CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

ORCA – Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository:https://orca.cardiff.ac.uk/id/eprint/131889/

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Tun, Tin A., Wang, Xiaofei, Baskaran, Mani, Nongpiur, Monisha Esther, Tham, Yih Chung, Nguyen, Duc Quang, Strouthidis, Nicholas G., Aung, Tin, Cheng, Ching-Yu, Boote, Craig and Girard, Michael J. A. 2021. Determinants of lamina cribrosa depth in healthy Asian eyes: the Singapore Epidemiology Eye Study. British Journal of Ophthalmology 105 (3) , pp. 367-373. 10.1136/bjophthalmol-2020-315840

Publishers page: http://dx.doi.org/10.1136/bjophthalmol-2020-315840

Please note:
Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See http://orca.cf.ac.uk/policies.html for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.

Determinants of Lamina Cribrosa Depth in Healthy Asian Eyes: The Singapore Epidemiology Eye Study

Tin A. Tun*, MD,[1,2] Xiaofei Wang*, PhD,[3,2] Mani Baskaran, DNB, PhD,[1,4] Monisha E Nongpiur, MD, PhD,[1,5] Yih-Chung Tham, PhD,[1] Duc Quang Nguyen, BEng,[1] Nicholas G. Strouthidis, FRCS(Ed), PhD,[1,6,7] Tin Aung, FRCS(Ed), PhD,[1,4,5] Ching-Yu Cheng, MD, PhD,[1,4,5] Craig Boote, PhD,[2,8] Michaël J.A. Girard, PhD[1,2]

1. Singapore Eye Research Institute and Singapore National Eye Centre, Singapore
2. Ophthalmic Engineering & Innovation Laboratory, Department of Biomedical Engineering, National University of Singapore, Singapore
3. Beijing Advanced Innovation Center for Biomedical Engineering, School of Biological Science and Medical Engineering, Beihang University, Beijing, China
4. Duke-NUS Medical School, Singapore
5. Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
6. NIHR Biomedical Research Centre, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, UK
7. Discipline of Clinical Ophthalmology and Eye Health, University of Sydney, Sydney, NSW, Australia
8. Structural Biophysics Research Group, School of Optometry & Vision Sciences, Cardiff University, Cardiff, UK

*TAT and XW contributed equally

Corresponding Author: Dr. Michaël J.A. Girard
Ophthalmic Engineering & Innovation Laboratory (OEIL)
Department of Biomedical Engineering, National University of Singapore
4 Engineering Drive 3, E4-04-08
117583, Singapore.
Email: mgirard@nus.edu.sg

This article contains additional online-only materials. The following should appear online-only: Table S1, Table S2, Figure S1, and S2.

Abstract Word Count: 244 **Text word count**: 3000 **References**: 38

Tables: 3 **Figures**: 2

Keywords: lamina cribrosa, optic nerve head, optical coherence tomography

Running Head: Determinants of anterior laminar depth in Asian eyes

Contributor Statement: Design of study (MB, TA, CYC, CB, NGS, MJAG); Conduct of the study (TAT, YCT, MB, MEN); Collection and management of data (TAT, XW, DQN, YCT, CYC); Analysis and Interpretation of data (TAT, XW, DQN, YCT); Preparation of manuscript (TAT, XW, DQN, CB, CYC, MJAG); Review or approval of manuscript (YCT, MB, MEN, NGS, TA, CYC, CB, MJAG)

License for Publication: "The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive license (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in BJO editions and any other BMJPGL products to exploit all subsidiary rights, as set out in our license (http://group.bmj.com/products/journals/instructions-for-authors/licence-forms/)."

Abstract

Aim: To investigate the determinants of lamina cribrosa depth (LCD) in healthy eyes of Chinese and Indian Singaporean adults

Methods: The optic nerve head (ONH) of the right eye of 1,396 subjects (628 Chinese and 768 Indian subjects) was imaged with optical coherence tomography (OCT, Spectralis, Heidelberg, Germany). LCD was defined as the distance from the Bruch's membrane opening (LCD-BMO) or the peripapillary sclera (LCD-PPS) reference plane to the laminar surface. A linear regression model was used to evaluate the relationship between the LCD and its determinants.

Results: Both LCDs were significantly different between the two races (LCD-BMO: 421.95 (95% CI, 365.32-491.79) µm in Chinese vs 430.39 (367.46-509.81) µm in Indians, P=0.021; and LCD-PPS: 353.34 (300.98-421.45) µm in Chinese vs 376.76 (313.39-459.78) µm in Indians, P<0.001). In the multivariable regression analysis, the LCD-PPS of the whole cohort was independently associated with females (β=-31.93, P<0.001), Indians subjects (β=21.39, P=0.004) (Chinese as the reference), axial length (Axl) (β=-6.68, P=0.032), retinal nerve fibre layer thickness (RNFL) (β=0.71, P=0.019), choroidal thickness (ChT) (β=0.41, P<0.001), vertical cup disc ratio (VCDR) (β=24.42, P<0.001) and disc size (β=-60.75, P=0.001). For every 1-year older in age, the LCD-PPS was deeper on average by 1.95 µm in Chinese subjects (P=0.01) but there was no association in Indians subjects (P=0.851).

Conclusions: The LCD was influenced by age, gender, race, Axl, RNFL, ChT, VCDR and disc size. This normative LCD database may facilitate a more accurate assessment of ONH cupping using OCT in Asian populations.

INTRODUCTION

The pathologic cupping of the optic nerve head (ONH) in glaucoma occurs due to thinning of prelaminar tissues and the neuro-retinal rim, widening of the scleral canal, loss of retinal ganglion cells and their axons, and posterior deformation of the lamina cribrosa (LC).[1–3] This cupping/excavation of the ONH is assessed clinically as the vertical cup-disc ratio (VCDR)[4] and the evaluation of cupping has been augmented recently with measurements from optical coherence tomography (OCT) that provides the cross-sectional information of the ONH, including cup volume,[5,6] rim volume,[7,8] rim width,[9,10] and lamina cribrosa depth (LCD).[3,11]

The LCD defines a distance from the anterior surface of the LC to a reference plane and is a measurement of the LC deformation. A large LCD has been reported in glaucoma eyes,[12,13] but not in eyes with other optic neuropathies.[14,15] Studies have reported an increase in the LCD measurement in glaucomatous eyes that progressed, and also a decrease in LCD after intraocular pressure (IOP) lowering treatment in glaucoma patients.[16,17] Moreover, experimental glaucoma studies showed that the changes in LCD were observed prior to thinning of the retinal nerve fibre layer (RNFL)[18] or functional loss[2] of the optic nerve. Although the LCD itself or the changes in LCD was used to study the ONH cupping in glaucomatous neuropathy,[12,18–20] glaucoma progression,[2,21] after acute IOP elevations,[22,23] and after the IOP lowering surgery,[17,24,25] studies also showed that the diagnostic power of the LCD was lower in some populations.[26,27] In order to use the change in LCD efficiently in diagnosis and management of glaucoma, the normative value of the LCD should be established from a large population-based study as performed herein.

Recent studies showed that the LCD is affected by the reference plane used,[3,19] age,[21,28] gender,[26,29] race,[21,28] and axial length (Axl).[11,29] The LCD was reported to be greater in subjects of African descent than in European descent subjects,[3,28] and the former had the greater prevalence of glaucoma than the latter. Luo et al reported that Asian and Native American descent participants had shallower LCD than African descent participants, but the number of Asian subjects in the study was only 19.[3] The reports of variation in LCD of Asians are limited and studies were mostly conducted in one ethnic group. There may have been variations in measurements where study design and methodology differed. Thus, the aim of the current study was to investigate variations of the LCD with age, gender, race and other ocular variables in a population-based cohort in Singapore.

METHODS

Subject Recruitment

Subjects were recruited from the Singapore Epidemiology of Eye Diseases (SEED) study, a population-based cross-sectional study of Singapore adults aged 40 years and older. The recruitment protocol and study design of the SEED study have been reported in detail.[30] In brief, the SEED study was conducted to detect the prevalence and impact of major eye diseases among adult Singaporeans.

After 6 years, 2,661 Chinese (87.7% response rate) and 2200 Indians (75.5% response rate) subjects participated in 6-year follow-up visit (SEED2). The right eyes of 1,465 (657 Chinese and 808 Indians) consecutive subjects from SEED2 were analysed in this sub-study. Written informed consent was obtained from all participants. The study

had the approval of the SingHealth Centralized Institutional review board and adhered to the tenets of the Declaration of Helsinki. We excluded the cases with glaucoma, glaucoma suspects and other optic neuropathies based on the investigations such as visual acuity assessment, slit-lamp examination done by an ophthalmologist, intraocular pressure measurement, gonioscopy, posterior segment optical coherence tomography, and Humphrey visual field test.

Optical Coherence Tomography Imaging and Analysis

The ONH of each subject was imaged using spectral domain (SD)-OCT (Spectralis, Heidelberg Engineering, Germany). Each OCT volume scan consisted of 97 serial horizontal B-scans (30 µm distance between B-scans; 384 A-scans per B-scan; 20 B-scan averaging) that covered a rectangular area of 15° x 10° centred on the ONH.[22,23] Raw SD-OCT images were post-processed and enhanced using adaptive compensation to reduce blood vessel shadows and to improve the visibility of the LC and the peripapillary sclera (PPS).[31] For each eye, post-processed OCT volumes were resampled with reference to the subject-specific fovea-ONH axis (**Figure 1**) and the central B-scan was chosen for analysis using custom-written MATLAB (MathWorks Inc., Natick, MA) algorithms.

Bruch's membrane opening (BMO) was defined as the end point of the Bruch's membrane (BM) layer (or the retinal pigment epithelium/BM complex) on either side of the ONH. The PPS was defined by a sharp increase in axial signal intensity extending laterally from anterior sclera to the LC through the LC insertion points.[32]

The two BMO points were manually marked and a peripapillary ring was automatically drawn from the centre of the BMO with an inner and outer radius of 1,200 µm and 1,800 µm respectively. The PPS surface within the peripapillary ring and the anterior surface of the LC were also manually delineated. (**Figure 1**)

The line joining two BMO points was defined as the BMO reference plane[10] (**Figure 1A**) and the line joining the outermost points of the peripapillary ring was defined as the PPS reference plane. (**Figure 1B**) The PPS reference plane was adopted to avoid irregularities and poor visualization at the anterior sclera opening.[19,28]

Using the aforementioned delineations, our custom algorithms derived the following parameters.[22,23]

1. *Lamina Cribrosa Depth (LCD)*

The LCD was defined as the perpendicular distance from anterior LC surface to the reference planes of BMO (**Figure 1A**) and PPS (**Figure 1B**). All LCD values in the region of central one-third of the length of the BMO were averaged and reported as the mean LCD from each reference plane.

2. Choroidal thickness (ChT)

The ChT was defined as the thickness between the BM and PPS boundary within the peripapillary ring and represented as the mean thickness in µm. (**Figure 1**)

3. Disc size

The disc size was defined as the distance between two BMO points and represented as “L” (BMO length) in **Figure 1**.

Validation of image grading

Reproducibility of the segmentation of the images was evaluated by performing intra- and inter-observer reproducibility tests on the measurements of the LCD-BMO and LCD-PPS. A subset of 40 images was selected using a random sampling method and delineated by the first observer. The second observer (masked to the results of the first grading) delineated the same set of images in a random order for the inter-observer reproducibility. The first observer repeated the image segmentation in a random order after a 2-week interval for intra-observer reproducibility.

Statistical Analysis

Statistical analyses were performed using R software version 3.22 (R Development Core Team (2008), http://www.R-project.org). Continuous variables were described as the median, and interquartile range (25^{th}-75^{th}). We used the independent T test to compare the differences in the distribution of continuous variables of two samples and used the Pearson correlation coefficient (r) to assess the association between the LCD and other determinants. We employed linear regression models to assess the relationship of LCD-BMO or LCD-PPS with its determinants after adjusting for potential confounders (that were significant in univariable analysis). We used Bland Altman analysis of MedCalc® (Windows v14.12.0, Mariakerke, Belgium) to compare the intra- and inter-observer reproducibility of segmentation of our customized algorithms. Statistical significance was set at $P<0.05$.

RESULTS

Demographic and Clinical Characteristics

Of the 1,465 consecutively recruited subjects, right eyes of 1,396 participants (628 Chinese and 768 Indians) were included in the final analysis after excluding 69 (29 Chinese and 40 Indians, 4.71%) due to poor visibility of the anterior sclera. **Table 1** shows the demographic and clinical characteristics of the study subjects. The median (IQR) of age of Chinese was comparable to that of Indians (58.73 vs 58.38 years, P=0.318). The weight, body mass index, diastolic blood pressure and mean arterial pressure were higher in Indians than Chinese subjects (**Table 1**). Indians subjects also had higher IOP, lower central corneal thickness (CCT), shorter Axl, lower RNFL thickness, greater VCDR and relatively smaller disc size than Chinese subjects in this study. The median (IQR) of LCD-BMO was 426.07 (365.82-00.04) µm and LCD-PPS was 365.89 (307.92-440.41) µm ; and both LCDs were significantly different between the two races (LCD-BMO: 421.95 (365.32-491.79) µm in Chinese vs 430.39 (367.46-509.81) µm in Indians, P=0.021; and LCD-PPS: 353.34 (300.98-421.45) µm in Chinese vs 376.76 (313.39-459.78) µm in Indians, P<0.001).

Intra- and Inter-observer reproducibility of image grading

Bland-Altman analysis of LCD-BMO measurement showed that the mean difference was 6.88 (95% confidence interval (CI), -3.057, 16.817) for intra-observer reproducibility and the mean difference was 7.923 (95%CI, -1.665, 17.511) for inter-observer reproducibility. The limits of agreement (LOA) for intra-observer reproducibility was from -54.019 (95%CI, -71.144, -36.894) to 67.78 (95%CI, 50.654, 84.905). The

LOA for inter-observer reproducibility was from -50.837 (95%CI, -67.36, -34.313) to 66.683 (95%CI, 50.159, 83.207). (online supplementary **Figure S1A and C**)

Bland-Altman analysis of LCD-PPS measurements showed that the mean difference was 2.899 (95%CI, -5.341, 11.14) for intra-observer reproducibility and the mean difference was 2.883 (95%CI, -4.555, 10.32) for inter-observer reproducibility. The LOA for intra-observer reproducibility was from -47.602 (95%CI, -61.804, -33.401) to 53.401 (95%CI, 39.199, 67.602). The LOA for inter-observer reproducibility was from -42.7 (95%CI, -55.519, -29.882) to 48.465 (95%CI, 35.647, 61.284). (online supplementary **Figure 1B and D**)

Association of LCD with clinical/ocular parameters

The LCD-BMO was associated with age, gender, Axl, spherical refractive error, VCDR, RNFL, disc size and ChT, while the LCD-PPS was associated with gender, Axl, spherical refractive error, VCDR, disc size and ChT. (online supplementary **Table S1**) Even though they showed statistical significance, these associations were weak (r value ranging from 0.068 to 0.193) with the exception of ChT. The association of ChT with the LCD-BMO was fair (r=0.489) but with the LCD-PPS was poor (r=0.228). Online supplementary **Figure S2** shows the histograms of LCD-BMO and LCD-PPS in the whole cohort as well as racial groups separately. The LCD from both reference planes showed a right-skewed curve (exponentially-modified Gaussian distribution) by the Shapiro-Wilk test (all P<0.001).

Table 2 shows the relationships of LCD for the whole cohort (n=1,396) with clinical/ocular variables. The multivariable regression analysis showed that the LCD-

BMO on average was shallower by 33.13 µm in females, was increased by 0.78 µm for every 1 µm thicker RNFL, was increased by 0.91 µm for every 1 µm thicker ChT and was increased by 19.01 µm for every 0.1 ratio increase of VCDR, after adjusting for age, race, and Axl. The LCD-PPS of the whole cohort was also shallower on average by 31.93 µm in females, was deeper by 21.39 µm in Indians when compared with Chinese, was shallower by 6.68 µm for every 1 mm increase in Axl, was increased by 0.71 µm for every 1 µm thicker RNFL, was deeper by 0.41 µm for every 1 µm increase in ChT, was increased by 24.42 µm for every 0.1 ratio increase of VCDR and was shallower by 60.75 µm for every 1 mm greater in disc size, after adjusting to age. (**Table 2**)

The relationships of LCD-BMO with its determinants are shown in online supplementary **Table S2**. The LCD-BMO was associated with age in univariable analysis (Chinese: β=-1.42, P=0.006, Indians: β=-1.34, P=0.007) but the association was lost when adjusting for the confounders of gender, race, axl, RNFL, ChT, VCDR and disc size. The multivariable regression analysis showed that the LCD-BMO was associated with RNFL and ChT in Chinese subjects; and it was associated with gender, RNFL, ChT and VCDR in Indians subjects, after adjusting for age and Axl.

Table 3 shows the relationships of LCD-PPS with its determinants. The multivariable regression analysis showed that the LCD-PPS in Chinese subjects was associated with age and ChT while that in Indians subjects was associated with gender, Axl, RNFL, ChT, VCDR and disc size, after adjusting for the cofounders. Similarly, after adjusting for the confounders, the association between the LCD-PPS and age achieved significance (P=0.009) in Chinese subjects, but not in Indians subjects (P=1).

Figure 2 shows a schematic, illustrating racial differences in ocular parameters between Chinese and Indians subjects.

DISCUSSION

In this population-based cohort, we studied anterior laminar depth of the ONH in Chinese and Indian adults in Singapore. The median (IQR) of LCD-BMO was 426.07 (365.82-500.04) µm and LCD-PPS was 365.89 (307.92-440.41) µm; and LCD of Indians was significantly greater than that of Chinese adults. The laminar depth was shallower in females, shallower in eyes with greater Axl, deeper in eyes with thicker RNFL, deeper in eyes with thicker choroid, deeper with greater VCDR and shallower in eyes with large disc size. The LCD from the BMO reference plane was fairly influenced by choroidal thickness, but that from the anterior sclera plane was not. To evaluate the health of the optic nerve, accurate assessment of ONH cupping is fundamental for screening, diagnosis and monitoring of glaucoma. In vivo imaging of the ONH using OCT provides a more objective and comprehensive way to assess cupping using the laminar depth; however, a consistent anatomical landmark for the reference plane, a normative database with a large sample size, and factors influencing the measurements are required. This paper reports the results from a large dataset of the two largest ethnic groups in Asia and provides a population-based normative value that has no selection bias and generalizability.

Normative value of anterior lamina cribrosa depth and racial variation

In this cohort, we found that the LCD was significantly different between the two races either using BMO or PPS as the reference plane. A multicenter study has

reported the LCD-BMO was 402±91 µm and LCD-PPS was 332±96 µm in 362 normal subjects, but their results could not represent the normative values for the Asian population because only 19 Asian subjects were involved in the study.[3] A study from Korea also showed similar findings (LCD-BMO = 402.06±101.46 µm) in 300 healthy eyes of 150 Korean subjects.[29] Since ethnic differences exist in the distribution of laminar depth, this disparity should be considered based on their respective ethnic-specific normative values while assessing the extent of ONH cupping in the clinic, or while designing clinical trials and research studies.

Laminar depth and choroid

Vianna et al. reported that the ChT influenced the LCD when the BMO plane was used; but the measurement from anterior sclera was not or less influenced by the choroid. Our results confirmed these associations in a large and population-based data. Morphologically, the choroidal layer is located between the reference plane of BMO and the anterior lamina surface so its thickness could be a part of the LCD and was influencing the measurement of the LCD-BMO.[19] Importantly, thinning of the choroid layers due to many factors such as ageing, high myopia, and uncontrolled diabetes and variations of choroid in racial groups have to be considered when the LCD-BMO is used.

Variation of lamina cribrosa depth with vertical cup-disc ratio and disc size

The VCDR was highly associated with the LCDs in this study suggesting that the LC was deeper in the eyes with a greater VCDR. Our results are consistent with the study conducted by Jung et al.[33] They reported that the LC was more deeply located

within the ONH of the eye with a higher VCDR when compared with the fellow eye with a lower VCDR.

Disc size was significantly different between Chinese and Indians in this study, but the difference was relatively small. We found that the LCD from the PPS reference plane was shallower in eyes with large discs. Luo et al. also found that the LCD was shallower in eyes with a large disc.[3] Large discs were thought to be susceptible to glaucoma especially in African populations.[34] However, other studies also reported that the disc size was not associated with the glaucoma susceptibility.[35] From a mechanical point of view, a large disc size may be associated with a larger total area of the LC, and thus more deformations when IOP increases.[34]

Variation of laminar depth with gender, axial length and age

We found that the LCD was shallower in females and in eyes with greater Axl especially in subjects of Indian descent. Our results are in concordance with previous studies which reported that gender and Axl influence LCD measurement.[3,29] It is unknown why the LCD was shallower in females, however, the disc area was larger in male than in female subjects.[36] A larger disc area may have a bigger eye ball and a deeper cup, but a longer eye ball was associated with shallower cup in the current study.

The LCD relative to the BMO plane decreased with age in the univariable analysis of our study and other studies;[3,21,28] but this association was lost after adjusting for the ChT in our study. (**Table 2**) After adjusting for the confounders, the LCD relative to the PPS plane in Chinese adults was deeper with increasing age, but this relationship was not found in the Indian adult cohort. The posterior migration of

BMO due to age-related choroidal thinning may influence the LCD from the BMO plane;[19,37] and aged-related remodelling of sclera such as PPS bowing posteriorly may also affect the measurement from the PPS plane. Investigation of age-related LC changes in a large ethnic-specific sample may facilitate or optimize the detection of local ONH changes in eyes at risk of glaucoma and the estimation of disease progression.

There are several limitations in the current work. First, only the central B-scan was used to measure the LCD. However the centre of the ONH has been shown to exhibit the maximum LC displacement following short-term IOP elevation[38] and, moreover, the central part provides a consistent measurement without the variable visibility of the peripheral lamina - especially under the area of blood vessel shadows nasally. Second, we excluded 4.71% of the sample due to limited visibility of LC and PPS even though we used customized algorithms to enhance the quality of the B-scans. Third, we used only two reference planes (BMO and PPS) in the current study, as in the previous studies.[19,28] Four reference planes (BMO, BM, scleral canal opening and PPS) had provisionally been proposed.[3] However, both the BM reference plane and the BMO plane are influenced by choroid; and the scleral opening plane was not chosen due to limited visibility.

In summary, the current study found that the laminar depth was shallower in females, in eyes with greater axial length and in eyes with larger disc size. The LC was deeper in Indians than in Chinese subjects, in eyes with thick retinal nerve fibre layers, in eyes with thicker choroids and in eyes with greater VCDR. Understanding the factors influencing the measurement of the LCD and its normative value in Asian eyes will

facilitate more accurate assessment of optic nerve cupping for diagnosis and monitoring of glaucoma in Asian populations using SD-OCT.

Acknowledgment

Funding/Support: The study was supported by the Singapore Ministry of Education Academic Research Funds Tier 1 (R-397-000-294-114 [MG]) and Tier 2 (R-397-000-280-112 and R-397-000-308-114 [MG]), by Beijing Municipal Natural Science Foundation (7194288[XW]), by the National Medical Research Council (TA; NMRC/STAR/0023/2014), and by the National Institute for Health Research, Biomedical Research Centre, Moorfields Eye Hospital National Health Service, Foundation Trust and University College London, Institute of Ophthalmology (NGS). The sponsor or funding organization had no role in the design or conduct of this research. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the UK Department of Health.

Financial Disclosures: No conflicting relationship exists for any author.

Other Acknowledgment: none

References

1 Quigley HA, Addicks EM, Green WR, *et al.* Optic nerve damage in human glaucoma: Ii. The Site of Injury and Susceptibility to Damage. *Arch Ophthalmol* 1981;**99**:635–49.

2 He L, Yang H, Gardiner SK, *et al.* Longitudinal detection of optic nerve head changes by spectral domain optical coherence tomography in early experimental glaucoma. *Investig Ophthalmol Vis Sci* 2013;**55**:574–86.

3 Luo H, Yang H, Gardiner SK, *et al.* Factors Influencing Central Lamina Cribrosa Depth: A Multicenter Study. *Investig Opthalmology Vis Sci* 2018;**59**:2357-2370.

4 Armaly MF. Genetic determination of cup/disc ratio of the optic nerve. *Arch Ophthalmol (Chicago, Ill 1960)* 1967;**78**:35–43.

5 Resch H, Deak G, Pereira I, *et al.* Comparison of optic disc parameters using spectral domain cirrus high-definition optical coherence tomography and confocal scanning laser ophthalmoscopy in normal eyes. *Acta Ophthalmol* 2012;**90**:e225-9.

6 El-Dairi M, Holgado S, Asrani S, *et al.* Optical coherence tomography (OCT) measurements in black and white children with large cup-to-disc ratios. *Exp Eye Res* 2011;**93**:299–307.

7 Leung CK, Medeiros FA, Zangwill LM, *et al.* American Chinese Glaucoma Imaging Study: A Comparison of the Optic Disc and Retinal Nerve Fiber Layer in Detecting Glaucomatous Damage. *Investig Opthalmology Vis Sci* 2007;**48**:2644-52.

8 Medeiros FA, Zangwill LM, Bowd C, *et al.* Evaluation of retinal nerve fiber layer, optic nerve head, and macular thickness measurements for glaucoma detection using optical coherence tomography. *Am J Ophthalmol* 2005;**139**:44–55.

9 Chauhan BC, O'Leary N, Almobarak FA, *et al.* Enhanced detection of open-angle glaucoma with an anatomically accurate optical coherence tomography-derived neuroretinal rim parameter. *Ophthalmology* 2013;**120**:535–43.

10 Tun TA, Sun CH, Baskaran M, *et al.* Determinants of optical coherence Tomography-Derived minimum neuroretinal rim width in a Normal Chinese Population. *Investig Ophthalmol Vis Sci* 2015;**56**:3337–44.

11 Yun S-C, Hahn IK, Sung KR, *et al.* Lamina cribrosa depth according to the level of axial length in normal and glaucomatous eyes. *Graefe's Arch Clin Exp Ophthalmol* 2015;**253**:2247–53.

12 Furlanetto RL, Park SC, Damle UJ, *et al.* Posterior displacement of the lamina cribrosa in glaucoma: In vivo interindividual and intereye comparisons. *Investig Ophthalmol Vis Sci* 2013;**54**:4836–42.

13 Lee EJ, Kim T-W, Weinreb RN, *et al.* Three-Dimensional Evaluation of the Lamina Cribrosa Using Spectral-Domain Optical Coherence Tomography in Glaucoma. *Investig Opthalmology Vis Sci* 2012;**53**:198-204.

14 Lee EJ, Choi YJ, Kim T-W, *et al.* Comparison of the Deep Optic Nerve Head Structure between Normal-Tension Glaucoma and Nonarteritic Anterior Ischemic Optic Neuropathy. *PLoS One* 2016;**11**:e0150242.

15 Ing E, Ivers KM, Yang H, *et al.* Cupping in the Monkey Optic Nerve Transection Model Consists of Prelaminar Tissue Thinning in the Absence of Posterior Laminar Deformation. *Invest Ophthalmol Vis Sci* 2016;**57**:2914–2927.

16 Lee EJ, Kim T-WW. Lamina Cribrosa Reversal after Trabeculectomy and the Rate of Progressive Retinal Nerve Fiber Layer Thinning. *Ophthalmology* 2015;**122**:2234–42.

17 Lee EJ, Kim T-WW, Weinreb RN, *et al.* Reversal of lamina cribrosa displacement after intraocular pressure reduction in open-angle glaucoma. *Ophthalmology* 2013;**120**:553–9.

18 Strouthidis NG, Fortune B, Yang H, *et al.* Longitudinal change detected by spectral domain optical coherence tomography in the optic nerve head and peripapillary retina in experimental glaucoma. *Investig Ophthalmol Vis Sci* 2011;**52**:1206–19.

19 Vianna JR, Lanoe VR, Quach J, *et al.* Serial Changes in Lamina Cribrosa Depth and Neuroretinal Parameters in Glaucoma: Impact of Choroidal Thickness. *Ophthalmology* 2017;**124**:1392–402.

20 Sousa DC, Leal I, Marques-Neves C, *et al.* Relationship between Intraocular Pressure and Anterior Lamina Cribrosa Depth: A Cross-Sectional Observational Study in a Healthy Portuguese Population. *Eur J Ophthalmol* 2017;**27**:295–300.

21 Ren R, Yang H, Gardiner SK, *et al.* Anterior lamina cribrosa surface depth, age, and visual field sensitivity in the Portland progression project. *Investig Ophthalmol*

Vis Sci 2014;**55**:1531–9.

22 Tun TA, Thakku SG, Png O, *et al.* Shape changes of the anterior lamina cribrosa in normal, ocular hypertensive, and glaucomatous eyes following acute intraocular pressure elevation. *Investig Ophthalmol Vis Sci* 2016;**57**:4869–77.

23 Tun TA, Atalay E, Baskaran M, *et al.* Association of functional loss with the biomechanical response of the optic nerve head to acute transient intraocular pressure elevations. *JAMA Ophthalmol* 2018;**136**:184–92.

24 Lee EJ, Kim TW, Weinreb RN. Reversal of lamina cribrosa displacement and thickness after trabeculectomy in glaucoma. *Ophthalmology* 2012;**119**:1359–66.

25 Lee EJ, Kim TW, Weinreb RN. Reversal of Lamina Cribrosa Displacement and Thickness after Trabeculectomy in Glaucoma. *OPHTHA* 2012;**119**:1359–66.

26 Lee SH, Kim TW, Lee EJ, *et al.* Diagnostic power of lamina cribrosa depth and curvature in glaucoma. *Investig Ophthalmol Vis Sci* 2017;**58**:755–62.

27 Lee EJ, Kim TW, Kim H, *et al.* In partnership with the Comparison between Lamina Cribrosa Depth and Curvature as a Predictor of Progressive Retinal Nerve Fiber Layer Thinning in Primary Open-Angle Glaucoma. *Ophthalmol Glaucoma* 2018;**1**:44–51.

28 Rhodes LA, Huisingh C, Johnstone J, *et al.* Variation of laminar depth in normal eyes with age and race. *Investig Ophthalmol Vis Sci* 2014;**55**:8123–33.

29 Seo JH, Kim TW, Weinreb RN. Lamina cribrosa depth in healthy eyes. *Investig Ophthalmol Vis Sci* 2013;**55**:1241–50.

30 Lavanya R, Jeganathan VSE, Zheng Y, *et al.* Methodology of the Singapore Indian Chinese Cohort (SICC) eye study: Quantifying ethnic variations in the epidemiology of eye diseases in Asians. *Ophthalmic Epidemiol* 2009;**16**:325–36.

31 Mari JM, Strouthidis NG, Park SC, *et al.* Enhancement of Lamina Cribrosa Visibility in Optical Coherence Tomography Images Using Adaptive Compensation. *Investig Opthalmology Vis Sci* 2013;**54**:2238.

32 Strouthidis NG, Grimm J, Williams GA, *et al.* A comparison of optic nerve head morphology viewed by spectral domain optical coherence tomography and by serial histology. *Investig Ophthalmol Vis Sci* 2010;**51**:1464–74.

33 Jung KI, Jeon S, Park CK. Lamina Cribrosa Depth is Associated With the Cup-to-Disc Ratio in Eyes With Large Optic Disc Cupping and Cup-to-Disc Ratio Asymmetry. *J Glaucoma* 2016;**25**:e536–45.

34 Hoffmann EM, Zangwill LM, Crowston JG, *et al.* Optic Disk Size and Glaucoma. *Surv Ophthalmol* 2007;**52**:32–49.

35 Jonas JB, Fernández MC, Naumann GOH. Correlation of the Optic Disc Size to Glaucoma Susceptibility. *Ophthalmology* 1991;**98**:675–80.

36 Varma R, Tielsch JM, Quigley HA, *et al.* Race-, Age-, Gender-, and Refractive Error—Related Differences in the Normal Optic Disc. *Arch Ophthalmol* 1994;**112**:1068-76.

37 Johnstone J, Fazio M, Rojananuangnit K, *et al.* Variation of the axial location of bruch's membrane opening with age, choroidal thickness, and race. *Investig*

Ophthalmol Vis Sci 2014;**55**:2004–9.

38 Levy NS, Crapps EE, Bonney RC. Displacement of the optic nerve head: Response to Acute Intraocular Pressure Elevation in Primate Eyes. *Arch Ophthalmol* 1981;**99**:2166–74.

Table 1. Demographic and ocular characteristics of the 1,396 study subjects

Variables	**Total (n =1396)**	**Chinese (n=628)**	**Indians (n=768)**	
	Median (IQR)	Median (IQR)	Median (IQR)	P value
Age, year	58.52 (53.94-65.03)	58.73 (54.18-64.99)	58.38 (53.69-65.04)	0.318
Gender, female	711 (50.97%)	332 (52.87%)	379 (49.41%)	0.219
Height (cm)	162.5 (156.5-169)	162 (156.57-168.62)	162.7 (156.5-169)	0.932
Weight (kg)	65.8 (57.9-74.53)	62.45 (55.29-69.5)	68.75 (61-77.28)	**<0.001**
Body mass index (kg/m2)	24.58 (22.37-27.49)	23.36 (21.37-25.85)	26.02 (23.39-28.53)	**<0.001**
Systolic blood pressure (mmHg)	134 (122-146.5)	134 (121-146.62)	133.5 (123-145.5)	0.673
Diastolic blood pressure (mmHg)	75.5 (70-82.5)	74.5 (68.5-81.5)	76.83 (71-83.5)	**<0.001**
Mean arterial pressure (mmHg)	95.17 (88.17-102.75)	94.67 (87.29-102.33)	95.69 (89.21-103.33)	**0.013**
Best corrected visual acuity, unit	0.1 (0-0.2)	0.1 (0.02-0.2)	0.1 (0-0.2)	0.579
Spherical equivalent, dioptre	0.2 (-0.9-1.12)	-0.16 (-1.6-0.75)	0.45 (-0.5-1.44)	**<0.001**
Intraocular pressure, mmHg	15 (13-16)	14 (12-16)	15 (14-17)	**<0.001**
Ocular perfusion pressure, mmHg	53.78 (49.11-58.78)	53.39 (48.75-58.78)	53.89 (49.33-58.67)	0.181
Central corneal thickness, µm	548 (526-570)	554 (532.25-575)	542 (522-564)	**<0.001**
Axial length, mm	23.53 (22.96-24.28)	23.81 (23.22-24.68)	23.35 (22.78-23.96)	**<0.001**
Vertical cup-disc ratio	0.35 (0.31-0.44)	0.33 (0.31-0.39)	0.38 (0.31-0.47)	**<0.001**
Retinal nerve fibre layer, µm	91.26 (84.84-98.94)	98 (91.78-104.49)	88 (81-94)	**<0.001**
Choroidal thickness, µm	153.52 (125.19-192.29)	147.72 (117.26-190.8)	158.63 (130.5-193.64)	0.131
Disc size, mm	1.64 (1.52-1.77)	1.65 (1.54-1.78)	1.64 (1.51-1.76)	**0.047**
LCD-BMO	426.07 (365.82-500.04)	421.95 (365.32-491.79)	430.39 (367.46-509.81)	**0.021**
LCD-PPS	365.89 (307.92-440.41)	353.34 (300.98-421.45)	376.76 (313.39-459.78)	**<0.001**

LCD-BMO is anterior lamina cribrosa depth from the reference plane of Bruch's membrane opening; LCD-PPS is anterior lamina cribrosa depth from the reference plane of anterior sclera; IQR is interquartile (25^{th}-75^{th}) range. A bold font denotes a statistically significant difference with p value less than 0.05.

Table 2. Linear regression model showing the relationship of lamina cribrosa depth of the whole cohort (n=1,396) with its determinants

Variables	LCD-BMO						LCD-PPS					
	Univariable			Multivariable			Univariable			Multivariable		
	Estimate	95% CI	P value	Estimate	95% CI	P value	Estimate	95% CI	P value	Estimate	95% CI	P value
Age, year	-1.4	(-2.1, -0.69)	**<0.001**	0.05	(-0.7, 0.8)	0.888	0.1	(-0.65, 0.85)	0.801	0.5	(-0.38, 1.39)	0.266
Gender (ref: male)	-38.32	(-48.55, -28.09)	**<0.001**	-33.13	(-43.67, -22.59)	**<0.001**	-32.25	(-43.18, -21.31)	**<0.001**	-31.93	(-44.34, -19.52)	**<0.001**
Ethnic (ref: Chinese)	12.3	(1.84, 22.77)	**0.021**	6.33	(-6.02, 18.68)	0.315	27.25	(16.21, 38.29)	**<0.001**	21.39	(6.85, 35.93)	**0.004**
IOP, mmHg	0.73	(-1.39, 2.84)	0.502				1.88	(-0.36, 4.13)	0.1			
OPP, mmHg	-0.36	(-1.07, 0.36)	0.327				0.01	(-0.74, 0.77)	0.978			
CCT, µm	-0.01	(-0.17, 0.14)	0.865				-0.13	(-0.29, 0.04)	0.141			
Axl, mm	-9.49	(-14.1, -4.88)	**<0.001**	-4.16	(-9.33, 1.01)	0.115	-11.29	(-16.19, -6.4)	**<0.001**	-6.68	(-12.76, -0.59)	**0.032**
RNFL, µm	0.68	(0.17, 1.18)	**0.009**	0.78	(0.28, 1.28)	**0.002**	0.06	(-0.49, 0.6)	0.836	0.71	(0.12, 1.3)	**0.019**
ChT, µm	0.98	(0.89, 1.08)	**<0.001**	0.91	(0.8, 1.02)	**<0.001**	0.49	(0.38, 0.6)	**<0.001**	0.41	(0.28, 0.55)	**<0.001**
VCDR (per 0.1)	17.63	(12.13, 23.13)	**<0.001**	19.01	(13.41, 24.6)	**<0.001**	20.69	(14.88, 26.51)	**<0.001**	24.42	(17.83, 31.01)	**<0.001**
Disc Size, mm	-36.45	(-64.53, -8.36)	**0.011**	-4.42	(-35.81, 26.98)	0.783	-57.94	(-87.69, -28.18)	**<0.001**	-60.75	(-97.71, -23.78)	**0.001**

LCD-BMO is lamina cribrosa depth from the reference plane of Bruch's membrane opening; LCD-PPS is lamina cribrosa depth from the anterior sclera reference plane; BCVA is best corrected visual acuity; IOP is intraocular pressure; OPP is ocular perfusion pressure; CCT is central corneal thickness; Axl is axial length; RNFL is retinal nerve fibre layer; ChT is choroidal thickness, VCDR is vertical cup disc ratio. A bold font denotes a statistically significant difference with p value less than 0.05.

Table 3. Linear regression model showing the relationship of lamina cribrosa depth from the anterior sclera reference plane with its determinants

Variables	Chinese (n=628)						Indian (n=768)					
	Univariable			Multivariable			Univariable			Multivariable		
	Estimate	95% CI	P value	Estimate	95% CI	P value	Estimate	95% CI	P value	Estimate	95% CI	P value
Age, year	0.82	(-0.19, 1.83)	0.11	1.88	(0.39, 3.37)	**0.014**	-0.4	(-1.47, 0.67)	0.464	-0.09	(-1.18, 0.99)	0.866
Gender (ref: male)	-19.48	(-34.26, -4.69)	**0.01**	-11.88	(-31.18, 7.42)	0.229	-41.06	(-56.64, -25.48)	**<0.001**	-44.32	(-60.2, -28.44)	**<0.001**
BCVA, unit	16.24	(-50.78, 83.26)	0.635				2.61	(-67.51, 72.74)	0.942			
IOP, mmHg	1.2	(-1.89, 4.29)	0.447				1.08	(-2.13, 4.3)	0.509			
OPP, mmHg	0.28	(-0.7, 1.26)	0.575				-0.37	(-1.48, 0.75)	0.518			
CCT, µm	-0.11	(-0.34, 0.12)	0.332				-0.01	(-0.26, 0.23)	0.921			
Axl, mm	-5.82	(-11.86, 0.21)	0.059	-0.24	(-8.83, 8.35)	0.957	-12.45	(-20.74, -4.16)	**0.003**	-13.31	(-21.71, -4.91)	**0.002**
RNFL, µm	0.63	(-0.31, 1.58)	0.191	0.64	(-0.35, 1.62)	0.207	0.64	(-0.12, 1.4)	0.101	0.84	(0.11, 1.56)	**0.025**
ChT, µm	0.33	(0.19, 0.46)	**<0.001**	0.34	(0.15, 0.53)	**<0.001**	0.65	(0.48, 0.82)	**<0.001**	0.49	(0.32, 0.67)	**<0.001**
VCDR (per 0.1)	5.41	(-3.23, 14.05)	0.22	10.63	(-0.67, 21.93)	0.066	27.34	(19.38, 35.3)	**<0.001**	30.04	(22.02, 38.05)	**<0.001**
Disc Size, mm	-59.21	(-98.01, -20.41)	**0.003**	-17.86	(-77.32, 41.6)	0.556	-49.51	(-93.2, -5.83)	**0.027**	-82.12	(-128.69, -35.55)	**<0.001**

BCVA is best corrected visual acuity; IOP is intraocular pressure; OPP is ocular perfusion pressure; CCT is central corneal thickness; Axl is axial length; RNFL is retinal nerve fibre layer; ChT is choroidal thickness, VCDR is vertical cup disc ratio. A bold font denotes a statistically significant difference with p value less than 0.05.

Figure legends

Figure 1. Illustration of measurement of anterior lamina cribrosa depth

LCD-BMO is anterior lamina cribrosa depth from Bruch's membrane opening reference plane (A) and LCD-PPS is anterior lamina cribrosa depth from anterior sclera plane (B).

Figure 2. Illustration of the determinants of anterior lamina cribrosa depth in eyes of Chinese Descent and Indian Descent