Evaluating Distribution of Foveal Avascular Zone Parameters Corrected by Lateral Magnification and Their Associations with Retinal Thickness

Qiang Li, BBioMedSc,[1,*] Peijun Gong, PhD,[2,3,*] Phuoc Hao Ho, BSc,[2,3] Brendan F. Kennedy, PhD,[2,3,4] David A. Mackey, FRANZCO,[1,5,7] Fred K. Chen, FRANZCO, PhD,[1,5,6,7,‡] Jason Charng, PhD[1,8,‡]

Purpose: To examine the distribution of foveal avascular zone (FAZ) parameters, with and without correction for lateral magnification, in a large cohort of healthy young adults.

Design: Cross-sectional, observational cohort study.

Participants: A total of 504 healthy adults, 27 to 30 years of age.

Methods: Participants underwent a comprehensive ophthalmic examination including axial length measurement and OCT angiography (OCTA) imaging of the macula. OCT angiography images of combined superficial and deep retinal vessel plexuses were processed via a custom software to extract foveal avascular zone area (FAZA) and foveal density-300 (FD-300), the vessel density in a 300-μm wide annulus surrounding the FAZ, with and without correction for lateral magnification. Bland—Altman analyses were performed to examine the effect of lateral magnification on FAZA and FD-300, as well as to evaluate the interocular agreement in both parameters. Linear mixed-effects models were used to examine the relationship between retinal thicknesses and OCTA parameters.

Main Outcome Measures: The FAZA and FD-300, corrected for lateral magnification.

Results: The mean (standard deviation [SD]) of laterally corrected FAZA and FD-300 was 0.22 mm^2 (0.10 mm^2) and 51.9% (3.2%), respectively. Relative to uncorrected data, 55.6% of corrected FAZA showed a relative change > 5%, whereas all FD-300 changes were within 5%. There was good interocular symmetry (mean right eye—left eye difference, 95% limits of agreement [LoA]) in both FAZA (0.006 mm^2, -0.05 mm^2, to 0.07 mm^2) and FD-300 (-0.05%, -5.39%, to 5.30%). There were significant negative associations between central retinal thickness and FAZA (β = -0.0029), as well as between central retinal thickness and FD-300 (β = -0.044), with the relationships driven by inner, not outer, retina.

Conclusions: We reported lateral magnification adjusted normative values for FAZA and FD-300 in a large cohort of young, healthy eyes. Clinicians should strongly consider accounting for lateral magnification when evaluating FAZA. Good interocular agreement in FAZA and FD-300 suggests the contralateral eye can be used as control data. *Ophthalmology Science 2022;2:100134 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyscience.org.

OCT angiography (OCTA) is an ophthalmological imaging technique used to visualize the retinal and choroidal vasculatures by measuring the reflection of light from moving red blood cells.[1] The main advantages of OCTA over traditional angiographic techniques are that it does not require the injection of intravenous dye, allows for micrometer-scale depth resolution,[2] and enables the extraction of quantifiable parameters. Foveal avascular zone (FAZ) refers to the region within the fovea that has no overlying capillaries,[3] and FAZ parameters have been shown to be useful biomarkers for diagnosing and monitoring retinal microvascular diseases such as diabetic retinopathy.[4,5] Commonly reported FAZ parameters include foveal avascular zone area (FAZA) and foveal density-300 (FD-300), the vessel density in a 300-μm wide annulus around the FAZ margin.

Numerous studies have reported normative values for FAZ parameters.[6-22] However, a recent study has estimated that an overwhelming majority (~90%) of OCTA studies do not account for lateral magnification when estimating the area of en face regions.[23] The difference in lateral magnification results in en face images subtending to different linear dimensions on the retina according to the axial length.[24] In other words, compared with an emmetropic eye, the same en face image will be larger in a myopic eye and smaller in a hyperopic eye. Therefore,

by not accounting for lateral magnification, one cannot accurately quantify en face OCTA parameters.

In this study, we provide reference data for FAZA and FD-300, corrected by lateral magnification, in a cohort of young, healthy adults. In addition, interocular symmetry of both FAZA and FD-300 was evaluated. We explore the clinical relevance of correcting lateral magnification of FAZA and FD-300 and the relationship between these parameters and foveal retinal thickness.

Methods

Study Participants

This cross-sectional, observational cohort study analyzed the ophthalmic data collected at the Raine Study Gen2 28-year follow-up. Based in Perth, Western Australia, the Raine Study is a prospective birth cohort study; the detailed methodology has been previously described.[25-28] In brief, a cohort of 2900 pregnant women (Gen1) were recruited between 1989 and 1991, and their offspring (Gen2) were enrolled to undergo a systematic series of medical tests and questionnaires at various intervals since the perinatal period. As part of the Gen2 28-year follow-up (April 2018 to May 2020), all active participants were invited to attend Lions Eye Institute (Perth, Western Australia) to undergo a comprehensive standardized ocular examination, which included OCTA (RTVue XR Avanti; Optovue, Inc, AngioVue software version A2018,1,0,43), ocular biometry using noncontact partial coherence interferometry (IOL Master V.5; Carl Zeiss Meditec AG), tonometry (iCare TAO1i Tonometer; iCare Finland, Oy), visual acuity testing, cycloplegic autorefraction (ARM-10; Tagaki Ltd.) after tropicamide (0.5%) instillation, OCT (Spectralis; Heidelberg Engineering GmbH), and fundoscopy (California; Optos). All individuals received a full explanation of the nature of the study, and written informed consent was acquired before participation. No participants received financial compensation. The Raine Study is registered in the Australian New Zealand Clinical Trials Registry (ACTRN12617001599369), and the G2 28-year follow-up was approved by The University of Western Australia Human Ethics Research Committee (RA/4/20/1038) and was conducted in compliance with the tenets of the Declaration of Helsinki.

Participants with concurrent macular OCTA and axial length scans in at least 1 eye were included in the analysis. Ocular exclusion criteria were self-reported ocular disease, amblyopia, strabismus, refractive surgery, and orthokeratology. Subjects with abnormal retina scans detected from fundus imaging and OCT were also excluded. In addition, OCTA images with signal strength < 7 (of 10) were also excluded from analysis.

OCTA Image Acquisition Protocol

OCT angiography scans were acquired in dilated pupils. The Angio Retina [3.0] recording protocol (3 × 3 mm scan size) was selected, which consists of a horizontal-priority (fast-x) and a vertical-priority (fast-y) OCT raster volume processed by 3-dimensional orthogonal registration (Motion Correction Technology; Optovue, Inc) to produce a single image with reduced motion artefacts. During acquisition, subjects were instructed to look at the central fixation point and avoid blinking. If required, the operator manually adjusted the center of the square to closely match the fovea before image acquisition. After scanning, if the operator detected obvious misalignment of blood vessels or poor image quality, the scan was retaken. For each eye, the "Retina" en face slab, which combines "superficial" and "deep" vasculature OCTA scan, was exported as an image file for post hoc analysis.

OCTA Image Processing

To correct for lateral magnification, a custom MATLAB (vR2017a, MathWorks) algorithm was developed. The program required the operator to first mark several points within the FAZ region, with FAZ defined as the largest area within the fovea with no overlying blood vessels. The algorithm would then, via a series of iterations, based on the Chan-Vese approach,[24] automatically outline the FAZ using the preselected seeding points. The operator terminated the iteration when visual inspection confirmed the FAZ boundary had been adequately delineated by the program. In instances where the algorithm failed to appropriately delineate the FAZ boundary, manual segmentation was performed. The segmented FAZ boundary was then smoothed and expanded radially from the center of the FAZ by 300 μm, which outlined the FD-300 zone. To define blood vessels within the FD-300 zone, the vessels were identified as pixels with the OCTA signal above a certain threshold. Because of the lack of access to the vessel threshold set by the Optovue OCTA device, a unique threshold value was empirically chosen for each uncorrected image by benchmarking against the AngioVue Analytics software provided by the Optovue OCTA device. In particular, the threshold was set at a value that best matched the resulting vessel density to the output vessel density by the AngioVue Analytics software in 9 square zones, as previously reported.[24] Vessel density was then calculated by dividing the total vessel area to the area of the FD-300 zone. The custom software then uses the axial length measurement provided to adjust for lateral magnification using the Littman and modified Bennett formulae.[24] The custom program exports OCTA parameters both uncorrected and corrected by lateral magnification. The uncorrected FAZA and FD-300 data were first used to validate the custom program by comparing against values output by the Optovue program. After validation, FAZA and FD-300 values corrected by lateral magnification were used for subsequent analyses.

Measuring Thickness of Retinal Layers

A raster scan (31 B-scans) was recorded in each eye, from which an ETDRS grid centered on the fovea was superimposed onto the retina. Delineation of the retinal layers for each image was conducted with the Spectralis software and was manually checked for correct segmentation. Full (inner limiting membrane to Bruch's membrane), outer (Bruch's membrane to outer nuclear layer), and inner (outer plexiform to inner limiting membrane) layers were extracted for the central 1-mm diameter circle.

Statistical Analysis

For cross-sectional analysis, only 1 eye per subject was included. The right eye was analyzed by default unless the image quality provided by the software was < 7,[29] in which case the left eye was used. The Bland−Altman method[30] was used to compare the uncorrected FAZA and FD-300 values extracted from the custom software to the raw data from AngioVue. Interocular limits of agreement (LoA) were calculated to quantify symmetry of FAZA and FD-300 in contralateral eyes with image scan quality ≥ 7.

Linear mixed-effects analysis was conducted to ascertain any association between retinal thicknesses and corrected FAZA/FD-300, adjusted for age and sex. We also adjusted for right and left eyes as a random effect. Unless otherwise stated, all data were summarized as mean ± standard deviation (SD). R statistical software (Version 4.1.0; The R Foundation for Statistical Programming) was used to conduct all statistical analyses.

Results

A total of 504 participants who met the inclusion and exclusion criteria, with at least 1 eye concurrent OCTA and axial length data (261 female participants [51.8%], 243 male participants [48.2%]; average [SD] age 28.2 [0.7] years), were included in the analysis. For cross-sectional analysis, 498 right eyes and 6 left eyes were used. The mean (SD) axial length was 23.7 (1.0), and median (range) scan quality was 9 of 10 (7 to 10).

Validating the Custom Program

In the majority of eyes, both the Optovue and the custom program delineated a similar FAZ boundary (Fig 1A). However, in some eyes, the demarcation of FAZ differed considerably between the 2 programs (Fig 1B). More specifically, the Optovue program tended to disregard faint blood vessels running through the central fovea when delineating FAZ, whereas using the semiautomated custom program, we were able to account for these vessels when determining the FAZ boundary.

By using 1 eye per subject, raw FAZA from the AngioVue software appeared normally distributed with a right skew (Fig 1C). The mean (SD) FAZA was 0.22 (0.10) mm^2. Uncorrected FAZA from the custom software showed similar distribution and a mean (SD) of 0.23 (0.10) mm^2 (Fig 1D). Bland−Altman analysis was conducted to evaluate the performance of the custom software compared with the Optovue program (Fig 1E). The mean (95% LoA) difference in FAZA between the 2 approaches was 0.004 (-0.02 to 0.03) mm^2, confirming the custom software tended to overestimate FAZA by an average of 1.8% compared with the Optovue program.

The distribution FD-300 from the Optovue program, by eye, appeared normally distributed with a left skew (Fig 1F), with a mean (SD) value of 51.8% (3.2%). With the use of the custom software, the distribution of uncorrected FD-300 (Fig 1G) was similar compared with the Optovue output, with the same rounded mean (SD) of 51.8 (3.2). Bland−Altman analysis (Fig 1H) showed a mean (95% LoA) difference of 0.01 (-0.42% to 0.45%) between the custom and Optovue programs.

Laterally Corrected Normative Values and Interocular Symmetry of FAZA and FD-300

The Littman and modified Bennett formula was applied to the FAZ and FD-300 boundaries derived using the custom program to correct for lateral magnification. In an eye with long axial length (Fig 2A, B, axial length 28.08 mm), the actual physical size of the FAZA is larger but the FD-300 boundary encapsulated a smaller retinal region in the corrected image (Fig 2B) compared with the raw image (Fig 2A).

The distribution of corrected FAZA appeared normal with a right skew (Fig 2C). The average (SD) corrected FAZA was 0.22mm^2 (0.10 mm^2). Bland−Altman analysis showed an average (95% LoA) difference between the corrected and uncorrected FAZA of -0.005 mm^2 (-0.05 to

0.04 mm^2) (Fig 2D). It is worth noting that the data points close to the upper LoA were due to longer axial length and those close to the lower LoA were due to shorter axial length. This was confirmed when the relative change in FAZA after lateral magnification correction in all eyes were plotted against their respective axial length (Fig 2E). By using a nominal ±5% error margin[24] (dashed lines), 96 of 504 eyes (19.0%) showed a relative difference > 5%, whereas 184 of 504 eyes (36.5%) had a relative difference <- 5%. Laterally corrected FD-300 appeared normally distributed (Fig 2F), with a mean (SD) of 51.9% (3.2%), with Bland−Altman showing an average (95% LoA) difference between corrected and uncorrected FD-300 of 0.11 (-1.03% to 1.25%) (Fig 2G). The relative change in FD-300 after lateral magnification correction, when plotted against the respective axial length, was within the 5% error margin in all eyes (Fig 2H). Cumulative distribution functions for both raw and laterally corrected FAZA as well as FD-300 are shown in Figure S1 (available at www.ophthalmologyscience.org).

Data from both eyes were available in 491 subjects. Bland−Altman analysis of FAZA showed a mean (95% LoA) interocular difference of 0.006 mm^2 (-0.05 to 0.07 mm^2) (Fig 3A). The FD-300, however, showed interocular (95% LoA) difference of -0.05% (-5.4% to 5.3%) (Fig 3B). There was a positive relationship between FAZA and FD-300 (Fig 3C; y = 18.1x + 47.9, R^2 = 0.32).

## Association between FAZ Parameters and Retinal Thickness

A total of 985 eyes (970 contralateral eyes from 485 subjects, 15 unilateral eyes from 15 subjects) were used for association analysis. There was a significant negative relationship (β = -0.0029, 95% confidence interval [CI], -0.0032 to -0.0027) between FAZA and central full retinal thickness (Table 1). Closer inspection of the data reveals that the association arose from the inner retina (β = -0.0035, 95% CI, -0.0038 to -0.0031) rather than the outer retina (β = -0.00018, 95% CI, -0.00063 to +0.00027). A negative relationship was also observed between FD-300 and full retinal thickness (β = -0.044, 95% CI, -0.056 to -0.033, Table 1). Similar to FAZA, a significant negative association to FD-300 was found in the inner retina (β = -0.053, 95% CI, -0.066 to -0.040) but not the outer retina (β = -0.0059, 95% CI, -0.017 to +0.029).

Discussion

The importance of rescaling OCTA images before quantifying en face dimensions is now widely recognized.[23,24] In this study, we established normative references and investigated interocular symmetry for lateral magnification corrected FAZA and FD-300 in a large cohort of young, healthy eyes. In addition, we explored the clinical relevance of preanalysis image scaling by determining LoA.

We determined lateral magnification corrected mean (SD) FAZA and FD-300 of 0.22 mm^2 (0.10 mm^2) and 51.9% (3.2%), respectively. Mean, lateral magnification
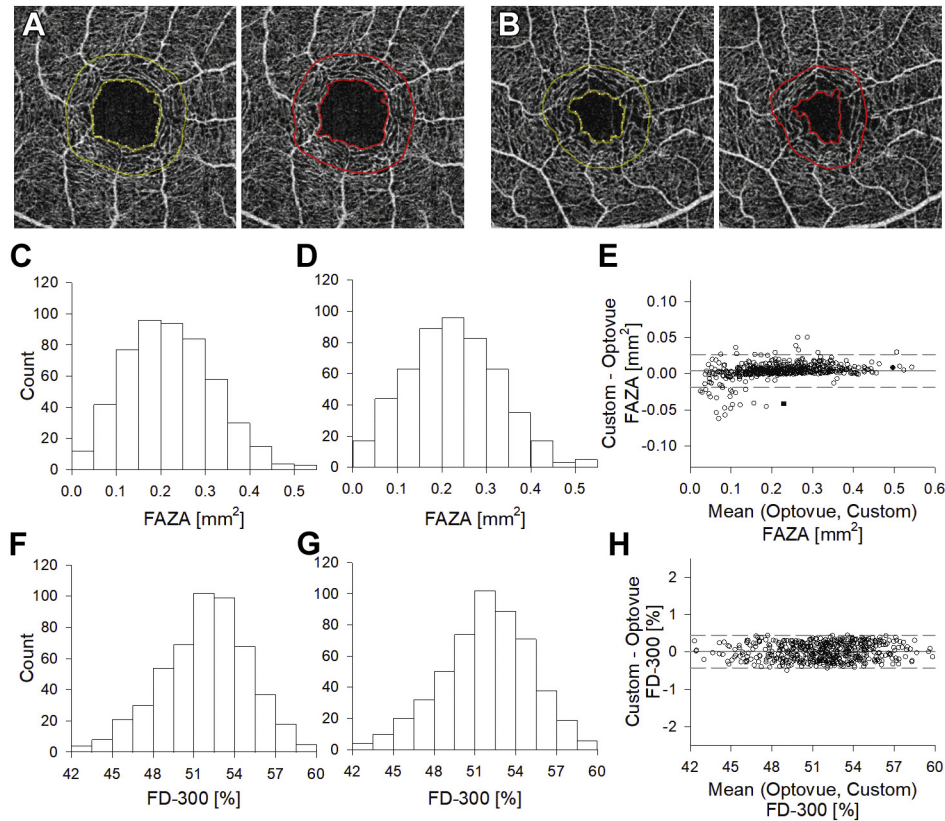
Figure 1. Comparing the custom program with the manufacturer's program. **A,** Example of good agreement in foveal avascular zone (FAZ) and foveal density-300 (FD-300) delineation with the manufacturer's software outlined in yellow **(left)** and the custom program in red **(right)**. **B,** Example of poor agreement in FAZ and FD-300 delineation with the manufacturer's software outlined in yellow **(left)** and the custom program in red **(right)**. **C, D,** Distribution of uncorrected foveal avascular zone area (FAZA) from the manufacturer's **(C)** and the custom **(D)** programs. **E,** Difference in FAZA (custom − manufacturer) is plotted against the mean of custom and manufacturer estimation of FAZA. **Solid line** indicates the mean difference, and **dashed lines** indicate the 95% limits of agreement (LoA). **F, G,** Distribution of uncorrected FD-300 from the manufacturer's **(F)** and the custom **(G)** programs. **H,** Difference in FD-300 (custom − manufacturer) is plotted against the mean of custom and manufacturer estimation of FD-300. **Solid line** indicates the mean difference, and **dashed lines** indicate the 95% LoA.

corrected FAZA of the superficial capillary plexus in normal eyes has been reported to range from 0.23 mm^2 to 0.32 mm^2,[20,31−33] with one study reporting mean corrected FAZA of 0.28 mm^2 and 0.36 mm^2 in the superficial and deep capillary plexus, respectively.[33] Our study analyzed FAZA from a combined superficial and deep retinal plexus slab, as per the manufacturer's current software update. Thus, direct comparison of FAZA and FD-300 between the current and previous studies must take into consideration the difference in retinal segmentation and the population-based difference. The clinical importance of correcting for lateral magnification when quantifying FAZA was apparent when examining our data (Fig 2E), which showed > 50% of data has relative change outside ±5%. To the best of our knowledge, no study has reported normative FD-300 values corrected by axial length. A previous study has shown that estimation of vessel density in the superficial retinal capillary plexus within a 0.5-mm and 1-mm annulus in macular OCTA scans is affected by axial length.[24] However, the relative change in vessel density reported in the aforementioned study was within ±5%, similar to our finding with FD-300. This raises the question of whether it is clinically relevant to correct FD-300. Our data suggest that, using an error margin of ±5%, it may not be necessary to correct for lateral magnification when estimating FD-300 in young, healthy eyes. In support of our postulation, it has been reported that changes of > 8% and 10% in superficial and deep vessel density acquired via OCTA, respectively, are considered clinically significant in a cohort of slightly older normal individuals.[34] We note that retinal capillary dropout in diseased or older eyes may result in > 5% decrease in FD-300 when lateral magnification is corrected for; thus, further studies are required to ascertain whether lateral magnification is clinically significant in FD-300 in other cohorts.

There appeared to be a good overall interocular symmetry in corrected FAZA, with a mean (SD) difference between the 2 eyes of 0.006 (0.03) mm^2. A previous study reported a similar mean interocular (SD) FAZA difference of 0.009 mm^2 (0.03 mm^2) in 50 lateral magnification corrected eyes from 50 subjects, but the OCTA signal was derived from the superficial retinal capillary plexus as opposed to both superficial and deep plexuses in the current study.[31] The FD-300 was also
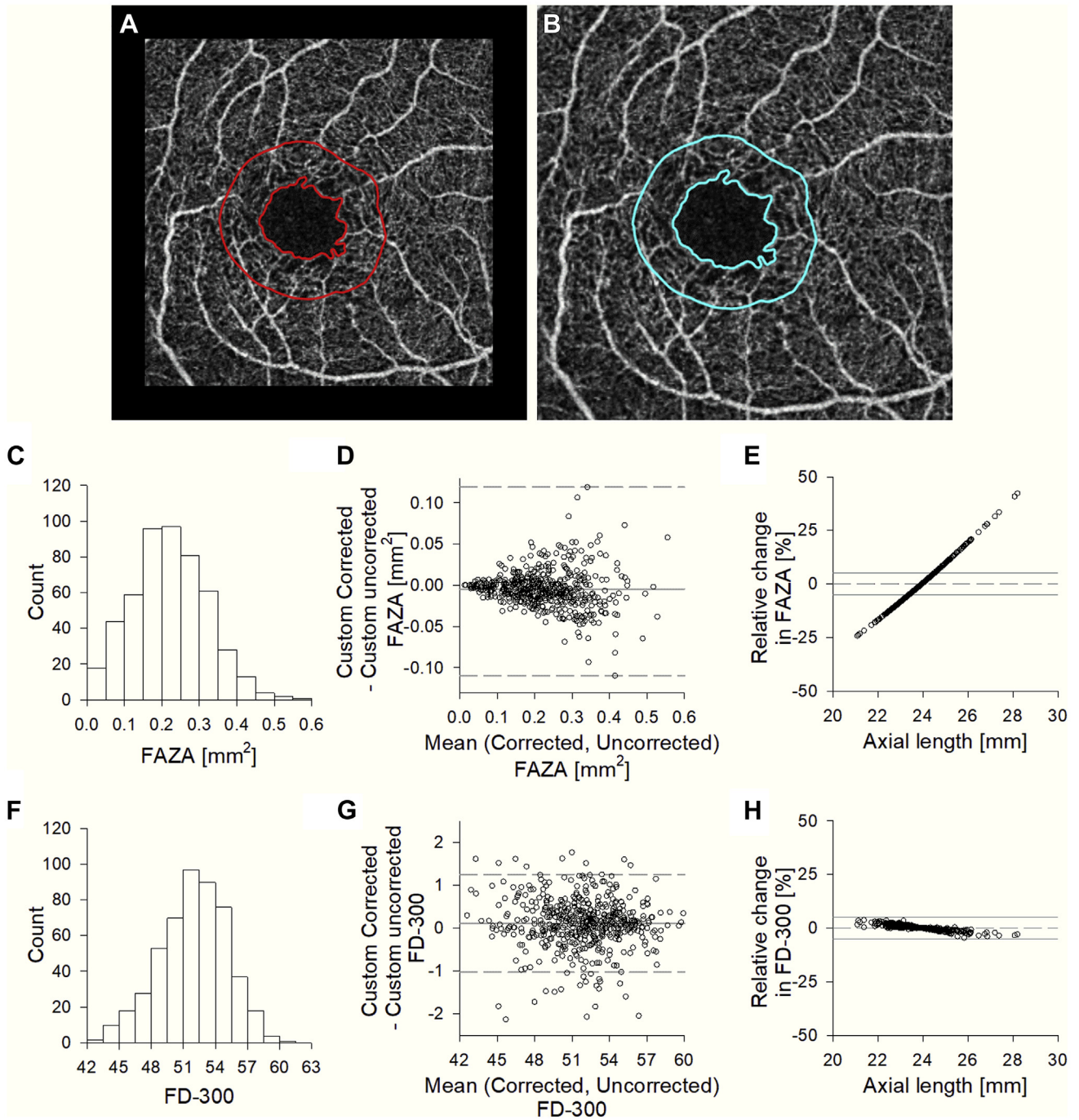
Figure 2. Effect of correcting for lateral magnification of foveal avascular zone area (FAZA) and foveal density-300 (FD-300). **A** and **B**, Representative example with long axial length (28.08 mm) demonstrating the effect of lateral magnification on the FAZA and FD-300 in uncorrected OCT angiography (OCTA) **(A)** and corrected **(B)** OCTA. Note that for FD-300, the outer portion of the annulus relative to the overall image differs in both images. **C**, The distribution of corrected FAZA. **D**, Difference in FAZA (corrected − uncorrected) is plotted against the mean of corrected and uncorrected FAZA. **Solid line** indicates the mean difference, and **dashed lines** indicate the 95% limits of agreement (LoA). **E**, Relative change in FAZA plotted against axial length. **Dashed line** indicates no relative change, and **solid lines** indicate error margin of ±5%. **F**, The distribution of corrected FD-300. **G**, Difference in FD-300 (corrected − uncorrected) is plotted against the mean of corrected and uncorrected FD-300. **Solid line** indicates the mean difference, and **dashed lines** indicate the 95% LoA. **H**, Relative change in FD-300 plotted against axial length. **Dashed line** indicates no relative change, and **solid lines** indicate error margin of ±5%.

relatively symmetrical overall, with a mean (SD) interocular difference of 0.05% (2.73%). Given that our data showed a positive relationship between corrected FAZA and corrected FD-300, eyes with larger interocular difference in FAZA tended to show a larger interocular difference in FD-300.
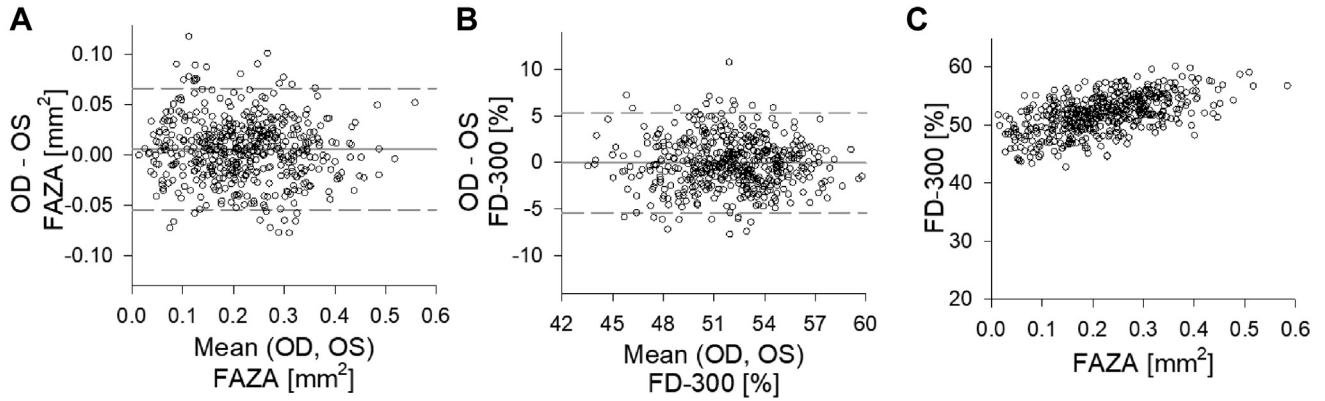
Figure 3. Interocular symmetry of limits of agreement foveal avascular zone area (FAZA) and foveal density-300 (FD-300). **A** and **B,** Difference between right eye and left eye is plotted between the mean of the right eye and left eye for FAZA **(A)** and FD-300 **(B)**. **C,** Corrected FD-300 is plotted against corrected FAZA. OD = right eye; OS = left eye.

Our findings support previous studies that reported a negative association between FAZA and central retinal thickness in both lateral magnification uncorrected[13,17,21] and corrected[20] eyes. In addition, we extended previous findings by showing that the negative relationship is driven by the inner, not the outer, retina. We also observed a negative relationship between FD-300 and central retinal thickness, as well as between FD-300 and inner retina. Again, there was no significant relationship with the outer retina. It has been shown that retinal vascular density derived from the entire 3 × 3 mm OCTA acquisition window is positively associated with central retinal thickness,[20] which differs from the negative association between FD-300 and central retinal thickness in the current study. We suspect the difference in methodology may underlie the contrary relationship observed. First, the age of subjects in the previous study was older, with a mean age of 42.1 years, and the retinal vessel density has been shown to decrease with age.[15] Second, the superficial capillary plexus was examined in the previous study, instead of combined superficial and deep plexuses in the current study. Last, the previous study evaluated capillary density within the entire macular scan, whereas the current study assessed a defined region around the avascular zone corrected by lateral magnification. Given that the outer retina is avascular in humans, anatomically, it is not unexpected that the relationships observed in FAZA and FD-300 are driven by the inner retina.

Study Limitations

Although past studies have already reported normative data on FAZA and FD-300, our study evaluated FAZA and FD-300 with correction for lateral magnification in a large cohort of young, healthy eyes. One weakness of our study is that the OCTA data were collected within adults of a narrow age range, and there may be an underlying age-related change in FAZ and FD-300. A recent, laterally corrected OCTA study of 144 eyes in 144 individuals reported no relationship between FAZA and age.[20] This is in contrast to an earlier study that showed an age-related increase in FAZA in normal eyes,[15] but the analysis did not account for lateral magnification. We could not find any literature on FD-300 changes with age. It has been shown that macular OCTA vessel density, both across the entire acquisition window[15] or in a defined circular region,[35] decreased with age. We note that neither study accounted for lateral magnification. For FD-300, the physical size of the annulus will depend on lateral magnification. However, given that there is a decrease in vessel density across the entire acquisition window, we postulate that there may be an age-related decrease in FD-300. A future cross-sectional or longitudinal study is required to assess whether there is a relationship between FD-300 and age.

In conclusion, we reported lateral magnification corrected FAZA and FD-300, as well as interocular symmetry, in a large cohort of young, healthy adults. The importance of correcting lateral magnification for FAZA is reiterated; however, adjusting for FD-300 may not be as critical clinically in young, healthy eyes.

Table 1. Association of Retinal Thicknesses with FAZ Parameters

	β	95% CI
FAZA		
Total thickness	-0.0029	**-0.0032 to -0.0027**
Inner retina	-0.0035	**-0.0038 to -0.0031**
Outer retina	-0.00018	-0.00063, +0.00027
FD-300		
Total thickness	-0.044	**-0.056 to -0.033**
Inner retina	-0.053	**-0.066 to -0.040**
Outer retina	-0.0059	-0.017 to +0.029

CI = confidence interval; FAZ = foveal avascular zone; FAZA = foveal avascular zone area; FD-300 = foveal density-300.
Model: FAZ parameter $= \alpha + \beta + age + sex$; β = change in FAZ parameter (mm^2 for FAZA, % for FD-300) per retinal thickness (in μm)
95% CIs are bolded if they exclude 0.

Footnotes and Disclosures

[1] Centre of Ophthalmology and Visual Science (incorporating Lions Eye Institute), The University of Western Australia, Perth, Australia.

[2] BRITElab, Harry Perkins Institute of Medical Research, Centre for Medical Research, QEII Medical Centre, The University of Western Australia, Perth, WA, Australia.

[3] Department of Electrical, Electronic & Computer Engineering, School of Engineering, The University of Western Australia, Perth, WA, Australia.

[4] Australian Research Council Centre for Personalised Therapeutics Technologies, Melbourne, Australia.

[5] Ophthalmology, Department of Surgery, University of Melbourne, Melbourne, Australia.

[6] Department of Ophthalmology, Royal Perth Hospital, Perth, Australia.

[7] Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, East Melbourne, Victoria, Australia.

[8] Department of Optometry, School of Allied Health, The University of Western Australia, Perth, Australia.

*Q.L. and P.G. are considered as equal first authors.

‡F.K.C. and J.C. are considered as equal last authors.

References

1. Gao SS, Jia Y, Zhang M, et al. Optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016;57: OCT27−OCT36.
2. Jia Y, Tan O, Tokayer J, et al. Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. *Opt Express*. 2012;20:4710−4725.
3. Bresnick GH, Condit R, Syrjala S, et al. Abnormalities of the foveal avascular zone in diabetic retinopathy. *Arch Ophthalmol*. 1984;102:1286−1293.
4. Ragkousis A, Kozobolis V, Kabanarou S, et al. Vessel density around foveal avascular zone as a potential imaging biomarker for detecting preclinical diabetic retinopathy: an optical coherence tomography angiography study. *Semin Ophthalmol*. 2020;35:316−323.
5. Takase N, Nozaki M, Kato A, et al. Enlargement of foveal avascular zone in diabetic eyes evaluated by en face optical coherence tomography angiography. *Retina*. 2015;35: 2377−2383.
6. Lavia C, Bonnin S, Maule M, et al. Vessel density of superficial, intermediate, and deep capillary plexuses using optical coherence tomography angiography. *Retina*. 2019;39: 247−258.
7. Acosta C, Gloria JM, Lavaque A, et al. Relationship of geographic altitude with foveal avascular zone metrics and

vascular density values assessed by OCT angiography. *Ophthalmol Retina*. 2020;4:394−402.

8. Linderman R, Salmon AE, Strampe M, et al. Assessing the accuracy of foveal avascular zone measurements using optical coherence tomography angiography: segmentation and scaling. *Transl Vis Sci Technol*. 2017;6:16.

9. Linderman RE, Muthiah MN, Omoba SB, et al. Variability of foveal avascular zone metrics derived from optical coherence tomography angiography images. *Transl Vis Sci Technol*. 2018;7:20.

10. Shahlaee A, Pefkianaki M, Hsu J, Ho AC. Measurement of foveal avascular zone dimensions and its reliability in healthy eyes using optical coherence tomography angiography. *Am J Ophthalmol*. 2016;161:50−55 e1.

11. Carpineto P, Mastropasqua R, Marchini G, et al. Reproducibility and repeatability of foveal avascular zone measurements in healthy subjects by optical coherence tomography angiography. *Br J Ophthalmol*. 2016;100:671−676.

12. Samara WA, Say EA, Khoo CT, et al. Correlation of foveal avascular zone size with foveal morphology in normal eyes using optical coherence tomography angiography. *Retina*. 2015;35:2188−2195.

13. Lim HB, Kim YW, Kim JM, et al. The importance of signal strength in quantitative assessment of retinal vessel density using optical coherence tomography angiography. *Sci Rep*. 2018;8:12897.

14. Hwang TS, Gao SS, Liu L, et al. Automated quantification of capillary nonperfusion using optical coherence tomography angiography in diabetic retinopathy. *JAMA Ophthalmol*. 2016;134:367−373.

15. Iafe NA, Phasukkijwatana N, Chen X, Sarraf D. Retinal capillary density and foveal avascular zone area are age-dependent: quantitative analysis using optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016;57:5780−5787.

16. Coscas F, Sellam A, Glacet-Bernard A, et al. Normative data for vascular density in superficial and deep capillary plexuses of healthy adults assessed by optical coherence tomography angiography. *Invest Ophthalmol Vis Sci*. 2016;57:OCT211−OCT223.

17. Kumagai K, Furukawa M, Suetsugu T, Ogino N. Foveal avascular zone area after internal limiting membrane peeling for epiretinal membrane and macular hole compared with that of fellow eyes and healthy controls. *Retina*. 2018;38:1786−1794.

18. Wang Q, Chan S, Yang JY, et al. Vascular density in retina and choriocapillaris as measured by optical coherence tomography angiography. *Am J Ophthalmol*. 2016;168:95−109.

19. Gadde SG, Anegondi N, Bhanushali D, et al. Quantification of vessel density in retinal optical coherence tomography angiography images using local fractal dimension. *Invest Ophthalmol Vis Sci*. 2016;57:246−252.

20. Fujiwara A, Morizane Y, Hosokawa M, et al. Factors affecting foveal avascular zone in healthy eyes: an examination using swept-source optical coherence tomography angiography. *PLoS One*. 2017;12:e0188572.

21. Shiihara H, Terasaki H, Sonoda S, et al. Objective evaluation of size and shape of superficial foveal avascular zone in normal subjects by optical coherence tomography angiography. *Sci Rep*. 2018;8:10143.

22. Choi J, Kwon J, Shin JW, et al. Quantitative optical coherence tomography angiography of macular vascular structure and foveal avascular zone in glaucoma. *PLoS One*. 2017;12:e0184948.

23. Llanas S, Linderman RE, Chen FK, Carroll J. assessing the use of incorrectly scaled optical coherence tomography angiography images in peer-reviewed studies: a systematic review. *JAMA Ophthalmol*. 2020;138:86−94.

24. 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.

25. McKnight CM, Newnham JP, Stanley FJ, et al. Birth of a cohort–the first 20 years of the Raine study. *Med J Aust*. 2012;197:608−610.

26. Sanfilippo PG, Huynh E, Yazar S, et al. Spectral-domain optical coherence tomography-derived characteristics of Bruch membrane opening in a young adult Australian population. *Am J Ophthalmol*. 2016;165:154−163.

27. Straker LM, Hall GL, Mountain J, et al. Rationale, design and methods for the 22 year follow-up of the Western Australian Pregnancy Cohort (Raine) Study. *BMC Public Health*. 2015;15:663.

28. Yazar S, Forward H, McKnight CM, et al. Raine Eye Health Study: design, methodology and baseline prevalence of ophthalmic disease in a birth-cohort study of young adults. *Ophthalmic Genet*. 2013;34:199−208.

29. Ali N, Sampson DM, Au Yong A, et al. Clinical validation of the RTVue optical coherence tomography angiography image quality indicators. *Clin Exp Ophthalmol*. 2020;48:192−203.

30. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res*. 1999;8:135−160.

31. Chen FK, Menghini M, Hansen A, et al. Intrasession repeatability and interocular symmetry of foveal avascular zone and retinal vessel density in OCT angiography. *Transl Vis Sci Technol*. 2018;7:6.

32. Li M, Yang Y, Jiang H, et al. Retinal microvascular network and microcirculation assessments in high myopia. *Am J Ophthalmol*. 2017;174:56−67.

33. Sugahara M, Miyata M, Ishihara K, et al. Optical coherence tomography angiography to estimate retinal blood flow in eyes with retinitis pigmentosa. *Sci Rep*. 2017;7:46396.

34. Yanik Odabas O, Demirel S, Ozmert E, Batioglu F. Repeatability of automated vessel density and superficial and deep foveal avascular zone area measurements using optical coherence tomography angiography: diurnal findings. *Retina*. 2018;38:1238−1245.

35. Lin R, Shen M, Pan D, et al. Relationship between cone loss and microvasculature change in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2019;60:4520−4531.