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The association between foveal floor measurements and macular hole size

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Abstract:	Purpose Determining which factors influence idiopathic macular hole (MH) size is important because it is a major prognostic indicator of treatment success. Foveal pit morphology is highly symmetrical within individuals and may influence MH size. Using a series of patients with unilateral MHs, we examined the foveal floor size of the fellow eye to evaluate its relationship with MH size and post-operative outcomes. Design A retrospective observational study Participants 241 participants with a unilateral MH treated with surgery and a fellow eye with no ocular pathology. Methods Spectral domain ocular coherence tomography (SD-OCT) imaged both eyes at the time of surgery. Minimum linear diameter (MLD) and base diameter (BD) defined MH size. Foveal floor width (FFW) and minimal foveal thickness (MFT) defined foveal pit morphology of the fellow eye. Main outcome measures Baseline characteristics, SD-OCT measurements and pre-operative variables were compared to determine their relationship with MH size and post-operative visual acuity in logMAR units (Va). Results FFW was correlated with MLD (r = 0.36; p=<0.001) and BD (r=0.30; p=<0.001) but not post-operative Va. MLD correlated with pre-operative (r=0.49; p=<0.0001) and post-operative Va (r=0.54, p=<0.0001). A two-stage regression model was developed to predict post-operative Va (r^2 = 0.28); pre-operative Va (beta = 0.36; p=0.002) explained 13% of variability and MLD (beta = 0.29; p=0.002) and MH duration (beta=0.23; p=0.004) explained a further 16%. Conclusion FFW of the fellow eye in patients with a unilateral MH was significantly correlated with MH size and may explain some of the variability in MH size observed between individuals. However, FFW could not predict post-operative vision.
Suggested Reviewers:	
Opposed Reviewers:	

Precis

Foveal Floor Width (FFW) is correlated with macular hole size but not post-operative vision.

Title: The association between foveal floor measurements and macular hole size

Short title: Foveal floor measurements and macular hole size

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Declarations

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Conflicts of interest/competing interests

DCM has no conflicts of interest

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Availability of data and material

Data and material can be made available upon direct request to the corresponding author

Authors' contributions

Authors name	Research design	Data acquisition and or research execution	Data analysis and/or interpretation	Manuscript preparation	Approved of final article
Declan C Murphy		Yes	Yes	Yes	Yes
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Louisa Wickham	Yes	Yes		Yes	Yes
David HW Steel	Yes	Yes	Yes	Yes	Yes

<u>Ethics approval</u>

All data and scans were collected as part of routine care and fully anonymised, and as such under UK guidelines this study was categorised as a service evaluation and did not require ethical approval

<u>Consent to participate</u>

All included participants provided informed consent for participation in this study

<u>Consent for publication</u>

All authors provide consent for publication

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None

<u>Human subjects</u>

The study abides to the declaration of Helsinki.

<u>Abbreviations</u>

logMAR: Logarithm of the Minimum Angle of Resolution

VA: Best corrected Visual Acuity

SD-OCT: Spectral Domain Ocular Coherence Tomography

MH: Idiopathic Macular Hole

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Precis

Foveal Floor Width (FFW) is correlated with macular hole size but not post-operative vision.

Abstract (251/350 words)

Purpose

Determining which factors influence idiopathic macular hole (MH) size is important because it is a major prognostic indicator of treatment success. Foveal pit morphology is highly symmetrical within individuals and may influence MH size. Using a series of patients with unilateral MHs, we examined the foveal floor size of the fellow eye to evaluate its relationship with MH size and post-operative outcomes.

Design

A retrospective observational study

Participants

241 participants with a unilateral MH treated with surgery and a fellow eye with no ocular pathology.

Methods

Spectral domain ocular coherence tomography (SD-OCT) imaged both eyes at the time of surgery. Minimum linear diameter (MLD) and base diameter (BD) defined MH size. Foveal floor width (FFW) and minimal foveal thickness (MFT) defined foveal pit morphology of the fellow eye.

Main outcome measures

Baseline characteristics, SD-OCT measurements and pre-operative variables were compared to determine their relationship with MH size and post-operative visual acuity in logMAR units (Va).

Results

FFW was correlated with MLD (r = 0.36; p=<0.001) and BD (r=0.30; p=<0.001) but not post-operative Va. MLD correlated with pre-operative (r=0.49; p=<0.0001) and post-operative Va (r=0.54, p=<0.0001). A two-stage regression model was developed to predict post-operative Va (r^2 = 0.28); pre-operative Va (beta = 0.36; p=0.002) explained 13% of variability and MLD (beta = 0.29; p=0.002) and MH duration (beta=0.23; p=0.004) explained a further 16%.

Conclusion

FFW of the fellow eye in patients with a unilateral MH was significantly correlated with MH size and may explain some of the variability in MH size observed between individuals. However, FFW could not predict post-operative vision.

Key words

Idiopathic macular hole; vitreoretinal surgery; fovea; foveal floor width

Introduction

It is known that most idiopathic macular holes (MH) result from anteroposterior traction occurring secondary to vitreomacular traction.[1] Once MHs form, they typically increase in size over time[2] which is predominantly related to tangential tractional forces.[3] Other factors which may contribute include retinal edge hydration[4] and the bistable foveal hypothesis, proposed by Woon et al which both result in retinal edge eversion and an increase in hole dimensions.[5]

The factors which determine MH size in individual patients are unclear. Some patients may present with short histories but large MHs and conversely long histories with small MHs. This has been explained before by the often uncertain clinical history and the unknown magnitude of tangential traction forces present, but clinical experience suggests that MHs differ significantly in size when they first form.

It is known that ethnicity can affect MH size[6] and possibly gender[7] but the variability in size cannot be explained by demographics and chronicity alone.

Determining which factors contribute to the size of a MH is important because it is known that MH size is a major prognostic indicator of treatment success both in terms of hole closure and visual outcomes.[7–10] Indeed, surgeons often formulate their surgical plan based on hole dimensions.[11] Elucidating which additional factors are relevant and can influence MH size, may lead to an improved understanding of the pathogenesis underpinning MH formation and better management decisions. Furthermore, although MH size, pre-operative visual acuity and duration have all been shown to be predictive of post-operative outcomes, their predictive value is limited so other currently unquantified person-specific factors may be important.

Another variable which may affect MH size is foveal pit morphology. The foveal centre is characterized by a foveal avascular zone (FAZ) which is comprised of an area of densely packed cone cells with elongated outer segments and surrounded by outwardly displaced inner retinal layers, which form the foveal pit.[12] It is known that there is significant inter-individual variability in pit size and shape although fellow eyes are highly symmetrical.[12,13]

We hypothesised that inter-individual differences in foveal floor size could predict MH size. Using a series of patients with unilateral MHs, we examined the foveal floor size of the fellow eye to investigate their relationship with MH size and visual outcomes after surgery.

Materials and methods

This was a retrospective observational study of a cohort of 241 patients with a unilateral MH who underwent surgery with vitrectomy, internal limiting membrane (ILM) peeling and gas tamponade at two specialist ophthalmic centres in the United Kingdom (UK) between 1st January 2016 and 1st January 2018. Data was obtained from two ophthalmic centres in the United Kingdom (UK), Sunderland Eye Infirmary and Moorfields Eye Hospital. Patients were identified from the surgical databases of the surgeons involved.

Participants with a unilateral full-thickness idiopathic MH and a normal fellow eye were eligible for inclusion. We excluded patients with traumatic MHs, chronic MHs (present for longer than twelve months), myopia greater than 6 dioptres, eyes with epiretinal membrane (ERM) and or epiretinal proliferation, eyes with axial lengths of less than 22mm and greater than 25.5mm, MHs associated with other retinal pathology, previous retinal surgery or ocriplasmin treatment, fellow eyes with other retinal pathology or abnormalities including vitreomacular traction, and eyes with inadequate imaging.

For each included dataset, participant age, gender, ethnicity, imaging modality and laterality of the affected eye were recorded. For patients from the Sunderland Eye Infirmary cohort, duration of MH symptoms at the time of surgery and the pre-operative and three-month post-operative visual acuity, as well as the anatomical success of surgery with hole closure (i.e. closure of MH without a neurosensory retinal defect) were also recorded.

Visual acuities (Va) were measured using a standard Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart and then converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis.

All patients in the Sunderland cohort had undergone trans-conjunctival 25 or 27-gauge vitrectomy by the same surgeon with the same equipment (Alcon Constellation, Alcon, Fort Worth, USA) using wide field non-contact viewing and combined phacoemulsification and intraocular lens implantation if phakic. Brilliant Blue G [ILM Blue, Dorc international, The Netherlands] was used to stain the ILM and peeled using a pinch technique and end gripping forceps (Grieshaber revolution DSP ILM forceps, Alcon Grieshaber AG, Schaffhausen, Switzerland). Either 25% SF6 or 20% C2F6 gas was used as a tamponade and the patients were instructed to remain in the face down position for one to three days post-operatively.

All participants had undergone imaging using spectral domain optical coherence tomography (SD-OCT) on the Heidelberg Spectralis (Heidelberg Engineering Inc USA) in one centre (Sunderland Eye Infirmary) and with a Topcon 3D OCT (Topcon, Tokyo, Japan) in the second centre (Moorfield's Eye Hospital) as part of their routine care.

Using the Spectralis, a high density central horizontal scanning protocol with 30µm line spacing was used in the central 15 degrees. All scans used a 15 automatic real-time setting which enabled multisampling and noise reduction over 15 images. Using the Topcon, a macular volume scan was performed for each eye consisting of 256 horizontal B-scans, centred through the fovea.

Image measurements

On the SD-OCT scans, the minimum linear diameter (MLD) and maximum base diameter (BD) of the eye affected by the MH were measured using tools on the imaging systems.[14] The presence of vitreomacular adhesions (VMA) to the edge of the hole was noted.

On the fellow unaffected eye, the minimal foveal thickness (MFT) at the base of the foveal pit was measured using the SD-OCT slice with the thinnest foveal floor measurements. The foveal floor width (FFW) was also measured and defined as the widest distance between the two points at which the outer nuclear layer/Henle's fibre layer reached the inner retinal surface on the SD-OCT slice with the widest floor dimensions. **(Figure 1)**

Two observers performed the SD-OCT measurements. One performed the MH measurements and the other the fellow eye measurements, with each masked to the others' findings. A third observer masked to the results repeated the measurements in a subset of cases to ascertain agreement.

Patients from both Sunderland Eye Infirmary and Moorfields Eye Hospital were combined to create a single patient cohort for analysis. Analyses which included pre-operative Va, post-operative Va, and symptom duration were performed using data from Sunderland Eye infirmary patients only due to data availability.

This study adhered to the tenets of the Declaration of Helsinki. All data and scans were collected as part of routine care and fully anonymised, and as such under UK guidelines this study was categorised as a service evaluation and did not require ethical approval

Statistical analysis

Statistical analysis was performed using SPSS v26.0. Participant demographic characteristics, and pre-operative and post-operative variables are presented as means, standard deviation (SD) and range or percentage (%) as appropriate. Two-sample non-paired t-tests or one-way ANOVA with Tukey's HSD post hoc testing compared continuous variables. Hierarchical multiple regression was used to analyse the effect of multiple variables. The repeatability of the FFW and macular holes measurements were tested using intra-class correlation (ICC). Statistical significance was defined by a p-value of 0.05 or less.

Results

Study characteristics

During the study period a total of 356 eyes of 324 patients underwent surgery for a MH. Eighty-three patients were excluded leaving 241 patients who fulfilled our inclusion criteria; 108 from Sunderland Eye Infirmary and 133 from Moorfields Eye Hospital.

The baseline characteristics of the study population are shown in **Table 1.**

241 participants were included in total. 181 were female. 178 were of Caucasian ethnicity, 25 were Afro-Caribbean and 38 were Indian/Asian. Average age was 68 years.

Measures of MH size and foveal shape were calculated. Mean FFW was 500.8µm, MFT was 193.9µm, MLD was 412.3µm and BD was 880.2µm.

Associations

Associations between foveal and MH measurements are displayed in **Table 2**. FFW showed a significant association with MLD (r=0.357, p=<0.001) **(Figure 2)**. BD and MLD showed a strong positive correlation (0.664; p=<0.001).

MHs were divided into two groups according to MH size (MLD<400µm (N=129) and MLD≥400µm (N=112)). There were no significant between-group differences in the associations between MH and foveal size parameters. Correlations between MFT and FFW, MLD and FFW, BD and FFW were not significantly different (p=0.08, p=0.12, p=0.11 respectively). Other correlations between MH and foveal parameters are almost identical regardless of MH size (p=>0.05 for all).

There were no significant associations between age or gender with FFW, MFT, MLD or BD. **(Table 3)**

Ethnicity had a significant influence on FFW (p=<0.001), MFT (p=<0.001), MLD (p=0.01) and BD (p=0.002). **(Table 4)**

FFW was significantly smaller in Caucasians compared with Afro-Caribbeans (468.4µm versus 602.2µm, p=<0.001)) and Indian/Asians (468.4µm versus 585.9µm, p=<0.001) **(figure 3)**, and MFT significantly larger in Caucasians compared with Afro-Caribbeans (199.8µm versus 183.0µm, p=0.048) and Indian/Asians (199.8µm versus 173.4, p=<0.001). No significant differences were observed between Afro-Caribbeans and Indian/Asians for FFW (p=0.867) or MFT (p=0.444).

MLD and BD were significantly smaller in Caucasians compared with Indian/Asians (395µm versus 487.4µm, p=0.007; 839.0µm versus 1069.1µm; p=0.001 respectively). There were no significant differences for MLD and BD between Caucasians and Afro-Caribbeans or between Afro-Caribbeans and Indian/Asians.

The intraclass correlation coefficient for repeat measurements of foveal floor width was 0.82 (F= 1.11, p=0.40), and for MH width 0.81 (F = 1.84, p=0.18) indicating moderate-high repeatability, and with no systematic difference between observers.

Post-operative vision outcomes

Of the 108 patients in the Sunderland cohort, 104 had primary closure and post-operative visual acuity data was available on 103 of those, all of whom were Caucasian. Visual acuity outcomes were all recorded at 3-months post-operatively as part of routine local practice.

MLD was positively correlated with both pre- and post-operative Va (pre-operative Va: r=0.49, p=<0.0001; post-operative Va: r=0.54, p=<0.0001). FFW or MFT did not significantly correlate with either pre-operative or post-operative Va.

MH duration was not significantly related with FFW (r=-0.06; p=0.61), MFT (r=-0.06; p=0.63), BD (r=0.13; p=0.26) or MLD, although MLD did approach significance (r=0.22; p=0.06)

A two-stage regression model was developed to predict post-operative Va. Variables included pre-operative Va, MLD, gender, laterality of MH, age, MH duration, FFW and an MLD/FFW ratio. Pre-operative Va was first entered (to control for it) and then other variables were entered in a single block. Pre-operative Va explained 13% of variability in post-operative Va when entered alone (beta = 0.36; $r^2 = 0.13$; p=0.002), with MLD (beta = 0.29; p=0.002) and MH duration (beta=0.23; p=0.004) explaining a further 16%, whilst other variables were non-significant, including FFW (p=0.72) and the MLD/FFW ration (p=0.57). The overall coefficient of determination for the final model was 0.28.

Discussion

There are wide inter-individual differences in foveal pit morphology and retinal thickness, and it has been postulated that these may affect an individual's predisposition towards developing retinal diseases and their severity.[15–18] Since retinal thickness and foveal morphology are highly symmetrical in an individual, inferences about features of the fovea can be made using the properties of the fellow eye.[12,13,15,19]

In this study we chose to investigate two measurements of the fellow eye's foveal anatomy, the FFW and MFT. The FAZ is significantly associated with foveal pit morphology particularly foveal pit area, depth, width and volume.[12,20–22] Although FAZ is between 100-200µm larger in diameter than the FFW as measured in this study, FFW is closely correlated with FAZ diameter and hence representative of foveal morphology.[22] Typically, foveal thickness is inversely related to its width however can vary independent of foveal pit width, so FFW and MFT were both measured separately.[12,15]

Our study demonstrated a significant association between FFW and MH size. Eyes with larger MHs had fellow eyes with broader foveal floor sizes. In a cohort of 46 eyes, Shin et al showed a similar positive correlation between MLD and the FFW of the fellow eye.[23] An important limitation in their study was that 17 of the 46 fellow eyes showed evidence of foveal abnormalities which could have influenced measurements. In this study we specifically excluded fellow eyes with foveal abnormalities and expanded the sample size to add credence to the finding. We found no association between MH size and MFT, although it is possible foveal thickness might be associated with the propensity to form MHs rather than its size.

We showed no significant association between FFW or MFT with gender. Females have been reported by others to have significantly thinner macular retinas than males[15,24–28] but without associated differences in foveal geometry.[15] The gender related differences in retinal thickness may be one factor which explains the higher incidence of MH in females compared to men. Furthermore, although we found no difference between the genders and MH size, others have. In a large database study of 1483 MHs, females had slightly larger holes measured by MLD than males.[7]

We identified no significant differences in foveal or MH measurements with age. Age-related changes in foveal pit shape are unclear. Some have suggested retinal thickness reduces in all macula regions with increasing age without affecting foveal pit morphology[25,29] however others have found no significant association[24] or that central retinal thickness increases with age.[18] There have been no reported differences between MH size and age to suggest that age-related changes in retinal thickness are important in determining the size of MHs.

We also showed that FFW was larger for Afro-Caribbean and Indian/Asian participants than Caucasians. To concur with our findings, Wagner-Schuman et al found that Afro-Caribbeans have deeper and larger diameter foveal pits compared with Caucasians although interestingly there were no significant differences in foveal slope which we did not measure.[15] We also found that the MFT was thicker in the Caucasian patients. Central foveal thickness has been found by others to be lower in Afro-Caribbeans than Caucasians.[15–18,30] Associated with wider and thinner foveas, we showed that MH size was significantly greater in Indian/Asian participants than Caucasians. Other authors have reported similar differences in MH size according to ethnicity.[6,31] Our findings combined with published literature suggest that these ethnicity-related differences in MH size may in part result from differences in foveal morphology rather than duration or other explanations.

Shin et al found a significant relationship between the ratio of MLD with the fellow eye's FFW, which they termed 'adjusted hole size parameter', and post-operative Va.[23] They hypothesised that as MH diameter was related to foveal floor size, this may represent the extent by which photoreceptors centrifugally retract after MH formation. They suggested that following surgery, photoreceptors may be repositioned to their original location relative to the inner retina and that size adjustments take this into account. However, we did not find any similar significant association and found no evidence of a moderating effect of the fellow eye's foveal morphology on post-operative outcomes. There are several possible reasons for this including the chronicity of MHs. The mean duration of the MHs included in Shin et al's study was three-months whilst in this study it was five-months, and the longer duration may have resulted in higher levels of outer retinal atrophy and less retinal plasticity to enable recovering to its normal position following surgery. Furthermore, it has been postulated that the zone of outer retinal disruption during MH formation varies according to the intensity and area of vitreomacular traction.[32] It may be that MHs in this current study were of a more disrupted type and less tissue recovery was possible, although the pre- and post-operative visual acuities of the two studies were similar.

Relevantly, we did not find any association between MH duration and MLD. We did however find associations between post-operative Va and other previously recognised predictors namely pre-operative Va, MLD and MH duration.[7,8]

This study has several limitations. Data were collected retrospectively which could affect the accuracy of our findings. Only horizontal line scans were used for measurements which risks off-centre scanning. MFT and FFW are single measurements derived using a single SD-OCT slice and therefore may not accurately measure MFT compared with other measurement methodologies. Our analysis was not conducted using automated analysis which may introduce inaccuracies due to human errors in measurement and analysis. Participants were selected from two UK centres which limits the generalisability of conclusions. Data for pre-operative Va, post-operative Va and MH duration were only available for patients from Sunderland Eye Infirmary which reduces the statistical power for these calculations and predisposes to type II errors. Although we found a correlation of 0.18 between FFW and post op Va it was non-significant. It is possible this was due to the limitations of the retrospective design of our study and sample size. Indeed, to detect a significant difference of this magnitude, with an alpha of 0.05 and power of 90% would require a sample size of 320. We did not have accurate axial length data on all patients so could not systematically adjust our lateral measurements for that parameter, but did confine inclusion to a narrow range of axial lengths to reduce magnification errors, and were also investigating relationships between measures not absolute values. We did not demonstrate a significant association between symptom duration and MH size which is not consistent with other published literature and therefore further investigation is required. Finally, the Caucasian population in our cohort predominated so our findings must be interpreted with caution in non-Caucasian ethnic groups.

Conclusion

We found that the width of the foveal floor in the fellow unaffected eye of patients with unilateral MH was correlated with MH size, which may explain some of the variability in MH size observed. Differences in foveal floor width and minimum thickness may explain some of the differences in macular hole size found between differing ethnicities. The FFW of the fellow eye did not offer any improved predictive ability on post-operative outcome over the size of the macular hole on its own.

References

1. Takahashi A, Yoshida A, Nagaoka T, et al. Idiopathic Full-Thickness Macular Holes and the Vitreomacular Interface: A High-Resolution Spectral-Domain Optical Coherence Tomography Study. *Am J Ophthalmol*. 2012;154(5):881-892.e2.

2. Madi HA, Dinah C, Rees J, Steel DHW. The Case Mix of Patients Presenting with Full-Thickness Macular Holes and Progression before Surgery: Implications for Optimum Management.

Ophthalmologica. 2015;233(3-4):216-221.

3. Chew EY, Sperduto RD, Hiller R, et al. Clinical course of macular holes: The Eye Disease Case-Control Study. *Arch Ophthalmol*. 1999;117(2):242-246.

4. Tornambe PE, Poliner LS, Grote K. Macular hole surgery without face-down positioning: A pilot study. *Retina*. 1997;17(3):179-185.

5. Woon WH, Greig D, Savage MD, et al. Movement of the inner retina complex during the development of primary full-thickness macular holes: implications for hypotheses of pathogenesis. *Graefe's Arch Clin Exp Ophthalmol*. 2015;253(12):2103-2109.

6. Chandra A, Lai M, Mitry D, et al. Ethnic variation in primary idiopathic macular hole surgery. *Eye*. 2017;31(5):708-712.

7. Steel DH, Donachie PHJ, Aylward GW, Laidlaw DA, Williamson TH, Yorston D. Factors affecting anatomical and visual outcome after macular hole surgery: findings from a large prospective UK cohort. *Eye*. March 2020:1-10.

8. Essex RW, Hunyor AP, Moreno-Betancur M, et al. The Visual Outcomes of Macular Hole Surgery: A Registry-Based Study by the Australian and New Zealand Society of Retinal Specialists. *Ophthalmol Retin*. 2018;2(11):1143-1151.

9. Gupta B, Laidlaw DAH, Williamson TH, Shah SP, Wong R, Wren S. Predicting visual success in macular hole surgery. *Br J Ophthalmol*. 2009;93(11):1488-1491.

10. Geenen C, Murphy DC, Sandinha MT, Rees J, Steel DHW. SIGNIFICANCE OF PREOPERATIVE EXTERNAL LIMITING MEMBRANE HEIGHT ON VISUAL PROGNOSIS IN PATIENTS UNDERGOING MACULAR HOLE SURGERY. *Retina*. 2019;39(7):1392-1398.

11. Madi HA, Masri I, Steel DH. Optimal management of idiopathic macular holes. *Clin*

Ophthalmol. 2016;10:97-116.

12. Tick S, Rossant F, Ghorbel I, et al. Foveal shape and structure in a normal population. *Investig Ophthalmol Vis Sci*. 2011;52(8):5105-5110.

13. Bradley A, Applegate RA, Zeffren BS, van Heuven WA. Psychophysical measurement of the size and shape of the human foveal avascular zone. *Ophthalmic Physiol Opt*. 1992;12(1):18-23.

14. Steel DHW, Downey L, Greiner K, et al. The design and validation of an optical coherence tomography-based classification system for focal vitreomacular traction. *Eye*. 2016;30(2):314-325.

15. Wagner-Schuman M, Dubis AM, Nordgren RN, et al. Race- and sex-related differences in retinal thickness and foveal pit morphology. *Investig Ophthalmol Vis Sci*. 2011;52(1):625-634.

16. Kelty PJ, Payne JF, Trivedi RH, Kelty J, Bowie EM, Burger BM. Macular thickness assessment in healthy eyes based on ethnicity using stratus OCT optical coherence tomography. *Investig Ophthalmol Vis Sci*. 2008;49(6):2668-2672.

17. Asefzadeh B, Cavallerano A a., Fisch B m. Racial differences in macular thickness in healthy eyes. *Optom Vis Sci*. 2007;84(10):E941-E945.

18. 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(3):496-502.e1.

19. El-Ashry M, Hegde V, James P, Pagliarini S. Analysis of macular thickness in British population using Optical Coherence Tomography (OCT): An emphasis on interocular symmetry. *Curr Eye Res*. 2008;33(8):693-699.

20. Dubis AM, Hansen BR, Cooper RF, Beringer J, Dubra A, Carroll J. Relationship between the

foveal avascular zone and foveal pit morphology. *Investig Ophthalmol Vis Sci*. 2012;53(3):1628-1636.

21. Chui TYP, Zhong Z, Song H, Burns SA. Foveal avascular zone and its relationship to foveal pit shape. *Optom Vis Sci*. 2012;89(5):602-610.

22. Chui TYP, VanNasdale DA, Elsner AE, Burns SA. The association between the foveal avascular zone and retinal thickness. *Invest Ophthalmol Vis Sci*. 2014;55(10):6870-6877.

23. Shin JY, Chu YK, Hong YT, Kwon OW, Byeon SH. Determination of macular hole size in relation to individual variabilities of fovea morphology. *Eye*. 2015;29(8):1051-1059.

24. Adhi M, Aziz S, Muhammad K, Adhi MI. Macular thickness by age and gender in healthy eyes using spectral domain optical coherence tomography. *PLoS One*. 2012;7(5).

25. Song WK, Lee SC, Lee ES, Kim CY, Kim SS. Macular thickness variations with sex, age, and axial length in healthy subjects: A spectral domain-optical coherence tomography study. *Investig Ophthalmol Vis Sci*. 2010;51(8):3913-3918.

26. Gella L, Raman R, Sharma T. Macular thickness measurements using Copernicus Spectral Domain Optical Coherence Tomography. *Saudi J Ophthalmol*. 2015;29(2):121-125.

27. Wong ACM, Chan CWN, Hui SP. Relationship of gender, body mass index, and axial length with central retinal thickness using optical coherence tomography. *Eye*. 2005;19(3):292-297.

28. Ghassemi F, Mirshahi R, Bazvand F, Fadakar K, Faghihi H, Sabour S. The quantitative measurements of foveal avascular zone using optical coherence tomography angiography in normal volunteers. *J Curr Ophthalmol*. 2017;29(4):293-299.

29. Kanai K, Abe T, Murayama K, Yoneya S. Retinal Thickness and Changes With Age. *Nihon Ganka Gakkai Zasshi*. 2002;106(3):162-165.

30. Grover S, Murthy RK, Brar VS, Chalam K V. Normative Data for Macular Thickness by High-Definition Spectral-Domain Optical Coherence Tomography (Spectralis). *Am J Ophthalmol*. 2009;148(2):266-271.

31. Papavasileiou E, Vasalaki M, Velissaris S, et al. Characteristics, socioeconomic status and ethnic variations of primary idiopathic macular hole repair in vitreoretinal centers in the United Kingdom. *Hell J Nucl Med*. 2017;20:160.

32. Chung H, Byeon SH. New insights into the pathoanatomy of macular holes based on features of optical coherence tomography. *Surv Ophthalmol*. 2017;62(4):506-521.

Figure legend

Figure 1

Measurements of the fellow eye. (A) Minimal foveal thickness (MFT) was measured as the retinal thickness at the base of the foveal pit using the SD-OCT slice with the thinnest foveal floor measurements. (B) Foveal floor width (FFW) was measured as the widest distance between the two points at which the outer nuclear layer/Henle's fibre layer reached the inner retinal surface on the SD-OCT slice with the widest floor dimensions.

Figure 2

Scatter plot with regression line and 95% CI which demonstrates a significant positive correlation between FFW and MLD, r=0.357, p=<0.001.

Abbreviations: 95% CI: 95% confidence interval; FFW: Foveal floor width; MLD: minimum linear diameter.

Figure 3

Box plots with mean, 95% CI and minimum and maximum values represented. Shows FFW is significantly smaller in Caucasians compared with Afro-Caribbeans (p=<0.001) and Indian/Asians (p=<0.001).

Abbreviations: 95% CI: 95% confidence interval; FFW: Foveal floor width

Title: The association between foveal floor measurements and macular hole size

Short title: Foveal floor measurements and macular hole size

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DCM has no conflicts of interest

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<u>Availability of data and material</u>

Data and material can be made available upon direct request to the corresponding author

<u>Authors' contributions</u>

Authors name	Research design	Data acquisition and or research execution	Data analysis and/or interpretation	Manuscript preparation	Approved of final article
Declan C Murphy		Yes	Yes	Yes	Yes
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Ethics approval

All data and scans were collected as part of routine care and fully anonymised, and as such under UK guidelines this study was categorised as a service evaluation and did not require ethical approval

Consent to participate

All included participants provided informed consent for participation in this study

Consent for publication

All authors provide consent for publication

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Human subjects

The study abides to the declaration of Helsinki.

Abbreviations

logMAR: Logarithm of the Minimum Angle of Resolution

VA: Best corrected Visual Acuity

SD-OCT: Spectral Domain Ocular Coherence Tomography

MH: Idiopathic Macular Hole

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Precis

Foveal Floor Width (FFW) is correlated with macular hole size but not post-operative vision.

Abstract (251/350 words)

Purpose

Determining which factors influence idiopathic macular hole (MH) size is important because it is a major prognostic indicator of treatment success. Foveal pit morphology is highly symmetrical within individuals and may influence MH size. Using a series of patients with unilateral MHs, we examined the foveal floor size of the fellow eye to evaluate its relationship with MH size and post-operative outcomes.

Design

A retrospective observational study

Participants

241 participants with a unilateral MH treated with surgery and a fellow eye with no ocular pathology.

Methods

Spectral domain ocular coherence tomography (SD-OCT) imaged both eyes at the time of surgery. Minimum linear diameter (MLD) and base diameter (BD) defined MH size. Foveal floor width (FFW) and minimal foveal thickness (MFT) defined foveal pit morphology of the fellow eye.

Main outcome measures

Baseline characteristics, SD-OCT measurements and pre-operative variables were compared to determine their relationship with MH size and post-operative visual acuity in logMAR units (Va).

Results

FFW was correlated with MLD (r = 0.36; p=<0.001) and BD (r=0.30; p=<0.001) but not post-operative Va. MLD correlated with pre-operative (r=0.49; p=<0.0001) and post-operative Va (r=0.54, p=<0.0001). A two-stage regression model was developed to predict post-operative Va (r^2 = 0.28); pre-operative Va (beta = 0.36; p=0.002) explained 13% of variability and MLD (beta = 0.29; p=0.002) and MH duration (beta=0.23; p=0.004) explained a further 16%.

Conclusion

FFW of the fellow eye in patients with a unilateral MH was significantly correlated with MH size and may explain some of the variability in MH size observed between individuals. However, FFW could not predict post-operative vision.

Key words

Idiopathic macular hole; vitreoretinal surgery; fovea; foveal floor width

Introduction

It is known that most idiopathic macular holes (MH) result from anteroposterior traction occurring secondary to vitreomacular traction.[1] Once MHs form, they typically increase in size over time[2] which is predominantly related to tangential tractional forces.[3] Other factors which may contribute include retinal edge hydration[4] and the bistable foveal hypothesis, proposed by Woon et al which both result in retinal edge eversion and an increase in hole dimensions.[5]

The factors which determine MH size in individual patients are unclear. Some patients may present with short histories but large MHs and conversely long histories with small MHs. This has been explained before by the often uncertain clinical history and the unknown magnitude of tangential traction forces present, but clinical experience suggests that MHs differ significantly in size when they first form.

It is known that ethnicity can affect MH size[6] and possibly gender[7] but the variability in size cannot be explained by demographics and chronicity alone.

Determining which factors contribute to the size of a MH is important because it is known that MH size is a major prognostic indicator of treatment success both in terms of hole closure and visual outcomes.[7–10] Indeed, surgeons often formulate their surgical plan based on hole dimensions.[11] Elucidating which additional factors are relevant and can influence MH size, may lead to an improved understanding of the pathogenesis underpinning MH formation and better management decisions. Furthermore, although MH size, pre-operative visual acuity and duration have all been shown to be predictive of post-operative outcomes, their predictive value is limited so other currently unquantified person-specific factors may be important.

Another variable which may affect MH size is foveal pit morphology. The foveal centre is characterized by a foveal avascular zone (FAZ) which is comprised of an area of densely packed cone cells with elongated outer segments and surrounded by outwardly displaced inner retinal layers, which form the foveal pit.[12] It is known that there is significant inter-individual variability in pit size and shape although fellow eyes are highly symmetrical.[12,13]

We hypothesised that inter-individual differences in foveal floor size could predict MH size. Using a series of patients with unilateral MHs, we examined the foveal floor size of the fellow eye to investigate their relationship with MH size and visual outcomes after surgery.

Materials and methods

This was a retrospective observational study of a cohort of 241 patients with a unilateral MH who underwent surgery with vitrectomy, internal limiting membrane (ILM) peeling and gas tamponade at two specialist ophthalmic centres in the United Kingdom (UK) between 1st January 2016 and 1st January 2018. Data was obtained from two ophthalmic centres in the United Kingdom (UK), Sunderland Eye Infirmary and Moorfields Eye Hospital. Patients were identified from the surgical databases of the surgeons involved.

Participants with a unilateral full-thickness idiopathic MH and a normal fellow eye were eligible for inclusion. We excluded patients with traumatic MHs, chronic MHs (present for longer than twelve months), myopia greater than 6 dioptres, eyes with epiretinal membrane (ERM) and or epiretinal proliferation, eyes with axial lengths of less than 22mm and greater than 25.5mm, MHs associated with other retinal pathology, previous retinal surgery or ocriplasmin treatment, fellow eyes with other retinal pathology or abnormalities including vitreomacular traction, and eyes with inadequate imaging.

For each included dataset, participant age, gender, ethnicity, imaging modality and laterality of the affected eye were recorded. For patients from the Sunderland Eye Infirmary cohort, duration of MH symptoms at the time of surgery and the pre-operative and three-month post-operative visual acuity, as well as the anatomical success of surgery with hole closure (i.e. closure of MH without a neurosensory retinal defect) were also recorded.

Visual acuities (Va) were measured using a standard Early Treatment Diabetic Retinopathy Study (ETDRS) letter chart and then converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis.

All patients in the Sunderland cohort had undergone trans-conjunctival 25 or 27-gauge vitrectomy by the same surgeon with the same equipment (Alcon Constellation, Alcon, Fort Worth, USA) using wide field non-contact viewing and combined phacoemulsification and intraocular lens implantation if phakic. Brilliant Blue G [ILM Blue, Dorc international, The Netherlands] was used to stain the ILM and peeled using a pinch technique and end gripping forceps (Grieshaber revolution DSP ILM forceps, Alcon Grieshaber AG, Schaffhausen, Switzerland). Either 25% SF6 or 20% C2F6 gas was used as a tamponade and the patients were instructed to remain in the face down position for one to three days post-operatively.

All participants had undergone imaging using spectral domain optical coherence tomography (SD-OCT) on the Heidelberg Spectralis (Heidelberg Engineering Inc USA) in one centre (Sunderland Eye Infirmary) and with a Topcon 3D OCT (Topcon, Tokyo, Japan) in the second centre (Moorfield's Eye Hospital) as part of their routine care.

Using the Spectralis, a high density central horizontal scanning protocol with 30µm line spacing was used in the central 15 degrees. All scans used a 15 automatic real-time setting which enabled multisampling and noise reduction over 15 images. Using the Topcon, a macular volume scan was performed for each eye consisting of 256 horizontal B-scans, centred through the fovea.

Image measurements

On the SD-OCT scans, the minimum linear diameter (MLD) and maximum base diameter (BD) of the eye affected by the MH were measured using tools on the imaging systems.[14] The presence of vitreomacular adhesions (VMA) to the edge of the hole was noted.

On the fellow unaffected eye, the minimal foveal thickness (MFT) at the base of the foveal pit was measured using the SD-OCT slice with the thinnest foveal floor measurements. The foveal floor width (FFW) was also measured and defined as the widest distance between the two points at which the outer nuclear layer/Henle's fibre layer reached the inner retinal surface on the SD-OCT slice with the widest floor dimensions. **(Figure 1)**

Two observers performed the SD-OCT measurements. One performed the MH measurements and the other the fellow eye measurements, with each masked to the others' findings. A third observer masked to the results repeated the measurements in a subset of cases to ascertain agreement.

Patients from both Sunderland Eye Infirmary and Moorfields Eye Hospital were combined to create a single patient cohort for analysis. Analyses which included pre-operative Va, post-operative Va, and symptom duration were performed using data from Sunderland Eye infirmary patients only due to data availability.

This study adhered to the tenets of the Declaration of Helsinki. All data and scans were collected as part of routine care and fully anonymised, and as such under UK guidelines this study was categorised as a service evaluation and did not require ethical approval

Statistical analysis

Statistical analysis was performed using SPSS v26.0. Participant demographic characteristics, and pre-operative and post-operative variables are presented as means, standard deviation (SD) and range or percentage (%) as appropriate. Two-sample non-paired t-tests or one-way ANOVA with Tukey's HSD post hoc testing compared continuous variables. Hierarchical multiple regression was used to analyse the effect of multiple variables. The repeatability of the FFW and macular holes measurements were tested using intra-class correlation (ICC). Statistical significance was defined by a p-value of 0.05 or less.

Results

Study characteristics

During the study period a total of 356 eyes of 324 patients underwent surgery for a MH. Eighty-three patients were excluded leaving 241 patients who fulfilled our inclusion criteria; 108 from Sunderland Eye Infirmary and 133 from Moorfields Eye Hospital.

The baseline characteristics of the study population are shown in **Table 1.**

241 participants were included in total. 181 were female. 178 were of Caucasian ethnicity, 25 were Afro-Caribbean and 38 were Indian/Asian. Average age was 68 years.

Measures of MH size and foveal shape were calculated. Mean FFW was 500.8µm, MFT was 193.9µm, MLD was 412.3µm and BD was 880.2µm.

Associations

Associations between foveal and MH measurements are displayed in **Table 2**. FFW showed a significant association with MLD (r=0.357, p=<0.001) **(Figure 2)**. BD and MLD showed a strong positive correlation (0.664; p=<0.001).

MHs were divided into two groups according to MH size (MLD<400µm (N=129) and MLD≥400µm (N=112)). There were no significant between-group differences in the associations between MH and foveal size parameters. Correlations between MFT and FFW, MLD and FFW, BD and FFW were not significantly different (p=0.08, p=0.12, p=0.11 respectively). Other correlations between MH and foveal parameters are almost identical regardless of MH size (p=>0.05 for all).

There were no significant associations between age or gender with FFW, MFT, MLD or BD. **(Table 3)**

Ethnicity had a significant influence on FFW (p=<0.001), MFT (p=<0.001), MLD (p=0.01) and BD (p=0.002). **(Table 4)**

FFW was significantly smaller in Caucasians compared with Afro-Caribbeans (468.4µm versus 602.2µm, p=<0.001)) and Indian/Asians (468.4µm versus 585.9µm, p=<0.001) **(figure 3)**, and MFT significantly larger in Caucasians compared with Afro-Caribbeans (199.8µm versus 183.0µm, p=0.048) and Indian/Asians (199.8µm versus 173.4, p=<0.001). No significant differences were observed between Afro-Caribbeans and Indian/Asians for FFW (p=0.867) or MFT (p=0.444).

MLD and BD were significantly smaller in Caucasians compared with Indian/Asians (395µm versus 487.4µm, p=0.007; 839.0µm versus 1069.1µm; p=0.001 respectively). There were no significant differences for MLD and BD between Caucasians and Afro-Caribbeans or between Afro-Caribbeans and Indian/Asians.

The intraclass correlation coefficient for repeat measurements of foveal floor width was 0.82 (F= 1.11, p=0.40), and for MH width 0.81 (F = 1.84, p=0.18) indicating moderate-high repeatability, and with no systematic difference between observers.

<u>Post-operative vision outcomes</u>

Of the 108 patients in the Sunderland cohort, 104 had primary closure and post-operative visual acuity data was available on 103 of those, all of whom were Caucasian. Visual acuity outcomes were all recorded at 3-months post-operatively as part of routine local practice.

MLD was positively correlated with both pre- and post-operative Va (pre-operative Va: r=0.49, p=<0.0001; post-operative Va: r=0.54, p=<0.0001). FFW or MFT did not significantly correlate with either pre-operative or post-operative Va.

MH duration was not significantly related with FFW (r=-0.06; p=0.61), MFT (r=-0.06; p=0.63), BD (r=0.13; p=0.26) or MLD, although MLD did approach significance (r=0.22; p=0.06)

A two-stage regression model was developed to predict post-operative Va. Variables included pre-operative Va, MLD, gender, laterality of MH, age, MH duration, FFW and an MLD/FFW ratio. Pre-operative Va was first entered (to control for it) and then other variables were entered in a single block. Pre-operative Va explained 13% of variability in post-operative Va when entered alone (beta = 0.36; r^2 = 0.13; p=0.002), with MLD (beta = 0.29; p=0.002) and MH duration (beta=0.23; p=0.004) explaining a further 16%, whilst other variables were non-significant, including FFW (p=0.72) and the MLD/FFW ration (p=0.57). The overall coefficient of determination for the final model was 0.28.

Discussion

There are wide inter-individual differences in foveal pit morphology and retinal thickness, and it has been postulated that these may affect an individual's predisposition towards developing retinal diseases and their severity.[15–18] Since retinal thickness and foveal morphology are highly symmetrical in an individual, inferences about features of the fovea can be made using the properties of the fellow eye.[12,13,15,19]

In this study we chose to investigate two measurements of the fellow eye's foveal anatomy, the FFW and MFT. The FAZ is significantly associated with foveal pit morphology particularly foveal pit area, depth, width and volume.[12,20–22] Although FAZ is between 100-200µm larger in diameter than the FFW as measured in this study, FFW is closely correlated with FAZ diameter and hence representative of foveal morphology.[22] Typically, foveal thickness is inversely related to its width however can vary independent of foveal pit width, so FFW and MFT were both measured separately.[12,15]

Our study demonstrated a significant association between FFW and MH size. Eyes with larger MHs had fellow eyes with broader foveal floor sizes. In a cohort of 46 eyes, Shin et al showed a similar positive correlation between MLD and the FFW of the fellow eye.[23] An important limitation in their study was that 17 of the 46 fellow eyes showed evidence of foveal abnormalities which could have influenced measurements. In this study we specifically excluded fellow eyes with foveal abnormalities and expanded the sample size to add credence to the finding. We found no association between MH size and MFT, although it is possible foveal thickness might be associated with the propensity to form MHs rather than its size.

We showed no significant association between FFW or MFT with gender. Females have been reported by others to have significantly thinner macular retinas than males[15,24–28] but without associated differences in foveal geometry.[15] The gender related differences in retinal thickness may be one factor which explains the higher incidence of MH in females compared to men. Furthermore, although we found no difference between the genders and MH size, others have. In a large database study of 1483 MHs, females had slightly larger holes measured by MLD than males.[7]

We identified no significant differences in foveal or MH measurements with age. Age-related changes in foveal pit shape are unclear. Some have suggested retinal thickness reduces in all macula regions with increasing age without affecting foveal pit morphology[25,29] however others have found no significant association[24] or that central retinal thickness increases with age.[18] There have been no reported differences between MH size and age to suggest that age-related changes in retinal thickness are important in determining the size of MHs.

We also showed that FFW was larger for Afro-Caribbean and Indian/Asian participants than Caucasians. To concur with our findings, Wagner-Schuman et al found that Afro-Caribbeans have deeper and larger diameter foveal pits compared with Caucasians although interestingly there were no significant differences in foveal slope which we did not measure.[15] We also found that the MFT was thicker in the Caucasian patients. Central foveal thickness has been found by others to be lower in Afro-Caribbeans than Caucasians.[15–18,30] Associated with wider and thinner foveas, we showed that MH size was significantly greater in Indian/Asian participants than Caucasians. Other authors have reported similar differences in MH size according to ethnicity.[6,31] Our findings combined with published literature suggest that these ethnicity-related differences in MH size may in part result from differences in foveal morphology rather than duration or other explanations.

Shin et al found a significant relationship between the ratio of MLD with the fellow eye's FFW, which they termed 'adjusted hole size parameter', and post-operative Va.[23] They hypothesised that as MH diameter was related to foveal floor size, this may represent the extent by which photoreceptors centrifugally retract after MH formation. They suggested that following surgery, photoreceptors may be repositioned to their original location relative to the inner retina and that size adjustments take this into account. However, we did not find any similar significant association and found no evidence of a moderating effect of the fellow eye's foveal morphology on post-operative outcomes. There are several possible reasons for this including the chronicity of MHs. The mean duration of the MHs included in Shin et al's study was three-months whilst in this study it was five-months, and the longer duration may have resulted in higher levels of outer retinal atrophy and less retinal plasticity to enable recovering to its normal position following surgery. Furthermore, it has been postulated that the zone of outer retinal disruption during MH formation varies according to the intensity and area of vitreomacular traction.[32] It may be that MHs in this current study were of a more disrupted type and less tissue recovery was possible, although the pre- and post-operative visual acuities of the two studies were similar.

Relevantly, we did not find any association between MH duration and MLD. We did however find associations between post-operative Va and other previously recognised predictors namely pre-operative Va, MLD and MH duration.[7,8]

This study has several limitations. Data were collected retrospectively which could affect the accuracy of our findings. Only horizontal line scans were used for measurements which risks off-centre scanning. MFT and FFW are single measurements derived using a single SD-OCT slice and therefore may not accurately measure MFT compared with other measurement methodologies. Our analysis was not conducted using automated analysis which may introduce inaccuracies due to human errors in measurement and analysis. Participants were selected from two UK centres which limits the generalisability of conclusions. Data for pre-operative Va, post-operative Va and MH duration were only available for patients from Sunderland Eye Infirmary which reduces the statistical power for these calculations and predisposes to type II errors. Although we found a correlation of 0.18 between FFW and post op Va it was non-significant. It is possible this was due to the limitations of the retrospective design of our study and sample size. Indeed, to detect a significant difference of this magnitude, with an alpha of 0.05 and power of 90% would require a sample size of 320. We did not have accurate axial length data on all patients so could not systematically adjust our lateral measurements for that parameter, but did confine inclusion to a narrow range of axial lengths to reduce magnification errors, and were also investigating relationships between measures not absolute values. We did not demonstrate a significant association between symptom duration and MH size which is not consistent with other published literature and therefore further investigation is required. Finally, the Caucasian population in our cohort predominated so our findings must be interpreted with caution in non-Caucasian ethnic groups.

Conclusion

We found that the width of the foveal floor in the fellow unaffected eye of patients with unilateral MH was correlated with MH size, which may explain some of the variability in MH size observed. Differences in foveal floor width and minimum thickness may explain some of the differences in macular hole size found between differing ethnicities. The FFW of the fellow eye did not offer any improved predictive ability on post-operative outcome over the size of the macular hole on its own.

References

1. Takahashi A, Yoshida A, Nagaoka T, et al. Idiopathic Full-Thickness Macular Holes and the Vitreomacular Interface: A High-Resolution Spectral-Domain Optical Coherence Tomography Study. *Am J Ophthalmol*. 2012;154(5):881-892.e2.

2. Madi HA, Dinah C, Rees J, Steel DHW. The Case Mix of Patients Presenting with Full-Thickness Macular Holes and Progression before Surgery: Implications for Optimum Management.

Ophthalmologica. 2015;233(3-4):216-221.

3. Chew EY, Sperduto RD, Hiller R, et al. Clinical course of macular holes: The Eye Disease Case-Control Study. *Arch Ophthalmol*. 1999;117(2):242-246.

4. Tornambe PE, Poliner LS, Grote K. Macular hole surgery without face-down positioning: A pilot study. *Retina*. 1997;17(3):179-185.

5. Woon WH, Greig D, Savage MD, et al. Movement of the inner retina complex during the development of primary full-thickness macular holes: implications for hypotheses of pathogenesis. *Graefe's Arch Clin Exp Ophthalmol*. 2015;253(12):2103-2109.

6. Chandra A, Lai M, Mitry D, et al. Ethnic variation in primary idiopathic macular hole surgery. *Eye*. 2017;31(5):708-712.

7. Steel DH, Donachie PHJ, Aylward GW, Laidlaw DA, Williamson TH, Yorston D. Factors affecting anatomical and visual outcome after macular hole surgery: findings from a large prospective UK cohort. *Eye*. March 2020:1-10.

8. Essex RW, Hunyor AP, Moreno-Betancur M, et al. The Visual Outcomes of Macular Hole Surgery: A Registry-Based Study by the Australian and New Zealand Society of Retinal Specialists. *Ophthalmol Retin*. 2018;2(11):1143-1151.

9. Gupta B, Laidlaw DAH, Williamson TH, Shah SP, Wong R, Wren S. Predicting visual success in macular hole surgery. *Br J Ophthalmol*. 2009;93(11):1488-1491.

10. Geenen C, Murphy DC, Sandinha MT, Rees J, Steel DHW. SIGNIFICANCE OF PREOPERATIVE EXTERNAL LIMITING MEMBRANE HEIGHT ON VISUAL PROGNOSIS IN PATIENTS UNDERGOING MACULAR HOLE SURGERY. *Retina*. 2019;39(7):1392-1398.

11. Madi HA, Masri I, Steel DH. Optimal management of idiopathic macular holes. *Clin*

Ophthalmol. 2016;10:97-116.

12. Tick S, Rossant F, Ghorbel I, et al. Foveal shape and structure in a normal population. *Investig Ophthalmol Vis Sci*. 2011;52(8):5105-5110.

13. Bradley A, Applegate RA, Zeffren BS, van Heuven WA. Psychophysical measurement of the size and shape of the human foveal avascular zone. *Ophthalmic Physiol Opt*. 1992;12(1):18-23.

14. Steel DHW, Downey L, Greiner K, et al. The design and validation of an optical coherence tomography-based classification system for focal vitreomacular traction. *Eye*. 2016;30(2):314-325.

15. Wagner-Schuman M, Dubis AM, Nordgren RN, et al. Race- and sex-related differences in retinal thickness and foveal pit morphology. *Investig Ophthalmol Vis Sci*. 2011;52(1):625-634.

16. Kelty PJ, Payne JF, Trivedi RH, Kelty J, Bowie EM, Burger BM. Macular thickness assessment in healthy eyes based on ethnicity using stratus OCT optical coherence tomography. *Investig Ophthalmol Vis Sci*. 2008;49(6):2668-2672.

17. Asefzadeh B, Cavallerano A a., Fisch B m. Racial differences in macular thickness in healthy eyes. *Optom Vis Sci*. 2007;84(10):E941-E945.

18. 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(3):496-502.e1.

19. El-Ashry M, Hegde V, James P, Pagliarini S. Analysis of macular thickness in British population using Optical Coherence Tomography (OCT): An emphasis on interocular symmetry. *Curr Eye Res*. 2008;33(8):693-699.

20. Dubis AM, Hansen BR, Cooper RF, Beringer J, Dubra A, Carroll J. Relationship between the

foveal avascular zone and foveal pit morphology. *Investig Ophthalmol Vis Sci*. 2012;53(3):1628-1636.

21. Chui TYP, Zhong Z, Song H, Burns SA. Foveal avascular zone and its relationship to foveal pit shape. *Optom Vis Sci*. 2012;89(5):602-610.

22. Chui TYP, VanNasdale DA, Elsner AE, Burns SA. The association between the foveal avascular zone and retinal thickness. *Invest Ophthalmol Vis Sci*. 2014;55(10):6870-6877.

23. Shin JY, Chu YK, Hong YT, Kwon OW, Byeon SH. Determination of macular hole size in relation to individual variabilities of fovea morphology. *Eye*. 2015;29(8):1051-1059.

24. Adhi M, Aziz S, Muhammad K, Adhi MI. Macular thickness by age and gender in healthy eyes using spectral domain optical coherence tomography. *PLoS One*. 2012;7(5).

25. Song WK, Lee SC, Lee ES, Kim CY, Kim SS. Macular thickness variations with sex, age, and axial length in healthy subjects: A spectral domain-optical coherence tomography study. *Investig Ophthalmol Vis Sci*. 2010;51(8):3913-3918.

26. Gella L, Raman R, Sharma T. Macular thickness measurements using Copernicus Spectral Domain Optical Coherence Tomography. *Saudi J Ophthalmol*. 2015;29(2):121-125.

27. Wong ACM, Chan CWN, Hui SP. Relationship of gender, body mass index, and axial length with central retinal thickness using optical coherence tomography. *Eye*. 2005;19(3):292-297.

28. Ghassemi F, Mirshahi R, Bazvand F, Fadakar K, Faghihi H, Sabour S. The quantitative measurements of foveal avascular zone using optical coherence tomography angiography in normal volunteers. *J Curr Ophthalmol*. 2017;29(4):293-299.

29. Kanai K, Abe T, Murayama K, Yoneya S. Retinal Thickness and Changes With Age. *Nihon Ganka Gakkai Zasshi*. 2002;106(3):162-165.

30. Grover S, Murthy RK, Brar VS, Chalam K V. Normative Data for Macular Thickness by High-Definition Spectral-Domain Optical Coherence Tomography (Spectralis). *Am J Ophthalmol*. 2009;148(2):266-271.

31. Papavasileiou E, Vasalaki M, Velissaris S, et al. Characteristics, socioeconomic status and ethnic variations of primary idiopathic macular hole repair in vitreoretinal centers in the United Kingdom. *Hell J Nucl Med*. 2017;20:160.

32. Chung H, Byeon SH. New insights into the pathoanatomy of macular holes based on features of optical coherence tomography. *Surv Ophthalmol*. 2017;62(4):506-521.

Figure legend

Figure 1

Measurements of the fellow eye. (A) Minimal foveal thickness (MFT) was measured as the retinal thickness at the base of the foveal pit using the SD-OCT slice with the thinnest foveal floor measurements. (B) Foveal floor width (FFW) was measured as the widest distance between the two points at which the outer nuclear layer/Henle's fibre layer reached the inner retinal surface on the SD-OCT slice with the widest floor dimensions.

Figure 2

Scatter plot with regression line and 95% CI which demonstrates a significant positive correlation between FFW and MLD, $r=0.357$, $p=<0.001$.

Abbreviations: 95% CI: 95% confidence interval; FFW: Foveal floor width; MLD: minimum linear diameter.

Figure 3

Box plots with mean, 95% CI and minimum and maximum values represented. Shows FFW is significantly smaller in Caucasians compared with Afro-Caribbeans (p=<0.001) and Indian/Asians (p=<0.001).

Abbreviations: 95% CI: 95% confidence interval; FFW: Foveal floor width

Figure 1

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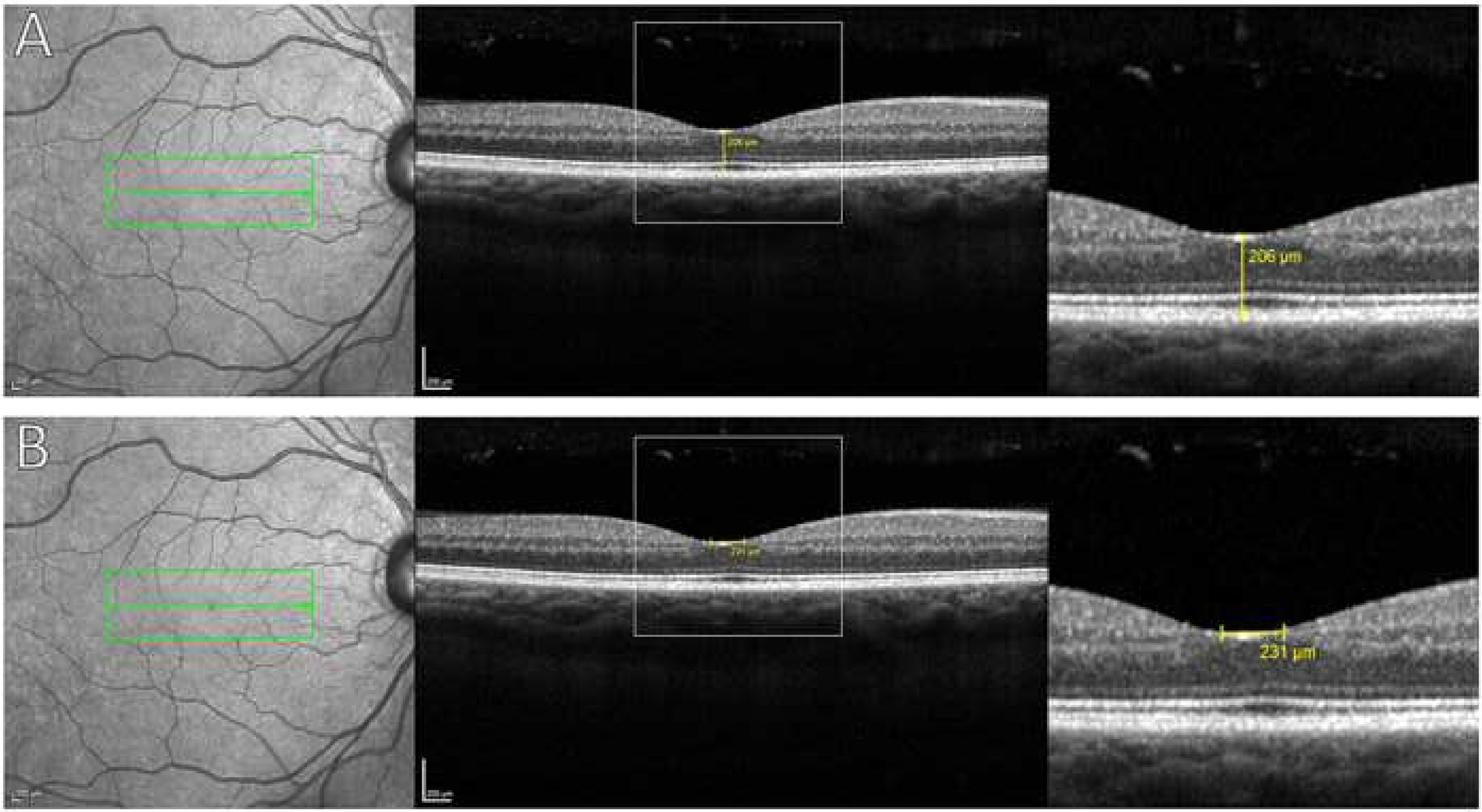
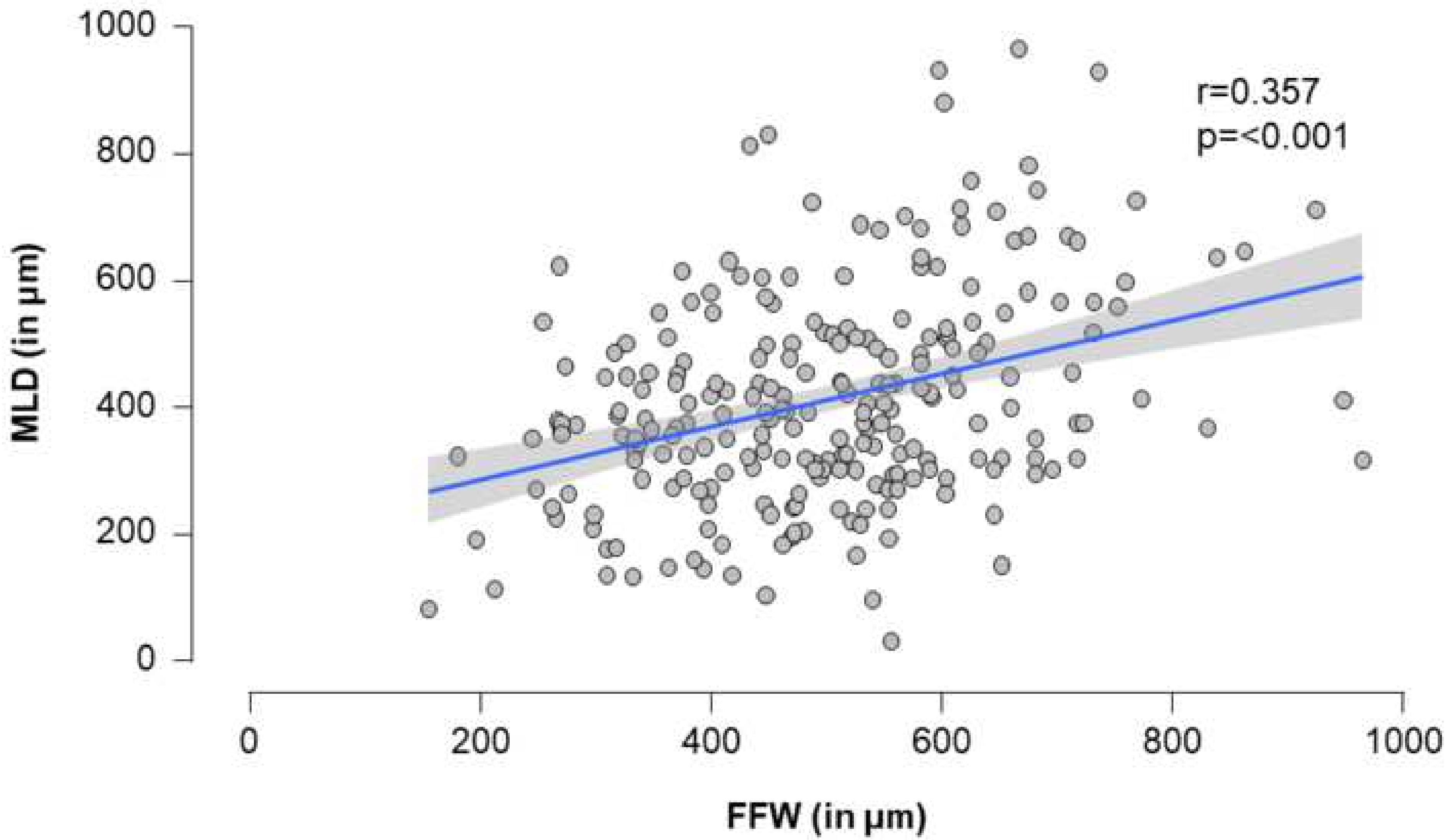


Figure 2


r=0.357
p=<0.001
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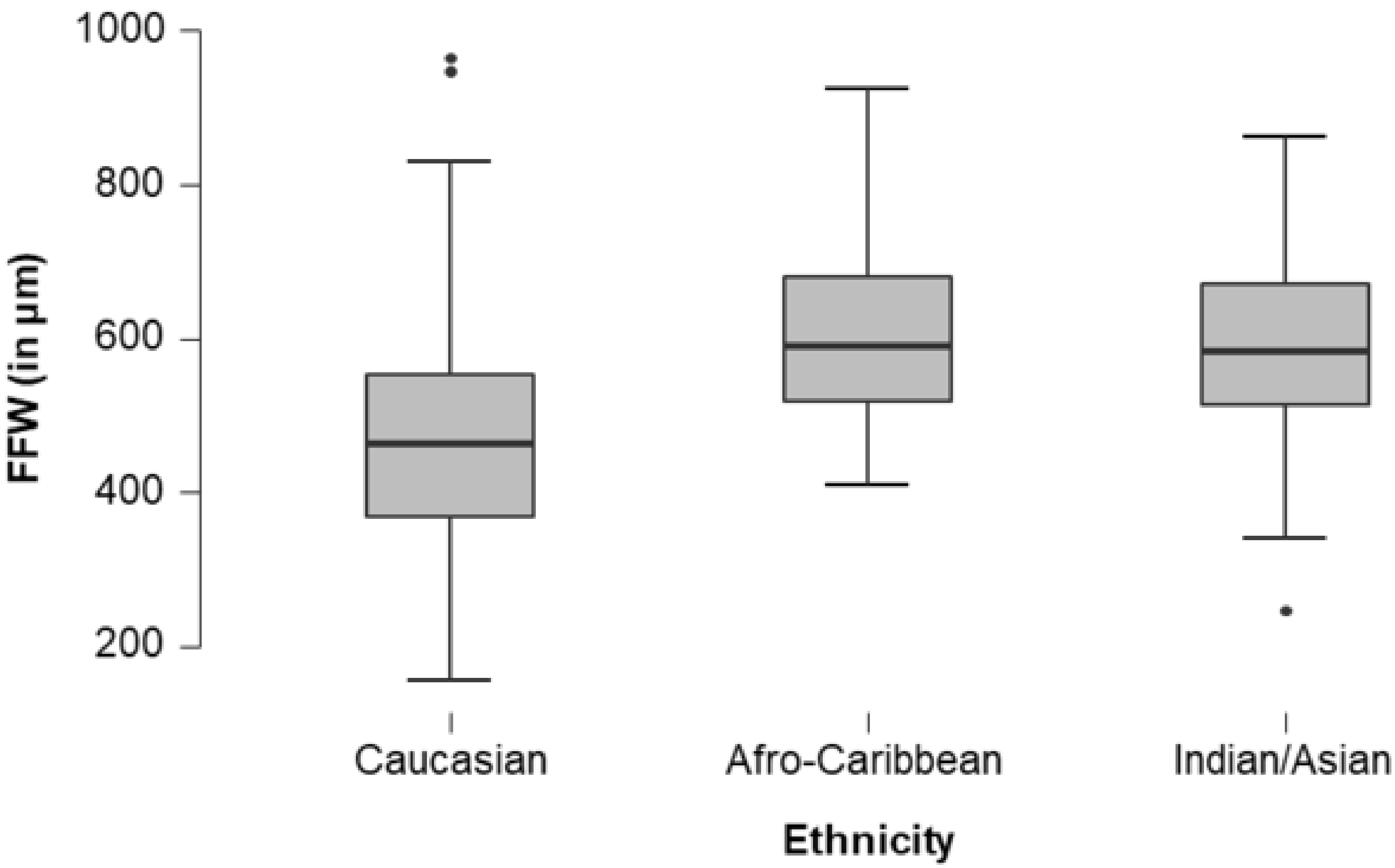
800
600
400
200
0
MLD (in µm)
0
200
400
600
800
1000
FFW (in µm)

Figure 3



1000
800
600
400
200
FFW (in µm)
Caucasian
Afro-Caribbean
Indian/Asian
Ethnicity

Table 1

Characteristic	Result
Entire cohort	
Number of participants (N)	241
Gender Male; female	60; 181
Ethnicity Caucasian; Afro-Caribbean; Indian/Asian	178; 25; 38
Laterality of MH Right; left	132; 109
Age in years (mean; SD)	67.95; 7.74; 48-91
MH measurements (mean; SD; range)	
MLD	412.31; 168.85; 31.5–965.0
BD	880.17; 316.49; 76.0-1979.0
Fellow eye foveal measurements (mean; SD; range)	
FFW	500.81; 144.97; 155-965
MFT	193.92; 45.60; 88-392
Sunderland Eye Infirmary cohort	
MH duration in months (N=103) (mean; ±SD; range)	5.06; 4.83; 1-12
Pre-operative Va in logMAR (N=103) (mean; ±SD; range)	0.84; 0.33; 0.5-2.0
Post-operative Va in logMAR	0.42; 0.26; 0.0-1.2

(N=103) (mean; ±SD; range)	

Table 1: Cohort characteristics

Characteristics for the patient cohort are displayed in table 1. The Sunderland Eye Infirmary and Moorfields Eye Hospital cohorts were combined and gender, MH laterality, ethnicity, laterality, age, macular hole measurements and foveal measurements are reported as such. Entire cohort calculations are based on N=241 patients. Macular hole duration, pre-operative Va and post-operative Va are reported for the Sunderland Eye Infirmary cohort only. Note: gender was self-reported by participants.

Abbreviations: Va: Visual acuity; logMAR: logarithm of the minimum angle of resolution; BD: Maximum base diameter; FFW: Foveal floor width; MFT: minimal foveal thickness; MH: Macular hole; MLD: maximum linear diameter; Visual acuity measured using logMAR units; SD: standard deviation.

Table 2

		Fellow eye measurements		Macular hole measurements	
		FFW r (p-value)	**MFT** r (p value)	**MLD** r (p value)	**BD** r (p value)
Fellow eye measurements	**FFW** r (p-value)	-			
	MFT r (p-value)	-0.189 (0.003)	-		
Macular hole measurements	**MLD** r (p-value)	0.357 (<0.001)	-0.155 (0.017)	-	
	BD r (p-value)	0.294 (<0.001)	0.154 (0.018)	0.664 (<0.001)	-

Table 2: Correlations between macular hole and foveal floor measurements

A correlation matrix which displays correlations (Pearson's correlation coefficient, r) between the mean value of macular hole and foveal floor measurements. Calculations are based on N=241.

Abbreviations: BD: maximum base diameter; FFW: foveal floor width; MFT: minimal foveal thickness; MLD: minimum linear diameter; r: Pearson's correlation coefficient

Table 3

	FFW	MFT	MLD	BD
Age r; p-value	-0.34 (0.60)	0.08 (0.21)	-0.02 (0.79)	-0.06 (0.35)
Gender Male; Female (p-value)	497.20; 502.15 (0.80)	194.53; 194.12 (0.95)	379.78; 423.27 (0.11)	895.04; 875.34 (0.71)

Table 3: Age and gender

Table displaying the associations between foveal floor and macular hole measurements with age and gender. Calculations are based on N=241 participants.

Abbreviations: BD: maximum base diameter; FFW: foveal floor width; MFT: minimal foveal thickness; MLD: minimum linear diameter; r: Pearson's correlation coefficient.

Table 4

	Fellow eye measurements		Macular hole measurements	
	FFW Mean (95% CI)	**MFT** Mean (95% CI)	**MLD** Mean (95% CI)	**BD** Mean (95% CI)
Caucasian (N=178)	468.4 (448.5 - 488.3)	199.8 (193.2 – 206.4)	395.2 (370.7 – 419.8)	839.0 (793.7 – 884.4)
Afro-Caribbean (N=25)	602.2 (549.1 – 655.3)	183.0 (165.4 – 200.5)	425.8 (360.3 – 491.3)	901.0 (780.1 – 1022.0)
Indian / Asian (N=38)	585.9 (542.9 – 629.0)	173.4 (159.2 – 187.7)	487.4 (432.8 – 542.0)	1069.1 (968.3 – 1169.9)

Table 4: Ethnicity

Differences in FFW, MFT, MLD and BD between ethnicities.

Abbreviations: FFW: Foveal floor width; MFT: minimal foveal thickness; MLD: minimum linear diameter; BD: maximum base diameter; 95% CI: 95% confidence interval

Supporting file for ethical approval

Ethical approval was not required for the study. The following URL states that ethical approval was not required according Health research authority and medical research council: http://www.hra-decisiontools.org.uk/ethics/

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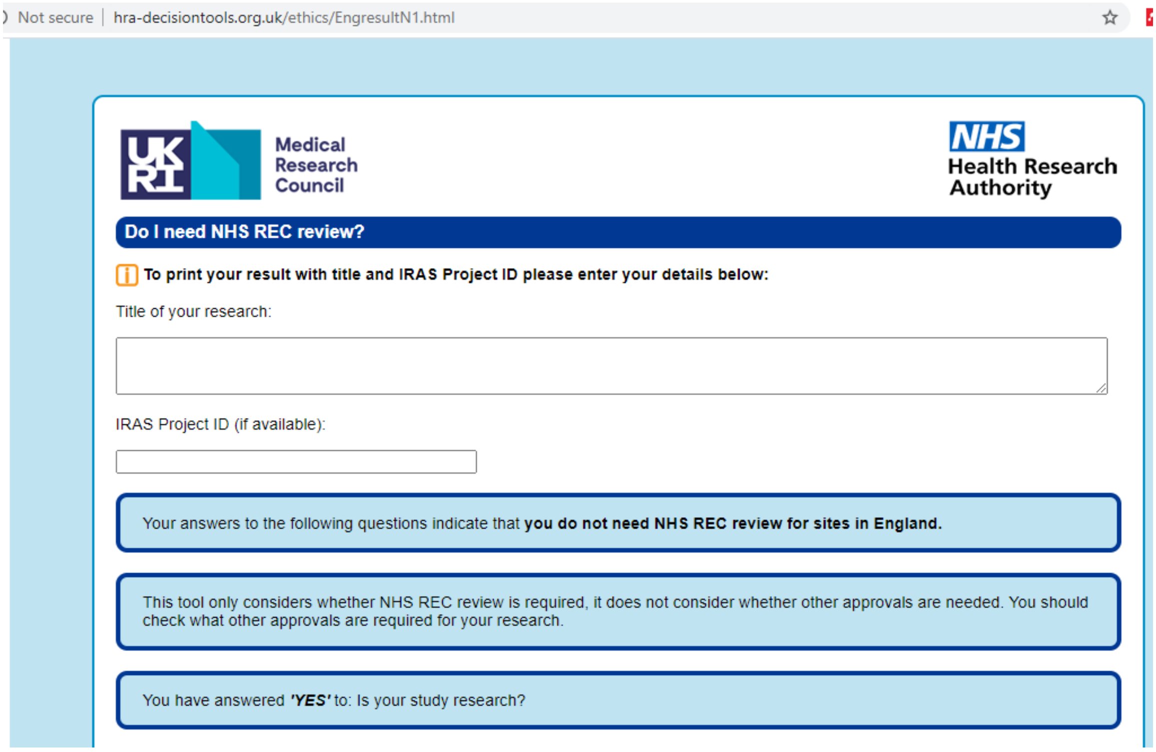

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AUTHORS: Declan C Murphy, Harry JR Melville; Grace George; Michael Grinton; Yunzi C

AUTHOR NAME	RESEARCH DESIGN	DATA ACQUISITION AND/OR RESEARCH EXECUTION	DATA ANALYSIS AND/OR INTERPRETATION	MANUSCRIPT PREPARATION
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Grace George	☐	✔	☐	✔
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Yunzi Chen	☐	✔	☐	✔
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Pallavi Tyagi	☐	✔	☐	✔
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AUTHOR NAME	RESEARCH DESIGN	DATA ACQUISITION AND/OR RESEARCH EXECUTION	DATA ANALYSIS AND/OR INTERPRETATION	MANUSCRIPT PREPARATION
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