Optic Disc Morphology Of South Indians: The Chennai Glaucoma Study

THESIS

Submitted in partial fulfillment
of the requirements for the degree of
DOCTOR OF PHILOSOPHY

by

Dr. S Hemamalini

Under the supervision of

Dr. L Vijaya

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE
PILANI (RAJASTHAN) INDIA
2008

Birla Institute of Technology and Science

Pilani, Rajasthan

Certificate

This is to certify that the thesis entitled "OPTIC DISC MORPHOLOGY OF SOUTH INDIANS: THE CHENNAI GLAUCOMA STUDY" submitted by S Hemamalini, ID No. 2003PHXF033 for the award of Ph.D. degree of the institute, embodies original work done by her under my supervision.

Signature of the Supervisor:

Name: **Dr. L VIJAYA**

Designation: Director, Glaucoma Service, Sankara Nethralaya, Chennai

DATE:

Dedicated to my parents who taught me faith, perseverance
and much more.

ACKNOWLEDGEMENTS

This thesis marks the culmination of a long and immensely rewarding learning process for me. My teacher and guide, Dr. L Vijaya, has been with me through this at every step - teaching, encouraging, and guiding me while at the same time, giving me space to find expression of my own thoughts. Words are inadequate to express my gratitude to her.

I am grateful to our Chairman, Dr.SS Badrinath, for his invaluable support to the Chennai Glaucoma Study, and for making this thesis possible by permitting completion of this thesis as a distance education programme. I am sure the Chennai Glaucoma Team would join me in thanking the Chennai Willingdon Corporate Foundation for their valuable financial assistance, and the Medical Research Foundation for institutional support to the study.

I must thank my friend and colleague Dr.Ronnie George for valuable intellectual input at the commencement of the study as well as during manuscript preparation. I would also like to thank Ms. Prema Raju and Mr.S Ve Ramesh, optometrists, whose expertise at optic disc photography made this thesis possible. The entire Chennai Glaucoma Study team consisting of, in addition to the above members, Dr. G Kumaramanickavel, Dr. M Baskaran, social workers Mr. Madan Raj and Mr. J Augustian and co-coordinator, Ms. Vijayalakshmi have been indispensable to the successful completion of the Chennai Glaucoma Study, and therefore to this thesis.

The software for this study was written by one of the brightest young men I have met-Mr. Prashant Kannan, engineering student at BITS Pilani, who wrote this software as part of his summer project. I thank him for this, as well as going out of the way to help refine and implement it during the course of the study.

The Research & Consultancy team at BITS have been extremely helpful during my work, by providing prompt replies to any queries and efficiently acknowledging and processing all necessary components of the PhD programme. I thank them for their support.

My family - my husband, mother and sister - have been immensely supportive during these busy, and sometimes stressful years. I can never thank them enough, but I hope I have done justice to their unquestioning faith and support.

Finally, I thank our patients without whom none of this bears any relevance. I thank them for their trust, their patience, and for being there so that our work has meaning.

S Hemamalini

ABSTRACT

Purpose: To report planimetric optic disc data for South Indians from a population-based study.

Design: Population-based cross-sectional study

Participants: 632 phakic participants of the Chennai Glaucoma Study with reliable, normal frequency doubling perimetry screening examinations, clear ocular media, and myopia <-8.0 D, if any.

Methods: Subjects underwent complete eye examinations including refraction, keratometry, frequency doubling perimetry (screening C-20-1), pachymetry, gonioscopy, grading of lens opacities and optic disc non-simultaneous digital stereo-photography. Planimetry was performed on photographs under stereo-viewing conditions using custom software by a single observer.

Optic disc area, cup area, vertical and horizontal disc and cup diameters, and rim width at 12, 3, 6 and 9 o'clock positions were measured. Torsion of the disc >15 degrees, tilting, morphological type of cupping (as no cupping, steep cupping, partly sloping or fully sloping temporal rim) and presence of cilioretinal arteries was noted.

Main Outcome Measures: Optic disc size and shape, optic cup size and shape, neural rim size and shape, cup-disc area and linear ratios were examined. The association of all the above outcomes with several ocular and systemic factors was studied. Asymmetry of the above optic disc parameters was studied in a sub-group where data of both eyes were available (n=565).

Results: Mean optic disc area in this study was 2.8 ± 0.5 sq mm. 2.5^{th} and 97.5^{th} percentiles for optic disc area were 1.9 and 4 sq mm respectively. No association with age, sex, refraction, central corneal thickness, presence of occludable angles, height or axial length were noted.

Mean vertical and horizontal disc diameters were 1.94 ± 0.2 mm and 1.81 ± 0.19 mm respectively. On average, optic discs were vertically oval with the vertical diameter about 8% longer than the horizontal. Disc shape was associated with torsion of the optic disc and showed weaker relationships with age and gender. Together, these 3 factors accounted for 10% of the variability of disc shape. Disc shape did not show any relationship with disc size, spherical or astigmatic refractive error, axial length, type of cupping or height. (25.8%) eyes had at least 1 cilioretinal artery (CRA).

Mean neural rim area in this study was 2.29 ± 0.39 sq.mm (2.5^{th} percentile 1.60 sq mm, 97.5^{th} percentile 3.18 sq mm). Rim area showed a significant positive correlation with disc area (r^2 change 0.44, $p<0.0001$) and type of cupping (r^2 change 0.195, $p<0.0001$). There was no

significant relationship with age, sex, height, refraction, corneal thickness, IOP, axial length, torsion, disc shape, or CRA.

The inferior rim was thickest (0.61± 0.11 mm), and temporal rim was thinnest (0.44 ± 0.12 mm, p<0.0001). On average, the inferior rim was 18% thicker than the superior rim. The lower 2.5th percentile of the ratio of inferior/superior rim width was 0.9. 7.1% of eyes had superior rims thicker than the inferior rim. Torsion of the disc increased the odds of a thicker superior rim (p=0.002, OR 4.8, 95% CI 2 -11.43). The temporal rim was not the thinnest in 12% of eyes (excluding nasal rims). Disc shape (low VDD/HDD) (p<0.0001), astigmatism (p=0.001) and type of cupping (sloping rims) (p=0.006) were significant contributors to this outcome.

Mean optic cup area was 0.53 ± 0.39 sq mm (2.5th percentile 0, 97.5th percentile 1.5 sq mm). Optic cup area also demonstrated a positive correlation with optic disc area (r^2 change 0.454, p<0.0001) and type of cupping (r^2 change 0.19, p<0.0001). When discs with no cupping were excluded from the model, the r^2 change values were 0.416 (p<0.0001) for disc area and 0.097 (p<0.0001) for type of cupping respectively. It showed no significant correlation with age, sex, height, refraction, corneal thickness, intraocular pressure (IOP), axial length, torsion, disc shape, or CRA.

In this population, 50.9% had discs with well demarcated cupping, 14.3% had no cups, 11.4% had partly sloping rims and 23.4% had entirely sloping temporal rims. Mean vertical and horizontal cup diameters were 0.720 ± 0.38 mm and 0.723 ± 0.37 mm respectively. Among eyes with physiological cupping, mean VCD/HCD was 1.0011 ± 0.14. Significant predictors of cup shape were disc shape (r^2 change 0.179, p<0.0001), disc area (r^2change 0.018, p=0.001), cup area (r^2 change 0.013, p=0.004), and type of cupping (r^2 change 0.019, p=0.002).

The mean (median) vertical and horizontal cup-disc ratios in the current planimetric study were 0.36 (0.39) and 0.39 (0.43) respectively. 97.5th and 99.5th percentiles were 0.63 and 0.68 for vertical CDR and 0.66 and 0.72 for HCDR. On average HCDR was 7% greater than VCDR. VCDR was significantly affected by disc area (r^2 change 0.223, p<0.0001) and type of cupping (r^2 change 0.535, p<0.0001). When discs with no cups were excluded, these two variables were still significant, though weaker (r^2 change 0.14, p<0.0001 for disc area, r^2 change 0.12, p<0.0001 for type of cupping).

The intraclass correlation co-efficient for agreement between clinical estimates and planimetrically measured VCDR was 0.74. Among discs with physiological cupping, clinical

assessment tended to underestimate small cups and overestimate large cups compared to planimetry.

No significant differences between right and left eyes were found for any of the planimetric measures. Mean asymmetries of disc, cup and rim areas were 0.19 ± 0.16 sq mm, 0.15 ± 0.15 and 0.18 ± 0.15 sq mm (median 0.15, 0.12 and 0.14 sq mm, 95th percentiles 0.49, 0.41 and 0.48) respectively. Rim area asymmetry showed a significant correlation with disc area asymmetry (r^2 change 0.359, $p<0.0001$) and IOP asymmetry (r^2 change 0.009, $p=0.004$. Optic cup area asymmetry correlated with disc area asymmetry (r^2 change =0.27, $p<0.0001$) and asymmetry in the presence of physiological cupping (r^2 change 0.06, $p<0.0001$).

Average disc shape (VDD/HDD) asymmetry in this population was 0.06 ± 0.05 (median 0.05, 95th percentile 0.15) (i.e., the VDD of one eye was an additional 6% longer than its HDD). The mean asymmetry in VCD/HCD was 0.16 (median 0.09± 0.23 (median 0.09, 95th percentile 0.85). Asymmetry in cup shape was significantly related to asymmetry of cup area (r^2 change 0.065, $p<0.0001$) and disc shape asymmetry (r^2 change 0.029, $p<0.0001$) and disc area asymmetry (r^2 change 0.024, $p<0.0001$).

Mean (median) planimetric vertical cup-disc ratio asymmetry in this study was 0.07 ± 0.08 (0.05). 97.5th percentile of VCDR asymmetry was 0.32, with the 99.5th percentile being 0.42. VCDR asymmetry was significantly higher among persons who had no physiological cupping in any one eye ($p<0.0001$). When persons with absence of cupping in any one eye were excluded, 97.5th percentile was 0.2 and 99.5th percentile was 0.27. VCDR asymmetry also showed a significant association with disc area asymmetry (r^2 change 0.08, $p<0.0001$).

Conclusions: We report normative optic disc measurements among South Indians. Their comparison with other racial groups, and implications for South Indians are discussed.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

- **Figure 3.5.4:** Correlation between clinical and planimetric estimates of vertical cup-disc ratio (VCDR)
- **Figure 3.6.1:** Scatterplot of rim area asymmetry (right minus left) versus disc area asymmetry (right minus left). Trend line displayed. Regression equation and R^2 (co-efficient of determination) value displayed in the top right corner.
- **Figure 3.6.2:** Scatterplot of rim area asymmetry (right minus left) versus intraocular pressure (IOP) asymmetry (right minus left). Trend line displayed. Regression equation and R^2 (co-efficient of determination) value displayed in the top right corner.
- **Figure 3.6.3:** Scatterplot of cup area asymmetry (right minus left) versus disc area asymmetry (right minus left). Trend line displayed. Regression equation and R^2 (co-efficient of determination) value displayed in the top right corner.
- **Figure 3.6.4:** Right eye (RE) and left eye (LE) optic disc photographs of the same subject demonstrating no physiological cupping in the RE and VCDR 0.54 in the LE.
- **Figure 3.6.5:** Scatterplot of vertical cup-disc ratio (VCDR) asymmetry (right minus left) versus disc area asymmetry (right minus left). Trend line displayed. Regression equation and R^2 (co-efficient of determination) value displayed in the top right corner.

ABBREVIATIONS

- ANOVA: Analysis of Variance
- APEDS: Andhra Pradesh Eye Diseases Study
- BDES: Beaver Dam Eye Study
- BEAS: Bridlington Eye Assssment Study
- BMES: Blue Mountains Eye Study
- CCT: Central Corneal Thickness
- CDR- Cup-Disc Ratio
- CGS: Chennai Glaucoma Study
- CI: Confidence Interval
- CRA: Cilioretinal artery
- CSLO: Confocal Scanning Laser Ophthalmoscope
- D: Dioptre
- DA: Disc Area
- DBP: Diastolic Blood Pressure
- ETDRS: Early Treatment Diabetic Retinopathy Study
- FDP: Frequency Doubling Perimetry
- HCDR- Horizontal Cup-Disc Ratio
- HDD: Horizontal Disc Diameter
- HRT: Heidelberg Retina Tomograph
- ICC: Intraclass Correlation
- IOP: Intraocular Pressure
- IR: Inferior Rim
- ISNT rule: Inferior Rim>Superior Rim>Nasal Rim> Temporal Rim
- LOCS: lens Opacities Classification System
- logMAR: logarithm of minimum angle of resolution
- OCT: Optical Coherence Tomography
- ONH: Optic Nerve head
- ONHA: Optic Nerve Head Analyser
- P: Probability

- R: Correlation Co-efficient
- R^2: Co-efficient of Determination
- RA: Rim Area
- RODA: Rodenstock Optic Disc Analyser
- SD: Standard Deviation
- SR: Superior Rim
- VCDR- Vertical Cup-Disc Ratio
- VDD: Vertical Disc Diameter
- VES: Vellore Eye Survey

CHAPTER-1

INTRODUCTION & REVIEW OF LITERATURE

Planimetry of the optic disc refers to measurement and study of the areas of the optic disc and its constituent parts – the cup and neuroretinal rim. However, in the literature, the term "planimetry" has been used to include linear (diameters, width etc.) as well as area measures[1, 2]. As a prelude to the current thesis that deals with planimetric optic disc data in perimetrically normal South Indians, this literature review deals with the importance of collecting this information, various methods described in the literature to do so and the results of various reported planimetric studies of the optic disc.

1.1. WHY IS OPTIC DISC PLANIMETRY IMPORTANT?

Optic disc examination is vital to the diagnosis of glaucoma. However, as is true of most biological variables, human optic discs exhibit a great range of variability in relation to shape, size, and relationships between its constituent parts. Several systematic studies have succeeded in accounting for a part of this variability by demonstrating its dependence on various factors like age, race[3], refractive error[4], height[4], axial length[5] and many more. However, there still persists a huge range of variability that makes it difficult to arbitrary limits of 'normal' and 'abnormal' with good diagnostic performance to large numbers of people.

In order to decrease some of this variability, cup-to-disc ratios (CDRs) have evolved as important clinical tools in evaluating the optic disc. Glaucoma progresses by expansion of the cup, and cup-disc ratios measure this expansion. It partly accounts for one of the most important physiological factors in variability of cup size- the size of its container, the optic disc. Cup-disc linear ratios have been a long standing and time tested method of documenting disc change in glaucoma[6] and are currently the most important single parameter for the diagnosis of glaucoma in epidemiological studies[7]. They are easy to measure and require no sophisticated equipment. Sectoral cup-disc area ratios are the basis for the Moorfields Regression Analysis of the Heidelberg Retina Tomograph (HRT) for detection of glaucoma[8] - either at first examination or on serial follow-up examination.

However, in spite of better consistency between people, the CDR is by no means a perfect measure and has been shown to exhibit a fairly wide range even among normal persons. A simple arbitrary cut-off value (e.g. vertical CDR of 0.6 or 0.7), would, therefore have poor

diagnostic ability, with high rates of under diagnosis or over diagnosis depending on the nature and distribution of these confounding factors in the population.

What we would like best, of course, is a clear definition of what constitute normal and abnormal, which is, however, easier stated than done. The first logical step would be to define the observed limits of normal from well -conducted population based studies with adequate sample sizes avoiding selection bias, and clear definitions of disease. The next step would be to study the relationships of these values with physiological factors to better define the limits of normality. Both these issues have been addressed by several studies,[4, 9, 10] though only in some racial groups. Planimetry enables a continuing search for quantitative and repeatable structural and spatial information about the optic disc, and exploration of the relationships between disc parameters and other biological parameters, thus contributing to the quest for earlier and better diagnostic indicators for glaucoma.

1.2. METHODS OF OBTAINING PLANIMETRIC DATA

A wide variety of methods have been used by different authors to obtain optic disc measurements. These range from simple measurement techniques used at the slit lamp to assessment of optic disc photographs by custom software, to automated optic nerve analysers (OHNA). With widespread availability and ease of use, more and more morphometric data are collected using the ONHA devices. Each method, however, has its own advantages and limitations. The different methods are discussed below.

Clinical Measurement

Direct ophthalmoscopy[11]

The 5 degree spot of light from the Welch–Allyn ophthalmoscope projects a circle of light with diameter of 1.5mm and an area of 1.8 sq mm on the retina when the ophthalmoscope is held in the usual range used for ophthalmoscopy. The spot may be aligned either over or adjacent to the optic disc and the size of the optic disc is compared to the size of the spot of light. If the optic nerve head is smaller than the spot of light, the disc can be estimated as small. If the optic nerve head is more than 1.5 times the size of the light spot, the optic disc is large.

Slit lamp indirect ophthalmoscopy[12]

These methods involve use of a fundus viewing lens - +90 D[13], + 78 D[14], +60 D[15], Goldmann lens[16] or the Zeiss 4- mirror lens[17]. Using either a slit beam of adjustable length, or an eyepiece graticule, and appropriate correction factors (X1.0 for + 60D lens, X 1.1 for 78D lens and X1.3 for 90D lens), the vertical and horizontal diameters of the optic disc and optic cup can be measured. The formula for the area of an ellipse can be used to obtain area measurements of the optic disc and cup, and neural rim area could be calculated as the difference between disc area and cup area[16]. The greatest advantage of this technique is that it requires no sophisticated equipment and provides the clinician with a working idea of the disc size. Measurements made with the +78 D and Zeiss contact lens have been reported to correlate well with computerized image analysis.[18] However, significant interobserver variation has been reported for clinical disc biometry.[19]

Use of a graded template of circles

This method was first described by Klein et al[20] and has been used to make optic disc measurements in the Beaver Dam Eye Study (BDES) as well as the Blue Mountains Eye Study[10] (BMES). The technique involved optic disc stereo-photography with a telecentric fundus camera, and processing of photographs to yield a pair of 2"x2" colour slides. The slides were placed on a slide sorter and examined using a Donaldson Stereoviewer. A plastic template with small circles ranging from 1/32 to 1 ¼ inches in diameter in 1/64 to 1/32 inch increments was used (Pickett, small circles no.1203). The grader placed it under the right slide of the stereo pair. The circle whose diameter coincided with the margins of the structure being measured was found for the longest and shortest disc and cup diameters. The rim width was calculated as the difference between disc diameter and cup diameter. The Blue Mountains Eye Study corrected for ocular magnificent using spherical equivalent correction as described by Bengsston and Krakau[21].

Good interobserver agreement was reported for this method,[10,20] which required no sophisticated equipment. However, it was not possible to directly obtain area measurements using this technique.

Use of projected photographs and digitized image analysis

This method was described and has been extensively used by Jonas et al.[22] Stereo optic disc 15 degree photographs were taken with a Zeiss fundus camera equipped with an Allen stereo separator. The slides were projected in a scale of 1:15. The outlines of the disc and cup were plotted on paper, which was digitized and morphometrically analysed using the Zeiss morphomat image analysis system. Ocular and photographic magnification was corrected using Littmann's correction (refraction and keratometry).[23] For disc and cup, area, horizontal and vertical diameters, maximum and minimum diameters, and a form factor were measured. Neural rim width, area, and sectoral areas were measured, as were areas of alpha and beta zones of parapapillary atrophy. Various ratios were calculated. Good interobserver repeatability has been reported by Jonas et al.[24]

Computer assisted planimetry of digital photographs

With the widespread use of digital photography with its inherent advantages of easier storage, retrieval and low cost, several centres have developed their own software for digital analysis of the photographs[25, 26, 27, 28, 29, 30, 31, 32]. Digital stereo pairs of optic disc photographs are obtained, which are displayed side by side on a computer screen. A stereo viewer is used and the margins of the disc and cup are marked on one of the digital images (usually with the computer mouse). Depending on the capabilities of the software, various measures are generated e.g. disc area, cup area, disc diameters, cup diameters etc. and other derived parameters can be calculated. Some examples of these systems are the DISC- DATA (used by Garway Heath DF et al),[25] the Discam stereo camera (Shuttleworth et al)[26] and the commercially available Zeiss FF450 fundus camera[27] and VISUPAC image archiving system. Other digital systems of morphometry are the AutoCAD R.14.0 Autodesk system (Sanchez-Perez et al),[28] soft imaging system analySIS (Nguyen NX et al),[29] and custom software used by Kwon YH et al,[30] Moya FJ et al,[31] Sekhar et al.[32] The systems used by Nguyen et al and Kwon et al utilized digitized versions of photographs that were originally captured on film. Good repeatability has been demonstrated with this technique of planimetry,[26, 28] which however, was better for an experienced observer compared to an experienced one.[25]

Different methods of correction for ocular magnification in fundus photographs has been described.[21,23,33] Some of the formulae correct for ametropia only (Bengsston & Krakau 2), some

for keratometry and ametropia (Littmann 1, Bengsston & Krakau 3) and some for axial length (Bennett, Rudnicka & Edgar 2, Littmann 2). A comparative study of 10 different formulae against one that uses most biometric information (Bennett, Rudnicka & Edgar 1) found that methods that include axial length provide most accurate values.[34]

All techniques described thus far require the operator to define the disc as well as cup margins. While the definition of the disc is fairly uniform (as the inner edge of the peripapillary scleral ring of Elschnig), studies differ in the way the cup edge is defined and this is an inherent source of variability between different planimetric studies. While some studies define the cup edge as the point where the rim contour steepens,[25] others define the cup edge as the point where cup first seems to deviate posteriorly,[26] Moya et al[31] define the cup margin at an imaginary intersection between the optic disc surface and a plane at the level of the sclera. The Ocular Hypertension Treatment Trial[35] provided a clear and simple definition – when the cup is cylindrical, the demarcation is clear; when the cup is conical, the plane midway between the surface of the disc and the depth of the cup is used as a reference plane. This definition has also been used by Kwon et al.[30]

Automated segmentation using pixel feature classification[36]

Pixel feature classification is a machine learning technique that can be used to assign a class to the pixels in an image, and thus automatically identify and measure optic disc landmarks. Pixel feature classification uses multiple pixel features, which are numeric properties of a pixel and its surroundings. Originally, pixel intensity was used, and later, its contrast with the surrounding region, its proximity to an edge, and so forth, were added. Horizontal stereo disparity can be incorporated as a pixel feature. As a supervised algorithm, it has two stages: a training stage, in which the algorithm "statistically learns" to classify pixels correctly from known classifications, and a testing or classification stage, in which the algorithm classifies new, previously unseen images.

Abramoff et al [36] evaluated an automated pixel-based algorithm developed by them and trained on a set of photographs taken with a fixed-base (Nidek) stereo-camera and graded planimetrically by 3 glaucoma experts. They reported that the algorithm performed as well as 3 fellows-in-training in estimating cup-disc ratios and concluded that the algorithm permits objective segmentation of the optic disc, and is a promising tool for objective evaluation of optic

disc cupping. However, the authors report about 12% incorrectly classified pixels with their method.

Rodenstock Optic Disc Analyser (RODA)[37]

This was among the earliest Optic Nerve head Analysers to be used on a large scale. It is now no longer manufactured, and better, more repeatable analysers have become available since. It is discussed in brief as it has been used in the past for collection of optic disc morphometric data.

The RODA uses a stereoscopic video camera to produce digitized images while projecting two sets of seven evenly spaced lines on the optic nerve head. Disparity between the corresponding points of light stripes of stereo pairs is used to generate vertical contour lines and 3 D contour maps. The disc margin is defined manually by selecting 4 points - the machine then fits an ellipse that outlines the disc. The cup margin is defined by constructing a reference plane corresponding to the level of the peripapillary retina. The parameters measured by the RODA are disc area, neural rim area, cup volume, cup-disc ratio, disc diameter and disc elevation. In addition to complexity and poor repeatability, the magnification correction was also not accurate in the RODA.

The Topcon Imagenet system

This semiautomated system of optic disc imaging and analysis was used by the Baltimore Eye Survey[9] and the Rotterdam Eye study[4.] to analyse optic disc photographs taken as part of the respective studies. Optic disc stereo photographs were first obtained using a Topcon SS simultaneous fundus camera. Stereo transparencies were digitized and analysed with the Imagenet system. For this, the technician marks four points along the edge of the optic disc and the machine fits an ellipse to represent the optic disc margin. The technician also defines a zero reference plane by marking five to eight corresponding points on both members of a stereo pair. The machine uses the parallax between pairs of corresponding points to determine the topography of 600-800 points within the optic disc margin. The cup margin is automatically defined as 150 microns lower than the most elevated peripheral point on the disc surface. Parameters generated are disc area, cup area, rim area and cup-disc ratios (vertical and

horizontal). Magnification correction is done using Littmann's correction (keratometry and ametropia). Repeatability has been reported to be very good between observers[4, 9].

The Glaucoma- Scope[38]

The Glaucoma scope consists of an optical head mounted on a slit lamp assembly, which includes a raster pattern projection system and a video camera to capture images. Approximately 25 parallel horizontal dark and light pairs are projected at an angle of 9° to the optic nerve head (ONH) using near infrared light (750 nm). As the lines pass over the surface of the ONH they are deflected proportional to the depth of the surface. A video image records these deflections and computer algorithms translate them into depth numbers. The reference surface for the depth measurements is defined by linear interpolation of data falling in two vertical columns placed 350 µm nasal and temporal to the disc margin. The operator selects a reference point for future image registration and outlines the disc margin (eight points) and major vessels to provide landmarks on the printout. The older version of the instrument only provided a greyscale and numerical thickness values of the disc and peripapillary nerve fibre layer. Version 3.12 also presents a three dimensional image with the calculation of different ratios and measurements - disc area, cup area, disc diameters, and cup-disc ratios. The cup edge is drawn at the 120 µm depth boundary inside the disc. Magnification correction is by the method of Bengsston and Krakau (ametropia).

Confocal Scanning Laser Ophthalmoscope[39]

Confocal scanning laser ophthalmoscopy (CSLO) is a real-time imaging technique that produces multiple coronal optical cross-sections of the retina and optic nerve head (ONH), which are then combined to give a three-dimensional image of the optic nerve head (ONH). It is based on the principle of spot illumination and spot detection. The system uses a pair of conjugated pinholes located in front of the light source and the light detector components. This pair ensures that only light reflected from a defined focal plane will reach the light detector. The device moves the focal plane to acquire sequential images. Reconstructing the series of scans at the various focal planes creates a three-dimensional topographic representation of the surface that is scanned.

The Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany) is a widely used CSLO device. The HRT uses a diode laser beam (wavelength, 670 nm) and captures a series of 32 sequential two-dimensional scans in a total acquisition time of 1.6 seconds. The optical transverse resolution of the HRT is 10 μm and the axial resolution 300 μm .

The operator is required to trace the ONH margin. Based on this contour line, the HRT operation software automatically defines the reference plane. This plane is located 50 μm posterior to the mean surface height along a 6-degree arc at the inferotemporal region of the contour line. The reference plane is then used as a topographic cut-off. Structures below the plane are defined as optic cup and structures above the plane as neuroretinal rim.

Among several stereometric parameters generated are disc area, cup area, rim area, cup-disc area ratio, cup volume, rim volume and cup depth. Measurements with the HRT have been found to be highly reproducible in numerous studies.[40, 41] Three versions of the HRT have been available-of these, HRT III is the most recent and HRT II is the previous version. Most planimetric data using the HRT available today has been obtained with the HRT II.

One method of HRT-II software analysis, Moorfields regression analysis (MRA), uses a program that compares the subject's optic nerve and RNFL parameters to a normative database of 112 subjects, all of whom were white and had ametropia of less than 6 diopters.[42] The HRT-III was designed to incorporate a new,expanded, race-specific database to account for this problem. This new normative database consists of 733 eyes of whites and 215 eyes of blacks.[43] This database was found to increase sensitivity with comparable specificity among white patients, but increased sensitivity at the expense of specificity among black patients.

The operator-marked contour line is an important source of variability in HRT measurements. Hatch et al[44.] assessed the interobserver agreement of HRT parameters reflecting the variation in contour line placement. The interobserver agreement was substantially better for parameters not dependent on the contour line than for those that are dependent on the contour line.

In many cases, the HRT analyses incorporate blood vessels into the neuroretinal rim. This inclusion has been suggested as the reason for the higher HRT rim measurements when compared with the findings of optic disk photograph planimetric evaluation.[45, 46]

The ease of use and widespread availability of the HRT have made it a useful tool to obtain normative optic disc measurements on large numbers of people [47, 48] However, the HRT does not directly make linear measurements i.e., linear disc diameters, cup diameters or cup-disc ratios, which are the most commonly assessed clinical parameters. This is one of the drawbacks of using the HRT to obtain normative planimetric measurements.

Though the HRT is the most popular CSLO, there are other CSLOs based on the same principle – the Rodenstock CSLO and TopconSS CSLO. The latter has been used mainly in Japan and Korea.

Optical Coherence Tomograph (OCT) [39]

Optical Coherence Tomography permits high resolution cross-sectional imaging of the human retina using light. It is based on the principle of Michelson interferometry. OCT is a non-invasive, non-contact technique that uses a light source consisting of a near-infrared, low-coherence superluminescent diode laser (wavelength 850 nm) split at a 50/50 beam splitter into two arms. One arm sends light to the actual sample (the eye), and the other sends light to a reference mirror. The distance between the beam-splitter and reference mirror is continuously varied. When the distance between the light source and retinal tissue is equal to the distance between the light source and reference mirror, the reflected light from the retinal tissue and reference mirror interact to produce an interference pattern. The interference pattern is detected and then processed into a signal. The signal is analogous to that obtained by A-scan ultrasonography using light as a source rather than sound. A two-dimensional image is built (analogous to a series of stacked A-scans) as the light source is moved across the retina. A transverse sequence of longitudinal measurements is used to construct a false colour topographic image of tissue microsections that appears remarkably similar to histological sections. The OCT image can be displayed on a gray scale where more highly reflected light is brighter than less highly reflected light. Alternatively, it can be displayed in colour whereby different colours correspond to different degrees of reflectivity. On the OCT scanners currently commercially available, highly reflective structures are shown with bright colours (red and white), while those with low reflectivity are represented by darker colours (black and blue). Those with intermediate reflectivity appear green. Digital processing aligns the A-scans to correct for eye motion. Digital smoothing techniques are used to further improve the signal-to-noise ratio.

The newer generation of OCT-spectral domain OCTs[49] - utilize the spectral properties of light to obtain very high resolution scans in rapid acquisition times. Their axial resolutions are claimed to be about 4 microns. However, it is still early days with these machines and further data may become available over time.

The ONH scan of the OCT3 which makes planimetric measurements is composed of six radial scans across the optic disc and centred at the optic disc centre. With the six cross-sectional line scans, the ONH analysis measures the amount of nerve fibre at the optic nerve head. The termination of the retinal pigment epithelium on either side of the ONH is identified as the disc margins. The distinction between the optic cup and neural rim is made at a line parallel to the line joining the 2 ends of the RPE across the optic disc, with an anterior offset of 150 microns. The cup offset is 150 μm by default and is adjustable. The placement of the disc reference points is also adjustable. Contour diagrams of the optic disc and optic cup are displayed as created from the data obtained from all six radial scans. The individual radial scan analysis gives rim area in vertical cross-section, average nerve width at the disc, disc diameter, cup diameter, horizontal rim length, and cup offset. The optic nerve head analysis results give vertically integrated rim area volume, horizontally integrated rim width, disc area, cup area, rim area, cup/disc area ratio, cup/disc horizontal ratio, and cup/disc vertical ratio.

Very high axial resolution and automatic definition of both disc and cup margins are inherent strengths of this method - however, limited transverse sampling may be a source of error. It is likely that the unscanned areas between the linear spokes and the unsampled points along each spoke also contribute to variation in OCT measurements. Also, errors in automatic detection of the disc margin in 53% of cases was reported in one study.[50]

Comparison Of Methods

A meta-analysis[51] of various studies of optic disc area measurements showed that compared to planimetry of photographs taken with the Zeiss fundus camera, the Topcon fundus camera, the HRT, the Topcon SS CSLO and the RODA made smaller measurements in similar populations. They calculated normalization factors of 1.04 for the Topcon fundus camera, 1.15 for HRT, 1.29 for the Topcon SS CSLO and 1.51 for the RODA compared to the Zeiss camera (1 by definition). Other studies have also shown consistently lower measures with the HRT compared to clinical planimetry[2, 45] and to the Imagenet system[2]. In the Beijing eye study, the

measurements obtained by planimetry of the digitised optic disc photographs (Canon fundus camera) and the measurements performed by confocal laser scanning tomography differed by a linear factor of 1:1.02 from each other.

Consistent with the above, in the VES, mean area of the optic disc was significantly smaller in the HRT than in the planimetric measurements of the clinical photographs . The mean difference in optic disc area between both techniques was 0.33 mm^2. Expressed as percentage of the disc area as measured by the HRT, it was 16.4% . Mean area of the optic cup was also significantly smaller in the HRT than in the planimetric measurements of the clinical photographs.[52] The area of the neuroretinal rim did not, however, differ significantly between the two techniques. Expressed as percentage of the disc area, the optic cup area covered a significantly larger proportion of the optic disc when examined by the photographic technique (37.0%) than that of measured by HRT (24.7%). The narrowest rim was temporal by both techniques, however the widest rim was inferior by photographic assessment but nasal by the HRT. As the optic cup area measurements were significantly larger in the photographic technique than that of HRT, the horizontal and vertical cup/disc diameter ratio were also significantly larger in the photographic method .

In contrast, Garway-Heath et al reported no difference in optic disc size estimates between planimetric and CSLO measurements in healthy subjects.[53] Measurements made with the HRT have been shown to have lower interobserver variation than planimetry, and also independent of observer experience.[25]

Measurements made by the OCT and HRT[54] have been shown to correlate highly, but with larger measures recorded by the OCT. In a study comparing CDRs measured by HRT II, OCT and stereophotographs, largest measures of VCDR were obtained with OCT and smallest with the HRT.[55]

1.3 RESULTS OF PLANIMETRIC STUDIES

For convenience, results of planimetric studies in the literature are divided into 3 parts – absolute values of disc measurements, interrelationships between optic disc structures, and relationship of optic disc structures with other biological variables.

Absolute Values Of Disc Measurements

Optic disc size

Large inter-individual variations in disc morphology have been have been reported, even within populations. Jonas et al reported that the optic disc area ranged from 0.80 to 5.54 mm^2 among normal subjects in their study population - an inter-individual variability of 1:6.9.[22] They also reported that discs with steep, punched out cups were significantly larger than discs with temporal, flat slopes and discs with no cups. In the same study, optic cup area ranged from 0 to 3.41 mm^2 and neuroretinal rim area displayed an interindividual variability of 1:5.8.

Ramrattan et al reported twofold variations in disc area and threefold variations in neuroretinal rim area in a sample of 894 eyes drawn from the target population of the Rotterdam eye study in the Netherlands[4]. In a recent study of optic discs of 70 randomly selected subjects from participants of the Vellore Eye Study,[56] Jonas et al reported an inter-individual variability of 1:3.6 for disc size. Among Chinese participants of the Beijing Eye Study, variability of 1:6.4 was reported.[57]

Table 1.3.1 presents the available planimetric data from different large studies in different populations. Note that methods of obtaining the planimetric information are different in different studies.

Optic disc and cup shape

Optic disc shape is an important determinant of the morphology of the optic disc, as the shape of the scleral canal can be expected to influence the position of nerve fibres on it, and recognition of normal variations are vital to avoid over-diagnosing diseased states.

Jonas et al in their study of 457 normal eyes, reported that on average, the form of the optic disc is slightly oval vertically, with the vertical diameter being 9% longer than the horizontal one. Average vertical diameter of the optic cup, on the other hand, was slightly smaller than the average horizontal diameter. They described 3 types of discs based on type of

Table 1.3.1: Planimetric Optic Disc Data From Different Studies

	Jonas et al [22] (Mean ± SD)	Ramrattan et al[4] (Mean ± SD)	Jonas et al (VES)[56] (Mean ± SD)	Sekhar et al (APEDS)[32] (Mean ± SD)	Varma et al[9] (Blacks)	Varma et al[9] (whites)	Healey et al (BMES)[10]	BEAS (47) (UK)	Beijing eye study (57)	Japanese study (48)
Method	Zeiss photography, digital morphometry	Topcon Imagenet	Zeiss photography, digital morphometry	Digitized photographs, custom software	Topcon Imagenet	Topcon Imagenet	Graded circles template	HRT 2	Canon photography, digital morphometry	HRT 2
Sample size	457	894	70	143	1534	1853	3654	918 eyes (459 pts)	4027	223
Optic disc area (mm2) (range)	2.69±0.70	2.42±0.47	2.58±0.65	3.36±0.68	2.94	2.63	Not available	1.98± 0.36	2.64 ± 0.52	2.16 ± 0.49
VDD (mm) (range)	1.92±0.29	Not available	1.87±0.24	2.12±0.231	Not available	Not available	1.51	NA	NA	NA
HDD (mm) (range)	1.76±0.31	Not available	1.7±0.22	1.97±0.19	Not available	Not available	Not available	NA		NA
Optic cup area (mm2) (range)	0.72±0.70	0.57±0.34	0.98±0.40	0.57±0.34	1.04	0.71	Not available	0.45±0.35	NA	0.59 ± 0.36
VCD (mm) (range)	0.77±0.55	Not available	1.06±0.23	Not available	Not available	Not available	0.66	NA	NA	NA
HCD (mm) (range)	0.83±0.58	Not available	1.16±0.23	Not available	Not available	Not available	Not available	NA	NA	NA
VCDR (range)	0.34±0.25	0.49±0.14	0.56±0.08	0.36±0.09	0.56	0.49	0.43	NA	NA	NA
HCDR (range)	0.39±0.28	0.40±0.14	0.66±0.07	0.38±0.09	Not available	Not available	Not available	NA	NA	NA
Cup/disc area ratio	Not available	Not available	0.37±0.08	0.16±0.07	Not available	Not available	Not available	0.22±0.14	NA	0.26±0.12
Neuroretinal rim area (mm2)	1.97±0.50	1.85±0.39	1.60±0.37	2.79±0.52	Not available	Not available	Not available	1.52±0.31	NA	1.57±0.33

VES: Vellore Eye Study

APEDS: Andhra Pradesh Eye Diseases Study

BMES: Blue Mountains Eye Study

BEAS: Bridlington Eye Assessment Study

cupping- no cups, steep, punched out cups and cups with temporal flat slopes. They reported that discs with steep cups had more circular cups than discs with temporal flat slopes.

In the Vellore Eye Study, again the vertical disc diameters (VDD) were about 6% longer than the horizontal disc diameters (HDD). They reported that in10 eyes (14.3%), HDD was longer than VDD. In another paper, the authors report that the horizontal optic cup diameter was significantly ($p < 0.05$) longer than the vertical cup diameter indicating a horizontally oval shape of the optic cup.[52]

Of 3583 participants of the BMES, inferior or nasal optic disc tilting was reported in 77 eyes of 56 participants (1.6%). Prevalence of tilted discs was significantly associated with astigmatism, myopic spherical refractive error, beta zone of peripapillary atrophy and visual field defects.

Neuroretinal rim shape

The healthy neuroretinal rim in normal eyes is usually broadest in the inferior rim, followed by the superior and nasal rims, and thinnest in the temporal disc region. This pattern of rim width is known as the ISNT rule (inferior > superior > nasal > temporal). The ISNT rule was originally described by Jonas et al after assessment of optic disc photographs of 457 normal eyes and is a useful rule to identify suspect eyes in clinical practice.[22] The most important aspect of this rule is that the temporal rim is the thinnest.

In the VES, while the neural rim was significantly thinner temporally, it was not significantly different between the other 3 regions.[56]

When the ISNT rule is not obeyed, glaucomatous damage must be suspected. This rule should be carefully evaluated, however, because the inferior sector of the optic disc may not show thickest rim in 37.8% of normal eyes.[58]

In another recent study that examined 66 normal subjects and 45 patients with glaucoma, the ISNT rule was intact in 52 (79%) of 66 normal eyes and 12 (28%) of 43 glaucomatous eyes ($P<.001$) Among subjects with normal eyes, the proportion of subjects adhering to the ISNT rule did not differ by race.[59]

In yet another hospital-based study from northern India, Sihota et al reported that the ISNT rule was applicable in 71% of normal eyes and 68% of early glaucoma eyes. The percentages reported are for rim area as calculated using the HRT. The characteristic

configuration of a normal optic disc with the rim width being greatest in the inferior disc region followed by the superior disc region was maintained even in most patients with early glaucoma.[60]

In a separate publication, Jonas et al evaluated the rim width ratios (inferior to temporal rim width and superior to temporal rim width) in normals, ocular hypertensive and glaucoma patients.[61] In the normal subjects, inferior to temporal rim width ratio was significantly higher than superior to temporal rim width ratio . They also found that both ratios were significantly higher the more vertically the optic disc was configured. The reason for this is that in horizontally oval shaped optic discs, the retinal nerve fibre bundles have a longer part of the disc circumference to enter the optic nerve head than they have in vertically oval optic discs. Correspondingly, the retinal nerve fibres in the inferior and superior disc regions are more crowded in vertically oval optic discs than in horizontally oval discs. This led to a broader neuroretinal rim in the inferior and superior disc regions, and consequently to higher inferior to temporal rim width ratio and superior to temporal rim width ratio in vertically elongated optic nerve heads than in horizontally shaped optic discs.

Due to the anatomy of the optic nerve head, the border of the optic disc can more easily be detected in the temporal, inferior, and superior regions than in the nasal region. Also, it is easier to demarcate the inner margin of the neuroretinal rim in the inferior and superior disc regions than in the nasal disc sector, as the central retinal vessel trunk and the major retinal vessels lie on the neuroretinal rim and its border with the optic cup. Since difficulties in outlining the margins of the optic disc and optic cup may lead to inaccuracy in measuring the neuroretinal rim, Jonas et al evaluated in another study of 649 normals and 1337 glaucoma patients how important the assessment of the nasal sector of the optic disc is for the detection of glaucomatous optic nerve damage.[62] They found that the highest diagnostic power for the separation between the normal group and glaucoma groups, had the sum of inferotemporal rim area plus superotemporal rim area, the sum of inferotemporal rim area plus superotemporal rim area plus temporal rim area, and the inferotemporal rim area as single parameter. The lowest diagnostic precision had the nasal rim area as single parameter or in combination with rim measurements in other disc sectors.

Interrelationships Between Optic Disc Structures

Disc area vs. cup area

A positive association between disc size and cup size has been reported by numerous authors and is a commonly accepted fact.[9, 10, 22, 56, 22, 47, 56] In Jonas' study, discs with no cups were significantly smaller than the average disc size.

Rim area vs. disc area and type of cup

Neural rim area has also been shown to correlate positively with disc area.[4, 22, 56]. Jonas et al also showed that the slopes of linear regression lines between rim area and disc area were dependent on configuration of the cups i.e., the slopes were steeper for cups with temporal flat slopes and less steep in discs with steep punched out cups.[63]

Cup-to-disc ratios

Cup-disc ratio also shows a positive correlation with disc size. [10, 32, 56, 64] Small discs tend to have lower cup-disc ratios while large discs have larger ones. This may cause erroneous diagnosis of glaucoma in large discs when, in fact, it is only a large physiological cup. On the other hand, early glaucoma is easily missed in small discs if disc size is not taken into account.

Cup size is related physiologically to disc size and enlarges pathologically in glaucoma. Therefore a measure that adjusts cup size for disc size – cup-to-disc ratio would be a simple, robust indicator of glaucomatous loss of the neuroretinal rim. Though it does serve as a clinically useful measure to assess relative amount of cupping, it is still not completely free of disc-size related and other biological variability.

The recent ISGEO classification of glaucoma[7] that provides a standardized definition of glaucoma for epidemiological surveys suggest that statistical limits of normal and abnormal cup-disc ratios be derived from normals in each population, for application to identify glaucoma in the same population, combined with other criteria. Thereby, the classification attempts to standardize diagnostic criteria for glaucoma, while accounting for racial variability of disc dimensions.

In the BMES, a linear relation between median VCDR and VDD was observed. The median VCDR increased from 0.33 for 1.2 mm optic discs to 0.55 for 1.9 mm optic discs. The 95th, 97.5th, and 99th percentiles showed a linear relation to vertical optic disc diameter. The 97.5th percentile increased from 0.6 for 1.2 mm optic discs to 0.75 for 1.9 mm optic discs, and from 0.62 to 0.83 for the 99th percentile.[65] They reported that small (1.1–1.3 mm) and large (1.8–

2.0 mm) discs formed a significant proportion of the population (16.1% and 9.0%, respectively). This suggests that approximately 1 in 4 optic discs require an adjustment to the 0.7 rule. Very small (microdiscs) and very large (macrodiscs) on the other hand are uncommon.

In an unselected cohort of 457 normal optic nerves, Jonas et al reported a range 0–0.87. Horizontal CDR was significantly larger than vertical CDR. In 31 of 338 optic discs with physiological cupping (9.2%), were horizontal CDR larger than VCDR. They also reported that vertical and horizontal CDR estimates were smaller in discs with temporal flat slopes compared to discs with steep cups.[22]

In the VES, too, the horizontal cup/disc diameter ratio was significantly ($p < 0.05$) larger than the vertical cup/disc diameter ratio. In 3 subjects (4.3%), horizontal CDR was greater than VCDR. Also, while horizontal and the vertical cup/disc diameter ratios were significantly correlated with the optic disc area ($p < 0.005$) , the ratio of horizontal to vertical cup/disc diameter ratio was statistically independent of the optic disc size ($p > 0.25$).[56]

Asymmetry of optic disc parameters

Optic disc parameters are largely symmetrical between both eyes of normal subjects. While this is true for absolute measures, it is even more so for ratios, and asymmetry of cup-disc ratio is considered one of the diagnostic indicators of glaucomatous cupping.[7]When examining genetic associations with cup- disc ratio assessed by direct ophthalmoscopy in a sample of 1098 subjects, Armaly found that 67% had no cup-disc ratio asymmetry, whereas 92% had cup- disc ratio asymmetry of 0.1 or less, and 99% had asymmetry of 0.2 or less.[66]

The Baltimore Eye Survey assessed 4877 subjects and reported vertical cup-disc ratio asymmetry of 0.2 or less in 98% of black subjects and in 96% of white subjects.[9] Jonas et al reported optic disc area differences of 0.5 mm^2 or less in 80% of normals and VCDR and HCDR asymmetry of 0.2 or less in 96% of normals. Asymmetry in type of cupping was detected in 10% of patients.[22] In the BMES, cup-disc ratio asymmetry of 0.2 or more was found in 24% of patients with OAG, compared with 1% of patients with OH and 6% of normal subjects. Corresponding rates for cup-disc ratio asymmetry of 0.3 or more in these three groups were 10%, 0%, and 1%, respectively. Cup-disc ratio asymmetry was associated with disc diameter asymmetry and intraocular pressure asymmetry. However, these two factors explained only 3%

of the variability of cup- disc ratio asymmetry and 20% of cup diameter asymmetry. Disc diameter asymmetry was related to refractive error difference between the eyes.[67]

The BEAP examined asymmetry in HRT parameters between the two eyes of 459 normal elderly people. Increases in the difference in disc area (larger disc minus smaller disc) were significantly related to increases in the difference in global rim area. However, increasing disc area difference was related to only a small change in the magnitude of global rim-to-disc area ratio asymmetry of marginal significance, confirming that ratio based parameters are less affected by disc size that absolute measurements.[68]

Relationship Of Optic Disc Parameters With Other Biological Parameters

Race

Racial differences in optic disc size have been reported by several authors.[3, 9, 69] Blacks have been consistently shown to have larger discs than whites. The Baltimore eye survey showed that on average, blacks had larger disc areas, larger cup areas, larger cup-disc ratios, similar rim areas and smaller disc area to rim area ratios. The Ocular hypertension Treatment Study, in their baseline CSLO study, report that blacks had larger disc area (12%), cup area and rim area compared to other participants - however the other associations disappeared on adjusting for disc size suggesting that larger discs among blacks were responsible for the other associations. [69] In another HRT-based study, Girkin CA et al reported similar results-significantly larger disc areas among black subjects that differences in optic disc parameters (including cup area, rim area, VCDR, cup-disc area ratio) between black and white populations were not significant after adjustment for differences in optic disc area and reference plane height.[70]

A meta-analysis of studies on optic disc size, which took into account different machines used by different studies also reported larger discs among blacks compared to white populations, with Asians falling between them.[51] The study of Indian eyes by Jonas et al[56] reported planimetric values similar to those of white people.

Age

Many of the large studies (Rotterdam study[4], Baltimore Eye Survey[9], Jonas et al[22] have found no association between planimetric variables and age among healthy adults. However, the Blue Mountains Eye Study did find larger cup diameter[81] and lower rim width among older age groups. After adjusting for IOP, however, the association was very weak. Tsai et al reported

smaller rim areas in elderly compared to young people. They however, also found smaller discs among the older people, which may have accounted for this finding.[71] Garway Heath et al reported significant and measurable decline in neural rim area of 0.28% to 0.39% per year.[51]

Gender

Several studies have reported slightly larger discs in men (2-3%) compared to women.[4, 5, 9, 51, 56] However, only some studies have reported a statistically significant association (Rotterdam, Japanese HRT study). No correlation between gender and planimetric variables was found by Jonas et al in their studies of Caucasians[22] or Indians[56] or Chinese (in the Beijing eye study).[57]

Refractive Error

The Rotterdam study[4] reported a weak relationship between myopia and larger discs (1.6% per D increase in myopia) as well as larger rims (1.4%). Their sample included high myopes and high hyperopes. Jonas et al found that when high myopes and hyperopes were excluded, there was no relationship between disc parameters and refractive error.[22] However, when high myopes and hyperopes were also included, a curvilinear relationship was seen with a steep change in disc size at myopia < -8D and hyperopia > + 4D.[74] A similar association was reported in the Beijing Eye study.[57]

The Baltimore Eye Survey found no significant relationship between refractive error and disc size. They found large variations in the extremes of refractive error, with no consistent relationship[9]. The Vellore Eye Survey, which had no high myopes or high hyperopes, also found no relationship between disc variables and refractive error.[56]

IOP

Among healthy individuals, two studies - the BMES [73] and the Baltimore Eye Survey[74] reported an inverse relationship between neural rim size and IOP. The Baltimore Survey reported that the relationship between IOP and neural rim area was linear among whites and quadratic among blacks.

Axial length

A positive association between disc area and axial length was reported by Miglior et al[5]. However, Britton et al, [75] Jonas et al[22, 56] found no association between morphometric parameters and axial length either among whites or among Indians. In another study (using HRT II) that

examined the relationship between axial length and disc area in 157 black and 124 white subjects, a weak correlation was found after adjusting for race ($r=0.13$, $p<0.035$). [76]

Others

A weak correlation inverse correlation between disc area and central corneal thickness (CCT) was reported recently[77] in a study of 72 glaucomatous eyes using HRT II images.

The Rotterdam Eye Study reported a weak linear association between height and disc size[4].

In view of reported racial variations in optic disc dimensions, Jonas et al examined association of disc size with iris colour, but found no such association.[78] In another study of 1973 eyes of 1012 Caucasian subjects with ocular hypertension or chronic open-angle glaucoma,[79] they reached the same conclusions.

The Thessaloniki eye Study examined 232 subjects planimetrically using HRT.[80] They found that in regression models, cup area, and cup-to-disc ratio were increased in subjects with normal diastolic blood pressure (DBP) that was the result of treatment, as compared with both the high DBP and untreated normal DBP groups. The authors discuss that this may have been due to the detrimental effect of low DBP and PP on optic nerve perfusion, and therefore, the neural rim.

The search for planimetric data continues. Large enough normative disc data are still not available for many population groups. These data, with enough numbers permitting exploration of relationships with adequate power are a necessary early step in the search for early diagnostic indicators for glaucoma. With newer, fully automated, and more repeatable measurements possible, this data is becoming technically easier to acquire. However, high cost is a restricting factor in the large-scale use of the ONH analysers in some countries. Planimetry of photographs, in spite of inherent shortcomings of greater variability and observer dependence, are more inexpensive and also present the optic disc to the examiner as he/she actually examines it. This permits qualitative studies and interpretations as well. With each technique having its advantages and limitations, each has its own place in glaucoma research.

1.4 Study Objectives

The aim of the current study was to collect normative optic disc data for South Indians.

The specific aims of the study were

1. To examine the optic disc size and shape in perimetrically normal subjects, and its dependence on ocular and other biological variables
2. To examine neuroretinal rim size, shape and morphological variations in perimetrically normal subjects and its dependence on ocular and other biological variables
3. To examine optic cup size, shape and morphological variations in perimetrically normal subjects and its dependence on ocular and other biological variables.
4. (a) To examine linear and area cup-to-disc ratios in perimetrically normal subjects and define limits of normal in the South Indian population.

   (b) To examine determinants of vertical cup-to-disc ratio

   (c) To examine the relationship between clinical and planimetric assessment of vertical cup-to- disc ratio

5. To examine asymmetry of the above optic disc parameters in perimetrically normal individuals.

CHAPTER-2

METHODOLOGY

The current study was part of the Chennai Glaucoma Study (CGS), [81] a population-based survey of glaucoma in Southern India. In brief, the CGS had rural and urban components. The urban component included 5 randomly chosen clusters in Chennai city. 960 permanent residents aged 40 years or above were enumerated from each cluster. Persons examined from last 2 clusters were included in the current planimetric study of optic disc characteristics.

2.1 Overview of the Chennai Glaucoma Study

The Chennai Glaucoma Study (CGS) was a population-based cross-sectional study. The aim of the study was to estimate the prevalence of glaucoma in persons aged forty years or above in rural and urban communities of South India. Eligibility criteria for the CGS were age 40 years or above and permanent resident status at the households. 4800 eligible persons each were enumerated from the rural and urban study areas. The rural study area consisted of 27 contiguous villages in Thiruvallur and Kancheepuram districts of rural Tamil Nadu, where it was estimated, based on the 1991 census, that the population of persons aged 40 years or above would approximate the required sample size.

Sample selection for the urban component of the study was done using a multistage sampling procedure. The total population of Chennai is 3.8 million according to the 1991 census.[82] Considering that 22% of the population is expected to be aged over 40 years, [83-85] the approximate number of persons in Chennai aged over 40 years is 0.85 million. The city is divided into 10 corporation zones, comprising 155 divisions. One division was randomly selected from each of those 10 zones and 5 divisions were randomly picked from those 10 divisions. The following areas of Chennai constituted the 5 randomly selected divisions:
(i) Dr. Radhakrishnan Nagar (ii) Siruvallore (iii) Anna Nagar Central (iv) Ashok Nagar and (v) Velachery. A simple random sample of 960 each from the above 5 randomly selected divisions were enumerated for the urban component of the CGS.

The current morphometric study is based on examination of optic disc photographs of subjects belonging to 2 out of the 5 clusters- Siruvallore and Dr.Radhakrishnan Nagar.

Field Operations And Enumeration

Social workers and volunteers belonging to the study area carried out the field operations, with the co-operation of local community leaders. The social workers conducted a door-to-door

survey of all the households in the study area to collect details regarding the number of families in the area, total number of members and eligible members in each family. They administered the household questionnaire through which collect demographic information was collected. Each eligible subject was assigned a unique nine-digit identification (ID) number. For the urban population, the first digit stood for the zone, the second for the area, the third and fourth for the street and the fifth and sixth digits indicated the door number. The seventh digit represented the household and the last two digits stood for the individual.

The social workers then motivated the eligible members to undergo clinical examination and photography on a convenient date. On the day of the examination, the social worker accompanied the subjects in the project vehicle to the hospital. Once the comprehensive evaluation was over, the subjects were transported back to their residence.

Awareness Programmes

Awareness programmes were periodically organized and conducted by the project staff in the study area to promote participation. The importance of glaucoma as a public health problem, the need to undergo eye examinations for early diagnosis and the need to collect more data on the disease were stressed during these meetings.

Examination and Diagnostic Procedures

On arrival at the examination centre, the subjects were registered and issued the previously assigned ID numbers. They were then requested to sign an informed consent form (left thumb impression in case of illiterate persons). They then proceeded through various ophthalmic examination and diagnostic procedures. IRB approval was obtained prior to commencement of the study and the study was conducted in accordance with the tenets of the Declaration of Helsinki.[86]

2.2 Tests Of Importance To The Current Study

A detailed medical and ophthalmic history was recorded, which included history of present and past eye problems, systemic illness, and personal history. They then underwent visual acuity testing with a logarithm of minimum angle of resolution (logMAR) chart. The Modified ETDRS chart (Light House Low Vision Products, New York, NY, USA) at 4 metres

was used to test the distance visual acuity.[87] Distance Visual Acuity Landolt's Ring Test (Light House Low Vision Products, New York, NY, USA) was used for subjects who cannot read English alphabets. Visual acuity was checked either unaided or with the subject's spectacles, if he or she is using any. Objective refraction was performed with a streak retinoscope (Beta 200, Heine, Germany) followed by subjective refraction. Spherical equivalent refraction was calculated as spherical error plus half of cylindrical error. Cylindrical error was noted in the minus form. Keratometry was performed with a Bausch and Lomb keratometer.

Frequency Doubling Perimetry (FDP)

Visual field screening was done with the FDP (Zeiss Humphrey Systems, Dublin, CA, USA). The test was performed on subjects with best-corrected visual acuity of 4/16(log MAR 0.6) or better.[88] Eligible subjects underwent the screening C-20-1 test twice.[89] The subject was given rest for at least five minutes between two tests. Repeated instructions at intervals during and between the tests are given to ensure reliable performance.

Pachymetry

The central corneal thickness (CCT) was measured using DGH 550 Ultrasonic pachymeter (DGH Technology Inc., Exton, PA, USA). The ocular surface was anaesthetised with 0.5% proparacaine eye drops (Sunways, Mumbai India). The measurement was made in auto mode with the subject in supine position while he or she fixates on a distant target. The probe tip was placed perpendicular to the central cornea and applanated. Ten readings were obtained and an average of these readings was recorded in microns.

External examination

External examination was performed using a handheld flashlight. The face and eyes were examined for the presence of strabismus, extraocular movement abnormalities or any other gross pathology.

Slit lamp biomicroscopy

The Zeiss SL 130 (Carl Zeiss, Jena ,Germany) slit lamp was used. Using a moderately wide beam, the eyelids, margins, lashes, canthi and puncta were systematically examined, followed by the palpebral and bulbar conjunctiva, sclera and cornea. Then, using a narrow parallelopiped beam, the cornea, anterior chamber and iris were examined for any abnormalities.

Applanation tonometry

Intraocular pressure (IOP) recording with the Goldmann applanation tonometer[90] (Zeiss AT 030 Applanation Tonometer, Carl Zeiss, Jena, Germany) was performed on all subjects. After applying 0.5% proparacaine eye drops for topical anaesthesia and staining the tear film with a 2 % flourescein strip, IOP was recorded in each eye. By convention, IOP was recorded first in the right eye.

Gonioscopy

Gonioscopy was performed in dim ambient illumination with a shortened slit that does not fall on the pupil. A Sussmann-type 4 mirror hand held gonioscope (Volk Optical Inc, Mentor, Ohio, USA) is used. The angle was graded according to the Shaffer system, [91] and the peripheral iris contour, degree of trabecular meshwork pigmentation and other angle abnormalities recorded. An angle was considered occludable if the pigmented trabecular meshwork is not visible in > 180^0 of the angle in dim illumination. If the angle was occludable, indentation gonioscopy was performed and the presence or absence of peripheral anterior synechiae was recorded. Laser iridotomy was performed in subjects with occludable angles after obtaining their consent. The rest of the examination was deferred to another convenient date following laser iridotomy.

Ocular biometry

Ocular biometry, using Alcon ultrasonic biometer (Ocuscan, Alcon laboratories Inc, Fort Worth, TX, USA) was performed on every fifth subject, the first subject having been selected at random (systematic random sampling). The axial length, anterior chamber depth and the lens thickness were measured. In addition to the randomised subset, all subjects diagnosed to have occludable angles or primary angle closure glaucoma underwent biometry measurements prior to laser iridotomy.

Grading of lens opacities

The subject's pupils were dilated with 5% phenylephrine with 1% tropicamide eye drops (Unimed Technologies, Halol, Gujarat, India). If phenylephrine was medically contraindicated, 1% homatropine eye drops (Warren Pharmaceuticals, Mumbai, India) was used instead.

Grading of lens opacities was performed using the Lens Opacities Classification System (LOCS II).[92] With a minimum pupillary dilation of 6 mm, the subjects' lenticular opacities were graded

by comparison with the standard set of photographs, which were retroilluminated by mounting on a light box.

Fundus examination

The binocular indirect ophthalmoscope (Appaswamy Associates, Chennai, India) was used to examine the entire ocular fundus, including the periphery. This was followed by examination of the disc and macula in greater detail using a +78 D lens (Volk Optical Inc, Mentor, Ohio, USA) at the slit lamp.

As part of optic disc examination, vertical and horizontal cup disc ratios and presence of any notching or thinning of the neuroretinal rim in each eye were noted.

Height

Height was recorded using a centimetre scale.

Visual acuity, refraction, keratometry, FDP, pachymetry and biometry were performed by one of two optometrists trained in glaucoma diagnostics. Slit lamp examination, applanation tonometry, gonioscopy, LOCS grading, disc and fundus examination were performed by one of two ophthalmologists, both of whom are glaucoma specialists.

2.3 Optic Disc Photography

All subjects with sufficient media clarity to permit good quality fundus photographs underwent fundus photography. The Zeiss FF450-plus fundus camera with VISUPAC digital image archiving system (Carl Zeiss, Jena, Germany) was used. Photography included one stereo-pair (non-simultaneous) of 20° optic disc photographs for each eye.

The labelled optic disc photographs were exported from the VISUPAC system as high quality JPEG images, and saved in an external storage device, to be analysed later.

2.4 Optic Disc Planimetry

Planimetry software

Planimetry was performed using custom planimetry software, which was developed specifically for this purpose, using MATLAB version 7 (Mathworks Inc, MA USA). The custom software was tested against the commercial VISUPAC software. Vertical and horizontal disc diameters and disc areas were marked on 50 optic disc pictures (of 50 subjects) and the values

were noted. The pictures were then exported as described and the same measurements were made using the custom software - excellent correlation was found between the 2 measurement methods. Mean difference between the 2 methods for vertical linear measures was 0.005 ± 0.004, intraclass correlation (ICC) coefficient 0.99; for horizontal lines it was 0.001 ± 0.004, ICC co-efficient 0.99; and for area measures it was -0.011 ± 0.02, ICC co-efficient 0.99.

Planimetry technique

Stereo pairs of photographs were displayed side by side on a 15" monitor. The *"Screenscope*" (Berezin Stereo Photography products, Mission Viejo, CA, USA) is a stereo viewer that can be used on digital stereo photographs on a computer screen, and was used for this study. All markings were made on the picture on the right side, under direct stereo-viewing conditions. The steps of planimetry were:

1. Marking the centre of the optic disc. This was taken as the centre of the longest and shortest axes of the disc-if these two points were not the same, their midpoint was considered the centre of the disc.
2. On confirming the centre, a "clock template" with markings along all 12 clock hours was superimposed on the photograph by the software with the marked point as centre.
3. The examiner marked the outer margin of the optic disc. The inner edge of the peripapillary scleral ring of Elschnig was taken as the disc margin.
4. The cup margin was marked. When the cup was cylindrical, the demarcation was clear; when the cup was conical, the plane midway between the surface of the disc and the depth of the cup was used was a reference plane.[35]
5. Vertical and horizontal disc diameters
6. Vertical and horizontal cup diameters.
7. Width of superior, temporal, inferior and nasal rims. Superior, temporal, inferior and nasal rim width were measured at 12, 3, 6 and 9 o'clock positions with respect to the optic disc centre. These was not measured for discs with no cups.

The software contains provision for making corrections for ocular magnification based on keratometry and refraction (Littmann's correction) - corrected values are recorded for all measurements.

Other parameters calculated from those measured so far are

1. Total rim area as disc area minus cup area
2. Vertical, horizontal and area cup-disc ratios
3. Ratio of vertical disc diameter to horizontal disc diameter as a measure of disc shape
4. Ratio of vertical cup diameter to horizontal cup diameter as a measure of cup shape

Other features noted were

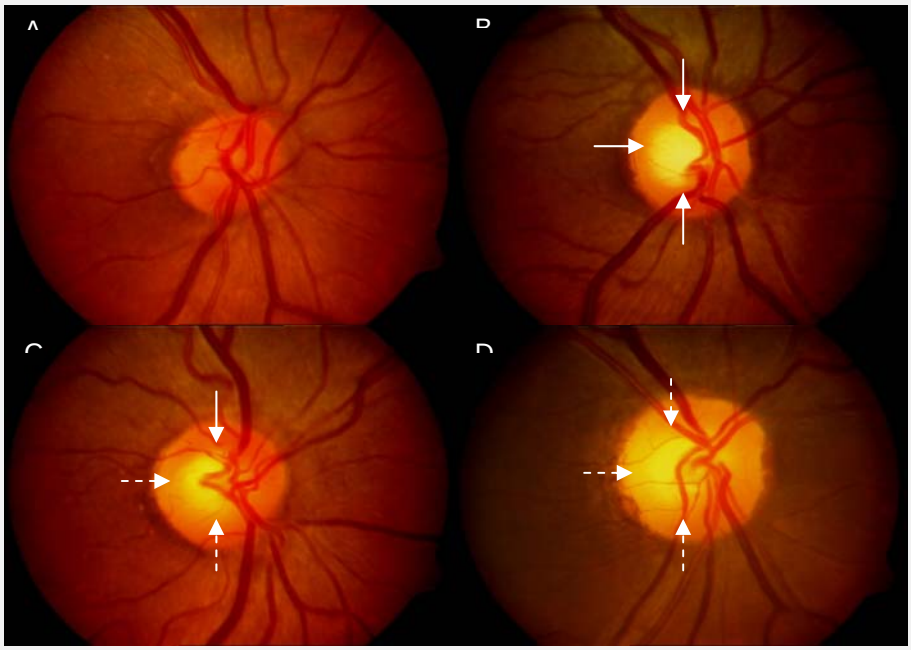
5. Torsion of the disc; direction and degree of torsion if present. The optic disc was considered torted when the vertical axis of the optic disc was rotated >15 degrees from the vertical meridian.[93]
6. Disc Tilting: The optic disc was considered tilted when there was (3-dimensional) angulation of the (antero-posterior) optic cup axis. [93]
7. Type of cup: Jonas classified discs into 3 types based on cup morphology- discs with no cups, discs with steep punched out cups and discs with temporal flat slopes. As a number of optic discs showed a sloping rim in a part of the temporal rim, this classification was modified to include a fourth category with partly sloping rim. (Figure 3.4.1).
8. Notching/ Thinning of rim; Location
9. Disc haemorrhages
10. Presence and number of cilio-retinal arteries (CRA)
11. Extent of beta-peripapillary atrophy. The extent in clock hours was noted.

Inclusion and Exclusion Criteria

Among persons from the last two clusters examined in the CGS, further eligibility criteria for the current planimetric study were absence of any cataract (LOCS II [92] grading NC0, N1, C0, P0), media haze or other ocular abnormality and normal FDP screening examinations. Reliability criteria for FDP were no fixation errors or false positives. Exclusion criteria from the planimetric study were any cataract or other media haze, aphakia, pseudophakia, non-availability of keratometry measurements, poor quality optic disc photographs including blurred photographs and/or poor stereo, any defect(s) on FDP and myopia >-8.0 D.

Figure 3.4.1: Examples Of Four Types Of Cupping

A: Disc with no cup, B: Disc with well demarcated cup, C: Disc with partly sloping rim, D: Disc with fully sloping temporal rim. (Steep rims marked with straight line arrows, sloping rims marked with dotted line arrows)



2.5 Statistical Analysis

Statistical Analysis was performed using SPSS XII software for Windows. Individual statistical methods are mentioned under the relevant sections. Kolmogorov-Smirnov test was used to test for normality. For 2 tailed distributions, 2.5^{th} and 97.5^{th} percentiles are presented, while for single-tailed distributions (absolute values of asymmetry measures), 95^{th} percentile values are presented to present the range within which 95% of values fall. In general, associations between 2 numerical variables were examined using Pearson's correlation. For associations between clinical and planimetric measures of the same variable (cup-disc ratios), intraclass correlation was used. Associations between 2 variables- one of them numerical and the other categorical were explored using t-test, with Welch correction if there was significant difference between the two standard deviations. The associations between categorical variables were explored using Chi-square test. For multivariate analysis, when the dependent variable was numerical, multiple linear regression was used with dummy coding for categorical explanatory

variables. When the dependent variable was categorical, logistic regression was used. Due to the large number of statistical associations explored, significance was detected at $p<0.01$ level in the interests of minimizing the risk of type 1 error. Histograms representing frequency distributions were generated using SPSS. Microsoft Excel was used to generate scatterplots.

CHAPTER-3

RESULTS & DISCUSSION

3.1. GENERAL & DEMOGRAPHIC INFORMATION

1,920 eligible residents were enumerated for the planimetric study. Out of them, 1,547 (80.57%) subjects responded. Of these , 896 persons were excluded from the planimetric study based on exclusion criteria described above i.e., cataract, aphakia, pseudophakia, glaucoma or other ocular pathology, abnormal FDP, poor performance of FDP , high myopia , non-availability of keratometry readings, or poor quality disc photographs. At least one eye was eligible in 678 persons, in 623 persons, right eyes were eligible, and in 645 persons, left eyes were eligible for inclusion and analysis. In order to maintain clarity and avoid repetition, only right eye data (n= 623) are presented in the first four sections. Asymmetry data in Section 4.6 are based on 565 persons for whom data of both eyes were available.

Mean age of the 623 participants was 48.3 $\pm$ 6.9 years. The mean age of all participants from the 2 clusters (n=1547) was 53.58 ± 10.61 years, the difference being significant ($p<0.0001$).

369 participants (59.2%) were women. Corrected visual acuity was 6/9 or better in all subjects. Mean spherical equivalent refractive error was 0.44 $\pm$ 1.15 D (-7.25 to 5D). Mean cylindrical error was -0.37 ± 0.48 D, mean intraocular pressure (IOP) was 15.9 ± 3.7 mm Hg. Mean central corneal thickness was 519.1 ± 31.1 microns, mean height was 157.3 ± 8.6 cm and mean axial length (n=159) was 22.78 ± 0.9 mm. 33 persons (5.3%) had occludable angles.

3.2. OPTIC DISC CHARACTERISTICS

3.2.1. Results

A. Optic disc size

a. Disc Area

i) Descriptive Measures:

Table 3.2.1 summarises the descriptive measurements pertaining to optic disc area.

ii) Distribution:

Figure 3.2.1 shows the frequency distribution of disc area, which was skewed to the right. (p=0.03, Kolmogorov-Smirnov test for normality)

Table 3.2.1: Optic Disc Area Measurements	
Description	***Value***
Mean ± SD	2.82 ± 0.52 sq mm
Median	2.76 sq mm
Minimum	1.52 sq mm
Maximum	5.06 sq mm
Variability	3.33 times
2.5th percentile	1.93 sq mm
97.5th percentile	4.01 sq mm
SD: Standard Deviation	

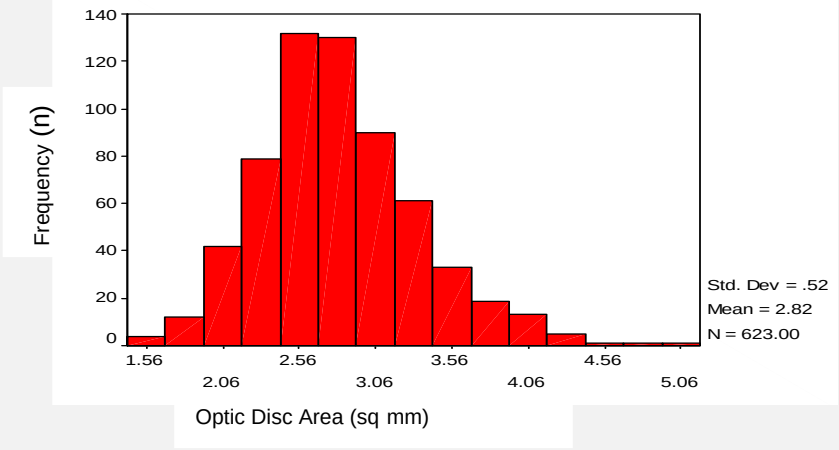


Figure 3.2.1: Frequency Distribution of Disc Area (n=623)

iii) Associations with Disc Area:

Disc area showed positive correlations with age (r = 0.08, p=0.043) and gender (mean disc area among men 2.88 ± 0.55 sq mm, mean disc area among women 2.78 ± 0.49 sq mm, p= 0.02, t-test) which were, however, not significant at the p<0.01 level. The mean disc area among

men was 3.6% larger in men than in women. Disc area showed no significant associations with spherical equivalent refraction (r=0.01, p=0.8), astigmatism (r=0.03, p=0.4), axial length (r=0.01, p=0.86), body height (r=0.07, p=0.07), presence of occludable angles (mean disc area in eyes with occludable angles 2.94 ± 0.48 sq mm, mean disc area in eyes without occludable angles 2.81 ± 0.52 sq mm, p=0.16, t-test), CCT (r=0.07, p=0.08), torsion of the disc (mean area of torted discs 2.68 ± 0.53 sq mm, mean area of non-torted discs 2.83 ± 0.52 sq mm, p=0.08, t-test), or tilting (mean area of tilted discs 2.56 ± 0.65 sq mm, mean area of non-tilted discs 2.82 ± 0.51, p=0.06, t-test).

Discs with no physiological cupping (mean disc area 2.41 ± 0.35) were significantly smaller than discs with cupping (2.89 ± 0.51, p<0.0001, t-test). Among the different types of cupping, however, disc area was not significantly different (p=0.18, ANOVA)

b. Disc Diameters

i) *Descriptive Measures:*

Table 3.2.2 summarises the important measurements pertaining to vertical and horizontal disc diameters.

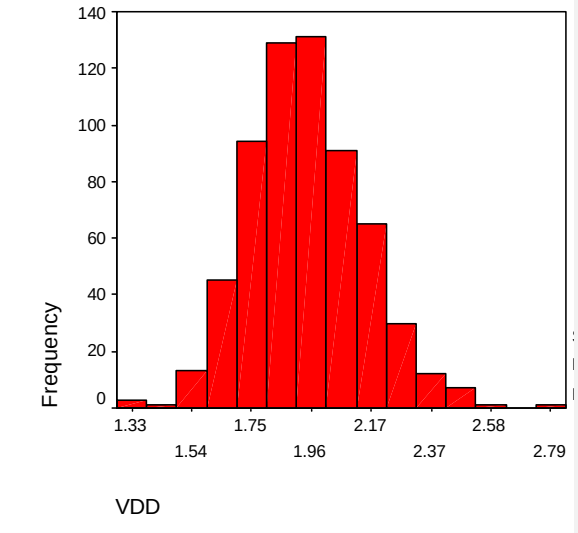
Table 3.2.2: Descriptive measures relating to Vertical and Horizontal Disc Diameters

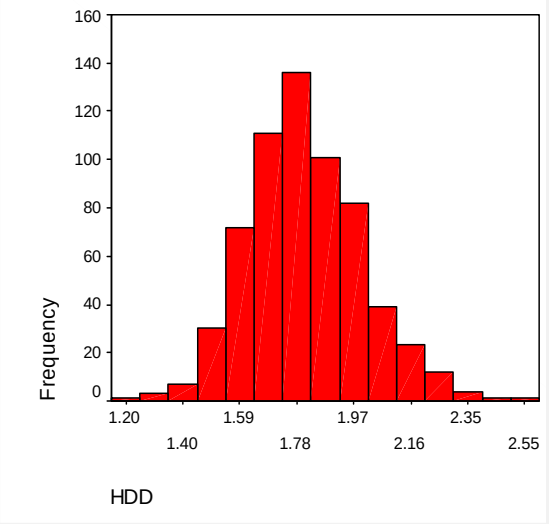
Description	***VDD***	***HDD***
Mean ± SD	1.94 ± 0.2 mm	1.81 ± 0.19 mm
Median	1.93 mm	1.79 mm
Minimum	1.31mm	1.21 mm
Maximum	2.82 mm	2.57 mm
Variability	2.15 times	2.12 times
2.5th percentile	1.57 mm	1.46mm
97.5th percentile	2.36 mm	2.23 mm

VDD: Vertical Disc Diameter, HDD: Horizontal Disc Diameter, SD: Standard Deviation

ii) Distribution:

Figures 3.2.2 a & b show the frequency distribution of vertical and horizontal disc diameters. Though slightly skewed to the right, both distributions were normal (Kolmogorov Smirnov test p=0.194 for VDD and p=0.3 for HDD).





Figures 3.2.2 a (left): Frequency Distribution of Vertical Disc Diameter (VDD), and b (right): Frequency Distribution of Horizontal Disc Diameter (HDD) (n=623 for both)

B. Optic disc shape

A. Torsion

Torsion of the disc > 15^0 was noted in 43 eyes (6.9%).

No significant associations with torsion were observed with age (mean age of persons with torted discs was 50.89 ± 7.9 years, mean age of persons with non-torted discs was 48.06 ± 6.73 years, p=0.028, t-test), gender (p=0.146, Chi-square tests), spherical equivalent refractive error (p=0.65), astigmatism (p=0.729, t-test), height (p=0.96, t-test) or the presence of beta zone of peripapillary atrophy (p=0.054, Chi-square test).

B. Tilt

Disc tilt as defined was noted in 14 eyes (2.2%).

Tilting showed significant associations with the presence of beta zone of PPA (50% of tilted and 14.5% non-tilted discs had beta zone of peripapillary atrophy, p<0.0001, Chi-square test).

Tilting showed no significant associations with age (p=0.19, t-test), gender (p=0.69, Chi-square test), spherical equivalent refraction (p=0.019, mean ref error in tilted discs -1.1 ± 2.1 D, mean error in non-tilted discs 0.48 ± 1.1 D, t-test), cylindrical refractive error (p=0.47), or height (p=0.11, t-test).

c. VDD/HDD

The ratio of vertical to horizontal disc diameter (VDD/HDD) was examined as an indicator of the disc shape.

i) Descriptive measures:

Table 3.2.3 summarises the descriptive measures relating to VDD/HDD

Table 3.2.3
Descriptive measures relating to VDD/HDD

Description	Value
Mean ± SD	**1.0769 ± 0.08**
Median	**1.075**
Minimum	**0.71**
Maximum	**1.36**
2.5th percentile	**0.92**
97.5th percentile	**1.24**

VDD: Vertical Disc Diameter, HDD: Horizontal Disc Diameter, SD: Standard Deviation

Mean VDD/HDD was 1.0769 ± 0.08 (median 1.075) indicating that on average, the VDD was 7.69% longer than the horizontal.102 eyes (16.4%) had VDD<HDD and 20 eyes (3.2%) had VDD=HDD.

ii). Distribution:

Figure 4.2.3 displays the frequency distribution of the ratio of vertical to horizontal disc diameter. The distribution of VDD/HDD was normal (p=0.943, Kolmogorov Smirnov test for normality).

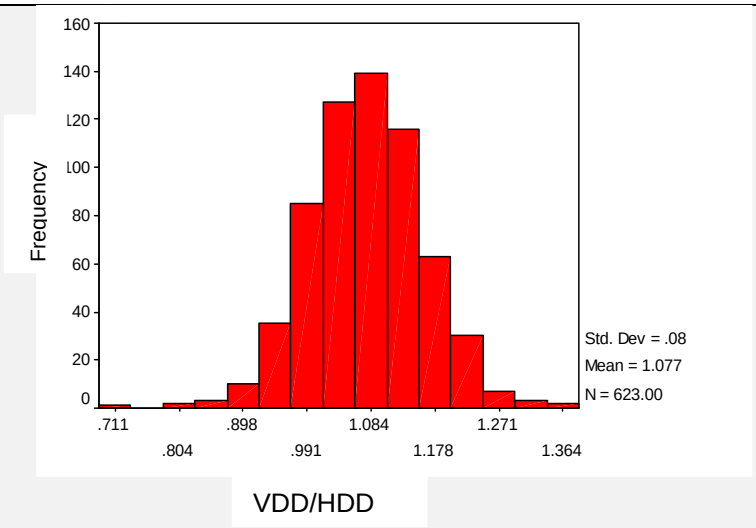


Figure 3.2.3: Frequency distribution of Vertical Disc Diameter (VDD)/Horizontal Disc Diameter (HDD) (n=623)

iii) Associations with VDD/HDD:

VDD/HDD was significantly related to torsion of the disc (mean VDD/HDD in torted discs 1.005 ± 0.09, mean VDD/HDD in non-torted discs 1.08 ± 0.08, p<0.0001, t-test). A weak, but statistically significant association with VDD/HDD was found with age (r=-0.15, p<0.001) and height (r=-0.15, p<0.001). VDD/HDD was also significantly different between the genders (mean VDD/HDD 1.06 ± 0.08 in men, 1.09 ± 0.08 in women, p<0.001, t-test).

Associations of VDD/HDD with disc area (r=-0.043, p=0.28), tilting of the disc (mean VDD/HDD in tilted discs 1.13 ± 0.16, mean VDD/HDD in non-tilted discs 1.07 ± 0.08, p=0.255, t-test), and presence or absence of physiological cupping (VDD/HDD 1.08 ± 0.1 in discs with no cups, 1.08 ± 0.08 in discs with physiological cups, p=0.99, t-test) were non-significant. It was also not significantly different between the different cup types (p=0.9, ANOVA) when physiological cupping was present. Other non-significant associations were with spherical equivalent refractive error (r=0.03, p=0.5), cylindrical refractive error (r=-0.096, p=0.02) and axial length (r=-0.122, p=0.126).

Multivariate analysis revealed that torsion (R^2 change 0.054, p<0.0001), age (R^2 change 0.016, p=0.001) and gender (R^2change 0.03, p<0.001) were significantly associated with VDD/HDD.

C. Cilioretinal Arteries (CRA)

161 (25.8%) eyes had at least 1 cilioretinal artery. 140 (90.3%) had a single CRA, 14 (9.0%) had two arteries and 1 person had 3 (0.2%).

Discs with cilioretinal arteries (CRA) (n=161) were significantly larger than discs without cilio-retinal arteries (mean area among discs with CRA 2.91 ± 0.51, mean disc area in discs without CRA 2.79 ± 0.52 sq mm, p=0.009, t-test). The association of rim area with the presence of cilio-retinal arteries (p=0.15, t-test) was non-significant.

3.2.2. Optic Disc Characteristics - Discussion

This thesis examines in detail the morphometric characteristics of the optic disc and its constituent parts, the neuroretinal rim and the optic cup, in a relatively large perimetrically normal population-based sample of South Indians. From this study, we present normative data for this ethnic group and also describe the distribution and determinants of various measures of optic morphology with particular emphasis on clinically relevant measures.

Mean optic disc area in this study was 2.8 ± 0.5 sq mm, with 3.3 times variability from the smallest to the largest measure. Table 1.3.1 presents a comparison of optic disc area measured by the current and other morphometric studies among different ethnic groups. The optic disc area reported by the current study was larger than the values reported among white Caucasian populations (2.69 ± 0.70 sq mm by Jonas et al in a German population,[22] 2.42 ± 0.47 by Ramrattan et al from the Rotterdam Eye Study,[4] 1.98 ± 0.36 sq mm by the Bridlington Eye Assessment Project (UK)[47] and 2.63 sq mm by Varma et al by from white participants of the Baltimore Eye survey[9]). It was also larger than measures reported among East Asian populations (2.64 ± 0.52 sq mm from the Beijing eye study [57] and 2.16 ± 0.49 sq mm by a CSLO study among Japanese participants[48]). However, the optic disc size of South Indians was smaller than that reported for African Americans by Varma et al (2.94 sq mm). It is noteworthy that measurements from different studies were made using different instruments, and systematic differences have been reported between the different methods. In a meta-analysis of different methods of estimating optic disc size, Meyer et al [51] calculated normalization factors of 1.04 for the Topcon fundus camera, 1.15 for HRT, 1.29 for the Topcon SS CSLO and 1.51 for the RODA compared to the Zeiss camera (1 by definition). Even applying these normalization factors, the optic disc area calculated for South Indians by the current study is larger than that reported for white Caucasians and East Asians, and is smaller than disc size reported for African Americans.

Morphometric optic disc data for South Indians have been reported by two other studies. Jonas et al in a planimetric study of 70 participants of the Vellore Eye survey [56] reported mean optic disc area of 2.58 ± 0.65 sq mm. In another study, Sekhar GC [32] et al reported mean optic disc area of 3.37 ± 0.68 in a study of 153 participants of the Andhra Pradesh Eye Diseases Study (APEDS). Our estimate falls between the other two reported measures. It is surprising that three studies conducted on populations that are geographically not very far away from each other should yield different results. We also have no reason to believe that the populations studied by

the three studies are actually very different from each other. These differences are therefore, most likely to be related to methodological differences between the studies. Sample sizes of both previous studies were much smaller than that of the current study, therefore we believe the current study is more likely to (have included a larger range of sizes and) be truly representative of the population. Also, as acknowledged by Jonas et al, magnification differences in the software programs used by the different studies may contribute to the differences.[56] In view of discrepancies in values reported by other studies, we took special care to ensure that the reported measurements are accurate. The software used in this study was validated against the widely available Zeiss-FF450 plus fundus camera and VISUPAC digital image archiving system, and showed excellent agreement with it. Care was taken to exclude all possible causes of alteration in magnification including any cataract, aphakia and pseudophakia.

The distribution of optic disc area in the current study showed a bell-shaped distribution with a skew to the right. This was consistent with patterns reported by Jonas et al in their studies of Caucasians[22] and Indians,[56] and by Ramrattan et al from the Rotterdam Eye Study.[4] For our population, microdiscs may be defined as optic discs of area < 1.9 sq mm (2.5^{th} percentile) and macrodiscs, as optic discs measuring > 4 sq mm (97.5^{th} percentile). The importance of this stems from the need to recognize abnormally small or large discs as this has important clinical implications in the interpretation of clinical findings (as discussed later).

In the current study, disc area was 3.6% larger in men than women, however, this difference did not reach statistical significance at the $p<0.01$ level. Several studies have reported slightly larger discs in men (2-3%) compared to women.[4,5,9,48,56] However, only some studies have reported a statistically significant association.[4,48]

We also did not find any statistical relationship between disc area and spherical equivalent refraction. In contrast, the Rotterdam study[4] reported a weak relationship between myopia and larger discs (1.6% per D increase in myopia) as well as larger rims (1.4% per D increase in myopia). Their sample included high myopes and high hyperopes. Jonas et al found that when high myopes and hyperopes were excluded, there was no relationship between disc parameters and refractive error.[22] However, when high myopes and hyperopes were also included, a curvilinear relationship was seen with a steep change in disc size at myopia < -8D and hyperopia > + 4D.[72] A similar association was reported in the Beijing Eye study.[57] The fact that we excluded persons with myopia>-8D and the highest level of hyperopia we had in this

study was 5D may be the reason we did not find any association between refractive error and disc area.

Although weak correlations of optic disc size with axial length,[5,76] height[4] and corneal thickness[77] have been reported before, we found no statistically significant associations with these parameters. In view of the fact that eyes with occludable angles generally represent shorter and smaller eyeballs[94] we looked for an association between disc size and the presence or absence of occludable angles, but found none.

Though optic disc area is the most commonly used indicator of optic disc size in studies, during clinical examination we measure, not area, but diameters of the optic disc as measures of optic disc size using the adjustable slit lamp beam or an eyepiece graticule with fundus viewing lenses. Correction factors have been suggested for the different fundus lenses - X1.0 for + 60D lens, X 1.1 for 78D lens and X1.3 for 90D lens[16] when the measurement is made in millimetres. In this context, the statistical range of disc diameters in this population as additional surrogates of disc size assumes importance.

Mean VDD in our study was 1.94 ± 0.2 mm and mean HDD was 1.81 ± 0.19 mm, with approximately two times variability of both measures. Compared to other studies that report disc diameters among other ethnic groups, the results of this study for VDD and HDD are consistent with results discussed above for disc area- the VDD and HDD were larger than reported by Jonas et al in Caucasians[22] and by Healey et al from the BMES[10]. Among Indian studies, our measurements fell midway between those reported by the VES[56] and the APEDS[32].

The frequency distributions for VDD and HDD were bell shaped and skewed slightly to the right. This was similar to the distributions for VDD reported by the BMES.[65] In this population, microdiscs based on disc diameters may be defined as discs with VDD and HDD lesser than 1.57mm and 1.46 mm respectively. Likewise, macrodiscs may be defined as discs with VDD and HDD larger than 2.36 mm and 2.23 mm respectively. It has been suggested that the formula for the area of an ellipse may be used to obtain area measurements of the optic disc and cup [16]. The formula for the area of an ellipse is πab where a and b are half the vertical and horizontal diameters respectively (semimajor and semiminor axes of the ellipse). When this formula is applied to our estimates of VDD and HDD, we get a mean disc area of 2.76 sq mm, the upper limit of microdiscs as 1.8 sq mm and lower limit of macrodiscs as 4.14 sq mm, which are quite close to the actual estimates of the same measures from Table 4.2.1.

Torsion and/or tilting of the optic disc is not an uncommon finding during clinical examination. If present, they may alter many of the commonly noted parameters during disc examination like rim width at 12, 3, 6 and 9 o'clock positions, cup-disc ratios etc. In order to study these possible effects, these parameters were noted and their influence on optic disc measurements were studied. We noted torsion of the disc >15 degrees in about 7% of eyes and disc tilting in about 2%. As expected, disc tilting showed significant associations with the presence of beta zone of PPA. However, these figures should not be considered population prevalence rates for torsion and/or tilting as we excluded all persons with any defects on FDP and all persons with myopia higher than -8.0D from the current morphometric study. As both myopia and perimetric defects are known to be associated with tilted discs[93], the actual prevalence of these conditions in the population is likely to be higher.

The ratio of vertical to horizontal disc diameter was examined as an index of optic disc shape. The significance of the optic disc shape, apart from theoretical interest, lies on the possible influence it may have on optic cup and neural rim configurations. Jonas et al suggested that a vertically oval disc has more space for arrangement of nasal and temporal retinal fibres, leading to correspondingly thicker superior and inferior rims and thinner nasal and temporal rims. They go further and mention that the vertically oval shape of the disc is the reason for the inferior and superior rims to be thicker than the nasal and temporal (ISNT rule).[22] Therefore, in addition to defining the 'normal' shape of the optic disc in this population, disc shape was studied as a possible predictor of other optic disc, cup and neural rim relationships.

The mean ratio of VDD to HDD was 1.08, indicating that on average, optic discs were vertically oval with the vertical diameter about 8% longer than the HDD. Only 16% eyes had VDD shorter than HDD. VDD/HDD values were distributed normally about the mean.

VDD/HDD did not show any relationship with spherical or astigmatic refractive error or axial length. It was, however, associated with torsion of the optic disc, age and gender. Together, these 3 factors accounted for 10% of the variability of disc shape. Torted optic discs tended to have more equal vertical and horizontal disc diameters. This easy to understand if we remember that VDD was measured from 12 to 6 position, and HDD was measured from 9 to 3 position, irrespective of the direction of the axes of the optic disc. Relative to men, women tended to have more vertically oval optic discs- the VDD was on average 6% longer in men and 9% longer in women than the HDD. Also, VDD/HDD showed a weak negative correlation with age, meaning

that older people tended to have relatively less vertically oval discs. Though statistically significant, the relationship was very weak, and age accounted for only 1.6% of the variability in disc shape.

Our findings regarding prevalence and associations with cilioretinal arteries were consistent with earlier reports. [95,96,97] About 26% of eyes examined had at least one cilioretinal artery. Discs with cilioretinal arteries were significantly larger than discs without cilioretinal arteries. However, the presence of cilioretinal arteries had no significant influence on neural rim area.

3.3. NEURAL RIM CHARACTERISTICS

3.3.1. Results

A. Neural rim area

i) Descriptive Measures:

Table 3.3.1 summarises the descriptive measurements pertaining to neural rim area.

Table 3.3.1 :
Descriptive Measures of Neural Rim Area

Description	Value
Mean ± SD	**2.29 ± 0.39 sq mm**
Median	**2.25 sq mm**
Minimum	**1.26**
Maximum	**3.66**
Variability	**2.9 times**
2.5th percentile	**1.60 sq mm**
97.5th percentile	**3.18 sq mm**

ii). Distribution

Figure 3.3.1 shows the frequency distribution of neural rim area, which was skewed slightly to the right but passed the Kolmogorov-Smirnov test for normality (p=0.14)

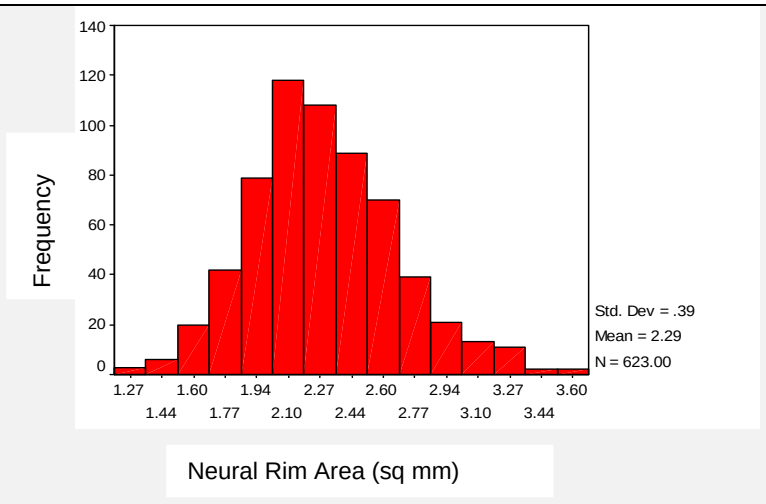


Figure 3.3.1: Frequency Distribution of Neural Rim Area (n=623)

iii) Associations with neural rim area

Rim area showed a strong positive correlation with disc area (r=0.67, r^2=0.44, p<0.0001). For every 1 sq mm increase in disc area, the rim area increased by 0.5 sq mm. Fig 3.3.2 displays this scatterplot with the associated linear regression line and equation.

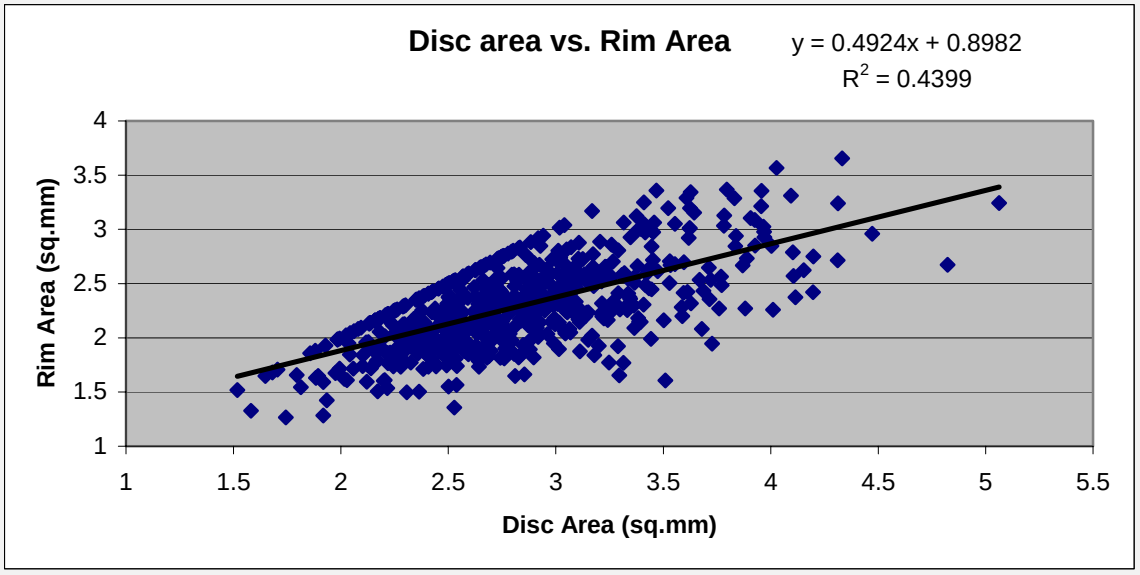


Figure 3.3.2 : Scatter plot of disc area versus rim area.

Trend line displayed. Regression equation and R^2 (co-efficient of determination) value displayed in the top right corner.

Rim area was significantly different between the different types of cups. When discs with cupping were compared with discs with no physiological cups, rim area was significantly greater in discs with no cups (2.39 ± 0.33 sq.mm) compared to discs with cupping (2.27 ± 0.39 sq.mm) (p=0.007, t-test). Among discs with physiological cupping, rim area was again significantly different between cup types (ANOVA, p<0.001) (Table 3.3.2).

Rim area showed a weak positive correlations with age (r=0.11, p=0.006). Mean rim area was also 3.1% greater in men than women, though the difference did not reach significance at the p<0.01 level (mean rim area in men 2.33 ± 0.4, mean rim area in women 2.26 ± 0.38, p=0.038). Associations of rim area with height (r=0.1, p=0.016), spherical equivalent refraction (r=0.03, p=0.5), axial length (r=-0.11,p=0.2), central corneal thickness (CCT) (r=0.05,p=0.2), IOP (r=-0.004,p=0.9), torsion (p=0.62) or tilting (p=0.12) of the disc, disc shape represented by the ratio

of vertical disc diameter (VDD) to horizontal disc diameter (HDD)(r=0.009, p=0.824), and presence of cilio-retinal arteries (p=0.15) were non-significant.

Table 3.3.2 : Comparison Of Rim Area By Type Of Cupping

	Type of cup	n	Mean rim area* (sq mm)	SD*	P value*	Mean# RA/DA	SD#	P value#
1	No cup	89	2.39	.35	<0.001	1	-	<0.001
2	Steep cup	317	2.19	.36		.77	0.09	
3	Partly sloping temporal rim	71	2.21	.42		.76	0.09	
4	Fully sloping temporal rim	146	2.48	.39		.85	0.08	

RA: Rim Area; DA: Disc Area

*** Data represent total RA; # Data represent RA adjusted for DA (RA/DA) ; For both parameters, P value calculated using one-way ANOVA.**

Tukey post-hoc multiple comparison test revealed significant difference in total rim areas and RA/DA between all pairs except between rows 2 and 3.

On multivariate analysis using multiple linear regression, only disc area (r^2 change 0.44, p<0.0001) and type of cupping (r^2 change 0.195, p<0.0001) retained statistically significant associations with rim area. Rim area / disc area (representing rim area adjusted for differences in disc area) was compared between cup types and was found to differ significantly (Table 3.3.2).

B. Neural rim shape

a. Comparison of superior, nasal, inferior and temporal rim widths

Comparison of mean width of the neuroretinal rim at the superior, temporal, inferior and nasal positions are presented in Table 3.3.3. Discs with no cupping (n=89) were excluded for all analyses of neural rim widths.

Table 3.3.3: **Comparison Of Mean Rim Width At Superior, Temporal, Inferior And Nasal Positions**			
Position	**Mean rim width (mm)**	**SD**	**p value***
Superior (n=534)	**.53**	**.11**	**<0.0001**
Temporal (n=534)	**.44**	**.12**	
Inferior (n=534)	**.61**	**.11**	
Nasal (n=534)	**.55**	**.11**	
*** p value calculated using one-way ANOVA.** **Tukey post-hoc multiple comparison test revealed significant differences between all pairs.** **Discs with no cupping were not included.**			

b. Comparison of superior and inferior rims

The mean ratio of the inferior rim (IR) to superior rim (SR) width was 1.18 ± 0.17, indicating that on average, the inferior rim was 18% thicker than the superior rim. The 2.5th percentile of this ratio was 0.9 and 97.5th percentile was 1.61 (minimum=0.84, maximum 2.32).

38 patients (7.1%) had superior rims thicker than the inferior rim (examples- Fig 3.3.3 A & B). The associations of thicker superior rims with ocular and other variables are summarized in Table 3.3.4.

c. Temporal rim

In 426 eyes (79.77%), the temporal rim was the thinnest rim. In 43 eyes (8.05%), the nasal rim was thinner then the temporal, in 44 eyes (8.24%), the superior rim was thinner and in 5 eyes (0.94%), the inferior rim was thinner. In the remaining 16 eyes (3%), more than 1 rim was thinner than the temporal.

Considering the clinically most relevant rim width measures in the context of glaucoma, the relationships of temporal with superior and inferior rims was evaluated, and the nasal rim was excluded from the analysis. Excluding the nasal rim, the temporal rim was thinnest in 469 eyes (87.8%). Examples of non-thinnest temporal rims are presented in Figure 3.3.4 A&B. Associations with the non-thinnest temporal rims are summarised in table 3.3.5.

Table 3.3.4:

Univariate And Multivariate Associations With Thicker Superior Than Inferior Rims

	IR > SR	SR > IR	P value (univariate)	P value (multivariate)[¶] (OR, 95% CI)
N (%)	496 (92.88)	38 (7.12)	-	-
Age (Mean ± SD) (years)	48.24 ± 6.87	48.36± 7.11	0.92*	0.59
Gender (M:F)	196:300	23:15	0.02[#]	0.04
VDD/HDD[§] (Mean ± SD)	1.08 ± 0.08	1.05 ± 0.09	0.03*	0.42
Disc Torsion (torted:non-torted)	26:470	8:30	0.001[#]	0.002 (4.8, 2 -11.43) for torted discs
Disc Tilt (Tilted:non-tilted)	12:484	1:37	1.00[#]	0.59
Type of cupping (Steep:Partial slope:Fully sloping)	291:69:136	26:2:10	0.28[#]	0.28
IOP (Mean ± SD) (mm Hg)	16.11 ± 3.86	15.26 ± 3.45	0.19*	0.23
CCT (Mean ± SD) (microns)	519.6 ± 31.39	525.76 ± 28.41	0.24*	0.11
Refraction (Mean ± SD) (D)	0.45 ± 1.15	0.28 ± 1.5	0.39*	0.7
Astigmatism (Mean ± SD) (D)	-0.35 ± 0.47	-0.46 ± 0.45	0.15*	0.16

IR: Inferior rim width, SR: Superior Rim width, OR: Odds Ratio, CI: Confidence Interval, SD: Standard Deviation, M: Male, F: Female, VDD: Vertical Disc Diameter, HDD:Horizontal Disc Diameter, IOP: Intraocular Pressure, CCT: Central Corneal Thickness, D: Dioptres

[§] As a measure of disc shape, *Calculated using t-test, [#] Calculated using chi-square test, [¶] Calculated using logistic regression

Table 3.3.5: Univariate and multivariate associations with non-thinnest temporal rims[¥]				
	Temporal rim non-thinnest	**Temporal rim thinnest**	**P value (univariate)**	**P value (multivariate)[¶]**
N (%)	**65 (12.2%)**	**469 (87.8%)**	**-**	**-**
Age (Mean ± SD) (years)	**50.11 ± 7**	**48 ± 6.84**	**0.02***	**0.78**
Gender (M:F)	**33:32**	**186:283**	**0.1[#]**	**0.7**
VDD/HDD[§] (Mean ± SD)	**1.02 ± 0.08**	**1.08 ± 0.08**	**<0.0001***	**<0.0001**
Disc Torsion (torted:non-torted)	**8:57**	**26:443**	**0.042[#]**	**0.85**
Disc Tilt (Tilted:non-tilted)	**2:63**	**11:458**	**0.6[#]**	**0.87**
Type of cupping (Steep:Partial slope:Fully sloping)	**27:13:25**	**290:58:121**	**0.007[#]**	**0.006**
IOP (Mean ± SD) (mm Hg)	**15.26 ± 3.59**	**16.16 ± 3.9**	**0.08***	**0.09**
CCT (Mean ± SD) (microns)	**515.52 ± 29.88**	**520.67 ± 31.36**	**0.22***	**0.30**
Refraction (Mean ± SD) (D)	**0.44 ± 1.6**	**0.44 ± 1.12**	**0.99***	**0.33**
Astigmatism (Mean ± SD) (D)	**-0.54 ± 0.63**	**-0.33 ± 0.44**	**<0.001***	**0.001**

SD: Standard Deviation, M: Male, F: Female, VDD: Vertical Disc Diameter, HDD: Horizontal Disc Diameter, IOP: Intraocular Pressure, CCT: Central Corneal Thickness, D: Dioptres

[§] As a measure of disc shape, [¥]Excluding nasal rims *Calculated using t-test, [#] Calculated using chi-square test, [¶] Calculated using logistic regression

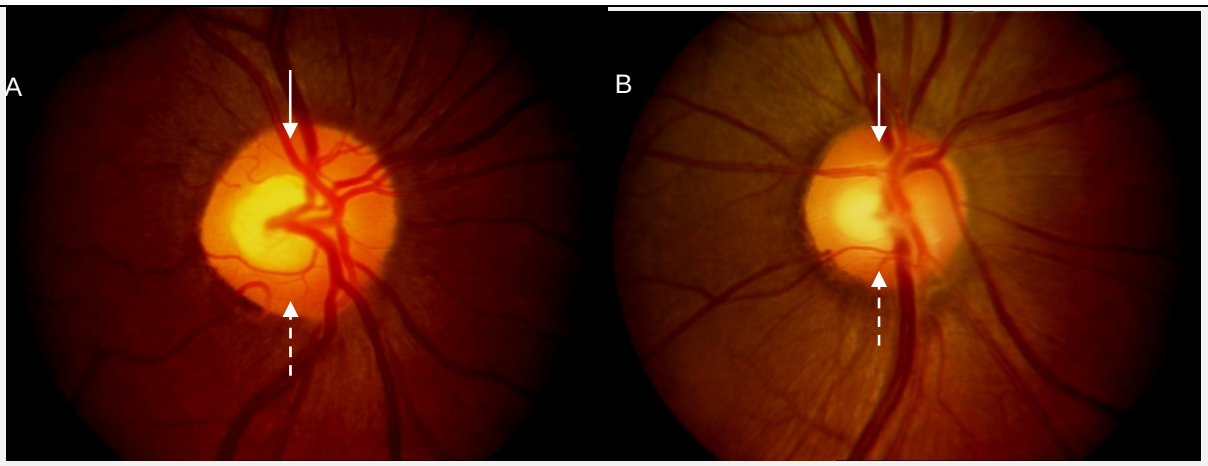


Figure 3.3.3: Examples of discs with thinner inferior (dotted arrows) than superior rims (straight line arrows). The difference is more pronounced in B than in A.

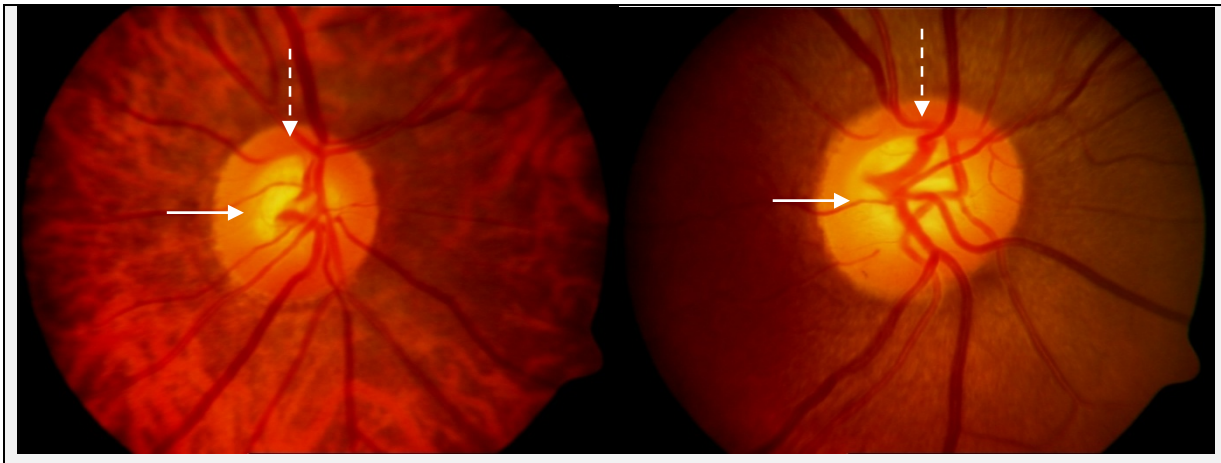


Figure 3.3.4: Examples of discs where the temporal rim is not the thinnest. In both pictures, the superior rim (dotted arrows) is thinner than the temporal (straight line arrows).

3.3.2. Neural Rim Characteristics - Discussion

The optic disc owes its importance to the neuroretinal rim - the collection of axons arising from the retinal ganglion cells which are bundled together at the scleral canal on their way to synapse with higher order neurons in the brain. Assessment of the health of the neuroretinal by direct (rim colour, shape) or indirect measures (cup-to-disc ratios) is the single most important component of a glaucoma work-up. This section discusses neural rim characteristics-size, configuration and associations- reported by this planimetric component of the Chennai Glaucoma Study.

Mean neural rim area in this study was 2.29 ± 0.39 sq mm, with nearly threefold variability from the smallest to the largest measure. In tandem with disc area values, rim area in the current study was higher than that reported among white Caucasians by Jonas et al [22] (mean rim area 1.97 ± 0.5 sq mm), Ramrattan et al (1.85±0.39), [4] Varma et al (1.92 sq mm)[9] and the BEAP (1.52±0.31)[47]. It was also larger than reported rim areas among Japanese subjects (1.57±0.33 sq mm)[48]. However, in contradiction to disc area measures, our rim area measures were larger than reported rim area for African Americans (1.9 sq mm, Varma et al) [9].

There are several possible reasons for differences in rim area measurements between studies. As discussed before, racial variations in disc area are well known and documented, and racial differences in rim area have been attributed to differences in disc area. Second, as stated earlier in the context of disc area, different methods have been used to collect the morphometric data in different studies, with systematic differences having been documented between them.[56] An additional source of variability while comparing rim areas is the way the optic cup was marked in each study. The Topcon Imagenet system used by the Baltimore and Rotterdam studies uses automatic definition at 150 microns lower than the retinal reference plane. The HRT used by the BEAP automatically defines the reference plane as located 50 µm posterior to the mean surface height along a 6-degree arc at the inferotemporal region of the contour line representing the disc margin. Jonas et al mention that the optic cup was marked using ‘contour and not colour’, and that red-free light was used to determine the cup margin in case of difficult situations. In the current study, the cup margin was marked in keeping with the OHTS protocol- i.e., in difficult situations arising from temporally sloping rims, the middle of the slope was taken as the cup margin. This was because in many sloping rims, it was difficult to determine the exact site of bending of blood vessels.

Table 3.3.6 presents a comparison of disc area, rim area and rim area/disc area between the different studies. Calculating the ratio of rim area/disc area allows more meaningful comparison of values as disc area differences and individual variations in software-related magnification factors are adjusted for.

Table 3.3.6:

Disc area, rim area and rim area/disc area from different studies

Author	Ethnic Group	Disc Area	Rim Area	Cup area	Rim Area/ Disc Area	Cup Area/Disc Area
Jonas et al[56]	Indian	2.58	1.6	0.98	0.62	0.38
Varma et al [9]	African Americans	2.94	1.9	1.04	0.65	0.35
Uchida et al [48]	Japanese	2.16	1.57	0.59	0.73	0.27
Varma et al[9]	White Caucasian	2.63	1.92	0.71	0.73	0.27
Jonas et al [22]	White Caucasian	2.69	1.97	0.72	0.73	0.27
Ramrattan et al [4]	White Caucasian	2.42	1.85	0.57	0.76	0.23
BEAP [47]	White Caucasian	1.98	1.52	0.46	0.77	0.23
Current study	Indians	2.82	2.29	0.53	0.81	0.19
Sekhar et al [32]	Indians	3.36	2.79	0.57	0.83	0.17

From Table 3.3.6, it is clear that accounting for magnification differences and disc area differences greatly brings down the racial variability in rim area. However, differences in the way the cup margins were marked would continue to be a source of variability.

Two other studies on smaller numbers of normal persons report rim areas among South Indians- 1.6 ± 0.37 sq.mm by Jonas et al in a planimetric study of 70 participants of the Vellore Eye survey[56] and 2.8 ± 0.53 by Sekhar GC et al [32] in a study of 153 participants of the Andhra Pradesh Eye Diseases Study (APEDS). As discussed for disc area, our estimate falls between the other two reported measures, and the factors already discussed- sample size, software differences, differences in marking the cup margin etc. may all play a role. As is evident from Fig 3.3.1, the values follow a normal distribution.

More important and clinically relevant than absolute measures are the inter-relationships between rim measurements and other optic disc variables. In agreement with previous studies among Indians[56] and white Caucasians,[22] rim area showed a significant positive correlation with disc area, which accounted for 44% of the variability in rim area. In addition, rim area was also significantly influenced by type of cupping, which accounted for 19.5% of rim area variability. As suggested by Jonas et al, sloping rims represent more horizontally or obliquely arranged nerve fibres at the optic nerve head, while steep rims represent a more compact arrangement of nerve fibres which bend posteriorly at almost a 90 degree angle at the optic disc.[22] In their landmark study of 457 normal white Caucasian eyes, they demonstrated steeper regression slopes in discs with sloping cups compared to punched out cups. The rim area/disc area measure that we examined in this study provides a similar estimate i.e., rim area per unit disc area, which was found to be maximum for discs with no cups, lesser for discs with fully sloping rims, and least for cups with partly sloping rims and punched out cups, indicating progressively more compact arrangement of nerve fibres at the optic disc. Although a significant correlation of rim area with age was found on univariate analysis, this disappeared on multivariate adjustment. Rim area showed no correlation with disc shape, IOP, corneal thickness, gender or refraction.

The ISNT rule (Inferior rim thicker than Superior rim, thicker than Nasal rim, thicker than Temporal rim) was suggested by Jonas et al based on findings from the above mentioned study of 457 Caucasian eyes.[22] However, as is true of most parameters in medicine, variability even within normals is not surprising, and must be expected. In a subsequent study of 193 normal eyes, [58] they reported violations of this rule- the thickest rim was located outside the inferior rim in 37.8% of eyes and in 24.9%, it was the superior rim. They also reported that the temporal rim was not the thinnest rim in 4.2% eyes. In another study that involved evaluation of masked disc photographs of 66 normal eyes of black and white subjects, Harizman et al[59]

reported violation of the ISNT rule in 21% of eyes. Of the 14 normal eyes that violated the ISNT rule, 7 had an inferior rim that was thinner than the superior rim, 5 had a nasal rim that was thicker than the inferior rim and 2 had a temporal rim that was thicker than the superior rim.

The nasal rim is usually the last to be affected by glaucomatous cupping, and it is often difficult to distinctly identify the borders of the optic cup in the nasal optic disc sector due to the presence of the large retinal vessels. For these reasons, it has been suggested that the nasal sector should be excluded from morphometric disc analysis.[62] Also, during clinical evaluation of optic discs using biomicroscopic examination, one usually evaluates 2 factors- the relative thickness of the inferior to superior rim as glaucomatous damage most commonly manifests as thinning of the inferior rim, and second, whether the temporal rim is the thinnest of the three rims as a thinner superior/inferior than temporal rim is considered highly suspicious of glaucoma. In an HRT study involving 136 normal North Indian eyes, Sihota et al reported that the inferior rim area>superior rim area>temporal rim area in 71% of normal eyes, and violation in the remaining 29%.[60]

In the current study, we found that on examination of mean values, the inferior rim was thickest, and temporal rim was thinnest, in accordance with the most important components of the ISNT rule as stated by Jonas et al. We also found that on average, the inferior rim was about 20% thicker than the superior rim. The lower 2.5^{th} percentile of the ratio of inferior/superior rim was 0.9, which indicates that in this ethnic group, an inferior rim that is 90% of the thickness of the superior rim may be considered the lower limit of normal. 7.1% of eyes had superior rims thicker than the inferior rim. Multivariate analysis of possible contributors to a thicker superior than inferior rim revealed that torsion of the disc increased the odds of a thicker superior rim by more than five times. Nasal or temporal torsion of the disc would change the relative rim positions measured at 12 0'clock (for superior) and 6 0'clock (inferior) positions, and contribute to relatively thinner rim measurement inferiorly than for a non-torted disc.

Of interest is the finding in the current study that the temporal rim was not the thinnest in 12% of eyes (excluding nasal rims). Disc shape (VDD/HDD), astigmatism and type of cupping were significant contributors to this outcome. A shorter vertical to horizontal disc diameter (i.e., a more horizontally oval disc) increases the relative availability of space for arrangement of nerve fibres at the superior and inferior poles, and decreases the space available nasally and temporally, necessitating that the nerve fibres be bunched thicker at the latter positions. The

same reasoning was mentioned by Budde and Jonas[58] to explain the occurrence of thicker nasal rims in eyes with lower VDD/HDD. However, in their study, very few eyes had thinnest rims outside the temporal zone (4.2%, 8 eyes), which may be the reason this parameter did not show significant correlations with VDD/HDD in that study.

The temporal rim was not the thinnest rim in 17.75% discs with any sloping rims, as against 8.5% discs with steep rims. Among discs with partly sloping rims, the temporal sector was sloping in 25 eyes (35.2%) in this sample. Oblique arrangement of fibres in the horizontal temporal region in discs with sloping cups in that region may contribute to measurement of wider rim widths temporally, analogous to the earlier discussion of the influence of type of cupping on rim area.

Revisiting racial variations in rim area in the light of the findings from this study, the arrangement of nerve fibres at the optic disc may be one more contributor to variability in measured rim areas between studies among different ethnic groups, and also may account for variability in rim area/ disc area Table 4.3.6. From this table, Indians have the highest measures of rim area/disc area. It is possible that the relatively larger rim/disc area ratio among South Indians from 2 studies may be because this population tends to have more sloping rims. This is further supported by our findings that a larger proportion of patients than reported among Caucasians had non-thinnest temporal rims, which was significantly associated with sloping temporal rims.

3.4 OPTIC CUP CHARACTERISTICS

3.4.1. Results

A. Optic Cup Size

a. Optic Cup Area

i) *Descriptive Measures:*

Table 3.4.1 summarizes the important measurements pertaining to optic cup area

Table 3.4.1: Descriptive Optic Cup Area Measurements

Description	Value
Mean ± SD	**0.53 ± 0.39 sq mm**
Median	**0.48 sq mm**
Minimum	**0**
Maximum	**2.15 sq mm**
2.5th percentile	**0 sq mm**
97.5th percentile	**1.5 sq mm**

ii) Distribution:

Figure 3.4.1 shows the frequency distribution of optic cup area. The distribution was bimodal and influenced by the high frequency of discs with no cups (n=89).

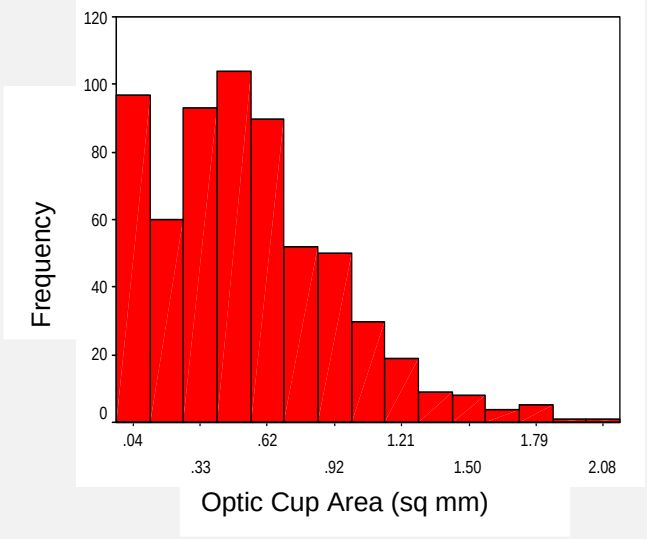


Fig 3.4.1: Distribution of Optic Cup Area

iii). Associations with optic cup area:

Optic cup area showed positive associations with disc area (r=0.67, p<0.0001) (Figure 3.4.2) and type of cupping (p<0.0001, ANOVA) (table 3.4.2).

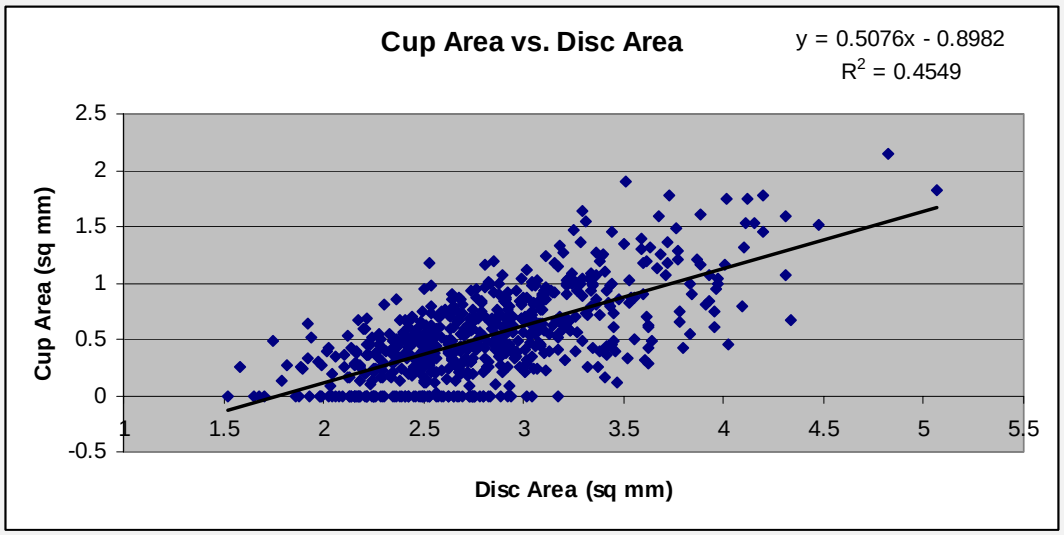


Figure 3.4.2 : Scatterplot of Optic Disc Area vs. Optic Cup Area. Trend line displayed. Regression equation and R^2 (co-efficient of determination) value displayed in the top right corner.

Table 3.4.2 :

Optic Cup Area in different morphological Optic Cup Types

	Type of cup	n	Mean cup area* (sq mm)	SD*	P value*
1	No cup	89	0		<0.001
2	Steep cup	317	0.67	.35	
3	Partly sloping temporal rim	71	0.70	.35	
4	Fully sloping temporal rim	146	0.47	.31	

Tukey post-hoc multiple comparison tests revealed significant differences between all pairs except 2 and 3.

IOP (r=0.082, p=0.04), presence of CRA (mean cup area in discs with CRA 0.59 ± 0.38, mean cup area in discs without CRA 0.51 ± 0.39, p=0.042, t-test), age (r=-0.001, p=0.972), height (r=0.05, p=0.181), gender (mean cup area among men 0.55 ± 0.42, mean cup area among women 0.52 ± 0.37, p=0.33, t-test), spherical equivalent refraction (r=-0.009, p=0.824), axial length (r=0.13, p=0.09), central corneal thickness (r=0.03, p=0.44), VDD/HDD (r=-0.067, p=0.09), torsion (p=0.06) and tilting (p=0.32) showed insignificant associations with optic cup area.

Multiple linear regression revealed that disc area (r^2 change 0.45, p<0.0001) and type of cupping (r^2 change 0.19, p<0.0001) were significant predictors of cup area. When discs with no cupping were excluded from the model, the r^2 change values were 0.416 (p<0.0001) for disc area and 0.097 (p<0.0001) for type of cupping respectively.

b. Optic Cup Diameters

i) *Descriptive Measures*

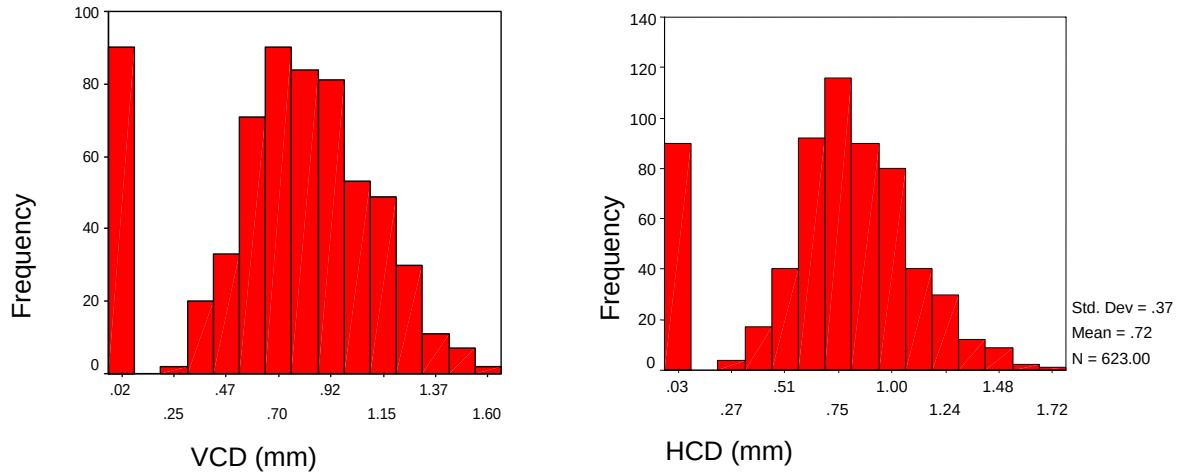
Table 3.4.3 summarises the important measurements pertaining to vertical and horizontal disc diameters.

Table 3.4.3:
Descriptive Measures of Vertical and Horizontal Optic Cup Diameters

Description	**VCD**	**HCD**
Mean ± SD	**0.720 ± 0.38 mm**	**0.723 ± 0.37 mm**
Median	**0.76 mm**	**0.78 mm**
Minimum	**0 mm**	**0 mm**
Maximum	**1.61 mm**	**1.74 mm**
2.5th percentile	**0 mm**	**0 mm**
97.5th percentile	**1.34 mm**	**1.40 mm**
VCD: Vertical Cup Diameter, HCD: Horizontal Cup Diameter		

ii) Distribution:

Figures 3.4.3 a & b show the frequency distribution of vertical and horizontal cup diameters. Both distributions show the influence of discs with no physiological cupping.



Figures 3.4.3 a (left) Frequency distributions of vertical cup diameter (VCD), and b (right): Frequency distributions of horizontal cup diameter (HCD)

B. Optic Cup Shape

a. Morphological Classification of type of cupping

Based on type of cupping, discs were classified into four types: discs with no cups (n= 89, 14.3%), discs with steep, well demarcated cups (n=317, 50.9%), discs with partly sloping temporal rims (n=71, 11.4%) and discs with fully sloping rims temporal to the retinal vessel trunks i.e., sloping supero-temporal, horizontal temporal and infero-temporal rims (n=146, 23.4%). Among discs with partly sloping rims, the slope was horizontal temporal in 10 (14.1%), infero-temporal in 42 (59.2%), supero-temporal in 4 (5.6%) and both temporal and infero-temporal in 15 (21.1%) of discs.

b. Optic Cup shape (VCD/HCD)

i). Descriptive measures:

Table 3.4.4 summarises the important descriptive measures relating to VCD/HCD

268 eyes (50.18 % eyes) had VCD/HCD <1, 12 eyes had VCD/HCD=1. (Discs with no cupping were excluded from analysis of VCD/HCD).

Table 3.4.4: Descriptive Measures of VCD/HCD	
Description	**Value**
Mean ± SD	**1.0011 ± 0.14**
Median	**0.99**
Minimum	**0.47**
Maximum	**1.42**
2.5th percentile	**0.71**
97.5th percentile	**1.31**

ii). Distribution

Figure 3.4.4 shows the normal distribution of vertical to horizontal cup diameter (Kolmogorov Smirnov test, p=0.53).

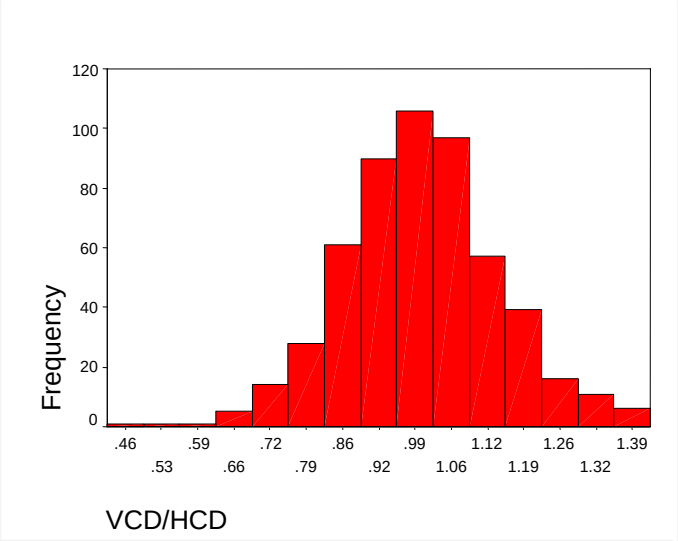


Figure 3.4.4: Frequency Distribution of VCD/HCD. VCD: Vertical Cup Diameter, HCD: Horizontal Cup Diameter

iii) Correlations with VCD/HCD

Significant associations of VCD/HCD were observed with disc shape as VDD/HDD ($r=0.4$, $p<0.001$), torsion of the disc (mean VCD/HCD in torted discs 0.92 ± 0.17, mean in non-torted discs 1.007 ± 0.14, $p<0.001$, t-test), type of cupping (longer VCD in sloping compared to steep rims, ANOVA, $p=0.003$; Tukey test - significant difference between steep cups and cups with entire temporal sloping rim only).

Associations with gender (mean VCD/HCD in men 0.98 ± 0.15, mean in women 1.01 ± 0.14, $p=0.011$, t-test), disc area ($r=0.11$, $p=0.014$), cup area ($r=0.101$, $p=0.019$), refraction ($r=0.099$, $p=0.022$), height ($r=-0.09$, $p=0.038$), age ($r=0.05$,$p=0.2$), astigmatism ($r=0.03$, $p=0.46$), axial length (-0.053, $p=0.532$), tilt (mean in tilted discs 1.086 ± 0.26, non-tilted discs 0.998 ± 0.14, $p=0.244$, t-test with Welch correction) and IOP ($r=0.05$, $p=0.289$) were non-significant at $p<0.01$ level.

Multiple linear regression revealed that significant predictors of cup shape are disc shape (r^2 change 0.179, $p<0.0001$), disc area (r^2change 0.018, $p=0.001$), cup area (r^2 change 0.013, $p=0.004$), and type of cupping (r^2 change 0.019, $p=0.002$).

3.4.2 Optic Cup Characteristics-Discussion

The optic cup represents the 'empty' portion of the optic nerve head-that part of the optic disc which does not contain nerve fibres. It therefore has an inverse relationship with the neuroretinal rim- loss of neural rim in glaucoma manifests as relative enlargement of the optic cup usually in the inferior and/or superior sectors. The classical description of the normal optic cup has been horizontally oval in a vertically oval disc, with thicker neuroretinal rims inferiorly and superiorly, and thinner rims nasally and temporally.[22] A vertically oval cup alerts the clinician to look for other evidence of neural rim thinning at the inferior and/or superior poles. Larger cups and vertically oval cups, therefore, are viewed with suspicion.

However, optic cups have also been known to demonstrate a wide range of variability among normal persons. This section attempts to describe optic cup characteristics in this perimetrically normal sample of South Indians, and describe norms, variability and determinants of optic cup size and shape.

Mean optic cup area in this population was 0.53 ± 0.39 sq mm. As for neural rim area, wide differences were observed in optic cup area determined in different racial groups (Table 4.3.6). As for neural rim area, the differences narrowed down after adjusting for disc area. Complementary to our findings for rim area, cup area/disc area was smallest for Indians, going by the findings from 2 out of 3 Indian (Sekhar et al and current) studies. The same reasons discussed previously for variability in rim area would hold good for variability in cup area.

Optic cups demonstrated a wide range of variability in size- ranging from no cupping to 2.15 sq mm, which was within the statistically normal range for optic disc area! The distribution of optic cup area was bimodal, the first peak occurred at 0 sq mm due to the presence of no physiological cupping in 14.3% of eyes.

Like rim area, optic cup areas also demonstrated a strong correlation with optic disc area. Larger cups were associated with larger discs. Cup area showed a weaker relationship with morphological type of cupping. Steep, well demarcated cups were significantly larger than cups with sloping rims. Both the above relationships have been described before by Jonas et al.[22] With increasing disc area, increase in cup area would be expected. We also noted earlier that disc area was not significantly different between different types of cupping among discs that had physiological cups. If steep rims represent more compactly arranged nerve fibres compared to sloping rims, it is logical that similarly sized discs with steep rims would have larger cups.

Akin to the preceding discussion about disc diameters, cup diameters are the commonly estimated surrogate measures of optic cup size. However, due to the strong dependence of 'normal' optic cup size on disc size, it would be often impractical to apply absolute measures of cup area to define limits of normality clinically. Rather, cup-disc ratios are much more meaningful measures of relative cup size and are much more commonly used. They will be discussed later.

The distributions of vertical and horizontal cup diameters are both bimodal, the first peak occurring due to the influence of discs with no physiological cupping.

Most glaucomatologists have encountered discs with sloping rims in their clinical practice and are aware of the difficulties posed by these discs in terms of assessment of cup-disc ratios, thinned vs. normal rims, and interpretation of relative rim widths in different parts of the optic disc in cases of sectoral sloping rims. In order to examine how rim slope affects measured optic disc parameters, we included a classification of type of cupping in the current study. Jonas et al described three types of discs based on the type of cupping- discs with no cupping, discs with steep punched out cups and discs with temporal flat slopes.[22] They described different regression slopes of rim area vs. disc area for each of the above disc types, and suggested that oblique arrangement of nerve fibres in temporal flat slopes vs. perpendicular arrangement in steep punched out cups may be responsible for the differences. As a number of discs were sloping in part of the temporal rim, but were compact elsewhere, we modified Jonas' classification to include a category with partly sloping rims. Most of the discs with partly sloping rims had their slopes inferotemporally, temporally or in both these regions. In this population, approximately half the discs had fairly well demarcated cupping, about 14% had no cups and the rest had at least part of the temporal rim sloping.

In this population, among eyes with physiological cupping, mean VCD was approximately equal to mean HCD (mean VCD/HCD was almost equal to 1) indicating, on average, fairly circular cups. VCD was shorter than or equal to HCD in 52.4% of eyes, and was longer than HCD in the rest. This differs from the findings reported by Jonas et al that horizontal cup diameter was significantly longer than vertical cup diameter in Caucasians,[22] and in Indians [56] (by about 11%).

In our study, the mean VCD and HCD were almost equal, though at the extremes of the distributions for VCD and HCD, values for HCD were greater than the values for VCD. VCD/HCD was normally distributed about the mean of 1.001.

The most significant predictor of cup shape in our study was disc shape, which accounted for about 18% of variability in cup shape. More vertically oval discs tended to have more vertically oval cups. Other, weaker predictors were disc area, type of cupping and cup area. Larger discs, discs with sloping rims and larger cups were associated with more vertically oval cups. Together, these three factors accounted for only 5% of the variability in cup shape. Spherical equivalent refraction, astigmatism, age, IOP and body height had no significant influence on the cup shape.

3.5. CUP-TO-DISC RATIOS (CDR)

3.5.1. Results

A. Cup-Disc area ratio

a) Descriptive Measures

Table 3.5.1 presents salient descriptive measures related to cup-disc area ratios.

Table 3.5.1:
Cup-Disc Area Ratio Measurements

Description	***Value***
Mean ± SD	0.179 ± 0.11
Median	0.18
Minimum	0
Maximum	0.54
97.5th percentile	0.415
99.5th percentile	0.477

b. Distribution

Figure 3.5.1 displays the frequency distribution of cup-disc area ratio, which is bimodal due to influence of discs with no physiological cupping.

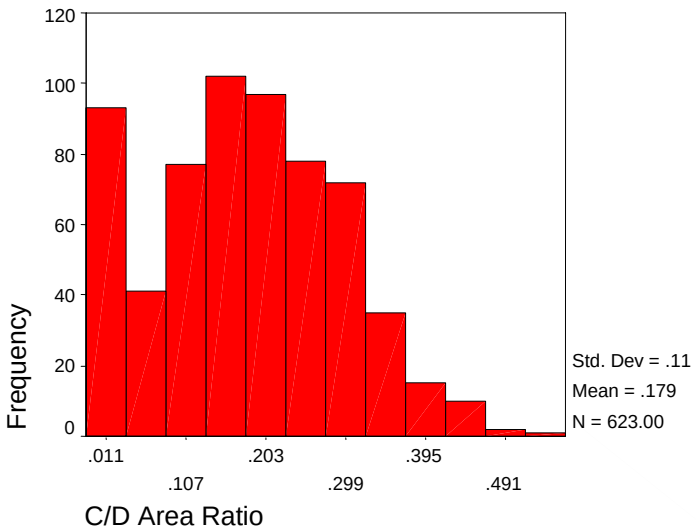


Figure 3.5.1: Frequency distribution of cup-disc area ratio

B. Linear Cup-Disc Ratios

a. Descriptive Measures

Table 3.5.2 summarises the salient descriptive measures of vertical and horizontal linear cup-disc ratios.

Table 3.5.2:
Vertical and Horizontal Cup-Disc Ratios

Description	VCDR	HCDR
Mean ± SD	**0.36 ± 0.18**	**0.39 ± 0.19**
Median	**0.396**	**0.43**
Minimum	**0**	**0**
Maximum	**0.74**	**0.75**
97.5th percentile	**0.628**	**0.665**
99.5th percentile	**0.68**	**0.722**

VCDR: Vertical Cup-Disc Ratio, HCDR: Horizontal Cup-Disc Ratio

b. Distribution

Figure 3.5.2 displays the frequency distributions of VCDR and HCDR, both of which are bimodal due to the influence of discs with no physiological cupping.

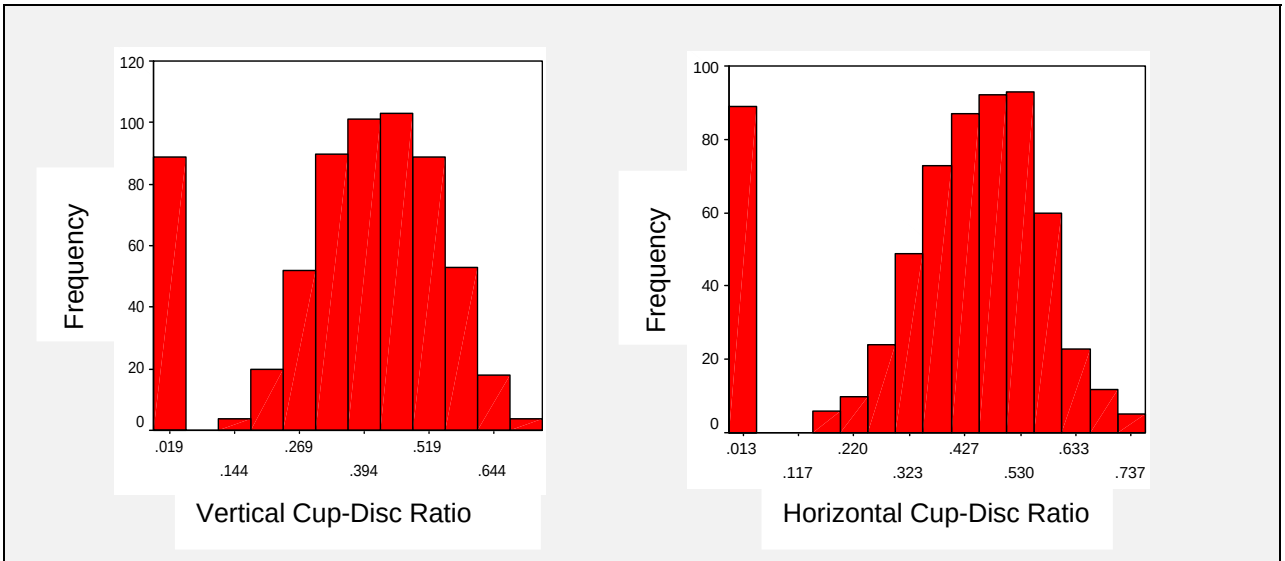


Figure 3.5.2 a (left): Frequency distribution of vertical cup-disc ratio, and b (right): Frequency distribution of horizontal cup-disc ratio

c. Ratio of Vertical to Horizontal Cup-Disc Ratio (Which is larger - VCDR or HCDR?)

Mean ratio of VCDR to HCDR was 0.93 ± 0.12 (minimum 0.45, maximum 1.33, median 0.93) indicating that, on average, HCDR was 7% larger than VCDR. 393 persons (73.6% of 534 persons with physiological cupping) had VCDR $\leq$ HCDR.

d. Associations with VCDR

Significant associations with VCDR were observed for disc area (r=0.46, p<0.0001, Fig 4.5.3) and vertical disc diameter (r=0.42, p<0.0001). When VCDR was compared among discs with different types of physiological cupping, there were significant differences. VCDR was obviously significantly different between discs with and without cupping (t-test, p<0.0001, mean VCDR in discs with no cupping=0, mean VCDR in discs with cupping=0.424 ± 0.11). When VCDR was compared between the different types of cups in discs with physiological cups, the difference was significant (p<0.0001, ANOVA).

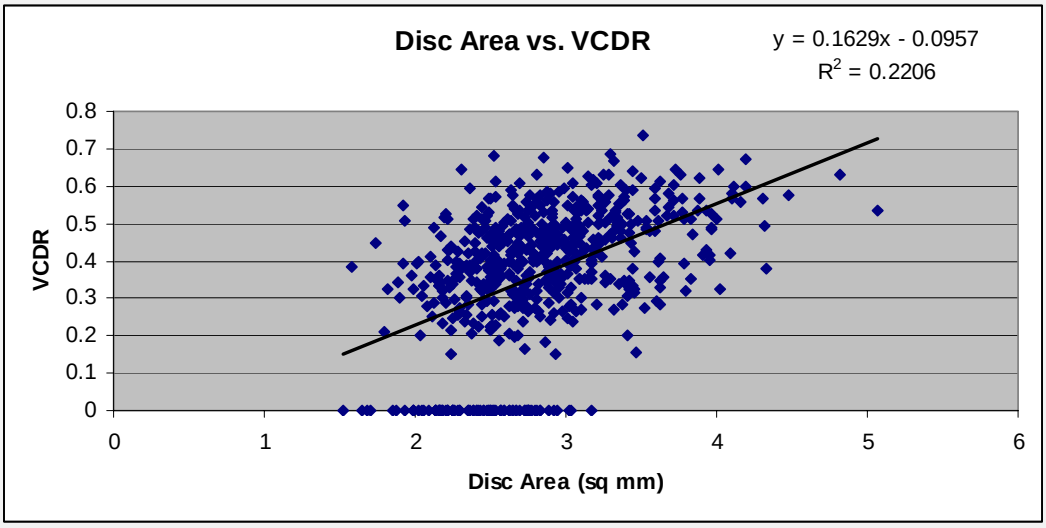


Figure 3.5.3: Scatterplot of Vertical Cup-Disc Ratio (VCDR) vs. Optic Disc Area. Trend line displayed. Regression equation and R^2 (co-efficient of determination) value displayed in the top right corner.

Table 3.5.3: **Comparison of VCDR between different cup types**				
Type of Cupping	**N**	**Mean VCDR**	**SD**	
Steep cups	**317**	**.4432**	**.1038**	**P<0.0001***
Partly sloping	**71**	**.4586**	**.1029**	
Fully sloping	**146**	**.3648**	**.1108**	
Total	**534**	**.4238**	**.1116**	
*** P value calculated using one-way ANOVA** **Tukey post-hoc test revealed significant differences between all pairs except steep and partly sloping cups.**				

Insignificant associations with VCDR were observed with presence of CRA (mean VCDR in eyes with CRA 0.39 ± 0.16, mean VCDR in eyes without CRA 0.35 ± 0.19, p=0.02, t-test), IOP (r=0.087, p=0.03), refraction (r=0.001, p=0.98), astigmatism (r=0.08, p=0.04), axial length (r=0.16, p=0.042), disc shape (r=-0.046, p=0.255), torsion (p=0.05), tilting (p=0.75) , age (r=0.007, p=0.85), gender (p=0.9), CCT (r=0.05, p=0.2) and height (r=0.01, p=0.74).

On multiple linear regression, disc area (r^2 change 0.223, p<0.0001) and type of cupping (r^2 change 0.535, p<0.0001) were significant factors influencing VCDR. When multiple linear regression was repeated after excluding discs with no cups from the model, these two variables were still significant, though weaker (r^2 change 0.14, p<0.0001 for disc area, r^2 change 0.12, p<0.0001 for type of cupping).

e. Correlation between clinical and planimetric assessment of CDR

Table 3.5.4 presents a comparison of clinical and planimetric measures of VCDR and HCDR in the same group of eyes (n=623).

Table 3.5.4:

Clinical And Planimetric Measures Of Linear Cup-To-Disc Ratios

	Mean ± SD	Median	Range	97.5th percentile	99.5th percentile
Planimetric VCDR	**0.36 ± 0.18**	**0.396**	**0 - 0.74**	**0.63**	**0.68**
Clinical VCDR	**0.43 ± 0.18**	**0.40**	**0 - 0.85**	**0.7**	**0.8**
Planimetric HCDR	**0.39 ± 0.19**	**0.43**	**0 - 0.75**	**0.67**	**0.72**
Clinical HCDR	**0.42 ± 0.17**	**0.40**	**0 - 0.85**	**0.7**	**0.8**

VCDR: Vertical Cup-Disc Ratio, HCDR: Horizontal Cup-Disc Ratio

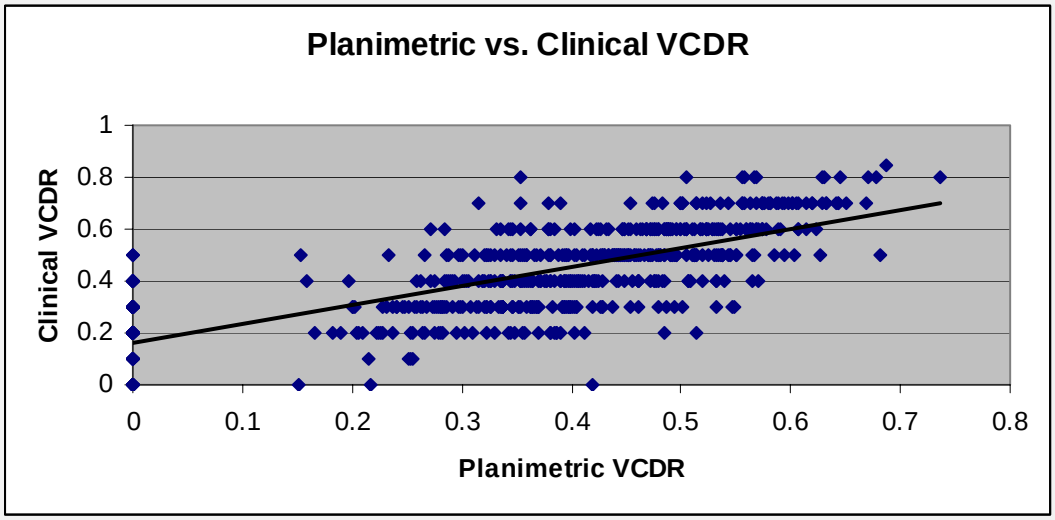


Figure 3.5.4: Correlation between clinical and planimetric estimates of vertical cup-disc ratio (VCDR)(n=623)

As VCDR is the more important measure from a clinical standpoint, this measure was explored in greater detail. Fig 3.5.4 is a scatterplot of clinical versus planimetric estimates of VCDR. In general, the two estimates correlated well. The ICC co-efficient for clinical vs. planimetric VCDR was 0.74. The mean difference between clinical and planimetric VCDR was 0.06 ± 0.13 (clinical minus planimetric VCDR; ranged from -0.42 to 0.50).

i) Clinical versus planimetric assessment of discs with no physiological cupping

92 discs were assessed to have no cupping by either clinical or planimetric estimates.

89 discs had no cupping by planimetric estimates, and 17 had no cupping by clinical estimates. The 2 methods agreed in 14 discs. There was significant difference between the proportion of discs considered to have no cups between the two methods (McNemar test, p<0.0001)

Among 89 discs with no physiological cups on planimetry, clinical VCDR estimate was 0 in 14 discs, 0.1 in 11 discs, 0.2 in 30 discs, 0.3 in 22 discs, 0.4 in 10 discs and 0.5 in 2 discs. In 1 eye with clinical assessment of 0 VCDR, planimetric assessment was 0.15 in 1 eye, 0.22 in 1 eye, and in one more, it was 0.42.

ii). Clinical versus planimetric assessment of discs with physiological cupping

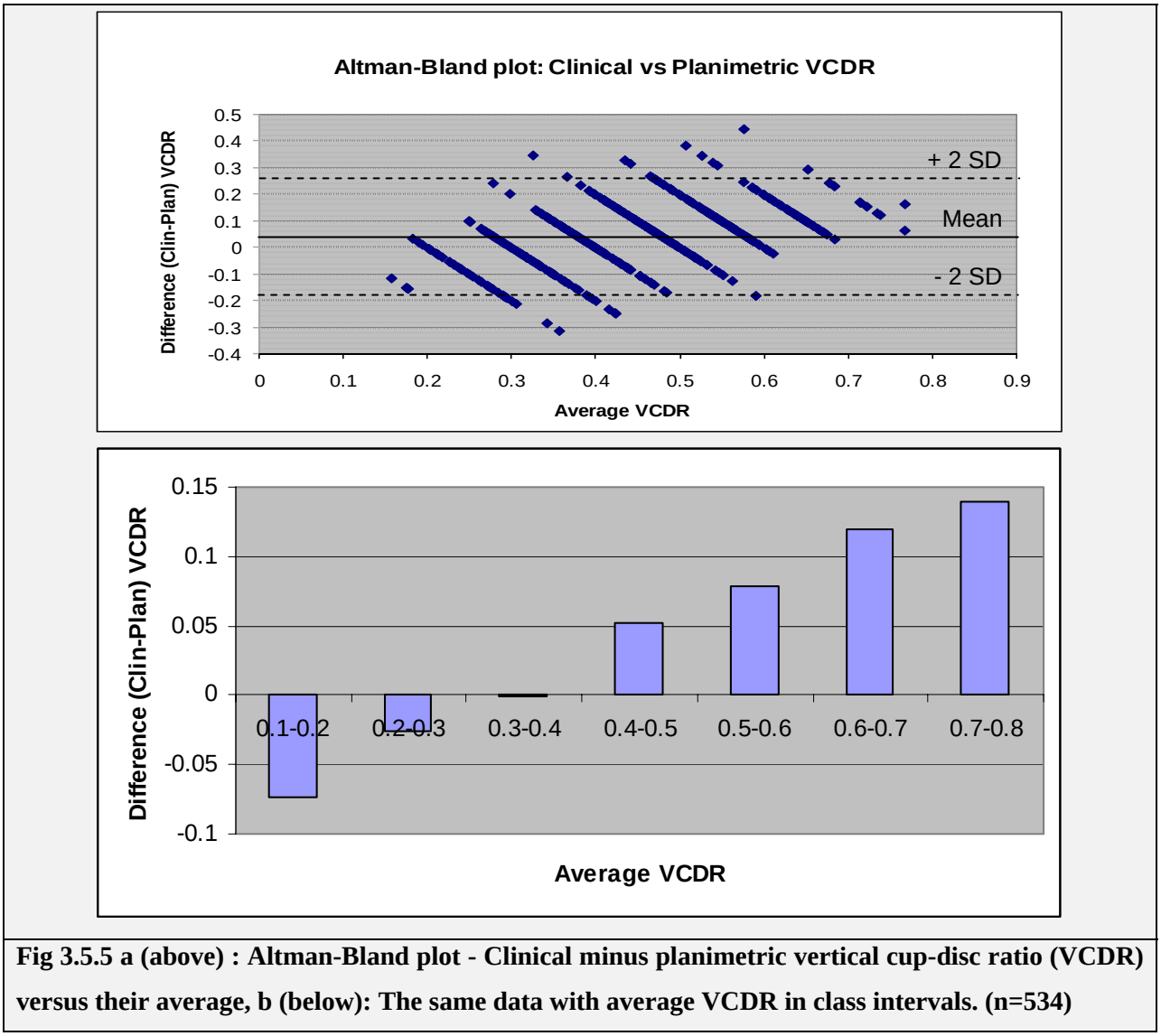


Fig 3.5.5 a (above) : Altman-Bland plot - Clinical minus planimetric vertical cup-disc ratio (VCDR) versus their average, b (below): The same data with average VCDR in class intervals. (n=534)

Plotting the difference between clinical and planimetric VCDR against the average of the 2 readings (Altman-Bland plot) [98] revealed that compared to planimetric estimation, clinical estimation tends to underestimate smaller cups and overestimate larger cups (Figure 4.5.5 a & b).

Difference between clinical and planimetric VCDR did not differ by cup type ($p=0.523$, ANOVA), torsion ($p=0.498$, t-test), disc shape ($r=0.02$, $p=0.58$), or disc area ($r=0.08$, $p=0.06$).

3.5.2. Cup-To-Disc Ratios (CDR) - Discussion

A. Cup-Disc Ratios

Optic cup size enlarges pathologically in glaucoma, however it also bears a physiological relationship to disc size. Therefore a measure that adjusts cup size for disc size – cup-to-disc ratio would be a simple, robust indicator of glaucomatous loss of the neuroretinal rim. This section deals with cup-to-disc ratios calculated as part of this planimetric study. We first discuss cup-disc area ratios briefly in keeping with the pattern adopted for discussion, and then move on to a more detailed discussion of linear cup-disc ratios, especially the VCDR which is most important in the context of glaucoma.

The cup-disc area ratio is the true measure of cup size relative to disc size. However, it is not routinely estimated as a clinical parameter. Linear cup-disc ratios are easier to estimate and are more popular clinical measures of cup size to disc size. With the increasing use of optic nerve imaging devices, however, familiarity with cup-disc area ratios is increasing. However, due to differences in the way the cup is identified by the different methods, as discussed earlier, the results of planimetric estimates of cup-disc area ratio may not be directly applicable to use with those instruments. Rather they would serve as, at best, a rough working guide.

Mean cup-disc area ratio was 0.18 indicating that on average, the optic cup occupied 18% of the optic disc area. 97.5^{th} and 99.5^{th} percentiles of this ratio were 0.42 and 0.48 respectively, indicating that 97.5% of perimetrically normal persons had optic cups that occupied lesser than 42% of the optic disc area, and 99.5% of them had optic cups occupying lesser than 48% of the disc area. There was a wide range of variability, from no optic cups on one end of the spectrum, to cups occupying 54% of disc area at the other end of the spectrum. Distribution of cup-disc area ratio was bimodal, influenced by the ratios of 0 in discs with no physiological cupping.

Linear cup-disc ratios, especially the vertical, have long been used as a measure of relative cup to disc dimensions to assess glaucomatous loss. The VCDR is an important measure to evaluate optic discs and traditionally, VCDRs $\geq$ 0.7 have been considered suspect for glaucoma.[99,100] The recent ISGEO classification of glaucoma[7] that attempted to provide a standardized definition of glaucoma for epidemiological surveys and maximize comparability of studies, suggested that statistical limits of normal vertical cup-disc ratios be derived from normals within each population, for application to identify glaucoma in the same population.

Thereby, the classification attempted to standardize diagnostic criteria for glaucoma, while accounting for racial variability of disc dimensions.

The mean (median) vertical and horizontal cup-disc ratios in the current planimetric study were 0.36 (0.39) and 0.39 (0.43) respectively. Mean VCDR and HCDR estimated by the current study were close to estimates by the APEDS[32] and by Jonas et al among Caucasians.[22] The values are smaller than those reported by other studies- The Rotterdam,[4] BMES[10] and the Baltimore Eye studies.[9] As discussed earlier, these differences may be related to methodological differences in the way the cup was marked (all studies that used the Topcon Imagenet i.e., Baltimore and Rotterdam, yielded larger CDRs than the current study), or real differences arising out of racial variations in the number or arrangement of nerve fibres at the optic disc. It is difficult to explain the rather wide difference in estimate of CDR between the current study and the VES (0.56 VCDR and 0.66 HCDR), except that the current study was larger and may have included a greater range of cup-disc ratios than the VES.[56]

97.5th and 99.5th percentiles which define the limits of normal CDRs were 0.63 and 0.68 for vertical CDR and 0.66 and 0.72 for HCDR. However, as discussed in detail later, we observed systematic differences between clinical and planimetric estimates of VCDR, and these statistical limits may not be directly applicable to clinical estimates. The frequency distributions of VCDR and HCDR were both bimodal, influenced by the discs with absent cupping (i.e., VCDR and HCDR of 0). Consistent with reports by earlier planimetric studies, mean VCDR in this study was smaller than mean HCDR. On average HCDR was 7% greater than VCDR, with approximately 74% of patients having VCDRs smaller than HCDR. Jonas et al suggested that this is due to the characteristic configuration of the neuroretinal rim, with the inferior and superior rims thicker than the nasal and temporal rims, leading to horizontally oval cups in vertically oval discs, and greater horizontal compared to vertical cup-disc ratios (by about 17%).[22] In the current study, optic discs were vertically oval, average VCD was approximately equal to HCD, and HCDR was approximately 7% greater than VCDR.

Glaucomatous change usually affects the inferior and/or superior poles of the optic disc, therefore VCDR is the more important measure in the context of detecting glaucomatous change. Therefore, determinants of cup-disc ratio were only examined for VCDR. Although VCDR by definition represents cup size corrected for disc size, it was still found to be dependent on disc size, though to a lesser extent than absolute measures of cup size. Dependence of VCDR on disc

size has been demonstrated before. Crowston et al [65] reported that median VCDR increased by 0.2 from small to large optic discs, and stressed the importance of routine evaluation of optic disc diameter in clinical practice. Garway-Heath et al[6] reported similar increase in VCDR with VDD. Jonas et al reported dependence of CDR on disc area as well as morphological type of cupping.[22] They reported that discs with temporal flat slopes had significantly lower VCDRs compared to discs with punched-out cups, which is what the current study reports as well. Oblique arrangement of nerve fibres in discs with temporal sloping rims, while increases measured rim area, decreases measured cup area and therefore results in lower cup-disc ratio estimates. Other factors- IOP, refraction, axial length, disc shape, age, gender, CCT and height had no significant influence on VCDR.

Clinical versus planimetric assessment

Clinical and planimetric estimates of cup-disc ratio are made under very different conditions. In the clinic, the physician is required to make a decision under constraints of patient discomfort under the bright light, eye movement and limited time. Planimetric assessment, on the other hand, affords more comfortable examination and accurate measurement without imposing time and other constraints. However, it is the clinical estimate that is more often used in practice and therefore is also more important from a treatment viewpoint. We therefore attempted to examine the relationship between clinical estimates and planimetrically measured VCDR in the current study and document systematic differences, if any, between the two methods.

The intraclass correlation co-efficient for agreement between the two methods was 0.74, indicating good agreement between the two methods. An inspection of Table 4.5.4 reveals that mean and median values of VCDR by clinical and planimetric evaluation were fairly close to each other. However, the differences between the two methods become wider close to the extreme i.e. 97.5^{th} and 99.5^{th} percentiles.

We then examined discs with and without physiological cupping separately to assess the concordance in estimation of no cupping between clinical and planimetric methods. Out of 89 discs assessed to have no cupping on stereophotographs, only 14 eyes (16%) received the same verdict during clinical examination. However, out of 17 discs considered to have no cups on clinical examination, 14 eyes (82.3%) were considered to have no cups on photographic assessment. These results suggest that discs were much more likely to be classified as having no

physiological cupping on evaluation of stereophotographs, compared to clinical examination of the patient.

Among discs with physiological cupping on clinical as well as photographic assessment, Altman and Bland plots were used to examine the relationship between clinical and planimetric measures and document systematic differences between them. The Altman-Bland plot [98] is a plot of the difference between the methods versus average of the two methods and is used to examine if the difference changes with change of the average of the 2 measures. Inspection of Figure 4.5.4 a suggests that the difference between the 2 methods does increase with average of the two measures. Figure 4.5.4 b presents the same data, but grouped into class intervals and displays the results more clearly. At average VCDR of 0.3-0.4, there was almost no difference between the methods. At lower average VCDRs, the difference was negative i.e., planimetric VCDR was greater than clinical VCDR. At average VCDRs higher than 0.4, clinical estimates of VCDR were higher than planimetric VCDR measures, and this increased progressively with average VCDR. Therefore, compared to planimetry, clinical assessment tended to underestimate small cups and overestimate large cups.

Two recent studies [101,102] that examined VCDRs measured using the DISCAM (planimetric) system with examiner assessment of VCDR from stereophotographs reported that planimetry overestimated small VCDRs and underestimated large VCDRs. While one of these studies[3] reported good correlation (ICC 0.7, similar to our findings) between ophthalmoscopic assessment and planimetric measures, neither of them reported systematic differences between ophthalmoscopic and planimetric VCDRs.

To the best of our knowledge, ours is the first study to directly examine systematic differences between CVCDR estimates and PVCDR measures. The studies mentioned above come closest in that assessment of stereophotographs, but not clinically (biomicroscopically) estimated CDR was compared with planimetric measurement. Theoretically, this may introduce differences as clinical measures are made under time constraints, and possibly an uncomfortable patient with moving eyes, while assessment of stereophotographs would be much more comfortable. Our results were very similar to those reported by the other 2 studies, suggesting that these constraints may not play an important part in creating the systematic differences. Rather, it may be an element of human error responsible for our finding that compared to planimetry, clinical assessment tended to underestimate small cups and overestimate large cups.

Biomicroscopic measurement of disc and cup diameters, although approximate, may help reduce the error.

3.6. INTER-EYE ASYMMETRY

3.6.1. Results

Data of both eyes were available for 565 persons. Their mean age was 48.18 ± 6.8 years. 334 subjects (59.1%) were women.

Table 3.6.1 presents morphometric data of right and eyes for this group of persons. No significant differences between right and left eyes were found for any of the measures

Table 3.6.1: Comparison Of Right Eye And Left Eye Values Of Planimetric Measurements

	Right Eyes (mean ± SD) (N=565)	Left Eyes (mean ± SD) (N=565)	P value
Disc Area (sq mm)	**2.84 ± 0.52**	**2.84 ± 0.52**	**0.82**
Rim Area (sq mm)	**2.29 ± 0.39**	**2.32 ± 0.42**	**0.25**
Cup Area (sq mm)	**0.54 ± 0.39**	**0.52 ± 0.38**	**0.37**
VDD (mm)	**1.94 ± 0.20**	**1.94 ± 0.20**	**0.90**
HDD (mm)	**1.81 ± 0.19**	**1.82 ± 0.18**	**0.35**
VDD/HDD	**1.08 ± 0.08**	**1.07 ± 0.08**	**0.19**
VCD (mm)	**0.73 ± 0.37**	**0.71± 0.37**	**0.43**
HCD (mm)	**0.73 ± 0.37**	**0.73 ± 0.37**	**0.80**
VCD/HCD	**1 ± 0.14**	**0.98 ± 0.13**	**0.05**
Cup Area/ Disc Area	**0.18 ± 0.11**	**0.18 ± 0.11**	**0.37**
VCDR	**0.37 ± 0.18**	**0.36 ± 0.17**	**0.45**
HCDR	**0.40 ± 0.19**	**0.39 ± 0.19**	**0.69**
VCDR/HCDR	**0.93 ± 0.12**	**0.91 ± 0.11**	**0.15**

VDD: Vertical Disc Diameter, HDD: Horizontal Disc Diameter, VCD: Vertical Cup Diameter, HCD: Horizontal Cup Diameter, VCDR: Vertical cup-disc ratio, HCDR: Horizontal cup-disc ratio

Inter-eye differences are presented as absolute values (larger minus smaller values) and as right minus left values. Right minus left values were used to explore associations in order to preserve side orientation with respect to all parameters examined.

Disc Size Asymmetry

a. Disc Area Asymmetry

i) Descriptive Measures:

Mean asymmetry of disc area was 0.19 ± 0.16 sq mm (median 0.15 sq mm, 95th percentile 0.49 sq mm, range 0-1.25 sq mm). Frequencies at different levels of asymmetry are summarized in Table 4.6.2. Considering right minus left differences, the mean was as -0.007 ± 0.25 sq mm (median -0.005).

Table 3.6.2: Frequency table: Disc Area Asymmetry (n=565)

Difference* (sq mm)	No. of subjects	Percentage	Cumulative percentage
0-0.1	184	32.57	32.57
0.11-0.2	175	30.97	63.54
0.21-0.3	102	18.05	81.59
0.31-0.4	46	8.14	89.73
0.41-0.5	34	6.02	95.75
0.51-0.6	12	2.12	97.87
0.61-0.7	7	1.24	99.11
0.71-0.8	2	0.35	99.46
0.81-0.9	1	0.18	99.64
0.91-1.0	1	0.18	99.82
>1.0	1	0.18	100

ii) Factors Influencing Disc Area Asymmetry

Disc area asymmetry did not correlate with average (of right and left) disc area (r=-0.048, p=0.25), asymmetry of spherical equivalent refractive error (r=-0.061, p=0.145) or average refractive error (r=0.004, p=0.93), asymmetry of CCT (r=0.011, p=0.796) or asymmetry in presence of physiological cupping (mean asymmetry in discs with cupping or no cupping in both eyes -0.006 ± 0.25, mean asymmetry in persons with cupping in one eye and no cupping in the other -0.025 ± 0.19, p=0.65, t-test). There were no significant gender differences (p=0.259, mean asymmetry in men 0.007 ± 0.25, mean asymmetry in women -0.02 ± 0.25, t-test) or correlation with age (r=-0.017, p=0.68).

b. Disc Diameter Asymmetry

i) Descriptive Measures:

Mean absolute value of VDD asymmetry was 0.09 ± 0.07 mm (median 0.08 mm, 95th percentile 0.23, range 0-0.56 mm). Considering right-left differences in VDD, the mean asymmetry was -0.001 ± 0.12 mm (median -0.002).

Mean absolute value of HDD asymmetry was 0.08 ± 0.07 mm (median 0.07, 95th percentile 0.22, range 0-0.50 mm). Considering right-left differences in HDD, the mean asymmetry was -0.01 ± 0.1 mm (median -0.008 mm).

VDD/HDD (disc shape) asymmetry

Descriptive Measures

Mean absolute value of VDD/HDD asymmetry was 0.06 ± 0.05 (median 0.05, 95th percentile 0.15, range 0.-0.28). Considering right-left differences in VDD/HDD, the mean asymmetry was 0.006 ± 0.08 mm (median 0.004).

Factors influencing disc shape asymmetry

Asymmetry of disc shape showed no significant relationship to age (r=-0.06, p=0.187), gender (p=0.17, t-test), asymmetry of astigmatism (r=0.03, p=0.5), asymmetry of spherical equivalent refraction (r=0.06, p=0.16), or disc area asymmetry (p=0.5, r=0.02).

Neural rim area asymmetry

Descriptive Measures

Mean absolute value of rim area asymmetry was 0.18 ± 0.15 sq mm (median 0.14, 95th percentile 0.48, range 0.-0.93 sq mm). Frequencies at different levels of asymmetry are summarized in Table 4.6.3.

Considering right-left differences in VDD/HDD, the mean rim area asymmetry was -0.03 ± 0.24 sq mm (median -0.013 sq mm).

Table 3.6.3: Frequency table: Neural Rim Area Asymmetry (n=565)			
Difference* (sq mm)	**No. of subjects**	**Percentage**	**Cumulative percentage**
0-0.1	**217**	**38.41**	**38.41**
0.11-0.2	**155**	**27.43**	**65.84**
0.21-0.3	**107**	**18.94**	**84.78**
0.31-0.4	**45**	**7.96**	**92.74**
0.41-0.5	**19**	**3.36**	**96.1**
0.51-0.6	**8**	**1.42**	**97.52**
0.61-0.7	**5**	**0.88**	**98.4**
0.71-0.8	**4**	**0.71**	**99.11**
0.81-0.9	**4**	**0.71**	**99.82**
0.91-1.0	**1**	**0.18**	**100**

Factors influencing rim area asymmetry

Rim area asymmetry correlated with disc area asymmetry ($r=0.59$, $p<0.0001$, Figure 4.6.1) and IOP asymmetry ($r=-0.12$, $p=0.005$, Figure 4.6.2). Insignificant associations were observed with asymmetry of refractive error ($r=-0.084$, $p=0.046$), asymmetry in morphological type of cupping (mean difference -0.015 ± 0.22 in symmetrical cupping, -0.047 ± 0.25 in asymmetrical cupping, $p=0.1$, t-test), CCT ($r=-0.02$, $p=0.6$) age ($r=-0.07$, $p=0.09$) or gender ($p=0.98$, t-test).

On multivariate analysis, disc area asymmetry (r^2 change 0.359, $p<0.0001$) and IOP asymmetry (r^2 change 0.009, $p=0.004$) were significantly related to rim area asymmetry.

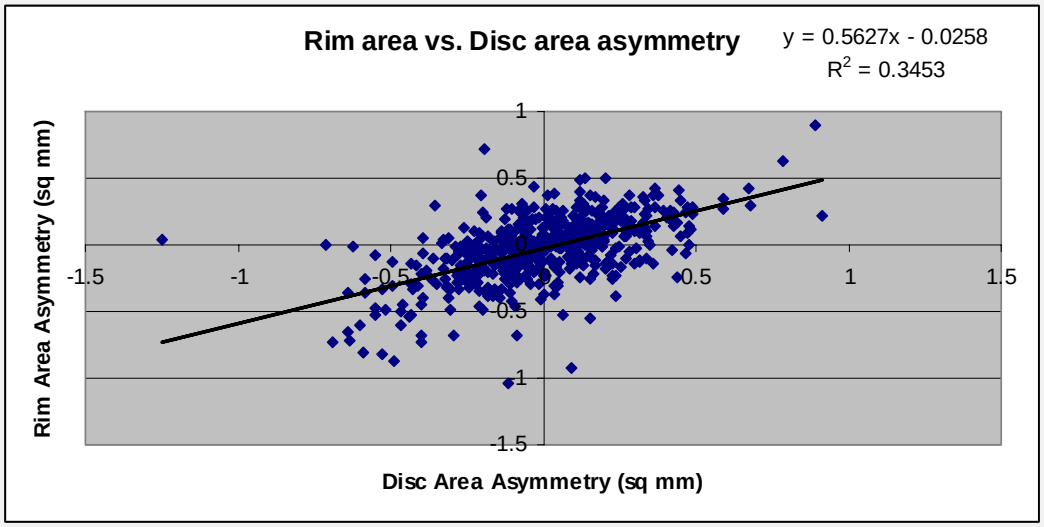


Figure 3.6.1: Scatterplot of rim area asymmetry (right minus left) versus disc area asymmetry (right minus left).Trend line displayed. Regression equation and R^2 (co-efficient of determination) value displayed in the top right corner.

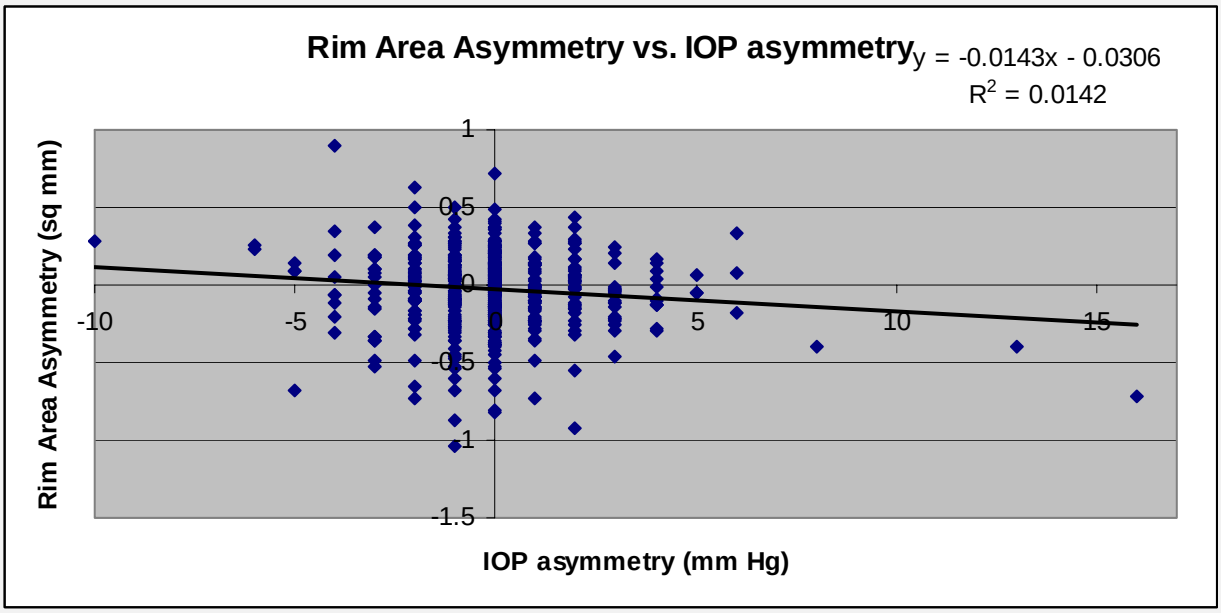


Figure 3.6.2: Scatterplot of rim area asymmetry (right minus left) versus intraocular pressure (IOP) asymmetry (right minus left). Trend line displayed. Regression equation and R^2 (co-efficient of determination) value displayed in the top right corner.

Asymmetry in type of cupping

Absence of Physiological Cupping

76 right eyes and 78 left eyes were adjudged to have no physiological cupping. Of them 60 eyes had bilateral absence of physiological cupping i.e., 10.62% of patients had no cupping in both eyes. In addition 34 patients (6.02%) had absence of cupping in any one eye (16 right eyes and 18 left eyes). There was a significant association between absence of cupping between right and left eyes (chi-square test, $p<0.0001$).

Discs with Physiological cupping

Among discs with cupping, the category was symmetrical in 288 patients (60.9%) and asymmetrical in the rest. There was a statistically significant association between type of cupping of right and left eyes ($P< 0.0001$, Chi-square test).

Optic cup size asymmetry

Cup Area Asymmetry

i) Descriptive measures

Mean absolute value of optic cup area asymmetry was 0.15 ± 0.15 sq mm (median 0.12 sq mm, 95th percentile 0.41, range 0- 1.29 sq mm). Considering right-left differences in optic cup area, the mean asymmetry was 0.02 ± 0.22 sq mm (median 0.00 sq mm).

Table 3.6.4: Frequency table: Optic Cup Area Asymmetry (n=565)

Difference* (sq mm)	No. of subjects	Percentage	Cumulative percentage
0-0.1	265	46.90	46.90
0.11-0.2	137	24.25	71.15
0.21-0.3	86	15.22	86.37
0.31-0.4	46	8.14	94.51
0.41-0.5	18	3.19	97.7
0.51-0.6	3	0.53	98.23
0.61-0.7	6	1.06	99.29
0.71-0.8	1	0.18	99.47
0.81-0.9	-	-	99.47
0.91-1.0	2	0.35	99.82
>1.0	1	0.18	100

ii) Factors influencing cup area asymmetry

A significant correlation between cup area asymmetry and disc area asymmetry (r=0.496, p<0.0001) was observed. (Fig 3.6.3)

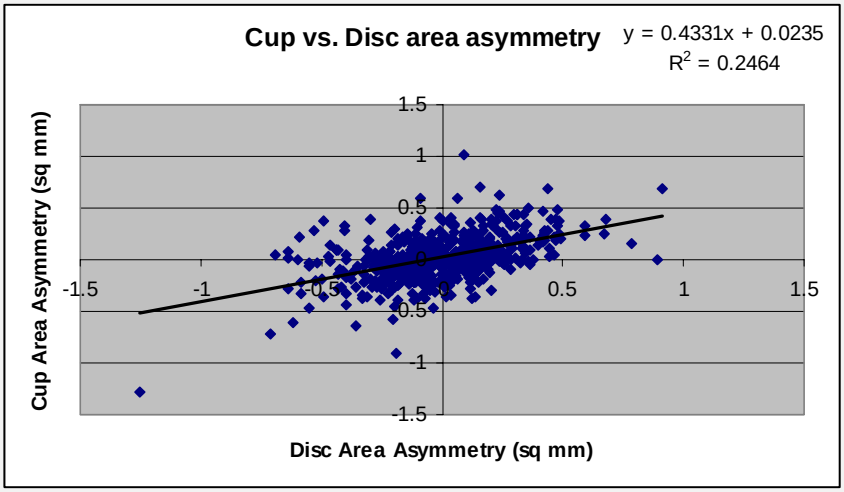


Figure 3.6.3: Scatterplot of cup area asymmetry (right minus left) versus disc area asymmetry (right minus left). Trend line displayed. Regression equation and R^2 (co-efficient of determination) value displayed in the top right corner.

When cup area asymmetry was compared between persons with no cups in any one eye and persons with physiological cupping in both eyes, the asymmetry was significantly higher among persons who had no cupping in any one eye (mean asymmetry in persons with no cupping in LE 0.25 ± 0.11 sq mm, mean asymmetry in persons with bilateral physiological cups 0.02 ± 0.22 sq mm , mean asymmetry in persons with no cupping in RE only -0.27± 0.2, p<0.0001, ANOVA) Tukey test revealed significant differences between all pairs. Insignificant influences on cup area asymmetry were observed with age (r=0.047, p=0.3), gender (p=0.3, t-test), asymmetry of refraction (r=0.02, p=0.54), asymmetry of cylindrical error (r=0.02, p=0.586), asymmetry of IOP (r=0.08, p=0.07) and asymmetry of CCT (R=0.04, P=0.29).

On multivariate analysis, disc area asymmetry (r^2 change 0.27, p<0.0001) and asymmetry in presence or absence of physiological cupping (r^2 change 0.06, p<0.0001) and were significant predictors of cup area asymmetry.

Asymmetry in optic cup diameters

Mean absolute value of VCD asymmetry was 0.15 ± 0.16 mm (median 0.11 mm, 95th percentile 0.47, range 0- 1.08 mm). Considering right-left differences in VDD, the mean asymmetry was 0.017 ± 0.22 mm (median 0.000).

Mean absolute value of HCD asymmetry was 0.15 ± 0.16 mm (median 0.10, 95th percentile 0.50, range 0- 1.04 mm). Considering right-left differences in HCD, the mean asymmetry was 0.005 ± 0.21 mm (median 0.000 mm).

Asymmetry in optic cup shape (VCD/HCD)

i) Descriptive Measures

Mean absolute value of VCD/HCD asymmetry was 0.16 ± 0.23 (median 0.09, 95th percentile 0.85, range 0.- 1.29). Considering right-left differences in VCD/HCD, the mean asymmetry was 0.02 ± 0.28 (median 0.000).

ii) Factors influencing optic cup shape asymmetry

Significant associations of VCD/HCD asymmetry were found with disc area asymmetry (r=0.15, p<0.0001), disc shape (VDD/HDD) asymmetry (r=0.17, p<0.0001) and cup area asymmetry (r=0.3, p<0.0001).

Insignificant associations were found with asymmetry in type of cupping (mean VCD/HCD asymmetry in symmetrical type of cupping 0.02 ± 0.15, 0.005 ± 0.17 in asymmetrical type of cupping, p=0.5, t-test), asymmetry of refractive error (r=0.005, p=0.9), asymmetry of astigmatism (r=0.04, p=0.33) and asymmetry of IOP (r=0.08, p=0.055).

On multiple linear regression, cup area asymmetry (r^2 change 0.065, p<0.0001), disc shape asymmetry (r^2 change 0.029, p<0.0001) and disc area asymmetry (r^2 change 0.024, p<0.0001) were significant predictors of cup shape asymmetry.

Asymmetry of cup-disc ratios

Cup-Disc Area Ratio Asymmetry

Mean Cup-Disc Area Ratio asymmetry was 0.05 ± 0.045 (median 0.04, range 0-0.31).

97.5th and 99.5th percentiles of Cup-Disc Area Ratio Asymmetry were 0.16 and 0.23 respectively.

In terms of right-left, the mean difference was 0.006 ± 0.07 (median 0.000).

Linear cup-disc ratios

i). Descriptive measures

Table 3.6.5 summarises the salient measures relating to vertical and horizontal cup-disc ratio asymmetries. Table 3.6.6 displays frequencies of different levels of VCDR asymmetry.

In terms of right-left, mean asymmetry of VCDR was 0.008 ± 0.11 (median 0.000) and that of HCDR was 0.004 ± 0.12 (median 0.000).

Table 3.6.5: Vertical & Horizontal Cup-Disc Ratio Asymmetry

	VCDR Asymmetry (n=565)	**HCDR Asymmetry (n=565)**
Mean ± SD	**0.07± 0.08**	**0.075 ± 0.09**
Median	**0.05**	**0.05**
97.5th percentile	**0.32**	**0.34**
99.5th percentile	**0.42**	**0.45**
Minimum	**0**	**0**
Maximum	**0.54***	**0.58**
*** Photographs of subject with asymmetry of 0.54 shown in figure 3.6.4.**		

Figure 3.6.4: Right eye (RE) and left eye (LE) optic disc photographs of the same subject demonstrating no physiological cupping in the RE and VCDR 0.54 in the LE.

Table 3.6.6: Frequency Table Of VCDR And HCDR Asymmetry (N=565)								
	VCDR Asymmetry * (N) (%) (n=565)	**Cumul - ative %***	**VCDR asymmetry§ (N) (%) (n=471)**	**Cumu-lative %§**	**HCDR Asymmetry* (N) (%) (n=565)**	**Cumu -lative %***	**HCDR asymmetry § (N) (%) (n=471)**	**Cumu-lative %§**
0-0.1	**439 (77.70)**	**77.70**	**379 (80.47)**	**80.47**	**441 (78.05)**	**78.05**	**381 (80.89)**	**80.89**
0.11-0.2	**87 (15.40)**	**93.1**	**82 (17.41)**	**97.88**	**82 (14.51)**	**92.56**	**79 (16.77)**	**97.66**
0.21-0.3	**24 (4.25)**	**97.35**	**10 (2.12)**	**100**	**20 (3.54)**	**96.1**	**11 (2.34)**	**100**
0.31-0.4	**13 (2.30)**	**99.65**	**-**	**100**	**18 (3.19)**	**99.29**	**-**	**100**
>0.41	**2 (0.35)**	**100**	**-**	**100**	**4 (0.71)**	**100**	**-**	**100**
N: No of subjects ; *Data of all 565 patients where both eyes data were available§ ; Only patients with bilateral physiological cupping (n=471), patients with no cupping in either one/both eyes excluded								

ii) Factors influencing VCDR Asymmetry

When VCDR asymmetry was compared between persons with no cups in any one eye and persons with physiological cupping in both eyes, the asymmetry was significantly higher among persons who had no cupping in any one eye (mean asymmetry in persons with no cupping in LE 0.28 ± 0.07, mean asymmetry in persons with bilateral physiological cups 0.01 ± 0.08, mean asymmetry in persons with no cupping in RE only -0.32± 0.10, $p<0.0001$, ANOVA) Tukey test revealed significant differences between all pairs. In persons with bilateral physiological cupping, VCDR asymmetry ranged from 0 to 0.28, 97.5th percentile was 0.2 and 99.5th percentile was 0.27. (Also see Table 4.6.6 for frequencies of VCDR asymmetries at different levels in the whole group vs. persons with bilateral physiological cups and example in Figure 4.6.4).

VCDR asymmetry was also significantly correlated with disc area asymmetry ($r=0.27$, $p<0.0001$, Figure 5), but not with IOP asymmetry ($r=0.08$, $p=0.07$), refractive error asymmetry ($r=0.03$,

p=0.5), asymmetry of CCT (r=-0.20, p=0.63) or disc shape asymmetry (r=-0.019, p=0.65). It also did not depend on the value of VCDR i.e., average of right and left VCDR (R=0.05, p=0.26)

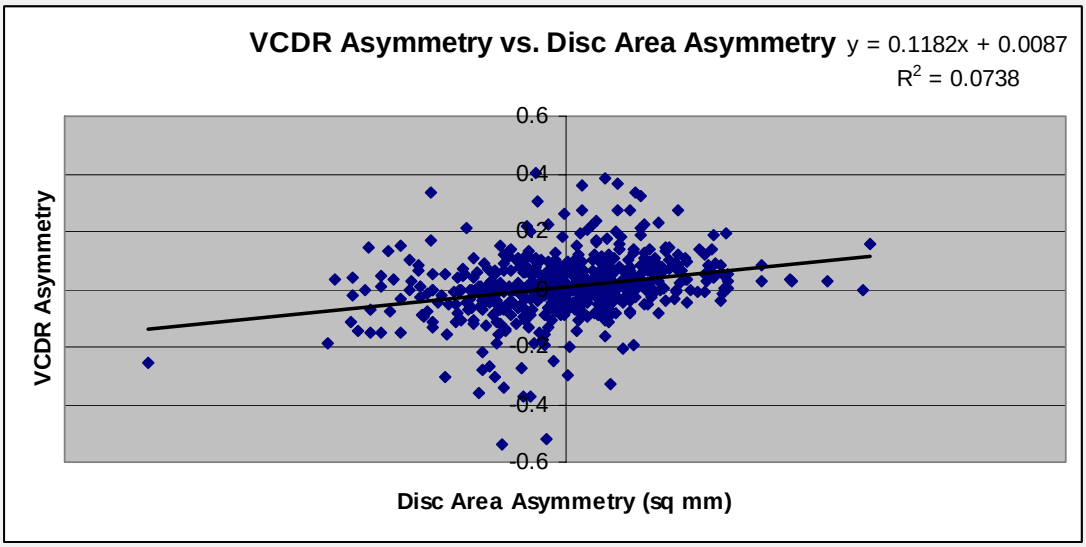


Figure 3.6.5: Scatterplot of vertical cup-disc ratio (VCDR) asymmetry (right minus left) versus disc area asymmetry (right minus left).Trend line displayed. Regression equation and R^2 (co-efficient of determination) value displayed in the top right corner.

On multivariate analysis, asymmetry in presence or absence of physiological cupping (r^2 change 0.43, p<0.0001) and disc area asymmetry (r^2 change 0.08, p<0.0001) were significant predictors of VCDR asymmetry.

3.6.2. Inter-Eye Asymmetry- Discussion

Optic disc parameters are largely symmetrical between both eyes of normal subjects. Determining asymmetry of optic disc parameters between the eyes of each patient potentially reduces parameter variability by adjusting for interindividual variations due to factors such as race, age, gender, and disc size. Asymmetry of vertical cup-disc ratio is considered one of the important diagnostic indicators of glaucomatous cupping.[7] In spite of the significance of asymmetry measures, there is relative paucity of population-based data on measures of asymmetry in normal individuals. Asymmetry data are available from the Baltimore,[9] BMES [67] and the BEAP [68]. Jonas et al also report side differences in a subset of 138 eyes from their hospital based sample of 457 patients[22]. To the best of our knowledge, there have been no reports of asymmetry of optic disc parameters among Indians.

In the current study, asymmetry data are presented as absolute values (larger minus smaller values) and also as right minus left values. Absolute values would be easier to relate to and apply clinically, and therefore are presented first. However, to explore relationships of optic disc parameter asymmetry with other ocular parameters, it is important that side orientation be maintained. For example, if a subject had right eye rim area of 2 sq mm and IOP of 10 mmHg, with left rim area of 1 sq mm and IOP of 20 mm Hg, the situation is very different from another patient having right rim area of 2 sq mm and IOP of 20 mmHg, with left rim area 1 sq mm and IOP of 10 mm Hg. If we considered absolute values to explore relationships, these two patients would be inappropriately considered to have identical values. Therefore, it is important to maintain right-left orientation while exploring relationships and for this reason, right minus left values have also been presented.

None of the optic disc parameters showed any significant differences between right and left eyes (Table 3.6.1). Mean asymmetries of disc, cup and rim areas were 0.19 sq mm, 0.15 and 0.18 sq mm (median 0.15, 0.12 and 0.14 sq mm) respectively. The BEAP[68] reported median disc area asymmetry of 0.14 sq mm among 517 normal persons, which is fairly close to our value of 0.15 sq mm. They however, do not report values of global rim and optic cup area. The Baltimore Eye study[9] reported disc, cup and rim area asymmetries of 0.29, 0.26 and 0.27 sq mm among blacks and 0.27, 0.24 and 0.28 sq mm among white participants. A CSLO study among Japanese participants[48] which examined interocular asymmetry in 174 participants reported mean asymmetries of 0.12, 0.16 and 0.16 for disc, cup and rim area respectively. In another HRT study

among normal Swiss participants, mean (median) asymmetries were 0.18 (0.14), 0.14 (0.11) and 0.19 (0.14) respectively.[103] 95% of our subjects had disc area asymmetry < 0.5 sq mm and optic cup area asymmetry < 0.41 sq mm. Jonas et al also report side differences in a subset of 138 eyes from their hospital based sample of 457 patients[22], and reported that 95% subjects had asymmetry < 1 sq mm.

Disc area asymmetry did not show any significant correlations with age, gender, or refractive error asymmetry. Though asymmetry was numerically greater (by 0.019 sq mm) in persons who had cupping in one eye and no cupping in the other, compared to persons with bilateral presence or absence of cupping, this difference was not statistically significant.

As expected, rim area asymmetry showed a significant correlation with disc area asymmetry, which accounted for 35.9% of variability in rim area asymmetry. The side with the larger disc tended to have the larger rim. Rim area asymmetry also correlated with IOP asymmetry. This was a little surprising in view of the fact that previous analysis of rim area vs. IOP values (not asymmetry) did not yield any significant correlations. However, the magnitude of the association was very small- IOP asymmetry only accounted for 0.9% of the variability in rim area asymmetry. As mentioned earlier, asymmetry analysis adjusts for interindividual variations of a number of known and unknown biological influences that may have an effect on optic disc parameters and this may have unmasked a weak, although clinically insignificant, association that exists between IOP and rim area among healthy eyes. There was no significant association between rim area asymmetry and other factors- age, gender, refractive error asymmetry and asymmetric type of cupping.

Optic cup area asymmetry was associated with disc area asymmetry, which accounted for 27% of the variability in optic cup asymmetry, and asymmetry in the presence of physiological cupping (which accounted for 6%). Other factors- age, gender, refractive error asymmetry, IOP asymmetry and CCT asymmetry did not show any significant influences on cup area asymmetry.

Mean (median) asymmetries of vertical and horizontal disc diameters were 0.09 (0.08) and 0.08 (0.07) mm respectively. Mean (median) asymmetries of vertical and horizontal cup diameters were 0.15 (0.11) and 0.15 (0.10) respectively. Previous data on VDD and VCD asymmetry have only been reported by the BMES,[67] which reported median VDD asymmetry of 0.08 and median VCD asymmetry of 0.09 mm, values which are quite similar to our results.

Asymmetry in the shape of the optic disc has, to the best of our knowledge, not been examined by any previous studies. As noted earlier, disc shape was found to have a significant influence on the shape of the optic cup. We examined disc shape asymmetry to document the normal limits of this parameter in our population, as well as to examine its influence on other parameters of interest i.e., asymmetry in cup shape and VCDR.

Average disc shape (VDD/HDD) asymmetry in this population was 0.06 (i.e., the VDD of one eye was an additional 6% longer than its HDD, compared to the other eye). This asymmetry ranged from 0 to a maximum value of 0.28, with 95% of values falling within 0.15. Though disc shape itself (not asymmetry) was significantly different between the genders, asymmetry in disc shape showed no relationship to gender. It also showed no relationship with asymmetry of disc area, age, asymmetry in spherical refractive error or asymmetry in astigmatism.

Just as a vertically oval cup alerts the clinician to look for other evidence of neural rim thinning at the inferior and/or superior poles, asymmetry in cup shape i.e., one eye with a more vertically oval cup than the other similarly alerts the examiner. We found earlier that optic cup shape in this healthy population is influenced by disc shape, disc area, type of cupping and cup area. We therefore examined asymmetry in VCD/HCD to examine asymmetry in cup shape, and also its association with other parameters.

The mean asymmetry in VCD/HCD was 0.16 (median 0.09, range 0- 1.29). The mean and range of inter-eye asymmetry of cup shape, were therefore greater than the asymmetry of disc shape. Asymmetry in cup shape was significantly related to asymmetry of cup area (the larger cup of the two eyes tended to be more vertically oval), disc shape (the more vertically oval disc tended to have a more vertically oval cup) and disc area (the larger disc tended to have the more vertically oval cup. However, these 3 factors together only accounted for 11.8% of the variability in cup shape asymmetry.

Mean (median) vertical cup-disc ratio asymmetry in this study was 0.07 (0.05). This compares with median VCDR asymmetry reported by the BMES[67] among normals (0.05) and mean VCDR reported by the Baltimore Eye Survey[9] (0.067 among blacks and 0.086 among whites).

More important are 97.5th and 99.5th percentiles of VCDR asymmetry, as they define limits of normal according to the 3 levels of evidence of the ISGEO criteria.[7] 97.5th percentile of

VCDR asymmetry was 0.32, with the 99.5th percentile being 0.42. Corresponding percentiles of clinically estimated VCDR asymmetry were 0.2 and 0.3 (median 0). VCDR asymmetry was significantly higher among persons who had no physiological cupping in any one eye (Figure 4.6.4). In persons with bilateral physiological cupping, 97.5th percentile of VCDR was 0.2 and 99.5th percentile was 0.27.

In the current study, 93.1% of patients had VCDR asymmetry of 0.2 or less, 96.1% had asymmetry 0.3 or less, 99.8% had CDR asymmetry 0.4 or less and 1 person had VCDR asymmetry of 0.5. When persons with absence of cupping in any one eye were excluded, VCDR asymmetry of 0.2 or less were seen in 97.9% of subjects, and all subjects had asymmetry lesser than 0.3.

Comparing these figures with planimetric estimates of CDR asymmetry from other studies, Jonas et al reported that asymmetry of 0.2 or less were present in 96% of 138 subjects, and asymmetry of 0.3 or less in 100% of them.[22] Ong et al reported CDR asymmetry of 0.2 or less in 99% and 0.3 or less in 100% of normals from the BMES.[67] The Baltimore Eye survey reported VCDR asymmetry of 0.2 or less in 98% black subjects and 96% white subjects.[9]

In addition to the above factor, VCDR asymmetry also showed a significant association with disc area asymmetry, which accounted for 8% of the variability in VCDR asymmetry. VCDR asymmetry did not show any significant association with IOP asymmetry, refractive error asymmetry, disc shape asymmetry, or the value of average VCDR of the 2 eyes.

CHAPTER-4

SUMMARY & CONCLUSIONS

4.1. SUMMARY OF RESULTS

Mean optic disc area in this study was 2.8 ± 0.5 sq mm, with 3.3 times variability. 2.5th and 97.5th percentiles for optic disc area were 1.9 and 4 sq mm respectively. The optic disc area was larger than the values reported among white Caucasian populations and measures reported among East Asian populations. It was smaller than that reported for African Americans. The distribution of optic disc area in the current study showed a bell-shaped distribution with a skew to the right. No association with age, gender, refraction, height or axial length were noted.

Mean VDD was 1.94 ± 0.2 mm and mean HDD was 1.81 ± 0.19 mm, with approximately two times variability of both measures. The mean ratio of VDD to HDD was 1.08, indicating that on average, optic discs were vertically oval with the vertical diameter about 8% longer than the HDD. Disc shape (VDD/HDD) was associated with torsion of the optic disc and showed weaker relationships with age and gender. Together, these 3 factors accounted for 10% of the variability of disc shape. VDD/HDD did not show any relationship with spherical or astigmatic refractive error or axial length.

Mean neural rim area in this study was 2.29 ± 0.39 sq.mm, with nearly threefold variability. In tandem with disc area values, rim area in the current study was higher than that reported among white Caucasians and reported rim areas among Japanese subjects. However, in contradiction to disc area measures, our rim area measures were larger than reported rim area for African Americans. Accounting for magnification differences and disc area differences greatly brings down the racial variability in rim area. However, differences in the way the cup margins were marked would continue to be a source of variability. The arrangement of nerve fibres at the optic disc may be one more contributor to variability in measured rim areas between studies among different ethnic groups, and also may account for variability in rim area/ disc area

In agreement with previous studies among Indians and white Caucasians, rim area showed a significant positive correlation with disc area, which accounted for 44% of the variability in rim area. In addition, rim area was also significantly influenced by type of cupping, which accounted for 19.5% of rim area variability.

In the current study, we found that on examination of mean values, the inferior rim was thickest, and temporal rim was thinnest, in accordance with the most important components of the ISNT rule as stated by Jonas et al. On average, the inferior rim was about 20% thicker than the superior rim. The lower 2.5th percentile of the ratio of inferior/superior rim width was 0.9,

which indicates that in this ethnic group, an inferior rim that is 90% of the thickness of the superior rim may be considered the lower limit of normal. 7.1% of eyes had superior rims thicker than the inferior rim. Torsion of the disc increased the odds of a thicker superior rim by more than five times. The temporal rim was not the thinnest in 12% of eyes (excluding nasal rims). Disc shape (low VDD/HDD), astigmatism and type of cupping (sloping rims) were significant contributors to this outcome.

Mean optic cup area in this population was 0.53 ± 0.39 sq mm. Like rim area, optic cup area also demonstrated a strong positive correlation with optic disc area. Cup area showed a weaker relationship with morphological type of cupping. Steep, well demarcated cups were significantly larger than cups with sloping rims.

In this population, approximately half the discs had fairly well demarcated cupping, about 14% had no cups and the rest had at least part of the temporal rim sloping. Among eyes with physiological cupping, mean VCD was approximately equal to mean HCD (mean VCD/HCD was almost equal to 1) indicating, on average, fairly circular cups.

The most significant predictor of cup shape in our study was disc shape, which accounted for about 18% of variability in cup shape. More vertically oval discs tended to have more vertically oval cups. Other, weaker predictors were disc area, type of cupping and cup area. Larger discs, discs with sloping rims and larger cups were associated with more vertically oval cups. Together, these three factors accounted for 5% of the variability in cup shape.

The mean (median) vertical and horizontal cup-disc ratios in the current planimetric study were 0.36 (0.39) and 0.39 (0.43) respectively. 97.5^{th} and 99.5^{th} percentiles were 0.63 and 0.68 for vertical CDR and 0.66 and 0.72 for HCDR. On average HCDR was 7% greater than VCDR. VCDR was significantly affected by disc size (disc area and vertical diameter) and by physiological type of cupping.

The intraclass correlation co-efficient for agreement between clinical estimates and planimetrically measured VCDR was 0.74, indicating good agreement between the two methods. Discs were much more likely to be classified as having no physiological cupping on evaluation of stereophotographs, compared to clinical examination of the patient. Among discs with physiological cupping, clinical assessment tended to underestimate small cups and overestimate large cups compared to planimetry.

Mean asymmetries of disc, cup and rim areas were 0.19 sq mm, 0.15 and 0.18 sq mm (median 0.15, 0.12 and 0.14 sq mm) respectively. Rim area asymmetry showed a significant correlation with disc area asymmetry, which accounted for 35.9% of variability in rim area asymmetry. Rim area asymmetry also correlated with weakly with IOP asymmetry which accounted for 0.9% of the variability in rim area asymmetry. Optic cup area asymmetry correlated with disc area asymmetry, which accounted for 25% of the variability in optic cup asymmetry.

Average disc shape (VDD/HDD) asymmetry in this population was 0.06 (i.e., the VDD of one eye was an additional 6% longer than its HDD). The mean asymmetry in VCD/HCD was 0.16 (median 0.09). Inter-eye asymmetry of cup shape was therefore greater than the asymmetry of disc shape. Asymmetry in cup shape was significantly related to asymmetry of cup area (the larger cup of the two eyes tended to be more vertically oval), disc shape (the more vertically oval disc tended to have a more vertically oval cup) and disc area (the larger disc tended to have the more vertically oval cup. However, these 3 factors together only accounted for 11.8% of the variability in cup shape asymmetry.

Mean (median) planimetric vertical cup-disc ratio asymmetry in this study was 0.07 (0.05). 97.5^{th} percentile of VCDR asymmetry was 0.32, with the 99.5^{th} percentile being 0.42. In the current study, 93.1% of patients had VCDR asymmetry of 0.2 or less, 97.35 % had asymmetry 0.3 or less, 99.65% had CDR asymmetry 0.4 or less and 2 persons had VCDR asymmetry of 0.5. VCDR asymmetry was significantly higher among persons who had no physiological cupping in any one eye. When persons with absence of cupping in any one eye were excluded, VCDR asymmetry of 0.2 or less were seen in 97.9% of subjects, and all subjects had asymmetry lesser than 0.3. VCDR asymmetry also showed a significant association with disc area asymmetry which accounted for 8% of the variability in VCDR asymmetry.

Most important outcomes

The most important outcomes of this study are those that would directly influence assessment of optic discs on an everyday basis. They are

- The dependence of neural rim area, cup area and VCDR on morphological type of cupping, in addition to disc area. This suggests the need to consider both

physiological variables in the assessment and interpretation of variations in rim area and VCDR.

- Deviations from ISNT rule in a significant minority of healthy subjects and the associations of these deviations with easily identifiable clinical parameters.
    - In this population, a normal disc need not necessarily have a thicker inferior than superior rim- in the absence of other glaucomatous features, an inferior rim with width at least 90% of the superior rim may be normal especially if the disc is torted.
    - In the assessment of discs with thinner superior or inferior than temporal rims, in the absence of any other features suggestive of glaucoma, disc shape, astigmatism and any oblique arrangement of nerve fibres must be considered as possible physiological reasons for this finding.
- While we defined 97.5^{th} and 99.5^{th} percentiles of VCDR as 0.6 and 0.7 (approximated to the first decimal place) planimetrically, it is also important to bear in mind that clinical estimation tended to overestimate large cups and underestimate small ones.
- Vertically oval discs tended to have vertically oval cups. To a smaller extent, vertically oval cup shape was associated with larger discs, larger cups and sloping rims. In the assessment and interpretation of vertically oval cups which are otherwise normal, these factors must be considered.
- We defined 97.5^{th} and 99.5^{th} percentiles of VCDR asymmetry as 0.32 and 0.42 respectively. VCDR asymmetry was markedly higher among persons who had no physiological cupping in any one eye. On excluding this group, 97.5^{th} and 99.5^{th} percentiles of VCDR asymmetry were 0.2 and 0.27.

4.2. ADVANTAGES & LIMITATIONS

The advantages of the study are its large sample size and population-based design. The large sample size permits exploration of a number of associations between optic disc parameters and other ocular/systemic factors. The population-based design permits extrapolation of results to the population that the sample represents i.e., South Indians.

Though time consuming, the technique of planimetry of digital photographs has its distinct advantages. First it presents the optic disc to the examiner as it is, and directly permits clinically relevant measurements with direct clinical applicability. The Heidelberg Retina Tomograph (HRT) is used more and more these days to obtain planimetric data,[19] however, it does not provide direct linear measures of disc diameters or rim widths, which are what the examiner usually estimates during a routine clinical disc examination. It also does not provide measures of such features as torsion and tilting of the optic disc.

All planimetry was performed by a single observer, which minimizes inter-observer variations. Also, except knowing that the subject was perimetrically normal, the observer was masked to all other clinical information about the subject, and was also masked to planimetric measures of the other eye while performing evaluation. This approach is likely to have minimized observer bias.

A possible limitation of this study was that the mean age of participants in the planimetric study was significantly lower than the mean age of the larger group of CGS participants from the two selected clusters. However, in the interest of obtaining true dimensions and in an effort to avoid inappropriate influences on ocular magnification, we took care to avoid all cataract, aphakia and pseudophakia, and therefore this age difference was unavoidable. The inclusion of only 2 out of 5 clusters is another possible source of error. The last 2 clusters were chosen due to logistic reasons - keratometry was performed only for these 2 clusters. The selection was not in any way based on, or influenced by, the nature of the data or findings. The inclusion of ocular hypertensives in the current study introduces the possibility that we may have included some patients with early (pre-perimetric) glaucoma.

4.3. CONCLUSIONS

In conclusion, we present normative values for (a) optic disc size and shape, (b) neural rim area and relative neural rim width (c) optic cup size and shape (d) cup-to-disc ratios and (e)

inter-eye asymmetry of all above parameters. From this population-based study on perimetrically normal persons aged 40 years or above, we present ranges within which 95% of readings would fall, defining statistical limits of normal for the South-Indian population.

We also report associations of the above measures with other biological factors. Optic cup and rim areas correlated with disc area and type of cupping. The occurrence of thicker superior compared to inferior rims was associated with disc torsion, and the occurrence of non-thinnest temporal rims with horizontally oval disc shape, astigmatism and sloping rims. Vertical cup-disc ratio was associated with disc size and type of cupping. Compared to planimetric evaluation, clinical estimates tended to underestimate small cups and overestimate large cups. Rim and cup area symmetries were significantly associated with disc area asymmetry. VCDR asymmetry was also associated with disc area asymmetry. Exclusion of discs with absent cupping in any one eye reduced the limits of VCDR asymmetry.

4.4. SPECIFIC CONTRIBUTION

To the best of our knowledge, this is the largest study of quantitative optic disc dimensions from this part of the world, which is home to approximately one-sixth of the world's population. As recommended by the International Society for Geographic and Epidemiological Ophthalmology (ISGEO) in recognition of racial variations in optic disc parameters, it is best that limits of normal parameters be derived from examination of perimetrically normal persons from the same populations.[7] From this study, we present statistical limits of normal optic disc parameters- optic disc, rim and cup sizes, disc, rim and cup shapes, and inter-eye asymmetry of disc, rim and cup measures for this ethnic group. This is the first study to describe these limits for relative neural rim width (rim shape), disc and cup shapes, cup-disc ratios, and inter-eye asymmetry of any optic disc parameters from India.

The associations described bear important clinical relevance. This is the first study to demonstrate dependence of deviations from ISNT rule with easily recognizable features – thicker superior rims with torsion and non-thinnest temporal rims with horizontally oval discs and type of cupping. It is also the first to show dependence of vertically oval cups on vertically oval (larger) discs, and dependence of VCDR on type of cupping, in addition to disc size. Though sloping rims are often recognized by ophthalmologists as potential confounders in assessment of many variables, this is the first study to document the relationships.

4.5. FUTURE SCOPE OF WORK

Future work may involve performing similar analysis in persons with different stages of glaucoma- early, moderate and pre-perimetric glaucoma. Comparison of findings with the current study may help refine the current norms, as well as assess the diagnostic capability of different optic disc measures in identifying glaucoma at various stages.

CHAPTER-5

REFERENCES

1. Bartz-Schmidt KU, Sundtgen M, Widder RA, Weber J, Krieglstein GK. Limits of two-dimensional planimetry in the follow-up of glaucomatous optic discs. Graefes Arch Clin Exp Ophthalmol. 1995;233: 284-90.,
2. Ikram MK, Borger PH, Assink JJ, Jonas JB, Hofman A, de Jong PT. Comparing ophthalmoscopy, slide viewing, and semiautomated systems in optic disc morphometry. Ophthalmology. 2002;109: 486-93.
3. Mansour AM. Racial variation of optic disc size. Ophthalmic Res. 1991;23(2):67-72.
4. Ramrattan RS, Wolfs RCW,.Jonas JB, Hofman A, de Jong PTVM. Determinants of Optic Disc Characteristics in a General Population-The Rotterdam Study. Ophthalmology 1999; 106:1588-1596.
5. Miglior S, Brigatti L, Velati P, Balestreri C, Rossetti L, Bujtar E, Orzalesi N. Relationship between morphometric optic disc parameters, gender and axial length. Curr Eye Res 1994;13: 119-24.
6. Garway-Heath DF, Ruben ST, Viswanathan A , Hitchings RA. Vertical cup/disc ratio in relation to optic disc size : its value in the assessment of the glaucoma suspect. Br J Ophthalmol 1998;82:1118-1124.
7. Foster PJ, Buhrmann R, Quigley HA, Johnson GJ. The definition and classification of glaucoma in prevalence surveys. Br J Ophthalmol. 2002;86: 238-42.
8. Miglior S, Guareschi M, Albe E, Gomaraska S, Vavarossi N, Orsalezi N. Detection of Glaucmatous Visual Field Changes using the Moorfields Regression analysis of the Heidelberg Retina Tomograph. Am J Ophthalmology 2003;136: 26-33.
9. Varma R, Tielsch JM, Quigley HA, Hilton SC, Katz J, Spaeth GL, Sommer A. Race-, age-, gender-, and refractive error-related differences in the normal optic disc. Arch Ophthalmol 1994;112: 1068-76.
10. Healey PR, Mitchell P, Smith W, Wang JJ. Relationship between cup-disc ratio and optic disc diameter: the Blue Mountains Eye Study. Aust N Z J Ophthalmol 1997;25 Suppl 1:S99-101.
11. Gross P, Drance S. Comparison of simple ophthalmoscopic and planimetric measurement of glaucomatous neuroretinal rim areas. J Glaucoma 1995;4:314-316.
12. Ansari-Shahrezaei S, Maar N, Biowski R, Stur M. Biomicroscopic measurement of the optic disc with a high-power positive lens. Invest Ophthalmol Vis Sci 2001;42: 153-157.

13. Ansari-Shahrezaei S, Stur M. Magnification characteristic of a +90-diopter double-aspheric fundus examination lens. Invest Ophthalmol Vis Sci. 2002;43: 1817-9.
14. Spencer AF, Vernon SA. Optic disc height measurement with the Zeiss 4-mirror contact lens and 78 dioptre lens compared. Eye 1996;10: 371-6.
15. Haslett RS, Batterbury M, Cuypers M, Cooper RL. Inter-observer agreement in clinical optic disc measurement using a modified 60 D lens. Eye 1997;11:692-7.
16. Jonas JB, Papastathopoulos K. Ophthalmoscopic measurement of the optic disc. Ophthalmology 1995;102: 1102-6.
17. Spencer AF, Vernon SA. Optic disc measurement with the Zeiss four mirror contact lens. Br J Ophthalmol 1994;78: 775-80.
18. Akman A, Oram O, Aydin P. Optic disc measurements with the 78 diopter lens, Zeiss 4-mirror contact lens and computerized image analysing system. Eur J Ophthalmol 1998;8: 22-7.
19. Pyott AA, Montgomery DM. Inter-observer variation in clinical optic disc biometry. Eye 1993;7: 452-6.
20. Klein BEK, Magli YL, Richie KA, Moss SE, Meuer SM, Klein R. Quantitation of Optic Disc Cupping. Ophthalmology 1985;92: 1654-1656.
21. Bengtsson B, Krakau CE. Correction of optic disc measurements on fundus photographs. Graefes Arch Clin Exp Ophthalmol 1992;230: 24-28.
22. Jonas JB, Gusek GC, Naumann GOH. Optic Disc, Cup and Neuroretinal Rim Size, Configuration and Correlations in Normal Eyes. Invest Ophthalmol Vis Sci 1988;29: 1151- 1158.
23. Williams TD. Determination of the True Size of an Object on the Fundus of the Living Eye. Optometry and Vision Science 1992;69: 717-720.
24. Jonas JB, Gusek GC, Guggenmoos-Holzmann I, Naumann GO. Variability of the real dimensions of normal human optic discs. Graefes Arch Clin Exp Ophthalmol. 1988; 226(4):332-6.
25. Garway-Heath DF, Poinoosawmy D, Wollstein G, Viswanathan A, Kamal D, Fontana L, Hitchings RA. Inter- and intraobserver variation in the analysis of optic disc images: comparison of the Heidelberg retina tomograph and computer assisted planimetry. Br J Ophthalmol 1999;83: 664-9.

26. Shuttleworth GN, Khung HC, Diamond JP. A new digital optic disc stereo camera: intraobserver and interobserver repeatability fof optic disc measurements. Br J Ophthalmol 2000;84:403-407.
27. Gili Manzanaro P, Carrasco Font C, Martin Rodrigo JC, Yanguela Rodilla J, Arias Puente A. Digital analysis of the optic disc with fundus camera: a study of variability. Arch Soc Esp Oftalmol 2004;79:125-30.
28. Sanchez Perez A, Honrubia Lopez FM, Larrosa Poves JM, Polo Llorens V, Melcon Sanchez-Frieras B. The Autocad system for planimetric study of the optic disc in glaucoma: technique and reproducibility study. Arch Soc Esp Oftalmol 2001;76:551-8.
29. Nguyen NX, Horn FK, Langenbucher A, Mardin CY. Conventional versus digital planimetry of optic disc photograph: a clinical comparative study. Klin Monatsbl Augenheilkd 2001;218:727-32.
30. Kwon YH, Kim YL, Pereira ML et al. Rate of optic disc cup progression in treated primary open-angle glaucoma. J Glaucoma 2003;12:409-416.
31. Moya FJ, Brigatti L, Caprioli J. Effect of aging on optic nerve appearance: a longitudinal study. Br J Ophthalmol 1999;83:567-572.
32. Sekhar GC, Prasad K, Dandona R, John RK, Dandona L. Planimetric optic disc parameters in normal eyes: a population-based study in South India. Indian J Ophthalmol 2001;49:19-23
33. Bennett AG, Rudnicka AR, Edgar DF. Improvements on Littmann's method of determining the size of retinal features from fundus photography. Graefe's Arch Clin Exp Ophthalmol 1994;232:361-367.
34. Garway-heath DF, Rudnicka AR, Lowe T et al. Measurement of optic disc size: equivalence of methods to correct for ocular magnification. Br J Ophthalmol 1998;82:643-649.
35. Feuer WJ, Parrish RK 2nd, Schiffman JC, Anderson DR, Budenz DL, Wells MC, Hess DJ, Kass MA, Gordon MO. The Ocular Hypertension Treatment Study: reproducibility of cup/disk ratio measurements over time at an optic disc reading center. Am J Ophthalmol 2002;133:19-28.

36. Automated Segmentation of the Optic Disc from Stereo Color Photographs Using Physiologically Plausible Features. Abra`moff MD, Alward WLM, Greenlee EC, Shuba L, Kim CY, Fingert JH, Kwon YH. Invest Ophthalmol Vis Sci. 2007;48:1665–1673.
37. Optic nerve head and retinal nerve fiber layer analysis. American Academy of Ophthalmology. Ophthalmology 1999;106:1414-24.
38. Lachkar Y, Cohn H. Sensitivity and specificity of optic disc variables and analysis of a new variable (MP/D) for glaucoma diagnosis with the Glaucoma-Scope. Br J Ophthalmol 1997;81:846-51.
39. Stein DM, Wollstein G, Schuman JS. Imaging in glaucoma. Ophthalmol Clin North Am 2004;17:33-52.
40. Miglior S, Albe E, Guareschi M, Rossetti L, Orzalesi N. . Intraobserver and interobserver reproducibility in the evaluation of optic disc stereometric parameters by Heidelberg Retina Tomograph. Ophthalmology 2002 Jun;109(6):1072-7.
41. Rohrschneider K, Kruse FE. Reproducibility of the optic nerve head topography with a new laser tomographic scanning device. *Ophthalmology* 1994; 101: 1044-1049.
42. Garway-Heath DG. Moorfields regression analysis. In: Fingeret M, Flanagan JG, Liebmann JM, eds. The Essential HRT Primer. San Ramon, California: Jocoto Advertising Inc; 2005:31–39.
43. Joseph R. Zelefsky, Noga Harizman, Ricardo Mora et al. Assessment of a Race-specific Normative HRT-III Database to Differentiate Glaucomatous From Normal Eyes. J Glaucoma 2006;15:548–551.
44. Hatch WV, Flanagan JG, Williams-Lyn DE et al. Interobserver agreement of Heidelberg retina tomograph parameters. J Glaucoma 1999;8:232-7
45. Jonas JB, Mardin CY, Grundler AE. Comparison of measurements of neuroretinal rim area between confocal laser scanning tomography and planimetry of photographs. Br J Ophthalmol 1998;82:362-6.
46. Dichtl A, Jonas JB, Mardin CY. Comparison between tomographic scanning evaluation and photographic measurement of the neuroretinal rim. Am J Ophthalmol 1996;121):494-501.

47. Vernon SA, Hawker MJ, Gerard Ainsworth G et al. Laser Scanning Tomography of the Optic Nerve Head in a Normal Elderly Population: The Bridlington Eye Assessment Project. Invest Ophthalmol Vis Sci 2005;46:2823–2828.
48. Uchida H, Yamamoto T, Araie M et al. Topographic characteristics of the optic nerve head measured with scanning laser tomography in normal japanese subjects. Jpn J Ophthalmol 2005;49:469–476.
49. Bigelow CE, Iftimia NV, Ferguson RD et al. Compact multimodal adaptive-optics spectral-domain optical coherence tomography instrument for retinal imaging. J Opt Soc Am A Opt Image Sci Vis. 2007 ;24: 1327-36.
50. Iliev ME, Meyenberg A, Garweg JG. Morphometric assessment of normal, suspect and glaucomatous optic disks with Stratus OCT and HRT II. Eye 2005; Epub date: September 23, 2005.
51. Meyer T, Howland HC. How large is the optic disc? Systematic errors in fundus cameras and topographers. Ophthalmic Physiol Opt. 2001;21:139-50.
52. Thomas R, George R, Muliyil J, Jonas JB. Correlation of confocal laser scanning tomography with planimetric photographic measurements of the optic disc in a normal South Indian population: The Vellore eye study. Indian J Ophthalmol 2005;53:289-294.
53. Garway-Heath DF, Wollstein G, Hitchings RA: Aging changes of the optic nerve head in relation to open angle glaucoma. Br J Ophthalmol 81:840--5, 1997.
54. Schuman JS, Wollstein G, Farra T, Hertzmark E, Aydin A, Fujimoto JG, Paunescu LA. Comparison of optic nerve head measurements obtained by optical coherence tomography and confocal scanning laser ophthalmoscopy. Am J Ophthalmol 2003;135:504-12.
55. Arthur SN, Aldridge AJ, Julio De Leo´n-Ortega et al. Agreement in Assessing Cup-to-Disc Ratio Measurement Among Stereoscopic Optic Nerve Head Photographs, HRT II, and Stratus OCT. J Glaucoma 2006;15:183–189.
56. Jonas JB, Thomas R, George R, Berenshtein E, Muliyil J. Optic disc morphology in south India: the Vellore Eye Study. Br J Ophthalmol 2003 Feb;87(2):189-96.
57. Wang Y, Xu L, Zhang L, Yang H, Ma Y, Jonas JB. Optic disc size in a population based study in northern China: the Beijing Eye Study. Br J Ophthalmol 2006;90:353–356.

58. Budde WM, Jonas JB, Martus P, Grundler AE. Influence of optic disc size on neuroretinal rim shape in healthy eyes. J Glaucoma 2000; 9:357–362.
59. Harizman N, Oliveira C, Chiang A et al. The ISNT rule and differentiation of normal from glaucomatous eyes. Arch Ophthalmol 2006;124:1579-1583..
60. Sihota R, Srinivasan G, Dada T, Gupta V, Ghate D, Sharma A. Is the ISNT rule violated in early primary open-angle glaucoma- a scanning laser tomography study? Eye advance online publication, 13 April 2007; Eye (2007), 1-6)
61. Jonas JB, Budde WM, Lang P. Neuroretinal rim width ratios in morphological glaucoma diagnosis Br. J. Ophthalmol. 1998;82;1366-1371.
62. Jonas JB, Budde WM. Is the nasal optic disc sector important for morphometric glaucoma diagnosis? Br J Ophthalmol 2002;86:1232–1235
63. Jonas JB, Gusek GC, Guggenmoos-Holzmann I, Naumann GO. Correlations of the neuroretinal rim area with ocular and general parameters in normal eyes. Ophthalmic Res. 1988;20(5):298-303.
64. Kashiwagi K, Tamura M, Abe K, Kogure S, Tsukahara S. The influence of age, gender, refractive error, and optic disc size on the optic disc configuration in Japanese normal eyes. Acta Ophthalmol Scand. 2000 Apr;78(2):200-3.
65. Crowston JG, Hopley CR, Healey PR, Lee A, Mitchell P. The effect of optic disc diameter on vertical cup to disc ratio percentiles in a population based cohort: the Blue Mountains Eye Study. Br J Ophthalmol 2004;88:766–770.
66. Armaly MF. Genetic determination of cup/disc ratio of the optic nerve. Arch Ophthalmol. 1967;78:5-43..
67. Ong LS, Mitchell P, Healey PR, Cumming RG. Asymmetry in Optic Disc Parameters: The Blue Mountains Eye Study. Invest Ophthalmol Vis Set. 1999;40:849-857..
68. Hawker MJ, Vernon SA, Ainsworth G et al. Asymmetry in Optic Disc Morphometry as Measured by Heidelberg Retina Tomography in a Normal Elderly Population: The Bridlington Eye Assessment Project. Invest Ophthalmol Vis Sci. 2005; 46:4153–4158.
69. Zangwill LM, Weinreb RN, Berry CC, Smith AR, Dirkes KA, Coleman AL, Piltz-Seymour JR, Liebmann JM, Cioffi GA, Trick G, Brandt JD, Gordon MO, Kass MA; Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study. Racial differences in optic disc topography: baseline results from the

confocal scanning laser ophthalmoscopy ancillary study to the ocular hypertension treatment study. Arch Ophthalmol. 2004 Jan;122(1):22-8.

70. Girkin CA, McGwin Jr G, Xie A, Deleon-Ortega J. Differences in Optic Disc Topography between Black and White Normal Subjects. Ophthalmology 2005;112:33–39.
71. Tsai CS, Zangwill L, Gonzalez C, et al. Age related decline of disc rim area in visually normal subjects. Ophthalmology 1992; 99:29-35
72. Jonas JB. Optic disk size correlated with refractive error. Am J Ophthalmol. 2005 ;139(2):346-8.
73. Healey PR, Mitchell P, Smith W, Wang JJ. The influence of age and intraocular pressure on the optic cup in a normal population. J Glaucoma. 1997 Oct;6(5):274-8.
74. Varma R, Hilton SC, Tielsch JM, et al. Neural rim declines with increased intraocular pressure in urban Americans. Arch Ophthalmol 1995;113:1001-5.
75. Britton RJ, Drance SM, Schulzer M et al. The area of the neural rim of the optic nerve in normal eyes. Am J Ophthalmol 1987; 103: 497-804.
76. Oliveira C, Harizman N, Girkin CA, et al. Axial length and optic disc size in normal eyes. Br J Ophthalmol 2007;91:37–39.
77. Pakravan M, Parsa A, Sanagou M, Parsa CF. Central corneal thickness and correlation to optic disc size: a potential link for susceptibility to glaucoma. Br J Ophthalmol 2007;91:26–28.
78. Budde WM, Velten IM, Jonas JB. Optic disc size and iris color. Arch Ophthalmol 1998 ;116:545
79. Jonas JB, Budde WM, Stroux A, Oberacher-Velten IM. Iris colour, optic disc dimensions, degree and progression of glaucomatous optic nerve damage. Clinical and Experimental Ophthalmology 2006; 34: 654–660.
80. Topouzis F, Coleman AL, Harris A et al. Association of Blood Pressure Status With the Optic Disk Structure in Non-glaucoma Subjects: The Thessaloniki Eye Study. Am J Ophthalmol 2006;142: 60–67.
81. Arvind H, Paul PG, Raju P, Baskaran M,et al. Methods and Design Of the Chennai Glaucoma Study. *Ophthalmic Epidemiology* 2003;10:337-48.

82. Census of India 1991, Govt of India Publication, Series 23, Part XII –B, District census handbook, Chengelpet MGR district, 214- 343.
83. Census of India 1991, Govt of India Publication Series, 23, part IV B – (ii), Religion (Table C-9), 22-29.
84. Census of India 1991, Govt of India Publication, Series 23; Part IV A, C Series) 25-54.
85. Census of India, Govt of India Publication. Table C-6, Part IV - Social and Cultural Tables, 56- 60..
86. World Medical Association. Declaration of Helsinki. Recommendation guiding physicians in bio-medical research involving human subjects. *JAMA* 1997; 277:925-926.
87. Ferris FL, Bailey I: Standardizing the Measurement of Visual Acuity for Clinical Research Studies-Guidelines from the Eye Care Technology Forum. Ophthalmology 1996; 103: 181-182.
88. Lester M, Capris P, Pandolfo A, Zingirian M, Traverso CE. Learning Effect, Short Term Fluctuation, and Long Term Fluctuation in Frequency Doubling Technique. Am J Ophthalmol 2000; 130:160-164.
89. Van Herick W, Shaffer RN, and Schwartz A. Estimation of width of angle of anterior chamber: incidence and significance of the narrow angle. Am J Ophthalmol 1969; 68: 626-629.
90. Kass MA. Standardizing the measurement of Intraocular Pressure for Clinical Research-Guidelines from the Eye Care Technology Forum. Ophthalmology 1996; 103: 183-185.
91. Shaffer RN. Symposium:primary glaucomas.III.Gonioscopy, ophthalmoscopy and perimetry. Trans Am Acad Ophthal Otol 1960; 62: 112.
92. Chylack LT, Leske MC, McCarthy D, Khu P, Kashiwagi T, Sperduto R. Lens Opacities Classification System II (LOCS II). Arch Ophthalmol 1989; 107: 991-997.
93. Vongphanit J, Mitchell P, Wang JJ. Population Prevalence of Tilted Optid Disks and the relationship of this sign to Refractive Error. Am J Ophthalmol 2002;133:679-685.
94. George R, Paul P G, Baskaran M, Ramesh S Ve, Raju P, Arvind H, McCarty C, Vijaya L. Ocular biometry in occludable angles and angle closure glaucoma: a population based survey. *British Journal of Ophthalmology* 2003;87:399-402
95. Justice J Jr, Lehmann RP. Cilioretinal arteries. *Arch Ophthalmol.*1976;94:1355–1358.

96. Mikelberg FS, Drance SM, Schulzer M, Wijsman K. Possible significance of cilioretinal arteries in low-tension glaucoma. Can J Ophthalmol. 1990 ;25(6):298-300
97. Budde W M, Jonas JB. Influence of Cilioretinal Arteries on Neuroretinal Rim and Parapapillary Atrophy in Glaucoma *Invest Ophthalmol Vis Sci.* 2003;44:170–174
98. Altman DG, Bland JM. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1 (8476): 307–10.
99. Wensor M D, McCarty CA, Stanislavsky YL, Livingston PM, Taylor HR. The prevalence of glaucoma in the Melbourne Visual Impairment Project. Ophthalmology 1998; 105: 733-739.
100. Leske MC, Connell AMS, Schachat AP, Hyman L, the Barbados Eye Study Group. The Barbados Eye Study: Prevalence of Open Angle Glaucoma. Arch Ophthalmol 1994; 112:821-829.
101. Jayasundera T, Danesh-Meyer H, Donaldson M, Gamble G. Agreement between stereoscopic photographs, clinical assessment, Heidelberg retina tomograph and digital stereoscopic optic disc camera in estimating vertical cup:disc ratio. *Clin Exp Ophthalmol* 2005;33: 259–263.
102. Correnti AJ, Wollstein G, Price LL, Schuman JS. Comparison of optic nerve head assessment with a digital stereoscopic camera (discam), scanning laser ophthalmoscopy, and stereo photography. *Ophthalmology* 2003; 110 : 1499–505.
103. Saruhan A, Orgul S, Kocak I, et al. Descriptive information of topographic parameters computed at the optic nerve head with the Heidelberg retina tomograph. *J Glaucoma*. 1998;7: 420–429.

PUBLICATIONS FROM THESIS

1. Hemamalini Arvind, Pradeep Paul, Prema Raju, M Baskaran, Ronnie George, Sukumar Balu, Sarangapani Sripriya, S Ve Ramesh, B N Mukesh, L Vijaya, G Kumaramanickavel, Catherine McCarty. **Methods and Design of the Chennai Glaucoma Study.** *Ophthalmic Epidemiology* 2003; 10: 337-348.
2. Hemamalini Arvind, Ronnie George, Prema Raju, S Ve Ramesh, Baskaran Mani, Prashanth Kannan, L Vijaya. **Agreement Between Clinical Estimates And Planimetric Measures Of Vertical Cup-Disc Ratio.** Accepted for publication in *Clinical and Experimental Ophthalmology* 2007;35:881-882.
3. Hemamalini Arvind, Ronnie George, Prema Raju, S Ve Ramesh, Baskaran Mani, Prashanth Kannan, L Vijaya. **Neural Rim Characteristics of Healthy South Indians- The Chennai Glaucoma Study**. Accepted for publication in *Investigative Ophthalmology and Visual Sciences*.

PRESENTATIONS FROM THESIS

1. **Neural Rim Characteristics of South Indians- The Chennai Glaucoma Study:** Presented at the AOGS-SEAGIG meeting, Cairns, September 2005 (Asia-Oceania Glaucoma Society – South-East Asia Glaucoma Interest Group).
2. **Optic disc characteristics of South Indians: The Chennai Glaucoma Study.** Scientific poster, SEAGIG meeting, Chennai, December 2006.

OTHER PUBLICATIONS FROM THE CHENNAI GLAUCOMA STUDY

1. Hemamalini Arvind, Prema Raju, Pradeep Paul, M Baskaran, S Ve Ramesh, Ronnie George, Catherine McCarty, L Vijaya. **Pseudoexfoliation in South India.** *British Journal of Ophthalmology* 2003; 87: 1321-1323.
2. Hemamalini Arvind, Ronnie George, Prema Raju, S Ve Ramesh, M Baskaran, Pradeep Paul, L Vijaya. **Effect of Cataract Surgery with Intraocular Lens implantation on Frequency Doubling Perimetry.** *Current Eye Research* 2005; 30(2): 123-128.
3. Hemamalini Arvind, Ronnie George, Prema Raju, S Ve Ramesh, M Baskaran, Pradeep G Paul, Catherine McCarty, L Vijaya. **Glaucoma in Aphakia and Pseudophakia in**

the Chennai Glaucoma Study. *British Journal of Ophthalmology* 2005; 89(6): 699-703.

4. Hemamalini Arvind, Ronnie George, M Baskaran, Prema Raju, S Ve Ramesh, L Vijaya. **Effect of Extracapsular and Manual Small Incision Cataract Surgery with Intraocular Lens on Scanning Laser Polarimetry.** *Asian J Ophthalmology 2006;8:86-90 - Won the South-East Asia Glaucoma Interest Group (SEAGIG) 2006 Writer's Award.*
5. Ronnie George, Pradeep Paul, M Baskaran, S Ve Ramesh, Prema Raju, Hemamalini Arvind, Catherine McCarty, L Vijaya. **Ocular Biometry in Occludable angles and angle-closure glaucoma- a population-based survey.** *British Journal of Ophthalmology* 2003; 87: 399-402.
6. G.Kumaramanickavel, Sarangapani Sripriya, Ronnie George, Hemamalini Arvind, L Vijaya. **Low Frequency of myocilin mutations in Indian primary open-angle glaucoma patients.** *Clinical Genetics* 2004; 65: 333-7.
7. Prema Raju, S Ve Ramesh, Hemamalini Arvind, Ronnie George, M Baskaran, Pradeep Paul, G Kumaramanickavel, Catherine McCarty, L Vijaya. **Prevalence of Refractive Errors in a Rural South Indian population.** *Investigative Ophthalmology and Visual Sciences* 2004;45:4268-4272.
8. Pradeep G. Paul, Ronnie J. George, Mani Baskaran, Hemamalini Arvind, Madan Raj V, Augustian, S. Ve Ramesh, Prema Raju, Govindasamy Kumaramanickavel, Catherine McCarty, Lingam Vijaya. **A Comparison of Participants and Non-Participants in the Chennai Glaucoma Study—Rural Population.** *Ophthalmic Epidemiology* 2005; 12 (2): 125 -132.
9. Vijaya L, Ronnie George, Hemamalini Arvind, M Baskaran, Pradeep G Paul, S Ve Ramesh, Prema Raju, Govidasamy Kumaramanickavel, Catherine McCarty. **Prevalence of Angle-Closure Glaucoma in a Rural South Indian Population.** *Archives of Ophthalmology* 2006; 124:403-409.
10. Vijaya L, Ronnie George, Pradeep G Paul, Baskaran M, Hemamalini Arvind , Prema Raju, S Ve Ramesh, Govindasamy Kumaramanickavel, Catherine McCarty. **Prevalence of Open-Angle Glaucoma in a Rural South Indian Population.** *Invest Ophthalmol Vis Sci* 2005; 46:4461- 4467.

11. Vijaya L, Ronnie George, Hemamalini Arvind , Baskaran M, Prema Raju, S Ve Ramesh, Pradeep G Paul, Govindasamy Kumaramanickavel, Catherine McCarty. **Prevalence and Causes of Blindness in a Rural South Indian Population.** *Br J Ophthalmol* 2006; 90:406-410.
12. Prema Raju, Ronnie George, S Ve Ramesh, Hemamalini Arvind , Baskaran M, Vijaya L. **Influence of tobacco use on cataract development.** *Br J Ophthalmol* 2006;90:1374-7.
13. Sripriya S, Nirmaladevi J, George R, Hemamalini Arvind, Baskaran M, Prema Raju, S. Ve Ramesh, T. Karthiyayini, Amali J, Job S, Vijaya L, Kumaramanickavel G. **OPTN gene: Profile of patients with glaucoma from India.** *Mol Vision* 2006; 12:816-820.
14. Ramprasad VL, Sripriya S, George Ronnie, Derek Nancarrow, Sandeep Saxena, Arvind Hemamalini, Dipak Kumar, Lingam Vijaya, Kumaramanickavel G. **Genetic homogeneity for inherited congenital microcoria loci in an Asian Indian pedigree.** *Mol Vision* 2005; 11:934-940.
15. Vijaya L, George R, Arvind H, Baskaran M, Raju P, Ramesh S Ve, Kumaramanickavel G and McCarty CA. **Prevalence of Angle-Closure Disease in an Urban South Indian Population and Comparison with Rural Population- The Chennai Glaucoma Study.** Ophthalmology 2008;115: 655-660.
16. Vijaya L, George R, Baskaran M, Arvind H, Raju P, Ramesh S Ve, Kumaramanickavel G and McCarty CA. **Prevalence of Open-Angle Glaucoma in an Urban South Indian Population and Comparison with Rural Population- The Chennai Glaucoma Study.** Ophthalmology 2008 ;115: 648-654.
17. Sripriya S, George R, Arvind H, Baskaran M, Raju P, Ramesh SV, Karthiyayini T, Vijaya L, Kumaramanickavel G. **Transforming Growth Factor beta-1-509 C>T Polymorphism in Indian Patients with Primary Open Angle Glaucoma.** Mol Diagn Ther. 2007; 11(3):151-4.

BIOGRAPHY OF THE CANDIDATE

Dr. Hemamalini Arvind has been an Associate Consultant at Sankara Nethralaya since 2000. After completing her graduation from the Madras Medical College, Madras in 1996, she underwent further postgraduate training in ophthalmology (MS) at the Post Graduate Institute of Medical Education and Research, Chandigarh from 1996-1999. She has been associated with Sankara Nethralaya since 1999, first as a fellow in glaucoma and then as faculty in the same department.

She has played a key role in the inception and execution of a large population-based project on the prevalence of glaucoma in South India, The Chennai Glaucoma Study, which has produced several publications in prestigious international journals. She has presented several scientific papers at both national and international conferences, and has won the best paper award at the annual meeting of the Glaucoma Society of India, 2002. At present, she is enrolled in a PhD program on optic disc morphometry with BITS, Pilani.

BIOGRAPHY OF THE SUPERVISOR

Dr. L Vijaya is the Director of the Department of Glaucoma, Medical Research Foundation, Sankara Nethralaya, Chennai. After completing M.B.B.S. from S V Medical College, Tirupati, in 1980, she commenced Ophthalmology training at Kurnool Medical College, Kurnool, first doing Diploma in Ophthalmology in 1984, and then M.S. Ophthalmology in 1985. She sub-specialized in vitreoretinal surgery at Sankara Nethralaya in 1986, and has been working as a consultant in Sankara Nethralaya since 1987.

A distinguished academic, she has published more than 50 papers in several national and international journals, and 2 chapters in textbooks. She has presented papers in various national and international conferences and has delivered lectures as an invitee guest speaker. She is the principal investigator in the Chennai Glaucoma Study, a major epidemiological project on glaucoma in the South Indian population. She serves on the editorial board of the Asian journal of Ophthalmology and the Tamil Nadu Ophthalmology Association Journal. She is a reviewer for several national and international journals in ophthalmology. Not only is she an excellent clinician and surgeon, she is also a dedicated teacher, and has been instrumental in training several ophthalmology trainees over the years.