12, 2021
Accepted: January 10, 2022
Published: February 3, 2022

Citation: Ma IH, Yang CM, Hsieh YT. The correlations of macular structure characteristics with idiopathic epiretinal membrane and its sexual preference—A matched comparison study. *Invest Ophthalmol Vis Sci.* 2022;63(2):10. https://doi.org/10.1167/iovs.63.2.10

Purpose. To measure the anatomical characteristics of the macula in fellow eyes of patients with unilateral idiopathic epiretinal membrane (ERM) and to compare them with normal controls.

Methods. A total of 83 fellow eyes with unilateral idiopathic ERM were gathered as the study group, and their age- and sex-matched subjects with no vitreomacular diseases were recruited as the control group. Macular structure parameters including foveal base width (FBW), central foveolar thickness (CFT), central subfield thickness (CST), area of foveal avascular zone (FAZ), and retinal artery trajectory (RAT) were measured using optical coherence tomography (OCT) and OCT angiography and were compared between two groups.

Results. For the study group, the FBW (463.8 ± 79.6 µm) and area of FAZ (0.39 ± 0.12 mm^2) were significantly larger than those in the control group (334.3 ± 76.5 µm, 0.31 ± 0.13 mm^2). Their CST was thinner and their RAT was wider than those of the control group ($P < 0.05$ for all). In the normal population, females had a wider FBW, a thinner CFT, and a wider RAT than males ($P < 0.05$ for all).

Conclusions. Fellow eyes of the unilateral ERM had a larger FBW, a larger FAZ, a thinner CST, and a wider RAT than the normal population. This implicates that some centrifugal tractional force may exist on their macula, which eventually may result in the formation of idiopathic ERM. Females had a wider FBW, a thinner CFT, and a wider RAT than males, which may explain the higher prevalence of idiopathic ERM in females.

Keywords: macula, epiretinal membrane, sex, fovea, retinal artery trajectory

Epiretinal membrane (ERM) has a range of clinical presentations, from the milder cellophane maculopathy to the more severe macular pucker. With similar clinical findings and treatment options, the underlying causes could be secondary to retinal pathologies or idiopathic.[1] Idiopathic ERM forms with the migration of cells and collagen deposition either along the posterior hyaloid surface or from the clefts of the internal limiting membrane (ILM), the innermost layer of the retina.[2–4] ILM is composed of interweaved footplate of the Muller cells, and natural ILM pores were found near the large vessels and toward the periphery of the normal retina. Clefts and deficits has been noticed in sections of the central retina where ERM coexists.[5] It has been proposed that these ILM clefts in the macula may be due to the separation of the posterior hyaloid membrane or by the tangential tractional forces exerted on the central macula.[6,7]

In our previous study,[8] a specific pattern of the fovea—wide-based foveal pit—was noted. Eyes with a wide-based foveal pit either had a similar wide-based foveal pit or some vitreomacular diseases including ERM and macular hole in their fellow eyes. The observed symmetry of foveal pit structure in bilateral eyes corresponded to the previous study, which demonstrated high consistency between bilateral foveal pits despite interpersonal variations in foveal pit parameters.[9] However, the high prevalence of vitreomacular diseases in the fellow eyes suggests that such foveal contour should be related to some vitreomacular interface pathology. Among the vitreomacular diseases in the fellow eyes, ERM is the most prevalent; therefore we propose that widening of the foveal base could be a result of tangential traction at the central macula and serve as one risk factor for ERM formation. To confirm this hypothesis, the foveal pit and the macular structure of presumed normal fellow eyes of unilateral ERM were analyzed and compared with normal controls in this study.

Materials and Methods

Study Subjects

In this matched comparison study, patients with unilateral idiopathic ERM diagnosed between November 2016 and August 2019 in National Taiwan University Hospital were retrospectively collected, and their normal fellow eyes were enrolled as the study group. During the same period, patients who received preoperative optical coherence tomography (OCT) examination for cataract or refractive surgery were screened. Those who had regular, smooth foveal contour and no obvious maculopathy in both eyes were enrolled as the control group. All eyes with posterior staphyloma, macular degeneration, previous retinal detachment, retinopathy of prematurity, retinal dystrophies, or retinal vascular diseases were excluded. Patients with diabetes were also excluded. Demographic data and ocular examinations including axial length, fundus photography, and OCT were collected. Axial length was measured with optical biometry (LENSTAR LS700, Haag-Streit AG, Koeniz, Switzerland), and eyes with an axial length longer than 26 mm were excluded. Macular structure characteristics were measured on B-scan OCT and en face OCT angiography using Optovue Avanti RTVue XR OCT (Optovue, Inc., Fremont, CA, USA). The fundus images were obtained using either color fundus photography, fundus autofluorescence, or infrared image. Cases with incomplete data were excluded from this study. Finally, 83 fellow eyes of unilateral ERM were recruited in the study group, and 224 normal eyes were recruited in the control group. Among the 224 normal eyes, 83 of them who were sex and age-matched (same sex, age difference $\leq$ 5 years) to the cases in the study group were chosen for further paired comparison. All enrolled study subjects were Taiwanese (East Asians). This study was approved by the Ethics Committee and Institutional Review Board of National Taiwan University Hospital (no. 202008011RIND) and adhered to the Declaration of Helsinki.

Parameters of Macular Structure Characteristics

The parameters of macular structure characteristics included the foveal base width (FBW), central foveolar thickness (CFT), central subfield thickness (CST), central subfield volume (CSV), foveal avascular zone (FAZ), and retinal artery trajectory (RAT). The FBW was measured at a line that is 10 μm above the lowest point of the pit and parallel to the underlying RPE layer in the B scan OCT image. Both the horizontal and vertical sections were used to measure the width of the foveal base and the mean value was recorded as the FBW (Supplementary Fig. S1). Because of the projection magnification that might occur on OCT images, the individual FBW was adjusted with its axial length, using the Sampson's model for modification.[10] The CFT was measured from the lowest point of the pit to the base of the retinal pigment epithelium layer. CST and CSV were measured at the central 1 mm-diameter area around the foveal pit; CST was the mean retinal thickness in this area, and CSV was the volume of the retina under this area. FAZ was measured according to the en face OCT angiography, also adjusted for the axial length. CST, CSV, and FAZ were all acquired automatically through the software of Optovue Avanti RTVue, and the centration was checked manually for precision. Posterior vitreous detachment was diagnosed by the visualization of Weiss ring on fundoscopic exam. The technique for measuring RAT was modified according to the method proposed by Yoshihara et al.[6] In short, the fundus images were rotated 90° clockwise for right eyes and 90° counter clockwise for left eyes using ImageJ (ImageJ version 1.47; National Institutes of Health, Bethesda, MD; available at http://imagej.nih.gov/ij/).[11] The arcade arteries were manually dotted, with the first being the site where the retinal artery emanating from the optic disc. Twenty dots were labeled in each fundus photograph, and the x-y coordination was generated with the "invert Y coordinate" function of ImageJ. Those coordinates were then fitted to the best fit curve with second degree polynomial equation (Supplementary Fig. S2).

Statistical Analysis

Student *t*-tests were used for comparison of parameters (axial length, FBW, CFT, CST, CSV, FAZ, and RAT) between different groups. A receiver operating characteristic curve was plotted using FBW to predict if the fellow eye has ERM, and the area under the curve was calculated. The data were analyzed using SPSS software (SPSS 22.0; SPSS Inc., Chicago, IL, USA). A P value < 0.05 was considered statistically significant.

Results

A total of 224 normal eyes and 83 fellow eyes of unilateral ERM were recruited for the study. The distributions of FBW in both groups are shown in Figure 1. For the normal population, most of the FBW was between 220 to 400 μm, whereas the distribution skews to the right with

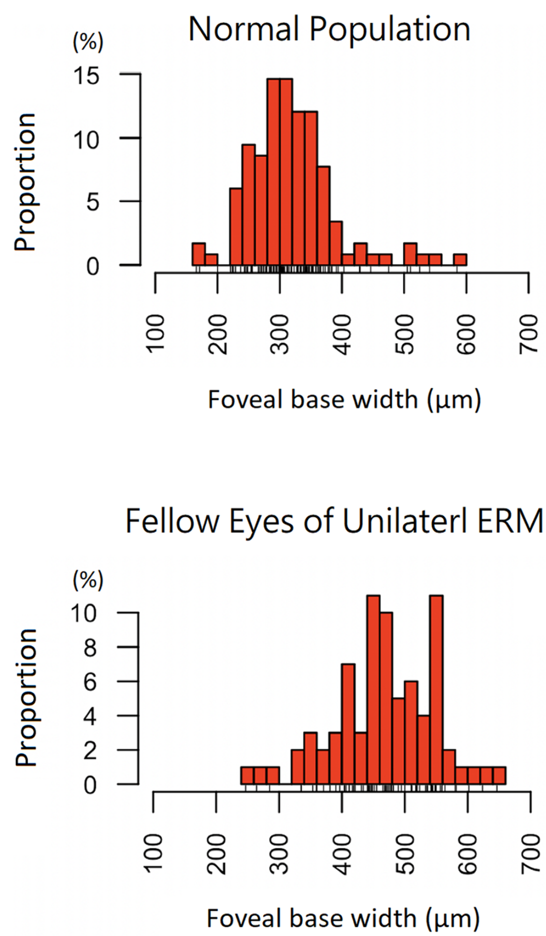

Figure 1. Histograms showing the distributions of foveal base width distribution in the normal population (only one eye was taken for illustration, n = 116) and in the fellow eyes of unilateral epiretinal membrane (n = 83).

Table 1. Comparisons of Demographic Data and Foveal Pit Characteristics Between Fellow Eyes of Unilateral Epiretinal Membrane Patients and Age-Matched Normal Subjects

	Fellow Eyes of Unilateral Epiretinal Membrane (n = 83)	Age and Sex-Matched Normal Controls (n = 83)	*P* Value
AxL	23.70 ± 1.26	23.44 ± 0.81	0.32
FBW	463.8 ± 79.6	334.3 ± 76.5	<0.001*
CFT	203.8 ± 20.6	207.2 ± 20.8	0.31
CST	238.8 ± 20.6	250.4 ± 14.9	0.020*
CSV	0.199 ± 0.020	0.199 ± 0.014	0.87
FAZ	0.39 ± 0.12	0.31 ± 0.13	0.002*
RAT	0.25 ± 0.16	0.35 ± 0.12	<0.001*

AxL, axial length (mm).
* Signifies statistical significance.

some FBW as large as near 600 µm. As for the fellow eyes of unilateral ERM, although the whole distribution ranges from 240 to 660 µm, most cases fall between 400 to 560 µm. Among the 224 normal eyes, the mean FBW was 321.7 µm, and the standard deviation was 72.3 µm. Hence, the mean plus one standard deviation, which was 394.0 µm, was chosen as the cutoff point for the definition of wide-based foveal pit in the study. In this regard, a total of 75.3% of eyes in the study group were recognized as having a wide-based foveal pit, in contrast to 10.2% in the control group ($P < 0.001$).

Among the 83 eyes in the study group, there were 53 female and 30 male patients. The mean age was 66.8 ± 7.5 (range, 51~81; median, 68) years, and the mean axial length was 23.70 ± 1.26 (range, 21.17~25.97; median, 23.57) mm. As for the 83 eyes from 83 age-matched persons chosen from the normal controls, their average axial length was 23.44 ± 0.81 (range, 22.39~25.80; median, 23.28) mm ($P = 0.32$). Compared to the age and sex-matched control group, the study group had a wider FBW (463.8 ± 79.6 vs. 334.3 ± 76.5 µm; $P < 0.001$), a thinner CST (238.8 ± 20.6 vs. 250.4 ± 14.9 µm; $P = 0.020$), a larger FAZ (0.39 ± 0.12 vs. 0.31 ± 0.13 mm^2; $P = 0.002$) and a wider RAT (0.25 ± 0.16 vs. 0.35 ± 0.12 µm; $P < 0.001$) (Table 1).

Sexual Difference in Macular Structure Characteristics

Table 2 shows the differences in macular structure characteristics between males and females in the normal population as well as in the study group. In normal population, females had a wider FBW (335.0 ± 78.9 vs. 307.6 ± 62.0 µm; $P = 0.004$), a thinner CFT (203.1 ± 19.2 vs. 221.8 ± 20.7 µm; $P < 0.001$) and a thinner CSV (0.198 ± 0.014 vs. 0.212 ± 0.015 µm; $P < 0.001$) than males. As for the study group, females also had a wider FBW (482.9 ± 73.4 vs. 432.4 ± 80.7 µm, $P = 0.009$) and a thinner CST (231.8 ± 18.2 vs. 244.0 ± 18.0 µm, $P = 0.014$) than males, but the difference in CFT or CSV was not statistically significant. Females had a wider RAT than males in the normal population (0.33 ± 0.11 vs. 0.40 ± 0.12; $P = 0.008$), whereas the RAT of the males in the study group (0.22 ± 0.14) was not only wider than males in the normal population but also wider than the females in the study group (0.26 ± 0.15), although not statistically significant ($P = 0.22$).

Table 3. Linear Regression Analysis for Correlations With Foveal Base Width in Normal Subjects and in the Fellow Eyes of Unilateral Idiopathic Epiretinal Membrane

	Normal Subjects		Fellow Eyes of Unilateral ERM	
Variables	Coefficient	*P* Value	Coefficient	*P* Value
Age	0.21	0.53	−2.25	0.063
Sex	−27.38	0.004*	−50.50	0.007*
AxL	−14.97	0.26	12.17	0.094
PVD	13.38	0.58	37.04	0.22
CFT	−0.83	<0.001*	−0.68	0.17
CST	−1.09	0.001*	−2.47	<0.001*
CSV	−2276.08	<0.001*	−500.72	0.275
FAZ	283.73	<0.001*	352.65	<0.001*
RAT	37.94	0.52	42.26	0.53

AxL, axial length (mm).
* Signified statistical significance.

Factors Associated With Foveal Base Width

Regression analysis was performed to evaluate the correlating factors for FBW. In the normal population, the FBW was inversely correlated with CFT, CST, and CSV, and positively correlated with FAZ ($P < 0.05$ for all). There was a significant correlation between females and a wider FBW ($P = 0.004$). In the study group, similar results were observed with FBW negatively correlated with CST ($P < 0.001$) and positively correlated with FAZ ($P < 0.001$). Females also tended to have a wider FBW ($P = 0.007$). The FBW was not correlated with age, axial length, RAT, or posterior vitreous detachment (PVD) status in either group (Table 3).

Predicting Epiretinal Membrane With Foveal Base Width of the Fellow Eyes

A receiver operating characteristic curve was plotted using FBW to predict if the fellow eye has ERM, and the area under the curve was 0.907. The best threshold of FBW was

Table 2. Comparison of Macular Structure Parameters Between Males and Females in Normal Subjects and in the Fellow Eyes of Unilateral Idiopathic Epiretinal Membrane

	Normal Subjects			Fellow Eyes of Unilateral ERM		
	Female (n = 115)	Male (n = 109)	*P* Value	Female (n = 53)	Male (n = 30)	*P* Value
Age	59.9 ± 14.0	56.5 ± 15.7	0.091	66.2 ± 7.7	68.7 ± 6.8	0.13
FBW	335.0 ± 78.9	307.6 ± 62.0	0.004*	482.9 ± 73.4	432.4 ± 80.7	0.009*
CFT	203.1 ± 19.2	221.8 ± 20.7	<0.001*	202.4 ± 19.5	206.1 ± 20.1	0.41
CST	246.8 ± 13.7	260.0 ± 21.5	0.20	231.8 ± 18.2	244.0 ± 18.0	0.014*
CSV	0.198 ± 0.014	0.212 ± 0.015	<0.001*	0.200 ± 0.022	0.200 ± 0.018	0.87
FAZ	0.32 ± 0.17	0.24 ± 0.09	0.12	0.41 ± 0.12	0.37 ± 0.12	0.20
RAT	0.33 ± 0.11	0.40 ± 0.12	0.008*	0.26 ± 0.15	0.22 ± 0.14	0.22

* Signified statistical significance.

Investigative Ophthalmology & Visual Science

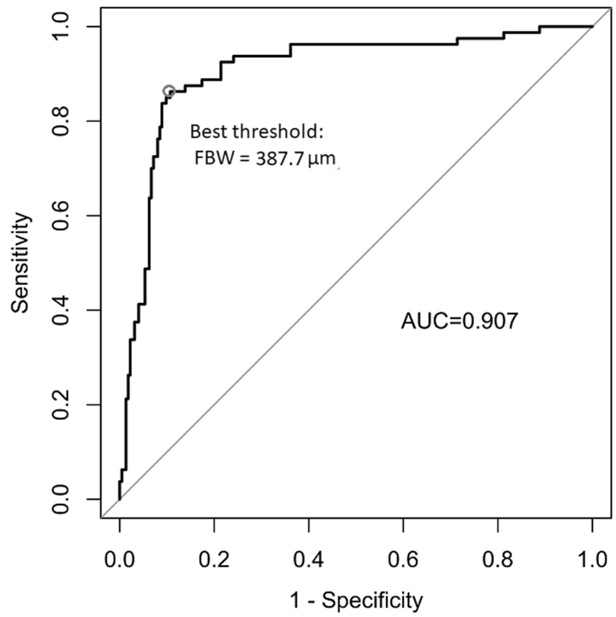

Figure 2. Receiver operation characteristic curve for predicting the presence of idiopathic epiretinal membrane using the foveal base width of the fellow eye. The area under the curve was 0.907, and the best threshold of foveal base width was at 387.7 µm.

at 387.7 µm, with a sensitivity of 86.3% and specificity of 89.3% (Fig. 2).

Discussion

Fovea development is visible at 22 weeks of gestational age and continues its maturing process in infants.[12] The foveal depression continues to deepen after birth until 15 months, and it is formed by a vertical contraction of the central Muller cells.[13,14] Afterwards, Muller cell processes contract horizontally, photoreceptors become more compact centrally, and these give rise to the base and the slope of the foveal pit. Under normal development, the fovea matures symmetrically in bilateral eyes[15]; this gives rise to the design of using the fellow eyes of unilateral ERM patients as the study group to find the possible macular structure–related factors for the formation of idiopathic ERM in this study.

In this study, it was found that the fellow eyes of unilateral ERM have a wider foveal base and a larger FAZ than the normal population. Not only was the average FBW much wider, but more than three-fourths of them had a wide-based foveal pit, which is wider than the mean value plus one standard deviation of the normal population. This finding corresponds to the proposal that the retracting force of astrocytes in central fovea widens the foveal base, and such centrifugal force may result in internal limiting membrane clefts at the central macula, which may stimulate glial cell proliferation and collagen deposition, and eventually lead to ERM formation.[3,6]

From the standpoint of macular structure, although astrocytes contract and exert centrifugal force on the central macula, not only the force would widen the foveal pit but also would make it thinner. Thus other anatomical parameters of the foveal pit might be influenced as well. This is compatible with our finding that CST was smaller in the study group than in normal controls. The results from the regression analysis also confirmed our assumption. The positive correlation of FAZ and FBW suggests that the widening of the foveal pit comes from outstretching of the fovea, not from pure thinning or atrophy of parafoveolar tissues. Furthermore, CFT, CST, and CSV were all negatively associated with FBW. Although CFT, CST, and CSV are three parameters representing similar concepts; there are still some differences among them. CFT is the thickness at the center of the foveola, whereas CST represents the average thickness of the central 1 mm–diameter area. The negative correlation between FBW and CST/CFT suggests that the widening of the foveal base is due to the thinning of the parafoveaolar area, rather than the thickening of the central foveola. Such correlation is compatible with our hypothesis that some centrifugal force results in both widening of the foveal pit and thinning of central foveola.

If a centrifugal force does exist at the macula, theoretically the RAT will be widened. The results did show that the RAT was much wider in the fellow eyes of unilateral ERM patients than normal controls ($P < 0.001$). However, the regression analysis did not show a significant correlation between FBW and RAT. It is possible that the RAT varies a lot among the normal population, so the correlation between FBW and RAT would be masked. As for other factors such as age and axial length, neither of them was correlated with FBW. Despite the fact that axial length poses an optical effect on image acquisition, which may lead to minimal measurement error,[10] the association of FBW is not correlated with the axial length within 21 to 26 mm. The status of PVD also had no correlation with FBW, which is reasonable because vitreomacular traction in non-PVD eyes is anteroposterior traction, rather than tangential traction that could affect the FBW.

Sexual difference in macular structure is a topic of interest. Previous studies have identified that the CST is thicker in males than in females.[9,16,17] Our previous study also observed a female preponderance in eyes with a wide-based foveal pit.[8] In this study, it was found that females had not only a wider FBW and a thinner CFT but also a wider RAT. This is compatible with the assumption that females may have a stronger centrifugal force at the macula that results in this phenomenon. Such result could also explain the finding by Poplin et al.[18] that the “hot spot” for sexual differentiation by deep learning models focused on retinal arteries in fundus photography. Furthermore, these observed sexual differences in macular structure could also explain the female preponderance in ERM and macular hole formation.[19–21] Interestingly, males who had an idiopathic ERM had the widest RAT in their fellow eyes among all in this study; this means that a really strong centrifugal traction force is needed for males to develop idiopathic ERM.

In conclusion, this study found that the fellow eyes of unilateral ERM had a larger FBW and FAZ, a thinner CST, and a wider RAT than the normal population. We postulate that centrifugal macular traction may result in the formation of idiopathic ERM. We propose that the centrifugal traction force at macula leads to widening of the foveal pit and thinning of central foveola, and it eventually may produce some cracks in ILM which harbor retinal glial cell proliferation and ERM formation. Females were found to have a wider FBW, a thinner CFT, and a wider RAT than males, which may explain the higher prevalence of idiopathic ERM in the female.

Acknowledgments

Disclosure: **I.-H. Ma,** None; **C.-M. Yang,** None; **Y.-T. Hsieh,** None

References

1. Snead DR, James S, Snead MP. Pathological changes in the vitreoretinal junction 1: epiretinal membrane formation. *Eye (Lond).* 2008;22:1310–1317.
2. Greven CM, Slusher MM, Weaver RG. Epiretinal membrane release and posterior vitreous detachment. *Ophthalmology.* 1988;95:902–905.
3. Bovey EH, Uffer S. Tearing and folding of the retinal internal limiting membrane associated with macular epiretinal membrane. *Retina.* 2008;28:433–440.
4. Kishi S, Shimizu K. Oval defect in detached posterior hyaloid membrane in idiopathic preretinal macular fibrosis. *Am J Ophthalmol.* 1994;118:451–456.
5. Wolter JR. Pores in the internal limiting membrane of the human retina. *Acta Ophthalmol (Copenh).* 1964;42:971–974.
6. Yoshihara N, Sakamoto T, Yamashita T, et al. Wider retinal artery trajectories in eyes with macular hole than in fellow eyes of patients with unilateral idiopathic macular hole. *PLoS One.* 2015;10(4):e0122876.
7. Yamashita T, Asaoka R, Tanaka M, et al. Relationship between position of peak retinal nerve fiber layer thickness and retinal arteries on sectoral retinal nerve fiber layer thickness. *Invest Ophthalmol Vis Sci.* 2013;54:5481–5488.
8. Ma IH, Yang CM, Hsieh YT. Wide-based foveal pit: a predisposition to idiopathic epiretinal membrane. *Graefes Arch Clin Exp Ophthalmol.* 2021;259:2095–2102.
9. Wagner-Schuman M, Dubis AM, Nordgren RN, et al. Race- and sex-related differences in retinal thickness and foveal pit morphology. *Invest Ophthalmol Vis Sci.* 2011;52:625–634.
10. Sampson DM, Gong P, An D, et al. Axial length variation impacts on superficial retinal vessel density and foveal avascular zone area measurements using optical coherence tomography angiography. *Invest Ophthalmol Vis Sci.* 2017;58:3065–3072.
11. Schindelin J, Arganda-Carreras I, Frise E, et al. Fiji: an open-source platform for biological-image analysis. *Nat Methods.* 2012;9:676–682.
12. Hendrickson AE, Yuodelis C. The morphological development of the human fovea. *Ophthalmology.* 1984;91:603–612.
13. Yuodelis C, Hendrickson A. A qualitative and quantitative analysis of the human fovea during development. *Vision Res.* 1986;26:847–855.
14. Bringmann A, Syrbe S, Gorner K, et al. The primate fovea: Structure, function and development. *Prog Retin Eye Res.* 2018;66:49–84.
15. Scheibe P, Zocher MT, Francke M, Rauscher FG. Analysis of foveal characteristics and their asymmetries in the normal population. *Exp Eye Res.* 2016;148:1–11.
16. Wong AC, Chan CW, Hui SP. Relationship of gender, body mass index, and axial length with central retinal thickness using optical coherence tomography. *Eye (Lond).* 2005;19:292–297.
17. Kashani AH, Zimmer-Galler IE, Shah SM, et al. Retinal thickness analysis by race, gender, and age using Stratus OCT. *Am J Ophthalmol.* 2010;149:496–502.e491.
18. Poplin R, Varadarajan AV, Blumer K, et al. Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. *Nat Biomed Eng.* 2018;2:158–164.
19. Duan XR, Liang YB, Friedman DS, et al. Prevalence and associations of epiretinal membranes in a rural Chinese adult population: the Handan Eye Study. *Invest Ophthalmol Vis Sci.* 2009;50:2018–2023.
20. Fraser-Bell S, Ying-Lai M, Klein R, Varma R, Los Angeles Latino Eye S. Prevalence and associations of epiretinal membranes in latinos: the Los Angeles Latino Eye Study. *Invest Ophthalmol Vis Sci.* 2004;45:1732–1736.
21. Miyazaki M, Nakamura H, Kubo M, et al. Prevalence and risk factors for epiretinal membranes in a Japanese population: the Hisayama study. *Graefes Arch Clin Exp Ophthalmol.* 2003;241:642–646.